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Agranulocytosis: its etiology, pathology, and treatment A survey of the recent literature

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Senior Thesis

McCleery Glazier

April 7th, 1936

Agranulocytosis; its etiology, pathology,
and treatment. A survey of the recent
literature.

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INTRODUCTION

In the past few years the condition known as agranulocytosis has apparently become much more common, both in this country and abroad. Its dramatic symptoms and signs, together with its high mortality rate, have brought the disease into sharp relief and have resulted in occasional expression of clear cut opinions as to its etiology, pathology, and treatment which are not, in all instances, entirely justified. In spite of our recently acquired familiarity with the disease, it still remains a mystery in many respects.

Certain authors, Rose and Houser (1), Brog-sitter and Von Kress (2), Zikowsky (3), Aubertin and Levy (4), regard the disease not as a clinical entity but rather as a syndrome common to many pathological conditions and their view may yet be proved correct. Before this question can be definitely answered a large number of cases must be carefully studied both from a clinical and a pathological point of view.

Rose and Houser (1) give a number of arguments in support of their belief that agranulocytosis is not a specific entity and their reasoning is similar to that of many authors who hold the same view. Leukopenia occurs, they say, under many conditions. Yet the fact that anemia occurs under many circumstances does not militate against the fact that pernicious anemia is an entity. They point out that there is no known etiological agent for agranulocytosis and that the condition has not been exactly reproduced in animals; yet it does not follow from these facts that there is no such disease. The etiology of myelogenous leukemia is unknown, nor has it been exactly produced in animals. Consequently I do not believe such arguments can so easily dispose of such a difficult question.

That extreme leukopenia and neutropenia alone does not constitute valid criteria for the establishment of a single disease should be obvious. Several authors, Brogsitter and Von Kress (2), Blumer (5), Pepper (6), Jackson (7), and Doan (8), have pointed out that

hematological pictures similar to that seen in agranulocytosis may be found in many diverse conditions. Yet because one disease may easily be confused with others does not argue that the first is not an entity.

Brogstetter (2), in a consideration of agranulocytosis, lists thirty-four patients with marked leukopenia and granulopenia in which the hematological picture was directly traceable to some other underlying cause. However, in this series of cases, fifty percent were males and in this fifty percent there were nineteen with noticeable anemia and in seventy-eight percent of the cases the platelets were markedly diminished. These are not characteristic findings of true agranulocytosis. Doan (8) believes that only twenty percent of the cases referred to his clinic with leukopenia could be regarded as falling into the narrow classification of true agranulocytosis, while Metteir (9) in a study of 1167 cases of leukopenia, found only six percent in which the cases were not explainable on the basis of some well recognized disease, of which the leukopenia

was but one striking sign. Moderate leukopenia is seen in the course of many infections; extreme leukopenia may occur as a sequel to overwhelming sepsis; it is seen as a result of Benzol poisoning and may be due to the toxic affect of gold, bismuth or arsenic; it is a prominent feature in aplastic anemia; it is not uncommon in severe pernicious anemia and is occasionally seen in both acute and chronic leukemia. There is no doubt but that the majority of patients with leukopenia have some well recognized fundamental disorder to account for this hematological abnormality and further that this disorder is in some instances unrelated, primarily to the hematopoetic system. Lack of appreciation of these undoubted facts necessarily leads to false thinking as regards the etiology, pathology, and treatment of the disease or syndrome, agranulocytosis.

Acute leukemia in the aleukemic phase very closely simulates agranulocytosis and the two diseases are not infrequently mistaken one for the other, (10), (11), (12). In fact, at the

present, the relationship of the two conditions must be regarded as problematical. Yet there would appear to be certain essential differences. Absence or marked diminution of platelets, anemia of moment, particularly if progressive, hemorrhages, especially from the mucous membranes of the mouth notable enlargement of the spleen and enlargement of lymph nodes, not readily explainable by adjacent ulceration and infection, all indicate acute leukemia. In acute leukemia, especially in adults, the blood smear shows a considerable number of very immature cells; often virtually all the white blood cells are stem cells and it is only in the most atypical cases that young forms are few in number, and occasional stem cell may be found in the blood of patients suffering from agranulocytosis. Any very considerable number, however, indicates the probability of a leukemia and the more there are the greater the probability. A level is reached, which is more than temporary, almost certainly means leukemia. During convalescence from agranulocytosis there may be, and in fact usually is, a transient outpouring of myelocytes, but this

stage is soon passed and clinical improvement is coincidentally evident.

