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Agranulocytosis

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AGRANULOCYTOSIS

Senior Thesis

by

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INTRODUCTION

Fifteen years ago the medical profession new nothing of the disease spoken of in this paper as agranulocytosis. Since Schultz, in 1922, gave an accurate description of a fulminating case, agranulocytosis has come to occupy more and more prominence in the medical field.

Today, the literature is fairly teeming with accounts of isolated cases of all descriptions. Added to this a confusing nomenclature, varied classifications, and heterogeneous forms of treatment; and the large question of whether it is a disease entity, a group of diseases, or only a symptom complex, and some idea may be garnered as to the progress made.

Time is a most important factor in diagnosis of this disease, and the prognosis at best is grave.

The treatment has gone through the maze of trials as that of any other new disease; there must be a cause and so there must be some specific treatment. In considering the age of the disease, it is but a child, and the medical profession may well be congratulated for the amazing discoveries so far made.

With a thought to the new, and with application of past knowledge gained, may we better able ourselves to become more accomplished and grasp these new diseases in the bud, and so better serve humanity.

DEFINITION: [1] Agranulocytosis is a grave disease of unknown etiology characterized by a marked reduction in the total number of white 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. The disease may be acute or chronic.

NOMENCLATURE:

Werner Schultz [2], in 1922, proposed the name agranulocytosis. There have been a wide variety of terms given to this disease. The name agranulocyte was originally chosen for "neutrophils without granulations" seen in blood smears from cases of leukemia. Friedeman[3] being impressed by the usual severe localization of the process in the throat, suggested the name "angina agranulocytica". This name is unfortunate because of its intrinsic ambiguity, and because it implies that one is dealing with an infections of the mouth which causes neutropenia instead of with a syndrome of utterly unknown etiology. It is now known, also, that cases do occur without angina. Many confusing terms have been suggested. Schilling[4] suggested the name "malignant neutropenia". Baldridge and Needles [5] proposed the term "idiopathic neutropenia", which is a very descriptive name. The term "hypogranulocytosis" has been used by Connor[6]. Other terms, such as mucosites necrotans agranulocytica, sepsis with granulocytopenia, monocytic angina and agranulosis have been used. The term "granulopenia" has been used by Harkin.[7] This author has also used the term Granulocytopenia.[8]

I will use the term Agranulocytosis forthwith as there seems to be a perponderance of this title in the material read and studied; and also seems to be most generally accepted.

HISTORY:

On the appearance of a newly described syndrome, one cannot help wondering under what diagnosis such a case would previously have been filed. This is peculiarly true of agranulocytosis because of the spectacular nature of the local lesions, the blood changes and the rapidly fatal course of most of the cases.

Schultz[2] in 1922, is given credit for recognition of the syndrome called agranulocytosis. The features emphasized by Schultz were a high fever, occuring generally in elderly women with necrotic throat infections, rapid exhaustian, slight jaundice, frequently leukopenia with few if any granular cells or platelets, and death with in a short time in almost every case. There is hardly anyone who believes that the condition had not previously been seen. For example, an editorial in The Journal[9] quotes Tink as describing similar cases in 1907. As far back as 1902 the disease was reported by Brown.[10]

Apparently there is little hope of finding any earlier reference to such cases in hematologic literature, but it would be surprising if such a startling angina had not been described. Reference to standard laryngologic works of 55 years ago seems to justify the view that it was.

In Tinks work he did not distinguish his cases from the more common leukopenia of overwhelming infection. He did call attention, however, to the low granulocyte count in some cases of severe sepsis.

In Morell Mackenzie's [11] "Manual of Diseases of Throat and Nose," one finds a condition defined as follows; "Primi-

tive gangrene of the pharyngeal mucous membrane, constituting an affection per se, and originating independently of any other malady, such as diphtheria, scarlet fever, etc".

Mackenzie credits Bubler in 1857, and Trousseau in 1865 with having clearly distinguished the condition from Diphtheria. Previously,"a majority of the profession were led to affirm the nonexistence of a primitive gangrene of the throat, but (thanks to Gubler and Trousseau) the existence of the malady has been clearly recognized, whilst the conclusion has been arrived at that the disease is an extremely rare one."

After Schultz's work became known, case reports began to appear in medical literature every where; now over 200 cases have been recorded. In 1927, Kastlin[12] collected reports of 43 cases and reported two more, with only three recoveries, a mortality of 93 percent. Stomatitis was always present in these cases, necrotic ulcers occurring in the mouth, larynx or esophagus. Petechial hemorrhages were found in twelve cases at autopsy. In some of these cases there were high platelet counts and again in others the counts were low. Because of the variationa in the cases reported, Kastlin believes that agranulocytosis is not a clinical entity. Many cases have been reported which vary even further from the original description. In some cases only a sore throat without ulceration and the typical lack of granulocytes are the diagnostic symptoms.

Blummer[13] reports a case beginning with numerous boils that became large abscesses, with the blood and the clinical course essentially the same as in the cases described by Schultz.

OCCUPATION: In the group of cases studied by Kracke and Parker[14] particular attention was paid to the occupation and some valuable and interesting information has been revealed. It is a striking fact that agranulocytosis is more prevalent among physicians and their relatives, nurses, hospital employees, and medical students than any other group of people. Based on the 1930 population census of the United States, it occurs fifty times more frequently in nurses than in female school teachers.

It will be noted that of the 200 reported cases in which the occupation is stated, including the housewives, approximately ten percent of there have been physicians and members of the medical group. The so-called medical group, including physicians, nurses, hospital employees, etc, constitute sixty percent of the reported cases of agranulocytosis in the United States in that group in which the occupation is definitely stated. It is not justified to explain this on the belief that this illness is diagnosed more promptly or efficiently in this group of people, since it is well known that physicians are most negligent concerning their own health.

Several writers have noted this same observation. Stellhorm and Amlosch[15] in 1931, summarized 42 cases of agranulocytosis from the region about Detroit, Mich. and made this significant statement; "It is rather curious to note that many of these patients were members of the medical or allied professions, or were relatives of physicians." In their series of cases were two nurses, two physicians, one dentist, and

seven immediate relatives of physicians. In a group of eight cases studied by Harkins[8] there was one Doctor, and one medical student and one nurse. In a series of about fifteen patients from Mayo Clinic the two cases of typical acute fulminant agranulocytosis occurred in a Doctor and a nurse. Madison and Squier[16] have reported from Milwaukee, Wisconsin, a valuable observation, in which fourteen patients were studied. Of the group five were physicians, physicians wives and nurses, and they stated" In this group as in the disease at large, there seems to be a most remarkable relation to the medical and allied professions. The only case report from Poland was one of a physician.

There is little doubt after the above observations and study of the table below but that agranulocytosis is a desease which is peculiar in its relation ot the medical profession.

STUDIES ON OCCUPATION

Housewives	102
Physicians	22
Nurses	17
Maides in Hospitals	4
Medical Students	3
Laboratory Technicians	1
Relatives of physicians	11
School teachers	2
Farmers	5
Business men	10
Clerks	2
Sailors	3
Dentists	1
49 other occupations	1 each
Occupation not stated	289

Conclusions;

1- The disease is extremely prevalent in physicians and their relatives, nurses and hospital employees.

2- It is fifty times more prevalent in physicians than in lawyers.

3- It is 200 times more prevalent in nurses than in female school teachers.

Above was based on population from U. S. Census.

GEOGRAPHIC DISTRIBUTION:

473 cases have been collected from the literature from 1922-1932 inclusive. There has been an increased number of cases reported each year, probably because of the larger number of cases and its more widespread recognition.During this same period there have been approximately 350 cases reported in Germany. The French literature reveals about 100 cases in that Country. The disease is apparently quite rare in Russia, Poland and the Far East. For some unknown reason it is extremely rare in Great Britain. It may be more prevalent in the Far East than we suspect, but the cases are probably not reported.

Dennis[17] has observed two cases in the University Hospital at Beiret,Syria, and states that he discussed the incidence of the disease with several physicians from Palestine and Egypt, and practically all of them had seen cases. Up to 1929 there had only been three cases reported from Russia. The rarity of the disease in England is of special significance. It is quite evident that it does not occur in the country to any appreciable extent. This may have its cause in the type of drugs that are employed by physicians in Great Britain.

GEOGRAPHIC DISTRIBUTION OF AGRANULOCYTOSIS 1922-1932

	No. of Cases.
United States	473
Germany	350
France	100
England	6 total
Italy	50 approx.

1. The disease is extremely prevalent in the U.S. and Germany.

2. It is extremely rare in England.

INCIDENCE OF AGRANULOCYTOSIS

No. of cases in the United States	473
No. of cases in the white race	442
No. of cases in the colored race	8
Race not stated	23
No. of cases in males	161
No. of cases in females	310
Sex not stated	2

1. The disease is essentially one of the white race.
2. It exists in the ratio of two females to one male.

A study of the above table reveals the highly significant finding that agranulocytosis is a disease primarily of the white race, since only eight reports of its occurrence in the colored race were found, and in the majority of these, the onset was preceded by arsphenamine therapy. It occurs in the ratio of two females to one male, and this is also true of the cases from other countries. It has no particular seasonal incidence as cases occur in about equal numbers throughout the months of the entire year. The average age is between forty and fifty, and ranges from under one year to above eighty. It is, therefore, a disease chiefly of middle life.

MYELOID TISSUE:

To accurately interpret the blood picture in this disease it is essentially necessary to have an understanding of the underlying mechanism of hematopoiesis. Since it is granulopoietic tissue that is concerned in this disease a review of the physiology of granulopoiesis will be given.

In the adult the myeloid blood elements, the red blood cells and the granulocytes, are produced exclusively in the bone marrow. This tissue fills out all the spaces in the bones. There are several kinds of bone marrow which differ by their macroscopical appearance; the most important varieties are the red and yellow or fatty bone marrow. The first has a red color and is very soft, while the second resembles subcutaneous adipose tissue. It is in the red marrow, which consists of myeloid tissue, that granulopoiesis takes place normally. In the embryo and the newborn, the cavities of all the bones contain only the red variety. With progressing age the red marrow is gradually substituted by the yellow, which consists mainly of fat cells. In the normal adult, the granulopoietic tissue(red marrow) is found in the vertebrae, the ribs, sternum, the "diploe" of the bones of the skull, and in the proximal epiphysis of the femur and humerus.

The subject of bone marrow as a hematopoietic organ means the consideration of the entire marrow as a unit. As shown by Wetzel[19] it is an organ of considerable size, having in the adult human being a volume of 1,419cc., which is thirteen times that of the spleen and almost equal to that of the liver. This whole structure will be found in a relatively

uniform structural state under normal conditions. This means that the proportion of the erythropoietic to granulopoietic tissue, as well as the proportions of the different levels of maturation within the two groups, is relatively constant. It can be roughly estimated, according to studies by Doan and Zerfas[20], that from three to twenty times more tissue is devoted to the production of granulocytes than to the production of erythrocytes, or in other words, the volume of the granulopoietic tissue is from nine and one-half to twelve times that of the spleen. In contrasting this with the great excess of erythroid over myeloid cells in the blood stream, the reverse in the ratio must be correlated with the greater length of survival of the erythrocytes in the blood stream. It would seem from this that the granulopoietic organ is manufacturing an extremely fragile and delicate product.

