Agranulocytic angina

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INTRODUCTION

In 1922, Werner Schultz (1) described a disease which to his mind, followed a typical course and which he considered to be a clinical entity. The syndrome had never before been described although it is doubtful whether his were the first cases ever to occur. Since that time there have been many cases reported in the literature, the first cases being reported in Germany. Subsequent to 1928 the literature in the United States has been flooded with reports of cases. There has been much diversity of opinion concerning the disease, many authors think the condition to be merely a symptom complex and belonging to a group of diseases. Still other men agree with Schultz in considering it to be a clinical entity. After a review of the literature it becomes apparent that there have been very many cases reported which do not coincide with the description as given by Schultz and whether these cases should be considered under the same classification is a difficult problem to decide. If we are to assume, as many clinicians do, that there is a secondary agranulocytic angina with a definite etiologic factor in the background, it would seem that many of the cases reported are a symptom complex and certainly not a clinical entity. On the other hand, there are certainly a number of cases reported which do coincide with Schultz's description, do not have an etiologic factor in the background and may be considered a valid clinicopathological entity in the same way that pernicious anemia is accepted as such. In contra-
distinction to pernicious anemia it may be considered to await the specific therapy to stamp it with unmistakable validity. It would thus seem that a thorough analysis of the case should be made in order to determine its primary or secondary classification. In this paper we shall deal chiefly with the primary or Schultz type of the disease which, until further proof is submitted, I believe should be considered a clinical entity.
NOMENCLATURE

The name that was first proposed for this disease was possibly chosen for its brevity, but certainly not to describe the condition. Werner Schultz (1) first reported a number of cases as agranulocytosis. Later Friedemann (2), impressed by the typical oropharyngeal lesions that were present in practically every case suggested the term agranulocytic angina. Although this name is unfortunate in that it implies that one is dealing with an infection of the mouth and throat which causes the neutropenia, it has held throughout the literature. It is now known, also, that cases without angina do occur. The terms agranulocytosis and agranulocytic angina are even at the present time being widely used, although they can be shown to be fallacious. The term agranulocytic angina is to be found in the Cumulative Medicus. Schilling (3) has stated that the term agranulocytosis is incorrect and he points out that the name "agranulocyte" was originally chosen for "neutrophiles without granulations" of leucemias. He further explains that the term "agranulocytosis" really means an increase in these atypical "neutrophiles without granulations", which was not intended by Schultz. He therefore considered the term malignant neutropenia to be much more appropriate and descriptive. Baldridge and Needles (4) pointed out that if the derivation of agranulocytosis is assumed to be agranulocyte - osis it would mean an increased number of these very special abnormal neutrophils. On the other hand, if the
derivation is a - granulocyte - osis it would mean an absence of increase of granulocytes, or a normal count. They, therefore, suggested the term "idiopathic neutropenia", thus making it analogous to idiopathic aplastic anemia and idiopathic thrombocytopenia. Many terms have been suggested, some of which are: mucositis necroticans agranulocytica; sepsis with granulocytopenia; monocytic angina; granulocytopenia; and agranulosis.(5) It would seem that "idiopathic neutropenia" is the most appropriate and descriptive term that has been suggested but because of the predominance of the term agranulocytic angina in the literature, in order to avoid confusion in this paper, we will refer to the condition by this name.
HISTORY

Upon the appearance of a newly described syndrome it is sometimes very difficult to determine under what name, if any, the cases have been previously described. This is especially true of agranulocytic angina. Because of the typical course and frequently fatal termination of the disease it would seem, on superficial examination, that the disease did not exist before Schultz (1) described it in 1922. Schultz is given credit for recognizing the syndrome later called agranulocytic angina by Friedemann (2), but the condition undoubtedly existed before this time. It is rather difficult to state definitely when the condition was first noted. There is little hope of finding references in hematologic works earlier than 1907. Pepper (6) states that Peter (7) in 1870 in writing of gangrenous angina, described the gross characteristics of the blood but no conclusions could be drawn from his description. Pepper also refers to Mackenzie's (8) "Manual of Diseases of Throat and Nose". Under the heading "Putrid Sore Throat" one finds a condition defined as: "Primitive gangrene of the pharyngeal mucous membrane, constituting an affection per se, and originating independently of any other malady such as diphtheria, scarlet fever, etc."

Mackenzie states that Peters observed that the history of this affection may be divided into three periods. First, the ancient period, when a belief founded on vague descriptions of Hippocrates and Aretaeus prevailed that the disease was a common one, while almost all cases described were cases of diphtheria.
Secondly, the period of Bretonneau, subsequent to 1821, when the researches of that observer proved that the so-called cases of gangrene were only cases of diphtheria and very rarely did a gangrenous lesion exist. Thirdly, the contemporary period in which the observations of Gubler (9) in 1857 and Trousseau (10) in 1865 clearly described the malady, and reached the conclusion that the disease was rare.

The descriptions of putrid sore throat would seem to conform perfectly with cases that would today be diagnosed as agranulocytic angina. No doubt the diagnosis "putrid sore throat" was applied to a variety of conditions and included Vincents angina and diphtheria but is easily conceivable that the rare case that provided the spectacular course with a fatal outcome was one of agranulocytic angina.

In 1902 Brown (11) described a fatal case of acute primary infectious pharyngitis with necrosis and an extreme leukopenia. The polymorphonuclear neutrophilic leukocyte count in this patient averaged from one to twenty-five per cent on differential examination. This possibly was the first case reported in this country. An editorial in The Journal (12) states that Turk (13) described, in 1907, cases with a low granulocyte count and severe sepsis. He thus did not differentiate them from the commoner leukopenia of overwhelming infection. Leale (14) in 1910 reported a case of "Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture". In this case "occasionally an ophthous patch developed on the buccal mucous membrane and this resulted in considerable necrosis". Leale refers to the blood picture as being leukopenic with an extreme
relative lymphocytosis. Baldridge and Needles (4) reported a case which on reexamination seems to come under their classification of idiopathic neutropenia. In 1922 Schultz (1) reported four cases and stated the belief that it was a clinical entity. After this original description (15) Lovett, in 1924, was among the first in this country to report a case. Lauter (16), in 1924, was the first to report a case of recovery in a young woman with agranulocytosis, tonsillitis and stomatitis. Since that time many cases have been reported both in this country and in Europe, especially in Germany.
PHYSIOLOGY

In the consideration of such a condition it is necessary to become acquainted with the mechanism of hematopoiesis, especially that of granulopoiesis. In the normal adult man the myeloid blood elements, the red blood cells and the granulocytes, are produced exclusively in the bone marrow. A brief description of the bone marrow with which we are particularly concerned has been taken from Maximow (17). This tissue fills out all the spaces in the bones. There are several kinds of bone marrow which differ by their macroscopical appearance; the most important varieties are the red and the yellow or fatty bone marrow. The first has a red color and is very soft, while the second resembles subcutaneous adipose tissue. Only the red marrow, which consists of myeloid tissue, plays a role in hematopoiesis. In the embryo and the newborn, the cavities of all bones contain only the red variety. With progressing age the red marrow is gradually substituted by the yellow which consists mainly of fat cells. In the normal adult, red marrow is found in the vertebrae, the ribs, the sternum, the "diploe" of the bones of the skull, and in the proximal epiphyses of the femur and humerus. It also forms a thin sheet at the periphery of the yellow marrow in the diaphyses of these bones.

In the myeloid tissue, as well as in the lymphoid, two structures have to be distinguished: (1) The supporting, spongelike framework or stroma which is intimately connected with the blood vessels and (2) the free elements in the meshes of the stroma. The stroma consists of an undifferentiated
cellular syncytium attached to the argyrophil fibers and of typical, phagocytic and storing reticular cells or histiocytes. The reticulum of cells and fibers is loose and its meshes are quite large. The free cells of the myeloid tissue present an extreme variety of forms. The various cell types are irregularly scattered and mixed throughout the tissue. The vast majority of them are represented by young forms of the myeloid elements.

In 1925 Doan and his co-workers (18a, 18b) reviewed the literature with regard to the formation of the blood cells. They found that a great number of hematologists accepted the theory of the formation of the blood cells from a single hematogenic stem cell, variously named. In their investigations, however, they outlined a theory that all blood-cells can be derived from two entirely different fixed tissue cells, both of which are distributed widely throughout the organism - the endothelial cell and the reticular cell, which makes up much of the framework of the marrow, proliferates and gives rise to a free primitive cell which in turn is the parent cell of all the cells of the granulocytic series. This was the first time this theory, which is now quite generally accepted, was advanced. In extrauterine life the granulocytes develop normally exclusively in the red marrow (19). The volume of this system has not been studied to any great extent. Only a few papers pertaining to bone marrow volume can be found in medical literature. Wetzel (20) reported a red marrow volume of 1419 cc. in
the skeleton of a twenty-year-old man. Nye (21) states that Mechanik (22) believed the red and yellow portions of the marrow were about equal and gave an average value of about 1300 gm. to the active portion. Doan and Zerfas (23) in three accident cases found the ratio of erythropoiesis to granulopoiesis was 1:20, 1:16, and 1:5.5. Other authors (5) have given a ratio of 1:3. Thus it can be roughly estimated that from three to twenty times as much tissue is devoted to the formation of granulocytes as there is to the formation of erythrocytes. Even with this great amount of granulopoietic tissue the number of white blood-cells in the circulation is far smaller than the number of erythrocytes. Thus, it can be seen that the granulocytes are fragile structures.

According to Doan (24) the arterial supply of the bone marrow is a closed system. It is secured by way of the medullary artery, the periosteal vessels along the shaft, and some vessels near the articular extremities which supply the epiphyses as well. The arterioles are relatively few in number. Normally there are a few "transition capillaries" functioning as the intermediary communication between arterioles and venous sinusoids. Sabin (25) states that the capillaries leading directly from the nutrient arteries of the third and fourth order, the "transition capillaries" of Doan are not the functioning capillaries, as in other organs, but rather they lead into tufts of sinusoids. The nature of these vessels was analyzed by Minot (26) in 1900 who introduced the term "sinusoid". These sinusoids
constitute the functioning vascular bed of the marrow and constitute the most characteristic thing about the gross circulation (24). They have walls like capillaries and appear like them when collapsed, but when open they have the diameter and lumen of large veins. When the sinusoids are dilated, there is a sluggish flow of blood, which brings the maturation factors to the right concentration for the white cells. Along the border of the marrow there is a narrow zone where the blood vessels of the marrow anastomose with those of the shaft of the bone. As granulopoiesis begins, every vessel of this narrow border is patent to the circulation; that is to say, there are no collapsed intersinusoidal capillaries. No other area of marrow has so constantly a maximum blood supply (25).

The granulocytes arise outside of the blood vessels, as stated above (19). They develop around the patent, dilated sinuses or vessels of the hematopoietic tissue in the peripheral vascular zone and move toward their borders as they become mature. The young granulocytes exist here in groups at the same stage of maturation and fill the sinuses. They are seen to move, en masse against the walls of the capillaries until the wall is bent inward, when the stretching reaches a certain point, a leukocyte close to the wall flows in between two endothelial cells and the rest follow in rapid succession (5).

The development of the mature granulocyte has been shown very well by Sabin (25) from which article the following has been obtained:
Maturation is represented as a series of varying factors, constantly changing; in some levels, the factors may increase together, in others some may increase while others decrease. The cells are shown in three levels, the original non-granular stages, the granular marrow cells or myelocytes, and the leucocytes, the three levels being separated by two critical points, shown as solid vertical lines. The first marks the point of the beginning of granulations and the second that at which the last cell division of the myelocyte has taken place, with the reduction to a cell of common size and state of maturity, the definitive leucocyte.
Level I. - In completely aplastic adult bone marrow only three types of cells can be seen: fat, endothelium, and reticulum. Of these three the fat is but accessory to blood formation. Red cells regenerate from the endothelium, while the white cells come from the reticulum. These reticular cells are not an hypothetical form; they can always be found in bone marrow, lymph glands, and spleen. Lang (27) describes them as certain cells of embryonic character, adjacent to the outer surface of the endothelium.

