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Agranulocytosis : a review with special consideration to etiology and treatment

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AGRANULOCYTOSIS
A Review
With
Special Consideration to
Etiology and Treatment

By

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SENIOR THESIS
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and
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Although it has been seventeen years since Werner Schultz, (108) in Germany, described a clinical syndrome, which he called agranulocytosis, and which he believed was a disease entity, there remains considerable confusion as to many phases of the condition. Many writers have refused to consider it as a true disease entity, and in reviewing the literature of the published case reports the reason for this becomes quite obvious. Many authors have included all cases that show a leukopenia and neutropenia regardless of the clinical picture. Such reports lead one to the conclusion that they are dealing with a group of diseases.

The literature is especially voluminous in regard to the etiology and treatment of agranulocytosis. Many ideas have been offered but few have been generally accepted. It is for this reason that the major portion of this paper will be given over to a review of the established observations concerning the etiology and treatment with an attempt to present the status of these phases at the present time. For the sake of completeness, brief consideration will be given to the history, pathology, symptoms and signs, and the blood picture of the disease.

Agranulocytosis may be defined as a grave condition of known and unknown etiology, characterized by a marked reduction of the total number of white blood cells, and

a great reduction in the percentage of granulocytes, accompanied by aplastic, normal or hyperplastic myeloid tissue. Following the peripheral neutropenia there may be any number of lesions and symptoms which might follow the removal from the body of such an important defense mechanism. Characteristically these lesions consist of necrotic ulcerations in the oral cavity but may also occur on the skin or mucous membranes elsewhere in the body. The disease may be acute, chronic or recurrent.

NOMENCLATURE

Werner Schultz, (108) in 1922, proposed the name agranulocytosis. The literature contains considerable criticism of this term and consequently many different ones have been offered in its stead. Friedemann, writing in 1923, being impressed by the usual severe localization of the process in the throat, suggested the name "agranulocytic angina". (121) This name has been used in the literature nearly as often as the original term given by Schultz. The term agranulocytosis came into the nomenclature, no doubt, on account of its brevity; many authors, however, believe it incorrect. Victor Schilling (107) said: "the term 'agranulocytosis' has come into the nomenclature on account of its brevity. It is incorrect; the name of 'agranulocytes' was originally chosen for 'neutrophils without granulations' of leukemias.

By 'agranulocytosis' is meant an increase in these atypical neutrophils which is not intended." The name agranulocytic angina has also been criticized because of its intrinsic ambiguity, and because it implies that one is dealing with an infection of the mouth which causes a neutropenia, instead of with a syndrome of indefinite etiology. Stillman, (118) and Baldrige and Needles, (2) have pointed out that the throat symptoms are not always present. Because of these confusing terms, many others have been suggested. Schilling (107) has stated that "Malignant neutropenia" is a more descriptive and appropriate term. Dameshek and Ingall (19) also prefer that term. Baldrige and Needles (2) have called it "idiopathic neutropenia". Fitz-Hugh and Krumbhaar (36) prefer the designation "pernicious leukopenia" which "suggests certain analogies between this disease and pernicious anemia". Linthicum (75) suggested the name "pyocyanic stomatitis with agranulocytic leukopenia" because of the etiological importance he attached to the *Bacillus pyocyaneus*. Pelnar, (88) in 1925, called the condition "malignant leukopenia". Because he believed that it was only one type of sepsis, Feer (33) preferred the term "sepsis agranulocytica". In order to give due credit to the man who aroused interest in the condition, Hueper, (49) has chosen the name, "Agranulocytosis (Schultz)".

Roberts and Kracke (100) prefer "granulopenia".

Rosenthal, (104) in his classification made according to the clinical manifestations and course, divided neutropenia into malignant (fatal) and benign (recovered) cases. In reference to this classification, Beck (3) stated that it might be well further to divide these into two main classes as follows: 1. primary benign and primary malignant neutropenia, the true cases of benign and malignant neutropenia, in which the etiology is unknown; 2. secondary benign and secondary malignant neutropenia, the cases in which the etiologic agents are evident or in which one is dealing with examples of well recognized clinical entities.

HISTORY

If agranulocytosis had existed to any great extent prior to 1922, it undoubtedly would have been described long before, since the disease runs such a dramatic course and often terminates fatally. Blood counts have been made as a routine procedure in most large hospitals for the past fifty years. Werner Schultz, (108) in 1922, first fully described four cases in middle aged women characterized by gangrenous throat lesions, severe leukopenia, a decrease or absence of granular cells in the peripheral blood, and a rapid septic course with death in from two to seven days. He noted the frequent association of jaundice, the persistence of a normal red blood cell count

and the scarcity of myeloid cells found in the bone marrow at postmortem examination. Schultz is thus given credit for recognizing the syndrome later named agranulocytic angina by Friedemann, but, Pepper (90) states: "no one believes that the condition had not previously been seen". An editorial in the Journal of the American Medical Association (31) quotes Turk as describing similar cases in 1907, although he did not distinguish them from the commoner leukopenia of overwhelming infection. Pepper, (90) in his history of agranulocytic angina, stated that standard laryngologic works of fifty years ago apparently described this disease under the heading "putrid sore throat" and "gangrenous angina", and he said that Mackenzie, in his manual of diseases of the throat and nose, credited Gubler, in 1857, and Trousseau, in 1865, with having clearly distinguished the disease from diphtheria.

In 1902, Brown (13) reported "a fatal case of acute primary infectious pharyngitis with extreme leukopenia". The case was that of a 28 year old married woman who died seven days after the onset of a sore throat. At the onset she experienced chilliness and a sudden rise of temperature to 103. The spleen and lymphnodes were slightly enlarged. The blood picture showed: leukocytes 1000 with one per cent polymorphonuclears, 83 per cent small lymphocytes and 16 per cent large lymphocytes. On the third

day of the illness the leukocytes were 400 and on the fourth day they were 320. The temperature at that time was 105.4. There was a gradual increase in swelling of the tonsils and pharynx. Cultures of the throat showed *Staphylococcus aureus* and *albus*. The urine showed albumin, casts and red blood cells. On the seventh day "so few leukocytes were found that neither a fair estimate of the total number could be made nor were enough found on six coverslips to make a differential count". The Patient died on the seventh day from edema of the glottis.

Leale, (72) in 1910, reported a case in a male child two and one-half months old under the title, "Recurrent furunculosis in an Infant Showing an Unusual Blood Picture". He described the case of a baby who was subject to repeated attacks of furunculosis, with accompanying fever and prostration all out of proportion to the clinical findings, and who also presented the unusual blood picture of leukopenia and lymphocytosis without other marked blood changes. He was at a loss to explain the unusual blood changes and carefully ruled out lymphatic leukemia, malaria, rickets, scurvy, and infectious disease. He concluded: "In all probability, the fever is to be accounted for by the toxemia generated by the *staphylococcus pyogenes aureus* during the attacks of furunculosis, but this does not

satisfactorily account for the peculiar blood findings." Baldridge and Needles (2) reported a case that occurred in 1910, pointing out that in former years it either was overlooked because the blood was not examined, or was interpreted as a symptom of exhaustion of the bone marrow, aleukemic leukemia or aplastic anemia.

In 1922, Schultz (108) reported the four cases as described previously, and applied the term agranulocytosis, and he stated the belief that it was a distinct clinical entity. From that date interest in this symptom complex has continually increased. In 1924, Lovett (76) reported the first case in this country following Schultz' description of the syndrome. She reported that about a dozen cases of the disease had been reported in Germany, and that her case was a similar one. She stated that the main features were ulcerative angina, usually accompanied by icterus, a great reduction in the white blood cells, affecting chiefly the polymorphonuclear leukocytes and a fatal outcome after an acute course. She added that there was no anemia and that the granular cells were absent not only from the blood, but also from the bone marrow. Since her report in 1924, many cases have been reported in this country and abroad and many theories as to the pathogenesis and treatment suggested.

Further interest was aroused in this country following

the report of R. R. Kracke, (65) in 1931, in which he first drew attention to the fact that his patient had used large amounts of benzene ring drugs for three years preceding her illness, and stated that the association between her illness and the drugs should be considered of etiological importance. Plumer's (93) report of a fatal case of agranulocytosis in April, 1937, which occurred following the administration of sulfanilamide, marked the opening of the latest chapter in the history of this interesting condition.

PATHOGENESIS

In reviewing the literature one finds many explanations and hypotheses of the pathogenesis of agranulocytosis. An attempt has been made to group these hypotheses so that they may be presented more clearly.

Predisposing Causes.--- It is exceedingly difficult to estimate the true incidence of the disease, first because an unknown number of cases are not recognized owing to the lack of an examination of the blood and, second, because all cases in which there is a marked leukopenia cannot be classified as instances of true agranulocytosis. For example, Doan (27) stated that only twenty percent of patients with leukopenia referred to his clinic have true agranulocytosis. It should be emphasized that extreme leukopenia may occur secondary to

sepsis in cases of various diseases of the blood, such as aplastic anemia, aleukemic leukemia and pernicious anemia. (121) Fitz-Hugh and Comroe (35) regard leukopenia which occurs in association with those blood diseases or following the therapeutic use of arsenic or gold preparations, or after exposure to benzene as a "mere hematological manifestation" of some other disease and not agranulocytosis.

Schultz described the condition as occurring in middle aged women. Hueper (49) reviewed 125 cases he found in the literature in the six years following Schultz's original article and concluded that 77.5 per cent of the cases had occurred in women. Kastlin, (62) in 1927, in a statistical review of the reported cases at that time found 43 cases reported with 34 of the cases appearing in females, or 78 per cent. Jackson (53) found that 82 per cent of the reported cases up to 1927 had been women. "Four women to one man" is the sex incidence as given by Kracke. (66) Roberts and Kracke (100) studied the problem of granulopenia in 8,000 ambulatory private patients, and found that one of every four patients in a general practice may be expected to have a mild granulopenia. However, they found that only 56 per cent of the mild granulopenias occurred in female patients. Beck (3) concluded that in the final analysis, it may be found that neutropenia, chronic and

acute, does not predominate in either sex.

Jackson (53) found that 76 per cent of the cases were in patients between the ages of 38 and 65 years. Kastlin (62) found the average to be 46 years. Kracke (66) stated that it may occur in infants or the aged. He has observed a patient 72 years old with agranulocytosis. Beck (3) stated that practically all of the typical cases of primary benign and malignant neutropenia have occurred in the fourth decade of life--from 41 to 58 years of age.

Jackson (53) observed that most of the cases have occurred in obese women complaining of gall bladder symptoms. Beck (3) also mentions the coincidence of previous disease of the liver and the gall bladder with malignant neutropenia. In his review of the incidence of the disease, Kastlin (62) found a negative history of past illness in 62.8 per cent of the cases. There seems to be no definite relationship of agranulocytosis to season. However, Kracke (66) believes that it may be somewhat more prevalent in the winter because of the "frequent association with influenza". As to geographical limitation Kracke stated that 80 per cent of the reports are found in German and American literature. He added that it was comparatively infrequent in France and England, rare in Italy, and extremely rare in the Orient. Kracke believes that this distribution can be correlated to the usage of

organic chemical compounds, because "in Germany and the United States is found the widest usage of organic chemical compounds and aniline dye products". Similarly, Beck (3) lists as other predisposing causes those drugs and chemicals containing the benzene ring, the arsenicals, trinitrotoluene, X-rays etc. She also believed that "certain infections" might be predisposing causes; such cases she groups under the headings of secondary benign and secondary malignant neutropenia.

Kracke (66) finds that the condition seems peculiarly prevalent in "ladies and gentlemen of leisure" or the "better class". He also states that the disease is practically confined to the white race. Madison and Squier (78) have found the condition especially prevalent in doctors, nurses, druggists, students, and other people associated with the medical profession.

Organisms as a Cause.-- The first reports of agranulocytosis show that the authors considered the condition as an infectious disease or at least the result of some form of sepsis. Schultz, with the idea that a nervous factor was involved, stated: "It may be assumed that the affection involves an extensive injury of the spinal cord in the domain of the granulocytic system, caused by infection". (40) Lovett, in 1924, (76) in the first report of the disease made in this country, said: "Is it a local

infection with a specific organism which produces severe gangrenous lesions, and has a toxic effect on the granulocytes, or is it primarily an injury to these cells at the site of their formation, with a consequent lack of general resistance, so that any infection goes on to necrosis and finally death?" She obtained *Bacillus pyocyaneus* in cultures from the oral lesions and from the spleen and attached great significance to this discovery. Experimentally Lovett claimed that this organism had the power of reducing the leukocytes in the blood of guinea-pigs, and causing degeneration of leukocytes in the peritoneal cavity. She concluded: "The disease appears to be due to an injury to the leukopoietic element of the bone marrow, with lowered bodily resistance and necrosis in various parts. The etiology and pathogenesis are not explained, but from the similarity of all cases so far reported, one must regard it as a clinical entity."

