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Neutropenia with special reference to differential diagnosis

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NEUTROPENIA
WITH SPECIAL REFERENCE
TO
DIFFERENTIAL DIAGNOSIS

by
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Introduction

The aim and purpose of this paper is to review the current literature upon a fairly recently described syndrome of malignant neutropenia.

This paper will include the history and first description, the nomenclature with the latest terms in use, a discussion of etiology and pathogenesis and a group of symptoms applicable to the malignant and secondary types. A review of pathology and typical blood pictures will also be included. As for treatment, only that which has seemingly given the best results will be discussed.

Due to the great amount of current discussion upon the topic of neutropenia in general, an attempt will be made to differentiate all neutropenias from the malignant type.

"Neutropenia 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." (1)

There is considerable confusion, at the present time, among investigators, many refusing to admit that neutropenia exists as a true disease entity. There is ample reason for this. In a review of published case reports within the past thirty years, it is evident that a group of diseases are being dealt with rather than a single one. The group includes any condition showing leukopenia and neutropenia, no matter what the cause or clinical picture.

Many terms have been used for the condition since Schultz' description in 1922. Schultz called the syndrome, agranulocytosis, a term which is misleading. Strictly speaking the term implies an increase of agranulocytes in the blood, this not being the case. A year after Schultz, Freedman called it angina agranulocytica. This name, again is misleading, implying that one is dealing with an infection of the mouth which causes neutropenia instead of a syndrome of utterly unknown etiology. The confusion has caused other terms to be suggested such as, mucositis, necroticans agranulocytica, sepsis with granulocytopenia, monocytic angina, granulocytopenia, granulopenia and Idiopathic Neutropenia. (4) From the confusion is arising more descriptive and appropriate terms. Schilling (5) has suggested the name Malignant Neutropenia. Rosenthal (6) has added to Schilling's term, benign neutropenia. He, stating malignant as fatal and benign

as those cases which recover. Beck (1) has gone further, adapting Rosenthal's terms and adding terms of her own. She claims that malignant neutropenia should be called either primary or secondary, primary, in those cases of unknown etiology and secondary when the etiology is known. The same is true with the benign type, primary when etiology is unknown and secondary in etiologically known cases.

Malignant neutropenia is comparatively a new condition. If the syndrome, as described by Schultz had been frequent before 1922, it would have no doubt been reported, as blood counts have been made as routine in hospitals for the past fifty years. Pepper (2) in a review of literature found that in 1857 a German, Gubler, distinguished the condition from diphtheria, as did a Frenchman, Trousseau in 1865. Morrell Mackinsie, in 1880, in a manual of diseases of the throat and nose, classified the condition as Putrid Sore Throat, differentiating it from Diphtheria and kindred disturbances, saying that it was a "primitive gangrene of the pharyngeal mucous membrane and originating independently of any other malady." The first report in America of a similar condition, was that given by Brown in 1902 in which he reported a fatal case of acute primary infectious pharyngitis with extreme leukopenia. Turk, a German, reported a case in 1907 and Leale (7) in 1910 reported upon recurrent furunculosis. From 1910 until 1922, no other cases of similarity were reported, then Schultz (2) reported four cases and applied the term agranulocytosis which was a clinical entity in his belief.