In regenerating marrow, this primitive reticular cell, with repeated divisions, gives rise to a primitive free cell. In this process a few mitochondria are elaborated in the cytoplasm and a basophilia is gradually built up. Finally, as the basophilia of the cytoplasm and the numbers of the mitochondria reach a maximum, the cell becomes the myeloblast. This period is one of growth and division, as well as one of maturation in regard to mitochondria and basophilia, the cells are to be found in varying sizes; but in normal bone marrow, it is the primitive free cell of small size, similar to the small lymphocyte, but differing from it in having fewer mitochondria and a less differentiated nucleus, which is to be found in the largest numbers.

It is now certain that lymphocytes may arise in bone marrow both under normal and under pathological conditions, but the usual cellular output of the marrow is limited to red cells and the three strains of the granulocytic leucocytes, so that the primitive free cell of bone marrow normally produces granulocytes in that location.
Level II. - The first step in the transformation of myelocytes from myeloblasts is the development in the cytoplasm of a small clump of neutrophilic granules or their precursors. This is the first evidence of neutrophilic granulation, and cells having a small clump of not more than ten to fifteen such granules have been designated as Myelocytes, Type A. (28)

The second stage in the development of the myelocyte consists in the increase of neutrophilic granules, with a decrease of mitochondria, and is designated as myelocyte, Type B.

The third stage of the myelocyte, or Type C, shows a predominance of neutrophilic granules, the mitochondria having been reduced to a narrow rim in the periphery in the cell. This is the type of myelocyte that predominates in normal bone marrow. The earlier leucocytes have a few mitochondria which are intermingled with the neutrophilic granules and move in the cytoplasm with them; such young leucocytes are occasionally found in the circulating blood but most of the leucocytes of the blood are without mitochondria.

Level III - The third level, marking the end of maturation is characterized by cells of approximately uniform size and content of the specific granulation. These factors mean functional maturity. The uniformity of size is due to the cessation of division which precedes the stage of polymorphism; the nuclei fragment and the cell frequently drops off bits of cytoplasm, but division no longer takes place. As is well known, ameboid movements are a constant phenomenon of the leucocytes,
whenever they have a surface to move upon. The leucocytes become more mature in the circulating blood according to the Arneth Pattern, involving the nuclear changes, and finally pass into the non-motile phase. The approximate hourly delivery of cells to the blood stream suggests that the time for the maturation from metamyelocyte to granulocyte might be expressed in units of hours or minutes, while the time for maturation from pro-myelocyte to metamyelocyte may possibly be expressed in units of days, probably from three to seven.

The mature granulocytes are normally delivered to the blood stream from the marrow. Sabin and Doan (29) showed that the chemical forces that act on the marrow cells as distinct from those that act on the endothelium, are divided into two activities: chemotactic factors (c) that attract the cells into the blood and growth-stimulating, or maturation (M) factors for both red and white strains.

Sabin and her co-workers (30) showed that there is a characteristic rhythm of the total white blood cells with an interval of approximately an hours duration. The total number of white blood cells is increased in the afternoon regardless of whether food has been taken or not, and this entire increase is the result of an increase in the number of neutrophilic leucocytes. These neutrophiles die out in showers, often of considerable proportions and the dead cells are promptly replaced either from some reservoir or directly from the bone-marrow.
Shaw (30) showed that the leucocytes of man exhibit twice daily a tidal rhythm of about twelve hours duration which is independent of certain recognized physiologic stimuli, the evidence being derived from a study of leucocytic variation in the peripheral blood of man and the distribution of leucocytes in the internal organs of animals. Two low points in the tide are consistent, one being between 9 p.m. and 11 p.m. and the other between 10 a.m. and 12 noon. The curve of the total neutrophil leucocytes closely follows the course of the tides and is largely responsible for the character of the latter. He also stated that the day and night tides are systemic and not confined to the periphery. Doan and Zerfas (23) in an interpretation of the occasional unexplained inconsistencies in clinical blood counting suggested that there is normally a more or less rhythmic variation in the numbers of white blood cells from moment to moment in each individual. In their work the total number of white blood cells was found to vary, within physiological limits and without abnormal external or internal stimuli, 100 per cent during the course of a day in a single, apparently normal, adult individual. In other words, rather than a relatively fixed individual "norm" or concentration of circulating cells, their concept of the normal for each person now is a wide zonal range, with a fluctuation for example of from 4000 to 8000 or from 6000 to 12,000 white blood cells, any chance single count being the resultant of at least three variables, the person, the physiological conditions of the moment, and the time of the day of the observation.

The method by which the mature granulocytes are de-
are delivered to the blood stream is dependent on chemotactic and maturation factors (29). The part vasomotor influences play in the mechanism is uncertain.

Concerning chematactic factors Doan and his associates (18) introduced suspensions of inactivated typhoid bacilli into the blood stream of normal rabbits and observed a bone marrow relatively free of developing and mature myeloid elements. They found that repeated injections of large numbers of bacilli deplete the bone marrow of its reserve of myelocytes only up to a certain point, beyond which the marrow returns to a perfectly normal condition. In this experiment there was apparently no maturation factor present. Later experiments conducted by Doan and his co-workers (32) revealed a prompt response of the bone marrow, in the delivery of new mature neutrophilic leucocytes to the circulation, after the introduction, intravenously of large doses of sodium nucleinate. There was shown to be a latent period in the replacement of the cells at the level of Myelocyte C, in bone marrow, as shown through the inability to reproduce a leucocytosis after too frequently repeated injections. Examination of the bone marrow confirmed the rapid depletion of the myeloid foci followed by only a gradual replacement. Thus sodium nucleinate and adenine and guanine nucleotides contain stimuli capable of calling forth new neutrophilic cells so long as there is an adequate reserve of myeloid cells at the level of Myelocyte C, but they lack any factors specifically active for the maintenance of this level.
Thus these substances would seem to be chemotactic in nature. The response of the bone marrow to chemotactic stimuli may be reflected in the general circulation through an absolute increase of young neutrophilic leucocytes within a period of less than an hour. Within this brief period there takes place maturation from myelocyte C and metamyelocyte into the early motile leucocyte, and the delivery of these just matured cells into the circulation. Later Doan (33) gave the conclusion that experimental and clinical observations formed the basis for his attributing to nucleic acid and the nucleotides chemotactic, maturation and initiatory stimuli for neutrophilic myelocytes when the basic mesenchymal tissues from which they arise are in a condition to respond. Nucleic acid is more likely to be a normal physiologic factor in the human organism than other substances with which experiments have been performed.

As far as maturation factors are concerned, there is but little known. Such bacteria that produce a leucocytosis may introduce such a factor for they produce an increased division, growth and maturing of the less mature leucocytes in the marrow far above normal. Bacon and his co-workers (34) believed that even in infections the stimulus for leucocytosis came from the breaking down of proteins and dehydration.

Granulocytes are very important to the human body. They are certainly one of the chief sources of immunity. The loss of polymorphonuclear neutrophilic leukocytes causes violent symptoms which appear to be illustrated by the agranulo-
cytoses. The granulocytes with their released ferments give much active daily immunity to the body. The leukocytes are thought to be the source of complement and complement is present in the plasma, owing probably to their continued disintegration. The leukocytes lead an active life from three to five days (35) both chemically and mechanically. Complement is probably the single most important factor in the destruction of the bacteria and the defense of the tissues. Roberts and Kracke (35) state, "We have evidence that the mere loss of granulocytes for seven days is incompatible with life. Let them decrease to any notable extent and the whole organism flops".
ETIOLOGY

It is rather generally admitted that the pathological process occurring in agranulocytic angina is located in the bone marrow, affecting the red marrow concerned with granulopoiesis. This would indicate that the etiological agent must act in some way upon the granulopoietic organ but at present such a causative agent has yet to be proven. Explanation of the pathogenesis of this disease rests mainly on hypothesis although some experimental work has been done which would seem to be the lead for future investigation. Such theories and experimental work pertaining to pathogenesis will here be briefly reviewed.

Predisposing Factors:-- As far as is known today there is no definite predisposing cause. Most authorities agree that the disease is seen predominantly in women. Schultz (1) found that it affected women from the ages of 38 to 61 in his group of cases. Later Kastlin (36) in his review of the literature, stated that it occurred 72 per cent in women and 22 percent in men with an age average of 46 years for women and 29 years for men. Hueper (37) found a ratio of three and one-half women to one man, or 77.5 per cent in women from 30 to 50 years of age. Roberts and Kracke (38) found that one out of two female patients between the ages of 40 and 60 may be expected to show a mild granulopenia. Similar findings were later reported by Mettier and Olson (39). Beck (5), in her excellent review of agranulocytic angina, has stated that practically all cases of both the malignant and benign type, have occurred in the fourth
decade of life from 41 to 58 years of age. Cases have been reported in children and people over 60 years of age but they are not common. More recently Kracke and Parker (62) in their very thorough review of the literature found that the disease is more common in the United States and Germany. The geographic distribution of reported cases from 1922 to 1932 inclusive, was found, by them, to be as follows: 473 cases in the United States; 350 in Germany; 100 in France; 6 in England; and 50 in Italy.

Other remarkable findings made by them were that the disease appears to be one of the white race, only 8 cases being reported as occurring in negroes and then only after anti-luetic therapy. They were also of the opinion that it occurred in the better classes of our people and was found more frequently in members of the medical and allied professions and their relatives.

These conclusions have been made with a definite purpose of implicating certain drugs and chemicals as etiologic agents. This question will be considered below.

Previous illness does not seem to play much of a part in the syndrome. The patient in the majority of cases will give a negative past history as to illness but according to certain investigators will give a history of contact with a drug or chemical (40, 62, 65, 63). Kastlin (36) was of the opinion that previous oral infection played a major role but this does not seem likely. Hueper and Garrison (41) and others have stressed the importance of previous gall-bladder and liver disease and have even carried this into the surgical treatment of cases.
From the literature at hand it would seem that as far as the secondary type of the disease is concerned drugs, chemicals mesorthium, trinitrotoluene, x-ray and the gamma rays of radium, etc., may play a very important part, but for those cases in which no such factor can be implicated it is open to question. There apparently is no seasonal incidence and the condition is not contagious.
Microorganisms: - Because of the peculiar necrotizing ulcerative process in the pharynx, mouth, gastrointestinal tract, anus, vagina; the sudden onset with high fever, and the not infrequent finding of positive blood and throat cultures have led many observers to consider the disease as being caused by a specific micro-organism. Such observers believe it to be an infectious disease representing a septicemia with an atypical reaction of the hematopoietic system (43) due either to bacteria with a special affinity and toxicity for the granulocytic system (43) or to an atrophy or hypoplasia of this organ because of the presence of a septic factor. The depression in the bone marrow may be caused by a hidden or latent infection that has been present for a long time, the depressed bone marrow then being unable to cope with an emergency. Fried and Damesheks (44), doing experimental work attempted to reproduce in animals a septic disease and to study the possible relationship between the hematopoietic system as seen in agranulocytosis in man and that of this form of sepsis found in the animal. They infected rabbits with Salmonella suispestifer by way of the blood stream. The animals infected with an overwhelming dose of bacteria rapidly developed severe leukopenia and almost complete agranulocytosis. There was but little tendency toward regenerative activity on the part of the granulocytes, and monocytosis did not develop to any appreciable extent. The animals died usually within forty-eight hours after infection. The bone marrow, post mortem, usually
showed but little evidence of regenerative activity. Injection of small doses of bacteria resulted in cases in which the animals recovered. They thus concluded that the results showed close similarities between the agranulocytosis resulting from the hematogenous infection of rabbits with Salmonella suispestifer and that observed in cases of agranulocytic angina in man. Piersol, and Steinfield (43) used inoculations of a small group of common bacteria in rabbits. The subcutaneous injections of suspensions of all the organisms used produced a leukocytosis varying in degree with the animal and with certain strains. No long-continued fall in leukocytes was induced by any of the filtrates or by the production of a state of hyperergy.

Lovett (44) found that cultures of B.Pyocyaneus have a toxic effect on the leukocytes of guinea pigs, producing vacuoles and irregular staining. She stated, however, that filtrates of fresh and old cultures had no toxic effect on human leucocytes in vitro.