Moore and Wieder, (83) in 1925, reported a case of a woman, aged 42, who recovered from a first attack but died of an attack two years later. From their observations of this case, these authors stated as to the etiology of the condition: "nothing definite has been found; it seems that an infectious toxin having an affinity for, and spending its force on, the neutrophil producing structure of the bone marrow is the important factor in causing the disease".

Zadek, (133) in 1925, concluded from the atypical cases of agranulocytosis, that it was not an independent disease, but only "an abnormal type of reaction". Piette, (91) in 1925, after histological examination of the liver, spleen, kidney, stomach, suprarenal and ovary from Skiles' (114) Case, concluded: "As far as the unfortunately incomplete microscopic examination permits me to form an opinion, the following is suggested as the possible pathogenesis: The lesions were due to bacterial emboli and were but secondary lesions as a consequence of the septicopyemia. Bacilli enter the human organism by some unknown route, rapidly destroying all the polymorphonuclear leukocytes; then they multiply and give rise to numerous embolisms throughout the body, meeting with no opposition or reaction. Only the reticulo-endothelial system of the spleen and to a lesser degree of the liver, which show progressive changes, make any attempt to combat the invader. The lymphocytes which are immune to the destructive virus are unable to entirely defend the body. Some elimination occurs through the kidneys, where the bacilli are most abundant and where they are found in large numbers within the excretory ducts." Piette (91) was unable to obtain positive blood cultures and thus "identify the causal organism". He said: "if they belong to the *Bacillus pyocyaneus* species they must possess some peculiarities in their biologic properties."

Pelnar (88) described a case of acute leukemia, in 1924, with a low leukocyte count (dropping from 4,750 to 1,070) and a low percentage of neutrophils. He felt that the low neutrophil counts seemed to be especially malignant when combined with low absolute counts. He did not feel, however, that agranulocytosis deserved separation as a different entity but grouped all the septic or leukemic conditions with this syndrome under the name, "malignant leukopenia". Feer (33) noted leukocyte counts below 3,000 in 186 of 29, 498 patients (0.63 per cent), among them 13 patients with counts below 1,000. All of the 13 died shortly afterward, with the exception of one woman with Banti's disease. Feer believed that agranulocytosis was only one type of sepsis.

Blanton, (6) in 1923, observed a 60 year old man with an unexplained temperature of 101, a slightly red and sore throat, and marked prostration. There were no definite localizing symptoms or signs. The leukocyte count was 1,340 with an entire absence of polymorphonuclears. Ten days later fluctuation was noted at the side of the neck and pus laden with hemolytic staphylococci was evacuated. Although multiple abscesses developed, the patient eventually recovered, and the blood picture changed to normal. Blanton concluded: "This might be cited as an illustration of an extreme leucolysis due to specificity of a bacterial

poison for white cells in the blood stream and bone marrow." In 1927, Hart (45) reported two cases of agranulocytosis occurring in sisters, ages 32 and 42. Blood cultures gave a pure growth of Friedlander's bacillus. The author believed that these cases were real septicemias and that the low blood count was merely indicative of an overwhelming infection. Linthicum, (75) in 1927, wrote: "agranulocytosis may be associated with a stomatitis caused by any of the pyogenic organisms". He believed, however, that there was a definite clinical entity, somewhat similar, which was always fatal and caused by the *Bacillus pyocyaneus*; thus he gave it the name "pyocyanic stomatitis with agranulocytic leukopenia".

Sachs, (106) writing in the Nebraska State Medical Journal in 1928, said that agranulocytosis was "probably not a disease entity but the failure of the bone marrow to respond to a severe infection of unknown etiology". He believed that the condition was not especially rare and that in all probability it was being mis-diagnosed as streptococcic sore throat. He was also of the opinion that agranulocytosis was very similar to a milder group of cases called "infectious mononucleosis" and that in all probability both were due to the same etiological factor. Stillman, (118) in 1928, expressed the belief that agranulocytosis was probably related to monocytic angina and

glandular fever, and that it might represent the severe form of these conditions. He thought that the condition was a special form of reaction on the part of the hemato-poietic system to infection, rather than the result of the activity of a special infective agent. He concluded: "Agranulocytosis is probably due to the activity of some external stimulus operating in individuals exhibiting a constitutional predisposition" and "This external stimulus is most frequently some form of infection, and conditions are such that even the *Bacillus pyocyaneus* may at times play a significant part in the etiology".

In 1928, Heuper (49) made an extensive review of the subject and concluded that the majority of workers up to that time were of the opinion that the condition was an infectious disease and represented a septicemia with an atypical reaction of the hematopoietic system due either to bacteria with a special affinity and toxicity to the granulocytic system or to an atrophy or hypoplasia of this organ because of the presence of a septic infection. According to his study, the investigators in the field believed that the bacterial causes were either specific or non-specific. Dayton, (23) in the same year concluded that absence or reduction of granular cells might be caused by a variety of toxic agents including bacterial invasion. Rose and Houser, (102) stated in 1929; "The available

evidence does not justify a conception of so-called agranulocytosis or agranulocytic angina as a specific disease entity. On the contrary, the known facts concerning the reported cases would indicate that the picture produced is the result of non-specific reaction to an infection of unusual absolute or relative virulence, and that a variety of infecting organisms may possibly play a part in its production."

Meyer and Rosenberg, (80) in 1930, would not believe that the condition was a disease entity and were "inclined to view it as a terminal reaction in a subject who had had a previous debilitating disease or overwhelming infection". Dameshek and Ingall, (19) in their review of 200 cases in 1931, found that most authors believed that the blood picture was due to a marked effect on the myeloid cells by a septic or toxic process the nature of which was unknown. They stated that Stocke concluded that there are imperceptible transitions from pure or typical agranulocytosis to the usual course of sepsis with rather an unusual type of leukopenia, and that agranulocytosis was not a special disease, but an abnormal reaction to sepsis.

With the prevalent belief that agranulocytosis was caused by an infection or septic process, it is not surprising to find the reports of many men describing their

attempts to reproduce the disease by injecting into animals organisms isolated from lesions, from the bone marrow and from the blood stream of patients suffering or dead from the disease. Lovett's (76) work, in 1924, of injecting Pyocyanæous bacilli into guinea-pigs and causing a reduction of the leukocytes was the first work of this type attempted. In 1928, Dasse (21) reported a case in which throat cultures gave an almost pure culture of Bacillus pyocyaneus. He made injections of living cultures of this organism subcutaneously into guinea-pigs and produced a slight reduction in the white blood count and "always a relative reduction of the granulocytes from 68 to 30 per cent". Kracke, (66) in 1932, expressed doubt in the results of Lovett's experiments. He felt that the granulopenia she produced was not below that which can often be observed in normal guinea-pigs. He isolated the Bacillus pyocyaneus from the blood stream in a patient dying from agranulocytosis but was not able to "disturb the blood picture" in rats and guinea-pigs with the bacteria. He said to his knowledge that "no one has been able to". "However," he added, "This does not mean that it should be ruled out as a possible causative factor." Kracke tried various organisms with no success and believed others had all failed. He stated that his results and those of others were "further

evidence that some other type of toxic agent depresses the bone marrow, resulting in an overwhelming infection by any or every organism that happens to be residing in the gastrointestinal tract". He did not attach etiological importance to pathogenic spirillum, which had been thought a factor in the disease due to the fact that a large number of reported cases had a history of being treated for Vincent's angina, but dismissed this point by saying that the mouth infection occurs because of a lowered cellular resistance of chronic granulopenia, or because of an unrecognized attack of acute granulopenia. Kracke has been unable to discover and spirillum in autopsy or biopsy studies under dark field.

Fried and Dameshek, (38) in their experimental work of producing neutropenia, infected rabbits with *Salmonella suispestifer* by way of the blood stream. By injecting small doses or overwhelming doses they could produce two types: 1. Cases in which the animals recovered; 2. fulminating cases ending fatally. The blood picture showed leukopenia and neutropenia. In the cases in which recovery occurred the bone marrow showed areas of necrosis with patches of proliferation. In the fulminating cases there was but little evidence of myeloid proliferation. These workers concluded: "The results have shown that there are close similarities between the agranulocytosis resulting from

Hematogenous infection of rabbits with *Salmonella* suispestifer and that observed in cases of agranulocytic angina in man."

Dennis (24) approached the problem from a slightly different angle in a group of experiments carried out to test the hypothesis that leucocidin producing organisms (*Staphylococcus aureus*, *Streptococcus hemolyticus*, *Streptococcus viridans*, and *Pseudomonas aeruginosa*) restrained from active invasion of the tissues, but so situated that their diffusible toxic products could be absorbed, were capable of producing granulopenia. The experiments were performed by inserting a "diffusion capsule", containing a serum broth culture of the organism to be studied, into the peritoneal cavity of a rabbit. In this way, he hoped to prevent any local tissue reactions to the organisms but hoped to cause an absorption of their toxic products. He found that *Staphylococcus aureus*, *Streptococcus hemolyticus* and a species of *Proteus* each produced a "more or less chronic granulocytopenia" which terminated with a fatal infection by a different bacterial species. *Streptococcus viridans* showed surprising virulence, producing an acute leukopenia within a few hours. Dennis believed that the picture produced in rabbits by *Streptococcus viridans* toxin was "analogous with that of acute agranulocytosis in man".

His concept of the usual origin of the 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 quantities and toxicity it injures the granulopoietic elements of the bone marrow." He thus suggested that agranulocytosis in man is due to the action of leucocidin, rather than to a specific microorganism. This work was not confirmed by Meyer and Thewlis (81), however, who attempted also to show that encapsulated pyogenic bacteria, acting as a focus, produce granulopenia. They used the same procedure that Dennis used and did produce an acute leukopenia and death of a rabbit in 40 hours but they found no "significant decrease in the per centage of neutrophils in the blood".

Harris and Schattenberg (44) in 1935, studied the effect on experimental animals of the subcutaneous, intraperitoneal and intracardiac injection of *B. enteritidis*, *B. welchi*, and *Streptococcus hemolyticus* and the toxic products derived from these bacteria. The toxic material was prepared from the exudate obtained from guinea-pigs with fatal peritonitis which was induced by these organisms and was then passed through a Berkefeld or Seitz-Wertz filter. When this filtrate

was injected parenterally into guinea-pigs, "granulopenia was induced". These workers concluded that there was some doubt as to whether the condition they produced was a true reproduction of the human disease, and also that their experiments indicated to them that agranulocytosis was due to varied causes. In 1936, Isaacs and his co-workers (51) stated "Despite various attempts it cannot be said that it is possible to produce true agranulocytosis in animals. This is not surprising if it is agreed that the condition occurs only in certain persons who are susceptible.

The idea that agranulocytosis was caused by a septic agent ~~was~~ met with considerable criticisms from many of the men interested in the subject who felt that the septic aspects of the condition were only secondary and not of importance etiologically. Vos and Staal (126) in reporting a case concluded that agranulocytosis was due to a lesion involving, exclusively, the leukopoietic function of the bone marrow and that the "gangrene and sepsis are secondary and the role of the tonsils is without importance in the etiology". Werner Schultz (109) in 1927, in reporting a case of "atypical tonsillitis" which he believed was actually agranulocytosis, stated that the tonsillitis appeared late which "speaks for the theory that the tonsil is only a point of

localization of the disease, not the portal of entrance". Hueper stated, in 1928, (49) that the demonstration of bacteria in the blood of patients with agranulocytosis "is not proof of the infectious character of the disease because bacteria are also frequently found in later stages of leukemias and their presence is due to invasion of the body through the areas of necrosis". Also in 1928, Dayton (23) stated "The necrotic condition of the mouth and throat and other mucous membranes is secondary to the agranulocytosis and due to the absence of the defensive posers of the leukocytes, since it is commonly found when this condition is present, regardless of the nature of the causative agent." Rosenthal (103) concluded in his observations, in 1930, that the septic manifestations "are of a secondary nature and produce pathological lesions which are common to septic conditions without the inflammatory reaction".