It is necessary to distinguish two structures in the myeloid tissue: 1.The supporting, sponge-like framework or stroma which is intimately connected with the blood vessels. 2. The free elements in the meshes of the stroma.[21]

The stroma of myeloid tissue has the same structure as in lymphoid tissue, being made up of fibers and fixed cells. The fibers are the argyrophil fibers of the reticular tissue, which are generally relatively thick and show distinct, paralleled, many fibrillations. This fibrous reticulum is everywhere intimately connected with reticular cells. It also consists of an undifferentiated cellular syncytium attached to the argyrophil fibers and of typical, phagocytic and storing reticular cells or histiocytes. The latter can become transformed into large, free macrophages. The reticulum of cells

and fibers is loose andits meshes are larger than in the lymphoid tissue. An important peculiarity of the stroma of the myeloid tissue is the constant presence of fat cells, which a are found everywhere scattered singly in the red marrow. In the yellow bone marrow they have crowded out practically all of the other cells; between them there remain, except the blood vessels and the reticular fibers, only scattered histiocytes and undifferentiated mesenchymal elements. The latter are probably the main source of the new blood cells when the yellow bone marrow is again transformed into re marrow. Lymph vessels have not been found in bone marrow.

Circulation in the bone marrow is accomplished by the main nutrient artery and its accompanying veins, passing toward either epiphysis, and its capillary branches to the venous sinusoids, together with numerous anastomoses of this system with small vessels of the bone along the shaft and with larger epiphyseal vessels in the mature bone.

The free cells of the myeloid tissue present an extreme variety of forms. The various cell types are irregularly scattered and mixed through out the tissue. The vast majority of them are represented by young forms of the myeloid elements.

The myeloid tissue which produces the elements that occur in the circulating blood always contains a ready supply of them, and in case of need, large quantities of them can be forwarded at once into the blood.

The young forms of the granular leukocytes together with the erythroblasts, are the most common cell type of the myeloid tissue and are, therefore, called myelocytes (marrow cells). Although the polymorphonuclear granular leukocytes of the blood are unable to divide and to become transformed into other cells, the myelocytes are intensely proliferating cells. Instead of a polymorphous nucleus they have a compact, round or oval or kidney-shaped nucleus.

In the myeloid tissue each of the three types of granular leukocytes has its own myelocytes which are already provided with the characteristic granulations. The myelocytes of each of the three types are specifically differentiated elements and cannot be transformed into myelocytes of another type or into elements of another kind. The myelocytes divide mitotically; one part of their progeny remains unchanged, while the other part undergoes progressive maturation which advances step by step with every division. Finally the last generation is reached by each type of myelocyte; the ability to divide is lost and then each cell is transformed individually into a mature polymorphonuclear granular leukocyte.

Myelocytes with Heterophil Granules(neitrophil myelocytes of man). They progress and grow and differentiate by menas of mitosis. The nucleus in there cells, as soon as it is reconstructed after the last mitosis, shows a beginning polymorphism and has the shape of a horse shoe. The visible expression of this metamorphosis is the progressive constric-

tion of the horse shoe-shaped nucleus which results in the highly polymorphous nucleus of the fully developed leukocyte.

Myelocytes with Eosinophil granules are less numerous than the above, but undergo about the same changes.

Myelocytes with Basophil granules are much more scarce and very difficult to study because their granules in man are easily soluble in water.

In addition to the erythroblasts and the three types of myelocytes, the myeloid tissue of all adult mammals contains large, ameboid, nongranular, basophil cells of lymphoid nature. They are scattered singly or in groups of two to four. These elements are the common stem cells of all the other myeloid elements. The most suitable name for them is hemocytoblast.[21]

The meylocytes, although capable of proliferation, are specific, differentiated elements which develope in their predestined direction and are finally transformed into mature granulocytes. Only some of the young forms in the tissue reach maturity; the rest remain unused in the tissue. This process is called homoplastic hemopoiesis-----the production of new mature cells by young elements of the same type. In the adult organism, under physiologic conditions, the needs of the organism for myeloid blood elements are usually supplied by homoplastic hemopoiesis. In all cases, however, in the very young organism or in the adult under pathologic conditions, homoplastic hemopoiesis does not suffice. The mitosis

of preexisting myelocytes continues, but, in addition, new cells of this kind develope through proliferation and diff-entiation of the hemocytoblasts. This is called heteroplastic hemopoiesis.

A most important role in the differentiation of the hemocytoblasts into myeloid elements is played by mitotic division. When an hemocytoblast divides, a peculiar unstable equilibrium of the cell developes at the height of the mitotic process. All of the various potencies of development which are present in the cells are in a latent condition; one of them is suddenly followed and both of the daughter cells which originate from such a mitosis at once show new properties. Their destiny apparently has been fixed during the mitotic processes and they have become either a pair of erythroblasts or a pair of myelocytes of one of the three types.

Function of Neutrophils: Roberts and Kracke[22] said, "We have evidence that the mere loss of granulocytes for seven days is incompatible with life." Their absence gives new slants and intimations on the part they play in immunity. Granulocytes are one of the chief sources of Immunity. With their disintegration and released ferments they give much active daily immunity to the body. They are thought to be the source of complement, and complement is present in the plasma, owing probably to the continued disintegration of neutrophils. Complement is probably the most important single factor in the destruction of bacteria and the defense of the tissues. There is some evidence to show that granulocytes may be the chief source of supply for many of the various types of immune bod-

ies, such as bacteriolysus hemolysius and precipitans. The role of neutrophils in infections is well known.

Mode of Entrance: The young forms of the myeloid elements in the bone marrow have an extra vascular location. It is obvious that to enter the circulation, the newly formed, mature, myeloid cells must in some way pass through the walls of the blood vessels. This happens in the venous sinusoids. Their walls, which are made up of littoral cells of the histiocytic system, are extremely thin and through them easily pass not only ameboid cells as the mature granular leukocytes, but also the non-motile erythrocytes. These, when ready for circulation, slip through the membrane into the blood stream in the lumen of the sinusoid. The mechanism of this phenomenon is probably regulated by changes in the permeability of the walls of the vessels and in the surface energy.

There has been much speculation as to the factor or factors which bring about this emmigration of cells into the blood stream. Two different processes must be analyzed: first, the mechanism of the delivery of the cells to the circulation, and second, the mechanism of maturation.

It is uncertain, if at all, that vasomotor influence plays any part in the mechanism of delivery. Experiments concerning the response of the marrow to nerve stimuli have not been sufficiently controlled with reference to the normal rhythm of delivery to allow the forming of any definite conclusions.

There is, however, more definite information available concerning chemotactic factors. Many agents are now known that will cause an increase in the percentage of polymorphonuclear

neutrophils in the peripheral circulation. Some of them are muscular exercise, change of position of the body, cold shower, atropine, foreign protein, toxemic conditions and ingestion of certain bacteria.

It is also possible to call the cells from the marrow by administrating inactivated Typhoid bacilli. This experiment was performed by Doan and his associates[23] and can be expressed as representing a condition due to a chemotactic factor minus a maturation element. The cells of the marrow showed no toxic effect, and the marrow readily regenerated after the experiment. Of the many substances that have been shown to call leukocytes from the bone marrow, nucleic acid is most likely to be a part of the normal mechanism.[24] Doan and others have made an excellent contribution on this subject, in a study of the effect of large doses of nucleic acid.

Nucleic acid was first isolated by Altman in 1877. Ames and Huntley were among the first to study nucleic acid experimentally from the stand point of its apparent production of a leukocytosis. They concluded from the hypodermic injection of nuclein solution into dogs that there was an increase in the number of leukocytes in the central and peripheral circulation, and, further, since they found an increase of young cells, that the response was a true delivery of cells from the bone marrow.

Doan and his co-workers study of the bone marrow showed clearly the chemotactic effect of the nucleic acid with the massing of leukocytes around the patent sinusoids, a marked

diapedesis into the vessels and the vacant areas of the marrow from which the granulocytes had been drawn. They also found that the granulocytes could be called from the marrow by the split products of nucleic acid, the purine bases, adenine and quanine. It is thus likely that nucleic acid and its derivatives are important physiologic factors in the chemotactic reaction, and that the showers of non-motile leukocytes in the circulating blood may give a rhythmic discharge of such products(nucleic acid, adenine, quanine,) into the circulation. In later experiments on nucleic acid and its degradation products, Doan[25] gives the following 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 tend neither to exhaust nor to 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 other wise injurious consequences, which is reflected by a relative or absolute increase in the amphophilic granulocytes in the blood stream of rabbits."

There is but meagre knowledge of maturation factors,but those bacteria that produce a sustained leukocytosis intro-

duce such a factor as they produce an increased division, growth and maturing of the less mature leukocytes in the marrow far beyond the normal amount. Bacon[26] and his co-workers considered that even in infections the stimulus to an increased activity of the marrow comes from altered body proteins. The relationship of the degree of leukocytosis to the resistance of the animal in infections has been repeatedly confirmed since Metchnikoff, and thus, as long as none of the substances involved in these reactions are known, variations in the response of the animal must be studied in terms of the amount of the infecttion and possibly differences in the power of the hemopoietic tissues to respond. One might venture to speculate, however, that the resistance of the patient may not depend on the power of the granulopoietic tissue to respond, but on the power of the tissues producing the maturation factor to respond. The only definite knowledge of maturation factors concerns erythrocytes. The recent application of the liver diet to patients with Pernicious Anemia and the isolation from liver of the specific substance by Cohn[27] and his associates involve the discovery of a maturation factor. Minot and Murphy[28] have shown that by the liver diet the normal mechanism is restored by the speedy appearance in the peripheral blood of reticulated erythrocytes of normal size. Liver extract does not supply a maturation factor for granulocytes. No doubt there is a similar maturation factor in the body to regulate the normal production of granulocytes.

The modern aspect of this problem involves an investigation of the chemotactic maturation factors which determine the granulocytes. These chemotactic factors are to be sought in certain organ extracts as well as in specific factors some of which may be vitamins.

Normal Destruction of Neutrophils: Weiskotten[29] experimenting with rabbits, showed that the life span of the neutrophils in the blood stream was about four days. The case studies by Roberts and Kracke[30] seem to prove that the life span of the human neutrophil is about the same. Some idea can thus be had as to the enormous numbers of granulocytes to be consumed daily, termed physiologic degeneration. Cells in the non-motile phase appear in the blood stream in showers, indicating that there is death of many granulocytes in the blood stream. There are various physiologic outflowings of granulocytes from the blood into the tissues, with consumption in the tissues. There is elimination of neutrophils into the saliva and probably into the entire digestive tract and onto all mucous membranes. There is apparently a gradual loss of granulopoietic tissue with advancing years. Custer and Ahlfeldt[31] studied the tibia, the femur, rib, sternum and vertebrae in an hundred unselected cases and found that the cellulairity of these marrows decreased with advancing years of life, the decrease corresponding in rapidity to the order named. The response of these marrows to a hemopoietic stim-

ulus of a given intensity is in the following order: vertebrae, sternum, femur, rib and tibia.

ETIOLOGY:

LIVE BACTERIA:

Lovett[32] noted in her case the presence of mouth ulcers infected with B. pyocyaneus and at once suspected this organism as etiologic. She injected numerous laboratory animals but failed to produce the condition.

Similar observations have been made by Linthicium[33], and Windham[34] and Keeney[35]. Also Friedeman[36] in a study of 23 cases found B.pyocyaneus in the blood stream of one. These findings have led many to suspect it as etiologic but up to this time efforts to reproduce the disease in laboratory animals with it have been unsuccessful. There is little support for the bacterial etiology of granulopenia since it has been well demonstrated by Roberts and Kracke[37] that the basic pathology is first the disappearance of the neutrophils and this in turn is followed by the invasion by any and every organism that is accessible, particularly throughout the entire length of the gastro-intestinal tract. Most writers are in accord with the conception that granulopenia is first a disease of the bone marrow, followed by disappearance of peripheral granulocytes, this in turn followed by varying degrees and types of infectious processes.

The following table shows at least 25 organisms that have been found to be blood stream invaders in this disease and that approximately20 percent show blood stream infection.