No conclusions can be drawn from the experimental work which has been done, in regard to organisms as a cause, because of the great variety of organisms so often isolated from the local lesions or from the blood stream and the resulting inconsistencies. Various observers have isolated such organisms as Vincents spirillum, B.fusiformus, B.Coli, B.Pyocyaneus, Streptococcus hemolyticus and S.viridous, pneumococcus and Staphylococcus from both the necrotic ulcerations and the blood stream, but no specific micro-organism has as yet been
to be present in every case.

In regard to a bacterium being present which has a special toxicity for the granulocytic cells, Channon and McLeod (47) and later Gay and Oram (48) showed that hemolytic streptococci produce a substance which has the property of destroying leucocytes. This substance was named leucocidin and was found to be very potent. Dennis (49) investigated this problem on the basis that certain of the pyogenic bacteria are capable of producing a toxin which is specifically lethal for leucocytes and that one or more of these organisms are almost constantly associated with focal infections, which in turn are frequently accompanied by granulocytopenia. Experiments were carried out in such a way that the bacteria used did not actively invade the tissue but the diffusible substance could be absorbed by the rabbit. He found that a similar picture to an agranulocytic angina in man was produced by pyogenic organisms, in rabbits under conditions simulating a focal infection. His conception of the usual origin of clinical agranulocytic syndrome is that there is a primary focus of infection by one of the leucocidin-producing organisms from which leucocidin is diffused into the blood stream where it affects the neutrophils, and if present in sufficient quantity and toxicity it injures the granulopoietic elements of the bone marrow. With the removal of the granulocytes and the cutting off of the supply, the body is liable to invasion and a fatal sepsis frequently results. Dameshek and Ingall (50) concluded that agranulocytosis
is a symptom complex, dependent upon an abnormal reaction of the bone marrow to a severe sepsis.

Thus, it can be seen that the question of a bacterium being the true etiologic agent in the disease is open to question, for every observation and experiment which would seemingly prove the syndrome to be due to such an agent, a toxic or septic process, there is one which tends to disprove it.

Zadek (5) expressed the belief that a virus of sufficient potency to destroy the granulopoetic tissue so completely could not uniformly spare all of the closely related contiguous cells. Roberts and Kracke (38) state that in the beginning there is no demonstrable infection, but only a selective hypoplasia or aplasia of the myelocytic cells of the bone marrow. About two days after the myelocytic series of cells disappear from the blood stream the classical clinical onset appears. If and when sepsis develops, it is a result and complication rather than a cause. The sepsis follows the disappearance of the granulocytes from the marrow and the blood. Furthermore, there may not be any demonstrable infection. Hamburger (51) states that none of his patients has suffered from any obvious infection before the development of the sore throat. He also states that once the agranulocytic state is established, local or general infection may follow. A further observation which tends to
eliminate the theory of a septic or toxic process acting on the myeloid tissue is that the neutropenia may be periodic. Rutledge and his associates (52) reported a case in which there were attacks of stomatitis associated with neutropenia, fever, and constitutional symptoms recurring at intervals of approximately three weeks throughout the life of a man twenty years of age. Biopsies and post-mortem studies may also show a peripheral neutropenia and leukopenia with myeloid hyperplasia. Blumer (53) stated that there are cases of local and general sepsis with an agranulocytic blood picture aside from the well recognized group of agranulocytic anginas, and it is not clear whether sepsis or the loss of power of the bone marrow to form granulocytes is the primary lesion.

Allergy: - A few authors believe the condition to be a form of allergy in which the bone marrow is the point of least resistance. Delatour (54) in his summary, states that recurrent agranulocytosis it would seem the bone marrow of some individuals is very sensitive. He reasoned that an overwhelming protein reaction on the bone marrow of a sensitive individual takes place, or that a sensitive granulocytosystem is affected by the noxious agent of a septic process. Schilling (3) was of the opinion that it is an allergic reaction. He produced a blood picture similar to malignant neutropenia experimentally in anaphylaxis, and
thus considers it to belong to this group of phenomena. Bromberg and Murphy (55) concluded that, since protein shock has been shown to be accompanied by local changes analogous to those in agranulocytic angina, as shown in their case, the agranulocytosis may have resulted from an overwhelming foreign protein reaction in a sensitive individual. Madison and Squier (56) in their summary state that they believe the appearance of primary granulocytopenia following the use of certain drugs may be the result of an allergic or an anaphylactic drug reaction. Pepper (57) appears to be very much in favor of the hypothesis that the leukopenia results from the entrance of a foreign protein into the body. He relates several cases, with which he has had contact, all of which showed the presence of allergy, by an asthma, urticaria, eosinophilia, etc. He also states that the literature contains no supporting evidence for this hypothesis. Kopelowitz (58) says there must be some factor, some idiosyncrasy or allergy or possibly an endocrine factor that renders the hemopoietic system susceptible to the noxious agent, but he offers no evidence to support the assumption. Kracke (59) stated, in 1931, that the question of typhoid prophylaxis as a whole or partial cause of the condition must be considered.

The question of allergy, the same as that of microorganisms, has still to be settled. Some authors think there is a definite possibility and hypothesis for etiology, but very few attempt to go so far as to submit proof. It must
also be remembered that we are in a period where it is quite common to explain everything on an allergic basis: as digestive troubles, migraine, and many others.

Chemical Theory: - The investigation of possible chemical etiology has been somewhat more successful than that of possible bacterial etiology. Although experimentally neutropenia and leucopenia have been demonstrated in animals, by the use of various organisms (44,45,46) the results are not entirely comparable to the clinical picture in man. Certain chemicals have long been known to be effective in the production of a leukopenia. Benzene is the only chemical that has been shown, for many years, to be capable of producing a marked depression of the leucocyte count to the point of complete agranulocytosis. An illustration of the cumulative and delayed effect of the chemical on the hematopoetic tissues was shown by Selling (60). One young girl, who had been working in a factory where she was exposed to benzene fumes, long after quitting her work, developed symptoms of fever, oral necrotic ulceration, loss of neutrophils, and finally died. Selling also reported two other cases with similar histories of exposure. After experimental work, he concluded (61) that benzene destroyed the white cells of the circulating blood and parenchymal cells of the hematopoetic system, but that the erythrocytes in the system were little affected. Kracke (62) showed experimentally that subcutaneous injections of benzene and olive oil, if given in small doses, resulted in clinical agranulocytosis in rabbits.
The smaller the dose, the more selective became the affinity for the myelocytic tissue. He states that it is probably the oxidation products of benzene which are directly responsible for its leucocytic depressing properties. Thus it might be possible that any drug containing the benzene ring could be an etiologic factor, such as the many coal tar derivatives on the market which have indiscriminate public use. These drugs may serve to weaken the hematopoetic tissue.

The arsenicals must be considered in this discussion because of their widespread use in the treatment of syphilis. Farley (63) in his discussion, states that there are reports of blood dyscrasias following arsphenamine treatment, under a variety of titles, as aplastic anemia, purpura hemorrhagica, bone marrow depression, agranulocytic angina, and so forth. All these are symptomatic depressions of the marrow, depending, no doubt, upon the degree of toxic action and the particular elements of the marrow suffering most injury. The condition is a rare one. Reported cases indicate that no one type of arsphenamine is more apt to produce depression than another. It is possible that those individuals in whom depression of the marrow occurs possess congenitally, a weak hematopoetic apparatus. Farley, in his summary, states that it seems likely that the direct cause is disintegration, in vivo, of the arsphenamine, so that benzol-like action occurs.

Recently Madison and Squier (56), after observing fourteen patients who developed agranulocytic angina, made
the following summary: (1) The increase in incidence of primary granulocytopenia has paralleled the increase in the use of the drugs containing amidopyrine and especially those containing amidopyrine with a barbiturate. (2) The disease has appeared most frequently in physicians, nurses, and those directly under the care of a physician. (3) The mortality in these patients who continue the use of amidopyrine after developing granulocytopenia is 100%, while discontinuance may retard the progress. (4) The appearance of primary granulocytopenia following the use of such drugs may be the result of an allergic or anaphylactoid drug reaction.

Since that time considerable work and observation has been under progress in an attempt to incriminate these drugs containing a benzene ring in their structure. Briefly, this work has brought forth hypothesis for the etiology of the condition. Kracke and Pariser (40) concluded that in the clinical or experimental development of granulopenia, it is necessary to presuppose the existence of a previously weakened, damaged, or idiosyncratic bone marrow, which may be congenital or acquired. They suggest that a careful history in each case be directed toward the previous use of known marrow depressing agents, and the usage of benzamine drugs in particular. They formulated the hypothesis that the disease owed its high incidence in nurses and physicians to their indiscriminate use of drugs containing the benzamine group, the more prominent members beings neoarsphenamine, arsphenamine,
benzene, acetanilid, phenacetine, and amidopyrine; the toxic effect produced by these drugs is caused by oxidation reactions. Herz (64) states that it has been proved beyond any reasonable doubt that amidopyrine is the most frequent cause of this condition. In his analysis of the structure of amidopyrine, he considers it to belong to a group other than the benzene drugs. He states it is a pyrazolon compound containing the highly toxic NH (imido-) radical, being derived from phenyl hydrazine and resembling the latter in its rapid reduction of granular leucocytes in the bone marrow and in the blood stream. By using safer antipyretics, granulocytopenia could be rapidly eliminated. In a special report of the Council of Pharmacy and Chemistry (64,65) the following was stated: (1) As far as can be learned from the evidence on hand, there can be no question that amidopyrine is very important in the production of granulocytopenia. In fact, no other agent has been found, either chemical or bacterial, which has been a factor in causing so many attacks. (2) No definite case has been reported in which a barbiturate alone is responsible. It appears that barbiturates have little or nothing to do with granulocytopenia. (3) There is also no doubt that many cases of granulocytopenia have occurred in which amidopyrine has never been taken, or any other drug, for that matter. (4) It is recommended that the indiscriminate use of amidopyrine, particularly the exploitation to the public in which individuals are importuned to self-medication, be discouraged.
From such evidence as appears above, the benzene ring compounds and those of pyrazolon derivation, especially amidopyrine, have certainly been implicated as being etiologic agents. It would seem that further investigation along this line is essential in order to determine just how often such a compound is the true causative factor. Here again, one is left with some doubt, for, although the evidence is strongly against such drugs, there still remain some cases which do not present such a factor in the history. Are these cases to be considered as belonging to the same group as those with an etiologic factor? Until this is proven, there will still be those cases of questionable causation.

Glandular Dysfunction: - The influence of the endocrine glands upon the output of both granulocytes and erythrocytes has been studied considerably and has long been suspected. Hubble (66), in his work, states that the hypothesis of the disorganization of a highly differentiated and relatively unstable tissue such as the adrenal cortex must be considered in etiology. He further suggests that a pituitary basophilic deficiency may be the fundamental cause of a depressed bone marrow. Corey and Britton (67) found that when the adrenal glands were removed from the cat, with the production of an adrenal insufficiency, the total leucocyte count was decreased, and there might be marked reduction in the neutrophil counts, sometimes almost to the disappearing point. The administration of cortico-adrenal extract to animals suffering from severe adrenal insufficiency and showing the above blood cellular disorganization resulted in the complete
restitution of normal cell values. The condition of the animals during the experiment did not, however, resemble very closely the clinical picture in man. Jackson and Merrill (68) in one publication and Thompson (69) in another, after observing similar cases of agranulocytosis in forty women, suggested a temporal correlation between the onset of neutropenia and the onset of menstruation. From their observations they concluded that it seems possible that, in some cases of agranulocytosis, a relationship exists between the hormones associated with menstruation and the neutropenic episodes. Although the evidence collected seems to indicate that the ductless glands exert an influence on the blood cellular elements, the proof of their specific action will have to await further confirmation.

