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Agranulocytic angina

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AGRANULOCYTIC ANGINA

by

LOUIS T. DAVIES

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University of Nebraska,
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INTRODUCTION

Agranulocytic Angina for the past seventeen years has been highly discussed both in medical centers and in literature. During this time the understanding of the disease has developed in the curriculum of the medical profession. Since 1922, when first described as a clinical entity by Schultz, it has been reported more frequently as the years passed until at the present time agranulocytosis is recognized widely as a disease process.

Just as with the development of any medical problem this has been laden with various opinions on its course, etiology, etc., all of which has served to confuse the searching medical mind as to its true standing. At the present time the literature is still presenting widely divergent views as to its interrelationships.

After a review of the literature, both from a clinical and an experimental angle, it has occurred to me that many of these rival views are in reality not such at all, but merely congruent or parallel facts or conclusions which are really more supportive than actually contradictory in nature.

While conducting experimental work in benzol

poisoning, an entity which closely simulates granulopenia, my interest in agranulocytic angina was first stimulated. The results of these experiments will not appear in this paper, but in a later paper. While working in this field, I was impressed with the argumentative basis of malignant neutropenia. This thesis is an attempt to bring together more closely these wandering views and to tie them together more firmly toward a central thought, that of agranulocytosis itself. The following will deal primarily with the clinical side of the question, bringing in experimental work only as a supportive measure to the clinical case.

DEFINITION

Agranulocytosis is a disturbance, constant or intermittent, chronic or acute, severe or mild, of the hematopoietic system, caused by various known or unknown factors. Clinically, it is more than a disease, falling more accurately in the classification of a syndrome. Characteristically, it incorporates a febrile course associated with ulcerative lesions of the mucous membranes, especially of the oral cavity, and a complete, or almost complete, disappearance of the granulocytin element from the circulating or peripheral blood stream. Mortality rates in this syndrome are high but are

decreasing with the advent of new therapeutic measures. Synonyms by which the entity is known are: granulocytopenia, granulopenia, agranulocytic angina, malignant neutropenia, idiopathic neutropenia and pernicious neutropenia.

HISTORY

The disease, or at least its modern conception, was first described by Schultz, a German writer, in 1922. However, we have the actual condition being referred to fifty years ago when standard laryngological works described the entity under the heading of "putrid sore throat" or "gangrenous angina". MacKenzie, in his manual of diseases of the throat and nose, credited Guber in 1857 and Trousseau in 1865 with having clearly distinguished the disease from diphtheria (7). MacKenzie and Marrel discussed a condition similar to the modern clinical conception in that they pointed out the stomadico-pharyngeal lesions and differentiated this condition from other lesions of the same area such as diphtheria, scarlet fever, etc. (93).

In 1902 Brown, although he did not describe the case under any of its present nomenclature, reviewed a typical case in a debilitated woman following a cervical

operation. He found the typical stomatitis and ulcerative lesions of this region associated with an enlarged liver. He reported a low white blood count and a differential which showed a complete lack of polymorphonuclear-neutrophelic leucocytes. At autopsy enlarged lymph glands were found in the cervical region. Blood specimens taken from various parts of the body showed no neutrophils. A bone marrow examination was not done. (15) Turk in 1907 reported what appeared to be a similar case, but he did not distinguish the disease from others. (51).

Leale described a clinical case in 1910 of a baby, age $3\frac{1}{2}$ months, with a white count of 3000, mostly lymphocytes. In fact, the polymorphonuclear count showed these cells to be only one percent. This case developed as a periodic fever accompanying furuncles and marked prostration. It was recurrent in this manner for one year's duration. The child was given immunizing vaccine which apparently cured him of his malady. (72)

Cases were described even before this date to quite an accurate extent as shown by Senator's article in 1888 and by Baldrige and Needles' paper in 1902. In 1913 Larson and Barron reported what seemed to be a typical case of agranulocytosis with ulceration of the upper jaw. The patient died a septic death. They considered

the fusiform bacillus as an etiological factor. This was the first mention of the etiology of the disease. It is interesting to note that many observers hold this to be an etiological factor today, and yet it was suggested before the actual description of the syndrome.(71)

It was not until 1922 when Schultz accurately described the disease and gave six cases that the attention of the medical profession was focused upon this condition. The importance of Schultz's observations, outside of calling forth attention and accurately recognizing the condition, was that he emphasized the fact that the red blood cells seemed to be little, if any, affected. (33).

It is of interest to note that the first case in this country was described by Lovett in 1924. He pointed out a reduction of white blood cells, chiefly of the neutrophilic variety, no anemia, and also a lack of neutrophils in the bone marrow. He accurately described the clinical symptoms and signs and stated that a cellular reaction to the local pharyngeal lesions was lacking. In addition, *B.pyocyaneus*, having been isolated from the spleen and local lesions, produced a low white blood count when injected into guinea pigs. (76).

Of further historical interest is the development of therapy in this field. The use of blood transfusions has long been recognized as a beneficial and

supportive treatment and a possible stimulative element in some blood dyscrasias. For these reasons transfusions have been a partial treatment of this disease. In late years liver therapy has been inaugurated into the therapy. Likewise, X-Ray treatment of the long bones has been and is used still as an aid in this condition. Its origin and use is obscure since this is a factor Roentgenologists have been taking advantage of for years in the treatment of certain blood dyscrasias.

Of more historical interest is the use of nucleic acid and its derivatives. This was first advocated by Huntley and Ames in 1897. However, we find that Vaughn as early as 1893 suggested nucleic acid as a treatment for leucopenia. Since then it has been used quite extensively from time to time, mostly upon a theoretical basis. In 1924 Jackson demonstrated pentnucleotidic acid as being normally present in the blood. Reznikoff in 1930 used this substance with beneficial results on six patients, and Jackson in 1931 said that clinical results were gained in 4-5 days, the blood picture being improved in 4-7 days. The excellent work of Doan in demonstrating its effect on the blood has proven conclusively its beneficial results. (33)

During the past year a new treatment with yellow

bone marrow extract has been subjected which seems to give even greater beneficial results.

Since Schultz's work in 1922 a voluminous amount of literature and experimentation has been done which seems to be growing with each succeeding year. As this is not important historically, the body of this paper will deal with the essential points of this material as they arise.

ETIOLOGY

The factors, both related and direct, which cause this disease are represented by a long list reported from several investigators. Many of these are the results of inductive and deductive logic. Some are backed by actual clinical material while a few have scientific experimentation to prove more or less conclusively their connection.

When the condition was first described, the sole cause was thought to be the peripheral effect of a circulating toxin or toxins of bacteria or else the paralytic effect of the same on bone marrow causing the hematopoietic tissue to become non-productive. This view is still held by some, but many others believe that the bacterial infection is only a complication made readily accessible by the lowered absolute count of the

polymorphonuclear neutrophilic leucocytes. (65)

For purposes of discussion the subject may be divided into several parts:

I. Predisposing causes:

It was at first reported that women between the ages of forty and fifty were the ones most likely to contract the disease. Figures now show that only 56% are female patients, which data seems to rule out the predisposing factor of women as contrasted to men. It is still most prevalent, however, in middle life.

The disease primarily affects the white race. Another factor is shown in that it has been found to arise many times coincident with previous diseases of the liver and gall bladder.

The use of drugs containing the benzene ring, the arsenicals, mesothorium, trinitrotoluene, X-Ray, and the Gamma rays of radium seem to affect the bone marrow in such a way as to simulate this entity (7).

II. Organisms as a cause:

The theory of a latent infection, which has been present for a long time, is superimposed by a new emergency with which the depressed bone marrow is unable to cope.

Many investigators believe that often the primary

infection is in the bone marrow or in the blood, or both, with the result of a marked leucopenia. (7). In support of this latter view it has been found that rabbits in which a hematogenous infection of *Talmonella surpestifer* has been produced often show agranulocytosis. This is accompanied by intense necrosis of the bone marrow without signs of regeneration. (26)

Other organisms have been isolated from the blood stream in this condition. These are usually the organisms of the mouth such as *Streptococci hemolyticus* and *viridans*, various *Staphylococci*, etc. The most constant offender found in the blood stream in this disease is Vincents' organism. (66).

Linthicum produced the disease in 1927 by injecting *B.pyocyaneus*, isolated from the throat of a woman suffering from granulopenia, into a guinea pig which resulted in a lowered white blood count. (75) However, Kracke demonstrated that in a large list of clinical and experimental cases the pathology was always first noted in the bone marrow. This was followed by a low white count. The infection was always a complication and followed the lowering of the peripheral circulating neutrophils. (64)

III. Septic and Toxic Processes:

Stocke believes that neutropenia is not a special disease but an abnormal reaction to sepsis. In contradiction to this view Zadek believes that a virus or bacterial-toxin of sufficient potency to destroy the granulopoietic tissue so completely would not spare so uniformly the closely related contiguous cells. (7)

Stocke's explanation is regarded by many investigators as a very plausible one. Many typical cases show a localized mouth infection and suggest a virulent circulating toxin which destroys the leucocytes of the blood and bone marrow. (62) Roberts and Kracke were unable to demonstrate any circulating agent which would affect the blood cells. After mixing normal blood with the serum of a diseased patient, they found no change in the cells after various periods of incubation. (105)

Blumer, however, reported a case in which agranulocytosis developed after sepsis was present. (12)

The whole problem of bacterial toxins as an entity in the production seems to be highly disputed. One investigator claims to have produced granulocytopenia by porous bags transplanted within the abdominal cavity. In these the bacterial culture was placed. The toxin could diffuse out, but the bacteria could not. Injections of the same bacteria would not cause granulopenia but

rather a typical septic rise in the white blood picture. No one has been able to reproduce his results.

IV. Hyperergic Inflammation.

Schilling believes that the phenomenon may be caused by a form of allergy in which the bone marrow is the point of least resistance. As a partial support of this view, Bromberg, Murphy and Kracke have observed the condition after prophylactic injection of typhoid toxoid (7). Patch tests on persons who have been suspected of having amidopyrine as the etiological factor sometimes shows an hypersensitivity with the same drug. (39).

V. Congenital and Familial Anomaly:

Hart, after observing malignant neutropenia in two sisters, suggested familial tendency. On the other hand, Wolf suggested a familial weak hemopoietic system when he observed a brother and sister, one with neutropenia and the other with myeloblastic leukemia. This latter view is held by Bickel (7).

VI. Chemical Poisoning.

This includes the entire class of drugs which may serve to weaken the hemopoietic tissue. Many do not produce a true agranulocytosis. For example, benzene usually does not produce a typical benign or malignant

neutropenia but rather a depression of all the bone marrow elements; so that anemia, purpura, and sometimes methemoglobinemia as well as leucopenia and neutropenia are produced.(7). Many others have been reported such as arsphenamine by Talley and Griffith, Kastlin, and others; gold preparations by Jacob and Dowody; arsenic by Dodd and Wilkinson, Wheelihan and Farley; mustard gas by Krumbhaar; and sulphanilamide recently by McGuire and others. Later, this list of drugs together with others producing agranulocytosis will be considered more thoroughly.

VII. Endogenous Disturbances; Production of Chemotactic and Maturation Factors.

It is known that two different processes are necessary to maintain production and amount of granulocytes in the circulation: (1) maturation, and (2) delivery to circulation. Animal experimentation, therefore, might be carried on by removing different glands of internal secretion. This might reveal valuable information concerning etiology and treatment.(7). For example, Richardson in 1933 reported agranulocytosis as being present in one of his patients who had Carcinoma of the Pancreas. He believe that this might be caused by toxins liberated from the growth (104).