Blood Stream Infection In Agranulocytosis.

Organism	No. of Cases.
Strep. Hemolyticus	8
" . Veridans	15
" . Type undetermined	9
Staph. Albus	3
" . Aureus	4
B. Friedlander	4
Pneu. Type two	3
" . " three	1
" . " four	2
" . " undetermined	2
Diplococcus	4
B. Pyocyaneus	3
B. Para Typh.B.	1
B. Coli	3
B. Protens	1
Streptothrix	3
Strep. with other bacteria	9
Fusiform Bacillus (gram)	1
Estivo-autumnal parasites	1
Varives cocci	3
Staph undetermined	1
Diphtheria bacillus	1
Vincent's organisms	1
Typhoid bacillus	1
Bacillus undetermined	1
Total number positive cultures	74
Negative or not stated	395

Conclusions:

1. Blood cultures are positive in about twenty percent of the total number of cases or positive in seventy percent of the examined cases.

2. The streptococci are the most frequent invaders.

3. The blood stream infection is probably secondary to the leukopenic state.

There are many reports in the literature concerning the efforts of various investigators to reproduce the disease in laboratory animals with organisms that have been isolated from their respective patients, but all of this work has been

unsuccessful. Piersol and Steinfeld[39] injected intravenously into rabbits inactivated cultures, Berkefeld filtrates, and supernatant fluids of cultures of many organisms and failed to reproduce the condition and called attention to the fact that a temporary leucopenia may be produced by the injection of peptones and a large number of other proteins.

It has been stated that agranulocytosis may be due to the continued absorption of toxins from sites of focal infection. The recent work of Dennis[17] is important. He was able to produce a sustained a marked leukopenia in rabbkts in which he allowed the Strep. Veridans to grow in the tissue under such conditions that the toxins were diffused throughout the animal body while the organisms remained in situ. It will be noted from a study of the last table that Strep. veirdans has been reported as the most frequent blood stream invader in this disease.

CHEMICALS: It has long been known that various chemicals will depress the marrow function, resulting in complete inhibition of all cellular types. For example, benzene poisoning has been recorded as a process in which hematopoiesis is completely inhibited in all of the three bone marrow elements, resulting in a picture simulating aplastic anemia. It has been shown by Kracke[37] that benzene may be introduced into the rabbit in such small doses that it exerts a selective affinity for the granulopoietic tissue only, leaving the erythrocytic and thrombocytic elements relatively undisturbed. This same

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situation is true with other bone marrow depressing agents, and no doubt, is true in the case of arsphenamine. Arsphenamine poisoning is a known etiologic agent in the production of bone marrow depression. The clinical picture resulting has chiefly been one of anemia, associated with granulopenia and thrombocytopenia as well.

It has been shown that the injection of the human being with certain preparations of gold will produce a condition closely simulating, if not identical with true agranulocytosis. Many such cases have been reported from Angeras and Ginsbourg.[38]

ALLERGY:

Some whose opinion show a trend towards belief in the allergic nature of the disease are Harkins[40] who reports the judgement of a group of physicians of the Chicago Uni, Hosps. based upon a study of 36 recurrent cases of agranulocytosis. Under their comments appears the statement,"Agranulocytosis may be due to some endogenous factor as allergy." In the same article Dr. Perry Pepper[41] of Philidelphia, is referred to as believing that"the disease may have and allergic basis." Dr. Pepper may further be quoted as saying in his writings that he is greatly impressed with the frequency of an allergic history in subjects of agranulocytosis.

Dr. Arthur F. Coca[42] has given an excellent basic explanation as to the nature of allergy, saying,"During the past twenty years we have witnessed the rapid growth of a

new medical specialty which is based upon the newly recognized principle of the causation of disease. This principle lies in the surprising paradox that antibodies, which had previously been known to medicine chiefly as protectors against disease, often represent the actual cause of disease."

A few authors believe that agranulocytosis may be a form of allergy in which the bone marrow is the point of least resistance. Schilling[4] 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. Kracke[42] reported a case and said, "The question of typhoid prophylaxis as a whole or partial cause of the condition must be considered." Bromberg and Murphy[43] reported a case following prophylactic vaccination against typhoid. It is known that inactivated typhoid bacilli have a marked chemotactic effect on the bone marrow.

CONGENITAL AND FAMILY ANOMALY: A familial tendency to diseases of the hematopoietic tissues of one type or anothe is a possibility. Hart[44] suggested a familial tendency, having observed agranulocytosis in two sisters. Congenital granulopoietic insufficiency seems to have been proved in some cases but the granulopoietic tissue in most of these patients had so far as is known, functioned normally for many years. The cyclic and recurring nature of many cases is hard to explain on the basis of a congenital lesion. Blumer[45] dismissed the possibility of a congenital anomaly with the following state-

ment: "The same patient has reacted with the usual leukocytosis and granulocytosis to an attack of an infection and has shown a neutropenic reaction and a leukopenic reaction to another attack." Whether certain patients have a constitutional and abnormal functionally limited bone marrow for making blood, is as yet a theoretical question.

Pepper[41] states that in all of his observations and reading, agranulocytosis is apparently not familial. The same with Fitz-Hugh and Comro[46], in none of their cases were they able to demonstrate even a suggestion of an hereditary or familial incidence of any blood dyscrasia.

CONSTITUTIONAL PREDISPOSITION: Roberts and Kracke[47] were among the first to recognize the importance of analyzing accumulated data in terms of white blood count level and symptomatology. In a study of the records of 8,000 private clinic patients, one out of every four was found to have had a mild granulopenia; one out of every two women patients between the ages of forty and sixty was neutropenic; and complaints of weakness, exhaustian and fatigue were twice as frequent in the granulopenic individuals as in those showing a normal white cell count. Furthermore, the severity of the symptoms to a remarkable extent were in direct proportion to the degree of granulopenia found.

In a very similar analysis of 10,000 case records of patients cared for in the U. of Calif. Hosp. between 1920and 1931 inclusive; Mettier and O"son[48] found that examinations of the blood counts revealed leukopenia in 1,167 or 11.7 per cent of the cases and that 52.4 percent of the cases of leu-

kopenia occurred in females and 47.6 percent in males. Leukopenia occurred frequently as a manifestation in patients with vague symptoms of one kind or another, chronic fatigue being the predominating symptom. The higher percentage obtained by Roberts and Kracke are probably due to their choice of 6,000 white blood cells per cubic millimeter of blood as the lower limit of normal while Mettier and Olson took 5,000 leukocytes as the lower limit of normal. Mettier and Olson are ardent supporters of the concept of agranulocytosis as suggested by Rosenthol[49] who said that in his belief the chief etiological factor in agranulocytosis is primarily a profound constitutional distrubance of granulopoietic tissue. His conclusions are based upon a personal observation of ninty cases of marked leukopenia.

After consideration of the various types of pathology found in the bone marrow(it may be hypoplastic, normal, or hyperplastic for granulopoietic elements) Miloslavich[50] expressed a quite similar belief as Rosenthal. He attributes these variations in reaction to pathological functional expressions of individual character of a constitutionally weak, functionally, readily insufficient and easily vulnerable bone marrow, depending also upon the type of virulence of the noxious agent. This constitutional (functional) inferiority of the bone marrow is vividly expressed in those instances in which an increased functional demand is urgently and vitally needed, but the bone marrow tissues respond with

an alarming collapse and a rapid, complete exhaustian.

It is not at all unreasonable to think of a decompensation of a granulapoietic organ that is functionally inadequate to with stand too great a load.

DRUG THERAPY:

Kracke and Parker[51] have investigated as carefully as possible the various etiologic factors in eleven cases in respect to drug therapy of true idiopathic granulopenia (agranulocytosis) with the following findings:

Case 1. An elderly white woman who had been subjected to repeated cystoscopic examinations over a period of nearly a year, during which time she was frequently given a large number of Peralga tablets (which contain 71 per cent of amidopyrine).

Case 2. A middle-aged white woman in whom the onset was preceded by a protracted period of illness diagnosed as influenza, during which time she was given practically daily amidopyrine and emperin compound for a period of several weeks; and prior to that time she had taken about three tablets two or three times per month over a four year period.

Case 3. A middle-aged white man had taken for more than a year as much as fifteen grains of amidopyrine daily for attacks of precordial pain, interspersed with a prescription containing phenacetin. Just before the clinical onset he was treated for a condition diagnosed as a mild attack of the Flu and was given a prescription of capsules containing phenacetin.

Case 4. A middle-aged white woman, the wife of a Dentist, had taken a proprietary preparation known as Jame's tablets several times weekly over a period of from five to ten years. According to her husband, he stated that his wife took these

tablets for every ache and pain. Investigation showed that each tablet contained grain one of acetanilid.

Case 5. A young white woman, a nurse in the Emory Uni. Hosp. had taken from five to fifteen grains of amidopyrine daily during hermenstrual periods for a period of several years and had taken them more frequently during the seven or eight weeks preceding the onset of her illness.

Case 6. A middle-aged white woman, librarian, had emotional stress during her last year of life. She was known to have suffered from profuse menstruation and, according to such information as was available, was thought to have been addicted to the use of the so-called coal tar drugs.

Case 7. A middle-aged white woman had received three doses of neo. and had taken emperin compound for her various minor symptoms.(phenacetin, asperin, caffeine.)

Case 8. An elderly white woman gave a history of prolonged use of a compound containing phenacetine which had been prescribed for her by her Dentist in connection with a long period of dental work.

Case.9. A middle-aged white woman had been given phenacetine for five years preceding the onset of her illness, and during this five year period had taken so much that when she was admitted to the hospital with agranulocytosis, she presented a typical picture of phenacetine poisoning with the marked slate blue color of sulphemoglobinemia.

Case 10. A middle-aged physician in general practice, was known by his brother, who was a dentist, to be a coal tar drug

addict, to such an extent, that his brother had even at times remonstrated that he took entirely too many of these drugs. His brother stated that he had taken such drugs as emperin compound, allonal, pyramidon, etc. almost daily for years for the slightest ache or pain.

Case 11. A middle-aged white man admitted to Grady Hospital, Atlanta, for treatment of rectal fistula, He was in the hospital for two months, during which time his medication covered a wide range of drugs. Included in this were generous doses of pyramidon. It is not known to what extent he took these preparations before his admission to the hospital. It is noteworthy that this patient developed agranulocytosis only after he had been in the hospital for two months, and is the only case of agranulocytosis that has been observed in the 600 bed Municipal Hospital of Atlanta.

The cases outlined above were of the true type of agranulocytosis, and all were the acute fulminating variety.

Kracke and Parker[51] have felt since 1930 that members of the medical profession have been prone to prescribe and use this class of drugs for their own ailments and for members of their families. They also feel that the average hospital nurse in the course of her duties, when seeking a mild analgesic will, because of her familiarity with these newer preparations, employ one of the coal tar products, instead of the older remedies such as asperin. They also feel that the average layman will use asperin when treating their own aches and pains unless they use some drug that has been prescribed by some

physician.

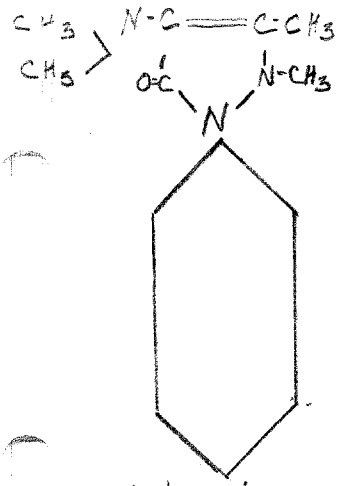
To varify the above points Kracke-Parker[51] conducted a study of several groups with particular reference to the usage of coal tar drugs. The information was obtained through history blanks which were filled out by the respective persons in each group. The following table shows their results.