Disturbance of the Chemotactic and Maturation Mechanism: - In 1932 Fitz-Hugh and Krumbhaar (83) reported a case in which there was a peripheral leucopenia and neutropenia, but which, at necropsy, showed a considerable myeloblastic hyperplasia in the femur, tibia, ribs, etc. Following this, they concluded that the "granulocytic aplasia" hypothesis is inadequate. They suggested that a maturation factor at work in this case either arrested development of white cells in their formative centers or produced degenerative changes in them before sufficient development for normal migration into the blood stream, or, possibly, a combination of both factors. This hypothetical factor would conceivably check
the granular series of blood cells at the myeloblast-myelocyte stage in the bone marrow. Later, Beck (5) considered this possibility and came to the conclusion that in typical cases with myeloid aplasia the part of the bone marrow that manufactures the granular leucocytes has ceased to function, or nearly so. She states that it seems reasonable to suppose that the primary lesion is not in the bone marrow, but is in the organ or tissue which gives rise to the substance that keeps the maturation of granulocytes regulated to a normal level, or regulated so that production and destruction is kept constant. Such a hypothesis would make the condition analogous to pernicious anemia, the principal alteration being the substitution of the granulopoetic centers for the erythropoetic tissues. There may be remissions in both. It is easy to see how a great reduction in granulocytes would be more rapidly fatal than a great reduction in erythrocytes. A maturation factor for erythrocytes has been found; it now remains to find a maturation factor for granulocytes.

Beck (5) considers the other group of cases showing peripheral neutropenia with slight hypoplasia normal, moderate, or masked hyperplasia of the myeloid tissue, as due to a lack of the chemotactic factors. The cells may be growing and maturing, but are not being called into the circulating blood. In support of this view it must be noted that the most successful therapeutic agents today are derivatives of nucleic acid.
Beck considers nucleic acid derivatives as supplying the chemotactic factors and considers it to be very useful in treatment when this factor is absent. On the other hand, Doan (33) considers these derivatives as supplying both a chemotactic and a maturation factor. Such a hypothesis must be considered because of the possibility of these factors being absent and causing the clinical picture just as the absence of the maturation factor in pernicious anemia causes that typical picture.

Constitutional Factors: - In 1931, Rosenthal (71), after observing 90 cases, stated that in his opinion the etiological factor of most importance is a profound constitutional disturbance of the granulopoetic tissue. He considers it more as an individual problem rather than being due to a factor which could cause the condition in every person. This hypothesis has been held by other investigators, and, from some observations, it would seem that it must be at least in mind. Miloslavich and Murphy (72), after studying the pathological reactions of the bone marrow, attributed the variations in reaction to pathological functional expressions of individual character of a constitutionally weak functionally readily insufficient and easily vulnerable bone marrow, depending upon the type of noxious agent. Roberts and Kraeke (38), in an effort to determine whether or not any relationship exists between the degree of granulopenia and certain signs and symptoms, made a statistical study of 8,000 records. Very few of these patients, between 1920 and
1930, showed any acute illnesses in which the hematological findings would be temporarily abnormal. In order to classify the 8,000 cases into either the normal or granulopenic group, an arbitrary standard for normality for the granulocytes was established. 6,000 leucocytes per cubic millimeter with 67% neutrophiles was accepted as being a low standard, and all counts were regarded as showing evidence of granulopenia if below this. In other words, any count showing less than 4,000 granulocytes per cubic millimeter was regarded as being granulopenic. They concluded that one out of every four patients may be expected to have a mild granulopenia: one out of two female patients may be expected to show a mild granulopenia; the complaints of weakness, exhaustion, or fatigue are twice as frequent in the granulopenic patients as in those with normal white cell counts; and the severity of the symptoms varies with the degree of diminution of the granulocytes. Later, Mettier and Olson (39) made a similar study of 10,000 case records of patients cared for in the University of California Hospital, between 1920 and 1931. Examination of the blood revealed leucopenia in 1,167 cases. Of these, 611 were from females, and 556 from males.

In opposition to this hypothesis, certain investigators have noted that certain patients have developed agranulocytic angina even though they have never shown a neutropenic trend at the previous time. Fitz-Hugh and
Camroze (73), in their series of 18 cases had records of normal white blood counts and granulocyte percentages prior to the onset of the disease in eight cases. In two of these they had noted a normal neutrophilic leucocytosis due to previous infection. These observations made it difficult for them to uphold the hypothesis of a "constitutional predisposition" to this disease. In their series of cases they found no suggestion of an hereditary or familial incidence of the disease. It would seem, however, that in their eight cases, where a normal granulocyte cell count previously was known to be present, the possibility of the granulopoietic system being compensated at that time would have to be considered. Reasoning in this vein, when the agranulocytic condition developed the granulopoietic system was unable to compensate.

Radiation: - Excessive exposure to radiation has been suspected as a possible etiologic factor (40). It is known that thorium will produce a marked neutropenia in animals and in the human being. It is conceivable that excessive roentgen radiation can produce marked bone marrow depressions, and it should be used in caution in therapy.
Classification

Due to the fact that the etiology of agranulocytic angina has not as yet been proven, a classification will necessarily have to be divided into those conditions in which no causative agent is suggested, and those in which there is a certain amount of evidence pointing to such an agent. Many of the cases which have been reported have very closely resembled those first described by Schultz (1), which have no suggestion of an etiologic agent. On the other hand, there are many which have undoubtedly have been due to some form of medication, infection, chemicals, constitutional predisposition, etc. Thus, it is probably too early to make a classification because of the revisions which will have to occur with new knowledge. For the present time, however, I believe the concept of a primary and a secondary condition existing should be followed. It is impossible to discuss all the secondary forms in this paper, but they are listed in order to give some idea of the scope of the problem of leukopenia and neutropenia. I would like to submit two classifications which vary slightly, but which are essentially the same. Both of these are recorded to show some of the possibilities of grouping of the various phases of the condition.

The "group of diseases" as referred to by Clough (74) is classified by Roberts and Kracke (35) as follows:

1. Agranulocytic states due to chemical poisons, as drugs with a benzene ring or derived from pyrazolon. Agranulotoxicosis.
2. Agranulocytic states due to radiation, as after radium and x-rays. Small doses upon the tissue stimulate; large doses destroy. Agranuloradiation.

3. Agranulocytic states due to bacterial infection. Agranulosepsis.

4. Agranulocytosis, a disease entity, in which an unknown cause results in marrow, blood, and clinical onsets in the order named. This is characterized by single or recurrent acute attacks.

5. Aplastic anemia, with or without acute terminal infection.

6. Pernicious anemia, terminal state.

7. Acute aleukemic lymphatic leukemia, with or without acute terminal infection.

8. Bizarre anemias and bizarre proportions of the lymphocytes and monocytes.

9. Roseola infantilis.

10. Acute infectious diseases associated with or followed by leukopenia and, rarely, near agranulocytic states - typhus, typhoid, mumps, measles, malaria, influenza, dengue, certain pneumonias, phlebotomus fever, and Egyptian splenomegaly.
Piersal and Steinfield (45), with a slight modification by Sachs (72), classify them as follows:

<table>
<thead>
<tr>
<th>Primary Granulopenia</th>
<th>Secondary Granulopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Acute (Schultz)</td>
<td>a. General infectious</td>
</tr>
<tr>
<td>b. Subacute</td>
<td>(Influenza, typhoid, some</td>
</tr>
<tr>
<td>c. Chronic, recurrent</td>
<td>exanthemasa, sepsis, etc.)</td>
</tr>
<tr>
<td></td>
<td>b. Focal infection</td>
</tr>
<tr>
<td></td>
<td>c. Chemicals, such as pyra-</td>
</tr>
<tr>
<td></td>
<td>zolon derivatives, benzene</td>
</tr>
<tr>
<td></td>
<td>ring compounds or arsenic.</td>
</tr>
<tr>
<td></td>
<td>d. Irradiation as X-rays and</td>
</tr>
<tr>
<td></td>
<td>radium.</td>
</tr>
<tr>
<td></td>
<td>e. Blood diseases as leukemia,</td>
</tr>
<tr>
<td></td>
<td>splenic diseases, aplastic</td>
</tr>
<tr>
<td></td>
<td>anemia, etc.</td>
</tr>
</tbody>
</table>
Symptoms and Clinical Course

There seem to be five distinct clinical types. These vary and are probably a reflection of the degree of injury to or dysfunction of the granulopoetic tissue. Kracke (76) lists these types as:

1. Acute, fulminant type with no infection.
2. Acute, fulminant type with localized or generalized infection.
3. Chronic type, with acute remissions.
4. Chronic type with no acute attacks.
5. Cyclic type (5)

The fulminating, acute type corresponds to the cases originally described by Schultz (1) with widespread necrosis of the granulopoetic system and a very high mortality. These patients may live long enough so they develop a localized or generalized infection, in which case even though the granulopoetic system shows signs of regeneration, the patient is usually overcome by the sepsis. On the other hand, the etiologic agent may be so potent that the patient dies even before any infection is manifest, possibly from terminal pneumonia.

A lesser form of the acute type is sometimes seen in which the illness is more prolonged, the average time being about one to three months. If such a condition appears, the prognosis is much more hopeful than in the above cases.

Patients showing the chronic type with remissions usually have two or more attacks, from several weeks to
to several months apart. The symptoms during the attacks may closely simulate those seen in the acute fulminating types. The patient may die in the second or later attack, or may completely recover, or the condition may become sub-chronic. There also exists a chronic type of neutropenia which may never show evidence of an acute attack. The patient may have a low white cell count with mild attacks of weakness, loss of activity, and depression, because of this lowered granulocytic count. In such a condition there is usually necrosis of the bone marrow, but it also shows evidence of active regeneration.

The cyclic type presents a chronic, regularly recurring periodic neutropenia (68, 69) Rutledge and his co-workers (52) and Doan (33) have reported cases which illustrate this particular type. In some instances these types may be mixed, in which case the etiologic factor is not acting constantly, or with equal force, during each attack.

unset: - For a number of years from the time of Schultz's first report, the majority of observers felt that the clinical onset of fever, angina, malaise, etc., was the starting point for the pathological process. They felt that the blood-cellular changes were secondary to an infective or causative agent which was primary. These observations are not at all to be discredited, for the physician would rarely see the patient before the occurrence of a localized
or even a generalized infection. Much credit must, therefore, be given to Roberts and Kracke (35) who, in 1930, were able to classify the problem of the onset of the disease. They had, under their observation, a woman, 72 years of age, who developed agranulocytic angina, recovered for a short time, and subsequently died in a second attack. During this time the patient was under close observation, daily blood counts being made from the first attack to, and through, the second attack. The leucocytes showed the first dramatic evidence of the second attack, the total white count dropping from 5,100 to 3,300 in one day, and the granulocytes dropping from 34 to 10, on differential count, during the same period. The patient felt well and had no complaints of any kind. From this time, the total white count and the granulocytic count dropped steadily until death supervened. On the third day following the first drastic leucocytic change the differential blood-cell count showed a complete absence of granulocytes. Even so, the patient had no symptoms whatever, actually dancing a few steps to show how well she was. On the morning of the fourth day, however, she seemed to collapse very suddenly, complaining of great weakness, which would not even allow her sitting up. At this time the throat was slightly reddened, but it was not until the seventh day that necrotic patches appeared in her oropharynx. She rapidly became stuporous, unconscious, and died on the twelfth day, apparently from a terminal bronchopneumonia.
From these observations Roberts and Krache concluded that there are three onsets: (1) The bone marrow onset - at this time the marrow has ceased to turn out the polymorphonuclear cells at a normal rate, while the destruction of these cells in the blood stream continues at a normal rate. The marrow evidently passes through a period of dysfunction to complete a function in a case presenting total absence of the polymorphonuclears. Weiskotten (77) agrees with Roberts and Kracke (35) in that cessation of the supply of neutrophiles from the marrow results in practically complete disappearance of neutrophiles from the circulating blood in a period between three and five days. The marrow onset, as reflected by the blood stream onset, may be acute, chronic, or recurrent. There are apparently no subjective or objective symptoms shown by the patient during this time.