Some investigators have advanced the theory that toxins from bacteria might act in such a way as to paralyze the stimulating endocrines which stimulate the bone marrow either for maturation or delivery to the peripheral blood channels. (5).

Other endocrine disturbances of marrow function have been noted. Hubble reported bone marrow depression accompanying pituitary basophilic insufficiency. Button and Corey produced neutropenia with adrenal insufficiency with a subsequent return to normal when the animal was fed cortico-adrenal extract. In thyroidectomized rabbits there ensued an aplastic anemia according to Kuncle et al (64).

Another important etiological agent is radiation. X-Ray in small doses tends to stimulate the hemopoietic centers but in moderate and large doses tends to destroy the germinal blood cells. Radium, thorium, X-Ray, and other radiating materials have a like effect. In supporting this belief Kracke stated that the disease is predominantly one of the white race, negroes being little affected. "Perhaps", he states, "it is due to the greater susceptibility of the white skin to radiations from the sun". This investigator was firmly convinced that most cases show a history of some chemical

toxin, or X-Ray, etc. He advanced some interesting statistics to hold forth his belief.

The disease has been high in incidence in both the United States and Germany where these drugs are sold most frequently. On the other hand, countries which do not vend these drugs to a very great extent have a low incidence. Also it is a disease of the "better class". And finally it is found most pronounced in the medical and associated professions, for here are the greatest offenders, if such be the case, of the consumption of products of the benzene ring. There are fifty times as many physicians as lawyers and one hundred times as many nurses as female teachers who suffer from the malady (64).

Other factors of etiologic importance have been listed: (a) Menstruation: Cases of women who have periodic attacks every twenty-eight days have been reported; (b) Fatigue: Many cases which give a history of restlessness, overwork, sleeplessness, or work. (18); (c) Pregnancy has been observed as a possible precursor of the disease. (66).

Aside from all these etiological factors of known or surmised value, there are found many cases of obscure origin. These are the so-called idiopathic agranulocytoses. Why? Is there an increased peripheral

destruction, an abnormal distribution, or a failure of cell development? There is no evidence of increased peripheral destruction. The spleen is a little enlarged and the red cells are not disturbed. Likewise, there is no evidence of abnormal distribution of cells.

Kracke in checking blood counts distributed over the entire body, both in venous and capillary systems, finds no striking deviation from Garrey's work, which shows a normal shift in the count in various places at various times. It is plain that a developmental cause is present many times since autopsy reports and sternal punctures show this to be true. Roberts shows that the sequence of events is bone marrow hyperplasia followed in four days by peripheral effect which is then superimposed by the clinical picture in about three or four days. This has been confirmed by many investigators.(105)

Is it, then, an entity, a deficient response of the patient, or a non-specific reaction to a factor of unusual absolute or relative virulence. The theory that bacteremia always precedes agranulocytosis has been disproved. That it is not always a bone-marrow hypoplasia is seen by patients who show a normal appearing marrow with a peripheral agranulocytosis. Perhaps a chemotactic as well as a maturation factor is present.

Perhaps anaphylaxis is more important than is supposed. Why should a person have a sudden leucopenia a few hours after taking a drug if he is not hypersensitive to this chemical so as to have "bone marrow shock" due to a sudden idiosyncrasy? (39).

It is seen, then, that although several etiological factors are of great importance, many are only theoretical and many more are entirely unknown. Perhaps the variations of individuals are being overlooked too much in this field. Some people may be born with weak or sensitive marrow just as other people may inherit other deficient functioning organs. Would this not explain many of the idiopathic cases? Beck believes the primary pathology to be not in the bone marrow but in the particular organ or tissue that regulates granulopoiesis. Those with a normal bone marrow lack chemotactic factors while damaged bone marrow shows a lack of maturation factors.

CLASSIFICATION

Several classifications have been advanced for the purpose of clearly defining the various types of agranulocytosis into a workable diagnostic pattern either from a clinical or a pathological point of view.

From the standpoint of a more thorough understanding of the disease, two classifications are necessary; one from an etiological angle and one from a clinical view point as far as the resultant symptoms are concerned. Inasmuch as this is a paper of primarily clinical aspects, the subject will be most thoroughly proposed without unnecessarily cluttering the field with detailed pathological classifications.

An etiological classification:

1. Agranulotoxicosis

(a) Caused by such myelotoxins as benzoe, arsenic and the benzene derivatives.

2. Agranuloradiations

(a) Caused by such elements as X-Ray, Thorium-X, and Radium. Usually involves erythropoiesis as well as granulopoiesis.

3. Agranulosepsis

(a) Caused by bacteria or their toxins.

4. Agranulocytosis

(a) Of unknown origin, consisting of depression of bone marrow and subsequent overwhelming of body in areas by bacterial invasion.

(b) Of unknown origin, with the usual depression of bone marrow and peripheral blood granulocytes, but without sepsis.

(c) Peripheral granulocytopenia without a depressed marrow.

5. A leukemic lymphatic leukemia

Granulocytes disappear from peripheral blood.

6. Acute infectious diseases

Examples: mumps, measles, malaria, influenza, dengue, tuberculosis and lues.

7. Roseola Infantum

A neutropenice of infancy. (105)

On the other hand, there should also be a classification which presents the clinical picture:

1. Acute agranulocytosis with or without sepsis.

Most common form, sepsis, may complicate, but the patient may die from prostration before inauguration of sepsis.

2. Acute Recurring Agranulocytosis with or without resulting sepsis.

(a) Differs from acute agranulocytosis in having two, three or more remissions.

3. Acute agranulocytosis of unknown cause.

4. Chronic agranulocytosis of unknown cause.

Another clinical classification which is perhaps more thoroughly symptomatic is the following:

1. Fulminating type:-

(a) Characterized by chill, high fever, necrotizing angina, occasional jaundice, and albuminuria, extreme leucopenia, and neutropenia. This usually involves necrosis of granulopoietic system and is generally fatal.

2. Sub-acute, prolonged:-

(a) Tender enlargement of lymph nodes and spleen; moderate to extreme leucopenia with reduction of polymorphonuclear neutrophiles.

(b) Usually reddened tender pharynx toward end of course.

(c) Of one to three weeks duration usually with recovery.

3. Recurring or relapsing type.

(a) Three or more attacks, weeks to months apart. Symptoms similar to either of other two above types.

4. Subchronic type.

(a) Leucopenia less intense.

(b) Bone marrow shows more active regeneration.

(c) Usually of one year or more duration with recovery.

5. Cyclic type.

(a) Regular, recurring, periodic neutropenia.

These then furnish the reader with a fairly accurate classification for clinical reasoning.

SYMPTOMS AND COURSE

In considering this phase of the subject, the discussion will be divided into five parts, namely; agranulotoxicosis, dealing with the chemical etiological factors; agranuloradiation, dealing with X-ray, etc.; agranuloseptic, dealing with bacteria and their products as etiology idiopathic agranulocytosis; and finally, miscellaneous causes either proven or suspected. Because it is the most true clinical type and the first described, the general classification will be based about agranulocytosis proper; the following four types will be described only inasmuch as their variations.

Agranulocytosis:

This disease cannot be a specific disease process and entity because: (a) there is a marked leucopenia in several types of infection; (b) there are a variety of necrotic foci; (c) epidemicity has not been reported; (d) it is not confined to class, age, sex etc.; (e) there is no constant etiological factor; (f) it has not been satisfactorily reproduced experimentally. (50).

The patient presents himself in a very pathetic state. He is wilted in appearance and his skin shows marked palor although the mucous membranes are of surprisingly good color. He is weak, sometimes almost

to the point of prostration, with a general toxic appearance. Jaundice is sometimes but rather rarely seen in this condition. The liver and spleen may be enlarged. He complains of easy fatigue and a constant drowsiness. He may also state that he seems to be easily infected with various organisms.

The severity of these symptoms is usually parallel to the degree of leukopenia. This is the condition and stage in which the physician usually sees the patient. It has been presented first in order that the idea might be gained as to the probable condition of the patient when diagnosis is made. (7)

The onset usually occurs in a period of seemingly good health, but may follow various chronic conditions. It is manifested by a sudden rise in temperature, sore throat, chills and malaise, and perhaps dysphagia, vomiting, headache, and general aching. A fetid odor of the breath is almost always present. The fever is from 10°P to 106° , and of continual type. (61)

The previous health may be characterized by lack of vitality and by weakness, but this is usually not true. The patient may also complain of palpitation of the heart and a murmur may be present. (7)

At this time an examination of the blood will show a lowered white blood count with a preponderance of the lymphocytes and a lowered polymorphonuclear count. Platelets are usually within normal limits, but in some types may be reduced. This will be discussed later. (37)

Coincident with or just following this period, ulcers of the gums, soft palate, uvula, pharynx or other oral locations usually develop. This is usually accompanied by marked edema of the surrounding tissue and a regional lymphadenopathy. A superimposed picture of sepsis is now present. A membrane, yellowish or green in color, forms over the ulcers which may be pulled free rather easily with no evidence of bleeding. These ulcers may be present on other mucous membrane surfaces such as the anus and vagina, but this is not constant. (89)

According to Kracke, the blood picture always precedes the clinical onset, but Green and Fitz-Hugh in 1933 state that it sometimes follows sepsis. (66) (37)

Many of these cases die with bronchial pneumonia. (66)

Most of the above described cases which are the typical acute variety may die, but some may recover to become chronic. In this type an acute future remission usually occurs. In another type the patient may

completely recover only to suffer another attack at a later date. According to its regularity or non-regularity, this would either be the cyclic or remitting type. In these types the blood count never returns to normal as far as the neutrophilic elements are concerned but always remains at a low normal.

In the chronic type with no acute attacks, the observer usually sees a constantly low (from 1,000 - 3,000) white blood count with a lowered neutrophilic element. The only constant symptom is weakness which is accentuated when the blood count drops. (66) In these long continued cases one usually sees monocytes and endotheliocytes in the peripheral blood. This is probably due to an extramedullary response. (42)

To bear out the above points, a few clinical cases might be reviewed briefly.

La Salle reports a case with the typical picture of an acute type of particular violence. Patient had been feeling ill for a few days with symptoms of weakness. One day he developed a headache. Upon the following day he was very weak with a sore throat; he stayed in bed with a cough. A physician was called who diagnosed the condition, Influenza. Two days later he was admitted to hospital in a comatose condition. His

throat was very red and his pulse rapid with a low blood pressure; respirations were 32 per minute. A red blood count showed 4,300,000; there was a white blood count of 4,300 with 2% neutrophils. The patient died seven and one-half hours later. (77)

Another case reported with fever, sore throat, malaise and prostration. The blood count was low on the white side with a low percentage of neutrophils. Treatment was of no benefit; the patient's condition became worse, his throat ulcerated and he died without sepsis. (103)

A case showed a white blood count of 3,500 six weeks before his death. He entered with sore throat, ulceration, lymph adenopathy, weakness, drowsiness, malaise. The white blood count was 160, polys 22%. The case progressed rapidly and resulted in death. (4)

Another case reported an anal swelling five weeks before, acute pain in the same region three weeks before, bleeding from anus and malaise. Patient was operated for hemorrhoids and an anal fistula noted. Directly afterwards he developed an anal ulcer. The white blood count was lowered to 1,700, predominantly lymphocytes. Clinically he showed malaise, fever, etc. His white count went steadily downward until he died. (17)

Another case with the same typical findings, except an additional skin necrosis was noted with an accompanying pharyngeal ulcer. Another case showed circumscribed ulcers on legs accompanying gum ulcers. In the latter case, although the platelets were decreased, no bleeding was noted. (21)

Marriott reports a typical case with a white blood count of 900, although the red count remained normal. The case recovered. Cannon reports a case with a white blood count of 400 that recovered. (80) (19)

When we come to the remission type of this entity we usually have a slightly less acute form, separated by periods of good health.

