Agranulocytosis: (agranulocytic angina) (malignant granulocytopenia)

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AGRNULOCYTOSES: (Agranulocytic angina)
(Malignant Granulocytopenia)

by
Howard Gessford

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INTRODUCTION

When new diseases, inventions or wars are brought to light the object holding our attention is exceeding interesting because of the mystery attached to it. At first the center of attention is viewed with awe. Then comes a desire to master the condition and many people accept the challenge. The method of solution is at first more or less a trial and error affair till some clue is found, and used in a scientific way to lead to new information and a better understanding of the problem. When at last mastery has been attained, the subject loses its interest and a search is made for more and deeper problems.

This is true in the field of Hematology. Agranulocytosis is a part of that vast field and one of the most recent challenges in blood dyscrasias, and its relation to the rest of the hematologist's work is not clearly understood yet. Although definite advancement has been made, there is still much to learn because it is not known why some drug causes the picture of Agranulocytosis in some patients and does not in others. Nor is it known why the same drug may cause other reactions such as dermatosis, another picture which is far from the outlined action that the textbook says the drug should follow.

Not all references read are listed as they
seemed to be repetition or merely brief case reports which add very little information to the solution of the problem, except as a matter of statistics. The literature is voluminous on this subject.

Since human life is involved, Agranulocytosis is one of the most interesting problems. The mortality which was, only 20 years ago, listed 100% fatal in the first five cases reported has now dropped to somewhat below 50%. This shows that the efforts of such outstanding men as Jackson, H. Jr., Pepper, C.H.R., Fitzhugh, T. Jr., Doan, C.A., Parker, F. Jr., Kracke, R.R., Kiznikoff, Paul and many others has not been wasted.

I have attempted to gather together all the important evidence in detail and put it into a picture that will give the fullest and concise as possible picture of the still mysterious disease, Agranulocytosis, probably better known as Agranulocytic angina, or pernicious leukopenia and called many other names by different authors.

It is my hope that this report is beneficial to all who read it and that the conclusions drawn will in the end turn out to be correct as new information on this disease is revealed.

I wish to thank Dr. Lynn T. Hall for help in outlining a plan to attack the subject. Also Miss Evans and Mr. Moe for help in getting reference material
from the library. I also want to thank Miss Pauline Daugherty and Miss Marian Lebeck for typing this manuscript. And most of all the the University of Nebraska College of Medicine for the opportunity to make this and many other studies that will enable me to live better and help others to live.
AGRAÑULOCYTOSIS

1. History

Agranulocytosis is a condition, and probably a specific disease, which is characterized by destructive ulcerative lesions of the throat, leukopenia, marked reduction of granular cells in the blood and bone marrow, and sometimes icterus. It occurs most often in middle aged females but has developed in patients from infancy to eighty-seven years of age. The prognosis is bad and mortality is reported from 40% to 90% by many authors, with occasional extremes on both sides.

The disease was first described by Schultz in 1922. He felt that it was a syndrome resulting from a depressant action on the bone marrow by micro-organism or chemical agents. The first case reported in the United States was by Moore, 1925 (2) in a woman who survived the first attack but died two years later in the second attack. All cases so far reported had been in middle aged women, all had throat symptoms resembling diphtheritic exudate and occasionally a tonsil sloughed out. The gums often ulcerate, the genitalia may ulcerate and the intestines occasionally show lesions. The most characteristic lesion was recognized in the bone marrow. Turk, 1907 first described a case with a blood smear showing a nearly complete lymphocyte count fatal in four days and with throat symptoms. He did not consider it a new disease and is given very little credit
in the study of the new disease. Schultz outlined the group of cases with gangrenous stomatitis and remarkable blood picture and suggested the name Agranulocytic angina (3) the name is still popular.

Kizinoff, 1930 (4) suggested the Nucleotide therapy, which is the best treatment today. Jackson 1931 (5) developed and established the therapy due to Kizinoff's work.

A Classification of the disease may be made as follows to simplify study. (From many writers)
1 Agranulocytic angina, ii cases due to sepsis as pneumonia, etc. and iii cases due to toxic influence, as radioactive substance and benzol. Certain drugs are important, the sulforamids, barbituric acid series, arsphenamine, hydroquinone and the greatest offender amidopyrine. The benzene ring is a common factor in all these drugs.

The differential diagnosis is not always easily made. The nature of the primary lesion in the bone marrow is not agreed on by all though this is fairly well established, to the satisfaction of most doctors. There is no proven specific treatment that all doctors accept. There are still many aspects of this new, rather interesting, and all too often fatal disease that must be studied yet.

Roberts and Aracke 1930 (6) states that it is known to be a disease primarily of the bone marrow.
"We are far from a full knowledge of the blood and its diseases. Agranulocytosis is probably just another discovery in this field, and with it comes a clearer appreciation of its allied states, of the function of the granulocytes, and of the part they play in immunity."

II Classification

There is evidence that a granulopenia is a more important biologic state and blood condition than it has been considered. Roberts and Kracke (7) have done most of the work in an attempt to completely classify the granulopenias, just as anemia has been divided into different groups depending on the cause. Agranulocytosis must be considered as one of the granulopenias and be differentiated from the other causes for lack of polymorphonuclear leukocytes in the peripheral blood stream. The classification may have to be revised as knowledge shows to be necessary. Their classification, however, gives us a mental picture of the leukopenia and a better idea of the divisions, of which Agranulocytosis, or pernicious leukopenia or agranulocytic angina is a part.
The list includes:

1. Acute granulopenia of unknown cause.
This includes the nervous and psychic individuals, the babies who have sore gums and a low granulocyte count of 0-50%. In other words those cases where no cause can be identified.

2. Chronic granulopenia of unknown cause.
If a low granulocyte count is the result of debility, a neurosis or a chronic exhaustion, it is relatively unimportant, but on the contrary it may be the cause and the origin of the syndrome, the primary lesion may still be found in the bone marrow.

3. Acute granulosis with or without sepsis.
This is the most common type of the disease and the one primarily intended for discussion in this research. But this cannot be understood to any degree without consideration of the rest and at best there is still much to learn. Many cases die before the onset of sepsis. There the overwhelming collapse from the mere and continued absence of granulocytes is so great that death occurs before ulceration, necrosis or septicemia have had time to develop.

Roberts and Arakke suggest a new name for Agranulocytosis which is shorter and also indi-
cates the pathology. The name is Agranulosis.

4. Acute recurring agranulosis with or without sepsis. This is the same as above but recur cases of allergy may be placed here.

5. Chemical granulopenia due to chemical poisons as benzol and arsenic. The pathology is the same for the last three classes listed.

6. Septic granulopenia as a result of general or localized septic processes.

7. Irradiation granulopenia.

8. Anemic granulopenia, the condition accompanying certain splenic, aplastic and pernicious anemias, acute alymphatic leukemia and certain secondary anemias with bizarre proportions of the lymphocytes and monocytes.

9. Infectious granulopenia, the condition accompanying certain acute diseases as typhoid, typhus, measles, mumps, malaria, influenza, dengue fever and certain pneumonias.

10. Granulopenia of Roseala infantum.

This classification has been based on a study of 8,000 cases. They (7) feel that the diagnosis and biologic importance of a leukopenia is as important as of leucocytosis.
Clinical picture.

The clinical picture of the malignant type of agranulocytosis is characterized by an acute onset of fever, sore throat, malaise, often chills, frequently jaundice, dysphagia, headache, muscular pains, herpes, vomiting, inflammation of the mouth or elsewhere, and usually some enlargement of the regional lymph nodes, the total leukocytes are decreased in very severe cases to 100 cells / cm³ and the myeloid cells are zero. (2,9,10,11,12,13)

There is little change in the erythrocytes, hemoglobin, platelets and coagulation time. Death may occur in four to eight days, or as late as from four to six weeks, however benign cases occur which eventuate in recovery. There is a marked tendency in these latter cases for the condition to recur. (10,14)

Jackson (15) and others differ in some of the points. (29) He states that death may occur 36 hours after clinical symptoms but it has been shown (4) that the disease may have progressed for 4 days before clinical symptoms are manifest. Clinical symptoms appear when infection has invaded the defenseless host. (30) Jackson (15) also says recovery is usually complete in 2 weeks.