	Nurses	Doctors	Laity
Total No. of Histories	154	100	100
No, using drugs	124	100	65
No. using Benzamine drugs	94	55	17
% " " " " "	75.8	55	26.1
No. using asperin	26	45	44
% " "	20.8	45	67.9
No. using drugs not classified	4		4
% " " " " " "	3.3		6.

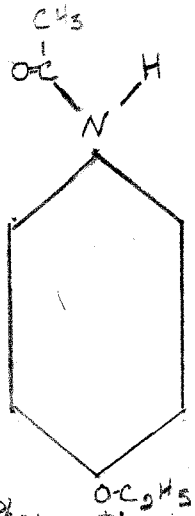
It can be seen, therefore, that there exists almost a direct proportion between the incidence of agranulocytosis in these groups and the incidence of drug usage in the same people. That there exists a direct relationship between the usage of these drugs to the incidence of agranulocytosis is believed by Kracke-Parker.[51]

The peculiar geographic distribution of agranulocytosis can also be correlated with usage of this class of drugs. The prevalence of the disease in Germany and the United States approximates the use of coal tar derivatives of this class

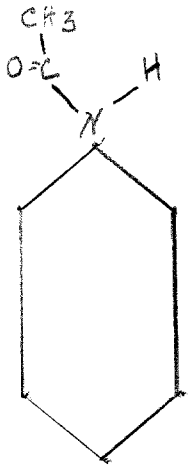
TABLE I



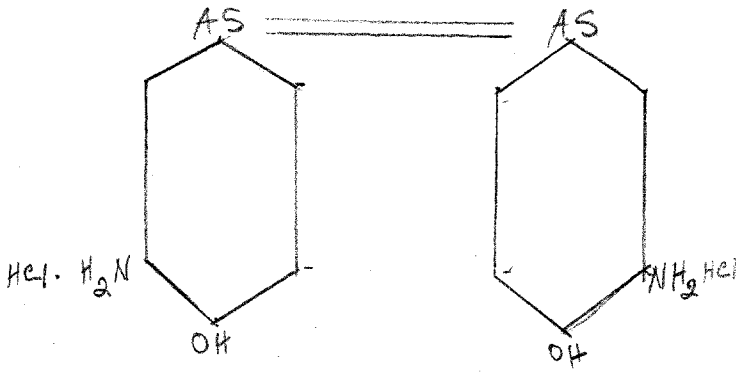
Amidopyrine.



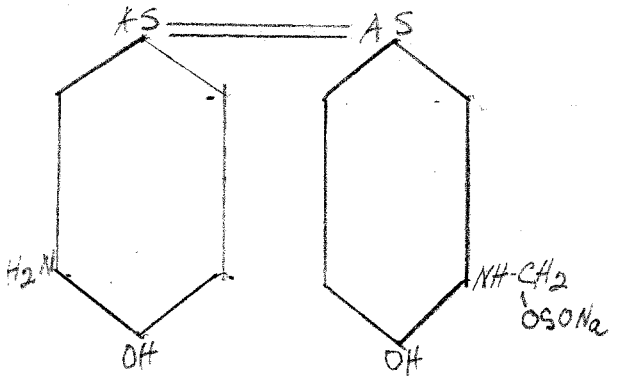
Phenacetine.



Acetonilid.

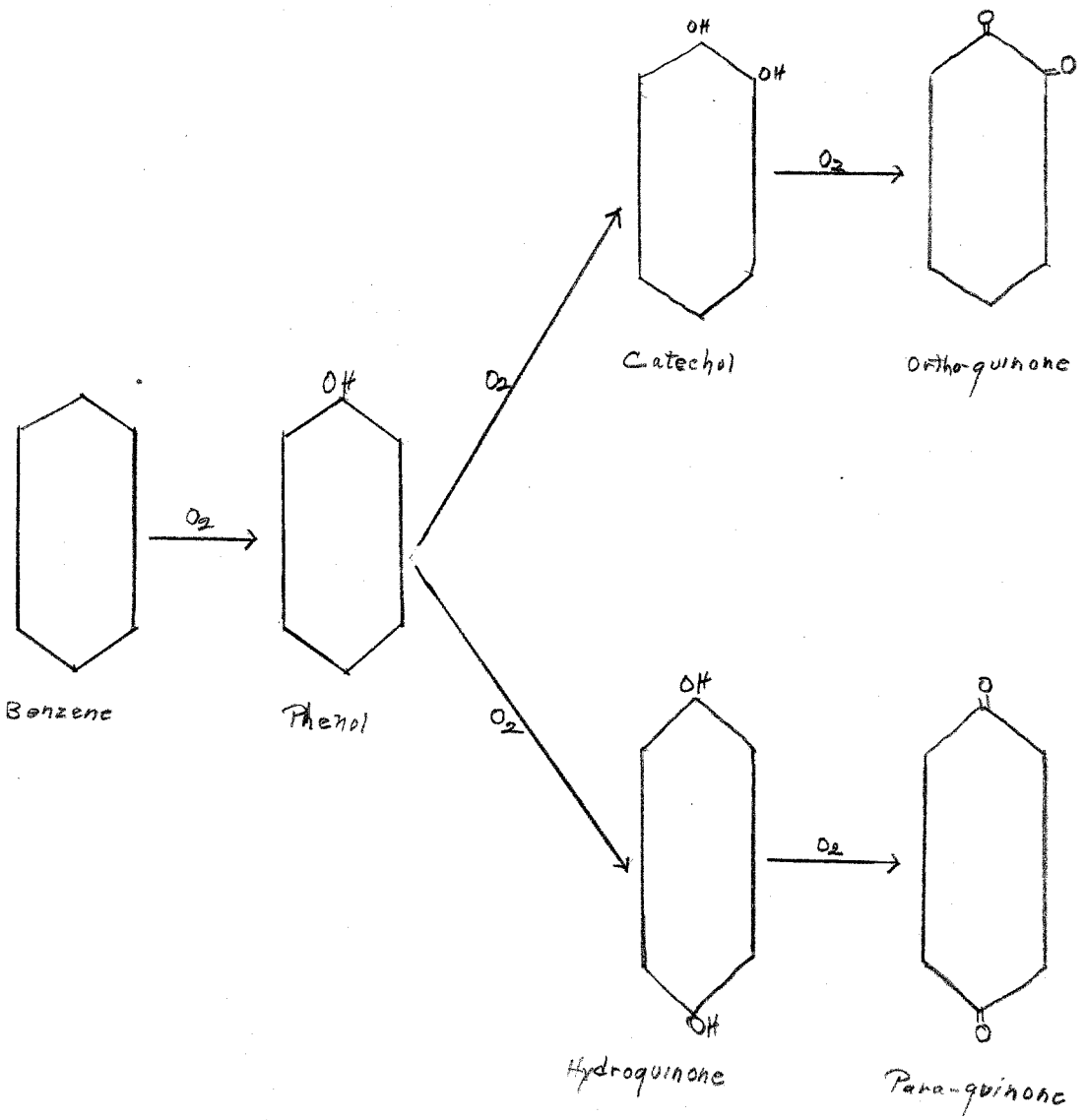


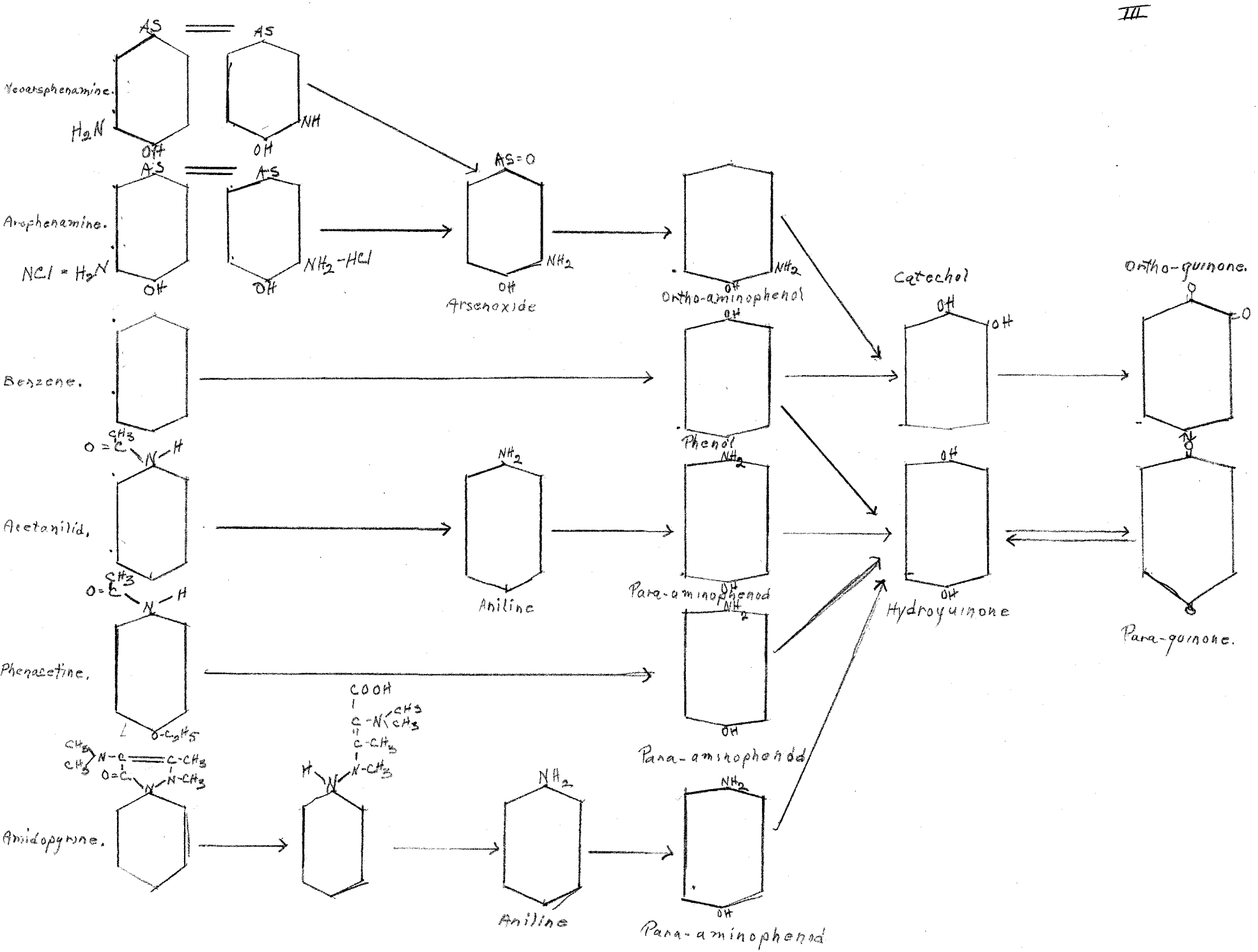
Arsphenamine



Neoarsphenamine.

TABLE II


OH
OH
O
O
O2
Catechol
Ortho-quinone
OH
O2
O2
Benzene
Phenol
OH
O
O2
OH
O
Hydroquinone
Para-quinone


Neoarsphenamine.
Arsphenamine.
Arsenoxide
Ortho-aminophenol
Catechol
Ortho-quinone.
Benzene.
Phenol
Acetanilid.
Aniline
Para-aminophenol
Hydroquinone
Para-quinone.
Phenacetine.
Para-aminophenol
Amidopyrine.
Aniline
Para-aminophenol

in these two countries. The practical absence of the disease in England is correlated with the fact that this class of drugs is used to a lesser extent in that country. It is also known that some of these drugs, notably those in combination with the barbiturates, have been introduced only with in the last ten or twelve years. This has been stated as the time period of Agranulocytosis. Therefore, this must be considered seriously as an etiologic factor.