It remained for Roberts and Kracke (99) in 1930 to offer definite clinical proof that the septic manifestations were of secondary importance in the disease. They reported in that year a case of a 72 year old woman who survived a first attack of agranulocytosis. Following her recovery she was confined to the hospital for observation. Daily blood counts were made although she was clinically well. Two months following her first attack it was noticed that there was a sudden drop in the leu-

kocyte count and that the polymorphonuclears entirely disappeared. The patient was clinically well even then, but on the fourth day following the first change in the blood picture she became acutely ill with typical symptoms and signs of agranulocytosis and died three days later. From their observation of this case Roberts and Kracke offered the following as an explanation of the mechanism involved in the production of the disease:

"The bone marrow before the clinical onset had ceased to manufacture granulocytes. The marrow evidently passes through a period of dysfunction to complete afunction in a case presenting total absence of the polymorphonuclears. But the primary lesion, the primary dysfunction, the primary afunction is in the myelocytic division of the marrow even before the clinical onset. The disease exists in the bone marrow before it appears in the blood stream and in the blood stream before it appears clinically." In 1931, Kracke (65) made similar observations in a case of a 44 year old woman who had recurrent acute attacks of agranulocytosis interspersed with prolonged periods of chronic granulopenia. By recorded blood counts during the periods of chronic granulopenia he again observed that the onset in the bone marrow preceded the appearance of clinical symptoms. In another paper written in 1932, Kracke (66) stated:

"I believe it can be reasonable assumed that agranulocytosis is primarily a disease of the myeloblastic tissues, followed by loss of resistance resulting in overwhelming infection." In the same paper he appeared, however, to attach some etiological importance to infection. He stated that it might be possible that the bone marrow depression was caused by "hidden or latent infection over a long period", so that when the "resistance fell to a low ebb", acute infection followed because the myelocytic tissues were "unable to meet the emergency" He felt that the number of cases he had seen following influenza after a variable length of time added support to this view. He said, "Since the infecting agent of influenza tends to produce a leukopenia, it is quite possible that the residuals of the infection produce a slow and gradual damage to the bone marrow from which it is unable to recover". In 1928, Heuper and O'Connor (50) wrote, "The infectious origin and character of the disease as asserted by numerous authors seems to us not proven. The presence of streptococci or other bacteria in the blood is not considered by us as a primary condition, but as a secondary one due to an invasion of these bacteria through the necroses in the mouth". They believed that all cases reported as agranulocytosis which developed this symptom complex following "a purulent infection and showing

evidence of suppuration, generalized hemorrhagic diathesis, secondary anemia, myelocytic reaction in the blood and bone marrow" could not be recognized as "essential" agranulocytosis but were "probably more correctly classified as septic infections with an agranulocytic symptom complex" which are also observed in many other diseases, as aleukemic leukemia, pernicious anemia, carcinosis of the bone and abdominal lymphogranulomatosis.

The case reported by Rutledge and his co-workers (105) of a patient showing periodic neutropenia tends to eliminate the hypothesis that agranulocytosis is due to a septic process acting on the myeloid tissue. Their case was one in which cyclic, agranulocytic angina associated with fever and constitutional symptoms, but without anemia, began at the age of two and one-half years and recurred at intervals of approximately three weeks, during the entire life of a man 20 years of age. This case is apparently unique in medical literature. This is the same case reported by Leale (72) in 1910 as "Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture" and was described earlier in this paper in the History. Case number three in Doan's (65) series also showed a periodic recurrence.

Hyperergic Inflammation.--A few authors believe that agranulocytosis may be a form of hyperergic inflammation (allergy) in which the bone marrow is the point of least

resistance. Schilling (107) has produced a blood picture similar to agranulocytosis experimentally in anaphylaxis so that he thinks it may be an anaphylactic condition instead of an individual disease. In a review of agranulocytosis in 1931, Pepper (89) stated: "Studying the cases I have seen for some common factor, I have been struck by the presence of allergy in each. This may, of course, be a mere coincidence, but this is unlikely for allergy occurs in only ten per cent of the race. I am sufficiently impressed by the evidence to suggest that agranulocytic angina may have allergy as the background." In 1929, Bromberg and Murphy observed a fatal case of agranulocytosis following prophylactic typhoid vaccination. They stated that the abnormal reaction of the hematopoietic system occurred so directly after the injections that it suggested that they "may have been the toxic agent that incited the clinical manifestations" of agranulocytosis. Kracke (65) reported a case in 1931 in which a woman failed to recover from the final dose of typhoid vaccine inoculation. She remained in bed with daily fever and extreme weakness for thirty days, culminating in three attacks of agranulocytosis. Kracke said: "The question of typhoid prophylaxis as a whole or partial cause of the condition must be considered." Beck (3) brought out the fact that inactivated typhoid bacilli have a marked chemotactic effect

on the bone marrow. She stated that a few of the cases had shown eosinophilia in further support of the theory of anaphylaxis, but she added that these cases may have resulted from an overwhelming reaction to foreign protein in a sensitive subject.

Congenital and Familial Bone Marrow Inadequacy.-- A familial tendency to diseases of the hematopoietic tissues of one type or another presents another possibility in the etiology of agranulocytosis. Hart (45), in 1927, suggested a familial tendency when he observed agranulocytosis in two sisters age 32 and 42. Harkins (43) reviewed 150 cases from the literature, in 1931, and made this statement: "One element in agranulocytic angina may be a constitutional defect of the bone marrow." Rosenthal (103), in 1930, from the fifteen cases he had observed and the others he had reviewed, concluded that he was inclined to the idea that agranulocytosis was a clinical entity, "related in some instances to a constitutional hypoplasia of the leukopoietic system; in other cases it may be a result of transitory hypoplasia". Beck (3) stated that congenital granulopoietic insufficiency seemed to have been proved in some cases, but that the granulopoietic tissue in most of these patients had, so far as was known, functioned normally for many years. The cyclic and recurring nature, mentioned previously, of some of the cases is hard to explain on the basis of a con-

genital lesion. Blumer (8) dismissed the possibility of a congenital anomaly with the following statement: "The same patient has reacted with the usual leukocytosis and granulocytosis to one attack of an infection and has shown a neutropenic and leukopenic reaction to another attack." Beck (3) concluded: "Whether certain patients have a constitutional and abnormal functionally limited bone marrow for making blood is as yet a theoretical question."

Endocrine Disturbances.-- The possible etiological importance of an endocrine disturbance in agranulocytosis was suggested by Thompson (124) in 1934. This author made a study of forty cases of the disease and found that in seventeen out of eighteen women, the onset of the subjective symptoms of agranulocytosis occurred within one or two days of the menstrual period. In six of those patients, one or more recurrences were seen, each appearing at the same time as catamenia. Two patients who had had attacks previously were followed with blood counts through a menstrual period and a definite neutropenia occurred without subjective symptoms a few days before catamenia. Thus, it seemed possible to Thompson that in some cases of agranulocytosis, there was a relationship between the hormones associated with menstruation and the neutropenic episodes. In the same year, Jackson (57) and his co-workers reported the case of a woman, age 30, who had four typical attacks of agranulocytosis in

two preceding years. Her relapses had occurred in each case with the onset of each menstrual period. Close observation of the blood picture revealed that with the onset of each menstrual period, the total number of polymorphonuclear neutrophils fell precipitantly, only to rise again to approximately the previous level. With each catamenia the fall in the count became greater and subsequent recovery less satisfactory. The authors felt that there was a definite "temporal relationship" between the menstrual cycle and the intensity of the leukopenia. It is interesting to note that a different possible endocrine relationship was observed by Corey and Britton, in 1932, (17) in their study of the blood cellular changes in adrenal insufficiency. They found that an agranulopenic syndrome was produced in adrenalectomized cats. Hubble (48) suggested that glandular dysfunction may play a role in producing the disease and stated that bone marrow depression might be caused by a pituitary insufficiency or granulopenia by cortical dysfunction. Baldrige and Needles (2) were also of the opinion that endocrine disturbance might possibly have a causal relationship to agranulocytosis. Generally speaking, however, the great volume of medical literature on this disease produces little evidence that endocrines are of primary importance in the etiology.

Etiologic Importance of Drug Therapy.--- Chemical poisoning of the hematopoietic system is well known, but usually

drugs do not have an affinity for just the granulopoietic tissue. Farley (32) reviewed from the literature, in 1930, thirty-nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and agranulocytosis, depending on whether the principal effect was on the granulopoietic, megakaryopoietic or erythropoietic tissues, or on all of these combined. In 1931, R. R. Kracke (65) made the first observation of the possible relationship between agranulocytosis and drugs containing the benzene ring. He reported the case of a 44 year old woman who gave a history of using large amounts of coal tar derivatives during the previous three years. He said: "Since it is known that benzene is a powerful leukocyte depressant, and that coal tar derivatives are for the most part altered benzene rings, the possible association should be considered." He added, significantly, that coal tar derivatives have had their widest usage since the world war. Dodd and Wilkinson (29) showed, in 1928, that arsenicals would depress the leukocyte count. Talley and Griffith (122), in 1930, reported one of the few cases of agranulocytosis that have been reported in negroes as following arsphenamine. Kracke, (66), in 1932, admitted that arsenical preparations should be considered as possible etiological factors until

definitely ruled out. He stated that Benzene, however, was the only chemical that has been shown for many years to be capable of producing a marked depression of the leukocyte count to the point of complete agranulocytosis. He stated; "Therefore it is the outstanding agent that should be considered as causative of agranulocytosis."

(66)
Kracke/⁽⁶⁶⁾found that one of the first observations of the toxic effect of benzene on the myeloblastic tissues was that of Selling, in 1910, who observed three young girls who had been working in a rubber factory where they had been exposed to benzene fumes and then entered Johns Hopkins Hospital with a clinical picture similar to agranulocytosis complicated by purpura and hemorrhages. Two of these patients died and the bone marrow was found to be hypoplastic. The interesting features of these cases were the early chronicity of symptoms, followed by sudden loss of neutrophils and rapid death. One of the patients had long before quit her work, which could be interpreted as illustrative of the cumulative and delayed effect of the chemicals on the hematopoietic tissues. Selling (112) followed this observation by experimental studies on rabbits. He injected benzene subcutaneously in rabbits and succeeded in producing a leukopenia down to 200 cells per cubic millimeter. He concluded that benzene destroyed white cells of the cir-

culating blood and "parenchymal cells of the hemato-poietic system", but that the circulating erythrocytes were little affected. Winternitz and Hirschfelder (130) showed that a pneumonic exudate in benzene treated rabbits contained erythrocytes, fibrin, and endothelial cells but not neutrophiles. Hektoen in 1916, (46) concluded that resistance of benzene treated animals was decreased by loss of neutrophiles, "Reduction in antibodies and reduction in phagocytic activity of leukocytes present". His experiments appeared to bear this out. Weiskotten and his associates, (129) in their experiments to determine the normal life span of the neutrophile in a rabbit, did a great amount of work on the action of benzene in the animal organism. They showed that benzene produced an aplasia of the myelocytic tissues, a marked granulopenia, and that the life span of the rabbit neutrophile was about four days. From these reports it seems that the ability of benzene to produce a reduction of neutrophiles with resulting death has been well demonstrated in both man and experimental animals.

There are those, however, who believe that the picture presented by benzene poisoning and that presented by agranulocytosis is not the same. Beck (3) states that benzene usually does not produce typical agranulocytosis, but a depression of all the bone marrow elements,

so that anemias, purpura and sometimes methemoglobinemia, as well as leukopenia and neutropenia, are produced. However, Kracke, (66) was of the opinion that the chief action of benzene was on the myeloblast tissues, and that it could be administered in such dosage to produce marked granulopenia with no apparent effects on either the erythrocytes or platelets. Therefore, in 1932, he conducted a group of experiments to prove his point, with the following conclusions: (1) Subcutaneous injections of benzene and olive oil, if given in sufficient small doses, so as not to affect the erythroblastic tissues, resulted in the development of clinical agranulocytosis. The smaller the dose, the more selective became the affinity for the myelocytic tissues. (2) The intravenous injection of benzene even in small doses resulted in the immediate death of the animal, "so it is probable that oxidation products of benzene are directly responsible for its leukocyte depressing properties". A marked leukopenia was produced by the subcutaneous injection of ortho-oxybenzoic acid and by the intravenous injection of hydro-quinone. (oxidation products.) (3) He was unable to depress the leukocyte count in animals with: aminophrine, phenacetine, peragla, dial, resorcinol, pyrocatechin, orthocresol, metacresol, paracresol, phenol, para-oxybenzoic acid, meta-oxybenzoic acid, or 50 per cent alcohol. Following these experiments,

Kracke concluded: "The etiology of agranulocytosis is unknown but the benzene ring must be strongly considered." In the same paper, he reported that eight of the nine patients with agranulocytosis that he had seen had taken drugs of the coal tar series prior to the onset of their illness. Following this report by Kracke, interest in agranulocytosis soon began to center about the role of certain drugs as etiologic factors in the causation of the disease.