Leukemic patients with temperatures of 102 degrees to 104 degrees F may seem comparatively well. This is rarely the case in agranulocytosis. In this latter disease such temperatures are almost invariably accompanied by marked prostration and symptoms of toxicity. In agranulocytosis, the fever is either steady or, more commonly, fluctuates within certain definite rather rather limits. In acute leukemia the temperature curve is often an extremely variable one. Afebrile periods are not rare, even at the height of the disease. It must be emphasized that the total white is of no vital importance in the diagnosis of leukemia whether the white count be 500 or 50,000 per c.mm. The character of the white cells, the concomitant alterations in the red cells, and platelet picture and the pathological changes in the bone marrow determine the diagnosis and serve, at least in the maj-

grity of instances, to mark the one from the other disease. Acute leukemia, furthermore, is the more likely the younger the patient and it is probable that the majority of the extreme leukopenias in children are traceable to leukemia or to some serious disorder of the myeloid system other than true agranulocytosis.

Those cases showing very low red cell counts depart more obviously from true agranulocytosis. The lower the red cell count the less likely the disease is to be true agranulocytosis. With marked anemia, pancytopenia or pernicious anemia with an unusually low white cell count is the more likely the diagnosis, but in certain instances the white cells in the peripheral blood of patients with pancytopenia fall far more rapidly and to a much greater extent than do the other formed elements and if sepsis should ensue one may have as in a case cited by Jackson and Parker (13) a picture more closely resembling true agranulocytosis.

However, this condition can be distinguished as a rule from agranulocytosis by the paucity of platelets, the progressive anemia, the presence of at least a few neutrophils in the peripheral blood and a tendency to bleeding from the mucous membranes. Yet, as with aleukemic leukemia, there may arise great difficulties as it is well within the realms of possibility that one disease may shade into the other.

Bearing in mind these diagnostic and nosological difficulties it does seem, however, that, after discarding the extreme leukopenias secondary to sepsis, a leukemic leukemia, a plastic anemia, pancytopenia and leukopenias of certain metastatic bone tumors, a senic, gold and benzol poisoning, there remains what for lack of a better term may be called agranulocytosis, agranulocytic angina or idiopathic malignant neutropenia. It is of this condition that I will discuss as to its etiology, pathology and treatment.

ETIOLOGY

The majority of the earlier authors regarded agranulocytosis as a direct result of overwhelming infection, Brogsitter (2). Yet gradually this point of view has been changing and there would seem to be considerable evidence that sepsis is not the cause, but rather the result of the disease. That such is the case is attested to by the fact that the white count has been found by many authors to be lowered for several days before any clinical signs or symptoms have been manifest. In a case of Jackson and Parker (13) the white count was 500 per c.mm. or lower for four days before the appearance of any clinical signs or symptoms whatsoever. On the fifth day the patient had an abrupt rise of temperature to 104 degrees F., chills, headache, prostration and severe sore throat. Bacteria has successfully invaded a defenseless organism. I believe it is difficult to envision an infection so potent as to virtually abolish leukopoiesis without

at the same time giving rise to some other outward and visible sign or symptom. It is more logical to assume that the depletion of the available leukocytes renders the organism liable to infection of a most virulent sort. This belief has been frequently expressed (6), (7), (8), (11), (14), and (16). Furthermore, in those instances in which infection appears to be the true cause of the leukopenia, the differential white count and histological picture in the bone marrow are quite different from that seen in agranulocytosis. In overwhelming sepsis the total peripheral white count may indeed be very low but polymorphonuclear neutrophils usually form a large percentage of the remaining cells. Myelocytes and young polys are common, even at the height of the leukopenia. In the unusually active bone marrow all stages of myelopoiesis are seen. Such a pathological picture is never seen in agranulocytosis when the disease is at its height. In this condition the neutrophils virtually disappear from the peripheral blood and in the bone marrow no forms more mature than stem cells, or at

best promyelocytes, are seen unless there has already been blood regeneration and the patient has died of some complication, as is occasionally the case. These pathological changes will be discussed in detail later.