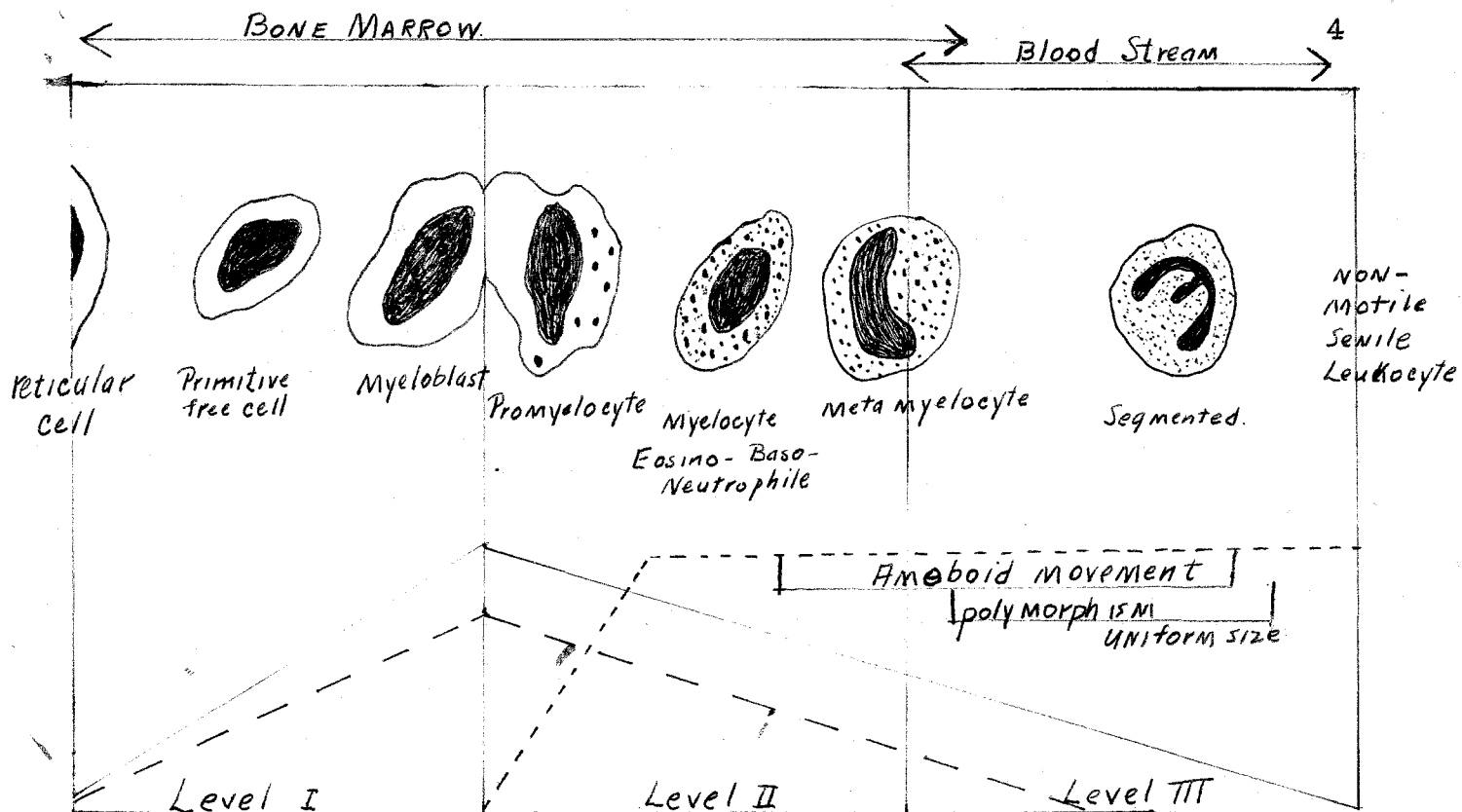
To understand and interpret the pathogenesis of the disease, one must have an understanding of the underlying mechanism of hematopoiesis. The pathogenesis is based upon the knowledge of the normal physiology.

The granulopoietic tissue in the adult is located in the red marrow which is to be found in the ribs, the vertebrae, the sternum, the bones of the skull and ⁰⁵innominatum. It is in the red marrow that

granulopoiesis takes place, normally. The size of the granulopoietic organ of the adult human being has been demonstrated by Wetzel (13) to be 1419 cc, thirteen times the size of the spleen, and about the size of the liver. It is roughly estimated that the ratio between erythropoiesis to granulopoiesis is 1-10. In contrasting the number of erythrocytes in the blood stream to the number of myeloid cells, it would seem that the cells manufactured by the granulopoietic organs are extremely fragile and a delicate product.

Granulocytes arise outside the blood vessels of the bone marrow and pass into them by their own motility. They develop around the patent, dilated vessels or sinusoids of the hematopoietic tissue in the peripheral, vascular zone, and move toward their borders as they become more mature. The young granulocytes exist here in groups at the same stage of maturation and fill the sinuses. They are seen to move en masse against the walls of the capillaries until the wall is bent inward. The stretching reaches a certain point, a leucocyte close to the wall flows in between two endothelial cells and the rest follow in rapid succession.

According to Sabin (14) the primitive cell is a reticular cell found in the interstices between the fat cells of the marrow. Following is a diagram of Sabin's:



In level 1, repeated divisions take place, giving rise to a free cell, - developing, to become a promyelocyte on level 2. In level 2, a change in chemistry of the cytoplasm ~~and~~ promyelocytes, eosinophilic, basophilic and neutrophilic myelocytes develop. In the beginning of level 3 amoeboid activity is at it's height, uniform in size, the cells are delivered into the blood stream, hence to become polymorphism in character, and to the senile stage.

There is a rhythmic delivery of granulocytes into the blood stream, (17) Under normal conditions the duration of time, from a myeloblast to a mature granulocyte is from five to seven days. Animal experimentation has shown that the chemotatic factor plays a part ~~in~~ Administration of inactivated typhoid bacilli, depletes the bone marrow of myelocytes leaving only promyelocytes and myeloblasts. Here is the chemotatic factor minus the maturation factor. The cells of the marrow show no toxic effect and the marrow readily regenerates after the experiment. It was also noted in this group of experiments

that nucleic acid and its derivatives caused the granulocytes to be called forth from the marrow.

The cause of maturation of the granulocytes is unknown. Bacteria that produce a sustained leukocytosis introduce such a factor, as they produce an increased division, growth and maturing of the less mature leucocytes in the marrow far beyond the normal amount. It is thought that the factor is that of altered body proteins. (18)

The pathogenesis of the disease rests upon theory alone. The exact cause of primary malignant and benign neutropenia is not known. Schultz advanced the theory that it might be the result of a depressant effect on the bone marrow of an unknown micro-organism or possibly of an unknown chemical agent. It is towards this goal that all work has been done upon etiology.