Most authorities agree that the red blood cell picture shows little change, and there is no notable loss of blood platelets. It must be realized
that a slight degree of anemia is not uncommon for various reasons in the middle-aged or elderly persons and, therefore, may well be an incidental finding, in true agranulocytosis. It is probably better to exclude those cases with marked anemia for the present from this category. Marked anemia and notable thrombocytopenia do not occur often in agranulocytosis. (10, 16)

The disease is far more common in women. (15, 9, 12) In Jackson's 103 cases eighty-three were female, twenty were male. (16) Norris found thirty-one males to forty-five females in 76 cases. (30)

Agranulocytosis occurs most commonly in mid adult life. In Jackson's series 29% were in the fifties. None were under ten years of age and two were over eighty. Beck (12) believes that practically every case occurs between forty-one and fifty-eight. The oldest reported case was found by Darling at age eighty-five (23) and the youngest a newborn boy by Keznikoff. (35)

The white cell count is rarely over 2500 and is often 1000 or less. Jackson (15) reports 30% having a count less than 500 at some time during the disease. When the leukocyte count is so low the granulocyte count is often zero or less than 5% with no young forms. (21, 30,) Neutropenia of an extreme grade is the rule. Eosinophils are rather consistently absent, not only during the disease but often for months.
afterwards. This is one argument against the allergic basis for the condition. Such neutrophils as remain are old and often degenerated. The lymphocytes make up most of the white cell count and show no noteworthy abnormalities. Occasional young lymphocytes can be seen in the smear. Some authorities believe that when monocytes are present in abnormally high percentages that the prognosis is more favorable (18,19) but there is little evidence to support this. Rarely, a few stem cells may be seen but never in the quantity that is found in acute Leukemia. (3,30) This is a very important point in differential diagnosis.

It is generally agreed that the platelet count is normal and may be elevated during convalescence but thrombopenia is reported in some cases (14) and some report it as a constant finding (2) and Roberts and Aracke (22,29) believe the platelet count to be markedly reduced. Most authors feel that if marked thrombopenia is seen in true idiopathic agranulocytosis, other diseases should be considered, notably aplastic anemia or acute leukemia. (10,12,16)

A few cases of classical agranulocytosis except for marked thrombopenia, showed at autopsy acute leukemia as reported by Hunter. (21,24,47)

Roberts and Aracke (22) state that it is "rare to see a case in which there is not some manifestation of the hemorrhagic trend and believe bleeding a common
symptom. Most authors believe on the contrary that bleeding is rare. This fits in with the quite well accepted finding that thrombopenia is rare. Kostlin found in forty-three cases that eight had hemorrhagic tendencies. Manifest bleeding during life, especially from mucous membranes, is strong evidence that one is dealing with some form of acute leukemia. This disease may be so fulminant that death occurs with coincident sepsis before definite anemia sets in. The life of the red cell is about three weeks in the peripheral circulation. Destructive invasion of the marrow with consequent sepsis and death may well occur inside this period.

Jaundice is regarded by some as very common. Schultz believed it was a necessary clinical symptom. Pepper (8) states it occurs in one half of all cases. Kostlin (10) found jaundice in seventeen of thirty-two cases. Jackson and Parker (16) found seventeen cases in one hundred and three cases. They feel that from the pathology (23, 24) of the disease there would be no good reason for supposing jaundice as a natural concomitant of the condition and this symptom when found is more properly to be regarded as the result of hemolysis due to secondary bacterial invasion. It cannot otherwise be adequately explained.

The spleen is occasionally enlarged but never greatly so. Splenectomy is suggestive treatment of
Agranulocytic angina by Jones. (25) This is not a well accepted treatment of most authors. The spleen does not destroy the granulocytes because there are none to be destroyed. Gross enlargement of the spleen indicates leukemia.

Ulceration and gangrenous lesions may be found in almost any part of the body; rarely they may be absent. The skin is not commonly involved. Lesions of the throat and pharynx are most prominent but lesions may be found in vagina, rectum, gastrointestinal tract and occasionally the skin. (16, 26, 27) Many cases were admitted under the guise of diphtheria to hospitals for contagious disease. (28)

Gangrene and sloughing may occur; this is particularly dangerous event when it occurs in the gastrointestinal tract. Two patients of the series by Jackson and Parker dies from rupture of necrotic intestine. In one the blood picture had already become normal, too late however to save the life. (16)

Owing to the absence of neutrophils there is none of the usual inflammatory reaction about the ulcerations but a peculiar brownly edema may be most extensive and in the throat constitute a great menace to the patient's life. This edema may be so great and so extensive as to preclude the possibility of swallowing and render breathing almost impossible. (16)
The fever has nothing characteristic about it. As a general rule the temperature reaches a maximum of 103°-104°F. Rarely it may rise to 106° or 107°F. In some patients only a very moderate hyperpyrexia is the rule. A steady, high unremitting temperature is of extremely grave prognosis. (7,16)

**Aetiology**

Most of the early authors consider agranulocytosis as a direct result of overwhelming infection. This point of view seems to be changing and there is considerable evidence that sepsis is not the cause, but rather the result of the disease. This is pointed out by the fact that many authors have found the white count to be lowered several days before any clinical signs or symptoms become manifest. (4,15,24) A patient of Jackson and Araeké (16) had a count of less than 500/ c mm or lower for four days before symptoms developed. Fever, chills, headache, severe sore throat and prostration developed on the fifth day. Bacteria had now invaded the defenseless organism. It is hard to see how an infection could be so severe as to destroy the granulocytes and yet produce no more visible signs or symptoms. It is more logical to assume that the organism attack a defenseless organism due to lack of granulocytes. Many authors express this view. (7,20,23,24,30)
There are cases where sepsis does appear to produce a picture similar to this, but the blood picture is different showing many developing granulocytes in all stages. (4)

There are some peculiar relations and facts concerning Agranulocytosis that have become established: The disease is a new and modern one, having appeared among us only since 1922 (2); it occurs mainly in the white race, and affects the better class of people; it is seen most often in middle-aged women, although no age is exempt; it has occurred most often in certain well defined geographic areas, chiefly in Germany and the United States; it has accounted for no less than 1600 deaths in the first ten years it was known in this country 1925-1935. It has a predilection for members of the medical and associated professions and members of their families. (16,47)

All these facts are factors in etiology and offers much aid toward a solution of its etiology.

Infection can probably be discarded as a common cause of true Agranulocytosis. It cannot be denied that it may be an occasional cause of the disease.

Allergy has been suggested first by Pepper (6) and the idea is still being studied at the present time. Hunter (47) feels that the primary cause of
Agranulocytosis is not known but may be limited to two causes... allergy and liver injury and gives argument for both. He concludes that it together with some allied blood disorders probably is an allergic phenomena and may be conditioned by functional damage to the liver.

That some endocrine disturbance is suggested by several as a cause. (37,38) It is doubtful whether any very large percentage of cases may be definitely traced to an endocrine disturbance. These cases are unique and the fact that many patients suffer from remissions or attacks at the onset of catamenia does not lay a solid foundation for an endocrine etiology for the disease.

Agranulocytosis has increased markedly in recent years. The leukotoxic effect of the benzene ring and the association of Agranulocytosis with administration of drugs containing the benzene ring makes this a most tempting theory to use. It is impossible to state the percentage of all cases following the use of drugs, and it seems quite reasonable that a certain number may have other etiological factors. However, Aracke and Parker (7) report they have never seen a case that could not be traced to some drug etiology. Other authors, especially in Germany, have had the same experience. Madison and Squier (1) had fourteen cases
of apparently true agranulocytosis in which amidopyrine, alone or with other drugs, were used extensively immediately before the onset of the disease. Hoffman, Butt and Hickey(45) Watkins(44) have drawn attention to this relationship between these drugs and the disease. Jackson(32) reports on the contrary in a group of twenty-seven cases that in only seven of them could the disease be regarded as directly traceable to these benzene ring containing drugs. Jackson (32) and Fitzhugh(31) made efforts to reinvestigate the drug history, but this was reported as unsatisfactory since the personal history of the patient was necessary and many patients were dead. Histories are hard enough to obtain on living patients. The problem is made more difficult by the large number of patented preparations containing amidopyrine, in which the name is not descriptive and the formula not available. This, with the wide spread use of proprietary pain relieving drugs, makes it well nigh impossible to rule out their use in any patient with any degree of certainty.

There is a question as to how much is required to produce the disease. Some people appear to be sensitive to it, and this may be a true allergy.(8) Recovered patients have had recurrence with as little as three grains and some authors have noted a fall in the granulocyte by patch test on the unbroken skin.(13)
A special report on the Council on Pharmacy and Chemistry of the American Medical Association (39) concludes that there is no question that amidopyrine is very important in the production of granulocytopenia. The report does not say, nor imply, that all cases are due to the drug, nor does it preclude the possibility that there may be some preexisting bone marrow dyscrasia which affords a fulcrum upon which the drug may work. (16)

Dinitrophenol has been shown to be the apparent cause of the disease in certain instances. Bohn (40) Davidson (41) Dameshik (42) and Silver (43) state that this drug must be considered as dangerous therefore, even in therapeutic doses.

A familial tendency is rarely seen. Kracke and Parker (11) report six such cases but say chance alone may account for this.

Sulfonamids are the latest causative agent. (15,18,19)

Arsphenamine and neoarsphenamine has been a factor in several cases (4,41,47) and should be used with care.