Overwhelming infection can in all probability be discarded as a common cause of true agranulocytosis.

Pepper (6) has suggested allergy to be of etiological importance in the production of agranulocytosis. However, little has been written to substantiate his suggestion.

Jackson, Merrill, and Duane (17) and also Thompson (18) have suggested that some endocrine disturbance is the basis for the condition by the fact that in many instances the disease occurs at the time of menstruation. Thayer and Hansen-Pruss (19) reported a case in which attacks occurred regularly for over twenty years at approximately twenty-five day intervals. This case would seem almost certainly to be of glandular origin. It is doubtful, however,

whether any very large percentage of the cases may be definitely traced to an endocrine disturbance. Thayer's patient appears to be unique and the fact that many female patients suffer from remissions or attacks at the onset of their catamenias does not necessarily lay any very solid foundation for an endocrine etiology of the disease.

The fact that agranulocytosis has increased markedly in recent years together with the known leukotoxic effect of the benzene ring, makes most tempting the theory that some, if not all, cases are due to the administration of amidopyrine and allied drugs, therapeutic agents which have lately become more and more widely used. Madison and Squier (20) draw the following conclusions from fourteen cases cited in their recent article. First, the increase in incidents primary granulocytopenia has paralleled the increase in the use of drugs containing amidopyrine and especially those containing amidopyrine with a barbiturate. Second, the disease has appeared most frequently in persons apt to be taking drugs: physicians,

nurses, and those directly under the care of a physician. Third, in each of fourteen patients the onset of primary granulocytopenia was directly preceded by the use of amidopyrine alone or in combination with a barbiturate. Fourth, the mortality in a group of six patients who continued the use of drugs containing amidopyrine was 100 percent. In a group of eight patients who did not continue the use of the drugs, only two died, and both died of the initial attack. Fifth, the administration of a single dose of amidopyrine to each of two patients who had recovered from the acute disease was followed by a rapid fall in granulocytes. Hoffman, Butt and Hickey (21), Watkins (22) and others have drawn attention to a similar relationship between the drugs and the disease. Seeman (23) however, noted that in thirteen of twenty-six cases amidopyrine or its allies had been taken, yet in fifteen there was definitely no history of such therapy. Similarly Jackson (24) in an analysis of twenty-seven of their cases in which complete and unequivocal data relative

to medication were at hand, found that in only seven of them could the disease be properly regarded as directly traceable to the administration of the compounds. There can be no question but that amidopyrine or its allies are of etiological importance, particularly as Madison and Squier (20) have produced with these drugs mild and transient, but definite granulopenia in patients who had recovered from a classical attack. But there is also no question but that in many other instances there is no such explanation of the cause of the disease. Furthermore, it has been pointed out that the drug may be taken in considerable amounts prior to the onset of the disease. Yet on careful analysis it may appear that it is of no etiological importance whatsoever. Eight of twenty-seven cases studied by Jackson (24) had taken amidopyrine or allied compounds in considerable quantities, yet it could be shown in these instances that the therapy had not the slightest causal relation to the actual disease. Therefore, it is safe to say that the etiological importance

of these drugs is undeniable, but they certainly are not the sole cause of the disease. A special report of the Council on Pharmacy and Chemistry of the American Medical Association (25) concludes that there is, "no question that amidopyrine is very important in the production of granulocytopenia". The report does not say, nor does it imply, that all cases are due to the drugs, nor does it preclude the possibility that there may be some pre-existing bone marrow dyscrasia which affords a fulcrum upon which the drug may work.

In a similar manner dinitrophenol has been shown to be the apparent cause of the disease in certain instances. Bohn (26), Davidson (27), Dameshek (28) and Silver (29) have substantiated this belief. This drug must therefore also be regarded as potentially dangerous, even in therapeutic doses. A familial tendency is rarely seen. In the articles that I have reviewed, I could find no suggestion in the histories of cases that would suggest familial tendencies.