A case has been reported in which a patient suffered sore mouth, fever, malaise, drowsiness, but of a less acute form and was able to walk about. His red blood count was little affected and although his platelets were decreased, he suffered no hemorrhage. His white blood count was lowered and his neutrophils were reduced. Between attacks he was able to carry on his activities in good health. Patient is 19 years old and still having his attacks. (108)

A case which had three relapses, each having the typical acute symptoms and signs, although treated with X-Ray, died. (42)

Chronic cases present same symptoms with no ulcers or extreme prostration. The blood count is usually higher and the percentage of neutrophils generally greater. Patients have weakness in proportion to the low white blood count.

Kracke et al, believes that infection actually stimulates the bone marrow, thus shortening the course of the disease. They believe that infection may weaken and serve to bring on second attacks, which may be accompanied by nervous symptoms. (65)

The next class to be dealt with is agranulosepsis.

Du Bray reports a very typically acute picture of this disease that had recurring attacks every few months for a duration of two years. The patient died in an acute attack. The throat was continually positive for Loefflers bacillus, and he offers the possibility of a bacterial, bodily balance which would shift one way and then the other. (33).

Another case was that of a woman who had Herpes zoster with recovery. After this she developed a coronary occlusion with apparent definite improvement. Later, a pulmonary infarct was contracted. She was progressing quite well following this when five days later, she had a temperature of 100.4. She had both a

sore rectum and a sore throat. The next day her temperature went up to 105°. Her throat was very reddened and her blood picture showed a white blood count of 1200; 100% of which were lymphocytes. One injection of nearsphenamine was given. Her temperature decreased, but the next day was again up to 105°. Her white blood picture showed 550 cells, all lymphocytes. She died shortly afterwards. (3).

Blumer describes a case with a tooth abscess that developed a weakness, cough, anorexia, fever, loss of weight and an enlarged liver. The blood picture showed a marked leucopenia and anemia. Death was due to sepsis and lobar pneumonia. The bone marrow showed strangely marked hyperplasia.

Swartz described a case with perinephritic abscess who recovered, developed gingivitis and died with typical agranulocytosis.

Strusberg describes a case following osteomyelitis which again showed the typical picture. (12)

Three cases were reported by Hard, including two sisters and one sister-in-law. All were typical cases. All showed a positive blood culture of Friedlanders pneumobacillus. Hard believes these cases were on an infectious basis, the location in the blood stream. (47)

Huncler pointed out a case following fracture of the tibia, cellulitis and erythema multiforme. (52)

An interesting case was published by Dwyer who described a boy, age six, with anemia, enlargement of salivary glands and spleen. He developed a leukopenia with complete absence of neutrophils. There was no extreme lymphocytic nor myeloid infiltration of organs as appear in leukemia. There was no evidence of primary disturbance of myelogenous marrow at autopsy. A streptococcus septicemia was found to be present at necropsy, which pointed to the infectious agranulocytosis. (34).

Rutledge et al, cite a case of a $2\frac{1}{2}$ year old child who had attacks of furunculosis every two to three weeks for six to ten days. These "attacks" had been present from early childhood and were accompanied by gastro-intestinal disturbance, lassitude, drowsiness, irritability, sore throat, sore mouth, cervical adenitis, fever of septic type, leucopenia agranulocytosis. Patient would be ill for four to six days, then mononucleus and transitional cells would appear and the case would improve. (108)

Babbit reported a case under his observation for some period, who developed a sore mouth from which

Vincent's was cultured; subsequently she developed a typical agranulocytosis. The patient recovered under local treatment supported with blood transfusions and X-ray of the long bones. (5).

A case cited where a combination of Streptococcus and Staphylococcus septicemia, together with Vincent's, seemed to cause the typical picture of granulopenia. (47).

All these case reports seem to point out that agranulocytosis may be etiologically produced by infection. The cases were briefly stated and in general showed the typical picture with one of sepsis imposed, i.e. septic temperature, etc.

On the other hand, some investigators as Hueper, O'Connor and Kracke, believe that the infection is secondary to the lowered blood count. In reviewing their cases, they have been able to prove this in most of them and never have showed the reciprocal to be true. Probably both happen, since one investigator was able to produce the picture with bacterial toxins but was unable to produce the symptoms with the bacterial cultures. It seemed from this that probable toxic etiology was an established fact, but that bacteria themselves seemed to raise the blood count, as is generally suspected, and not lower it. (28).

Agranuloradiation has been described as another type of the entity.

Although radiation is used as a stimulant to the bone marrow in the form of X-ray, it is not without its dangers. A dose of the radiation which would stimulate one person's marrow to hyperplasia, might definitely impede another. The exact dosage is, therefore, uncertain and only very small doses should be given at the beginning of treatment and these only by a competent radiologist.

In the same manner doses of radioactive substances as radium and thorium act. Thorium used in stimulating doses causes first an anemia and brief leucopenia which is followed by a lymphocytosis and a polynucleosis. The platelet count is reduced and a delay in bleeding time with poor clot retraction is present after two days of 5cc injections (2 injections). If the dosage is kept up, a gradual depletion or a complete aplasia of all elements of the blood is noted. (113)

Often radioactive substances are deposited in the spleen, bone marrow and liver from small continuous doses. In these cases the first effect is a stimulatory effect on all blood elements which continues until the blastic cells are irritated too long; then we get

destruction and the resulting aplastic anemia.

Thorium and mesothorium and radiothorium are more active than radium in this manner.

One employee, working from five to six years, may easily have one mg. of radioactive substance deposited in bone, allowing a liberal amount as excreted. Such a case was admitted to a hospital with a temperature of 101° - 102° and a pulse of 120/ minute. His gums contained ulcers. The laboratory work showed hemoglobin 33%, red blood count 1,400,000 and white blood count of 400 with 40% neutrophils, 2% histiocytes and 58% lymphocytes. There were areas of hemorrhage and petechial about the body. The bone marrow was deep red, resembling pernicious anemia, except that there were no iron deposits (hemosiderin) and no destruction of red cells. The spleen showed atrophic malpighian corpuscles and diffuse fibrosis. The peripheral blood was that of a profound anemia with anisocytosis, megaloblasts, and a leucopenia. Electrometer tests were positive. The patient died. (81).

The reticular endothelial cells of the liver and spleen show cloudy swelling and macrophages are present.(113)

In this form of poisoning, then, we do not see a strict agranulocytosis, but rather an associated

agranulocytosis with accompanying anemia and reduction of other cellular elements including thrombocytes. Since the granulocytes are affected first, a disease process resembling agranulocytosis is obtained.

Agranulotoxicoses forms that group of clinical granulopenias whose etiology is benzol and its derivatives mainly.

Many chemicals which are by some generally thought to produce this entity are innocent of it. It would be well to consider these briefly.

Lead is considered sometimes to be a leucotoxin, but only affects the red blood count.

Cases reported preceded by arsenic ingestion, but experimentally a great majority of clinical cases again show only erythropoiesis to be affected.

Mercury is primarily an effector of red blood cells as is vanadium. Phosgene increases leucocytes and neutrophiles but later a reduction of red cells, hemoglobin results. Hydrogen sulphide stimulates lymphocytes, also the polymorphic elements.

Of course, if one believes in the monophylitic theory of blood production, it is easy to see how a primary erythropoietic toxin might in time become a leucocytic toxin by destroying the stem cells of both

white and red elements. Likewise, any substance which stimulates leucocytic stem cells may, if continued long enough or in high enough doses, injure the cells; so the clinical reported cases with these substances may be authentic even if only one is reported.

The most important chemical poisons to the leucocytic system are, benzene and its derivatives. Benzene in industry is a frequent offender. The symptoms are ushered in by dizziness, incoordinated movements and twitching of muscles which may last for hours. Bright red spots of petechial hemorrhage appear on the body; cynosis is prevalent and there may be massive hemorrhage from the gastro-intestinal tract. A marked weight loss is generally noted. A hemic murmur may be present. No benzene can be demonstrated in the blood, but the phenols in the blood and urine increase in concentration. The blood picture shows a leucopenia, a reduced hemoglobin, an anemia and a thrombopenia. The red cells show anisocytosis and poikilocytosis. The neutrophils are reduced, and the mononuclear cells are elevated. There may be a complete absence of white blood corpuscles. A strange factor enters when one finds that recovery is possible even after almost total aplasia of the bone marrow. (45)

Amidopyrine usually, if taken in large enough doses, produces the same results. Trinitrololuene produces the same results as do other benzene derivatives.

It has been shown experimentally that benzene is primarily a leucotoxin. Most observers think even more specifically and designate the neutrophiles. Thus clinically many of the benzene derivatives may cause almost typical agranulocytic angina. A few clinical cases might be briefly mentioned.

Kracke mentioned a case that took several benzene derivatives for three years before an attack of agranulocytic angina. The attack was accompanied by methemoglobinemia which further points to the etiology of benzene. (67).

One patient took over ten gallons of elixir of phenobarbitol in five years together with luminol, gr. ~~fss~~ when she woke up at night. She developed a severe anemia, a white blood picture of 1,500 with a low neutrophile percent. Although these never completely disappeared, the patient recovered.(54)

Another patient was a heavy user of aspirin for several years. This person showed a typical agranulocytosis with a low white blood count (470), with low percentage of neutrophiles. The patient recovered from

this attack but later died in a second attack after extraction of some teeth. (86).

Berg and Holtzman report a case that took 5 gr. of amidopyrine every 4 hours for five days and developed fever, cramps and nausea. The medicine was discontinued for four days and the symptoms were alleviated. Then she took one tablet after meals for seven days and the symptoms returned. After she again felt well, two tablets a day were taken for eleven days following which nausea, vomiting, fever of 104^o, prostration and abdominal pain developed. The next morning the temperature was 107^o; a marked leucopenia was noted in which no neutrophils were seen. The larynx became edematous and after three days, ulcers of pharynx developed. The patient died. (11).

A patient entered a hospital with a history of ingestion of three tablets of Causalin (equal parts hydroquinoline and amidopyrine) a day for one month. A week before, a sore throat and a fever developed. She had a white blood picture of 1,200 of which only 4% were neutrophils; the red blood picture was also reduced to 3,300,000. The patient died.

Another patient took 200 tablets of the same drug in three weeks. On the eleventh day she developed ulcer of the tongue, chills and a fever. At the end of three

weeks her white blood picture showed 1,600, 63% lymphocytes, 35% monocytes, 2% basophiles and no neutrophiles. The red blood count was reduced to 3,830,000 and

The patient recovered. (55).

Fitz-Hugh states that amidopyrine is an important factor but will not cause agranulocytosis by itself, as it needs an idiosyncrasy to enhance its action. There is no way of telling which patient will show this idiosyncrasy. Patch tests frequently show sensitivity to amidopyrine. Once established, the patient usually dies with this poisoning. (39).

Sulphanilamide was given to an old syphilitic patient, 5 gr. for two days, 3.75 grs. for three days, 2 grs for 13 days. On the fifteenth day, the white blood picture was 3,900, the red blood count was 4,170,000. After eighteen days, the white blood picture showed 2,000 cells, 100% lymphocytes. A high fever and a sore throat developed. The patient died. Edema of larynx, edema of Kupfercells of liver, atrophy of splenic malphigian bodies, marrow depleted of polys, stem cell hyperplasia and reduction, degeneration of nucleated reds were seen at autopsy. (109).