In Oct. 1933, Madison and Squier[52] presented a report of fourteen cases of agranulocytosis, and in every instance the onset of the illness had been preceded by prolonged or intensive administration of drugs of this class, and they stated, "In each of the fourteen cases there was a definite history of amidopyrine in combination with a barbiturate or pyramidon in practically all of the cases we have seen."

It has been shown by repeated animal experiments that the subcutaneous injection of benzene will produce a depression of the bone marrow with a blood picture in which the leucocytes count falls to 200 or 300 cells with complete absence of granulocytes. This effect is produced, not by the direct action of benzene upon the bone marrow, but by the action of some of its exidation products. In support of this contention, rabbits were injected subcutaneously with a mixture of equal parts benzene and olive oil and the tissues at the site of injection were analyzed eighteen hours later for some of these products. The findings showed benzene to be present

only in traces while phenol and catechol were present in considerable amounts. Analysis of a noninjected control animal showed these products to be absent. At the same time bone marrow from the injected animals was analyzed and showed the presence of both phenol and catechol but no trace of benzene. Similar control animals gave entierly negative results. This indicated that benzene as such did not reach the bone marrow but did not exclude further oxidation products of the benzene ring as the causative factor in the leucocyte depression. The oxidation of hydroquinone or catechol to para-quinone and ortho-quinone respectively, can easily be carried out both in vitro and in vivo. In the latter case this reaction is activated by an enzyme, phenolase, which is present in the leucocyte.

Certain drugs of the coal tar series have been constantly associated with the cases of agranulocytosis.[53] It must be noted that there drugs all have as a nucleus the benzene ring with an attached amine(NH_2) group, making them substituted primary amines. This basic structure sets them apart (so far as their reaction are considered) from other coal tar derivatives, such as ,asperin etc., which do not contain the primary amine. For this reason <u>benzamine drugs</u> have been arbitrarily designated to facilitate reference to them as a group. The drugs contained in this group are amidopyrine, phenacetine, acetanilid, arsphenamine, neoarsphenamine, and those proprietary preparations which contain one or more of the above mentioned.

It is well known that the presence of an amine group of the benzene ring greatly increases the ease with which the structure can be oxidized. This property is little influenced by the substitution of additional side-chains either upon the ring or upon the amine group itself. With these facts in view, the possible oxidation products of these drugs have been worked out in an attempt to arrive at an end-product common to both benzene and the benzamine compounds. These reactions are logical and sound chemically, in that they have proven themso; but, physiologically, they are highly theoretical, in that they have not been proved so to take place in the animal organism.

The oxidation of acetanilid and phenacetine to para-aminophenol both in vitro and in vivo is well established. The compound has been isolated from the urine[54] and the blood serum[55] of patients.to whom these drugs have been administered. The further oxidation of para-aminophenol to quinone is easily carried out in vitro, but as yet, has not been demonstrated in animal metabolism. Hydroquinone is probably formed as an intermediate in this oxidation. These reactions are attended by the splitting off of acetic acid in the case of acetanilid, and of acetic acid and ethyl alcohol in the case of phenacetine. The side chains probably are oxidized further as straight chain carbon compounds.

The literature affords little information as to the ultimate fate of amidopyrine in normal or abnormal animal metabolism. Current opinion is summed up in the statement that it

is excreted either unchanged or as related substances[56] but no mention is made as to what such related substances might be.

Several aspects of the toxicity of arsphenamine have been dealt dealt with by Voegtlin[57]. He explains these either on the physical changes that the drug undergoes when injected into the blood stream, or upon the chemical action of trivalent arsenic with glutothione. It is pointed out that this latter reaction upsets the normal tissue oxidation reduction equilibrium with a resulting tissue asphyxiation. He mentions the occurrence of "aplastic anemias" in some instances, subsequent to the administration of arsphenamine, but does not explain this marrow depression other than by saying that it may be due to the longer retention of arsenic in the bone marrow than in any other tissue.

This lack of action of arsenic tended to center attention upon the benzamine nucleus of the compound. It is well established that arsphenamine or neoarsphamine, when administered intravenously, is readily decomposed by breakage of the double bond between the arsenic atoms, with resulting formation of two molecules of arsenoxide.[57] According to Voegtlin, it is this compound which by virtue of its trivalent arsenic, reacts with the SH of glutathione. He also shows that arsenous acid, when administered to animals, is more toxic than either arsphenamine or arsenoxide. This would point to the probability that trivalent arsenic may

exert its toxic effect equally well regardless of whether or not it is attached to the benzene ring. Therefore, removal of the arsenic from the ring with its hydrolysis to arsenous acid would leave the benzamine group, ortho-aminophenol, free to be oxidized to catechol, and finally to ortho-quinone. On the other hand, if arsenic is not split from the ring, the hydroxy and the amine groups can be oxidized, without interference, to the quinone form.

From the above reactions, it is obvious that the progressive oxidation of benzene, acetanilid, phenacetine, amidopyrine, and arsphenamine gives rise to several compounds in common. These intermediate and end-products are hydroquione, catechol, ortho-quinone, and para-quinone. It is, therefore, believed that one or more of these compounds are responsible for the depressant action of benzene upon the bone marrow, and so would point to the benzamine group as also being primary agents in the production of agranulocytosis.

The therapeutic effect of most of these drugs is based on one of the oxidation products. It is also true that the bone marrow depressing effect of benzene is due to one of its oxidation products and not to the drug itself. Therefore, it seems probable that bone marrow depression should be produced by the intravenous injection of one or more of these products.

In the production of this disease, a weakened or inferior bone marrow must be presupposed. This is brought to light by the fact that from a population of 120,000,000 in the U.S.

only 500 cases hve been reported. Only an occassional human being developes agranulocytosis while many thousands of individuals have taken benzamine drugs indiscriminately and have shown no depression of the bone marrow.

Under "chemistry and drugs" must be placed the pictures of depressed white blood cells with lowering or absence of the leucocytes which occurs in people exposed to benzol, hydrocarbon, Trinitrotoluene, and also the cases that occurred following the treatment of some condition with arseno-benzol, bismuth, bisimarsen, amidopyrine, barbitol, dinitrophene, and other drugs of that group.[58]

Stephen Bohn[59], SOlomon Silver[60], and Davidson and Shapiro[61] reported cases following injestion of dinitrophenol. Madison and Squire[52] reported fourteen cases in which the onset was directly preceded by the use of amidopyrine alone or in combination with a barbiturate. Allonal was the drug used in six of the cases.

MORBID ANATOMY:

Bone Marrow: According to Fitz-Hugh and Krumbharr[62] the current concept of the bone marrow changes in so-called agranulocytosis is that there exists, at least terminally, a more or less complete absence of white blood cells of the granular (myeloid) series. This granulocytic aplasia concept has developed partly on the basis of bone marrow studies indicating an apparently selective disappearance of the granular leucocytes and their progenitors; and partly on the basis of analogy to establish findings in certain other conditions, such as, benzol poisoning with its "selective" attack on formative tissues of the granular cells and blood platelets.

The possibility that such a concept may not be entirely well founded in fact, and may be misleading in implication, has come to mind from from their personal study of the bone marrow in fatal cases. In one of these, the marrow of most of the bones examined contained "active hemopoietic areas" filled with myelocytes, promyelocytes, and myeloblasts, while the peripheral blood contained only 200 white blood cells per cc, (all lymphocytes). Similar, although less obvious, absence of myeloid white cell aplasia was found in the marrow of the other two cases. One of these died after months of illness characterized by repeated severs relapses and incomplete remissions. This patients marrow, in most of the bones, was more nearly aplastic as regards granular series cells than any other marrow of such cases examined; but even this one show-

ed numerous myeloblasts and a few myelocytes in the rib marrow, whereas the terminal white blood cells was only 500 cells per cm. Necropsy was performed in these cases within two hours after death, and fresh bone marrow, spleen, and lymph nodes smears were stained at once.

According to Fried and Dameshek[63] there is often a widespread necrosis of the leukopoietic tissue in the severe forms of agranulocytosis. In two cases of Agranulocytosis found by above men foci of necrosis were found in the bone marrow liver and spleen.

In the bone marrow deprived of its granulated elements small lymphocytes are often present in great numbers, and the small lymphefollicles which are common in normal bone marrow may be inconspicuous.

In the first cases of agranulocytosis which were described by Schultz, the complete absence of granulated cells from the bone marrow of the ribs and femur was the outstanding feature. The bone marrow was fatty with small islands of lymphoid cells among which a few myeloblasts could be distinguished. Many of the subsequent investigators were able to confirm this statement, stressing the integrity or hyperplasia of the erythropoietic tissue and magakaryocytes in striking contrast to the complete aplasia of the granulocytes. Several authors observed severe alterative changes of the myeloblasts and myelocytes. Rose and Houser[64] observed cells with indistinct, ragged outlines and with hyaline droplets in the

cytoplasm in the hyperplastic bone marrow in a typical case of agranulocytosis. The nuclii of these cells were either pale and ballooned or pyknotic, and some of the cells were completely transformed into a hyalin mass.

The cases of agranulocytosis in which the bone marrow reveals severe alterative changes or complete exhaustion of the granulopoietic tissue are in contrast to those cases in which the bone marrow is found to be normal or hyperplastic without apparent injury to the granulopoietic tissue. In one of the cases of Dameshek and Ingall[65] in which a sternal biopsy was done during life the bone marrow showed nothing abnormal. Zikowsky, who had at his disposal numerous, carefully studied cases of agranulocytosis, observed considerable difference in the cellular picture of the bone marrow. He believes that in the early stages of agranulocytosis there is a blockage of the bone marrow which prevents the mature granulocytes from entering the blood stream. If this blockage persists over a long period of time, the parental cells of the granulocytes degenerate and break down. Fitz-Hugh and Krumbharr[62] came to the conclusion that at least occasionally death may occur in an uncomplicated agranulocytosis with a profound peripheral leucopenia while the leucopoietic centers are well supplied with parental cells. They consider it likely that a maturation factor is at work either arresting the development of the white cells or producing degenerative changes in them before sufficient development has taken place for the migration

into the blood stream. In a subsequent paper with Comroe, Fitz-Hugh[46] again put the maturation arrest before the primary aplasia of the granulopoietic tissue of the bone marrow. The presence of apparently normal myeloblasts and myelocytes in the bone marrow in some cases of agranulocytosis has also been stressed by others.

In the acute fulminating and the chronic severe cases of agranulocytosis, the pathological findings vary widely, according to Lambe,[66] depending on whether or not the infection has become generalized. Until recently, reports of the condition of the bone marrow have stressed the fatty, hypoplastic, liquified state of marrow, with an absence of myeloblastic cells. Erythrocytic regeneration has been noted repeatedly.

Thus the bone marrow changes at necropsy may exhibit aplasia or hyperplasia of the granular cell progenitors. The operation of an hypothetical maturation arrest factor in the peripheral leucopenia, and it is not impossible that the cases of terminal aplasia may have passed through a transitory hyperplastic stage. It is reasonable to conclude, that in a disease with as many variants as neutropenia, the underlying pathology is not uniform. The acute fulminating case, dead in from four to six days after the onset of symptoms, and the case of a mild chronic agranulocytosis are poles apart clinically, and no doubt, to a great extent pathologically. About the only common denominator is the diminished number of neutrophils, and that a matter of degree.