In October of 1935, Madison and Squier (77) reported before the Central Society of Clinical Research that "the increased incidence of primary granulocytopenia has paralleled the increase in use of drugs containing a barbiturate combined with amidopyrine". In a later article, (78) these same authors reported that in 1931 they observed a case which suddenly took a turn to the worse with abrupt decrease in granulocytes. They found that the patient had been given a sedative dose of a barbituric acid derivative on the preceding evening. The drug was withdrawn and not repeated and the patient recovered. They later discovered that immediately before the onset of the illness, the patient had taken allonal (allyisopropyl barbituric acid with amidopyrine) and for some time previously had been in the habit of taking that drug frequently. Soon after they saw a woman who had had acute cholecystitis and was treated by rest, diet, and two allonal tablets each nite for a period of two weeks. At the end of that time blood examination revealed the presence of only 1,200 white blood cells

with a complete absence of granulocytes. It was these two cases that so emphasized in the minds of Madison and Squier the importance of drugs in this disease that they studied the relationship in all cases seen subsequently. Since these two cases, these authors reported, in 1934, that they had treated twelve more. In each of the fourteen cases there was a definite history of the taking of amidopyrine in combination with a barbiturate, amidopyrine alone, or in one instance in combination with other drugs, immediately prior to the clinical discovery of the agranulocytosis. Amidopyrine with a barbiturate had been used in seven of the cases, amidopyrine alone in six, and amidopyrine in combination with other drugs in one. They stated: "The mortality in a group of six patients who continued the use of drugs containing amidopyrine was one hundred per cent. In a group of eight patients who did not continue the use of these drugs, only two died, and both of these in the initial attack." To obtain further evidence of the ability of these drugs to depress the granulocytic tissue, drugs suspected of etiologic relationship were given to each of two patients who had clinically recovered from acute agranulocytosis. The first patient, a man aged 40, who eighteen months previously had had his initial attack following the use of allonal and who had had a normal granulocyte count for ten months, was given five grains of amidopyrine. In

three hours he had a chill with return of symptoms of the acute illness and in twelve hours the granulocytes had almost completely disappeared from the peripheral blood. The second patient, a woman, responded with similar results after the administration of amytal and amidopyrine. Amytal alone was tried in the latter case but failed to produce the effect. Unaware of Kracke's (66) experiments with these drugs on rabbits, Madison and Squier (78) attempted similar ones. One rabbit was given allonal by mouth in relatively large doses. There was an abrupt drop in granulocytes and the rabbit died on the thirtieth day. Preceding death there was complete absence of granulocytes in the peripheral blood. Seventeen other rabbits were given allonal or amidopyrine, but they failed to show any marked change in the blood picture. These authors, therefore, concluded: "We believe that amidopyrine alone or in combination with a barbituric acid is capable of producing primary granulocytopenia in certain individuals who have developed sensitivity to the drug. We believe that the appearance of primary granulocytopenia following the use of such drugs may be the result of an allergic or anaphylactoid drug reaction."

In 1934, Kracke and Parker (68) stated that they found agranulocytosis was more prevalent among physicians and their relatives, nurses, hospital employees, and

members of allied professions, than in any other group in the United States. The fact that such drugs as amidopyrine was especially available to this group seemed especially significant to these writers. In the same paper, they presented eleven cases in which the patients were addicted to the use of prescriptions or tablets containing amidopyrine (peralga tablets), phenacetine, acetanilid, aspirin, caffeine, empirin compound, allonal, or pyramidon. Rawls, (95) in 1934, stated that amidopyrine had been used extensively in the arthritis clinic of the New York Polyclinic Medical School and Hospital. Two patients in this clinic developed neutropenia while taking the drug. One case was fatal. The other patient returned to normal nine days after amidopyrine was omitted, without any other form of treatment. After a period of rest the drug was resumed and the neutropenia recurred. This time pentnucleotide therapy and omission of the amidopyrine brought the blood to normal in eight days.

Watkins (128), at the Mayo Clinic, reported 32 cases of agranulocytosis. Twenty-four of his patients had taken amidopyrine or barbital derivatives. Watkins concluded: "I do not feel that these cases prove that amidopyrine, or derivatives of barbituric acid are etiologic factors in producing agranulocytosis, but I do believe that there is a possibility that certain individuals have an idiosyncrasy

to the drugs, which is manifested by agranulocytosis. Randall (94) reported in 1934 the case of a twenty-five year old woman house physician who developed an acute and alarming leukopenia following the use of barbiturates and amidopyrine "may therefore occur only in those individuals who are unusually susceptible to the benzene chain." Hoffman and his associates (47) reported that in twelve of their fourteen cases of agranulocytosis a history was obtained of the taking of some form of amidopyrine. Thirteen of their cases were fatal. They explained that the common factor in amidopyrine, benzene, arsphenamine, dinitrophenol, orthoxybenzoic acid, and hydroquinone, "all of which have produced neutropenia experimentally or clinically," is the benzene ring. "Whether", they wrote, "The latter is the actual toxic agent in the production of neutropenia needs further experimentation. Our work points to amidopyrine as having a definite effect on myeloblastic tissue similar in man and rabbits." They gave rabbits doses of amidopyrine, 0.2 to 0.9 grams per kilogram, by mouth. An almost immediate leukocytosis occurred which was followed by a depression of the white cell count. In some of the rabbits the polymorphonuclears were as low as eight per cent and in all they were twenty per cent or under.

The fact that a person ingests a certain drug immediately

before the onset of a disease is suggestive but not conclusive evidence that it is the cause of the condition. The strongest evidence of this view, however, lies in such cases as those reported by Madison and Squier (78), Sturgis and Isaacs (120), and Plum (92) who produced leukopenia in patients who had recovered from agranulocytosis promptly after small doses of amidopyrine were administered.

The relationship between amidopyrine and agranulocytosis has been studied by the Council on Pharmacy and Chemistry of the American Medical Association (98) with the conclusion that "as far as can be learned from the evidence at hand there can be no question that amidopyrine is very important in the production of granulocytopenia. It appears that barbiturates alone have little or nothing to do with the condition." They advised, "The indiscriminate and unnecessary administration of amidopyrine, and the self administration by the public is certainly dangerous and should be discouraged." Plum (92) reviewed comprehensively the relation of amidopyrine to agranulocytosis and stated, in 1935, that in a year and one-half 128 cases had been reported in which the disease developed after therapeutic doses of amidopyrine. Sturgis (121) emphasized that this drug is not the sole cause of the condition and Jackson (56), in 1934, reported a whole series of cases in which there was definitely no history of such therapy. Of

course it is possible that in some of the cases in which the patient reported that he had not taken amidopyrine as such, he may have taken it in combination with a barbiturate or some other drug under a trade name.

Kracke and Parker (69) wrote in 1935 a very comprehensive article on the etiology of agranulocytosis and concluded that a great deal of evidence had been accumulated which indicated that the administration aminopyrine alone or in combination with one of the barbiturates was responsible for the disease in a large number of patients. They emphasized that it is almost impossible to obtain an accurate history as to the ingestion of drugs after a patient is dead. They cited examples which illustrate how difficult it may be to secure a reliable history even from a living patient and concluded that a "negative drug history is a worthless one."

In his paper in 1935, Gordon (41) was not in accord with the more prevalent view that aminopyrine was an important factor in the production of agranulocytosis. After questioning 59 patients, he concluded that in only one case could any therapeutic agent have related to the etiology of the disease. In his opinion a number of factors may be responsible for the disease, but he considered that its absolute etiology still had not been recorded in the literature. Jackson (54), in 1935, wrote that aminopyrine

had an important etiologic significance in some cases, but he expressed the opinion that conclusive evidence had not demonstrated that it was the sole or even the major cause of the disease. In urging that caution be used in accepting this drug as an important cause of the agranulocytic state, he stated, in regard to its etiologic relationship to the disease, that some patients recover even though the aminopyrine therapy is continued; and that in other patients there was no evidence to indicate that the drug was taken prior to the attack. He has observed patients who took aminopyrine and became ill with the disease, but despite the fact that the drug was discontinued one or more relapses occurred. In other patients, in whom the attack was precipitated by aminopyrine, there had been no evidence that after recovery they continued to be sensitive to it. He stated that it had been suggested that the incidence of the disease was becoming less, and that this had been attributed to the withdrawal of the drug from the market, and yet he found that the sales of aminopyrine had actually increased in the six months prior to the time his paper was written.

Squier and Madison's (116) article, in 1935, presented observation on two patients which showed the effect on the granulocytes in the peripheral blood of ten grains of amytal compound (amytal with aminopyrine), five grains of aminopyrine alone, and the application of a ten per

cent solution of the latter drug to the unbroken skin. A significant granulopenia developed following the administration of the foregoing drugs, but there was no important change in the white blood cell count when amytal alone was given. They concluded that the cause of the disease was an "allergic response to certain drugs" rather than a "heightened pharmacologic or physiologic response." Kastlin (63) has made the observation that there must be a variability of susceptibility in "sensitive" persons if aminopyrine plays an important etiologic role in this disease. He reported the case of a patient who had taken this drug for years on account of insomnia. A marked granulopenia developed (800 white blood cells per cubic millimeter), but recovery followed despite the daily administration of amytal and aminopyrine and of an allylisopropyl barbituric acid with aminopyrine. The granulopenia recurred, however, and the drugs were withheld. After a temporary recovery the disease again progressed and terminated fatally.

Limarzi and Murphy (73) reported a case, in 1935, of a young woman, age 24, who had four recurring attacks of agranulocytosis over a period of about two and one-half years. She had taken from fifteen to twenty grains of aminopyrine, with or without acetylsalicylic acid, each

week for the previous four years and yet showed no clinical evidence of agranulocytosis in the interim between the attacks. Furthermore, during the last attack, at which time the leukocyte count fell to 1700 per cubic millimeter, with twelve per cent polymorphonuclear neutrophils, a total of 370 grains of aminopyrine was given. Despite this, the blood returned to normal, and the patient made a complete recovery. On the basis of this case, these writers believe a patient "may become specifically susceptible from which a selective toxic action on the bone marrow may arise." They made a skin patch test in this case, but it was found to be negative.

Stenn (117), in 1935, was unable to produce the disease in guinea-pigs, rabbits or monkeys when aminopyrine was given orally, subcutaneously, intraperitoneally and intravenously. He also was unable to produce the disease when the drug was injected into animals in which an attempt had been made to sensitize them to it. He used a total of 120 animals in his experiments and concluded that there was no evidence that agranulocytosis could be produced in animals by aminopyrine under the following circumstances: (1) When there was severe anemia as a result of bleeding; (2) after the "bone marrow had been previously injured by the administration of benzene and olive oil"; after the

animals had been infected for one month with *Bacillus subtilis*, *Streptococcus viridans*, and *Salmonella suis-pestifer*, and (4) after a complete fast of five days. Similarly, Kunde and his co-workers, (70) in the same year, were unable to diminish the number leukocytes in the circulating blood of normal rabbits by the administration of Cibalgine (aminopyrine and diallyl malonyl urea) orally in large doses for seventeen consecutive days. They also studied the effect of this drug on rabbits with "sniffles" or a "certain gastro-intestinal infection" in which there is normally a marked leukocytosis. This leukocytosis was not depressed by administration of the drug for seventeen to thirty days. Smith and Mack (115) likewise were unable to produce agranulocytosis although they did produce some degree of leukopenia in experimental animals. Working on the hypothesis that a deficient diet plus the toxic effect of drugs was of possible etiologic importance, these men tested the action of amytal and amidopyrine on the blood picture of twenty-six, sixty day old albino rats weakened by a deficient diet. They found that the white blood count was reduced approximately fifty per cent but that the differential counts showed no significant reduction of granulocytes. A control group of rats received the same deficient diet but no drugs and their blood showed no change in the white cell count.

Climenko (16) , in 1935, studied the inhibiting effect of aminopyrine, antipyrine, alpha-dinitrophenol, phenylhydrazine hydrochloride, catechol and orthoquinone on the leukocytosis which is ordinarily produced in the rabbit by the parenteral injection of nucleic acid. He found that the intramuscular injection of five milligrams of nucleic acid per kilogram of body weight produced a maximum white blood cell count of 15,000 in four hours, 34 per cent of the cells being polymorphonuclear neutrophils. After the rabbit had received 0.3 grams of aminopyrine orally for eighteen days, a similar dose of nucleic acid was given intramuscularly. No significant response was evoked in the white blood cell count. The other drugs mentioned produced similar inhibitions to leukocytosis.

The theory that aminopyrine may be responsible for agranulocytosis in certain susceptible persons has received fairly widespread acceptance. It is known, however, that many persons may take large amounts of the drug without producing the syndrome. Nor can it be said that it is the sole etiologic agent, as other drugs, such as dinitrophenol, apparently have been responsible for its production in some instances. In 1934, Hoffman and his associates (47) reported the first case of dinitrophenol causing agranulocytosis in a patient who had taken the drug for reduction purposes for a period of two weeks. She recovered. Bohn, (10) in the same year, described a case which developed in a patient after the ingestion of 21.8 grams of dinitrophenol

sodium over a period of four months. Dameshek and Gargill (18) reported two cases of agranulocytosis following the use of dinitrophenol therapy.