It was first thought that there was a predisposition to elderly females but the most recent statistics (17) show that the percentage of females is fifty-six, and all the typical cases of primary neutropenia, age of incidences, is forty-~~2~~ to fifty-eight.

Very little success has been obtained trying to demonstrate an organism that would cause the identical picture. *Bacillus pyocyaneus* (9) has been isolated from human cases and injected into the blood stream of guinea pigs. There was a marked reduction of leucocytes and a degeneration of the leucocytic forming elements of the bone marrow. There is a close similarity between agranulocytosis resulting from hematogenous infection in rabbits with *Salmonella suispestifer*, (8) and that observed in case of agranulocytic angina in man, but it takes an overwhelming infection in the animals to produce the persistent neutropenia and necrosis of bone marrow with signs of regeneration.

The pyogenic organisms have been used in animal experimentation, such as *staphylococcus aureus*, *streptococcus haemolyticus* (10) and *streptococcus viridans*, but none produce the correct picture in human cases.

There has been more success obtained by investigators in regard to chemicals being the etiology. Depressing effects of bone marrow have resulted upon the administration of benzine, ortho-oxybenzoic acid and hydro-quinone. (1) Animal experimentation showed similarity in the chemical and pathological picture. The drugs contain the benzine ring, and it is upon this basis that most of the late experimental work has been done.

Arsphenamine, containing a double benzine ring, has been studied and reported. (2) Similar is a case seen on out call from the University of Nebraska.

Case Report: Mrs. J. K. age 21, white, had received four treatments for syphilis with neoarsphenamine, the treatments being February 12th, 19th and March 5th and 12th, 1934. On March 14th the patient noted headache and weakness. On March 15th, ulcers upon the tongue and mucous membrane of the buccal cavity. An alkaline mouth wash was advised, but the condition progressed until ^alarge, deep, ulcerated necrotic lesion was present upon the tongue and several smaller ulcers of similar character upon the buccal cavity. The temperature at this time ranged from 101 to 102.6. On March 21st the patient complained of pain in the rectum. The mouth condition was more severe and the temperature 104. The patient was admitted to the University Hospital. Cultures were taken of the lesions of the mouth and found to be mixed with a few Vincents and pyogenic bacteria.

Proctoscopic examination disclosed four ulcerated areas in the rectum, the largest, two centimeters in diameter, the other three, one-half to one centimeter in size.

Blood count for the duration of her stay in the hospital is as follows:

	7 A.M	11 A.M 5 P.M.										
	3-24	3-24	3-24	3-26	3-27	3-28	3-29	3-30	3-31	4-1	4-3	
Blood												
Hb.	73%											
R.B.C.	4,340,000											
W.B.C.	4,150	5,000	4800	4600	4800	5200	5000	4900	8000	6300	5500	
Poly.Seg.	0	3	2	3	4	9	19	28	31	36	39	
Poly staff	15	11	9	12	24	19	22	16	19	17	17	
Poly Young	3	10	9	7	4	2	3	2	1	1	1	
Myel	15	5	9	4	2		1	1				
S Lymph	60	40	48	45	45	50	44	39	43	36	28	
Lymph	1											
mono	32	24	14	24	13	19	9	1	4	6	12	
Unidentified	1											
Premyel		4	5	1	1							
Blast		2	3	2	4	1	1	3	1	2	1	
Baso			1		1			1	1	1	1	
Eosin					2		1	1		1	1	

The treatment was symptomatic. Alkaline antiseptic mouth wash, mineral oil in the evening and Sodium Bicarbonate every four hours.

The general condition of the patient became better with the increase of the granulocytes in the blood stream. The temperature gradually descended from 104, on March 24th, to normal on March 29th. The symptoms of headache and weakness diminished in the same proportion.

In commenting, one can say that the history and progress are not complete. Just when did the granulocytes begin disappearing from the blood stream?

The necrotic ulcers were in keeping with the syndrome of Schultz. The case parallels that reported by Dodd and Wilkinson (12) in 1928.

Another possible source of etiology is that of the barbiturates. (15) (16) Fifteen cases reported, showed patients in the habit of using barbiturate derivatives. During the active course of the disease, allonal, amipopyrine, neonal, phenobarbital and amytal were given, immediately following the administration the granulocytes decreased in number. The average age of these patients was forty-eight years, with a sixty per cent mortality. It was thought by these authors that an allergic reaction weakened the granulopoietic tissue.

The general symptoms of primary neutropenia are fairly constant, according to a great number of investigators. (19) All patients have the complaint of weakness and fatigue, the duration depending upon the extent. Malaise and fever is recorded in all patients. The fever with a chill is the usual onset. The temperature ranges from 101 to 106. The disturbing feature being that the patient is in great distress and the toxic appearance is out of proportion to the physical findings. They are wilted in appearance, the skin pale but the mucous membrane has a good color. Some patients are nauseated and vomit. There is an offensive, fetid odor to the breath and the tongue heavily coated. It is believed that lesions of the mouth are due to the break down of the natural barriers which combat the normal habitat of many virulent organisms. Oral sepsis reduces the frequency of lesions in the mouth.