EPITHELIAL LESIONS:

The local lesions seen in agranulocytosis usually occur on the mucous membranes, more rarely on the skin. Lesions of the mucous membranes when present, are localized mainly in the mouth and involve various structures, such as the gums, tonsils, softpalate, lips, pharynx and buccal mucous surface. More rarely the nose, uterus, vagina, rectum, anus and skin are involved. Local lesions may also occur any place along the gastro-intestinal tract or in the lungs, and the symptoms are according to the areas involved. There may be regional adenopathy with necrosis and sloughing of the overlying tissues and skin. The tonsils, when involved, have in some cases sloughed away.

Richards[67] gives us a very vivid description of the typical agranulocytic lesion. He says, the most common site is on the tonsils, which at first are enlarged and reddened, but soon become covered with a greyish or yellowish exudate which may cause sloughing of the involved areas. The typical mucous membrane lesion of the disease is characterized first by an intense local exudative inflammation not unlike that caused by Diphtheria. This is soon followed by an ulcero-gangrenous process which often causes sloughing of the involved mucous membrane, producing additional or multiple ulcerative lesions, of identical appearance. These may coalesce to produce an irregular, extensive lesion, or there may be isolated ulcers on various parts of the mucous surface. The

base of the ulcer is usually filled with a thick, yellowish or greyish necrotic exudate which emits a strong, fetid odor. Fortune [68] says the usual findings are those of an acute infection with extensive necrosis in the local lesion without polymorphonuclear infiltration.

In the Annals of O.R.L.[69] we find the the mucosa change in agranulocytosis is always an ulcer or slough which follows a sudden undermining of normal mucosa with clinical and histological evidence of the lack of cell reaction or leucocyte accumulation for defense. The lesion may first be seen as a mottled, yellowish spot in the center of the anterior piller before the surface of the mucosa has broken down. It is also seen as a lemon-yellow dot about one-half cm. from the gum margin, when the lesion has begun as an ulcerative gingivitis. Exudates and gangrenous sloughs sloughs of the soft palate or mouth with exfoliation of bone must be regarded as late lesions.

Microscopically[70] there is present an outer structureless layer of necrotic tissue with ulceration, containing numerous colonies of bacteria. This is surrounded by an inner edematous zone of tissue showing varying degrees of nuclear degeneration, permeated by fibrin and at times containing plasma cells and lymphocytes. The vessel walls show necrotic changes and their lumina are filled with hyalin and fibrin thrombi. Absence of polymorphonuclear leucocytes occurs in most cases.

Summary of Observations gleaned on Analysis of Autopsies:

1. The lungs in many instances have shown fibrinous confluent broncho-pneumonia, with little , if any, evidence of inflammatory cellular reaction. Pleurisy with effusion and

and subpleural petichiae have been noted a few times.

2. The liver has sometimes been found to be enlarged, often with perivascular lymphocytic collections. Focal and bacterial emboli have been noted.

3. The spleen is frequently noted as enlarged. Bacilli and inflammatory exudate are found in and beneath the capsule. Marked proliferation of endothelial cells with little if any increase in lymphocytes has been a common feature.

4. In the lymph nodes, small hemorrhages and occasionally hyperplasia of endothelial cells, have been observed.

5. The heart has shown parenchymatous degeneration, subpericardial and endocardial hemorrhages, and in one of Kastlins cases, acute ner endocarditis.

6. The kidneys are mentioned as showing numerous bacterial emboli which were present also in the suprarenal bodies.

7. In the stomach and intestines there may be superficial necrotic foci with a surrounding zone of lymphocytes, bacterial emboli and petechial hemorrhages in the mucosa.

8. The tonsils and pharynx have almost constantly shown ulcerative or gangrenous lesions of greater or less degree. These are often surrounded by an edematous zone and sometimes by a profusion of bacterial collections.

Miscellaneous: Pneumonia may occur and the picture is characterized by the appearance of a diffuse edema. The gross picture is similar to that of influenzal pneumonia if death occurs during the neutropenia. Subpleural hemorrhages are

frequently observed. Microscopically, there is no evidence of pneumonia, but a diffuse acute hemorrhagic edema with little phagocytosis and no signs of inflammation are seen.[71]

CLINICAL CLASSIFICATION:

Type 1. Physiological:

Digestive---normally white blood cells and constituents change during the day.

Storage-----spleen, liver, bones, etc.

Type 2. Leucocytic:

Exogenous---external noxious agents, i,e, bacterial, chemical,allergic, etc.

Endogenous---endocrine, metabolic, or constitutional. allergic.

Type 3. Digestive:

Increased permeability of leucocytes and their appearance in digestive juices in increasing numbers concurrently with their decrease in blood. (seen with pyramidon)

Type 4. Malignant: Primary bone marrow disease.

a). Deficiency.
1. congenital changes in anlage.
2. decrease or absence of a necessary substance.

b). Paralytic.
1. Suppression in formation (maturation arrest)
2. Suppression in delivery

c). Destructive.
1. Congenital changes in anlage.
2. Decrease or absence of a necessary substance.
3. Malignancy.
4. Metastatic bacterial invasion.

Under the heading Physiological, there is little to say, since it is a commonly accepted fact that the leucocyte level varies at different times of the day under normal conditions.

Under the heading Leucolytic, the exogenous is caused by external agents, such as bacterial, chemical agents, allergy, etc. and the endogenous is caused by endocrine, metabolic, constitutional, or allergic changes. These produce a decrease in the peripheral circulation of the white blood cells by their destruction. Examination of the bone marrow reveals no changes and these patients usually improve from their leukopenia.

Under Digestive, an increased permeability of the leucocytes and their appearance in the digestive juices in increasing numbers occurs concurrently with their decrease in the blood stream. This has been described by Sturgis and his Associates of Ann Arbor in their studies with pyramidon in the treatment of Rheumatism. They found that in one case treated with forty grains of pyramidon daily for rheumatism, after a period of about three weeks, the white blood count which was done daily began to fall and reached about 2800 with a 48per cent of Polys. As soon as the pyramidon was stopped, the blood count gradually returned to normal.

Under Malignant type, there exists primary bone marrow disease. The first type of this condition is the congenital deficiency due to changes in the anlage of the primary bone cell. These patients have always been ill, and have always shown an atypical blood count. They are the patients who

develope the fulminating type of this disease, and do not react to any type of treatment. The other type is characterized by an inability of the primary cell to reproduce because of an absence of a necessary substance. These cases are the ones in whom treatment give good results.

The second or paralytic type is the type where there is suppression in the formation of the cells. This suppression is due either to a paralysis of the primary reticulo-endothelial system or to the lack of some substance such as a hormone that is necessary in the formation of the cells. This is termed a maturation arrest. There also may occur a dimindshed supply of this substance or hormone which results in a failure of the cell to reach its normal size. Thesuppression in delivery of the cells is due to a loss in power of the bone marrow to perform this function. In these cases there is an increased number of white blood cells in the bone marrow and a decreased number in the blood stream.

The third or destructive type is subdivided into three parts. The first two causes are well described under deficiency. The third is caused by an invasion of the bone marrow with malignant cells, destroying the bone marrow, and consequently less or no white blood cells are produced. The fourth is caused by metastatic bacterial invasion of the bone marrow producing a similar destruction. There also may be a gangrene of the bone marrow as a result of a deficient or paralytic bone marrow.

LABORATORY DATA:

The results of laboratory examinations in this disease are of the greatest importance, since without following the total leucocyte count, as well as the differential count, at frequent intervals, an accurate diagnosis cannot be made and the progress of the disease followed. It is necessary to distinguish this syndrome from a number of other diseases characterized , in part, by low total leukocyte counts, as well as by lymphocytosis. As a rule, this is not difficult, and can be done easily on a basis of results of clinical and laboratory examinations. It is probable that many cases with characteristics of agranulocytosis are over looked because of inadequate laboratory studies. For comparable results, counts should be made in these at the same hours each day; thereby, cognizance is taken of the rhythmic delivery of granulocytes to the blood stream. Daily leukocyte and differential counts are essential in following the results in any form of treatment. In some cases it is well to make two or three examinations in the twenty-four hour period.

Total Leukocytes: One of the outstanding laboratory findings in this disease is, of course, the marked leukopenia. In a severe, fulminating case, the total leukocytes may be so low as to be practically uncountable. It is necessary in these low counts to use a 1:10 dilution of the blood instead of the usual 1:20. In the mild cases with a relatively slow

course, the number of total white cells may be quite normal at first but may gradually fall to 1,000 or less per cm. The entire drop in the leukocyte count at the beginning of the disease is due to the disappearance of granulocytes. In fulminating cases, when first seen, the total leukocyte count may be 700 or 600. In some cases the counts are reported as low as 200 total white cells. In practically all cases the counts are below 2,000.

Granular Leukocytes: The second most outstanding laboratory finding in this disease is the neutropenia. The neutrophilic granulocytes may range from around forty or thirty per cent in the most chronic and less severe cases to a total absence in the fulminating cases. One striking feature is that their morphology, in practically all cases, is normal. Complete studies on the changing differential counts of the white blood cells have been made in but relatively few of the reports recorded in the literature, chiefly, it is presumed, because of the rapid course of the disease, and secondly, because of the extreme leukopenia, which makes finding of the cells difficult. Dameshek and Ingall[73] repoted in one case the gradual disappearance of granulocytes, most of which were immature forms. A terminal rise in minature granulocytes has been commented upon by Krumbharr[74] who, observing this phenomena in fatal cases of mustard gas poisoning associated with marked leukopenia, walled it a "myelocytic crises." Schilling explained its mechanism thus:[75] "The toxic or infectious agent destroys most of the granulopoietic tissue; the remaining

granulocytes, however immature, gradually or suddenly appear in the blood stream, until finally the available stock of granulocytes becomes totally exhausted, the total count gradually decreasing during this time. Schilling called this a "degenerative shift." In most of the fatal cases of this disease, the maturation factor is absent, but the chemotactic factor is present, causing the granulocytes to continue being delivered to the circulation until the supply is exhausted. The amount of the chemotactic factor could determine the rate of delivery. In cases of "maturation arrest", the normal supply or an oversupply of granulocytes is in the hematopoietic tissue, but a chemotactic factor to call them to the circulation is absent. In these cases when a chemotactic factor is supplied, mature cells are ready to be delivered to the circulation and a few young forms are seen. These observations make it impossible to say at times, from the appearance of the blood slide alone, whether the patient is recovering or whether there is just an "agonal" outpouring of the remaining young cells. The total count in conjunction with the differential count aids in making the decision.

In practically all of the cases reported in the literature the eosinophils were either absent or present in normal or slightly increased percentage. In all of the cases to be reported, they were absent during the attack. The basophils are either absent or in normal percentage.

Viability of Granulocytes: Rutledge[76] and his associates studied the viability of the granulocytes in a case of benign agranulocytosis by supra vital staining. They found that just before and during an attack the motility of the neutrophilic granulocytes became much reduced, and their vitality, as well as there capacity to take the neutral red dye, was much diminished. Their viability was frequently no more than half of the normally expected time of life, and their motility between attacks never approached normal. The eosinophils during this time (they were always increased during an attack in this patient) showed on the contrary, great motility and increased viability.

Lymphocytes: The lymphocytes may at first be present in their normal absolute numbers, the entire drop in the total leukocyte count being due to the disappearance of neutrophilic granulocytes. As the disease becomes more and more severe there is a relative increase, but in most instances an absolute decrease, of lymphocytes. Although they may become greatly reduced, the morphological characteristics, as arule, remain perfectly normal. The mechanism of the reduction in lymphocytes is obscure, as there is no evidence of the destruction of lymphoid tissue. Only theiries can be advanced. If the pathological changes in the lymph nodes as reported by Huefer and Garrison[77] are present in all cases, they may account for the diminution of lymphocytes.