(2) The blood stream onset - Here the number of circulating granulocytes depends entirely upon the type of marrow onset. This may be acute, chronic, or recurrent, and causing symptoms both objective and subjective, according to the degree and severity of the neutropenia. From the study on the life span of the neutrophiles, it would seem that from three to five days following the marrow onset the blood stream cellular change would occur. From a review of the literature it seems that the consensus of opinion attributes to neutropenia, in certain cases, the symptoms of weakness, fatigue, exhaustion, malaise, nervousness, etc. (38,39) The degree to which these
complaints are noted is dependent on the severity of the neutropenia and, in some cases, a chronic neutropenia would seem to be the causative factor of some of these vague complaints. The acute loss of granulocytes, from the above evidence, may cause violent symptoms which appear illustrated by agranulocytosis. Fitz-Hugh and Comroe (73) feel that, although weakness and fatigue are the most common symptoms, they are over-emphasized. They state that they have seen patients with agranulocytic angina (as well as patients with leukemia and other diseases) whose total granulocytes have varied from zero to supernormal numbers without any other symptomatic or objective changes of status. Jackson et al (78) believe there is a primary type in which the leukopenia may precede any symptoms by several days. They cite a case in which the white blood cell count was for three successive days at approximately 500 cells per cubic millimeter, and yet the patient felt perfectly well and was at her work. Thus, they conclude that the blood changes precede and condition the striking anginal symptoms. Certain observers (33, 35, 39) have found that in chronic leukopenia states, some individuals have rather vague symptoms, but which condition is not incompatible with health. As long as there is an efficient and satisfactory cellular equilibrium, even though functioning at a lower level than in the normal adult, the health of the patient, and his
resistant reaction to mild infection, does not seem to be impaired. In still other chronic leukopenic individuals the demands upon the granulopoetic system above the normal may cause a fall in granulocytes with resulting symptoms of weakness, fatigue, etc. During the blood stream onset the symptoms are thus dependent on the degree of granulopenia and, in conclusion, the statement made by Roberts and Kracke (35), "We have evidence that the mere loss of granulocytes for seven days is incompatible with life" must be remembered. (3)

(3) The clinical onset - The typical and striking symptoms, both objective and subjective, are here noted. These symptoms have been covered to a certain extent in the blood stream onset, but it is my desire here to give the picture as seen and originally described by Schultz (1) and reported subsequently by many other authors. It must be noted first, however, that these three onsets have been accepted by most authors at the present time, as being the course of the disease and many of them have submitted evidence. (33, 57, 78)

When the marrow has ceased to turn out the polymorphonuclear cells at a normal rate, and they quickly disappear or nearly disappear from the blood stream, it is only natural that the most desperate symptoms should arise from two chief causes - (1) the loss of the powerful, normal, active immunity of the tissues conferred in large measure by the granulocytes, and (2) the easy infection that results. Fever, chill, and sore throat are the usual mode of clinical onset,
which may be sudden or gradual, but in the acute is usually sudden and dramatic. The temperature ranges from 101 to 106 F., and is one of the continual type. The patient may have one or more chills at the onset, and then soon develop a sore throat. Neutropenia is frequently associated with lesions of the mouth and throat (5), probably because it is here that so many virulent organisms are harbored, and its natural barriers are subject to frequent insults. The patient may also complain of general malaise, and weakness which is marked, dysphagia, and shortness of breath. A rash, herpes labialis, vomiting, and abdominal pains may occur, but are rather uncommon. There may be slight jaundice in 50% of the cases (37), and diarrhea may or may not be present. There is an offensive, fetid odor to the breath, and the tongue is usually heavily coated. There may be added to these, headache, marked palpitation, and a tumultuous heart beat, general aching, drowsiness, and, occasionally, delirium.

In 1927, Kastlin (36) made the following charts, after collecting 43 cases from the literature:

I. Mode of Onset of the Disease

| Acute Onset, During Good Health | 28 cases |
| Acute Onset, During a Period of Ill Health | 15 cases |
| Malaise, one week to five months | 5 cases |
| Malaise, with jaundice, three weeks | 1 case |
| Tonsillitis, with recovery | 1 case |
| Infections, purulent | 2 cases |
| Influenza | 1 case |

II. Situation of Inflammatory Processes, Necrosis

| Tonsil | 19 cases |
| Throat | 13 " |
| Gums | 9 " |
| Tongue | 6 " |
| Larynx | 5 " |
| Esophagus | 2 " |
In 1933 Fitz-Hugh and Camroe (73), in their summary of 18 cases, recorded the onset of symptoms thus:

- weakness - 100%, fatigue - 100%, malaise and feverishness - 100%,
- sore throat - 79%, sore mouth - 47%, cough - 34%,
- chills - 34%, vomiting - 26%, rectal distress - 18%, and dysphagia - 10%.

From these two summaries it is possible to get some idea as to the symptoms and their incidence. As can be seen by Chart I (Kastlin), the majority of the patients are attacked during a period of good health. Apparently there is no predisposing cause (see: Etiology). Recently, certain investigators (40,64) have implicated certain drugs, especially the pyrazolone derivatives, and it is apparently along this line that further investigation should be carried.

For the present time, however, it suffices to note that a complete and detailed history should be taken with regard to drugs and chemicals used.

Fitz-Hugh and Camroe (73) found the course in the acute type to be very short, and fatal in over 90% of the cases. The course may cover two to ten days, or, possibly, in the non-fulminating type, be continuous for about three
months. It is easily understandable, with such evidence, why the diagnosis should be made early, and intensive treatment instituted.

**Physical Findings:** - Fitz-Hugh and Camroe (73) recorded the significant physical findings as follows: Fever - 100%, oro-pharyngeal lesions - 84%, rectal or vaginal lesions - 44%, dental sepsis - 44%, slight cervical adenopathy - 36%, jaundice - 18%, moderate splenomegaly - 18%, moderate splenomegaly, extending 1 inch or more below the costal margin, and barely palpable spleens - 10%.

According to Ordway and Gorham (79), the patient usually looks severely ill. During the first few days, however, some cases fail to betray by their general appearance the very serious prognosis which lies ahead. In the majority of cases there is no pallor of the skin and mucous membranes. The sensorium is particularly clear, a sense of exhaustion is common, but the mind is quite normal as a rule just before death, when coma may supervene.

Inflammatory changes of varying degree in the oral cavity accompany practically all cases. Of these, ulceration and necrosis with membrane formation are the most frequent. Tonsils, throat, gums, tongue, larynx, and even the esophagus may be the site of the necrotic processes. The membrane which forms may be attached to healthy tissue as well as to ulcerated areas. Lesions arise in the area due to the infective organisms which are always present.
Ulcers in other portions of the gastro-intestinal tract, in the skin, and in the vagina may accompany the oral lesions. According to Kastlin (36), in his Chart IV:

IV. Location of Extra-Oral Ulcers

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach, multiple small lesions</td>
<td>6 cases</td>
</tr>
<tr>
<td>Stomach, large ulcers</td>
<td>3 &quot;</td>
</tr>
<tr>
<td>Duodenum</td>
<td>2 &quot;</td>
</tr>
<tr>
<td>Ileum</td>
<td>6 &quot;</td>
</tr>
<tr>
<td>Colon</td>
<td>5 &quot;</td>
</tr>
<tr>
<td>Anus</td>
<td>4 &quot;</td>
</tr>
<tr>
<td>Rectum</td>
<td>2 &quot;</td>
</tr>
<tr>
<td>Cervix</td>
<td>2 &quot;</td>
</tr>
<tr>
<td>Vagina</td>
<td>8 &quot;</td>
</tr>
<tr>
<td>Symphysis</td>
<td>2 &quot;</td>
</tr>
<tr>
<td>Hip</td>
<td>1 &quot;</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>1 &quot;</td>
</tr>
</tbody>
</table>

Whatever their location, the ulcers have a similar appearance, due to the peculiar lack of cellular response.

The membranes may be described as non-marginated, with overhanging edges, or with no surrounding inflammatory reaction. The microscopic examination of the membrane shows very little cellular reaction, and, as a rule, a complete absence of polymorphonuclear leucocytes.

The skin may show petechial hemorrhages. Spontaneous hemorrhages into the viscera may occur, but these are not the rule. Such hemorrhagic tendency appears to be independent of the number of platelets, which is usually normal.

Lymph glands may be enlarged in the region of oral drainage in about half of the cases. The liver and the spleen may or may not be enlarged. Jaundice of moderate degree was found in about 50% of the cases.
Blood pressure may be somewhat lowered (37); the heart is normal except for increased activity. At first the lungs are negative but later there may be signs similar to those in bronchopneumonia. Palpation of the abdomen may give some tenderness in the epigastric area, especially over the gall-bladder area.

Laboratory Findings.-- The results of the laboratory examinations in this disease are very important, for without following the total leucocyte count, as well as the differential count, an accurate diagnosis cannot be made and the progress of the disease followed. On the basis of laboratory and clinical examinations it is usually not difficult to distinguish this syndrome from a number of others.

Blood: The outstanding laboratory finding in this disease is, of course, the marked leukopenia. In a severe fulminating case the total white-blood-cells may be exceedingly low. When first seen the total leucocyte count may be 700 or 600, the lowered count being due to the decrease in granulocytes. In the more chronic, relatively slow course, the total number of white blood-cells may be almost normal at first and then gradually fall to below 1000 or less per c. mm. In practically all cases the counts are below 2000.

The granulocytes, with which we are particularly interested in this syndrome, may range from a total absence in the acute fulminating cases to 30 or 40 per cent. in the slower forms (5). Their morphology in practically all cases
is normal. Immature forms of these cells are very seldom present but degenerative forms are noted (37). The cases showing myeloid aplasia have a chemotactic factor present but are lacking in a maturation factor. When the chemotactic factor is absent, the mature forms in the marrow are not called to the circulating blood stream. These are the cases with myeloid hyperplasia or normal myeloid tissue.

The lymphocytes may at first be present in their normal absolute numbers, but as the disease progresses there is a relative increase, but an absolute decrease in most cases. The morphologic characteristics of all the lymphocytes are, as a rule, perfectly normal. The pathologic changes in the lymph nodes (41) may account for the decrease in lymphocytes.

The monocytes and transitionals of the reticuloendothelial tissue may be either increased or decreased. The oxydase reaction is always negative for these cells. Schilling (3) believes them to be greatly increased. When present in normal numbers, their morphology is apparently normal.

In typical cases the erythrocytes and hemoglobin are not affected. If they were low before the attack, it is impossible to say that the neutropenia caused it. If, however, the course lasts longer than usual the erythrocytes and hemoglobin may decrease. In like manner the blood platelets are either normal or increased unless the course of the disease has been prolonged. Coagulation and bleeding times are usually normal.

Cultures: Cultures from the mouth or throat lesions have yielded a great variety of organisms with no one type
predominating. Borrelia vincenti, Fusiformis dentium, streptococci, pneumococci, and staphlococci have all been found but it must be remembered that these organisms are oftentimes found in routine cultures and it is only natural that after the defensive granulocytes have disappeared the organisms will become more abundant. Positive blood cultures with hemolytic streptococci, staphylococcus, pneumococcus, B. coli and B. pyocyaneus have been most frequently reported.

Urine: The urine in this disease shows nothing but that which might be expected during any febrile attack. Albumin and casts might be present in varying amounts. Sugar is usually absent unless the patient previously had diabetes. Urobilin and urobininogen may be present in patients with jaundice.

Miscellaneous: The Widal and Wassermann reactions are usually negative unless the patient has had the disease. According to Kracke (76), there are more and more reports of associated hemorrhages appearing in the literature. In these cases he believes this phenomenon to be due to diminished or absent platelets and he states that there can be no hard and fast line drawn between those cases showing neutropenia only and those showing the same condition complicated by diminished platelets, purpura bleeding, etc.
MORBID ANATOMY

Bone Marrow.— In reviewing the literature with regard to the pathology that exists in the bone marrow, one is very much disappointed in the variety of findings and the diversity of opinion concerning the pathological process. This is especially true since, with the evidence presented above that the first onset in the disease is one of bone marrow, one would expect to find a definite pathology which could at least be correlated in every case. Because of the variance in pathological reports we are made to wonder whether this is a disease entity or a symptom complex. Again there is some doubt raised as to whether all these reported cases should be included under the title of this disease. A still more disturbing fact is that many cases with a very similar clinical course, show anything but consistent findings both by biopsy and at necropsy. A general review of the pathological findings can thus only be attempted.