Gold has been reported as a cause (10,41,47) and arsenic and its compounds are suspected. (15,36,39,41)

"When all is said and done it must be confessed that the etiology of this disease still remains in a large part, obscure, that some cases appear to be caused
by the administration of certain chemicals or by action of certain toxices or sera and should not be regarded as indicating that the disease is but a syndrome. Pernicious anemia may be due to lack of an intrinsic factor, to radical surgical interference with the gastro-intestinal tract or to malignant disease preventing the proper functioning of such factors as cause a proper maturation of the red cells. In a similar manner a variety of agents, known and unknown, may prevent proper maturation of the granular white cell and so produce the disease agranulocytosis." (14)
The impression seems to prevail that the diagnosis of Agranulocytosis present little difficulty and this is true in the typical acute fulminant case, in which there is usually marked prostration, fever, oral ulcerations, or other evidence of sepsis, and a profound neutropenia with a total leukocyte count below 1,000 and red cell picture unaffected. However, atypical types of the disease are apparently being recognized more frequently and in these the diagnosis oftentimes is extremely difficult.

The chronic type of granulopenia has been described (7) in which the patient is usually a middle-aged female who complains of easy fatigue and lassitude, but with no positive physical findings. In this patient, the leukocyte count may be as low as 2,000 cm³ with few granulocytes. This probably differs only in degree from acute Agranulocytosis and such a patient may be regarded as one with impending bone marrow failure or one with a narrow threshold of bone marrow reserve. In such a case the marrow would probably fail to meet the emergency of an acute infection and an acute Agranulocytosis might result. (11)

Some patients appear to be in good health but have occasional intervals with attacks when the leukocyte count drops as low as 1000 cm³. They may have
sore throat or even ulcers but recover in a few days. This appears to be mild agranulocytosis.

A few diseases imitate agranulocytosis. A patient is reported (11) with typhus who had a leukocyte count of 1000/ c mm. but developed the classical typhus picture and recovered.

Hooe feels the greatest pitfalls in diagnosis are (2) from Aplastic anemia, Aleukemic leukemia, Leukemia with radiation, monocytic angina and septic processes.

In leukemia the leukocyte count may vary from 500,000 to 500. In Aleukemic leukemia the granulocyte count and the total white count may resemble the count in Agranulocytosis. The patient will usually die in such an attack if they are profoundly ill with evidence of sepsis and possibly hemorrhages. Here careful laboratory work is needed. In Agranulocytosis the granulocytes are old worn-out cells. In Aleukemia leukemia the cells are early blast types. (21,30)

In Aplastic anemia the clinical picture may be identical, especially in the terminal stage. The patient with Aplastic anemia usually presents a hemorrhagic diathesis, some may not. This disease is characterized by marked leukopenia with a low granulocyte count, or entirely absent; marked thrombopenia, which accounts for the hemorrhage; and a severe normocytic type of anemia. It is probable that Aplastic
anemia represents a failure of marrow activity in all its functions, whereas agranulocytosis is the same marrow failure, but restricted only to the granulocytes. (11)

When leukemia has been treated by x-ray the resulting inhibition of the blood forming cells may cause a picture very similar to Agranulocytosis. In this case however the cells do not develop to the stem cell stage but lie dormant or the marrow may become aplastic.

There are many various atypical varieties of bone marrow failure or "marrow insufficiency" in which the hematologic findings do not fit into the accepted criteria for any of the blood dyscrasias. Some have a typical picture of aplastic anemia yet recover with appropriate therapy. If the conception that Aplastic anemia is fatal, they cannot be classed as such.

Infectious mononucleosis usually occurs in young adults often in the early twenties. The patients are not as prostrate as in acute neutropenia. Lymphadenopathy in infectious mononucleosis is often generalized, the spleen is palpable in many cases, leukocytosis is common, and the lymphocytes may show fine stratification or vacuolization of the nuclei. (3) Moreover, the absolute number of neutrophils is usually
not reduced and many of them are immature. The heterophile agglutination test of Paul and Runnell is practically diagnostic. (35)

The chronic leukopenias rarely offer difficulties of diagnosis because the neutrophils usually are not as markedly depressed as in acute neutropenia. In many of these conditions splenomegalia is marked. However, chronic neutropenia is occasionally encountered in patients who have no other complaints but fatigue. (7) Neutropenia is sometimes seen in patients with no complaints or in the course of other diseases.

In differentiating neutropenia from other conditions affecting the white blood cells the blood picture is of paramount importance. The depression of neutrophiles is the chief characteristic and changes in the other blood elements are moderate or conspicuously absent. (35)
VI. Pathology

Numerous theories have been advanced to explain the disease or symptom complex of agranulocytosis. The pathology of the disease is much in dispute. This is due partly to the fact that there has been very little attempt to differentiate, either clinically or pathologically, the various conditions giving rise to the striking but far from pathognomonic sign, that of extreme granulopenia. Confusion also arises because of different interpretation and reliance on smears of bone marrow.

The hematologist of today is still confronted with the problem of identifying agranulocytosis as a disease entity and especially the cause for the pathological findings in the neutrophilic white cell series.

Specificity of the disease is denied by some, asserted by others and regarded by still others as unimportant. From a pathological point of view there is still too much chaos. This is due largely to an uncritical choice of cases studied and a lack of appreciation of such variations in cellular composition as normally occur from one bone to another, even in healthy individuals. (21)

Hubertin and Levy (21) make no attempt to separate agranulocytosis pure and simple from pancytopenia. Dodd and Alkinson (48) describe aplastic bone marrow but do not say which bones were studied. Dameshek and
Angell (24) reported nine cases and drew their conclusions from these. (48) One of these developed anemia from 4,000,000 red blood cells per cm. to 850,000 per cm. within one month. The other case was a four year old girl with severe sepsis, bleeding from the mucous membranes and a red cell count of 1,500,000 per cm. Of the white cells, a large percentage were of the premature forms. They say in summary: "It is felt that agranulocytosis is a symptom complex, dependent primarily upon an abnormal reaction of the bone marrow to severe sepsis. Gradations can be seen between the typical case with angina, and those cases of sepsis with an atypical leukopenia." (24)

Ladek (21) found lymphocytes in the bone marrow and felt they crowded out the cells of the myeloid series. Two of his patients became leukemic and a third developed a leukocytosis of 11,000 cells per cm. and lymphocytic nodules in the bone marrow. It is questionable whether reports such as these advance our knowledge of the pathology of agranulocytosis.

Campbell and Murdock (4) describe a case resulting after pneumonia with septicemia and describe the marrow of the tibia as fatty, while this is a normal finding after early childhood. Schultz has been quoted as saying the bone marrow in agranulocytosis was aplastic. (49) Leon, who reported on the histological changes of Schultz's cases, says that neither adult
polymorphonuclear neutrophils nor myelocytes were seen and that grossly the femur was partly red and partly fatty. Luchtenstien, with eighteen cases all well worked out and Koch, Kommerell and Baltzer, with smaller groups, found a lack of polymorphonuclear neutrophils and at times absent. There were seldom myelocytes, and myeloblasts were present in small numbers, with scattered lymphocytes, normal or increased numbers of megakaryocytes and plentiful red cells in all stages of development. These works were all European and were reported by Darling. (21)

Some authors emphasize degenerative changes. Rotter reports a case with many degenerated myeloblasts but says the patient had marked anemia and was questionably diagnosed as agranulocytosis. Jaffe (5) found the bone marrow more cellular than normal with signs of degeneration in the granules of the myelocytes. These granules were said to "fuse with the cytoplasm". He believed the majority of the white cells to be myelocytes with a moderate or considerable number of plasma cells and lymphocytes. Megakaryocytes he found in normal or increased numbers.

Fitz, Hugh and Krumbhaar (7) postulate a maturation arrest at the stem cell stage with the added possibility of an end stage which might be regarded as aplastic. Darling and Parker (21) and Jackson and Parker (16) agree with this view. Fitz, Hugh and
Krumbaaar note that at post the marrow of most bones contain "actively hemopoietic areas" filled with myelocytes, promyelocytes and myeloblasts while the peripheral blood contains only 200 white blood cells, all lymphocytes. They studied both the blood and the marrow from different parts of the body. They feel the marrow tends to become aplastic but is not so at the start of the primary bone lesion. They studied (1) blood from the vena cave; (2) blood from the right heart; (3) marrow from the ribs; (4) sternum; (5) vertebra; (6) femur; (7) tibia; and (8) spleen. They found a hyperplasia in the bone marrow in the early stages and this tended to become more hypoplastic as the disease drew out and became chronic. (8)

They suggest a maturation factor at work, either arresting development of the neutrophils series in formation centers or producing degenerative changes in them before sufficient development for normal migration into the peripheral blood stream or possibly both. This hypothetical factor checks the granulocyte series of blood cells at the myeloblast-myelocyte stage in the bone marrow and may check the lymphocyte series at lymphoblast stage in nodes and spleen. (16)

Analogies to pernicious anemia are obvious. Remissions and relapses occur. It is often an idiopathic disorder and probably also constitutional background is of primary importance. It may be, and often is,
mimicked by other disorders. Relapses are characterized by megaloblastic hyperplasia of bone marrow caused by some maturation inhibiting factor directed against the red cell series. This concept, when transposed to the granulophilic series, fit agranulocytosis. For these reasons they suggest the name pernicious leukopenia for the syndrome. (16)

Custer (52) confirmed and amplified these results. He studied eleven cases of typical agranulocytosis and found that in the true disease the bone marrow showed marked proliferation of myeloblasts, a failure of these cells to mature beyond that stage. He found the number of megakaryocytes increased and a moderate infiltration with lymphocytes and plasma cells. He concludes by saying: "the presence of a lesion of maturation specifically confined to the granulopoietic series, not reduplicated by diseases of known etiology, entitles idiopathic agranulocytosis, tentatively at least, to a place as a disease entity".