Therefore, when all is summed up, it must be confessed that the etiology of this disease still remains, in large part at least, obscure. That some cases appear to be caused by the administration of certain chemicals or by the action of certain toxins should not be regarded as indicating that the disease is but a syndrome. Pernicious anemia may be due to lack of an intrinsic factor, to radical surgical interference with the gastro-intestinal tract or to malignant disease preventing the proper functioning of such factors as cause a proper maturation of the red cells. In a similar manner a variety of agents, known and unknown, may prevent proper maturation of the granular white cells and so produce the disease, agranulocytosis.

PATHOLOGY

The pathology of this disease is in dispute. Much of this confusion arises from failure on the part of many even to attempt the differentiation, either clinically or pathologically, of the various conditions giving rise to the striking but far from pathoneumonic sign, that of extreme granulopenia. Confusion also arises from too great reliance being placed on the interpretation of stained smears taken from the bone marrow. Such smears are of importance in identifying certain cells not easily recognized in sections stained with eosin-methylene-blue. But from smears of bone marrow one gets absolutely no idea of the number or arrangement of the cells and upon such factors, as well as upon the nature of the individual cells, the diagnosis of any marrow lesion is based. Custer (30) and Peabody (31) have expressed this opinion. Roberts and Kracke (16) say, "there is an unanimity of opinion that the essential pathology is a marked hypoplasia of the myelocytic tissues". In one of their cases

sternal puncture (smears) showed a marrow entirely devoid of granular cells of any type, including even myeloblasts. In the photomicrograph illustrating this feature one would be at a loss to identify any cell according to one author. Dodd and Wilkinson (32) state that the bone marrow is aplastic, but it should be pointed out that they describe the marrow of a colored girl of eleven years with hereditary syphilis who after treatment with sulpharsphenamine developed extreme leukopenia. The condition can hardly be regarded as one of true idiopathic agranulocytosis. Schultz, who originally described this disease entity, is often quoted as believing the marrow to be aplastic. Yet Leon (33), who described the marrow in Schultz's cases, merely says that there were neither mature neutrophils nor myelocytes to be found and that the femur was partly red, partly fatty. Such statements can not be construed as indicating that the author considered the marrow "aplastic". In other instances when

the marrow is said to be aplastic, examination of the original sources discloses the fact that in the case under consideration the tibia or midfemur was examined. It is not surprising, therefore, that the histological picture of the disease is regarded as confusing.

Jaffe (34) found the bone marrow rather more cellular than normal with signs of marked degeneration in the granules of the myelocytes. These granules were said to "fuse with the cytoplasm". Jaffe believed the majority of the white cells to be myelocytes with a moderate or considerable number of plasma cells and lymphocytes. Megakaryocytes, he found in normal or in increased numbers. Fitz-Hugh and Krumbhaar (35) in a most important contribution, postulate a maturation arrest at the stem cell stage with the added possibility of an end stage which might be regarded as aplastic. This seems to be the general trend of thought.

Jackson and Parker (52) studied the marrow of twenty-five cases which they diagnosed as agranulocytosis. The following generalizations were made. The marrow of the ribs, sternum and midfemur

and vertebrae was essentially the same. The degree of cellularity was usually normal. Rarely the femur remained fatty, as in the normal adult. It would seem that in these instances death occurred too soon for the marrow activity to spread peripherally, although this view is not entirely agreed upon. In some sternal and vertebral marrows, particularly in patients dying later in the disease, a certain amount of hypoplasia existed. On the other hand in the fulminating cases the marrow was perhaps unusually rich in cells. The degree of cellularity, however, varied but little and is, they believe, an unessential feature of the condition. There was little or no disturbance in the red cell series. Erythroblasts, normoblasts and nucleated reds occurred in normal or slightly increased numbers and showed no abnormal features. The megakaryocytes also were found in the usual numbers and histologically appeared perfectly normal. With this latter finding of Jackson and Parker, Rotter (36) and Jaffe (34) agree. This seems important since

Roberts and Kracke (16) believe that they hemorrhagic tendency which they regard as a very common symptom to be due to marrow disfunction involving megakaryocytes and a decrease of platelet formation. Most writers have not found such a dyscrasia to exist.