Another patient received 110 gr. of sulphanilamide in treatment of a Bartholine abscess. He received in seventeen days, two 15 gr. doses, and after first dose felt dizzy, drowsy, headache, nauseated and his heart showed palpitation. The white blood picture showed 17,500, 87% of which were polys. The red count was normal. Two more days passed in which 80 grs. of drug were given. The red blood count dropped to 3,960,000 and the white blood count to 2,900 with 64% neutrophiles. Nine days later no neutrophils in blood. The drug was stopped and the patient returned to normal. (1)

Sulphanilamide was given to another patient at the rate of 15 grs. per day for thirty days. The patient developed typical neutropenia with white blood count of 450 and no neutrophiles. After ceasing the drug, the patient recovered. Sulphanilamide at $7\frac{1}{2}$ grs. per day was given with a rapid fall in white blood picture and neutrophiles being noted. (87).

Neoarsphenamin upon its first dose caused fever and chills in a patient. After one year's treatment it caused nausea, vomiting and pain in abdomen of three weeks duration. Later bismuth and neoarsphenamin were continued. Forty eight hours after the last injection chills, fever, malaise were noted. Platelets count was

84,000; the white blood picture showed 2,000 with 1/3-1/2 of them neutrophils. The patient recovered in four days after stopping the treatment. (10).

A case showed typical agranulocytosis. After two weeks treatment with silver salvarsan, the patient recovered after cessation of treatment. (82).

Thus it seems that both benzene and its derivatives react the same or practically the same on man.

A few other myelotoxins may be mentioned briefly by citing a few cases as examples. Two doses of sodium theosulphate of 40 mg. in injections were given one week apart. A night following the second dose the patient developed a typical agranulocytic angina as far as the blood picture was concerned. The next day clinical symptoms were ushered in. The patient recovered with K 96 treatment in ten days. (101).

In a case of cerebral injury, potassium arsenite was given for 36 days, starting at 6 minims and building dose to 39 minims daily. Phenobarbitol was given at the rate of gr. $\frac{1}{155}$ per day. The white blood picture decreased from 14,000 to 1,300 with a decrease in neutrophiles from 62 to 3%. Recovery followed in two weeks after cessation of treatment. (125)

Another case (developed after a case of mercurial injection) which was quite typical except for a profound

anemia, and thrombocytopenia with purpura. Typical agranulocytic symptoms prevailed, since the anemia secondary to thrombopenia, as shown by marrow which was aplastic for granulocytic elements but hyperplastic for erythrocytic elements. The case died. (35).

Thus it is seen that the chemical myelotoxins do not strictly hold to the granulocytes, but can and usually do, incorporate destruction of other blood elements with the production of the symptoms typical of depletion of these same elements.

Miscellaneous types:--

In other blood dyscrasias such as lymphatic leukemias, etc., the myelogenous elements may be "crowded out"; so that neutrophiles are not developed or are greatly in minority. Symptoms of agranulocytic angina usually are superimposed by the symptoms of the other disease.(27)

Added insulting of the system with bacterial or other toxins may produce the typical picture. Cases of carcinoma and other debilitating diseases have been complicated with this picture of agranulocytic angina, probably also from toxic effects on bone marrow of the liberated toxins.

Call reports a case of an eight months pregnant woman who developed abdominal pain, tremor, fever,

rigors, laryngitis, throat ulcers and a temperature. The white blood picture was low, with a low percentage of neutrophils and a low red blood picture. The mucous membrane of the rectum, vagina and vulva was swollen and red. Typical agranulocytosis resulted. (18).

Other etiological factors such as fatigue, sleeplessness, worry, etc., are accredited with causing the typical picture.

It is seen, then, that regardless whether or not the etiological agent is known, the basic ^{diene} synchronone is very similar.

As additional elements, variations such as anemic symptoms of benzol poisoning or the hemorrhage signs of the same or the septic symptoms of agranulosepsis may occur.

EXPERIMENTAL WORK

This section will not be inclusive of this work, but will only deal with that portion of clinical experimental work or animal experimentation which directly bears out some clinical point or seems to disprove some clinical conception which has been mentioned in previous sections of this thesis. The animal experimental points therefore, will be mentioned very briefly since this is primarily a clinical thesis.

Dr. Plum had treated a patient with 20 grains of amidopyrine (who had suffered from agranulocytosis several years previously). The patient developed chills and fever and was indisposed one hour after injection. His sedimentation rate decreased in five days from 28 mm. per hour to 10 mm.

The white blood picture dropped from 9,000 to 1,500 in one hour and one half. In double that time it had climbed to 11,500, then slowly down to 2,000 in 24 hours. It then climbed to 10,400 in eight days and leveled off gradually. Granulocytes dropped from 5,700 to 1,450 in one and one half hours. Twenty four hours later the count decreased to 1,150 and remained in this neighborhood for ten days, after which it returned to normal. There was a marked shift to the left in these elements; the non-granular elements had a primary fall in the first hour to 150, then gradually climbed to normal in ten days. (95).

From this it may be seen that drugs undoubtedly do produce the entity, and also that the more primitive cells, the lymphocytes, are greatly affected. Since here is a disturbance of potential stem cells, one may gather how serious and persistent the leucopenia may become.

Harris and Schattenberg extracted the toxins from cultures of bacteria which were isolated from stools of an agranulocytic patient. Animals injected with this toxin produced a low white blood count, predominately of a lowered neutrophil type. Injections of bacterial cultures showed a raised count. Different organisms producing this effect were *B. enteritidis*, *Streptococcus hemolyticus*, *Staphylococcus aureus*, *B. typhosis*, and *B. welchii*. (46)

In another experiment, bacteria from focal infections of patients were cultured. These cultures, mostly *Staphylococci* and *Streptococci* were implanted intraperitoneally. They produced a leucopenia, some acute, but only the granulopoietic elements were affected, the mononuclears remaining constant. Controls were negative. Cultures injected caused a leucocytosis.

These experiments showed that toxic products of bacteria may have a similar effect, but that bacteria themselves do not. (28).

Benzol experiments in general bear out clinical experiments in that an agranulocytosis is produced and also a depletion of red elements; occasionally various other or all of the other elements may be depressed such as: the thrombocytes, lymphocytes, etc. Many clinical

symptoms may also be noted in these animals such as loss of weight, malaise, anorexia, oral ulcers, bone marrow, spleen and lymphatic tissue changes, etc. The same can be said in general for the products of benzene, amidopyrine, acetaphede, trinitrololuene, and other benzene ring products. Perhaps it is of interest that benzol products with an amino group attached to the ring seem more often offenders than those that are not. Selling explains this by saying that these are the ones most easily oxidized to toxic products such as phenol and catechol, etc. He attempts to prove this by showing increased excretion of phenol after benzene and an increased amount of phenol in body tissues. Nowhere could he demonstrate benzene, except at site of injection. This clinical paper is not to be laden with further indirect experimental evidence, since it can never be directly applied to the clinical case, but will refer the reader to articles of this nature, should he desire to acquaint himself with this part of the work. (110), (118), (113), (82), (78), (102), (13), (97), (23), (53) (91), (20), (120), (121), (122), (123), (124),

PATHOLOGICAL ANATOMY

In writing the section on pathology, it is well to cover a few physiological points and to deal with the

pathological state more as a physiological mechanism since it is only in this manner that effects can be visualized.

The granulopoietic system is located in the red bone marrow which is found in the ribs, the vertebrae, the sternum, the bones of the skull and as innominatum. It is in the red marrow that granulopoiesis takes place normally. The size of the granulopoietic organ in the adult has a volume of about 1,420 cc, which is thirteen times as great as that of the spleen and about the same as that of the liver. There are from three to twenty times as much tissue devoted to granulopoiesis as there is to erythropoiesis. The life span of the neutrophil is about four days after it reaches the blood stream. There are various physiological outflowings of the granulocytes from the blood into the tissues with consumption in the tissues. Neutrophils are eliminated into the saliva, the entire digestive tract, and through all the mucous membranes. A gradual loss of granulopoietic tissue ensues with advancing years. (7). The granulocytes have an hourly fluctuation. There is a reciprocal relationship between myelocytes and the mature neutrophils. It is suggested, then, that this fluctuation is caused by withdrawal of the mature

neutrophiles from the peripheral circulation. (30). Besides this hourly fluctuation, there are two general tides of leucocytes. The tide is high in the early afternoon and in the hours after midnight. This is largely due to the neutrophilic element and is not influenced by any factor of daily life. There is little individual variation in this process. The fluctuation is not confined to the periphery, but is generalized over the entire body. (111). Sabin showed rhythmic occurrence of young polymorphs in the periphery after occurrence of old non-motal neutrophiles. This may account for the occurrence of an hourly tide, probably by reflex stimulation. This further substantiated by the fact that the blood during these tides shows a neutrophilic shift to the left. (29).

In neutropenia a cessation of the bone marrow supply of neutrophiles results in a peripheral shortage in about three to four days. This may proceed gradually until the total peripheral count is 1,000 or less. At the beginning of the disease the granulocytes fall rapidly, usually to 700 or 600 cmm. Thus the granulocyte shows 30 to 40% of the total count in chronic cases to absolute absence in severe forms. In almost all cases their morphology is normal. However, it is found that the

motility, vitality, and phagocytic ability of the cells is decreased. It is interesting to note that besides the absent maturation factor which would plainly call forth these changes, there is, many times, a normal or hyperplastic granulopoiesis which also suggests a chemotactic factor. (7).

Besides the change in neutrophiles there may be a small to great absolute decrease in the lymphocytes. This may be without evidence of destruction in the lymphatic tissues. A depression of the reticular endothelial system may cause a decrease in number of monocytes. To compensate for this the macrophages may be increased, and many times these and the clasmatocytes elaborate granules and seemingly take over the function of the granulocyte.

The erythrocyte is usually not decreased except in chronic cases. Here the hemoglobin is also effected. Likewise, in long cases, the blood platelets may show a reduction. (7). In contradistinction to the latter statement, Danashek, in a review of many cases, states that thrombocytes are decreased only in the first two weeks. Most investigators hold that this is not true and that if a change in thrombocytes is noted in the first two weeks, it is an increase rather than a decrease. (25).

It must be remembered that the drop in leucocytes occurs before the clinical onset is evident, and that the observer usually sees these changes at completion of his examination of the clinical case. (6).

At the depth of the disease, a shift to the left of myelocytes can be observed. It has been suggested that there are not only young cells but abnormal young cells which might further suggest an abnormal chemotactic factor as well as the maturation factor. This phenomena is often seen in cases with hyperplasia of the marrow.(38)

It is sometimes confusing to see the generality of this description confused by infection. Many times this changes the entire picture. Here if the observer will merely consider the effects of this process and the initial cells which it has to effect in the blood, he can interpret the changes. (65)

The toxicity of the blood serum itself has been suggested by several observers. Beck mixed normal leucocytes with serum of a patient suffering from agranulocytosis. The leucocytes were seen to become rounded and lose their mortality in about 45 minutes.(7)

It might be interesting here to consider a theory of antigen and its reactivity which has long been suggested by clinical observers. Shiff found that by injecting benzene, an etiological factor of this disease,

intraperitoneally in animals, the reactivity of antigen was increased. Rush found that rabbits injected with this substance reduce lysin formation for sheep blood corpuscles and praecipitin for horse serum in the conditioned rabbit. Simmonds and Jones found a reduction of lysins for dog corpuscles and for typhoid apsonin in conditioned rabbits (114). Winternitz found same to be true for pneumococcus. (7). Hektoen repeated this work and stated that at high antibody production benzene has little effect on leucocytes and also that it lowered leucocytic activity. (49).

This then points out that benzene may effect the white cells in another indirect way.