The lesions that are present are located upon the mucous membranes, rarely upon the skin. The most common site is that of the mouth. The tonsils and posterior pharynx is most frequently involved or in seventy-eight percent of cases(19). The gums, tongue and buccal mucous are involved in about forty percent of cases. The next most frequent involvement is the rectum and vagina. The ulcers are most generally inflammatory, with marked edema and gangrenous. The areas quite frequently slough. The membrane, if present, is a dirty yellow or gray in appearance.

There are five distinct clinical types (1) that one must consider in making a diagnosis. The type described by Schultz is the fulminating or acute type, in which the onset is sudden with a necrotizing angina and the bone marrow shows a widespread necrosis of the granulopoietic system. Another type is the subacute type in which the patient may carry a fever and illness is quite prolonged, last; two to three weeks. The greatest

percent of these patients recover(20). The third type is the relapsing type, in which the patient has had previous attacks and seemingly recovered. The symptoms may parallel the fulminating or subacute types either being fatal or recovering. The fourth type is the subchronic. This type presents few symptoms. They fatigue easily, otherwise they are quite normal. There is a low granulocyte count and may carry along from one to six years and recover, spontaneous. The fifth type is the cyclic type in which there is a chronic, regularly recurring periodic neutropenia. (2) Of course the five clinical types may be mixed.

The diagnosis of neutropenia must be made early if the mortality is to be reduced. The most important is the blood picture showing a lack of or diminished number of granulocytes in the blood stream. The symptoms and blood picture are as typical as that of pernicious anemia. In the subacute and subchronic types frequent blood counts should be done as a follow up.

In discussing pathology, one must consider the lesions, changes in the bone marrow, spleen, liver and lymph nodes. The local lesions have been discussed as inflammatory, microscopically there is not an infiltration of polymorphonuclear leukocytes. The infiltration that does occur is mainly lymphatic and endothelial leukocytes. The bacteria present in the lesions are those that are most common at the site of the ulceration.

In the bone marrow is found the most typical changes. (1) In fatal cases the bone marrow is degenerated and varies in color from red to straw. Normoblasts and megakaryocytes are present in normal numbers, but myelocytes and polymorphonuclear cells are absent. In some cases, granulocytes may be absent, but erythrocytes, lymphocytes and endothelial leukocytes are present. The aplasia of the marrow involves the granulocytes only. According to Rosenthal (6) there are two types of bone marrow pathology, "In one type, maturation of granulocytes has ceased, and there are peripheral neutropenia and myeloid aplasia;

in the other type, there is arrest of maturation with peripheral neutropenia and normal or hyperplastic myeloid tissue."

Pathology of the spleen, shows an enlargement, which in some cases is due to the great increase in the reticulo-endothelial cells, which out number lymphoid cells. The lymph follicles are not prominent in the cut surface. The sinuses are filled with erythrocytes and lymphoid cells.

The liver is enlarged and shows some fatty degeneration and cloudy swelling and a few small multiple foci of necrosis. The lymph glands that are involved are usually those of the cervical chain. They are enlarged and contain hemorrhage, and reveal atrophy of the lymph follicles.

The point of major importance is the pathological blood picture. The average range of leukocytes is from 1000 to 2500, with extremes as low as 200, and as high as 4000. The average being 2000. (1)

The diagnostic feature is the finding of neutropenia. In average chronic cases there are 30 to 40 percent. While in fulminating types the granulocytes are entirely absent.

The lymphocytes are not disturbed in the beginning of the disease. The total number of lymphocytes in a normal individual being 1500. With the progress of the disease the lymphocytes become relatively increased, but in absolute numbers there is a decrease. The monocytes are normal at first but relatively increased over the granulocytes, but they eventually follow as the lymphocytes.

The erythrocytes and blood plateletes are normal and not effected.

As yet, a specific and satisfactory treatment has not been discovered for neutropenia. After the syndrome of Schultz was described the literature was flooded with different types of therapy, many without rational

The treatment for this disease must be considered under two headings. First, treatment in the acute cases, which means the employment of an agent that will stimulate maturation of the granulocytes and cause their

delivery to the circulating blood in the shortest time possible. The second consideration is the treatment of the patients with the chronic cases with the object of preventing a recurrence if possible.

In the large percent of cases local lesions are present and must be treated. The lesions, as have been stated are necrotic in nature and without the proper mechanism of defense present, so they must be handled with care. An antiseptic that will not cause too great a tissue destruction should be used. The necrotic areas should never be incised and removed. There is not a danger of abscess formation, because granulocytes must be present before such a phenomenon takes place. Surgical intervention should only take place after the granulocytes have begun to reappear in the blood stream.

A miscellaneous group of agents have been used to produce a stimulation of the granulopoietic tissue. Intra-muscular infections of milk and typhoid vaccine, with idea of foreign protein stimulating production. Turpentine (10) was used without rational. When there was thought of a micro-organism being present, intra-venous injection of gentian violet and acriflavine were used. (1) The gentian violet and acriflavine did not in any way stimulate the production of granulocytes. The use of fetal liver and extract of bone marrow (27) have been used but without gratifying results. Splenectomy (1) and immunotransfusions and administration of calcium gluconate are also numbered among unsuccessful therapy methods.