In the first cases of agranulocytosis which were described by Werner Schultz (1), the complete absence of granulated cells from the bone marrow of the ribs and femur were the outstanding anatomic features. The bone marrow was fatty with small islands of lymphoid cells among which a few myeloblasts could be distinguished. Many subsequent investigators (80, 81), especially those in Germany, were able to confirm these views, noting the apparently normal marrow with regard to the formation of red cells but with
an almost complete disappearance of its leukocytic elements. In 1929, Rose and Houser (82) found an outstanding scarcity of myeloid cells. Many of those present showed a distinct degeneration; their outline was indistinct and ragged; the cytoplasm tended to take on an eosin stain, or contained hyaline droplets. No leukocytes of any kind were found.

They found an active erythrocytic regeneration and a myelocytic destruction. According to Fried and Dameshek (44), there may be a widespread necrosis of the leukopoietic tissue in the severe forms of agranulocytosis. In one case reported by Dameshek and Ingall (50), in which a sternal biopsy was done during life the bone marrow showed nothing abnormal.

In 1932, Fitz-Hugh and Krumbhaar (83) observed that the current concept of the bone marrow changes in so-called agranulocytic angina was that there existed, at least terminally a more or less complete absence of white-cells of the granular (myeloid) series. (1, 36, 38, 82) This "granulocytic aplasia" developed partly on the basis of bone marrow studies indicating an apparently selective disappearance of the granular leukocytes and their progenitors and partly on the basis of analogy to established findings in certain other conditions, such as benzol poisoning, with its "selective" attack on formative tissues of the granular cells and blood platelets.

Fitz-Hugh and Krumbhaar made the following statement at that time: "The possibility that such an aplasia concept may not be entirely well founded in fact,
and may be misleading in implication, has come to mind from the personal study of the bone marrow of three recent fatal cases. In one of these the marrow of most of the bones examined contained "actively hematopoietic areas" filled with myelocytes, promyelocytes and myeloblasts, while the peripheral blood contained only 200 white blood cells per c. mm. (all lymphocytes). Similar, although less obvious, absence of myeloid white cell aplasia was found in the marrow of the other two cases. One of these died after months of illness characterized by repeated severe relapses and incomplete remissions. The patient's marrow, in most of the bones, was more nearly aplastic as regards granular series cells than any other marrow of such cases personally examined; but even this one showed numerous myeloblasts and a few myelocytes in the rib marrow, whereas her terminal white blood-cell count was only 500 cells per c. mm. (all lymphocytes). Necropsy was performed in these cases within two hours of death. There are several reports of myeloblastic and myelocytic hyperplasia on record" (4, 50).

Rosenthal (71), in 1931, made the observation that there is sufficient evidence to indicate that the histological examination of the bone marrow usually shows changes which correspond to the blood alterations, but he adds that in some cases there is marked discord between the leukopenia and the hyperplastic histological picture of the bone marrow, especially in benign cases of agranulocytosis.

The above observations of Fitz-Hugh and Krumbhaar led them to object to the current hypothesis of
"granulocytic aplasia" as constituting the "primary" pathologic mechanism of the disease and in its place they suggested a hypothesis of "maturation arrest" for consideration and future study. This has been referred to above under etiology. This hypothesis was strengthened when Fitz-Hugh and Comroe (73) later reported nine cases that came to necropsy. In these cases none of them showed what they called an aplasia. They referred to a "femur exhaustion", a "scarcity of myeloid cells", and "no evidence of aplasia". In opposition to this they reported "marked myeloid and erythroblastic hyperplasia", considerable myelocytic and myeloblastic hyperplasia in the femur, fibs and tibia", or "marked erythropoietic and myeloblastic hyperplasia" in seven of the nine cases. They did not include, in this series, cases of acute benzene poisoning, arsen-amine poisoning, and so forth.

In 1933, Jaffe (84) gave an excellent review of the pathology of the bone marrow as seen in these cases and added some impressions of his own. He presented a series of cases in which he observed peculiar changes in the myelocytes. In three of the cases of apparently idiopathic agranulocytosis and in one of the cases in which the history suggested relations between the agranulocytosis and anti-luetic treatment, the bone marrow of the femur was found to be much more cellular than the age of the patients would lead one to expect. In this hyperplasia the granulopoietic tissue took an active part and it seems in some instances
the agranulocytic catastrophe is preceded by proliferation of the young myelocytes. In the remaining five 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.

Jaffe found that in both types, hyperplastic and non-hyperplastic bone marrow, the granulopoietic cells revealed severe regressive changes. He obtained the impression that the specific granulations is the first to become affected while the nucleus remains intact for some time and may even divide by mitosis. The specific granules swell, their outline becomes indistinct, and small vacuoles often appear around them. Their granules later dissolve into these vacuoles. In the meantime the chromatin of the nuclei has become separated into coarse, sharply defined clumps, and the nucleoli have disappeared. The mitoses are, however, atypical. Finally the nucleus shrinks and disappears, the cytoplasm coagulates and the cell is dead. When present the myeloblasts appear intact, which suggests that therapeutic attempts are not absolutely hopeless even in the acute forms of the disease.

After this observation and study, Jaffe decided that the explanations Fitz-Hugh and Krumbhaar (83) offer for these cases sound logical, since it is possible that disturbances in the maturation of the myelocytes or emigration of the mature myelocytes may precede visible changes in the structure of these cells.
The great majority of the cases of agranulocytosis shows histologic evidences of a severe injury to the granulopoietic tissue. The few neutrophilic leucocytes which are occasionally found in the blood films from this disease are most severely altered. The giant cells in the bone marrow may be conspicuous and the megakaryocytes besides showing proliferation may show degenerative changes.

As far as erythropoiesis is concerned, a moderate anemia develops, usually in cases of more prolonged course, but it does not assume the character of an aplastic anemia. The bone marrow in typical cases of agranulocytosis shows a normal or increased erythropoiesis.

In all the cases Jaffe observed lymphocytes and plasma cells were present in the bone marrow. The reticulo-histiocytic elements of the bone marrow were not strikingly affected. From these observations he concluded that agranulocytosis is a symptom complex rather than a disease entity.

Grossly, the bone marrow shows very little. In practically all fatal cases the bone marrow shows various stages of degeneration and its color may vary from red to straw.

Ulcerative lesions: These lesions are present in a great majority of the cases and may occur in the mouth, pharynx, any place along the gastro-intestinal tract, in the vagina, on the cervix and indolent ulcer of the anus has been noted. (5, 84, 85, 35, 36, and others). These lesions are thought to be the consequence of the absence of circulating granular leucocytes. In all of these areas the surface is normally well
supplied and covered with granulocytes and with a lack of development of the protective inflammatory barrier to infection, such an infection results. These lesions are most commonly seen in areas where bacteria are normally abundant. All in all, the ulcerative processes are similar, being characterized by the absence of polymorphonuclear infiltration. The membranes which form have been variously described as non-margined, with an over-hanging edge, or with no surrounding inflammatory reaction (79).

Taking a necrosing process in the mouth as an example, the lesions may vary considerably. Only a few superficial ulcerations may be present on the tonsil, or there may be extensive, multiple, deep gangrenous constrictions involving the esophagus and the larynx. They are sometime surrounded with a zone that is wine-red in color. Microscopically, (37) the bottom of the ulcer is composed of three layers. A necrotic, granular material, intermingled with numerous bacteria, forms the uppermost layer. In the next one underneath, which usually extends into the muscle tissue, the tissue is also necrotic, but the cellular outlines are preserved. Streak-like accumulations of bacteria may be found in the intercellular spaces. The vessels in this region are thrombotic and contain hyalin or fibrinous material or clotted blood in which the absence of leucocytes is striking. In the still deeper edematous layer, areas of living and necrotic tissue alternate. Smaller and larger accumulations of lymphocytes and plasma
cells may be present in varying numbers. Leucocytes are absent or nearly so in these infiltrations.

Because of their common occurrence the early diagnosis of these ulcerative lesions is of prime importance so that treatment may be instituted early, before the case becomes hopeless.

The mucosal change, as described as Costen (86), is always an ulcer or slough, which follows a sudden undermining of normal mucosa with clinical and histological evidence of the lack of cell reaction or leucocyte accumulation for defense. The process is evident to the examining eye at the very beginning. It may be seen as a mottled yellowish spot in the center of the anterior pillar before the surface of the mucosa has broken down. It is also seen as a lemon yellow dot \( \frac{1}{2} \) cm. from the gum margin, when the lesion has begun as an ulcerative gingivitis. The necrotic tissue is always white or gray but the pastel shade of yellow is imparted to the very early sign by the white substance shining through what remains of pink or red mucosa.

The remaining morbid anatomy is not characteristic and various findings at necropsy have been reported. As a general rule the various authors have reported similar changes and here a general review as given by Huper and Garrison (41) and Beck (5) will be reported.

Lungs: Subpleural hemorrhages are rather frequently observed. A fibrinous exudate may cover the pleura in places where dark red, solid, irregular, small foci are present in
the lung. Such areas are rather regularly found, especially in the lower lobes which show also hypostatic hyperemia and edema. The capillaries of these solidified foci of lung tissue are hyperemic. The alveoli are filled with erythrocytes intermingled in places with bacteria. The absence of leucocytes in these foci is remarkable. Gangrenous changes may occur. When pneumonia occurs, it is characterized by an appearance of diffuse edema. The gross picture is similar to that of influenza pneumonia, if death occurs during the neutropenia.

Heart: Subepicardial and subendocardial hemorrhages do occur.

Liver: This organ usually shows some enlargement and evidence of cloudy swelling. Microscopically, there exist varying degrees of fatty degeneration, occasionally multiple, small, focal necroses, and in general an increase in kupffer's cells. The bile capillaries frequently contain bile casts and the liver cell bile pigment. These liver changes are probably the cause of the jaundice frequently seen.

Spleen: The reaction shown here is thought to be dependent on the predominance of toxic or septic symptoms. A swelling of the spleen is common, but usually not considerable. In some cases this enlargement has been found to be due to the great increase in reticulo-endothelial cells which outnumber the lymphoid cells. The lymph follicles are not prominent on the cut surface. It is dark red and moderately firm but never soft as in septicemia. Microscopically, the sinuses
are filled with erythrocytes, proliferating reticulo-endothelial cells and lymphoid cells. Oxydase positive cells are in general completely absent, or only scantily present. The lymph follicles are small and atrophic, especially the germinative centers which are usually only composed of mature lymphocytes.

Kidney: This organ usually shows evidence of cloudy swelling. Numerous, red, pinhead-size points are seen underneath the capsule in the cortex representing swollen, hyperemic glomeruli. On the cut surface the cortex and medulla are not well demarcated. The tubular epithelium is in general markedly degenerated or necrotic. The lumina are filled with casts.

Lymph-nodes: The submaxillary, cervical, peribronchial and mesenteric lymph-nodes are in general enlarged. They sometimes contain hemorrhages. The microscopical examination reveals an atrophy of the lymph follicles, as present in the spleen, and a proliferation of the reticulo-endothelial cells.
PROGNOSIS

It is somewhat difficult to give the prognosis in this condition because of the variance in the case reports. The evaluation and classification of cases, with their various types of reactions and therapy, is a difficult problem for the case may be one of a primary type or one of a secondary type and there are probably many cases that recover, never having been diagnosed. The prognosis depends apparently largely upon the extent of the injury to the bone marrow. The mortality as recorded by various clinicians, varies, due possibly to the time of diagnosis, the type of treatment instituted, and the complications which arise.