Erythrocytes: In typical cases the erythrocytes are not affected. If, however, the illness lasts more than the usual ten days, the erythrocytes may be affected and diminished. In fulminating cases the erythrocytes are not affected because there is not time. The erythrocytes and hemoglobin may have been low before the attack, in which case the decrease cannot be said to be due to the neutropenia, When anemia is present, it is of the secondary type with the erythrocytes more or less achromic and their average diameter less than seven microns.

Blood Platelets: Most authors are agreed as to the normal or the increased number of blood platelets. They may become reduced if the disease is of fairly long duration and the bone marrow becomes more or less aplastic, but ordinarily the patient dies before this eventuality occurs. In agranulocytosis due to benzene and other drugs, the blood platelets are reduced.

Blood Cultures: Many cases have shown positive blood cultures, Strep. viridans, and haemalyticus, Staph. aureus, Pneumoccus, B. Coli and B. Pyocyaneus being most frequently found. These blood cultures have not been sufficiently ignored, especially if they occur late in the disease, since the disease is characterized by an early breaking down of the normal protective mechanism. Many cases have had negative blood cultures.

SYMPTOMS:

The patients arewilted in appearance, the skin is pale, but the mucous membranes are of good color. The weakness, marked prostration and toxic appearance are out of all proportion to the few physical signs. The liver and spleen may be enlarged. The patients are characterized by weakness, easy fatigue, drowsiness and tendency to infection, especially in the oral cavity. The fulminating cases are rapid in progress, with c comatose condition usually preceding death. The disease may last from three days to three months, in rare cases a number of years, and end with death or with recovery. The benign cases usually correspond to the fatal group of cases as far as the early symptoms are concerned.

ONSET:

Fever, chill and sore throat are the usual mode of onset, which may be sudden or gradual. The temperature ranges from 101 to 106 F and is of the continual type. There may be cases however, with no temperature at all. There may be added to these headache, marked palpitation with a tumultous heartbeat general aching, drowsiness and occasionally delirium. Nausea and vomiting present in some patients. There is usually an offensive, fetid odor to the breath, and the tongue is heavily coated.

CLINICAL TYPES:

1. Fulminating, acute type, like the original cases of Schultz. The onset is sudden, with a chill, high fever and necrotizing angina; occasionally there may be jaundice, and albuminuria is frequently present. The blood shows an extreme degree of leukopenia and neutropenia, and the bone marrow reveals a wide spread necrosis of the granulopoietic system. This type is rapidly fatal.

2. Subacute type in which the illness is more prolonged. This type presents the following clinical picture: There are several days of fever, followed by a moderate, soft, tender enlargement of the lymph nodes and spleen, accompanied by moderate to extreme leukopenia and a reduction in neutrophils, often reaching an almost complete absence. There is a relative increase in the endothelial leukocytes, and abnormal forms are sometimes seen. Toward the end of the disease the pharynx becomes red and sore, and scattered, round, superficial, whitish spots appear on the posterior pharyngeal wall. The disease lasts from one to three weeks, and most patients recover promptly and completely.

3. Recurring or relapsing types. The patients with this type have two, three or more attacks several weeks or months apart. The symptoms during an attack may be similar to those in the fulminating or subacute types. Death may occur in the second or third attack; the patients may make a complete recovery, or the process may become subchronic.

4. Subchronic type. In this type the onset begins insidiously. The leukopenia is usually less intense, and the number of granulocytes is higher than in the other types. Some show a high percentage of endothelial leukocytes. There is necrosis of the bone marrow, but it shows an active power of regeneration. The patients may be ill for a year or more and finally recover.

5. Cyclic type. These cases present a chronic, regularly recurring, periodic neutropenia. There have only been two cases of this type recorded in the literature.

Occasionally the five types may be mixed, as subchronic recurring or subacute recurring. These varying types and the degree of severity of the neutropenia may depend on the type and degree of reduction of the maturation factor or the chemotactic factor for granulocytes.

DIAGNOSIS:

Agranulocytosis must be diagnosed early if the nortality is to be reduced.[1] There shoubd be more critical cytologic examinations of the blood, as there is much evidence in the literature that the neutropenia preceded all other symptoms. To wait for the appearance of sore mouth, sore throat, fever and prostration is only giving the army of organisms time for invasion. The patient is ill from several days to several weeks, or perhaps months, before the acute stage in many cases. The history of some of the cases shows that the patients were treated for a week or more for influenza, sore throat, or diphtheria. Diagnosis in a typical case is fairly easy. The symptoms and the blood picture are as characteristic as those occurring in Pernicious Anemia. A typical history is the appearance of sore throat in a middle-aged patient, usually debilitated, accompanied by chills and fever, ulcerations and then membrane formation in the throat and on the buccal mucous membrane. If angina is absent, with only fever of more or less long duration and with but few clinical signs, the diagnosis is mor difficult. The rule should be to follow up each case of continued fever with frequent leukocytic and differential counts. If angina and fever are both absent and there are only weakness, malaise, and drowsiness, a frequent leukocytic and differential count should be made. Since many cases are reported to have followed Vincent's Angina and Trench Mouth, a careful study of the blood should be made in these cases. Other cases have been reported following

the extraction of teeth and tonsillectomy, so that a total leukocyte and differential count should precede these operations. The diagnosis is made on the low total count and the neutropenia. Some authors state that normal numbers of circulating erythrocytes and thrombocytes are essential to the diagnosis and do not accept as agranulocytosis any case in which there is a significant absolute increase in lymphocytes or endothelial leukocytes. A sternal marrow biopsy would aid in the diagnosis.

DIFFERENTIAL DIAGNOSIS:

Chronic Agranulocytosis: There is a small group of apparently normal individuals who persistently have a neutropenia or a total white count of 5,000 or below, due to a reduction in the number of granulocytes. These people are in good health, respond normally to infection, and apparently do not in any way belong to the pathological grouping of neutropenia.[78] There is another similar group, however, of chronic neutropenic individuals in whom there is frequently a loss of the sense of well being, loss of energy, abnormal fatigability, a relative lymphocytosis, and a mild shift to the left. Any condition, as an acute infection in these people, calling for more than the usual physiological demands upon the bone marrow, results in a still more marked neutropenia rather than a leukocytosis. The chronic neutropenic, then, loses his normal defense against infection when it is most needed, the infection depresses the marrow still more, so that a vicious circle is formed, and the patient rapidly passes into the malignant type of neutropenia. In such cases the sense of well being is often directly proportional to the total white count. Just why these persons begin with a chronic insufficiency of the bone marrow is not clear unless some specific toxic agent can explain it.

Aplastic Anemia: This usually occurs in young individuals who are in a fair state of nutrition. The patients show a definite yellowish or grayish pallor of their skin, usually with hemorrhages into the skin and mucous membranes. An angina is usually present accompanied by a septic type of temp-

erature. The blood picture shows: 1.A leukopenia with a relative lymphocytosis; 2. A severe anemia often as low as 500,000; 3. Thrombocytopenia; the platelets are usually less than 75,000. In other words there is an aplasia of the bone marrow as a whole, and at autopsy the bone marrow is found to be soft, yellow, and almost completely replaced by fat. The outcome in all cases is fatal and no form of treatment has proved efficacious.

Leukemias: Agranulocytosis can be differentiated from lymphatic reactions by the fact that in lymphatic reactions there is an absolute increase in lymphocytes, which replace the neutrophils to make the total leukocyte count normal or increased. In the lymphatic reactions there are usually many abnormal lymphoid cells, while in agranulocytosis most of the lymphocytes are normal. The differential diagnosis between acute leukopenic lymphatic leukemia and agranulocytosis may be so difficult as to be well nigh impossible.[1] In rapidly developing acute leukemia, the leukocytes may fall as low as 1,200 or 2,000. The biopsy on the bone marrow will establish the diagnosis in doubtful cases. In the leukemias there is a crowding of the marrow with lymphoid cells. Chronic leukemial with low values for leukocytes also must be ruled out.

Diphtheria: This is to be differentiated by appropriate clinical means, and also the difference in bacteriological and pathological respects. A positive blood culture will cinch the diagnosis.

Acute Leukopenic Leukemia and Aleukemic Leukemias can be distinguished from agranulocytosis by the existence of a generalized hemorrhagic diathesis, secondary anemia, thrombopenia, lengthened bleeding time, tenderness of the lower part of the sternum and characteristic pathologic alterations such as leukemic infiltrations in the liver, spleen, lymph nodes and kidney.[79]

Influenza and Typhoid fever are differentiated from agranulocytosis in their course and their bacteriologic and pathologic manifestations in spite of the existence of a certain resemblance in acute cases in the beginning.

Infectious Mononucleosis: In this disease there occassionally may be seen low values for leukocytes. In this condition, the injection of foreign protein will result in an increase in the circulating neutrophils. The clinical manifestations are usually much less severe than in agranulocytosis.

PROGNOSIS:

In the beginning, the mortality was reported as 100 per cent. Kastlin[12] in 1927, reported a mortality of 95 per cent. Harkins,[8] in 1931, reviewed the literature and stated that up to the date of writing at least 150 cases with 27 recoveries had been reported, the approximate mortality rate being 82 per cent. In 1931, Rosenthal[49] reported a series of 26 cases, twelve of them being fatal, giving a mortality of 46.2 per cent. Many of the remaining fourteen patients who recovered had been under observation for six years. Taussig and Schnoebelen[80] in a review of 328 cases, found that the mortality was 75 percent 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[81] reported a mortality of 30 per cent in 54 typical cases of agranulocytosis in which treatment consisted of nucleotides. It will be seen that since 1927 the reported mortality rate has steadily decreased. The increase use of blood counts will probably cause the reported mortality rate to continue to decrease. Fulminating cases are rapidly fatal, while recoveries are to be expected in those cases which are more prolonged and milder. Very few patients recover if the total count falls below 1,000. Kracke[42] reported one case in which the leukocytes fe fell as low as 470 and the patient recovered, only to die in a second attack.

Wyatt[82] reported one case in which the patient recovered after surgical drainage of multiple abscesses. Many recoveries are reported following neucleotide therapy, the mortality with this form of treatment being the lowest. A great many patients are reported to have recovered without any active form of treatment. Recoveries and deaths are reported with all forms of treatment. It can be seen that reduction in mortality cannot be ascribed solely to any one mode of treatment. It seems more probable that the reduction is due to the recognition of more cases, owing to more critical studies of the blood and thereby the inclusion of the more chronic cases in the group. In the early stages of the disease the outcome cannot be determined, as in the cases showing myeloid aplasia it depends entirely on whether maturation of the granulocytes will be resumed. In the cases showing peripheral neutropenia and normal or hyperplastic myeloid tissue, the out come depends on the resumption of delivery of the cells to the circulation.

TREATMENT:

A review of the literature reveals that a specific and satisfactory treatment has not been discovered. Most of the authors have the same idea, believing, that recovery, when it does take place, is spontaneous, and not influenced by the type of treatment. Many cases areon record in which spontaneous recovery took place in what seemed , in the beginning, to be a fatal case. Such a case was reported by Hamburger[82] in a patient with 1,500 white cells and two per cent neutrophils. This patient recovered in four weeks with out any active treatment, and was still well five years later. Beck [1] had a patient under her observation that recovered without any active treatment except a diet rich in Vitamin B. There are also many cases in which recovery occured where several types of treatment was used. In this way it is impossible to draw any decisive conclusions as to the efficacy of the measures that were used, or to say which, if any, was responsible for the cure.

In treating this disease, it is necessary to put it under two headings. 1. Treatment in the acute, fulminating cases, which means employment of some agent to stimulate maturation of the granulocytes and cause their delivery to the circulating blood in the shortest time possible. The mere absence of granulocytes from the blood stream for seven days is probably incompatible with life, and in a system devoid of granulocytes infection quickly takes place.