In acute fulminating cases of idiopathic nature, the pathology is usually limited to the marrow of the long bones. Here is seen usually a hypoplastic granulopoiesis. The erythroblastic elements are usually unaffected. (65). The bone marrow changes are the same in the living patient as in the necropsy specimen. This has been shown by sternal biopsys. (61). The bone marrow in fatal cases usually shows marked degeneration. The marrow shows patchy necrosis, with the myelocytes and neutrophiles absent, or nearly so. The megakaryocytes and normoblasts are usually uneffected so that the

hypoplasia involves the granulocytes only. However, this is not always true since three distinct types have been noticed; in one, a maturation of myelocytes had ceased; in another type, there was myeloid aplasia; while a third type showed normal myeloid elements. (7).

The myelocytes themselves are usually degenerative or necrotic. Some cells have deeply basophilic and vacuolated cytoplasm with large pale staining nuclei. Some contain several nuclei. Rose and Houser saw hyalin drops in the cytoplasm with pale falloned or picnotic nuclei. Van der Wielen describes cells with no granulation and small picnotic nuclei. Offenorde spoke of large cells with a pale cytoplasm and various forms of nuclear degeneration. Fried, Danashek, Naegele and Koch spoke of wide necrosis of the marrow. Koch added that the bone marrow was often deprived of granulopoietic elements but that lymphoblastic elements were greatly increased. The reticuloendothelial elements are often hypertrophic and show erythrophagocytosis and phagocytosis of iron pigment. Perchenbach's patient showed a fatty bone marrow with cellular areas composed chiefly of promyelocytes. Fitz-Hugh and Krumbhaar found that many times the mature granulocytes are absent and that there is an abnormal number of young neylocytes with pale nuclei

and many neutrophilic granules. Many times death may occur when there is an abundance of these parental cells but a peripheral leucopenia. Here the maturation factor is deficient at work. Zekowsky believed that in hyperplastic marrows a bloch (chemotactic factor) existed. If this held for a period of time, degeneration would begin. Many cases at death show myeloid hyperplasia.

Following are a few concrete examples of some of these cases:

In three cases of idiopathic agranulocytosis the bone marrow was found to be much more cellular than the age of the patient would suggest. In this hyperplasia the granulopoietic tissue of the patient took an active part. It seems, therefore, that in some cases the agranulocytic catastrophe is preceded by a proliferation of the young myelocytes. In some cases, the cell content of the bone marrow of the femur was not increased, and the destruction of the granulopoietic tissue did not follow an initial hyperplasia. In both the hyperplastic and the non-hyperplastic bone marrow, the granulopoietic cells revealed severe regressive changes, and it was often only by comparison with the less altered cells that the young myelocytes could be identified as such.

Specific granulation is the first to become affected

while the nucleus remains intact for some time and may even divide by mitosis. Specific granules swell, their outlines become indistinct, and small vacuoles often appear around them. The granules later dissolve into these vacuoles and pale purple pink droplets result, which fuse together, giving a vacuolated appearance to the cells. In the meantime, the chromatin of the nuclei has become separated into coarse, sharply defined clumps, and the nuclei have disappeared. An occasional mitosis may be detected in a cell which has been deprived of its granulation. The mitosis is, however, atypical with short and clumsy chromosomes and do not seem to pass beyond the metaphase. The nucleus finally shrinks and disappears; the cytoplasm coagulates and the cell dies. With the dissolution of the granules into the vacuoles the oxidase reaction becomes negative. When present, the myeloblasts appear intact which suggests that therapeutic attempts are not absolutely hopeless in the acute forms of the disease.

The great majority of cases of agranulocytosis show histological evidences of a severe injury to the granulopoietic tissue.

In many cases, the giant cells are increased in number and many young forms with signs of multiplication of the nuclei were present. Thus the megakaryocytes may

may be involved also.

In cases of long standing granulopenia, a moderate anemia may develop. The normoblasts vary considerably in size, and some of them were large and hyperchronic. Segmentation of the nucleus infrequently seen before picknosis is complete.

Lymphocytes and plasma cells are always present (59]. The liver shows perivascular lymphocytic infiltration; Kupfer cells containing much pigment and Glisson's capsule is often overlain with a thin inflammatory exudate. (94). An increase in Kupfer's cells is often present. The liver cells themselves show cloudy swelling and small areas of necrosis. (7).

The spleen often shows tremendous development of the reticular endothelial system at the expense of the lymphatic elements. The sinus are empty, with the exception of a few lymphocytes, plasma cells, and red blood corpuscles. The reticulum of the white pulp contains scattered lymph and plasma cells. Megakaryocytes are present. (94). The whole organ might be enlarged due to the reticuloendothelial hypertrophy. No young cells or lymphoblasts are seen in the atrophic lymph follicles, but only mature lymphocytes. Anemic infarcts are occasionally seen.

The lymph nodes are sometimes enlarged with hemorrhages. Atrophy of follicles is present with no young lymphocytes in the germinal center. A proliferation of reticular endothelial cells is also seen here. (7).

In the kidney, in cases with sepsis, cloudy swelling bacterial embolin, marked degeneration of tubules and acute nephritis is seen. (94).

Necrotic lesions of the mouth, anus and cervix show an absence of a surrounding inflammatory zone, no granulocytes being present. Often edema and gangrene are seen. The gastro-intestinal tract may also present ulcerations. The lung shows sub-pleural hemorrhages with bacteria. Complications by generalized infection, toxic myocarditis, cloudy swelling, fatty degeneration and multiple areas of necrosis of the liver may be encountered. (65). These ulcerative sites are secondary to blood changes and due to lack of body resistance. (61).

The pathological changes in septic forms has already been mentioned and shown how it might change and complicate the picture both in hematological and local pathology.

Changes due to radiation or to drug influence are essentially the same as described above. The differences are merely that the red elements and negakaryocytes seem

to be more prone to changes than in the idiopathic form. These changes are however, the same as those listed above as far as clinical facilities can be determined but tend to advance with the granulopenia rather than only in old chronic cases as it was described under in the above disertation. However, even here, granulopenia and effect on granulopoiesis is much more marked.

These points are born out by experimental production on laboratory animals, and by accidental poisoning in clinical cases. (32), (90), (69), (88), (113).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

This is usually rather simply made if one observes all of the material with which he has to work. Beck states that if one has the clinical picture, accompanied with a persistent ulcerative lesion, a study of the blood picture, with perhaps a sternal biopsy, will cinch the diagnosis. (7). A clinical syndrome might be described as: (a) weakness, (b) easy exhaustion, (c) tendency to fatigue, (d) loss of strength and inertia, (e) a loss in the number of granulocytes. The severity of the disease almost parallels the degree of depletion of the bone marrow elements.

A few entities might be confused with this picture. Ludwig's angina differs in that the membrane of agranulocytosis is a tenacious gray membrane which does not bleed on removal. This also is easily ruled out by the blood picture. Some investigators class thorium, arsenic, benzol and x-ray as acute poisons with secondary granulopenia. Differential diagnosis is made here by history. X-ray also first attacks the lymphocytes and the granulocytes secondarily. Acute leukemia presents a high fever, a mucous membrane with petechial hemorrhages, enlarged nodes and spleen and a stomatidis with a leucocytosis. Sepsis also shows a leucocytosis. An aleukemic leukemia presents abnormal lymph forms, presence of polymorphonuclears and the same clinical picture as leukemia. (61) A lymphosarcoma may cause a leucopenia but may be differentiated by clinical course and biopsy findings. Aplastic anemia shows a reduction of all blood elements. Infectious mononucleosis will show an increase in circulating neutrophiles upon the injection of foreign protein.

THERAPY AND PROGNOSIS

Discussion of this phase of the subject will necessarily be laden with many procedures that have

been proven to be of little value. If the latter is true, indication will be given after the discussion.

Local lesions are present in the form of ulcers of the various mucous membranes. The most important are found in the oral and pharyngeal cavities. These are primarily treated by cleanliness subsidized by application of antiseptic solutions. (65) A method of treatment can be outlined as follows: A saturated solution of potassium chlorate is sprayed on the cleansed lesion. The denuded area is then painted with a solution of ten grains of copper sulphate per ounce of water. The phlegmonous masses are then excised and any abscesses are drained. It is well to mention here that surgical procedures should be avoided unless absolutely necessary since the lowered concentration of white blood cells make it a dangerous enterprise. (7)

Nucleic acid and its derivatives were probably the most important development ever advised with the possible exception of the yellow bone marrow extract recently advocated. Nucleotides were first advocated in 1897 by Ames, Delano and Huntley, as a treatment for leucopenia. They claimed a rise of the white blood cells in five to ten minutes after injection of the material in both the peripheral and central circulation.

They stated that the polymorphonuclears were little effected, but that many young mononuclears were present. In normal patients white blood count could be raised to 25,000 in forty-five minutes. (2). It is interesting to note that even before this experimental work was done in 1897, Vaughan, who had evidently noted some of its action upon patients, recommended its use in 1893 as a germicide when given intravenously. (117). The treatment was used intermittently in therapy of leucopenia with no advancement being made in either its use or its understanding until 1924 when Jackson isolated from human blood a substance which he believed to be adenine nucleotide. This was combined, or mixed, with an equal amount of pyrimidine nucleotide. (56). In 1925 Jones and Perkins prepared B. Nucleoprotein and from this formed crude nucleotides. They then separated guanine and adenine fractions and finally obtained the brucine salt from the pancreas. (60) In 1931 Reznikoff suggested the following treatment: Adenine sulphate injected at the rate of 0.5 grams in 25cc of normal saline per day. In six hours he noticed a rise in the white blood cells, the polymorphs appearing normal. He treated two cases this way and both recovered. (100) Dameshek, in a review of this work, stated that this therapy alone had lowered the mortality rate of

granulopenia from 80-90% to 25%. He also published some of his own case work and gave three cases, all of the relapsing or recurrent type, which had recovered under use of these derivatives. To case I he gave 10 cc of pentnucleotide intramuscularly daily for four days. After 72 hours from the time the first injection was given, the white blood count began a gradual climb which ended five days later with a count of 16,800. It then gradually returned to normal, remaining thus. Case II was given adenine sulphate. One injection of 0.5 grams of material caused definite improvement. The leucopenia recurred and was treated with pentnucleotide with essentially the same results as obtained in case I. His third case was also treated with pentnucleotides which showed definite improvement in 72 hours. (24) Fitz-Hugh injected 0.7 grams of the substance intramuscularly twice daily for four days. This caused definite improvement in two days after cessation of injection. Granulocytes were seen here for the first time in two weeks. (37). Marriott, in one instance, gave 2.8 grams (of pentose nucleotide) intramuscularly, for ten days and then 0.7 grams via the same method for five days. Transfusions were also given along with calf liver. The patient recovered. (80)

Adenine sulphate usually produces a speedier improvement in patients but also gives a more severe reaction, (i.e. chills, etc.) than does pentnucleotide. If the leucopenia is secondary to sepsis, aplastic anemia, or aleukemic leukemia, there will be no improvement. Following the administration of these drugs, there occurs a sharp dyspnoea, precordial distress, bradycardia, and sweating if it is given intravenously. The latter is not so marked if the drug is given intramuscularly. Following injection these symptoms usually last for about one hour. The first change in the blood picture is histiocytemonocytosis followed by an increase in immature granulocytes and a rise in the entire white blood count. The order of appearance of the granular cells is first myelocytes, metamyelocytes and finally mature neutrophiles. The white blood count rises about two days after the appearance of the immature cells. Clinical improvement which is coincident with quite a noticeable rise in the white blood elements, does not occur until five to seven days. The counts rise to 18,000 - 20,000, on the average, after ten days of treatment. Some investigators found improvement in three or four days, after injections were started, until clinical improvement was noticed. (24), (40).