In the series of 25 cases studied by Darling, Parker and Jackson, these were divided into three groups on the basis of symptoms before death. The first group includes seven where death occurred within four days of clinical onset. In this group they showed that the essential lesion consisted of an increase of the very early granular cells (stem cells) and a lack of further maturation. These findings were the same as Custer's after
they agreed on terminology. For this lack of maturation they suggest the term "granulocytic anakmesis as proposed by Dr. John Finley of Harvard. (21)

In the second group were eleven patients who died in five to ten days after the onset and gave a somewhat less uniform picture in the bone marrow; and two had a picture typical to the first group. Of the remaining nine, one was described as typical of the group. "The vertebral bone marrow, the only specimen obtained, was grossly dark red. Microscopically, the cellularity was about normal, the red cell series present in normal proportions, and megakaryocytes were very numerous. The myeloid series were represented by scattered stem cells and a very rare myelocyte. Polymorphonuclear neutrophils were entirely absent. Plasma cells and lymphocytes were numerous, the latter usually in small clumps." The other cases varied only slightly from this reported case. (21)

The third or last group, of six are where death occurred over ten days after the first onset of clinical symptoms. One typical case died on the eighth day of treatment with pentnucleotide (NNR) of 50cc. daily per intramuscular injection, and some three weeks after clinical symptoms. Her course was steadily down hill. Her white blood count of 1000 per cmm. dropped in eight days to 500 per cmm., all lymphocytes; platelets were always
numerous. (21)

Autopsy showed ulcers of tonsil, pharynx and the entire gastrointestinal tract, early bronchopneumonia, congestion and edema of lungs, liver and brain. Grossly, the bone marrow from the vertebra and sternum was dark red, that of mid-femur and humerus pale yellow. The vertebral sections showed an occasional stem cell, in all other sections they were very rare.

Agranulocytosis is a new disease and an important addition to the list of dangerous diseases. A condition exists in which the granulocytes are greatly diminished in the blood stream and do not develop to maturity in the bone marrow. It necessitates a thorough study of the peripheral blood and the factory where these cells are made. The granulocyte is apparently a biologic necessity for life. This opens up a whole new world for research upon the blood. No other condition has so clear an opportunity to study possible functions of these cells that have been so poorly understood in the past. A brief illustration from Roberts and Kracke give the picture so often seen: "for four days a strong man fifty-eight years of age feels sluggish and tired; the fifth day has a chill and fever; the sixth day a higher fever; the seventh day a slight redness of the throat and a restless stupor; the eighth day coma and death. (21) There is a negative history of infection, a negative blood culture, only an absence of granulocytes,
myelocytes and myeloblasts. What is it and why is it?" (51)

In their previous paper, Roberts and Kracke (50) list four steps that can be seen in the typical disease process. They are as follows:

1) Agranulocytosis or granuloleukemia, characterized by the bone marrow onset.
2) Septicemia identified by the blood stream onset.
3) Clinical picture often with mild symptoms or apparent recovery.
4) Stupor and death in about 70%, recovery in 30%. The sepsis may precede or succeed the granulopenia. The question has been answered by many men and the majority feel that "the sepsis follows the agranulocytosis rather than precedes". (50) and (21, 24, 49)

There seem to be two types of lesions which are sufficiently constant to be accepted unreservedly, the first the bone marrow lesion described and the other. The lesions seen during life, and secondary to the bone marrow lesions, in the mouth, the pharynx, larynx, the rectum or vagina, and found at necropsy at various points along the gastrointestinal tract. In the mouth the ulcers are seen most commonly along the gingival margin, and in the throat it is the tonsils and pharyngeal piliars which are involved. The skin is rarely involved. (8)

Wherever the lesion, it passes similar char-
acteristics; it is a necrotic process, with little or no reactive erythema about it. This is more evident in lesions on the gums than on the tonsils and pillars, but even there the lesion is distinctive. Dr. Fielding Lewis feels he can diagnose the syndrome from the local throat lesions and that he never saw those pathoneumonic lesions until recent years. (8) However the disease is usually well advanced when throat lesions occur to be effective; treatment must be started before these lesions develop.

The tissue looks dead and its sloughing verifies its necrotic state. It improves in the blood count and general improvement there seems to be an increase in the reactive erythema about the lesion. Where improvement fails the tissue seems to melt away. The lymph glands enlarge. The spleen may enlarge. The liver also may enlarge and jaundice has occurred in perhaps half of all reported cases. (8)

In summary it may be said that it is now quite well settled that the primary lesion is in the bone marrow, and there is possibility that it may be due to an allergic reaction to certain drugs and toxins or to functional abnormalities of the liver. (47)
VII. Drug Reactions

Agranulocytosis as a disease was divided into three types in the early part of this paper. True angina is caused by Ludwig's spirochete and the treatment is quite satisfactory. Agranulocytosis due to sepsis and exhaustion of the debilitating condition can and must be treated in part as a secondary condition. This is not to be discussed here.

True agranulocytosis as a primary disease, whether it be syndrome (47) or entity (16), is not understood. The most common cause of the disease at the present time seems to be drugs containing the benzene ring or metal such as gold or arsenic. There are many other possible etiological factors such as allergy, and it may be true that an allergy to the drug is developed; endocrine dysfunction, and familial tendencies have been suspected. Overwhelming infection as a cause cannot be denied in some cases. X-ray may be a cause. None of these has been ruled out.

There has been marked interest in the disease since it was described by Schultz. There were over sixty papers published in the first half of 1932, and more were coming out regularly. In 1933 a German author, DeVries, (47) first suggested that amidopyrine might be a cause of agranulocytosis. From then on the interest in the disease has become much keener till it is nearly impossible to study and classify all the cases of the
disease so new in 1927. In October, 1933, Madison and Squier (1) read a paper on this subject. Watkins (44) published a report for a group of patients. He was the first to publish and call attention to the etiological importance of this class of drugs.

It is now well established that drugs containing the benzene ring are the leading cause of agranulocytosis in this country and Germany. This is not true in France and other countries where the drugs from the coal tar series are not used so extensively.

Amidopyrine is still considered the chief causitive agent. Hunter (47) gives a list of 53 drugs that contain amidopyrine that have been listed as a cause of agranulocytosis.

When this paper was started the plan was to list all the drugs and find the amount of each that was necessary to cause symptoms. The problem of prevention can not be approached that way. Three types of cases have been reported which show this rule can not be followed. Hunter (46) reports a case which had a long history of amidopyrine usage which developed agranulocytosis. Her case was not severe but she recovered even though she increased the use of the drug. Another case was reported (11) where agranulocytosis developed. She recovered and later took amidopyrine again without serious results. No explanation is offered. Still another type is the patient who after amidopyrine therapy
developed agranulocytosis and recovered. However, she later had recurrence of the disease without any history of drugs containing the benzene ring. (31) These cases do not fit into any picture. On the other hand some authors have reported enormous doses of the drug with harmful effects. (14,18) Other cases are reported after taking only the minimum dose accepted as official (47) and some patients show a lowered granulocyte count four or five hours after a patch test, for a long time after an attack. (53,54)

There must be some reason for the reaction which, too often, follows the administration of certain ordinarily useful drugs. There is some factor in the body of the patient which is responsible and this might be in the bone marrow or it could be functional liver reaction to drugs containing benzene ring, gold, arsenic and serum and other protein solutions. The nearest approach to the new concept of drug idiosyncrasy before Pepper's work (8) was that injury from drugs was based on supposedly orthodox toxic reactions. (56) These include anemia from lead poisoning, mercury, arsenic, phenylhydrazine, trinitrotoluene, benzene, radium, and methemoglobinemia from potassium chlorate, antipyrine, acetanilid, acetphenetidin, analine and nitrobenzene. Although these reactions were viewed as toxic, it was recognized that individual susceptibility to such special effects existed, and to this extent something akin
to idiosyncrasy was implied. After 1930, centering about the mystery of that relatively new disease called agranulocytic angina, there developed knowledge of hitherto unrecognized effects of acquired (drug) sensitivity involving the formed elements of the blood and bone marrow in very special and dramatic ways." (55)

In Fitz Hughes's paper (51), the terms sensitivity, hypersensitivity and allergy are synonymous and the term idiosyncrasy used to mean drug allergy. This drug allergy is probably a drug protein combination (57) reaction following the repetition of contact with a drug, by an allergic response. This response need bear no resemblance to the drugs normal pharmacologic and toxic action and may be precipitated by a troffing dose (55).