The treatments that have obtained the best results and will be discussed in order are, pentose nucleotide (24) (25) (26), adenine sulphate (23) fetal calf spleen (28) sodium thiosulphate (1) and irradiation of bones.(22)

In 1924 Jackson demonstrated pentose nucleotide in normal human blood. It was suggested at the time that the bone marrow may normally be stimulated by the disintegration products of leukocytes. In 1931

a non-irritating solution of pentose nucleotide was prepared under the trade name of K 96, and administered to twenty patients (24) with agranulocytic angina. Fourteen of the patients recovered. Another series (25) reporting sixty-nine cases gave good results. Of fifty-four cases of agranulocytic angina, thirty-eight recovered, seven recovered and after a relapse responded to treatment again, two cases who recovered died later in fulminating relapses. The average duration of the disease before treatment was started was 7.2 days.

It is noted that the recovery in this group of cases is quite satisfying. The K 96 was injected intramuscularly in 10 c.c. doses. There was not a clinical or hematological improvement until after the fifth day. This again agreeing with the theory that a granulocyte reaches the blood stream in four to six days.

There is not any definite evidence as to why the reaction takes place, but it was thought by the investigators (25) that the nucleic derivatives had an effect upon the inactive bone marrow, causing the formation and maturation of the granulocytes.

Adenine sulphate has been used with quite satisfying results. As has been stated nucleic acid has been recognized as stimulating leukocytes. The derivatives of nucleic acid, adenine and guanine have the same property. The latest report on the use of adenine sulphate is given by Reznikoff. (23) The dosage for an adult was one gram boiled in 30 c.c. of physiological saline and administered intravenously. The temperature was maintained at 100 to prevent precipitation, and administered three times a day for three days. According to Reznikoff this is not a maximum dose but the results were quite favorable. There was a decline in fever, and an increase of granulocytes within forty-eight hours. In some of the patients as high as 10.4 grams were administered within seven days without ill effects.

In the first group are fifteen patients of primary agranulocytosis. Eleven of the patients recovered, three died within fifteen hours after the administration of adenine sulphate was begun, and the fourth died within two days.

In three of the patients that recovered, there was slight improvement in granulocyte count before the administration of adenine sulphate was begun. This fact must be kept in mind as some observers feel that recovery is spontaneous. As evidence of the increase in granulocytes the temperature dropped and there was symptomatic improvement.

In the second group are eight patients with questionable diagnosis of agranulocytosis. There may have been either a primary disease or a serious complication of agranulocytosis dominating the picture. There was not a clear cut clinical entity represented. At any rate the condition had a neutropenia and was treated as such. Only one of the patients recovered. This group can not be considered as clear cut cases as the complications of anemia, lymphadenitis, multiple bone marrow abscesses, and cardiac decompensation were present.

Reznikoff summarized the report by putting emphasis upon neutrophilic response from adenine sulphate in uncomplicated agranulocytic angina cases. One must consider, though, that only fifteen cases of primary agranulocytosis was reported, before saying that adenine sulphate is the specific treatment.

Fetal calf spleen (28) has been used upon the same basis as nucleotides and adenine sulphate. Spleen substance contains nucleic acid. In a report of five cases (28) of primary agranulocytosis, three recovered from the administration of raw fetal calf spleen. Here again the number of cases is not sufficient to draw any conclusions. The author (28) of the report states: "While it is entirely possible that the patients may have recovered without any specific treatment, and also that they may have a recurrence at any time, I feel that raw fetal spleen is of definite,

specific value in the treatment of agranulocytic angina. The only objections to its use are the frequent difficulty in obtaining a fresh, adequate supply, and the distastefulness of it."

As has been discussed, neutropenia occurs due to the depressing effect of neocarsphenamine. Treatment in this type of cases means removal of the cause and administration of sodium thiosulphate.(1) Sodium Thiosulphate is non-toxic up to two grams. It is administered in 20 c.c. of distilled water by daily injections for four days. Patients have quite a rapid recovery of neutropiles, again in cases of this kind, recovery may have been complete without medication.

Irradiation of bones was first suggested by Friedeman (29) in 1928. Irradiation in large doses inhibits activity of the bone marrow. Smaller doses causes a stimulation to activity. Friedeman used measured amounts, one twentieth of an erythema dose of roentgen rays to the bones of the skeleton, using 6 m.m. of copper as a hard filter. He irradiated the long bones in four cases, giving from one to three treatments, at intervals of from two to several days. He reported that improvement from roentogen treatment may begin within from twenty-four to thirty-six hours, both in the symptoms and in the blood picture. According to Friedeman there is not a standard amount of roentogen ray dosage. One irradiation with one-twentieth skin unit dose may produce a blood crisis in one patient, and in another it may take three doses to produce a change in the blood picture.

In another report (30) of five cases, four recovered and the fifth was moribund when first seen.

Treating by irradiation is not constant in dosage. As an illustration of treatment, one-fourth of an erythema dose was used upon a left femur, with neutrophilic response. Twenty-four hours later the same amount was used upon the right femur. This particular patient (22) on the third day had a relapse, with a neutrophile count of ten percent. Again

irradiation was used to both upper extremities with good response.