Historically a case of so-called "putrid sore throat" carried a very bad prognosis and if this condition were an agranulocytic manifestation, the early observers considered it to be almost hopeless. Schultz (1), in his original description, considered the mortality to be 100 per cent. A few years later Kastlin (36), in reviewing the cases he could find in the literature, found the mortality to be 95 per cent. In 1930 Hueper and Garrison (41), made the statement that about 10 percent of all cases on record were cured. In the same year Rosenthal (87) stressed the point that, in patients with counts below one thousand, death will likely occur, and in those with counts above that figure and a negative blood culture, the chance for recovery is good. He made this statement after observing ten of his patients who presented a mortality of 50 per cent. In 1930, Kracke (76) found that
approximately 250 cases had been reported with a mortality of 85 percent, but he felt that final reports on many patients, the mortality rate would appreciably increase. In the same year Harkins (88) found that out of 150 cases reported, 27 had recovered, giving a mortality rate of 82 per cent. In 1931, Taussig and Schonebelin (86), in analyzing the results of therapeutic measures, excluded all those cases which terminated fatally within 48 hours of the time that treatment was instituted and found these facts:

| Cases treated by means of irradiation | 64 | 34 | 53 |
| Cases treated by means of transfusion | 53 | 34 | 64 |
| Cases treated with arsphenamine | 33 | 34 | 73 |
| Cases treated with other measures | 178 | 133 | 75 |
| Cases without special therapy | 328 | 245 | 75 |

More recently Jackson et al. (78), in reviewing 54 cases which had been adequately treated with Nucleotide K 96 found a mortality rate of only 30 percent. In the same year Doane (33) found the mortality rate to be with arsphenamine 72 percent; with blood transfusion 64 percent; with irradiation 53 percent; and with Nucleotide only 25 percent. In 1933, Reznikoff (90) reported a series of 15 uncomplicated cases treated with adenine sulphate with a mortality of only 27 percent.

Thus it can be seen that the prognosis at best is grave, although not hopeless. It appears that various forms of treatment may in the future change the prognosis to a brighter outlook, dependent entirely on the ability of the therapeutic agent to bring about the resumption of granulopoietic function.
DIAGNOSIS

As can be seen from the discussion, the outstanding phenomenon in this disease is the blood picture. This, along with the symptoms should make the diagnosis fairly easy in the typical case. A typical history is the appearance of sore throat in a middle aged patient who may have been perfectly well. Chills occur and fever develops and the patient is extremely prostrated, out of proportion to the clinical picture. Ulceration and membrane formation in the throat and on the buccal mucous membrane very frequently occurs. If angina is absent the diagnosis is made more difficult. The patient may go on to a secondary infection, severe sepsis, coma and death.

The early diagnosis of the condition is essential if the mortality is to be lowered. To wait for the appearance of sore throat, sore mouth, fever and prostration, is to give way to secondary infection and a hopeless situation. Thus it should be a rule to make cytologic examinations of the blood more frequently, especially if there is a fever of any duration at all. A careful blood study should be made in all patients who complain of frequent mouth and throat infection. The final diagnosis is made from the low, total white blood cell count and the absence or near-absence of granulocytes in the circulating blood. There is some difference of opinion as to whether these changes in the erythrocytes and blood platelets contraindicate such a diagnosis, but this can usually be decided by following the course of the disease.
Differential Diagnosis

In the differential diagnosis it is necessary to learn whether one is dealing with the primary Schultz type or a secondary type of the disease manifestation. Notable among the causes of the secondary type is poisoning, which may be acute or of the slow insidious form. The possibility of a chemical or drug bringing about the condition is best ruled out by a careful, complete history. More often in the secondary type there is an associated anemia and thrombocytopenia.

1. Schultz (1) in differentiating from a septicemia with gangrenous stomatitis, noted that there is always an outspoken anemia, decrease in blood platelets, a hemorrhagic diathesis, a positive blood culture, and a soft, septic type of spleen at autopsy. He thus excluded such cases from the agranulocytic angina classification.

2. Leukopenia: This may be caused by toxic agents which have to be ruled out by the history. Other conditions at time cause a leukopenia and it may be necessary to exclude them. Patients with streptococci sore throat, with streptococcus hemolyticus septicemia, occasionally have leukopenia, but rarely less than 5000 or 4000 cells, with probably at least 85 percent neutrophils. In typhoid fever and influenza, the total white cell count is rarely less than 4000, and the neutrophilic percentage is at least 25. Generalized, rapidly advancing Tuberculosis may show a marked leukopenia, as low as 3000 cells, but the neutrophils comprise from 90 to 99 percent, mostly
immature forms. Pneumonia may at times cause leukopenia, rarely below 6000 cells, and there is always a preponderance of neutrophils. In any case, with a leukopenia without angina, frequent leucocyte and differential counts should be made until the diagnosis is established (5).

3. Diseases with similar necrotizing processes in the mouth but without an agranulocytic symptom complex (41).

(a) Diphtheria: The differential diagnosis in this condition has been discussed very ably by Gordon and Litvak (91). These men have made a chart which is too detailed to be included in this paper. The fulminant type of this disease resembles in its general and local symptoms sometimes very closely those present in agranulocytosis, but it is different in hematological, bacteriological, and pathologic respects.

(b) Vincents Angina: This may show also, locally, similar alterations as those found in agranulocytosis as it may agree with this disease by the presence of a fusospirillosis. The correct diagnosis rests upon the general condition of the patient, the blood findings, the good prognosis, and the pathologic alteration.

(c) Infectious Mononucleosis: This occurs as Vincents Angina at an earlier age than agranulocytic angina. The necroses are usually restricted to the tonsils. There is a generalized enlargement of the lymph-nodes, liver and spleen. A definite leukocytosis is present at some stage of the disease and white counts of a few hundred cells with almost total absence of the polynuclear cells are not encountered. The
disease is apparently contagious, has a protracted course and carries a good prognosis.

(d) Acute Follicular Tonsillitis: This should be differentiated by appropriate means and routine leucocyte and differential count. There is usually an increase in total white blood cell and angranulocyte counts.

4. Acute Leukemia: The resemblance of agranulocytic angina to atypical cases of acute leukemia may be marked, especially to those with an aleukemic or subleukemic blood pictures (79). The similarity extends even farther if there is an actual decrease in the total white count. The increase in the number of leucocytes in the beginning of acute leukemia is often of only slight degree and counts as low as 3000 or less have been recorded. (78) As a rule the count increases during the course of the disease to 30,000 or more. There are, however, cases which have shown subnormal counts through the entire course of the disease. Besides certain clinical manifestations, which are similar in both conditions, acute leukemia usually presents added features of bleeding from the mucous membranes, hemorrhagic diathesis and a fall in red blood cells and hemoglobin. The presence of a high percentage of abnormal primitive cells, either myeloblasts or lymphoblasts, in the blood smear is strong evidence that the case is either acute myeloblastic or acute lymphoblastic leukemia. In general the course is shorter in agranulocytic angina and the excessively low white counts are usually not encountered in leukemias. The differential diagnosis during
life may be difficult, but the post-mortem examination should serve to distinguish the two diseases. In acute leukemia there is a widespread leukemic cell infiltration of all organs, which separates it from the pathology of agranulocytosis where the bone marrow shows an absence of granular cells, and the ulcerative processes show no inflammatory reaction.

(5) Aplastic Anemia: The classical symptoms are subacute course, tendency to affect young persons, striking pallor, hemorrhages under the skin, bleeding from the mucous membranes, (nose, gums, and vagina) and ulcerative lesions in the larynx (79). The onset of the fever is usually not so abrupt. The blood picture shows a leukopenia, neutropenia, thrombocytopenia and rapidly advancing anemia of the hyperchromic type. The color index is irregular. There is a relative increase in lymphocytes. If anemia is present in agranulocytosis it is of the secondary type, the erythrocytes being more or less achromic. Examination of the bone marrow shows a striking difference. In aplastic anemia there is extensive atrophy of the marrow, the latter being yellow and completely barren of erythrocytes, leucocytes, and megakaryocytes. In agranulocytic angina the leucocytes only are damaged and the red cells are relatively intact.
A review of the literature indicates that most authors believe that a specific and satisfactory treatment has not yet been discovered for neutropenia, many believing that when recovery does occur it is spontaneous and very little influenced by the type of therapy. Some cases have been reported which have appeared to be hopeless but recovered without any active treatment. (51) In considering therapy in such a condition several factors are encountered. There are the local lesions, the absence of granulocytes, and the septic, toxic, processes which occur subsequent to an infection. There is also the problem of the prevention of this pathological process if it is at all possible. Thus, we become concerned with prophylaxis, with chronic cases and the prevention of recurrences, and the treatment during the acute phase.

Prophylaxis: There is little definite information available as to the prevention of this disease. Until the true etiology is known this matter is only met with logic and methods similar to those that might be employed in preventing any disease. It is apparently not an infective, contagious thing and thus isolation at the present time does not appear to be indicated. Recently, it has been recommended that the indiscriminant use by the public of drugs and chemicals containing the benzene ring be stopped. From a review made by Kracke and Parker (40) it would seem that the use of the benzamine drugs by nurses and physicians should be controlled so as to cut down on the incidence of the disease. If we are
to believe such investigators as Herz (64), the use of amidopyrine will be curtailed as well as other drugs of pyrazolon derivation. The Council on Pharmacy and Chemistry has made the statement that as far as can be learned from the evidence on hand, there can be no question that amidopyrine is very important in the production of granulocytopenia. They found that no other agent, either chemical or bacterial, had caused so many attacks. Thus it would seem that until further investigation is reported the use of such marrow-depressing drugs and chemicals, those of pyrazolon derivation or containing a benzine ring should be restricted in use and even then a close watch of the blood picture in the patient should be kept.

As to the management of chronic cases and the prevention of recurrence of acute attacks, there is little that has been advised. Roberts and Kracke (38), Doane (33), and Mettier and Olson (39) have all made statistical studies of the neutropenic state with special reference to its chronicity. The evidence accumulated indicates that weakness, exhaustion, fatigue, and tendency to sleep are the chief results of a slightly depressed granulocyte count. This is important to note for the severe type of neutropenia is more apt to occur in those patients with a granulopenia. Roberts and Kracke found that many patients improve with rest in bed alone. This form of therapy is very important, especially in those cases who develop a myocardial heart involvement during the granulopenia. The rest should be complete with freedom from emotional
and mental stress. These patients should also refrain from using drugs which have any depressing effect on the bone marrow. Beck (5) reports a case that recovered with no active treatment other than rest and a diet rich in vitamin B.

The problem of diet in this disease may play a more important part than is now imagined. Doan (24), in experimental work with pigeons, reduced the bone marrow to an extreme hypoplasia with under-feeding. All that was left after this starvation were the blood vessels, fat cells, and a minimal framework of reticulum and reticular cells. Thus it would seem that the state of nutrition is important and if this can be proven and a dietary factor that has a specific influence be found, it will have a most practical bearing.

All foci of infection should be eliminated if possible, but operative procedures on these patients should be approached with considerable caution, as the granulopenic state may develop at any time and prevent proper healing. Hueper and Garrison (41) advise drainage of the gall-bladder in those cases which have a definite gall-bladder history in an attempt to remove toxic products of a causative nature. Routine blood counts should be studied with great care, and all patients having a granulopenia should be under careful observation and frequent blood counts should be made.

The treatment in this paper will be concerned chiefly with that therapy instituted during the acute period. In reviewing the literature the value of such treatment is very difficult to analyze. Many authors have reported highly
successful results with certain type of treatment, while others have been very much disappointed with that same type of therapy. It must also be remembered that the efficacy of the type of treatment used depends largely on the time at which, during the course of the disease, it was instituted. It is only logical that, if a patient is not seen until secondary infection with toxemia and possibly septicemia have occurred, the treatment will be of very little value, even with a well functioning bone marrow, let alone when the great defensive mechanism of the body has been destroyed. Thus the greatest factor in recovery lies in early recognition. If we accept the conception that in the disease there is an inability of maturation and delivery to the blood stream of granulocytes, only that type of treatment which will re-institute granulopoiesis will help. Thus in the acute case our therapy is directed to the employment of an agent that will stimulate maturation of the granulocytes and cause their delivery to the circulating blood in the shortest time possible. The management of the local lesion must also be considered.