The problem presented by such acquired states of sensitivity has three sides: first, identification of the reacting agent or drugs; second, identification and study of the specifically conditioned responses of the sensitized subject and third, investigation of the conditioning factors responsible for the sensitization. The last phase must include investigation of the still inexplicable fact that only one person out of many thousands to whom the drug is administered becomes sensitized or conditioned. (42, 55, 54, 58, 59, 60)

The mechanisms of acquired drug idiosyncrasy and human allergy is, in general, obscure. To this may be added (hypothetic) dysfunction of the liver (as a
major organ of detoxification) and the spleen (as an important site of destruction of red blood cells and platelets and perhaps granulocytes). (25, 14) In addition to the lesion of the bone marrow, there is the phenomenon of the granulocytic crisis (4) which has to be considered in any concept of the pathologic changes of agranulocytic angina. Fitz Hugh (55) feels that the granulocytes disappear from the blood stream too quickly to be due to a maturation arrest, while Jackson (13, and 11, 12, 14, 21, 35) feels that the first clinical symptoms may come on only after the maturation arrest has been in progress about four days and the old cells have died off. Fitz Hugh (20, 55) believes the condition to be a shock conditioned sticking of leukocytes to the vascular endothelium. Several episodes may be necessary to produce the arrest status of the bone marrow in the disease proper. "If this peripheral depopulation of leukocytes can be proved, it may remove the necessity for hypothesizing a maturation arrest as the primary cause. Fitz Hugh's work in this one point is not sustained by other authors.

Drugs which have been suspected or proven to be idiosyncratic causes of individual attacks of agranulocytosis are amidopyrine, denitrophenol, arsphenamine and neoarsphenamine, gold salts, and neostibosan (55), acetophenetidin, sodium phenylmethyl, pyrozolan, methylaminomethane sulfonate (novaldin) (65) preparation containing about equal molecular parts of amidopyrine and eight
Hunter (47) outlined the arguments in favor of an allergic basis for agranulocytosis and says the evidence is indirect and scattered but uses them to support a hypothesis: 1) There is no one organism or drug constantly present in the disease nor does one drug uniformly produce the clinical, blood, nor pathological picture. He believes the condition a syndrome, not an entity. Fried and Daneshek (73) verify this.

2) The drugs of the benzamine group do not produce the syndrome except in certain individuals it has often been made. (14, 16, 20, 22, 26, 28)

3) The sudden onset of chills, fever and malaise is similar to foreign protein reactions.

4) Neutropenia, similar to agranulocytosis, is seen constantly in acute allergic shock in animals, and has also been observed in serum sickness in human beings.

5) Signs and symptoms often return upon future injection of the drug which was first suspected as the cause of the syndrome. This was shown by many authors especially for amidopyrine. (1, 74, 75, 76) Flum has done special work in this field but his work is in a foreign language.

6) It has not been demonstrated that drugs of the adiopho-
adiphatic series (straight chain carbon compounds) can produce clinical agranulocytosis. Barbital alone has not been proven a cause of agranulocytosis. This was a statement (39) made in 1934 and has not been disproved yet as far as this research shows.

7) There seems to be a close relationship between certain of the blood dyscrasias due to drugs. Observations (78, 79) and Jackson (16) believe that agranulocytosis, leukemia and purpura are closely related.

8) Agranulocytosis has been noted after injections of foreign protein, such as vaccines, serum and malaria. (80, 81)

9) Drugs which have been implicated in the causation of agranulocytosis; namely, amidopyrine group, arsphenamines and sulfanamides at times produce skin eruptions without changes in the blood picture. (82)

10) Agranulocytosis has been observed in patients known to be allergic. (31, 81)

11) Most observers agree that a high proportion of the reactions occurring during the course of arsphenamine or gold therapy such as dermatitis, jaundice, and disturbances of the blood, occurs in the second course of treatment or after the second or third injection following a period of no treatment.

Hunter also lists the arguments for liver injury as a cause for agranulocytosis. (47)

1) Leukopenia, sometimes accompanied by neutropenia, has
been observed in a number of conditions in which it is
known that the liver was, if not anatomically, at least
functionally damaged. Leukopenia often occurs during
cirrhosis and is a constant finding in typhoid fever, with
focal liver necrosis.

2) There is a high incidence of jaundice in agranulocytosis,
both in the idiopathic type and in the type due to
drugs and in particular, in the group caused by arsenical-
mines.

3) Eosinophilia has been observed not only as a finding
in certain forms of allergy but occasionally in patients
with liver disease. The significance of this is obscure
since eosinophilia occurs in parasitic infections, after
splenectomy, and at times in cases of pernicious anemia
adequately treated with liver extract. The "eosinophilia
of cure" has been noted by many authors but explained by
none. (76)

4) There is repeated reference to vacuolization of the
liver cells, central necrosis or even early cirrhosis
in some postmortem cases of agranulocytosis. (43, 76, 87)

5) Drugs of the benzol group have a tendency to injure
the liver. (88) Jaundice or central liver necrosis of
the liver is at times seen in chronic benzol poisoning.
That cinchophen at times produces acute yellow atrophy
is generally accepted and Quick believes this to be an
allergic phenomenon. (85) Finally, a study of the pro-
tective effect of certain food substances in agranulo-
cytosis may, in the future, throw some light on the problem, as Benanno (from 47, 54) has been able to produce agranulocytosis in guinea pigs by means of X-ray irradiation only in those animals placed on an alkaline diet.

6) The liver is known to be an important store house for hematopoietic maturation factors in pernicious anemia, and it might be assumed that there is a factor for the granulocytic cell series stored in the liver and that this store may be depleted without giving specific microscopical changes. Beck (33, 89) feels there are two factors in white cell development; (a) a growth stimulating substance probably manufactured in the liver and not contained in liver extract; and (b) a chemotoxic factor which causes the neutrophils to be delivered into the blood stream. Custer (52) says idiopathic agranulocytosis can be differentiated from the type caused by drugs, by a study of the bone marrow, and feels that the lack of a maturation factor in the idiopathic type is unique and therefore a clinical entity. If the liver should be found to contain a specific maturing factor for granulocyte formation a new field of investigation will be opened and possibly many conflicting opinions reconciled.

In conclusion, it seems that agranulocytosis may be a syndrome (47) or a clinical entity. (16) The etiology is not established. The idea is fast gaining ground that agranulocytosis probably must be placed in
the category of allergic phenomenon, and may even be conditioned by functional damage to the liver.

**Action of Leukopoietic Drugs**

Before going into the treatment of the drugs used for agranulocytosis, one should know the action of the drug, the reaction wanted due to the disease, agranulocytosis, and the results to be expected from drugs used in curative therapy. There is no universally accepted specific drugs for treatment of agranulocytosis, although many have been tried. Some have brought about recovery but it was not proven that the drug was the cause of the recovery. Koch's postulates might well be applied to the specificity of drug action. The question was asked why does a drug act differently in different conditions? (16)

The neutrophil leukocytes are the fighting forces of the body and since this has been known, attempts have been made to find a drug capable of calling forth young cells from the bone marrow. Leukocytosis, due to an increase of neutrophils, has been observed in a number of drugs but rarely have attempts been made to find out if the leukocytosis was due simply to mobilization of cells which normally stagnate in the viscera or to the actual proliferation of new cells in the bone marrow.

Perhaps the most extensive work on this problem was carried out by (C.R. Das Gupta) (76) which was...
received for publication December 31, 1938. The work was all done on rabbits in a research laboratory in London. Most of the rabbits were about one year old and weighed between 2000 and 3000. The blood of each rabbit was examined several times before any experiment was started. Definite precautions were taken to prevent mobilization of the leucocytes from the viscera to the peripheral blood stream. All blood specimens were taken at 10 a.m. The drugs tested were grouped as:

1. Substances generally reputed to be leukopoietic, e.g., pentnucleotide, sodium muchinate and liver extract.
2. Toxic substances, e.g., colchicine.
3. Sympathetic stimulants, e.g., adrenaline chloride.
4. Parasympathetic stimulants, e.g., atropine.

Leukocytosis may be the result of (1) re-distribution of circulating leukocytes, (2) mobilization of the granulocytic reserves of the bone marrow, or (3) increased maturation of granulocytes. If health more leukocytes are present in the visceral blood than at the periphery, and a variety of agents can induce temporarily a more uniform distribution of white cells throughout the vascular system, probably as a result of capillary dilatation and contraction of capsular and trabecular smooth muscle. This re-distribution of leukocytes may occur within a few minutes and subside in a few hours, especially when given by intravenous injection. A peripheral leukocytosis of this type is more apparent than
real and unlikely to be of therapeutic value. It may also be proceeded by a period of peripheral leukopenia.