Alternating the femurs and humeri for six treatments the patient seemed to be in good condition. The seventh and eight treatments included both legs and arms. The eighth treatment was the last, the patient recovered.

From the reports reviewed it seems that irradiation of long bones has left a question of rational. In the adult, the marrow in the shaft of the long bones is mostly adipose tissue having little or no blood forming function. Yet, when there is excessive or pathological demand there is a formation of new centers of differentiation of the myelocytes, the adipose tissue of the bone marrow being replaced by the newly-formed tissue. It is possible that irradiation may aid in the formation of the new tissue. (30)

Although the results of irradiation of the bone marrow in agranulocytic angina is not definitely certain, the few scattered, good results would justify further investigation and treatment in this manner.

Diagnosis in a typical case of malignant neutropenia is fairly easy. There is a history of a sore throat. The patient is debilitated accompanied by chills and fever and an ulceration and membrane formation in the throat and on the buccal mucous membrane. The blood picture is as characteristic as the one for pernicious anemia.

In cases where angina is absent and with only fever of more or less long duration and with but few chemical signs, the diagnosis is more difficult. So in making a differential diagnosis, all diseases of similarity will be considered.

First, those diseases that have local lesions similar, such as acute tonsillitis, Vincent's angina, diphtheria, septic sore throat, and tubercular and syphilitic ulcerations of the mouth and pharynx.

In acute follicular tonsillitis the symptoms and onset are similar to malignant neutropenia. The tonsils are swollen and have a yellowish-

white exudate filling the crypts. The cervical lymph glands are usually quite large. The mucous membrane of pharynx is a dark dusky red. In malignant neutropenia, involvement of the tonsils is that of ulcerations, and not limited to the crypts alone. There may be slight enlargement of the cervical lymph glands but not to the same extent as in the acute tonsillitis. Another differential point is that of color of the mucous membrane of the pharynx. All mucous membranes in malignant neutropenia are a bright red and quite normal in appearance. Of course, the deciding point in diagnosis would be a differential blood count.

Ulceromembranous stomatitis is a condition described by Vincent in which there is a predominance of fusiform bacilli and spirochetes. The onset and symptoms are mild as compared to acute tonsillitis. The lesions are ulcerative upon the gums spreading posterior to the pharynx. There is a tenderness with considerable bleeding. The lesions become necrotic forming a yellowish exudate which sloughs. The patient suffering with this condition does not have the systemic disturbances as compared to malignant neutropenia. The differential diagnosis is made from a smear of one of the lesions and a differential blood count. One must remember that Vincent's Angina has been suggested as etiological factor in malignant neutropenia, therefore a careful blood analysis is necessary.

The local lesions in diphtheria again simulates those of malignant neutropenia. Upon the tonsils are degenerative changes in the epithelial cells and an abundant fibrinous exudation from the blood-vessels into the underlying tissues. The epithelial cells may be necrotic and the destructive process involving the underlying tissue, the membrane formation extends into the submucosa. The symptoms and onset compare to malignant neutropenia, but the differential point is the appearance of the membrane. The diphtheric membrane is tenacious, being of fibrinous content: The leukocyte count in diphtheria ranges from 15000 to 25000, thereby eliminating a neutropenia.

Septic sore throats of streptococcic origin may simulate malignant neutropenia. The onset is sudden, and the symptoms of fever, pains and sore throat, but the mucous membrane is much infected, more so than the membrane of the neutropenia. The blood count may be low due to the overwhelming infection but the differential count would eliminate a neutropenia.

Ulcerations of the pharynx of tubercular and syphilitic origin do not have the systemic disturbances that accompany malignant neutropenia. A tubercle may ulcerate to the surface and discharge its contents. The discharge is a semi-fluid or fluid pus and does not tend to form a membrane over the jagged edged, deep ulcer. Although tuberculosis is characterized by a leukopenia, a differential count shows neutrophiles present as high as ninety-five percent.

Lesions of the mouth and throat in syphilis are usual nodules which disappear leaving an atrophic brownish area which later becomes white. There is a tendency for the nodules to ulcerate and form large areas of necrotic tissue. The exudate forms a crust, breaking down, and reforming again. These lesions do not carry with them a great amount of pain.

The second group of diseases that need be differentiated from malignant neutropenia are those that have similar clinical symptoms as well as blood dyscrasias. This group includes aplastic anemia, acute leukemia, aleukemic leukemia, infectious mononucleosis, lympho-sarcoma, Hodgkin's disease, metastatic carcinoma to bone marrow and pernicious anemia.

Aplastic anemia (32) is a term applied to a group of anemias which are characterized clinically by a progressive and frequently fatal course and pathologically by deficient or totally absent blood formation.

Two types are recognized, an idiopathic and a secondary type. The idiopathic type was first described by Ehrlick in 1888. The disease occurs in young adults, ages ranging from fifteen to thirty years. The

etiology is unknown but it is thought to be a congenitally defective bone marrow, or an infection with a toxic agent having a special affinity for blood forming tissues.