Care of Local Lesions: These lesions require care but the most important point to remember is that an antiseptic that will cause a chemical destruction of the tissue should certainly not be used. As long as the area is kept as clean as possible and the slough cleared away, any other mild measures may be taken. Hamburger (51) prefers the use of a saturated solution of potassium chlorate as a spray, following this with the swabbing of each ulcerated area with a copper sulphate
solution. This is usually done quite frequently until improvement occurs. Other men (54) prefer hot saline irrigations every three hours, followed by the local application of sodium perborate or hydrogen peroxide. Griffith (92) is of the opinion that when streptococci are found in these lesions, erythematous doses of ultra-violet light are of value, analogous to the great value of ultra-violet light in erysipelas.

It is well known that no incisions should be made in these local lesions because of the absence of an inflammatory reaction, and the possibility of merely disturbing the patient and giving rise to a septicemia. If the granulocytes are made to return to the circulating blood, the local lesions will usually clear up spontaneously. The formation of new necrotic and ulcerative processes due to septic technique in making biopsies and venipunctures must be avoided. Many men refuse to do any type of surgical procedure due to the absolute lack of any resistance in the body.

Symptomatic Treatment: This type of treatment differs not at all from that given in any other acute illness. It is concerned with making the patient as comfortable as possible during the acute stage, carrying him through this stage, and anticipating any complication. As in other acute diseases, the patient must be kept in bed, at complete rest, both physically and mentally. A diet high in caloric content and vitamins (B) is desirable, but the forcing of such a diet on an extremely ill and prostrate patient is probably inadvisable.
In order to combat the toxemia, intravenous glucose-saline solution, as well as transfusions, should be tried. This should be started early and continued intensively. If there is difficulty in swallowing, tube feeding may be necessary. As in other toxic conditions digitalis may be used as well as stimulants to keep the patient going. Because of the fact that a broncho-pneumonia often develops, hyper-ventilation of the lungs by means of carbon dioxide inhalations at intervals may be a life-saving measure.

Aside from symptomatic treatment, the chief methods of therapy tried in any considerable number of cases of agranulocytosis are: (a) radiation, (b) transfusions, (c) purine or nucleotide therapy. These latter chemicals are grouped together, because in all probability the active principle in them is the same. (90)

Radiation: Some of the most ardent supporters of radiation therapy are Taussig and Schnoebelin (89) and Gager and Speer (93). In 1931, in their analysis of treatment Taussig and Schnoebelin excluded from consideration those cases which terminated fatally within 48 hours after treatment was instituted. They found that the results of treatment by means of irradiation, as recorded in the literature, showed only a 53 percent mortality. In their own four cases there was a mortality of 50 percent under this type of treatment. They thus concluded that irradiation of the long bones gave the best result in treatment at that time. They used a set up which, with an exposure of about 45 seconds, corres-
ponded to about one-twentieth erythema dose. With this ar-
angement the time of exposure was two and a half minutes. 
In 1932, Gager and Speer reported two cases of agranulocytosis 
with recovery, roentgen irradiation being the only general 
therapeutic agent employed in the crisis of the disease.

These investigators were of the opinion that stimu-
lating doses of x-ray were an effective therapeutic measure 
in agranulocytosis providing the injury to the bone marrow 
was not too extreme. They felt that minimal doses, applied 
to the long bone, caused a definite rise in the granulocyte 
level, even in healthy tissue, while the effect was much more 
pronounced and more rapid in diseased tissue. They also 
felt that transfusions at the same time were of value.

The value and rationale of this type of therapy is 
apparently open to question. Doane (33) made the following 
statement: "There is some difference of opinion as to the 
primary effect of minimal exposure to x-rays or radium. That 
many tissues and especially the hematopoietic tissues are 
highly radio sensitive and may be inadvertently destroyed by 
a variable exposure to such active rays, particularly in in-
dividuals of a more readily susceptible constitution, makes 
of this therapeutic measure a two-edged sword to be wielded 
with great caution, when stimulation rather than destruction 
is the end desired. Granting that there is a stimulatory 
threshold below which a primary destruction of cells does not 
precede regeneration, this must vary considerably from indi-
vidual to individual and hardly yet be susceptible to recog-
nition and control by the roentgenologist. In patients with
malignant neutropenia but in whom the marrow is hyperplastic and shows only a arrest of maturation, the mechanism by which a response is obtained may well be that of a primary destruction of some of the intact myeloid foci with a liberation of autogenous nucleotide, which then could initiate the maturation and delivery of leucocytes from the remaining myeloid foci."

This statement summarizes very well the doubt many authors have, as to the efficacy of roentgen therapy. It may be of very great value, but on the other hand it may precipitate a complete aplasia and fatal termination in those cases having a hypoplastic bone marrow (5,57,86). If radiation stimulates the granulocytic elements of the bone marrow by hyperemia or fixed tissue cell proliferation, subsequent atrophy of the granulocytes may result; in which case there would be a complete relapse in which radiation would be completely ineffective.

Transfusion: This form of treatment has been given constantly in agranulocytosis although no extensive series of cases, treated by this method, has been reported. As far as is known, transfusions or intramuscular injections of blood have never been shown to stimulate the production of polymorphonuclear leucocytes (90). Reznikoff (94), in 1931, found that in some instances large transfusions tend to markedly decrease the polymorphonuclear cells in the peripheral blood. Sabin (25) has definitely proven that transfusions lower the rate of erythropoiesis and it is only natural to wonder if the same does not hold true for granulopoiesis, although it has
not been proven. Griffith (92) and Delatour (54) and many others (57 and 86) are highly in favor of frequent small transfusions, but the rationale for such a procedure is doubtful, although it may be of some value, merely as a supportive measure and not as a specific. Most authors agree that if they are used they should be started at the earliest possible moment and continued. Sachs (75) feels that transfusions should be used, their only contraindication being a severe reaction or depression of granulocytes after transfusion. Many men have pointed out that if the disease becomes subacute or chronic it may become more and more difficult to find a donor whose blood will match that of the patient.

Thus it can be seen, both from clinical and experimental work (25) that there is no rationale for the use of blood transfusions in agranulocytic angina. They may be of some value as a supportive measure, but they certainly cannot be considered as specific therapy. The use of transfusions in an effort to tide the patient over will undoubtedly be used continuously until some more specific therapy is found.

Purine or Nucleotide Therapy: For many years investigators have felt that this disease should lend itself to treatment by the stimulation of the polymorphonuclear elements by some substance. The first work done on leukocytosis, its occurrence in nature, produced by nucleinic acid was done by Ames and Huntley (95), in 1897. Later Doan et al. (32) showed the chemotactic effect of large doses of nucleic acid. They found that if nucleic acid were used a
leukopenia preceded the leucocytosis, due to the storage of granulocytes in the spleen, but if the split products of nucleic acid, guanine and adenine, were used there was a direct leucocytosis without the leukopenia. In 1930, Reznikoff (94) described four cases of agranulocytic angina treated with transfusions of blood and intravenous injections of the purine basis, adenine and guanine. Three of his patients recovered. In the next issue of the same journal he pointed out (95) that he used purine basis and not nucleotides in these four patients. Nucleic acid is a complex molecule made up of two pyrimidine and two purine nucleotides linked together. These nucleotides in turn are made up of a purine or pyrimidine base together with pentose and phosphoric acid. These compounds can be further broken down to nucleosides by the loss of phosphoric acid and still further to the purine and pyrimidine bases with the loss of pentose. It is these purine bases that Reznikoff (94,95) used. These substances given to rabbits, intravenously, caused a marked increase in the granulocytes without any effect on any other cells. In 1931, Jackson et al. (96) used the unbroken nucleotide known as K 96. They treated 20 cases of profound leukopenia. Of these, thirteen were typical agranulocytic angina cases; five patients had marked leukopenia; and two had extreme neutropenia and anemia secondary to benzene poisoning. Of the thirteen agranulocytic angina patients, seven recovered and all of them showed definite signs of clinical improvement on the third or fourth days after treatment was begun, irrespective of the duration of the disease before treatment.
The first sign of improvement in the blood picture occurred almost invariably between the fourth and the seventh day — usually on the fifth day. They considered the consistency with which reaction occurred on or about the fifth day to be of great importance. It is at this time, they observed, that the reticulocyte rise begins to take place following the liver therapy in pernicious anemia; also, it is at this time that the bone marrows of experimental animals subjected to a single injury begin to recover. They found the total and differential white blood cell count to be invariably normal ten days after treatment was begun. In each case 0.7 Gm. of Nucleotide K 96 in 100 cc. of saline solution was injected intravenously, daily for four days.

In 1933, Reznikoff (90) summarized the results obtained with adenine sulphate injected intravenously, in a group of fifteen cases. He found the mortality in this group to be only 27 percent, which is about the same as that obtained by Jackson (97). Of the patients who recovered in the Reznikoff series, almost all showed evidence of response to adenine sulphate within 24 hours after the administration of the purine salt, as evidenced by the beginning increase in granulocytes, drop of temperature and symptomatic improvement; and most of the patients showed very distinct improvement within 48 hours. This quick reaction is important, of course, because of the acuteness of the disease. Adenine sulphate was found to have no effect in the complicated cases. One gram of adenine sulphate was given in saline solution, intravenously three times.
a day, for at least three days. This dosage was found to be non-toxic for adults.

Thus it would seem that the pentose nucleotide or adenine sulphate is the most effective treatment, for the case of acute agranulocytic angina. The adenine sulphate may prove to be more efficacious because of its quicker action, but production of experimental agranulocytosis more nearly simulating the disease, is essential before more definite proof of the value of therapeutic agents can be established. It is to be noted that adenine sulphate does not seem to cause any reaction in the individual, while pentose nucleotide may at times cause some sort of an undesirable response.

Miscellaneous: Since the original description of the disease, many substances have been tried in the treatment more or less blindly with great hope. These have included diphtheria antitoxin, foreign proteins, bone marrow extract, foetal liver, streptococcus antitoxin, and convalescent blood serum. None of these have proven effective in bringing granulocytes to the peripheral circulating blood. The secondary blood stream infection has also been treated with various antisepsics but with little success.

Arsphenamine: Some men, especially in the past, have been vigorous supporters for this type of treatment. The efficacy of adding neoarsphenamine to the blood transfusion has been stressed, but today it appears to be a dangerous procedure. Suffice it to say that Farley's (63) review of 39 cases of depressed bone marrow function due to arsphenamine should be enough warning for discontinuance of the practice.
SUMMARY

The consideration of a status of agranulocytic angina has been given after a review of the literature. The consensus of opinion is that the prognosis of the disease is grave but not hopeless. It is characterized by a marked leukopenia and an absence or near absence of granulocytes with no infection, localized infection, or generalized infection. It is rapidly increasing in incidence. Whether it is a clinical entity or a symptom complex is debatable, but it may be considered an entity in the same sense as pernicious anemia is - only it awaits a specific therapeutic agent to stamp it with validity.

A definite etiologic agent for all cases is still unproven. From evidence presented it would seem that it is a disease of the white race; of the better class of people; and has a peculiar predilection for members of the medical and allied profession. Bacterial agents have given inconsistent findings experimentally, while certain chemical agents have simulated the clinical picture more closely than anything else. It seems that the benzamine drugs and those of pyrazolon derivation, especially amidopyrine, should be used with discretion.

The main pathological processes are to be found in the red bone marrow, effecting the myeloid tissue which may show a hypoplasia to an aplasia, an apparently normal state, or a hyperplasia. The reaction of the bone marrow is probably the result of the constitutional inadequacy and the potency of noxious agent. The local lesions and ulcerations are charac-
terized by necrosis, sloughing, and a lack of any inflammatory reaction.

The diagnosis, which should be made early, is fairly easy in a typical case, and is made by the blood picture. The characteristics of this are: marked leukopenia with absence or near absence of granulocytes; no young white blood cell forms; normal erythrocytes, platelets, lymphocytes and monocytes.

In treatment the desirable thing is to prevent the condition if possible by the restriction of marrow depressing substances and the proper care of patients with chronic leukopenia. If the disease develops, early diagnosis is essential. Care of the local lesions, symptomatic and supportive treatment must be instituted. Pentose nucleotide or adenine sulphate are apparently, at the present time, the most efficient of the (specific) types of treatment. If improvement takes place under this treatment it will usually occur between the fourth and seventh days with pentose nucleotide K 96 and within 24 to 48 hours with adenine sulphate.
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