A second group of agents, such as protein shock, mobilizes the immature polymorphonuclear cells which are normally present in bone marrow. This requires hours to reach a peak but is usually back to normal in a period of 24-48 hours. (Bunker) (90) Although there are numerous chronic diseases, in which protein shock and the mobilization of granulocytes from the bone marrow may be helpful, it can do little good in agranulocytosis, in which the patient has already been exposed to the powerful chemotactic influence of infection, fever or toxin, the reserves of granulocytes being empty. (91)

The reserves are normally replenished by the proliferation and maturation of myeloblasts and premyelocytes. Being a process of growth, stimulation of leukopoiesis requires much more time than the mere redistribution or mobilization of pre-formed granulocytes, and is a matter of days, the leukocytosis not being evident for about four days and reaching a maximum in about ten days. The leukocyte crises which is strictly comparable to the reticulocyte crises of pernicious anemia. Although it is convenient to discuss separately the three processes of re-distribution, mobilization and new formation of leukocytes, they are closely associated and merge insensibly into one another. The first two pro-
bably pay a part in artificial fever (Cohn and Warren) (1935) (92). After protein shock, there may be successive waves of leukocytosis for some days, suggesting the maturation and subsequent delivery of fresh crops of leukocytes (Murry and Calhoun, 1919) (93). The essential lesion in agranulocytosis is a failure in the differentiation of granulocytes from the primitive myeloid tissue, and until this has been repaired all efforts to stimulate a leukocytosis must fail. "Without leukopoiesis there can be no enduring leukocytosis." (93)

To distinguish between mere re-distribution and true increase in the number of leukocytes in circulation it is essential to count the nuclear lobes of the neutrophils. Bone marrow contains cells of class one and a few of class two in the Arneth count, but none of classes III, IV, or V. If a leucocytosis is not accompanied by any departure from the normal leukocytic formula in the Arneth count and there is no increase in the cells of Class I or II, it can be concluded that the increase is due to the re-entry into the blood stream of that part of the normal population of leukocytes, which had been aggregated in the tissue spaces. (Cook and Ronder) (94).

In order to replace the usual expression for distribution of the cells in the Arneth count by single figure, Ronder and Flint (95) advocated taking the weighted mean of the observations by multiplying the cells
of class one by one of class two by two and of class three by three and so on through class five, the results being finally used as it has the advantage that it could be graphically recorded and fluctuations, however small could be noted. A low value indicated the presence of larger numbers of young cells of class one and two in the peripheral circulation and as such is of great value in distinguishing whether the leukocytosis is merely due to re-distribution of cells from stagnant viscera or is due to young cells from the bone marrow.

All workers are unanimous over the great variations in the white blood cells in normal men and animals, even at rest, and recent investigations have demonstrated that these variations are independent of the digestive process. Sabin, making total and differential white cell count on a series of subjects at 15 minute intervals, reported a characteristic rhythm and a definite rise in the afternoon count, which was independent of any digestive process. (Sabin) (96)

Shaw, 1927, corroborated Sabin's findings in the main and found two high peaks in the course of 24 hours, one in the afternoon and the other at about midnight, these day and night tides occurring regardless of food.

In the same way there is an unanimity of opinion with regard to the leukocytosis produced by exercise. A short bout of severe exercise caused leukocytosis
up to 100 or more, while the increase is much more after long strenous exercise, as has been shown in Marathon runners, in one of whom the leukocytes went up from 3,700 to 20,800 during a race. (Garrey and Brogan) even change in posture is supposed by many to produce leucocytosis, and Cheng (91) reports a difference in the leucocyte counts of rabbits dependant upon stomach up or back up positions. Psychic stimulation without any obvious muscular activity is also said to produce a certain amount of variation in the leucocyte count. Thus the intense odour of food and aromatic and even the thought of food are sufficient to cause leucocytosis, and variations in the leucocyte count has been noted under different emotional conditions in rabbits e.g. leucocytosis when teased, Cohnstein and Zuntz (76) relative monocytosis when excited (Menkin) (100) and leukopenia when emotional. (Nice and Katz 34) (101)

Leukocytosis observed before operation in uninfected cases has been attributed to fear or apprehension and even slight pain, such as the prick of a needle, may be sufficient to produce leukocytosis, which has been regarded as being due to liberation of a histamine-like substance. Findley, 1928 (102) The leukocytosis noted under all the above conditions are physiological, being due to redistribution of cells from center to periphery without any change in the nuclear lobe count.

The results of the experiments of Das Gupta are
as follows:

Nuclein therapy was suggested as early as 1893 to increase the germinal power of the blood in bacterial disease, (Vaughn, Nory, and McClintock, 1893) (103)

In the course of examination of normal living blood cells, there were found "non-motile" polymorphonuclear neutrophils which accrued in "showers" in the peripheral circulation. (97) Doan and Zeofas (104) correlated these showers of non motile leucocytes in human pathological conditions with subsequent increase of young motile neutrophils. Both these observations suggest that the "zonal range" of the leucocytes is maintained by the disintegrating products of cells of the same type, nuclear derivatives are an important component of these. Later (Jackson 1924) (105) found pentose-nucleotide in normal blood which strengthened the suggestion. (Riznikoff 1929) (106) showed that nucleotides noted a shift to the left in the Armerh count. Later (Riznikoff 1930) (4) tried the effect of nucleotide and its derivatives in agranulocytosis and meant with immediate success, as three out of four cases recovered. More reports of success followed, mainly from America. (Witts 1936) Summarizing the effect of pentnucleotide in Agranulocytosis in Great Britain concluded that "the rate of cure was little better than the spontaneous course of the disease. An account of the conflicting reports of the efficacy of the drug in Agranulocytosis
as well as negative results obtained by Reich and Reich (34) in experiments on rats with the drug experiments with pentnucleotide and sodium nucleinate were conducted on normal rabbits.

Leucocytosis, which was preceded by leukopenia and which was due to an increase in neutrophiles, was seen after both pentnucleotide and sodium nucleinate. The leukocytosis observed after pentonucleotide, given intravenously appeared one hour after the injection and persisted only for three hours whereas leucocytosis after sodium nucleinate, intramuscularly, did not manifest itself for six hours but persisted for a longer period. Occasionally a myelocyte was found at the height of the leucocytosis after a single injection. Daily repeated injection of either drug, however, failed to maintain a sustained leucocytosis and no immature cell was found at any time. With both single and repeated injections the weighted mean of the nuclear lobes remained almost constant and there was no increase in staff neutrophils. These rabbits received 6.3 grams of pentonucleotide, almost twice the dose which was given by Joan to his rabbit but still no striking Granulocytosis was observed in the peripheral circulation nor was there any shift to the left in the Arneth count as claimed by Joan. (32)

It is seen from Joan's (104) chart that biopsy
of bone marrow was done on January 24, pentnucleotide was started on January 26th only two days later and was given at irregular intervals and the whole experiment was completed within one week from date of biopsy. It is also seen from the charts that the total leucocytes varied from 10,000 to 15,000 per c.mm. and the total neutrophils from 3,500 to 7,200 and not from 2,700 to 8,200 per c.mm. as is claimed by Doan, if, as is only fair the initial count be taken before biopsy of the bone marrow and not after. It is further to be noted that the maximum leukocytosis in most cases came shortly after the injections were given.

Das Gupta's experiments and an analysis of Doan's charts tend to show that the leukocytosis observed by Doan was well within normal limits. It was due mostly to redistribution of cells but partly to the inflammatory process following biopsy, and the latter was enough to account for the shift in the Arneth count. This view is further supported by the absence of any immature white cells in the peripheral circulation. (95)

Liver Extract. From Das Gupta's experiments and from those of Rowers and Murphy (108), Meyer, Middleton and Tewlis (76) and Rowers, J.C. (109) on human beings that single injection of liver extract in large doses produces a leukocytosis of short duration due to an increase in the neutrophils. The leukocytosis is ob-
served 3-4 hours after an intravenous injection and 6-7 hours after an intramuscular injection. Evidently the leukocytosis is not merely due to re-distribution of cells from the viscera but to a certain extent to influx of pre-formed cells from the bone marrow, as is evident from an increase of staff forms and consequent lowering of the weighted mean. That the leukocytosis was not due to squeezing of the spleen was almost conclusively proved by Myer and others who demonstrated leukocytosis with the injection of the drug in one case of Banti's disease and in another case of hemolytic icterus, both before and after splenectomy. Powers feels that the leukocytosis was due to direct or indirect stimulation of the marrow. Das Gupta (76) doubts this because if due to stimulation of the marrow, repeated injection should have caused a sustained leukocytosis if the marrow was not completely devoid of leukopoietic cells, but no leukocytosis is maintained as was shown by blood examination. The bone marrow, however, was slightly hyperplastic. If the hyperplasia of the bone marrow was due to the stimulating effect of the drug, that stimulation was not sufficient to induce a sustained leukocytosis in the peripheral blood. The leukocytosis observed within 3-7 hours after the injection of the drug is probably due to some transient chemotactic action by which pre-formed reserve cells from the marrow are temporarily drawn into the peripheral circu-
lation, but after only a short stay the cells leave to stagnate in the various viscera of the body.