Although all observers are not in accord, Rawls (95) claimed, in 1936, that sufficient data have been accumulated to indicate that aminopyrine bears some causal relationship to agranulocytosis. He administered over 100,000 tablets of aminopyrine or aminopyrine mixed with magnesium carbonate to 400 patients in clinic or in private practice. In four (one per cent) of these patients agranulocytosis developed, and three died of it. Exclusive of the four patients, there were no significant changes in the white blood cell picture of 100 patients who received an average daily dose of about thirteen grains for a mean interval of approximately eighty-four days. Rawls concluded that aminopyrine does not produce hematologic changes "except in isolated cases, in which there probably is an idiosyncrasy to it."

The blood of one hundred patients with various diseases, chiefly rheumatism and infections of the upper respiratory tract, who were treated with salipyrene (combination of salicylic acid and antipyrine) was studied by Nammack and Thorsteinson. (85) They explained that antipyrine contained a benzene ring and was closely related in chemical structure to aminopyrine. Their repeated examinations of the

blood of the patients failed to show a significant change in the total white blood count or in the percentage of neutrophils, nor was there any change of importance in the Schilling count. From their experience and a review of the literature, the authors concluded: "Neutropenia in connection with drugs containing the benzene ring probably depends on individual idiosyncrasy to this type of drug."

Witts (131), in 1936, aptly stated that the evidence incriminating aminopyrine as the chief cause of agranulocytosis may be classified as circumstantial, experimental and direct. Circumstantial evidence includes the many reports in which a history of the taking of the drug prior to illness was obtained. Experimental evidence lies in the production of the disease in laboratory animals by the administration of aminopyrine. Direct evidence is found in those cases which have recovered from an attack thought due to the drug, and which another attack has been precipitated by administration of the drug. Witt mentioned in the same paper that in England the "Poisons List Confirmation Order", which went into force on May 1, 1936, makes it necessary to have a written order before aminopyrine can be supplied.

Parker and Kracke, (87) in attempting to produce the disease experimentally, cause leukopenia of "usually less than 1,000 leukocytes " in rabbits by the subcutaneous injection of benzene in olive oil and showed that these animals had a marked depletion of the biologically active or

reduced glutathione in the bonemarrow and the blood. They suggested that a depletion of this form of glutathione in human blood and bone marrow may lead to various leukopenic states.

Benjamin and Biederman (4) reported observations on the blood of a patient after the oral administration of 10 grains of Novaldin, a drug which is closely related to aminopyrine. This preparation was given to a woman who previously had had several attacks of agranulocytosis after the ingestion of aminopyrine. Eight hours after the drug was given subjective symptoms appeared and within twenty-four hours the white cell count had fallen from 5,300 to 2,800 and the polymorphonuclear neutrophil cells had been reduced from 72 to 46 per cent. Intracutaneous, patch and passive transfer tests with Novaldin gave negative results. The authors concluded that this drug may "produce the same deleterious effects as aminopyrine on the hematopoietic system". Klump (64) substantiated this view when he reported the cases of a patient in whom agranulocytosis developed after the use of Novaldin for headache. The patient expired after a fulminating illness of six days, during which time the leukocyte count fell to 150 with a complete absence of polymorphonuclears. In attempting to answer the question, "Is there a safe method for administration of aminopyrine and its derivatives?" Klump concluded, "The abrupt onset without warning and fulminating course of

this case, and others I have seen, lead inescapably to the same conclusion that there is no entirely safe method of administering aminopyrine."

Goldman and Haber (39) reviewed the literature concerning the relation between dinitrophenol and granulopenia and added the report of an additional case which they had observed. Their patient, a girl of 13 years, had taken 0.1 grams of dinitrophenol daily for forty-six days. Weakness, malaise, feverishness, sore throat and vomiting appeared and she suddenly became acutely ill and irrational. The white blood cell count was 700 with 100 per cent lymphocytes. The patient died and no changes were found in the granulopoietic system at autopsy. Goldman and Haber concluded in reference to this case: "The fatality can be attributed either to cumulative toxicity or to an idiosyncrasy to the drug."

Davis and Frissel (22), in 1937, reported that they had given aminopyrine daily to thirty-two patients for varying periods up to three months without demonstrating any alterations in the white blood cell count. They also observed patients who had used the drug for more than four years without dangerous clinical symptoms. Of fifty patients who received cutaneous tests with aminopyrine, only one, who was sensitive to the drug, reacted positively. However, these writers did report that in their series of twenty cases of agranulocytosis, ten of the patients were known

to have taken aminopyrine or allied drugs. Shapiro and Lehman (113) reported that they observed a man in whom agranulocytosis developed after he had taken cinchophen, 0.5 grams three times daily for about three weeks. They pointed out that cinchophen under "certain Conditions" may yield benzene or nitrophenol, either of which "can cause a paralyzing effect on the bone marrow". Dowds (30) reported a fatal case of agranulocytosis in a patient with syphilis. He concluded that intramuscular injections of a bismuth preparation caused the condition, and he stated specifically that aminopyrine was not a contributing factor.

Davis and Frissell (22) summarized the literature regarding aminopyrine hypersensitivity and found discussions of three theories to explain the role of aminopyrine intoxication in the production of granulocytopenia; 1. All drugs with the benzene nucleus, or the benzene nucleus in association with an amino group, are per se toxic, presumably to the bone marrow. 2. Aminopyrine is semispecific for the bone marrow and produces a direct intoxication of the leukopoietic tissue. 3. The hemopoietic changes are the result of an allergic reaction.

Sulfanilamide, the remarkable drug which has proved to be of so much value in the treatment of beta streptococcus infections, gonorrhoea, pneumonia, and other infections, is not without its dangers to the blood. These dangers include

the development of methemoglobinemia and cyanosis, acute hemolytic anemia and now agranulocytosis. (67) In a letter written April 17, 1937, Plumer (93) described the case of a woman of 54, suffering from subacute bacterial endocarditis of about five months duration. Her blood culture was positive for streptococcus viridans. She was given one gram of prontosil a day for four days, and 1.3 grams for thirty-one days, when it was discontinued because of nausea and vomiting. Three days, thereafter, the white count had fallen to 400, with no neutrophils; it rose the next day to 1600, but extensive gangrenous infection of the mouth and pharynx had already developed and death occurred on that day. As no other drugs were administered and no history could be obtained that she had taken other drugs, Plumer concluded that the agranulocytosis was due to prontosil. Plumer's case is the first reported in which agranulocytosis has been attributed to sulfanilamide. Three months later, however, Young (132) reported agranulocytosis with fatal outcome in a man suffering from acute rheumatism, who had taken 3 grams of prontosil album for eighteen days. The day before death the total white count was 1800 with no neutrophils. A feature of the case was the failure of serial leukocyte counts to give warning of the impending disaster. The bone marrow showed complete aplasia at autopsy. The only benzene ring drug administered within twenty-four days of the development of agranulocytosis was sulfanilamide.

Less than a month after Young's report, Model (82) reported the case of a man of 20, suffering from a recurrence of rheumatic fever. Three grams of "proseptasine" (para-aminobenzenesulphonamide) were given for eighteen days and then discontinued. Two days later the leukocyte count was found to be 600 per cubic millimeter. In spite of blood transfusions and pentnucleotides, death occurred the following day. Model said: "Although there is no proof that the agranulocytosis was due to the sulfanilamide, this case and Young's case suggest the advisability of a daily leukocyte count in cases in which this drug is given over long periods."

Borst (11) reported a case of a woman, age 61, being treated for pyelocystitis. She received 6 tablets (300 mg. each) of prontosil flavum daily for nine days following which her urological symptoms subsided and the drug was stopped. About a week later, however, the symptoms reappeared and the drug was again prescribed in the same dosage for a period of eleven days after which the dosage was increased to 8 tablets daily. A week later the patient complained of general discomfort, difficulty in swallowing and had a temperature of 102.3. A blood count at that time showed 960 leukocytes per cubic millimeter with only one per cent polymorphonuclears. The patient died that day. Borst concluded: "There can, I think, be no doubt about the close connexion between the use of prontosil flavum and the

occurrence of agranulocytosis in this case."

Jennings and Southwell-Sander (60) observed agranulocytosis in a 39 year old woman who suffered from ulcerative colitis. Sulfanilamide, 4.5 grams per day, had been given for three weeks and discontinued because her symptoms had disappeared. Two days later evidence of agranulocytosis began and increased in severity for four days, when the total white count was less than 400, none of which were polymorphonuclear cells. Under pentonucleotide therapy, there was a rapid rise in the polymorphonuclear count and general improvement and recovery. This is the first case of agranulocytosis attributed to sulfanilamide in which recovery has occurred. Schwartz and his associates (111) in January of 1938, reported the case of a man of 32, treated for a penile ulcer with sulfanilamide over a period of twenty-one days, during which time he took a total of 56.6 grams. The typical symptoms of agranulocytosis, with a leukocyte count of 2000 and an absence of polymorphonuclear cells, developed. They attempted to stimulate leukopoiesis by an intravenous injection of killed typhoid bacilli. The temperature increased but the leukocytes continued to drop to 800 with an absence of granulocytes on the smear. The patient became increasingly toxic and died. The authors stated that they believed that sulfanilamide was the only drug that could be directly incriminated because the patient was in good general

health prior to receiving the drug and then, coincident with the intensive administration of it, granulocytopenia developed abruptly. They emphasized that sulfanilamide has a multiplicity of serious toxic properties, particularly with reference to the hemopoietic system and therefore that it should be administered only under careful observation and with frequent examinations of the blood.

Berg and Holtzman (5) reported a fatal attack of agranulocytosis in a man who took 38 grams of sulfanilamide in eleven days for acute gonorrhoea. They state: "If there is any question as to whether sulfanilamide can induce the granulocytopenic state, this third reported fatal case adds it weight to the belief that the relationship is actually causal." Jones and Miller (61) reported, in November, 1938, a case of a man who had taken sulfanilamide for eight days following which he developed a fever and generalized aching pains. Two attempts to resume therapy were followed by a return of symptoms, the last time accompanied by severe neutropenia, with a total white blood cell count of 2,300 of which only five per cent were neutrophils. The authors recorded the sulfanilamide concentration in the blood in relationship to the leukocyte count and concluded that there was apparently an "increasing susceptibility to the drug". Allen and Short described a case in July, 1938, in which an eighteen year old school girl was treated by sulfanilamide

therapy for a Bartholin's abscess, presumably due to the gonococcus. The patient made a spontaneous recovery. She had received no other drugs "which might have been indicted as possible causes of granulocytopenia, so that sulfanilamide can be considered, at least presumptively, as the cause of her agranulocytosis."

It will be noted that these cases have all been reported since April, 1937, and that the average age of the group is about 37 years and over half of the cases were in young adults, only three of which were females. In every instance rather large amounts of the sulfanilamide were administered before the disease made its appearance. Kracke (67) believes that this indicates that the mechanism of granulopoietic depression may be different from that following the administration of a single dose of aminopyrine. On the basis of his study of such cases, Kracke concluded: "Sulfanilamide should be added to the list of drugs that are capable of producing agranulocytosis." He felt that because of the increasing use of this drug there will probably be an increasing number of cases of the disease following its administration. He said: "It is reasonable to assume that the market will shortly become flooded with patented remedies containing sulfanilamide and that the dangers of agranulocytosis will become more accentuated."

In a study of the relation of drug therapy to neutro-

penic states, Kracke (67), in October, 1938, drew attention to a chart which he took from Plum's investigation of agranulocytosis in Denmark. The chart reveals that the consumption of aminopyrine in Denmark before the disease made its appearance was practically nil, and that there was a gradual increase in the use of aminopyrine paralleling the increasing number of cases of agranulocytosis, the peak being reached in 1934. At that time the use of the drug was practically abandoned, and the disease practically disappeared.

Kracke (67) has compiled a list of drugs and preparations that are known to be capable of producing agranulocytosis. They are presented in the table below:

*(A) Preparations that should be used with caution because they may depress the leukocytes.

Allonal	Amidonine	Aminol	Barb-Amid
Alphebin	Amidophen	Am-Phen-Al	Benzedo Comp.
Amarbital	Amidos	Ampydin	Cibalgine
Amidol	Amidotol Comp.	Amytal Comp.	Compral
Amido-Neonal	Amifein	Baramid	Cronal
Dymen	Gardon	Neurodyne	Phenopyrine
Dysco	Lumodrin	Nod	Pyramidon
Eumid	Midol	Optalidon	Pyraminol
Gynalgos	Mylin	Peralga	Seequit
Hexin	Neonal Comp.	Phen-amidol	Yeast-Vite

(B) Drugs Known to Produce Depression of the Marrow:

Dinitrophenol	Antipyrine
Arsphenamine	Sulfanilamide
Novaldine	Sedordmid

*Preparations listed under (A) contain aminopyrine.