2. One must consider the treatment of patients with chronic cases with the object of preventing a recurrence if possible.

The mouth and throat are the sites of the most frequent local lesions. An antiseptic that will not cause a chemical destruction of the tissue is advised. Hamburger [82] advised the following: 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, ten grains to the ounce. This may be given as often as five times per day, and less frequently as improvement takes place.

Phlegmonous masses in any locality should not be incised unless absolutely necessary, since no local abscess forms under the existing granulopenic state. After the neutrophilic granulocytes return to the blood stream in sufficient numbers, abscesses may form, and incision and drainage may be instituted if necessary.

PREVENTIVE TREATMENT:

There is little definite information available as to the management of chronic cases and the prevention of recurrence of acute attacks. Roberts and Kracke [83] made a statistical study of 8,000 records of leukocyte and differential counts from a series of ambulatory patients seen between 1920 and 1930. Their study points out many interesting facts. In the granulopenic group of this series, the count

ranged from 4,000 down to 1,000. There were 1,881 patients with a granulopenia, or one of every four. This number is significant, since agranulocytosis developes chiefly in patients with granulopenia. In this group the chief complaint was weakness. The evidence accumulated indicates that weakness, exhaustian, fatigue, and tendency to sleep are the chief results of a depressed granulocyte count. Patients who have had more than one attack know by their feelings when granulopenia is present. A great many patients give an history of great mental stress or emotional shock. A number of patients with chronic cases improve with rest. Therefore, rest and freedom from mental and emotional stress should be advised. It would also seem advisable that such patients should refrain from using any drugs shown to have a depressing effect upon the granulopoietic tissue, such as those containing the benzene ring. It would be advisable, also, to attempt to clear up any foci of infection, being especially solicitous concerning oral hygiene. A generous amount of vitamin B. should be included in the diet. Routine blood counts should be studied with great care, and all patients having a granulopenia should be under careful observation and frequent blood counts should be made.

Diet heretofore had not been credited with much importance in the role of treatment. Doan [84], experimenting with pigeons by underfeeding, reduced the red marrow of the radius to an extreme hypoplasia. There were only three components left: blood messels, fat cells and a minimal residue frame-

work of reticulum and reticular cells. It has also been found that the total number of cells per cc. mill, in childrens marrow, seemed to be dependent on the state of nutrition. If this can be proved and the dietary factor that has a specific influence found, it will have a most practical bearing. A diet rich in vitamin B. has been suggested, especially in the chronic, recurring and cyclic cases.

Treatment of Agranulocytosis due to Arsphenamine:

Foster[85] successfully treated patients with agranulocytosis due to arsphenamine by the intravenous use of sodium thiosulphate. Similar successes have been reported by Kennedy [86], and O'Leary and Connor [87]. Although sodium thiosulphate may be given by mouth, the best results are obtained through the intravenous administration. McBride and Dennis [88] advised that it be given in not more than 20cc of distilled water, with dauly intravenous injections as may be necessary, in doses starting with 0.3 gram and increasing by 0.5 gram daily. Sodium Thiosulphate is nontoxic in doses up to two grams. It has been proven that there is no stimulating or specific action attributed to transfusion in these cases. There seem to be warning or prodromal symptoms in these patients as seen by Moore and Keidal [89]. They are manifested by itching, mild rash, prolonged fever, malaise or any tendency toward purpura.

TRANSFUSIONS:

Transfusions have been used in many of the cases reported some of the patients recovering and others dying. Transfusion is essentially empirical. No definite conclusions as to its efficacy could be frawn from the literature. In practically all of the cases, other measures were employed along with the transfusions. It is an established fact that repeated transfusions lower the rate of erythropoiesis [90], and perhaps granulopoiesis. There is no evidence that transfusions actually stimulate granulopoiesis or that the neutrophils added in 500 cc of blood would be os any assistance, as the life of the neutrophil is short (five days), and the number added would be quite small compared to the number needed.

IMMUNOTRANSFUSION:

The word immunotransfusion means a transfusion of blood which has been immunized by an autogenous vaccine of the patient.

In June, 1930, Fisher [91] reported the successful treatment of a patient with agranulocytosis by immunotransfusion. The patient was a nurse, aged 24, who had suffered with sore gums and malaise for two weeks. As Vincent's organisms were found on the gums, she was given 0.4 grams of neoarsphenamine intravenously. The next day she was much worse; sore throat developed, and she was admitted to the hospital. The white cells totaled 1,200 with 6 per cent granulocytes. The second

and third day she was treated with an ordinary transfusion of 500 cc of unmodified blood, 25,000,000 dead typhoid germs and an ampule of sodium nucleate. There was no improvement in the symptoms or the blood picture. On the fourth day of her illness a donor of the same group, who had recovered from this disease in 1927, was secured, and 500 cc of his blood was given to the patient. The third day after this transfusion, or seven days after the diagnosis had been made, the total count was 7,800 and there were 21 per cent granulocytes. (In a spontaneous recovery, improvement occurs at about this time also.)

In Nov. 1930, Harkins [8] also treated a patient with agranulocytosis successfully by giving a transfusion of 500 cc of blood from a patient who had recovered from the disease. However, no definite conclusions can be drawn from these two cases.

On the other hand we know, if a recovered patients serum contained immune bodies, relapses and recurrences should not be the rule. One attack does not give immunity from further attacks.

Rational of Roentgen Treatment:

The marrow in the shafts of the long bones in an adult is mostly adipose tissue, having little or no blood-forming function. When pathology or excessive demand exists, there is a formation of new centers by differentiation of the myeloblasts into granular myelocytes, the adipose tissue of the

bone marrow being replaces by this newly formed tissue. One theory is that irradiation may aid in the formation of this new tissue. The only way of proving just what effect, if any, the roentgen ray has directly on the yellow marrow would be through biopsy as soon as the young granulocytes were appearing in the blood stream. Some investigators say that one cannot be sure whether the apparent stimulation is the result of chemical changesin the blood or is due to the roentgen ray itself, or whether the recovery is spontaneous. Certainly, there is no evidence that a cell per se is affected by the roentgen ray other than in a destructive manner.

Some emminent investigator has said,"It is evidently essential that as large a surface of the body as possible be subjected to irradiation. Whether, thereby, a direct effect is exerted upon the bone marrow, or an indirect effect by the irradiation of other tissues is also an open question." Also, the effect of the roentgen ray may be indirect, stimulating organs of internal secretion to produce maturation products for granulocytes. Doan's [25] theory is that the roentgen ray benefits the type of case showing peripheral neutropenia with hyperplastic myeloid tissue. The roentgen ray in these cases brings about a primary destruction of some of the intact myeloid foci with a liberation of autogenous nucleotide, which then initiates the maturation and delivery of granulocytes from the remaining myeloid foci. Coll and his associates [92] reports that it appears that the roentgen ray might have an important role in the stimulation of the granulopoietic tissue, but definite proof is lacking.

NUCLEOTIDE THERAPY:

The nucleic acids of the animal body occur mainly in combination with protein material in the so-called nucleoproteins of which they form the characteristic radicals. The amount and character of the protein with which the nucleic acid molecule is combined vary, and the acid may, in certain cases, be found in cells in a free form. Those tissues are richest in nucleic acid which contain the largest amount of nuclear material and of nucleoprotein, such as glandular tissue, thymus, spleen, liver and hematopoietic tissue. The nucleic acids are a distince class of substances, characterized by their decomposition products. Nucleic acid on hydrolysis yield the purine and pyrimidine nucleotides. The purine nuccleotides on further hydrolysis finally yield the purine bases, adenine, and quanine.

The first work done on the nature of leukocytosis produced by nucleinic acid was by Ames and Huntley.[93] Jackson[94] was the first to demonstrate that pentose nucleotide existed in normal human blood. This substance is known to exist principally in the nuclei of living cells. Doan and his Co-workers,[24] in their experimental work with large doses of nucleic acid, showed clearly its chemotactic effect. They also found that with nucleic acid there was a leukopenia preceding the leukocytosis, owing to a temporary storage of the granulocytes in the spleen. Then they found that the granulocytes could be called from the marrow by the split products of nucleic

acid, adenine and guanine, and that after giving these substances the leukocytes were not withdrawn from the circulation by the spleen, so that there was a direct leukocytosis without the temporary leukopenia. Reznikoff [95] reported four cases of agranulocytosis, in three of which the patients recovered following treatment with nucleotides. This investigator actually used purine bases, a decomposition product of nucleotides, as he himself pointed out in a later issue of the same journal.[96] These substances given intravenously to rabbits, caused a marked increase in the number of neutrophilic granulocytes without any effect on the temperature or any other cells. Adenine sulphate or guanine hydrochloride was used. Other therapeutic agents were used along with this, so no precise conclusions can be drawn. Jackson and his associates [97] in their series of cases, used the unbroken pentose nucleotide, called nucleotide K-96. Twenty patients were treated. Thirteen had agranulocytosis, five leukopenia and neutropenia due to an infection, and two benzene poisoning. Of the thirteen patients with agranulocytosis treated, seven 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. They 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

Pernicious 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. There is no definite experimental proof, however, that nucleotide K-96 supplies a maturation factor for granulocytes.

It seems only reasonable to presume that if the cells are not developing they cannot be called to the circulation. Jackson and his co-workers concluded: "We believe that these nucleotides may have a definitely favorable effect on the average inactive bone marrow and in certain cases of agranulocytosis, and we believe that the substance is worth further trial in such cases.

Jackson, Parker, and Taylor [81] reported a series of 69 cases collected from various sources of which 74 per cent recovered after pentnucleotide treatment. Cases treated with pentnucleotide have also been reported in England by Bulmer, Fairley and Scott [98] and Marriott; of these two recovered, the case of Fairley and Scott being fatal.

Wilkinson [99] presented a case to the Therapeutic Trials Committee of the Medical Research Council. This case was treated with pentnucleotide and full recovery was made. This case presented the typical features of agranulocytosis; namely, rapid onset, mouth lesions, low pathogenicity of organisms isolated from these lesions, and a myelocytic response following pentnucleitide therapy. The question arises again-

Is the recovery truly due to the therapeutic agent involved, or is it a spontaneous recovery. However, before Nuclein therapy agranulocytosis seems nearly always to have ended fatally.

Smith [100] presented a table worked out by Doan in 1932, showing the per cent mortality of this condition and how it varies with different treatment.

TREATMENT	CASES	DEATHS	% MORTALITY
Untreated	--	---	90 plus
Miscellaneous	198	133	74
Arsphenamine	33	24	72
Blood Transfusion	53	34	64
Irradiation	64	34	53
Nucleotide	44	11	25

Smith also presented a case in which pentnucleotide therapy was used and on the fourth day improvement was noted and four weeks later the patient was discharged from the hospital fully cured.

SUMMARY

The literature today is full of case reports of the disease just described. It is most difficult to give everyone's view as to etiology, morbid anatomy, treatment, etc.

In this paper I have tried to give you, in a more or less concise way, a general summing up of what we know today of agranulocytosis. It may well be called a disease of the blood, but whether it is one of failure of the bone marrow to produce the needed cells, or failure to deliver them to the blood stream has not, as yet, been definitely decided.

I have given you some ideas of various investigators on etiology, also where the pathology lies, and a brief description of differential diagnosis.

The diagnosis of this disease lies in the blood picture and it depends on the clinician for accurate and early blood counts and differential counts for the early diagnosis.

The pentnucleotid treatment, at present, is the most favored, and this is because this form of treatment has proven itself by giving the desired results.

There is yet much to be done, and it will only be by alertness and desirability to the make the correct, early diagnosis, that we can combat this new disease.

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