Colchicine: The leukocytosis induced by a single large dose of colchicine may be divided into two phases—one due to increase in the lymphocytes which appears at the third hour after injection and continues up to the eighth hour, and the other due to increase in the neutrophils, which does not manifest itself until about the 24th hour. This is probably explained by the two distinct pharmacological actions of the drug. Dixon and Malden contended that the polymorphonuclear leukocytes at the later stages was suggestive of some powerful influence exerted by the drug on the bone marrow, whereby its elements were swept out into the general circulation. This may be either a positive chemotactic action on the bone marrow or a disturbance of the regulating mechanism of the hemopoietic organs which normally prevent the passage of immature cells into the blood stream. This action of colchicine is not confined to the leukoblastic cells, but effects the erythroblastic cells as well as along with myelocytes and metamyelocytes; normoblasts are very often seen in the peripheral circulation. It appears, therefore, that it is not chemotactic in nature, or the action would be more selective, affecting some particular elements of the marrow. It seems more reasonable to suppose that the regulating mechanism of the hemopoietic organs is thrown out of gear, as a result of the toxic action of the drug and
the response is the result of actual injury. When the drug is administered daily in small doses, its effects are not of sufficient magnitude to produce a sustained leukocytosis, although it still exerts some influence on the bone marrow, as is shown by the frequent presence of the immature cells in the blood, and the lowered weighted mean of the nuclear lobes in the Arneth count.

When the animals were killed, at the end of 21 injections the bone marrow was very cellular; hemoblastic areas were far in excess of the erythroblastic areas and it was crowded with granular cells.

Adrenalin chloride: Although certain investigators find no change after the injection of adrenaline chloride, yet in general the literature constantly records leukocytosis and polycythemia and in most cases the action is the same whether the spleen was normal, enlarged or absent. (Patch and Deland) Kennedy and Thompson found a shift to the left in the Arneth count while hyperplasia of the bone marrow was observed by Walter Hoffer (76) and Schon and Berchtold (76).

Histamine: Moon (112) worked on cats, monkeys and human volunteers. In each case leukocytosis followed histamine injections due to an increase of granular cells. The maximum leukocytosis occurred in 3-5 hours and returned to normal within 24 hours. Frequently the leukocytosis was preceded by leukopenia. Das
Gupta found little change in the weighted mean in his experiments.

Acetyl choline and cashaminoyl choline: Bachman (25) noted that acetyl choline increased the platelet count but did not produce leukocytosis. Das Gupta showed that parenteral administration of parasympathetic stimulants leads to great increase in the peripheral white cell count. An immediate leukocytosis was probably due to action on visceral organs. The late leukocytosis after the injection in all cases was probably due to mobilization of pre-formed reserves from the marrow as is evident from the occasional presence of immature cells and the lowering of the "weighted mean".

Atropine: Hirich, 1919, did not find any change in the leukocytes after ordinary doses of atropine, but Bachman et al. (76) found atropine cause a great increase in leukocytes. The slight leukocytosis observed in Das Gupta's experiment after atropine was probably due to re-distribution of cells from internal organs.

Physostigmine: Das Gupta injected subcutaneously physostigmine gr.1-6 and gr. 1-20 respectively and both injections were tolerated well. There was more influence on the red than the white blood cells.

Knowing the wide range of leukocytic variations possible, even with the needle prick and the
slight manipulation necessary to take a sample of blood from an animal as excitable as a rabbit, it is rather difficult for one to say with any degree of certainty whether the leukocytosis unaccompanied by any change in the nuclear lobe count, which has been noticed for many drugs, is due to the drug or not. But considering the great amount of leukocytosis noted after most of the drugs and taking into account that leukocytosis of this degree was never seen in the control animals even after injections of an indifferent solution such as fresh normal saline, it is reasonable to conclude that leukocytosis was probably due to the action of the drug. With the exception of colchicine, the leucocytosis was more apparent than real and was attributable to re-distribution of the white cells in circulation and to more or less outpouring of pre-formed granulocytes from the bone marrow. In certain instances, as with adrenalin and parasympathetic stimulants, these two phases appeared to be represented by successive peaks in the white cell count. The leukocytosis was transient, and with pentnucleotide and liver extract it was impossible to produce a sustained rise in the white count or evidence of increased proliferation and saturation of the leukopoietic cells in the marrow, even though injections were frequently repeated. Colchicine undoubtedly stimulates the formation of new cells in the marrow, and induces immature cells of both the red and the white
series to appear in the peripheral blood, but it is frankly toxic and its destructive powers outweigh its stimulant effects.

It may be considered disappointing and surprising that no evidence was found that pentnucleotide or liver can stimulate the new formation of leucocytes in health. Everyone accepts the fact that iron and liver will not raise the red cell count beyond the normal level and "a priori" there seems no reason why the leukopoietic tissues should behave differently when they are supplied with an excess of hemaeric principles. The immediate leukocytosis which followed the injections of these drugs is transient and more apparent than real. No enduring leukocytosis, no myelocytosis, and no outpouring of immature leucocytes follow their repeated administration, unless the experiments are of themselves sufficient to account for any changes reported in the white cells. It may be that, like the liver principle in pernicious anaemia, pentnucleotide and liver act only in conditions of pathological leukopenia. (76)

"My experiments allow me no right to speak on this matter though I may be forgiven for pointing out that evidence of their therapeutic value in agranulocytosis is not convincing." (Mitts) (76)
VIII. Treatment.

The treatment of any disease, the pathogenesis and nature of which is uncertain, is at best unsatisfactory and the more so when that condition may be easily confused with other pathological entities of probably a different fundamental nature. Many measures have been advocated to combat Agranulocytosis. None is specific. Almost all authorities agree that the major problem is that of restoring the bone marrow to its normal activity and thus raising the peripheral white count, for the loss of leucocytes removes one of the body's greatest defenses against infection. Without bone marrow recovery there can be no cure. (16)

Jackson and Tighe (15) wrote a critical analysis of the efficacy of various forms of treatment of Agranulocytic angina. This is a difficult problem and open to many fundamental objections. First, there is a tendency to report more of the successes and forget to report the failures. However, it is not likely that any one type of treatment suffers more than another though the percentage of success may be high for all. The analysis is a report of 390 cases reported with complete history, treatment, and prognosis. (15)

Another objection is that in a disease so little understood cases may creep in which are not true Agranulocytosis. On the other hand, the results may be more significant if the patients are reported from
various studies rather than all from one doctor. They started with 448 cases but discarded 5 and because the report failed to substantiate the diagnosis but was aplastic anemia, pernicious anemia, overwhelming sepsis, Hodgkin's disease, leukemia or some other fundamental disorder associated with chronic leukopenia. (15)

Of the 390 cases, seventy-five received no treatment directed toward the bone marrow dyscrasia. Mortality in this group was 78% or very near that of other authors. (15)

There were 130 cases that received inadequate treatment or died before the beneficial action resulted. The result, as would be expected, was about the same as for untreated cases or 73%.

Non-specific therapy, such as the injection of sterile milk or turpentine is conceded by almost everybody to be useless. The theory of this treatment is that the sterile abscess will call out white cells (17) and this is what happens in normal patients but there is no reason that it will work in Agranulocytosis. There seems to be no cells to be called out. (16)

Transfusions have been suggested by some as a useful form of treatment. (8, 15, 16) Some recoveries have occurred. Aside from this there is little good
evidence that blood transfusions have a stimulating
effect on the bone marrow or a curative effect on
agranulocytosis. Often the white cells are definitely
lowered after a blood transfusion. The number of cells
given is comparatively small and their life is short
and the patient does not need plasma or red blood cells.
Jackson (16) treated a series of patients with
pentnucleotide and some with transfusion and pentnucleo-
tide and found the mortality rate the same in both
series. Seventeen cases have been reported to 1939
treated with transfusion alone. Fourteen cases or 82%
died. This is about the percentage of untreated cases.
Fifty-six cases have been treated with transfusion and
other therapy. Twenty-nine of these cases or 53% died.
(15)

In the presence of sepsis when the white count has
risen to normal levels, small multiple transfusions may
be of value. Transfusion cannot be considered specific
therapy for Agranulocytosis.

Stimulating doses of x-ray were first advocated
by Friedemann and Sikeles (16) in Germany in 1930. They
treated 43 cases. Of these 23 died before x-ray could
be of help and were not counted. They reported a 47% 
mortality but when the complete unexpurgated series are
considered the mortality is 82%. Laussig (82) treated
four cases and two recovered. Several authors un-
enthusiastically recommend radiation. (15, 17, 21, 28, 47)
Rezinkoff (36) and (16) believe that even small doses of x-ray tend to depress the bone marrow and they point out that four or five days must elapse before the effects of any maturant agent can be seen in the peripheral blood. Pepper (8) does not use x-ray and one author treated twenty cases with seven recoveries but one year later only two were alive.