Endogenous Disturbances in the Bone Marrow.-- According to Beck, (3) two different processes must be considered concerning the mechanism to maintain production and destruction of granulocytes at a constant level: 1. The mechanism of delivery of cells to the circulation. 2. The mechanism of maturation. As far back as 1927, Kastlin, (62) in discussing the pathogenesis of agranulocytosis, said: "The hypoplasia of the granular cells is not a terminal event and the decrease of the cells in the blood stream appears to be due to failure of development of the cells in the bone marrow". The early writers nearly all believed that the bone marrow in these cases was always aplastic. Leon (74), who wrote one of the first papers on this subject, in 1923, stated that the bone marrow did not contain leukocytes nor myelocytes. However, Buck (14), in 1928, reported a case in which postmortem examination of the bone marrow revealed evidence of acute hematopoiesis with cells normal in number and character and even myeloid hyperplasia. Kracke (66), in 1933, reported that he had studied the bone marrow removed during life from five patients with agranulocytosis and found "an apparent cessation of activity of the myelocytic elements and in some cases the complete absence of those elements". Dameshek and Ingall (19), and Baldrige and Needles (2) were of the opinion that the bone marrow was not aplastic.

Thus the literature presented a picture of chaos as far as the pathology of the bone marrow and the pathogenesis of the disease was concerned. It remained for Fitz-Hugh and Krumbhaar (36), in 1932, to clarify the situation. They reported a case in which myelocytes and myeloblasts were found in the bone marrow at necropsy in more than normal numbers. The case was that of typical agranulocytosis, clinically, and the antemortem white blood cell count was 200, all of which were lymphocytes. Based on these findings and similar ones recorded in the literature, these writers raised objection to the then current hypothesis of "granulocytic aplasia" as constituting the primary pathologic mechanism of the disease, and in its place they proposed the hypothesis of "maturation arrest". The following year, Fitz-Hugh and Comroe (35) reported that necropsy studies had shown in more than half of the cases examined, by them, a plentiful supply in the leukopoietic centers of the progenitors of the blood leukocytes. They pointed out that this virtual hyperplasia was in marked contrast to the profound peripheral leukopenia characteristic of the disease, and "strengthens the previous suggestion of an hypothesis of primary 'maturation arrest' rather than primary 'aplasia' to account for the hematologic phenomena of the disease." Thus these writers entertained the opinion that "agranulocytic angina exists as a

valid clinicopathologic entity in the same sense that pernicious anemia is accepted". They explained that it was not many years ago that it was difficult to "defend the nosologic purity" of pernicious anemia but that it is now possible to exclude certain obscure pernicious-like anemias from the category of pernicious anemia by virtue of their failure to respond to adequate specific therapy. They concluded: "In a similar way agranulocytosis should be viewed as a disease entity which awaits the discovery of a specific therapy to stamp it with unmistakable validity." It was from these observations that the authors suggested the name "pernicious leukopenia", which suggests certain analogies between agranulocytosis and pernicious anemia.

Beck (3) stated that in typical cases of agranulocytosis there is a myeloid aplasia, and the part of the bone marrow that manufactures the granular leukocytes has ceased to function, or nearly so. She pointed out that the life of the granular cells in the blood stream in normal conditions of health is considered to be from three to five days; therefore, when manufacture of the granulocytes ceases and the supply of promyelocytes and metamyelocytes is exhausted, the granulocytes of the blood stream would totally disappear in from three to five days after the exhaustion of the supply. Beck added that there was little evidence that the granulocytes are abnormally destroyed in the blood

stream and that the bulk of all evidence pointed to the fact that the primary lesion in these cases, so far as known, was in the granulopoietic areas of the bone marrow, and that this condition preceded the clinical symptoms and local infections. Therefore, Beck was drawn to the same conclusion that was reached by Fitz-Hugh and Krumbhaar (36), relating to a "maturation factor". She said: "It seems reasonable to suppose that the primary lesion is not in the bone marrow but in the organ or tissue which gives rise to the substance (factor) that keeps maturation of the granulocytes regulated to a normal level or regulated so that destruction and production are kept constant." In the same paper, Beck (3) pointed out that the textbook descriptions of pernicious anemia could be made to apply astonishingly well to this type of agranulocytosis, the principal alteration being the substitution of the granulopoietic for the erythropoietic tissue. Beck stated: "The maturation factor for erythrocytes has been found. It now remains to find a maturation factor for granulocytes". Similarly, Gordon (41) stated: "The cause of the disease may be a deficiency of some substance that will correspond to ventriculin in pernicious anemia."

Roberts and Kracke (101) have presented a logical theory concerning the mechanism of the production of the disease, as follows; First, there is the onset in the

bone marrow with a failure of myelocytic function. This may be due to myelocytic aplasia or cessation of maturation. Second, after a few days there is an onset in the blood stream with a gradual diminution of the granulocytes until the number is greatly reduced or they completely disappear. Third, there is the clinical onset, with the appearance of the characteristic symptoms. Fourth, with a loss of protection, bacterial invasion begins and sixth, recovery or death occurs.

In his review of the present day findings and hypotheses of agranulocytosis in 1937, Thomas Fitz-Hugh (34) showed some dissatisfaction with the theory he originally introduced that a "maturation arrest" was the principal underlying factor in the pathogenesis of the disease. He stated: "The sudden changes in the granulocyte count of the peripheral blood (of 'sensitized' individuals making contact with a drug) occur too rapidly to be mediated by a 'maturation arrest' mechanism." Such sudden changes he has referred to as "granulocytoclastic phenomena". He explained that Clarke's work on the changes of the capillary endothelium might offer a possible mechanism for the sudden changes in the granulocyte count. (Clarke and Clarke (15) showed by means of a glass rabbit's ear chamber, in which they could observe the cells within the capillaries, that minute stimuli of a mechanical, thermal or chemical nature

resulted in changes of the endothelium which resulted in the adhesion of the leukocytes to the capillary wall.)

"One might hypothesize", concluded Fitz-Hugh, "Several such granulocytoclastic episodes might precede the final bone marrow arrest which in turn initiates the usual clinical syndrome."

PATHOLOGY

In the previous section attempt was made to show that in the earlier writings there was much disagreement as to the pathologic picture of the bone marrow in agranulocytosis. At the present time, however, there is quite general agreement that the bone marrow changes are variable. Boyd (12) has summed up this view as follows: "As a rule it (the marrow) is aplastic and appears to be completely exhausted, as is seen in experimental benzol poisoning. In others it is normal, and in still others it may be hyperplastic." Beck (3) stated that in practically all fatal cases the bone marrow was degenerated to a great extent, often liquid, and varied in color from red to straw. This author also stated that there may be areas of patchy necrosis in the marrow and that normoblasts and megakaryocytes were present in their normal numbers, but the myelocytes and polymorphonuclear cells were absent or nearly absent. However, in 1936, Darling, Parker and Jackson (20) made an analysis of 25 typical cases of agranulocytosis

and concluded that , as Fitz-Hugh and Krumbhaar (36) first suggested, in rapidly fatal cases the bone marrow shows stem cell hyperplasia and myeloid anakmesis, (the word they have given to maturation arrest) without notable changes in the red cell series and that as the survival of the patient became longer the cells gradually and somewhat irregularly gave way to plasma cells and lymphocytes. They hypothesized that early in the disease there is a compensatory increase of the number of normally occurring stem cells (myeloblasts) in a vain effort to overcome the maturation arrest and that in the latter stages these stem cells disappear and a coincident increase of lymphocytes and plasma cells occurs. They found that in the recovery stage there was a rapid development of the stem cells into myelocytes, metamyelocytes, and polymorphonuclear neutrophils. These changes, in the authors' opinion, substantiate the previous contention of other investigators that the condition in the bone marrow is one of arrested maturation.

There is little mention made in the literature of the pathology of agranulocytosis excepting that which refers to the changes which occur in the bone marrow. The sharply outlined necrotic lesions in the oral cavity and elsewhere, according to Ordway and Gorham, (86) are "characterized by a peculiar reactionless type of inflammation", that is, a complete absence of polymorphonuclear leukocytes, and only

a few lymphocytes and plasma cells. These authors pointed out that such necrotic ulcerations may occur in varying degree, in the mouth, esophagus, intestinal tract, vulva, vagina or skin. Beck (3) stated that it is possible that the lesions along the gastro-intestinal tract are affected by the usual bacterial inhabitants which gained entrance to the tissues as a result of the removal of the protective mechanism of the granular leukocytes.

The enlargement of the spleen in some cases has been found to be due to a great increase in the reticulo-endothelial cells, which outnumber the lymphoid cells. The lymph follicles are small and atrophic, and there are no young cells or lymphoblasts in the germinal centers, only mature lymphocytes. The liver may be somewhat enlarged and show cloudy swelling. Microscopically, some cases have shown fatty degeneration, and occasionally small multiple foci of necrosis. The submaxillary, cervical, peribronchial and mesenteric lymph nodes are in general enlarged, and they sometimes contain hemorrhages. Microscopic examination reveals atrophy of the lymph follicles; there are no young lymphocytes in the germinal centers, only mature lymphocytes being present. There is a proliferation of the reticulo-endothelial cells. (3)

SYMPTOMS, SIGNS, AND BLOOD PICTURE

The clinical symptoms, signs, and blood picture of agranulocytosis have been reviewed by many authors in the

literature, each presenting almost identical descriptions, the one phase of this condition in which there is, apparently, quite wide-spread agreement. For that reason only brief consideration will be given in this paper. Thompson's (125) description is typical; The onset of the acute case is abrupt, usually during good health. The first symptoms are fever and prostration. The temperature rises within a few hours to 104 to 105 degrees; malaise rapidly progresses to exhaustion. During the first one or two days these are often the only symptoms. A severe infection is suspected, but there is no subjective or objective evidence of localization. A diagnosis can be made at this stage only by the finding of the extreme neutropenia which has existed from the onset. Jaundice may or may not be present. The early writers stressed this finding as appearing in the majority of cases, but modern writers find that it is rare in typical cases. The end of the second day usually marks the appearance of the gangrenous lesions of the gums and throat. These begin as small discrete patches of edematous redness. They spread rapidly, the centers become ulcerated and necrotic, and they tend to coalesce into irregularly shaped areas of gangrene covered by a thick, tenacious, grayish white membrane; and surrounded by a similar raised, spreading, red margin. Similar ulcerations may appear in the rectum and vagina. As a rule there is relatively

little reaction in the neighborhood of these lesions, the contiguous lymph nodes are only slightly enlarged and are rarely tender. The spleen is not enlarged as a rule. (125) Jackson and Parker (58) stated that the finding of an enlarged spleen should indicate a leukemia instead of agranulocytosis. Kastlin (62) found the spleen palpable in 33 per cent of the cases.

Although gangrenous stomatitis is by far the most frequent lesion, the infection may appear in various other places and assume various forms. Occasionally the lungs are the site of an extensive bronchopneumonia; acute pyelitis with pyelonephritis has been seen. Several instances of gangrenous vaginitis and endometritis have been reported, as have cases of proctitis and perirectal abscess. Abscesses tend to develop during convalescence. The chronic form of the disease is characterized by a persistent leukopenia of from 2,000 to 4,000 with 25 to 50 per cent neutrophils. There is moderate malaise and weakness of a chronic type. There is no angina or ulcerations except following a period of extreme leukopenia and neutropenia when an acute attack is ushered in. (125)

The typical agranulocytic type of blood picture presents few difficulties in diagnosis. There is a marked decrease in the total number of white blood cells, the counts ranging usually from 1,000 to 3,000 per cubic millimeter; white counts as low as 150 to 300 are not at all uncommon. Examinations of the stained smear shows a great

scarcity of white blood cells. Many low-power fields may have to be examined before a single cell is found. Of the white cells that are seen, all, or nearly all, are adult, mature, small lymphocytes. A rare large lymphocyte and an occasional monocyte may be encountered. When complete agranulocytosis exists, no polymorphonuclear leukocytes are found. With the less severe degrees of depression, it is possible to find occasional granular cells, rarely more than ten per cent of the total number. The polymorphonuclear leukocytes, when found, are almost invariably adult, mature cells with a nucleus of from three to five lobes. Eosinophils are absent as are the young forms of granulocytes. (Thompson (125))

Concerning the erythrocyte count, Sturgis and his associates (121) said: "There is rarely if ever a significant degree of anemia. When this is present it usually indicates that the leukopenia is associated with some other disease." Jackson and Parker (58), however, pointed out that since the disease is most frequently found in middle-aged to older women, the finding of a moderate degree of anemia would be of no great consequence.