From this it is seen that nucleic acid and its derivatives are primarily chemotactic. If maturation is absent, chemotaxis would be of little value; so it is not the utopia of therapy. (7). Chemically, nucleic acid yields, upon hydrolysis, phosphoric acid, a sugar or a derivative of a sugar, basis of purine or pyrimidine. The plant, nucleic acid, has an extra sugar (d-rebose), and animal nucleic acid has thymine and desoxyribose. In the digestion of nucleic acid, it is found that neither the gastric nor pancreatic enzymes play much of a part. The succus entericus, however, contains a nucleinase that converts tetranucleotides to mononucleotides. It also contains a nucleinase, nucleotidase, nucleosidase; so the end products as phosphoric acid, nucleosides, sugar, guanine and adenine go to the liver. These facts might be useful as a factor in administering these products orally or in administering animal products rich in tetranucleotides. (44)

A few experimental phases of this form of treatment might be mentioned. The induction of nucleinate on rabbits produces a primary leucopenia for several hours. This is followed by an increased delivery of new forms causing leucemia. Both are due to the granulocytes.

Bone marrow slides show a speeding up of later stages of granulocyte production. The primary leucopenia is caused mostly by the spleen since splenectomy shortens the primary leucopenia greatly. The spleen actually increases in size during the leucopenic period. Adenine and guanine sulphate cause no initial leucopenia. (29)

When nucleic acid and its derivatives are injected intravenously with phosphate buffers, a short primary leucopenia is noted. This was not produced when normal saline solution was substituted for the buffer solution. The leucopenia was caused by decrease in lymphocytes. Nucleoproteins also produce a leucopenia. (99) Climenko found that nucleic acid and its derivatives do not react when given after or with benzol derivatives. (22)

Doan kept animals on nucleinate for 102 to 116 days with a constant hyperplasia of marrow but found no harm done to this organ after this length of time; so this therapy seems to be quite safe. (31)

Transfusions have been used quite extensively with this disease but with very doubtful beneficial results. It is evident that frequent transfusions of a large enough quantity might serve in keeping a much distressed patient alive until some more potent form of therapy may be tried. Fisher used immune serum from a donor who

had recovered from granulopenia. Ordinary blood had previously been tried with negative results. After this transfusion the patient seemed materially aided, and he recovered. (36) It seems that such a procedure would be rather trying, however, since the donor was none too sure of not needing all of his own blood in a remission.

Radiation of bones with X-ray seems to be definitely beneficial. The exact dose varies greatly with individuals. One-twentieth of a skin unit might be satisfactory for one individual but quite insufficient for another. Too large a dose of this material is definitely dangerous, since the very disease one is trying to cure may be listed as being caused by excessive X-ray as a etiological agent. Small doses should be administered first and only then by a competent roentgenologist.(7) Many clinical cases may be found which when this treatment was used, had very definite improvement, both hematologically and clinically.

Calcium gluconate has been reported as giving a granulocytic response five days after injections were started. (7). Orange juice, brewers yeast, bone marrow extract and cod liver oil have all been used with dubious results. Other miscellaneous items that have

been tried include milk, gentian violet, fetal liver, Squibb's leucocytic extract, Armour's extract of spleen, intravenous antistreptococcus serum, diphtheria anti-toxin, non-specific proteins, etc., All of these produced little, if any, effect upon the patient, either clinically or hemotologically. (65)

One investigator used typhoid vaccine with a report of recovery. (6) Some cases show an "allergic state" in which they tremble, etc. This is especially manifested at the onset of clinical symptoms. Adrenalin seems to combat this state. (39). Massive doses of liver therapy, have been used with no definite results. In cases where symptomatic cardiac discomfort is developed colloidal sulphur seems to be of some value.(65) In cases produced by arsphenamine therapy, intravenous sodium theosulphate seems to present therapeutic advantages. The dosage suggested being 0.3 grams, increasing 0.15 grams daily until 2 grams have been given. Prophylactic treatment includes rest, cessation of all types of toxins, and a high vitamin B. diet. (7)

There are three types of treatment that are rather late developments which have been left purposely to the last for discussion. For two of these there is no clinical data. The first of these substances is

glutathione. This is found normally in all body cells. In cases of benzol poisoning, it is reduced. In myloid leukemia, it is especially elevated and in leucopenia it is decreased. It was reasoned, therefore, that if this substance be given, an increase in division of myelocytes may be obtained. It is found that beneficial results are obtained in animals with benzol poisoning, a leucopenia being present in these same animals. In normal animals, however, no leucocytic response was gained. (92).

Greer, in working with rats with experimental granulopenia resulting from benzol poisoning, introduced another form of therapy. This was fetal calf spleen. In animals treated, a 25% mortality rate was established. In those untreated, 66% mortality rate was obtained. In his experiments he found fetal spleen nucleoprotein, raw fetal spleen and fetal spleen powder to be ascending in that order in benefit derived. Pentnucleotid also increased the white blood count, but a higher mortality rate was noted. Powdered beef spleen and fetal spleen cystosine groups were no better off than the control group.

The third of this last group is a development of the last year which gives more promise than any treatment

developed to date. This is extract of yellow bone marrow introduced by Marberg and Wiles in 1938. Yellow bone marrow was saponified with an excess of potassium hydroxide. The unsaponifiable portion was then extracted in vacuum. This portion was found to contain almost all of the active ingredient by clinical tests. The oil extracted was then absorbed in some bland oil, such as cotton seed oil, so that 0.05 cc contained 2 grams of the strained yellow bone marrow. Of the normal persons tested only one responded. The blood count in this instance (after one teaspoonful taken orally of the concentrate) was raised from 7,000 to 21,000 in twenty four hours. One case was given 10 drops three times daily for two days followed by half that dosage. The white blood picture went from 2,600 to 5,400 and the polymorphonuclears from 27% to 35% in nine days. Another patient had been on pentnucleotides but the treatment was considered unsatisfactory. With the blood count at 4,500, the patient was given 105 drops of oil per day. In four days the count was up to 7,500. The treatment was discontinued and the count dropped to 3,500 in four days. Then starting with 65 drops per day, it resulted in a count of 7,500 in five days. Of seventeen cases treated, almost all of whom had been treated unsuccessfully with other known forms of treatment, mostly

nucleotides, ten recovered and seven died. Of the seven who died, three had aplastic anemia and one had diabetes. Of the ten who recovered, six had agranulocytic angina and four had leucopenia without angina. The response was both clinical and hematological in forty-eight hours. The authors state that clinical recovery followed immediately the return of the blood picture to the phase expected by the local lesions.(79)

The prognosis has been discussed with the types of treatment. Here may be given a few generalities. The prognosis depends upon the severity of the neutropenia. Rosenthal states that a white blood below 1000 cells per cm. gives a poor prognosis, while one over 1,000 gives a good prognosis. It must never be forgotten, however, that the individual might die from a subsequent attack. (66). A mononucleosis developing in the course of treatment is a favorable sign. (100) When the disease was first described, the prognosis was practically 100% mortality. In 1927 it was still 90 - 95%. In 1931 it dropped to 50%, and at the present time is only 25%. From this, it is seen that treatment has not been without its effect.

DISCUSSION AND SUMMARY

From the body and discussion of the subject, one can see that there are still contraversial points. Most of these are not, however, antagonistic points of a true nature but merely isolated facts about which the intermediate is still obscure or not yet worked out.

The history of the disease reveals the fact that while the recognition of the syndrome itself is only seventeen years of age, the picture has been described, sometimes quite completely, all through this century and had been suggested in the fifty years preceding 1900. In the last ten years knowledge has become widely distributed, and the disease is being recognized with more and more frequency. Aside from this, the actual incidence seems to be growing since men who have been recognizing the syndrome for a number of years advance the opinion that it has, of late years, been more prevalent. Perhaps this is due to the cumulative effect of etiological agents such as benzene ring derivatives. The etiological agents may be divided into four general classes; (a) Agranulocytosis: The idiopathic form of the disease which shows perhaps the most truly typical form of the syndrome. (b) Agranulosepsis, which is caused by bacteria or their products. It is probably

more true to say just the products since, on normal animals, bacteria produce the typical septic picture, and only the products when injected will produce the entity similiar to the clinical phase of agranulocytosis. There is also no evidence to show that bacterial septicemias, when found in these cases, are not really secondary. In fact, evidences of the bacteremia have never been demonstrated before the clinical onset of the complex. (c) Agranuloradiation is that form of the entity developed when excessive X-ray, radium products or any radioactive substance has been ingested to any marked degree. This form of granulopenia is prone to be accompanied by anemia and effects on the erythroplastic portions of the bone marrow; so many authors consider it as more truly classed in the realm of aplastic anemias. (d) Agranulotoxicosis is that portion of the syndrome caused by toxic substances such as benzene and its derivatives. Small doses of these substances over periods of time seem to produce the typical picture. Larger doses, however, seem to cause a condition more congruent with complete aplasia of the bone marrow. Several investigators believe that in nearly every case of agranulocytosis a history of one of these toxins can be gained. If this is true, the

class of idiopathic agranulocytosis is being almost eradicated. In a review of the literature it is apparent that many people can and do take tremendous quantities of these drugs without ill effects upon the hemopoietic system. There is, then, undoubtedly a factor of inherent weakness of this system. As long as this is true, it is not justified in ruling out completely, at least, agranulocytic angina idiopathica.

The clinical onset is rapid and follows a hemotological onset of days to weeks or even months. The point of onset as relative to the blood picture is variable but is usually after the white blood picture showed fifty percent of its original concentration and one half of its customary granulocytic element. The severity of the symptoms are usually parallel with the severity of the hemotological deviation. The onset is marked with weakness, malaise, lassitude, inertia, etc. This is followed by sore mouth and subsequent formation of ulcerative lesions in these localities. The physician usually finds the patient well advanced in the disease. The clinical types may be divided into acute fulminating, with a high mortality; chronic with a low mortality; acute and chronic recurring, with corresponding mortality rates; cyclic variety which is regular, periodic; and

of either the acute or chronic variety with various gradations of these general classes. Recovery is rapid or gradual, depending on the etiology (whether or not it can be removed), the severeness of the disease, the condition of the patient, etc. Death, the other alternative is likewise based on the severity, advancement and etiology of the syndrome. Chronic patients may show only one sign, that of weakness, for years on end.

The pathology of the local lesion is a non-infiltrated, denuded, inflamed area. That of the blood is a decrease to total lack of granulocytes with a total decrease of the white blood cells. The bone marrow shows a corresponding loss of granulopoietic elements to a complete aplasia of these factors. There may or may not be an associated decrease in the other elements of the blood. Some investigators would argue the associability of this as contiguous with the syndrome, but when one considers the common origination of all blood cells, one can readily realize that these related elements may become affected merely as a matter of course in the disease itself. Could one not, therefore, consider this entity as a step in one of the processes of production of aplastic anemia? And if this is true, why would not benzol and its derivatives be a true, or

partial, etiological factor since the degree of benzol poisoning seems to determine just what type and how many of the cellular elements of the marrow and blood are affected. Likewise, the spleen and nodes, or the lymphatic elements, often show atrophic processes. Experimental evidence indicates that many of these points are true.

Treatment of this disease entity has progressed rather rapidly. The value of nucleic acid and its derivatives had been known even before the syndrome itself was described. Its application has done much in offering a better prognosis. Its value is chiefly chemotactic in nature. Glutathione offers a possible addition in that it might supply the maturation factor. Both of these factors are supplied with both fetal calf spleen and yellow bone marrow extract with the latter being much more successful as far as can now be determined. Radiation of the long bones seems to be stimulatory, but the danger of its use and its inaccessibility place it in a less desirable group. Transfusions are helpful only as a direct treatment to prolong life until another form of treatment has time to exert its influence. Actual stimulation from blood transfusions in recovered cases has been reported as beneficial,

but its possible reaction on the donor makes its use of doubtful value from a practical standpoint. Other forms of treatment with the exception of local ulcer treatment are of doubtful value.