Roberts and Kracke (7) believe that "sepsis and necrosis are the great hope of every patient with complete Agranulocytosis." This hope is only too often fulfilled. They say however there is death with sepsis unless the granulocytes reappear. The idea is that necrosis stimulates the bone marrow to regenerate and thus restore the granulocyte to the peripheral circulation. Just how sepsis stimulates leukocytosis in normal patients is not clear. The sepsis of Agranulocytosis is admitted by all to be the result and not the cause of the leukopenia. Sterile abscesses of turpentine and sterile milk have been advocated.(8,37).

Griffin and Watkins (114,115) suggested that yellow bone marrow might be of value in Agranulocytosis on the theory that it contains a factor that overcomes the maturation arrest of the leukocytes. They suggest 300-500 gms. of desiccated bone marrow taken by mouth. Marberg and Wiles (116,117) have used the drug and report that a reaction may be expected in 24-48 hours.
They have treated twenty-six cases and have reported wonderful results with the marrow drug. Four recovered when only the bone marrow extract was used and three when other pentnucleotide was used. Only one of their cases died or a mortality of 20%. Of the other 18 cases reported on the record the mortality was not so high leaving a total mortality of 33% but they question the work and efficiency of the authors whose work they review.

Less than 100 cases have been reported and this is too small a series for definite calculations but yellow bone marrow extract appears to be the drug of choice if present expectations hold up. Is is hard for a patient with a sore mouth, necrosis and lesions of the tonsils and pharynx to swallow 500 grams of extract and the drug is expensive.

Leukocytic cream injections have been advocated by Strumia (118) as a means of specific therapy. He used the "cream", from 100-150 c.c. of normal whole blood as a dose. The cream is obtained by letting defibrinated blood settle, and removing the portion between the plasma and the red blood cells as the cream. Strumia says a favorable response should be expected in one to three days. He reports five cases where this method alone was used with 100% recovery. Another case was soon reported which died and six cases have been report-
ed up to 1939 treated with leukocytic cream and other
therapy. This leaves two deaths out of twelve cases
or a mortality of 17%. This is too small a series to
base any conclusions on. The cream is expensive and
has not been used extensively. However the success
of these treatments does show that the possibilities
deserve further study.

Adenine sulfate as a specific was first ad-
vocated by Riznikoff(4) in 1930. This treatment is
on the basis of pentnucleotide treatment, a stimulant
to the granulopoietic tissue by use of glandular pro-
teins with the purine nucleotides. He recommends a
dose of 0.5 grams injected intravenously twice daily.
In 1937 Riznikoff reported on fifteen cases and set
the standards for his treatment(4). The dose then was
1 gram given intramuscularly three times daily and
recovery was expected in 24-48 hours. Of the fifteen
cases reported only five lived 24 hours but all of these
lived. This treatment has been used quite extensively
but the mortality rate is no lower than for pentnucleo-
tide which is cheaper.

Pentnucleotide (N.N.K.) has been used with
apparent success by many. (4,5,7,13,14,15,18,19,22,
29,35,39,41,46,48,62,68,71,113)

Jackson (5) first suggested this therapy as a
specific after they showed that normal human blood con-
tained appreciable quantities of nucleotide (105) and later Doan (113) proved that injections of pentnucleotide, intravenously, raised the peripheral white cell count in normal rabbits. Pentnucleotide may be given in 10 c.c. intravenously or intramuscularly four times daily until the white count has definitely risen and young neutrophils have appeared. In favorable cases, this change usually occurs from the third to the sixth day after the initiation of treatment. If there is no response in ten days, further therapy is probably useless (16) and therapy changed. However very few cases ever go that long.

Zia and Forkner (119) use pentnucleotide in cases of Agranulocytosis complicating Kala Azar. They say, 'it would appear that the administration of pentnucleotide or of purine bases offers by far the most satisfactory treatment, not only for Agranulocytosis but also for conditions of Agranulocytosis, the result of pyogenic infection or of chronic benzene poisoning'. Others have had less success in treatment with Nucleoprotein therapy (17,120).

It has been suggested by Beck (12) and (121) that surgical intervention is contraindicated. Jackson (16) disagrees especially in treatment of the mouth ulcers or opening of abscesses. They say, 'such surgery should be done as would be indicated for a patient with a normal
blood'. An operation of election should be avoided.

In certain cases edema of the throat may interfere with deglutition and inspiration be difficult or impossible. Tracheotomy should be done only as a last resort but may be necessary. All drugs of the benzene group should be stopped at once. These include all drugs that may be considered causitive.

Intelligent bedside care, careful nursing, adequate nourishment and fluids are a necessary and obvious part of the treatment. The patient must be protected from infection, but the ulcers cannot be sterilized. Saline gargles may allay the pain, reduce the amount of secretion and make the patient more comfortable.

Nordenson states (122) that his study of 915 cases from the literature together with 59 personal cases verifies the generally accepted view that there is not at present any specific or reliable treatment for agranulocytosis (or malignant granulocytopenia). He points out that in mild cases expectant treatment may be given because of a tendency to spontaneous recovery; while in cases of grave involvement, the choice of treatment depends to a certain degree on the results of the examination of the bone marrow. When there are grave changes, x-ray may be tried for three days. If less grave, pentnucleotide therapy for seven days is
indicated.

Blood transfusions and liver therapy, he says (122) as well as mixed treatment often give good results and treatment with leukocyte and bone marrow extract and with transfusion of leukemic blood should be given further trial.
IX. Prognosis

In a study of 390 cases Jackson and Tighe (15) found the mortality in untreated cases to be 78% in a series of 75 cases.

The mortality in 43 cases which received no specific therapy but received more than three days general hospital care was 70%.

The mortality in 130 cases receiving inadequate amounts of any supposedly specific therapy was 77%.

They found that neither x-ray nor transfusion seemed to alter the mortality rate.

Doan (113 and many English authors disagree with this sharply.

Treatment by yellow bone marrow extract, leukocytic cream of adenine sulphate has not been widely enough reported upon to permit any of the low mortality in the cases so far reported, three measures deserve further trial. (15) The mortality in 26 cases treated with adequate amounts of liver extract was 62%.

The mortality in the 85 cases treated with pentnucleotide was 35%. This figure is close to that given by Jackson and Parker. (16). One of the later cases are included in the above analysis. (15)

Doan offers a chart which shows some contrast
to the findings above.

Mortality Statistics of Malignant Neuropenia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cases</th>
<th>Death</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untolerated</td>
<td>Many</td>
<td>---</td>
<td>90%</td>
</tr>
<tr>
<td>Miscellaneous Therapeutic Measures</td>
<td>178</td>
<td>133</td>
<td>74</td>
</tr>
<tr>
<td>Phospheneine</td>
<td>33</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>54</td>
<td>34</td>
<td>64</td>
</tr>
<tr>
<td>Nucleotide</td>
<td>64</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>Leukopoietic cream and Nucleotide</td>
<td>44</td>
<td>11</td>
<td>25</td>
</tr>
</tbody>
</table>

From these figures it is evident that the prognosis is bad. Prevention of the disease by care in prescribing and legislation to prevent the promiscuous sale of suspected drugs are the best and safest way of avoiding death by this method. When the disease is diagnosed early, adequate treatment with pentnucleotide, liver extract and yellow bone marrow extract seem to be the safest and best treatment.
CONCLUSION

1. It cannot be said with certainty yet, whether Agranulocytosis is a disease entity or a syndrome, but it is probable that such a disease entity does exist.

2. The etiology of the condition still remains uncertain. There is a growing feeling that Agranulocytosis is on an allergic basis with possible functional liver involvement to precipitate the bone marrow, blood and last...clinical picture of Agranulocytosis.

3. The final diagnosis requires a study of the bone marrow as well as subjective and objectives about the mouth and other parts and a careful study of the blood.

4. The primary lesion in Agranulocytosis is located in the bone marrow and sepsis is the result of, not the cause of Agranulocytosis. The bone marrow picture shows changes consisting of a maturation arrest at the stem cell stage in the development of the granulocyte series. At first there is marked hyperplasia with an abnormally high number of plasma cells, and myeloblasts with a sudden stop in development with few myelocytes and no young staff or adult forms found in the bone marrow. The reason for this break is still unknown as well as the way that it is produced.
5. Pentnucleotide (N.N.R.) intramuscularly or intravenously given, 40-50 c.c. in four divided doses for 7-10 days is at present the best method of stimulation of bone marrow activity. It is probably aided by the use of liver therapy.

6. There is no specific treatment for Agranulocytosis.

7. Definite progress has been made as shown by the lowered mortality rate from about 90% to a low of 33% in a large series of cases.

8. Adequate nursing and intelligent general care and asepsis are essential and important factors in treatment.

9. Until the nature, etiology and pathology of Agranulocytosis are better understood and placed on a firm basis the diagnosis, prognosis and treatment of the condition must remain undetermined to a large extent.
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