There is a controversial point in regard to the blood picture as far as the platelets are concerned. The majority of observers agree that the number of platelets is normal or increased. Others believe the number is

reduced. Roberts and Kracke (101) stressed that a hemorrhagic tendency was common in the disease, whereas most observers have stated this finding is rare. Schultz and Jacobowitz, (110) in 1925, emphasized the absence of hemorrhagic diathesis and thrombopenia and the practically normal erythropoiesis as strict criteria for the diagnosis of the disease. Likewise, Jackson and Parker (58) stated that cases showing reduced platelets and marked anemia are probably acute leukemia or aplastic anemia.

PROGNOSIS

In the beginning the mortality of agranulocytosis was reported as 100 per cent. The first recovery from the disease was reported by Lauter, (71) in 1924, who reported the case of a young woman with "agranulocytic tonsillitis and stomatitis". In 1927, Kastlin (62) reviewed the forth-three cases he found in the literature and discovered only three recoveries or a mortality of about 94 per cent. Harkins, (43) in 1931, found twenty-seven recoveries had been reported in the one hundred and fifty recorded cases, the approximate mortality rate being 82 per cent. Taussig and Schnoebelen (123) reviewed three hundred and twenty-eight cases and found that the mortality was 75 per cent., without special therapy and with miscellaneous forms of treatment; 63 per cent with transfusions of blood, and 53 per cent with roentgen treatment. Jackson and his co-workers, (55) in 1933, reported a mortality of 30 per cent

in fifty-four typical cases in which treatment consisted of nucleotides. From these various reports, it would seem that the mortality rate has been steadily decreasing since 1927. On the other hand, Fitz-Hugh (34), in 1937, stated that his present mortality was 75 per cent. Similarly, Ordway and Gorham, (86) in 1937, stated that the mortality was "at least 75 per cent".

Very few patients recover if the total count falls below 1000. (3) Kracke (65) reported one case which showed a leukocyte count as low as 470 and recovered, only to die in a second attack. It is possible that the apparent decrease in mortality in some reports is due to the fact that closer observations of the blood picture have caused some writers to include so-called "benign" or "chronic" forms in their statistics. Ordway and Gorham (86) have pointed out that recovery from the first attack, with death in a second or third episode, may occur. They state that in general, the outlook will depend on the kind and degree of marrow injury, the degree of secondary infection, and the general recuperative power of the bone marrow.

TREATMENT

There have been recorded many different suggestions as to the proper treatment of agranulocytosis. Most authors, however, believe that a specific and entirely satisfactory treatment has not been discovered. Many

believe that recovery, when it does take place, is spontaneous and not influenced by the type of treatment. Hamburger (42) reported a case in a patient with 1500 white cells and two per cent neutrophils. This patient recovered in four weeks without any active treatment, and was still well five years later. In many cases in which recovery occurred, several types of treatment were used, so that it is impossible to draw decisive conclusions as to the efficacy of the measures that were used, or to say which, if any, was responsible for the cure.

Treatment of Local Lesions.-- The most frequent complication of agranulocytosis is infection, local or general. The local lesions are most frequently found in the mouth and throat. All authors agree that the lesions require careful and intensive treatment. Babbit (1) stated, in 1930, that combined antiseptic and cauterizing measures should be employed. For a cauterizing measure, he prefers the use of 25 per cent trichloroacetic acid and ten per cent neo-arsphenamine. He reported recovery in the case of a patient in which the leukocytes were down to 600 with a complete absence of granulocytes. Hamburger (42) advised the following for local treatment: After nourishment, the mouth and throat are sprayed with a saturated solution of potassium chlorate. Following the spraying, each ulcerated area and the gums are swabbed with a solution

of copper sulphate, 10 grains to the ounce. This oral treatment is given as often as five times a day, and less frequently as improvement takes place. It is obvious that in the absence of granulocytes no frank abscesses will form but with the onset of recovery and the return of these cells to the blood stream such lesions are not uncommon. Any abscesses that form, of course, should have proper surgical incision and drainage. Beck (3) emphasized the importance of refraining from any surgery in these patients that can be possibly avoided. She stated that such a procedure may bring about sloughing of tissue, as healing cannot take place normally in the presence of leukopenia and neutropenia.

Miscellaneous Agents Used.-- The use of Neo-arsphenamine, intravenously, was mentioned by Moore and Wieder, (83), in 1925. Rosenthal (103), in 1930, advised the use of neo-arsphenamine and blood transfusions. His series at that time showed six recoveries in fifteen cases. However, such treatment would certainly seem paradoxical in the face of Farley's (32) finding of thirty-nine cases recorded in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. Diphtheria antitoxin, intravenous mercurochrome, iron, arsenic, streptococcus serum, typhoid vaccine and other forms of foreign protein, have all been tried without apparent success. (40)(114) Intravenous injections of gentian violet and acriflavine have been tried with

the idea that there was a blood stream infection. (3)

Roberts and Kracke, (101) in 1934, said: "Sepsis and necrosis are the great hopes of every patient with complete granulopenia". This was based on the theory that these conditions stimulated the myeloblastic activity of the marrow and thus caused leukocytosis. They believed that in cases without sepsis and necrosis that one would not be doing wrong to inject living staphylococci into the skin. They have shown that turpentine intramuscularly in a rabbit causes necrosis and leukocytosis and have used this treatment on one human case with good results. Jackson (54) condemned sepsis as a therapeutic agent as there is "no evidence that it can stimulate a paralyzed bone marrow". Strumia, (119), in 1934, pointed out that the reason for the good results reported in some cases in which X-ray therapy was used, was the destruction of a number of cells and the liberation of disintegrating products. It occurred to him that injections of leukocytes intramuscularly in cases of agranulocytosis might furnish such products of disintegration, "containing large amounts of nucleic acid salts in a form probably well tolerated and active". He therefore prepared a "leukocytic cream" from human whole blood. He said: "Clinical response and the hematologic improvement following the injections of leukocytic cream have been, on the whole, strikingly parallel, and have progressed con-

tinuously after they have begun." Blanton (6) reported a case with recovery in which he gave 50 cc. of leukocytic extract daily. Sturgis and his associates (121) stated that there was no evidence that leukocytic cream was of therapeutic value.

Splenectomy was performed in one case reported by Baldrige and Needles (2), in 1931. The patient died thirty-five days after the operation. There was not the usual rise leukocytes after the operation seen in other cases, but there was the usual platelet response. At necropsy the bone marrow showed an overgrowth of myelocytes and myeloblasts almost as marked as in myelogenous leukemia.

Marberg and Wiles, (79) in 1938, reported seven cases of agranulocytosis which were treated with yellow bone marrow concentrate per os. All of the patients recovered. Whether used alone or jointly with other medication "it usually causes a response in forty to forty-eight hours." From their clinical tests these authors have concluded that the yellow bone marrow concentrate contains a substance or substances which act to stimulate the maturation or liberation of leukocytes of the granulocyte series. They stated that their results had confirmed the fundamental clinical observations C. H. Watkins, of the Mayo Clinic, made on patients treated with whole yellow bone marrow. They added

that the concentrate they developed contained the active principles without the bulky inert neutral fats which made the whole bone marrow unpleasant for clinical use.

Blood Transfusions.-- Transfusions have been used in many of the reported cases, some of the patients recovering and others dying. There can be no definite conclusions drawn as to its efficacy because in practically all cases other measures were used along with the transfusions. There can be no great argument made in defense of transfusions as there is no convincing evidence that they will actually stimulate granulopoiesis. Certainly the number of cells would be small as compared to the amount needed. Doan (36) supplied a possible defense for the advocates of blood transfusions when he pointed out that it had been shown that he normal blood contains nucleotides and the neutrophils on disintegration yield nucleic acid. Thus in transfusion "an addition is made of the active principle". He hastened to add, however, that the concentration is very small and would probably be insufficient in severe cases of myeloid hypoplasia. Jackson (54) is "decidedly against transfusion" stating that in some instances the white blood cell count may fall following them. In spite of these facts, many men have used this form of therapy and are still using it. Such a use would seem to be essentially empirical. However, such writers as Ordway and Gorham (86), in 1937,

advised frequent small transfusions as a supportive measure, and Sturgis and his co-workers (121) stated that "multiple small transfusions of blood may be beneficial". Meyer and Rosenberg, (80) after reviewing the literature concluded that transfusions seem to give favorable results.

Irradiation of Bones.--Friedmann, in 1927 first reported the results of irradiation. At that time four of his cases showed improvement. A year later he reported two more. More recently Friedmann has reported a series of 43 cases treated exclusively by X-ray. Of these 13 were reported as cured. He selected one-twentieth of an erytherma dose as the proper dosage based on the Arndt-Schultz law that "small doses stimulate, large doses destroy." (127) From the cases in the literature it is apparent that this dosage has been quite universally accepted. Waters and Firor (127), stated that a variety of voltage factors have been used, from 130,000 to 200,000 volts. In 1931, these authors reported the cases of five patients treated with roentgen rays; four were still living and the other was moribund when first seen. Their technic was as follows: The lower extremities, the pelvis, the upper part of the humeri, and the shoulder girdles were irradiated in the course of three

or four treatments. Voltage values of 200,000 with aluminum and copper filtration, both separately and combined, with effective wave lengths ranging from 0.197 to 0.161 angstrom units, were used. The measurement of dosage was effected by a dosimeter reading in roentgens, 600 units being adopted as the erythema dose, which was agreed on at the International Conference of Radiologists at Stockholm in 1928. These writers explained the rationale of X-ray treatment by pointing out that the marrow in the shafts of the long bones in the adult consists mostly of adipose tissue with little or no blood forming function. Also that when excessive or pathological demand exists, there is a formation of new centers of differentiation of the myeloblasts into granular myelocytes, the adipose tissue of the bone marrow being replaced by this newly formed tissue. They believe that it is possible that irradiation might aid in the formation of this new tissue. They concluded: "The results of irradiation of the bone marrow in angina agranulocytica, though not definitely ascertainable as yet, justify, in our opinion, a trial of such therapy whenever possible for the unfortunate patients." Doan (26), in 1932, believed that X-ray was theoretically correct on the basis that if maturation arrest is present, irradiation might work by "first destroying some of the

myeloid foci and thus release some of the autogenous nucleotides which then supply the necessary stimulus for maturation." He stated, however, that because of the potentially destructive affinity of irradiation for hematopoietic tissue, this form of therapy must be used with great caution when stimulation is desired. Taussig and Schnobelen (123) reviewed the literature as to the results of the various treatment, and, in 1931, reported that the lowest mortality rate was found in those patients who had been treated by irradiation. They said: "Of the methods of treatment at present in use, the most promising appears to be the irradiation of the long bones by means of minimal doses of X-rays. Jackson (54) stated that Roentgen therapy was useless. Witts (131), in 1936, stated that in his opinion Roentgen, and other forms of treatment, were not specific therapeutic agents. Ordway and Gorham (86), stated: "The stimulating action of X-ray has been suggested but has proved of little value, and may even be harmful." At the present time there seems to be few advocates of Roentgen therapy for agranulocytosis.

Liver Extract.--In 1931, Harkins (43) reported two cases of agranulocytosis that recovered following the use of liver extract as the chief therapeutic agent.

Foran and his associates (37) reported remissions in all five of their cases following liver extract therapy. One died later in a recurrence during an attack of lobar pneumonia; the other four have remained well. They said: "The resemblance of the leukocytic increase to the reticulocyte rise in pernicious anemia was very striking in four cases." They used the equivalent of 100 grams of liver every eight to twelve hours intramuscularly or intravenously. Jackson (54), in 1931, said: "At present the ultimate value of liver therapy in agranulocytosis cannot be estimated. It can only be said that a few patients have been successfully treated." Ordway and Gorham (86), in 1937, stated that liver extract may be effective. They advocate that it be given intramuscularly in large doses, 3cc. of concentrated liver extract every three hours, amounting to 10 or 12 cc. daily. They suggested that frequent white blood counts be made during the day "to gauge the effect". They observed that results apparently vary widely according to different writers; "in some instances brilliant success has been reported, in other cases, disappointing failure." Parker and Kracke (87) made determinations on various preparations of liver extract and found the presence of a large amount of reduced glutathione. They suggested that this substance may be partially responsible for the therapeutic effect of liver

extract in some of the leukopenic diseases, based on their experiments which showed a depletion of glutathione in the bone marrow and blood of animals with a depressed bone marrow. Murphy (84), in 1936, reported that he had treated six typical cases of agranulocytosis with daily, or more frequent injections of liver extract, with recovery in each instance. He believes that usually liver therapy has not been adequate where recovery has not followed. However, he considered that sufficient evidence had not been furnished to establish such therapy as the treatment of choice, but suggested that further experience may demonstrate that this preparation is "as valuable in the control of this disease as it is in pernicious anemia."