The secondary type may arise from chronic intoxication with chemical poisons, excessive exposure to roentgen rays and radio-active substances, overwhelming infections, and it may be the terminal stage of pernicious anemia.

Chronic intoxications with chemicals have been reported from arsenical (33) compounds and benzine. Arsenicals are used quite frequently in treatment of disease and the untoward results obtained do not seem to follow the use of the arsenical but rather, it is thought, to the susceptibility of the individual patient with congenital weakness of the hematopoietic tissue. The same theory is advanced in cases of malignant neutropenia from arsphenamine infection.

Many cases have been reported from benzine poisoning. As has been stated on preceding pages the benzine ring seems to be the factor that causes the depression of the bone marrow. The granulocytes seem to be the most susceptible to benzine, the red corpuscles, the least, while the blood platelets are intermediate of the two. The red corpuscles may be affected by the hemorrhage associated with platelet involvement and purpura, and true aplastic anemia may result either primary or as a consequence of exhaustion following hemorrhage or hemolysis.

Exposure to radio-active substances and roentgen rays have depressing effects upon the hematopoietic tissues causing aplastic anemia.

The overwhelming infections inhibit the production of granulocytes and erythrocytes by the toxins produced. The marrow becomes necrotic and unable to produce blood cells.

The symptoms are predominately those of weakness and fatigue. The patient is pale and waxy in appearance. The mucous membranes bleed easily and petechia of the skin are very common.

The blood changes correspond very closely to malignant neutropenia. The red corpuscles are normal in appearance although low in count seldom exceeding 2,000,000 cells. The hemoglobin is proportionate to the number of red cells present. The platelet count is very low. The white corpuscles show marked similarity to malignant neutropenia. The cells formed on the bone marrow, or the granulocytes, are almost entirely absent, while the small lymphocytes predominate, being between eighty and ninety percent of the total white count.

Definite diagnosis of the disease is usually made at autopsy. The bone marrow reveals hypoplasia or complete aplasia. Yellowish-white fat is seen in the marrow cavities. Only occasionally is hterehyperplastic bone marrow.

When one encounters malignant neutropenia without the symptomatic lesions, it would cause some difficulty in distinguishing from aplastic anemia. The marked difference would be the number of erythrocytes present, the number of platelets and the hemoglobin. The autopsy findings in both cases are aplasia or hypoplasia, of the bone marrow, but with some hyperplasia occasionally present in malignant neutropenia.

Acute leukemia (34) may well confused with malignant neutropenia. The symptoms are marked headache, fever, prostration and general malaise. Petechial and purpuric spots may appear. Ulcerations, necrosis and gangrene may appear in the mouth and throat. The clinical course is quite rapid. If blood examinations are made immediately, very little anemia is found. The well cell count in the early stages may not exceed the normal, or even be below normal, then rising 20,000 to 25,000.

Although neutropenia and acute leukemia are similar and could be mistaken in their early stages of symptoms, onset and rapid course, the differentration rests in a very careful leukocyte study. The lymphocytes present account for eighty to ninety percent of the cells in either case, but in acute leukemia there are many immature cells.

Aleukemic leukemia is the term applied to those types of leukemia, myeloid or lymphatic, in which the total white cell count remains normal. The condition is in other respects identical with the more usual form of leukemia and is identified by the qualitative changes in the blood and the leukemic changes in the tissues.

Infectious mononucleosis (1) occasionally has low values for leukocytes. There is mononuclear leukocytosis. With the increase of the mononuclear cells there is an absolute reduction in the number of polynuclear granular cells per cubic millimeter. 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 benign and malignant neutropenia.

Lymphosarcoma or lymphoblastoma often has a blood picture simulating malignant neutropenia. Leukocytosis may occur, if so, the lymphocytes are prominent. The lymphocytes vary slightly from normal appearing cells. The small lymphocyte is slightly larger than normal and containing normal elements. A differential diagnosis would be made clinically.

Clinical differentiation marks Hodgkins' disease. The blood picture is that of slight anemia. The leukocytes are usually normal in number or slightly decreased. The shapes of the cells are also normal.

Metastotic carcinoma to bone marrow involves the hemopoietic tissue. The blood picture at first gives evidence of intense stimulation or irritation of the bone marrow. The blood is marked by anisocytosis, with many macrocytes and nucleated red cells. Irritation of the leukocytic tissue is evidenced by neutrophelic leukocytosis with the presences of myelocytes and myeloblasts. Following the stage of irritation of the bone marrow, there is a crowding out of the hemopoietic tissue, and the condition terminates as an aplastic anemia.

Case Reports. (35)

I Miss A. N., age 24, laboratory technician, entered the Clarkson Memorial Hospital on December 29, 1926.

Chief Complaints: Sore throat, general malaise, and generalized aching.

Past History: Essentially negative.

Present Illness: During the past year, patient complained of feeling "below par". She tired easily in her daily routine of work. Three days before entrance, she was taken suddenly sick with an upper respiratory infection - diagnosed nasal pharangitis. The treatment at that time was local and symptomatic. She seemed on the road to recovery until twenty-four hours before entrance in the hospital there was a sudden elevation of temperature, an acutely sore throat, and generalized swelling and tenderness of the lymph glands. At this point, she entered the hospital. The temperature was 105.8. Pulse-122, respiration-22.