Diagnosis is made upon the clinical symptoms, combined with the blood picture. All other forms can be ruled out by using these two phases, but all other diseases can not be ruled out by using only one of them. For example, the blood picture of aleukemic leukemia has been confused with that of this syndrome, and some leukemias with oral sepsis may closely simulate this disease clinically.

Agranulocytic angina may be rather simply and accurately diagnosed and may usually be treated successfully as demonstrated by the fall in mortality. It is, therefore, a disease in which medical science from an experimental and clinical angle, should be congratulated. Yet, much remains to be gathered about its intricate mechanisms, and even greater success should be procured with a fuller understanding of this entity.

CONCLUSIONS

1. Agranulocytosis is a disease of recent recognition but of probably much older history.
2. Its etiology may be divided into idiopathic agranulocytosis, agranulosepsis, agranulotoxicosis, and agranuloradiation.
3. Its clinical course is characterized by weakness, prostration, inertia, formation of mucous membrane ulcers and a low white blood count with a granulopenia.
4. Pathological changes in the bone marrow may be either conducive with the clinical blood picture which shows an abnormal maturation factor, or the marrow might be normal or hyperplastic, showing abnormal chemotactic factor.
5. Diagnosis is made upon clinical symptoms with the help of the blood picture and perhaps sternal biopsy.
6. Treatment is successful in so far as the prognosis has been considerably improved. The successful forms of treatment, besides the local management of ulcers are; Irradiation of bones - stimulative but dangerous in as much as aplasia may be instigated; Nucleic acid and its derivatives - chemotactic; Glutathione - maturative; Foetal spleen - both chemotactic and maturative, and yellow bone marrow

extract, both maturative and chemotactic and of greater potency than any of the others.

7. Prognosis has improved from 100% mortality to 25% in the last fifteen years. The prognosis varies almost directly with the abnormality of the blood picture and the severity of the attack.

BIBLIOGRAPHY

1. Allen, J.G. and Short C.L.,
Granulocytosis Associated with Sulfanilamide
Therapy,
New Eng. J. Med., 219:6-8, (July 7,)1938
2. Ames, DeLano, and Huntley, A.A.,
The Nature of the Leucocytosis Produced by
Nucleinic Acid: A Preliminary Experimental
Study,
J.A. M.A., 29:472, 1897
3. Argue, T.H., and Schafer, R.J.,
Granulopenia: Case Report,
New York State J. Med., 33:1385, 1933
4. Ashworth, O.O. and Maphis, E.C.,
Agranulocytic Angina. With Report of a Case,
Virginia M. Monthly, 54:237, 1927
5. Babbitt, J.A. and Fitz-Hugh, T. Jr.,
Agranulocytic Angina: Report of a Case with
Apparent Recovery,
Arch. Otolaryng., 12:439, (Oct.), 1930
6. Baldrige, C.W. and Needles, R.J.,
Idiopathic Neutropenia,
Am. J. M. Sc., 181:533, 1931
7. Beck, Regena, C.,
Benign and Malignant Neutropenia:
Present Status of Knowledge of this Condition,
with Report of Four Cases,
Arch. Int. Med., 52:239-288, 1933
8. Beck, Regena, C.,
Drug Idiosyncrasy and Neutropenia,
Virginia M. Monthly, 61, 643, 1935
9. Beck, Regena C.,
Neutropenic Syndrome,
Virginia M. Monthly, 60, 336, 1934
10. Behnke, A.R.,
Neutropenia Following Administration of
Neoarsphenamine,
U.S. Nav. M. Bull., 36:108-110, (Jan.),1938

11. Berg, S. and Holtzman,
Fatal Agranulocytosis Following
Sulfanilamide Therapy,
J.A. M.A., 110:370-371, (Jan.29,), 1938
12. Blumer, G.,
Agranulocytic Blood Picture in Conditions
Other Than Angina,
Am. J. M. Sc., 179:11-16, 1930
13. Bolton, V.L.,
Laboratory Study of Amedopyrine, Barbitol,
Phenyl Hydrazine, and Benzene in Relation to
Agranulocytic Angina.
J. Lab. and Clin. Med., 20:1199-1203, (Aug.)
1935
14. Bromberg, L. and Murphy, P.,
Agranulocytic Angina Following
Prophylactic Typhoid Vaccination,
J.A.M.A., 92:1266, 1929
15. Brown, P.K.,
A Fatal Case of Primary Infectious
Pharyngitis with Extreme Leukopenia,
Am. Med., 3:649, 1902
16. Brugman, Francis and Lewis, Edgar J.,
Treatment of Agranulocytic Angina with
Nucleotide K 96,
Northwest. Med., 32:336-338, 1933
17. Buck, R.W.,
Agranulocytosis Associated with Anal Ulcer,
J.A.M.A., 93:1468-1469, (Jan. 9,) 1929
18. Call, M., Gray, B.H., and Hodges, F.M.,
Agranulocytic Angina. Report of One Case
with Recovery,
Am. J. Roentgenol., 20:550, 1928
19. Cannon, A.B.,
Some Unusual Peumatoses,
South. M.J., 20:141-147, 1927
20. Camp, W.E., and Baumgartner, E.A.,
Inflammatory Reactions in Rabbits with
Severe Leukopenia,
Jour. Exp. Med., 22:174-193, 1915

21. Chown, G. and Gelfand, A.S.,
Agranulocytosis,
Canadian Med. Ass. Jour., 29:128, 1933
22. Climenka, D.R.,
Inhibition of Leukogenic Activity in
Rabbit by Certain Cyclic Compounds,
Proc. Soc. Exper. Biol. and Med., 32:
823-825, (Mar.,) 1935
23. Climenko, D.R.,
Modification of Hematopoietic Function in
Rabbit by Certain Cyclic Compounds,
J. Lab. and Clin. Med. 21:913-922, 1936
24. Dameshek, Wm.,
Agranulocytosis, Report of Three Cases
Treated with Nucleic Acid Derivatives,
New Eng. Jour. of Med., 209: 1054-1061, 1933
25. Dameshek, Wm.,
Benzene Poisoning and Agranulocytosis,
J.A.M.A., 93: 712, 1929
26. Dameshek, Wm.,
Granulocytopenia,
J.A.M.A., 102:950, 1934
27. Darnall, J.R.,
Granulopenia,
Military Surg., 74: 187, 1934
28. Dennis, E.W.,
Experimental Granulopenia Due to Toxins
Elaborated in Vivo,
J. of Exper. Med., 57:993-1008, 1933
29. Doan, C.A., Zerfas, L.G., Warren, S., and Ames, O.,
A Study of the Mechanism of Nuclemate Induced
Leucopenic and Leucocytic States, with Special
Reference to Roles of Liver, Spleen, and
Bone Marrow,
J. Exper. Med., 47: 403-435, 1928
30. Doan, C.R. and Zerfas, L.G.,
Rhythmic Range of White Blood Cells in Human
Pathological Leucocytic and Leucopenic
States, with Study of Thirty-two Human Bone
Marrows,
J. Exper. Med., 46, 511, 1927

31. Doan, C. R.,
Neutropenic State: Its Significance and
Therapeutic Rationale,
J.A. M.A., 99: 194, 1932
32. Dodd, K., and Wilkinson, S.J.,
Severe Granulocytic Aplasia of Bone Marrow,
J.A.M.A., 90: 663, 1928
33. Du Bray, E.S.,
Agranulocytic Angina: A Pitfall in Its
Recognition and Comments on Recent Advances
in Its Treatment,
Northwest. Med., 32: 331-336, 1933
34. Dyer, H.L. and Helwig, F.C.,
Agranulocytic Angina,
Am. Jour. Dis. Child., 35: 1041, 1928
35. Farley, D.L.,
Depressed Bone Marrow Function From the
Arsphenamines,
Am. J. M. Sc., 179: 214, 1930
36. Fisher, R.L.,
Case of Agranulocytic Angina Successfully
Treated with Immuno-Transfusion,
J. Michigan M. Soc., 29: 435, 1930
37. Fitz-Hugh, G.,
Agranulocytosis,
New. Eng. J. Med., 209: 1051, 1933
38. 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
39. Fitz-Hugh, T. Jr.,
Pernicious Leukopenia, Clinical and
Experimental Background and Its Present
Status,
M. Clin. North Am., 19: 103-122, 1935
40. Fitz-Hugh, T. Jr.,
Pernicious Leukopenia (Agranulocytic Angina),
Penn. Med. J., 37: 579, 1934

41. Folin, O. and Denis, W.,
The Excretion of Free and Congugated
Phenols and Phenol Derivatives,
Jour. Biol. Chem., 22: 309, 1915
42. Goldenberg, C.,
Agranulocytosis - Report of A Case with
Three Relapses,
Virginia M. Monthly, 58: 391, 1931
43. Gordon, M.B. and Lituaic, A.M.,
Differential Diagnosis Between Diphtheria
and Oral Lesions of Blood Dyscrasias,
M.J. and Rec., 131: 35, 1930
44. Greer, A.E.,
Experimental Study of Treatment of Benzol
Produced Agranulocytosis in Albino Rats,
South. M.J., 28: 1114-1123, 1935
45. Hamilton, Alice,
Industrial Poisons in the United States,
New York, The MacMillan Company, 1929
46. Harris, W.H. and Schattenberg, H.J.,
Experimental Studies in So-Called
Agranulocytic Angina; Effects of Toxic
Products of Certain Bacteria Recovered from
Stool and Blood of Human Being Upon
Leucocytes of Animals,
J. Lab. and Clin. Med., 20:1053-1062, 1935
47. Hart, V.K.,
Combined Ludwig's Angina, Agranulocytic
Angina, and Septicemia,
Laryngoscope, 57: 357, 1927
48. Hart, V. K.,
Further Observations on Agranulocytic Angina,
Laryngoscope, 37: 798, 1927
49. Hektoen, Ludwig,
The Effect of Benzene on the Production of
Antibodies,
Jour. Inf. Dis., 19: 69-84, 1916
50. Houser, K. M., and Rose, E.,
Angina; Blood Stream Infection and
Agranulocytosis: Case Report,
Tr. Coll. Phys. Philadelphia, 50:368, 1928

51. Hueper, W.C. and O'Connor, D.,
Agranulocytic Angina,
Laryngoscope, 38: 679, 1928
52. Hunter, R.J.,
Agranulocytic Angina: Report of a Case
with Fractures of Tibia,
Tr. Coll. Phys. Philadelphia, 47:490, 1925
53. Hurwitz, S.H. and Drinker, C.K.,
The Factors of Coagulation in the Experimental
Aplastic Anemia of Benzol Poisoning,
J. M. Res., 21: 421, 1915
54. Jacobsen, A.W.,
Agranulocytosis,
Canad. M.A. J., 22: 814, 1930
55. Jackson, H.,
Agranulocytosis Following Ingestion of
Causalin,
J.A. M. A., 111: 523, 1938
56. Jackson, H. Jr.,
Studies in Nuclein Metabolism; Isolation of
a Nucleotide from Human Blood,
J. Biol. Chem., 59: 529, 1924
57. Jackson, H. Jr., Parker, F. Jr., Rinehart, J.F.,
and Taylor, F.H.L.,
Studies of Diseases of the Lymphoid and
Myeloid Tissues: VI The Treatment of
Malignant Neutropenia with Pentose Nucleotides,
J.A.M.A., 97: 1436, 1931
58. Jacobsen, W.C.,
Neutropenia following Excessive Use of
Phenobarbitol. Case,
Med. Rec., 148: 148-150, 1938
59. Jaffee, R.H.,
Bone Marrow in Agranulocytosis (Pernicious
Leukopenia)
Arch. of Path., 16: 611-629, 1933
60. Jones, W. and Perkins, M.E.,
Occurrence of Plant Nucleotides in
Animal Tissues,
J. Biol. Chem., 62: 291, 1925