Nucleotide Therapy.--The nucleic acids are present in the nuclei of cells of the animal body. According to the prevailing view, the nucleic acids are combined with protein, thus constituting the so-called nucleoproteins. On partial hydrolysis, nucleoproteins yield a protein residue and a protein-nucleic acid complex which has been called nuclein. If the cleavage is carried somewhat further, the nuclein yields protein and nucleic acid as cleavage products. Of the foodstuffs, glandular tissues, such a thymus, pancreas, liver, and kidney, are especially rich in nucleic acid. On hydrolysis nucleic

acid yields purine and pyrimidine nucleosides and phosphoric acid. The purine nucleotides on further hydrolysis finally yield the purine bases, adenine and guanine. (Bodansky (9)).

Doan (26), in 1932, stated that nuclein therapy was suggested, on purely empiric grounds, as early as 1893, to "increase the germicidal power of the blood in diseases of microbio origin." He stated that it is now known that the increase in leucocytes reported and attributed to nucleic acid in the earlier investigations was well within the normal range of physiologic fluctuation and not of sufficient magnitude to influence any pathologic process. Doan and his associates (28), in 1928, obtained a definite and usually considerable leukocytosis following intravenous injections of one gram of sodium nucleinate into normal rabbits. They found that a preliminary leukopenia occurred, sometimes lasting for a number of hours, which they attributed to a temporary storage of the granulocytes in the spleen. In 1924, Jackson (52) demonstrated the existence of pentose nucleotides in normal human blood. Doan and his co-workers (28) secured adenine and guanine nucleotides from Jackson's laboratory, and chemically pure crystalline adenylic and guanylic acids from P. A. Levene of the Rockefeller Institute. All of these products gave an immediate neutrophilic response without pre-

liminary leukopenia. Reznikoff (96), in 1930, reported the first clinical application of nucleic acid derivatives. He stated that, since the other blood elements are usually not affected, this disease should lend itself to treatment by "the stimulation of the polymorphonuclear elements by nucleotides such as adenine sulfate and guanine hydrochloride." He reported three cases with recovery by the administration of 0.5 gram of the nucleotide twice in twenty-four hours. He found that within six hours there was some response and usually the increase in granulocytes was marked after the second dose. In 1931, Jackson and his associates (52) reported recovery in fourteen out of twenty cases of profound leukopenia following large doses of nucleotides. They used the unbroken pentose nucleotide, called K-96, which was prepared by Smith, Kline and French Company. In the patients who recovered the first sign of improvement occurred between the third and seventh day, usually on the fifth day. The total and differential counts were invariably normal in ten days, sometimes in eight. These writers commented: "The consistency with which the reaction occurred on or about the fifth day is of great significance. It is at this time that the reticulocyte rise begins to take place following liver therapy in per-

nicious anemia. "This reaction would tend to show that the time for the maturation of the granulocytes is about the same as that of the erythrocytes. However, Beck (3), in 1933, stated that there was no definite experimental proof, that nucleotide K-96 supplied a maturation factor for granulocytes. Doan (25), experimenting on normal rabbits with pentose nucleotide, in 1932, produced not only an extensive degree of myeloid hyperplasia, but also an extramedullary myelopoiesis in the kidneys and spleen. He (25), later, stated that the average effective dosage of Nucleotide K-96 in human cases of agranulocytosis had been four to six grams in his experience at that time. He stated that the experimental studies he had made on normal rabbits justified three conclusions: (1) Nucleic acid and its degradation products exert a chemotactic effect on normal myeloid foci with a prompt effective increase in the delivery of granular leukocytes to the peripheral circulation under a controlled physiologic or rhythmic mechanism; (2) Repeated large intravenous injections do not tend to exhaust nor cause a malignant hyperplasia of the myeloid elements in normal animals. (3) A short course of injections stimulates a myeloid hyperplasia of normal marrow without otherwise injurious consequences. Attention should be called to the fact that

Doan admitted that his experiments were done upon normal animals. To draw conclusions as to the possible effect of such therapy in the case of human agranulocytosis hardly seems logical. Doan (26) based his work on the hypothesis that the degradation products of senile and disintegrating cells are an integral part of the normal mechanism for maintaining cellular equilibrium in the Marrow and the blood stream. He, therefore concluded that in those cases "presenting an etiology essentially intrinsic and related to an insufficiency of the myelopoietic function of bone marrow, the more rational treatment should be the supply to the body of a concentrated preparation of the active principle affecting directly the myeloid centers". Doan included the following table to show the efficacy of nucleotide therapy. These figures are based on the literature to 1931:

<u>Therapy</u>	<u>Cases</u>	<u>Deaths</u>	<u>Mortality</u>
1. Untreated	Many		90 %
2. Miscellaneous	179	133	74 %
3. Arshpenamine	33	24	72 %
4. Blood Transfusion	53	34	64 %
5. Irradiation	64	34	53 %
6. Nucleotide	44	11	25 %

In 1933, Jackson (55), reported that he began treating systematically cases of agranulocytosis and "malignant neutopenia secondary to sepsis" with pentose nucleotides (Pentnucleotide, N.N.R., formerly Nucleotide K-96).

He stated that he had treated, or had reported to him, 91 cases treated with pentnucleotide with a mortality of but 30%. However, he emphasized the tendency to relapse and the possible occurrence of death in the second or third attacks. In the usual case of agranulocytosis, Jackson uses 10 cc. of pentnucleotide intramuscularly two or three times daily until the white count has definitely risen. Thereafter 10 cc. are given once a day until the white count has been normal for three successive days. He recommends larger doses in the most severe cases up to as much as 40 cc. per day. Given intramuscularly this preparation usually produces no marked untoward reactions although there may be some local pain and not rarely there is nausea or vomiting shortly after administration. Jackson pointed out that no definite beneficial results are to be expected before the fourth or fifth day.

In 1933, Reznikoff (97), reported fifteen cases of agranulocytosis in which he used adenine sulphate. There was total recovery in eleven patients and almost all of them showed response in twenty-four hours. He used, for an adult, one grain of adenine sulphate boiled in 35 to 40 cc. of physiologic saline, administered by vein three times per day for a least three days. This writer emphasized the fact that in a disease such as agranulocytosis,

spontaneous recovery is so common that any evidence such as he has reported may be only circumstantial.

Jackson, Parker, and Taylor (59) made an analysis, in 1932, of 69 cases of malignant neutropenia treated with pentose Nucleotide (K-96) and found that 74 per cent of the patients had recovered. They stated, "The favorable clinical and hematologic response took place rather sharply about the fifth day of treatment, irrespective of how long the patients had been ill. Sturgis and his associates (121) concluded, in 1935, that there was more data in support of the effectiveness of pentnucleotide therapy than of any other form of treatment. The report of Jackson and Parker (58), in 1935, offers more confirmatory data. These authors reported a series of 103 patients treated with Pentnucleotide (N.N.R.) in which the mortality rate was but 33 per cent. Jackson (54), in a later paper, written in the same year, suggested that one reason that some unfavorable results with pentnucleotide had been reported was because less than 40 cc. daily, his recommended dose, had been given. He admitted that, unfortunately, this dose may cause such severe reactions in some patients that it cannot be tolerated. He added also that a complete absence of granulocytes in the peripheral blood is probably incompatible with life and therefore despite an adequate dosage, the patient may die

before the beneficial result occurs. Of all forms of treatment discussed thus far, the reports of cases and series of cases treated with nucleic acid derivatives would certainly indicate that that form of therapy comes the nearest to being of value in agranulocytosis. There are on the other hand, several observers who have failed to note any benefit from such treatment. In 1937, Fitz-Hugh (34) reported that the treatment in his hands had been of no apparent value. However, he stated that a possible explanation for his failure lay in the fact that he did not stop the use of such drugs as aminopyrine in his cases until after the report of Madison and Squier in 1934. In Witts' (131) opinion neither pentnucleotide, transfusions, liver extract nor Roentgen treatment are specific therapeutic agents.

^Preventive Treatment.--There was little definite information in the literature concerning the prevention of agranulocytosis or the prevention of recurrence of acute attacks until after 1931 when R. R. Kracks first drew attention to the possible etiologic importance of certain benzene ring drugs. Roberts and Kracke (100), who found an incidence of a mild granulopenia in one out of four of 8,000 private ambulatory patients, stated that the complaints of weakness, exhaustion or fatigue were twice as frequent in such patients as in those with normal white

cell counts. From this finding it would seem that rest, and freedom from mental and emotional strain, would be advisable in patients showing a low granulocyte count as a possible preventative measure against the development of agranulocytosis. With the great accumulation of data supporting the etiologic relationship between certain drugs (related to aminopyrine or the benzene ring), and the disease under discussion has lead the majority of authors to the opinion that all such drugs should be withdrawn in the event of beginning development of granulopenia. Many authors go further and say that such drugs should not be used or should be used only rarely and sparingly. Kracke and Parker (69) expressed the belief, in 1935, that the most valuable therapeutic measure for agranulocytosis is to refrain carefully from the use of drugs containing aminopyrine. Fitz-Hugh (34), in 1937, reported that in his series of such patients the best results, as far as therapy was concerned, were in the group of patients who stopped ingesting aminopyrine. He said: "It would seem reasonable that the earlier the diagnosis is established, and the earlier the offending drug is stopped, the better the outlook."

Kracke, (67) in 1938, expressed the views of the majority of writers when he wrote that in an effort to control the incidence of agranulocytosis, the physician

should refrain from the use of aminopyrine or analgesic agents that contain it; second, he should warn his patients against the dangers of self medication, particularly the purchase and use of pain-relieving remedies for which the formula is not available; third, the physician who is using agents such as sulfanilamide in the treatment of severe infectious states, or is using arsphenamine and other organic arsenicals, should watch the patient carefully for signs of possible hematologic depression by frequent studies of the blood; fourth, the physician should take an active part in the program of public instruction relative to the dangers of these preparations, for only if he does so can the public become informed as to these dangers. Certainly it will not get this information from drug stores and pharmaceutical manufacturers.

SUMMARY

1. The term agranulocytosis, although criticized by numerous writers because of its intrinsic ambiguity, has become so firmly imbedded in the medical literature and the vocabularies of the clinicians that it is believed that it should be retained. The various other names suggested are, admittedly, more descriptive and perhaps more accurate, but a common brief term, universally accepted, will always be more desirable.

2. Although there was no great interest in the disease until after the appearance of the original article by Schultz, (108) in 1922, data has been offered to show that there is no reason to believe that the disease did not exist prior to that time.

3. The report of Lovett, (76) in 1924, of the first case in this country, Kracke's report of a case, (49) in 1931, in which the relationship of coal tar drugs was first stressed, Fitz-Hugh and Krumbhaar's suggestion, (36) in 1932, that a maturation arrest was the principal pathology, and Plumer's (93) report of the first case due to sulfanilamide, in 1937, are other high points in the history of agranulocytosis.

4. The numerous theories of the etiology and pathogenesis have been discussed at some length. One definite conclusion can be drawn from the voluminous literature on this subject: There is, although gradually being reduced, a certain number of cases of agranulocytosis in which the cause cannot be determined at the present time.

5. Biopsy and autopsy studies have confirmed, in the minds of most authorities, that there is present in the bone marrow an arrest of the maturation of the granulocyte development not unlike the arrested maturation of erythrocytes in pernicious anemia. The cause of the maturation arrest, however, remains obscure.

6. Sufficient evidence has been presented, I believe, to incriminate certain drugs, notably aminopyrine and its derivatives, dinitrophenol, arsphenamine, and sulfanilamide, in a large number of cases. The mechanism by which such drugs produce the disease is not understood. The evidence does not show, however, that the drugs, per se, are toxic to all individuals. An allergic or idiosyncratic phenomenon must be assumed on the basis of the available data.

7. For the sake of completeness, a brief discussion of the pathology, symptoms, signs, blood picture, and prognosis of the disease has been included.

8. A review of the treatment employed for agranulocytosis reveals that almost innumerable agents have been prescribed. The fact that spontaneous recoveries are known to occur make it difficult to draw definite conclusions as to the efficacy of the various forms of treatment.

9. Nucleotide therapy in adequate dosage, according to statistics, offers the best hope for the patient as far as active treatment is concerned. Recent good results with liver extract and yellow bone marrow concentrate are encouraging but not conclusive.

10. The withdrawal of any drugs, especially those containing a benzene ring, which might possibly have an etiologic bearing on the disease is to be definitely

recommended. Such passive treatment in many cases has resulted in the patient's recovery.

11. Physicians should refrain from the use of aminopyrine drugs or analgesics containing it as much as possible. Close observation of the patient's blood picture during the administration of drugs containing the benzene ring is essential as a prophylactic measure. Patients should be warned of the danger of the indiscriminate use of pain-relieving drugs for which the formula is not available.

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