Physical Exam: Wilted appearance, throat was swollen to such an extent that it was difficult to open her mouth. The cervical lymph glands were enlarged and tender.

Course and Treatment: The patient grew worse in clinical signs and symptoms, dying on the third day after entrance. Treatment was symptomatic, antiseptics to mouth and throat. The pharynx and larynx became so edematous that adrenalin was applied locally, but without relief. On the third day tracheotomy was done, the patient died twenty minutes later.

Blood Picture	12-29	12-29	12-30	12-31
Hb.	_____	Not observed	_____	
R.B.C.	_____	Not counted	_____	
W.B.C.	1350	1650	1500	900
Neutrophiles		3(degenerative)		
Lymph, L.	20	20		
Lymph, S.	80	77		

II Mrs. M. L. age 56, white, housewife, entered the Clarkson Memorial Hospital on February 28, 1928.

Chief Complaints: Pain on left side of throat and neck, feeling of fullness in throat, and difficult swallowing.

Past History: Essentially negative.

Present Illness: The patient had not been feeling in the best of health for over a month - she was easily fatigued. Three days before entrance, she noticed a sore throat with difficult swallowing, she became worse and entered the hospital.

Physical Examination: Infected pharynx, left tonsil much larger than the right - ulceration upon the anterior pillar. T. 104.6, P-120, R-30.

Treatment: Injections of antistreptococcus and scarlet fever serums - also sterile milk into the gultaeus. Exit, eighth day.

Blood Picture:

	2-28	2-29	3-1	3-2	3-3	3-4	3-5	3-6
Hb.	70	70	70	70	70	70	70	65
R.B.C.	-----Not Counted-----							
W. B. C.	800	800	400	300	400	400	400	600
Neutrophiles	-----None-----							
Lymph, L.	32	-----Not differentiated-----						
Lymph, S.	60	-----"-----						
Young forms	8	-----"-----						

III Mrs. A. T. age 45, white laborer, entered the Clarkson Memorial Hospital March 21, 1932.

Chief Complaints: Severe Sore throat.

Past History: Three months before present complaint, patient underwent appendectomy, rather a stormy convalescence, but regained good health in two months.

Present Illness: Two days before entrance the patient noted a sore throat, not very severe - but enough to send him to his family physician - the condition progressed, and there was noted a dryness of the mouth and throat - difficult swallowing.

Physical Examination: Tongue swollen and coated, pharynx ulcerated tender - enlarged lymph glands in the cervical region.

Temperature on entrance 99.8 - twelve hours later, 104.8.

Treatment: Fluids and opiates - died 24 hours after entrance.

Blood Picture: Only two blood counts obtained which showed W.B.C-600, and 21 W.B.C on two stained slides, none of which were granulocytes.

Mrs. M. L. age 65, white housewife, entered the Clarkson Memorial Hospital on November 23, 1932, complaining of: severe sore throat, and sore tooth.

Present Illness: The patient noted a tooth ache, consulted a dentist and a second molar was removed one week before entrance. The pain increased and three days before entrance a severe sore throat developed.

Physical Examination: The throat was very much infected, with some edema. There was found an ulceration in the region of the second molar, lower left. The left jaw was swollen and tender.

Laboratory: Smears were made of the ulcerated area in the molar region. Vincent's organisms were found.

Treatment: Forcing fluids, opiates.

Nucleotide, -10 c.c. B. i. d.

Neocarsphenamine .3

Blood Picture:

	11-23	11-24	11-25	11-26	11-27	11-28	11-29
Hb.	70%	-----	-----	-----	-----	-----	-----
R.B.C.	3,890,000	-----	-----	-----	-----	-----	-----
W.B.C.	2050	1000	850	750	760	780	450

Summary

One can receive only a meager knowledge of malignant neutropenia from the preceding pages. I feel that the most definite thing is the pathology found at autopsy.

There is much confusion among investigators as to whether malignant neutropenia is a symptom complex or a clinical entity. The reports on treatment are so varied that one does not know which type to accept. I acknowledge that nucleotide and adenine sulphate therapy reports good results, but the question arises as to whether the cases reported were suffering from malignant neutropenia as described by Schultz, or types of neutropenia secondary to overwhelming infections, chemical poisonings and drug intoxications.

Five case reports are included. One cannot draw conclusions on so few. One case report is that of a secondary benign type, a case seen upon out call at the University of Nebraska. The case represented a toxic reaction to neoarsphenamine, wherein the granulopoietic tissue was paralyzed inhibiting the production of neutrophiles.

Four case reports were found in the files of the Clarkson Memorial Hospital. The case, Miss A. N. was the first case of malignant neutropenia in Omaha. Medical men at that time were very much in the dark as to the condition and its treatment. Two of the other three cases were treated symptomatic, the fourth with nucleotides but of no avail.

To me, malignant neutropenia is a clinical entity and not a symptom complex, ~~but~~ it is a field in medicine, broad with possibilities of research as to etiology and treatment.

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