61. Kastlin, G.J.,
Agranulocytic Angina,
Am. J. Med. Sc., 173: 799-813, 1927
62. Keeney, N.J.,
Pyocanic Angina, with Agranulocytosis,
Calif. and West. Med., 33: 503-505, 1930
63. Kracke, R.R.,
Agranulocytosis with A Report of An
Unusual Case,
Am. J. Clin. Path., 1: 385, 1931
64. Kracke, R.R. and Parker, F.,
Etiology of Granulopenia (Agranulocytosis),
with Particular Reference to Drugs Containing
Benzene Ring,
J. Lab. and Clin. Med., 19: 799-818, 1934
65. Kracke, R.R.,
Review of Granulocytopenia (Agranulocytosis),
J. Lab. and Clin. Med., 17: 993-1005, 1932
66. Kracke, R.R.,
Significance of Leukopenias, With Special
Reference to Agranulocytosis,
U.S. Nav. M. Bull., 30: 16-26, 1932
67. Kracke, R.R.,
The Experimental Production of Agranulocytosis,
Am. J. Clin. Path., 1: 385, 1931
68. Kracke, R.R.,
Thrombopenic Granulocytopenia (Agranulocytosis
with Hemorrhage)
South. M.J., 25: 448, 1932
69. Krumbhaar, E.B. and Krumbhaar, Helen D.,
Blood and Bone Marrow in Yellow Cross Gas
(Mustard Gas) Poisoning,
J.M. Research, 40: 497-507, 1919
70. Krumbhaar, E.B.,
Role of the Blood and Bone Marrow in Certain
Forms of Gas Poisoning 1. Peripheral Blood
Changes and Their Significance,
J.A. M.A., 72: 39, 1919

71. Larson, W.D. and Barron, M.,
Report of A Case In Which the Fusiform
Bacillus Was Isolated From the Blood Stream,
J. Infect. Dis. 13: 429, 1913
72. Leale, M.,
Recurrent Furunculosis in An Infant Showing
Unusual Blood Picture,
J.A.M.A., 54: 1854, 1910
73. Leuchtenberger, R.,
Beitrag Zur Frage der Agranulozytose,
Folia Hemat., 39, 63-101, 1929
74. Lewis, E.J.,
Treatment of Agranulocytic Angina with
Nucleotide K 96,
Northwest. Med., 32: 336, 1933
75. Linthicum, F.H.,
Experimental Work on Bacillus Pyocyanus,
Ann. Otol. Rhin. and Laryng., 36: 1093, 1927
76. Lovett, B.R.,
Agranulocytic Angina,
J.A.M.A., 83: 1498, 1924
77. La Salle, M. and La Salle, C.,
Agranulocytosis, Fulminating Case,
M. Rec. 148: 9-11, 1938
78. Mack, L. and Smith, E.
Effect of Deficient Diet, Amytol (Barbitol
Preparation) and Amidopyrine on Blood Picture
of Albino Rat,
Proc. Soc. Exp. Biol. and Med., 32: 1633-1624,
1935
79. Marberg, C.M. and Wiles, H.O.,
Granulocytopoietic Fraction of Yellow Bone Marrow,
Arch. Int. Med., 61: 408-429, 1938
80. Marriott, H.L.,
Agranulocytic Angina and Pentose Nucleotide,
Lancet, 1: 448-451, 1934

81. Martland, H.S., Conlon, P. and Knef, J.P.,
Unrecognized Dangers in Use and Handling of
Radioactive Substances,
J.A. M.A., 85: 1769-1776, 1925
82. Miller, D.K. and Rhoads, C.P.,
Experimental Production in Dogs of Acute
Stomatitis, Associated with Neutropenic and
Maturation Defect of Myeloid Elements of
Bone Marrow,
J. Exper. Med., 61: 173-182, 1935
83. Millman, M. and Fureolo, C.L.,
Relapsing Agranulocytosis: Case Report,
New Eng. J. of Med., 208: 440, 1933
84. McAlpin, K.R.,
Lymphocytosis, Its Clinical Importance,
New York State J. Med., 28: 1103, 1928
85. McCord, C.P.,
The Present Status of Benzene (Benzol)
Poisoning,
J.A.M.A., 93: 280-283, 1929
86. McDougall, C.,
Trans. Am. Laryn. Rhinol. and Otol. Soc.,
392, 1931
87. McGuire, J.P. and McGuire, P.R.,
Agranulocytosis Following Use of Sulfanilamide,
Illinois M.J., 73: 425-426, 1938
88. Nakaharce, W.,
Changes in the Lymphoid Organs After Small
Doses of X-rays,
J. Exper. Med., 29: 83-87, 1919
89. Ortway, T. and Gorham, L.W.,
Agranulocytic Angina,
Oxford Monographs On Diagnosis and Treatment,
New York, Oxford Univ. Press, 9: 204, 1930
90. Panton, P.N.,
The Effect of Trinitrotoluene on the Blood,
Lancet, 2: 77-82, 1917

91. Pappenheim, A.,
Zur Benzolbehandlung der Leukämie und
Sonstiger Blutkrankheiten,
Wein. klin. Wchnschr., 76: 48, 1913
92. Parker, F. P. and Kracke, R.R.,
Further Studies in Experimental Granulopenia,
with Particular Reference to Sulphydryl
(Glutathione) Metabolism in Blood Dyscrasias,
Am. J. Clin. Path., 6: 41-56, 1936
93. Pepper, O.H.P.,
History of Agranulocytic Angina,
J.A.M.A., 97: 1100, 1931
94. Piette, E.C.,
Histopathology of Agranulocytic Angina,
J.A.M.A., 84.2: 1415-1416, 1925
95. Plum, P.,
Agranulocytosis Due to Amidopyrine,
Experimental and Clinical Study of Seven
New Cases,
Lancet, 1: 14-20, 1935
96. Potter, H.W.,
Myelogenous Leukemia with Aleukemic Stage
Simulating Agranulocytosis: A Case Report,
Virginia M. Monthly, 58, 739-743, 1932
97. Reich, C. and Reich, E.,
Further Studies in Treatment: Effect of
Injections of Liver Extract and Milk Protein
on Blood and Bone Marrow of Rat,
J. Lab. and Clin. Med., 22: 503-505, 1937
98. Reznikoff, P.,
Etiological Importance of Fatigue and
Prognostic Significance of Monocytosis in
Neutropenia,
Am. J. M. Sc. 195: 627-633, 1938
99. Reznikoff, Paul,
Experimental Leukocytosis and Leukopenia,
J. Clin. Investigation, 6: 16, 1928
100. Reznikoff, P.,
Nucleotide Therapy in Agranulocytosis,
J. Clin. Investigation, 9: 381, 1931

101. Rheinheimer, E.W., and Smith, L.M.,
Granulopenia: Report of Case Following
Infection of Gold and Sodium Theosulphate,
Southwest. Med., 17: 239-240, 1933
102. Rhods, C.P.,
Etiology of Pernicious Anemia,
Symposium on Quantitative Biology,
5: 410, 1937
103. Richardson, J.K.,
Agranulocytic Angina: Case Report with
Autopsy Findings,
Virginia M. Monthly, 58: 545, 1931
104. Richardson, C.H.,
Granulopenia Associated with Carcinoma of
the Pancreas,
South. Surg., 2: 234, 1933
105. Roberts, S.C. and Kracke, R.R.,
Agranulocytosis: Its Classification Cases
and Comments Illustrating Granulopenia Trend,
from 8000 Blood Counts in the South,
Ann. Int. Med., 5: 40, 1931
106. Roberts, S.R. and Kracke, R.R.,
Agranulocytosis. (Report of a Case)
J.A.M.A., 95: 780-786, 1930
107. Rosenthal, N. and Kugel, M.A.,
Hypoleukocytic Angina: Unusual Form of
Infectuous Leukopenia,
J. Lab. and Clin. Med., 19: 344-358, 1933
108. Rutledge, Bitt, Hanson, Pruss, O.C. and Thayer, W.O.,
Recurrent Agranulocytosis,
Bull. Johns Hopkins Hosp., 46: 369, 1930
109. Schwartz, W.F., Garwin, C.F. and Koletsky,
Fatal Granulocytopenia from Sulphanilamide,
J.A.M.A., 110: 368-370, 1938
110. Selling, L.,
Benzol as a Leucotoxin. Studies on the
Degeneration and Regeneration of Blood and
Haematopoietic Organs,
Johns Hopkins Hosp. Reports, 17: 83-135, 1916

111. Shaw, A.F.B.,
Diurnal Tides of Leukocytes of Man,
J. Path. and Bact., 30, 1-19, 1927
112. Shea, J.J.,
The Blood in the Various Anginas,
Arch. Otolaryng., 12: 366, 1930
113. Shute, E. and Davis, M.E.,
Histologic Changes in Rabbits and in Dogs
Following Intravenous Injection of Thorium
Preparations,
Arch. of Path., 15: 27-34, 1933
114. Simonds, J.P. and Jones, H.M.,
The Effect of Injections of Benzol Upon the
Production of Antibodies,
Jour. Med. Res., 33: 197, 1915
115. Smith, J.W., Jr.,
Reaction of Leukocytes After Vaccination
with Army Triple Lipovaccine,
J.A.M.A., 72: 257-259, 1919
116. Stites, J. and Stites, F.M.,
Agranulocytosis
Kentucky J.J., 36: 324-328, 1931
117. Vaughan, V.C., Novv, F.G. and McClintock, C.T.,
The Germicidal Properties of Nucleins,
Medical News, New York, 62: 536, 1893
118. Watkins, C.H.,
Acute Leukopenic Leukemia and Its Differential
Diagnosis
Wisconsin M.J., 32: 156, 1934
119. Watkins, C.H.,
Possible Role of Barbiturates and Amidopyrine
in Causation of Leukopenic States,
Proc. Staff. Meet. Mayo Clin., 8: 713, 1934
120. Weiskotten, H.G.,
The Normal Span of the Neutrophil Leukocyte,
Am. J. Path., 32: 183-189, 1930

121. Weiskotten, H.G. and Brewer, R.K.,
Action of Benzol. III The Urinary Phenols
with Special Reference to the Diphasic
Leucopenia,
Jour. Med. Res., 35: 71-78
122. Weiskotten, H.G., Schwartz, S.C. and
Steensland, H.S.,
The Action of Benzol. II The Deuterphase
of the Diphasic Leukopenia and Antigen-
Antibody Reaction,
Jour. Med. Res., 35: 63-67, 1916
123. Weiskotten, H.G., Schwartz, S.C. and
Steensland, H.S.,
The Action of Benzol. I On the Significance
of Myeloid Metaplasia of the Spleen,
Jour. Med. Res., 33: 127-140, 1915
124. Weiskotten, H.G. and Steensland, H.S.,
The Action of Benzol. V. The Diphasic
Leukopenia as a Polynuclear Anophophite
Phenomenon (Rabbit)
Jour. Med. Res., 39: 485-494, 1919
125. Wheelihan, R.G.,
Agranulocytic Aplasia of the Bone Marrow
Following the Use of Arsenic
Am. J. Dis. Child., 35: 1024, 1928
126. Wyatt, T.C.,
Agranulocytic Angina; Report of Case with
Recovery,
New Eng. J. Med., 199, 525, 1928