The most marked bone marrow changes naturally occur in the cells of the granular series. No mature granulocytes, either neutrophils or eosinophils, are found in the marrow, nor is there any true myelocytes. Practically every cell that belongs to the granular series is a stem cell. The other cells found are plasma cells or lymphocytes. That this may be construed as a maturation arrest, Fitz-Hugh and Krumbhaar (35), rather than failure to deliver, is evidenced by the fact that the parent cells were often inactive mitosis. These stem cells seem to be able to produce their own kind of profusion. Further maturation is denied.

Rotter (36) finds that in those patients who survive the ravages of infection for a considerable period (eight to twenty days) the bone marrow picture was somewhat different.

It was found to be relatively hypoplastic. Gradually as the disease progressed, the stem cells diminished in number and their place was taken by lymphocytes and plasma cells and in cases dying as late as the fifteenth day after the apparent onset of the disease, the cells constituted virtually the only white cells in the marrow. This late stage would appear to correspond to the terminal "aplastic" stage postulated by Fitz-Hugh and Krumbhaar (35). Phagocytic macrophages were at all times present in considerable numbers, particularly in the late stages of the disease. Such cells have also been remarked upon by Jaffe (34).

It must be recognized that until further work is done we cannot speak dogmatically of the pathology of the disease, the nature of which is still obscure. At present the view of Fitz-Hugh and Krumbhaar regarding a maturation arrest with a predominance of lymphocytes and plasma cells seems most likely.

TREATMENT

The treatment of any disease, the pathogenesis and nature of which is uncertain, is at best unsatisfactory and the more so when that condition may be easily confused with other pathological entities of probably a different fundamental nature. Many measures have been advocated to combat agranulocytosis. None is specific. Most all authorities agree that the major problem is that of restoring the bone marrow to its normal activity and thus raising the peripheral white count; for the loss of leukocytes removes one of the body's great defenses against infection. Without bone marrow recovery, there can be no cure.

Non-specific therapy, such as the injection of sterile milk or turpentine, is conceded by almost everybody to be useless. That one gets a white cell response in normal patients by such therapy is not the slightest reason for supposing that a similar response should occur in agranulocytosis. The probable affect of such treat-

ment in patients with normal bone marrows, is chemotactic, that is the calling force of such mature and slightly young polys as are readily available in the bone marrow, and their rapid and efficient replacement. There are no neutrophils in the bone marrow of agranulocytic patients to call forth.

Transufision of blood has been endorsed by some, (1) and (6), and without question recoveries have followed one or more such transfusions. Aside from the fact that there is not good evidence that blood transfusion has a stimulating affect in agranulocytosis. Indeed, it is not uncommon experience to find the peripheral white count definitely lower after transfusion than before. The number of white cells actually given the patient is small; their life short; and further more, the patient, as a rule does not need either plasma or red cells. In the presence of sepsis, when the white count has risen to normal or abnormally high levels, small multiple transfusions may be of value. There seems to be little convincing evidence that they tend permanently to raise

the white count or stimulate the marrow.

Stimulating doses of X-Ray were advocated by Freidemann and Elkeles (42). They treated forty-three patients. Of these, twenty-three either had sepsis or pneumonia or died within thirty-six hours and all were discarded by Freidemann and Elkeles in evaluating the effects of roentgen therapy. Of the twenty remaining cases there appear to be but seventeen individuals and of these eight died, a mortality of forty-seven percent. It should be recorded for accurate comparison of mortality statistics that in the complete unexpurgated series the mortality was eighty-two percent.

Taussig and Schnoedelen (43) treated four cases by X-Ray with a mortality rate of fifty percent. Other authors unenthusiastically recommend radiation. Reznikoff (44) has expressed the opinion that even small doses of X-Ray tend to depress the bone marrow and he points out that four or five days must elapse before the effects

of any maturant agent can be seen in the peripheral blood. It is usually claimed by those who advocate radiation therapy that hematological changes of a favorable sort were seen in the peripheral blood in a few hours. When such changes have occurred, according to Reznikoff (44) it is due to either a re-distribution phenomena or a spontaneous rise and not to genuine stimulation of a dormant or suppressed marrow. Pepper (6) is not enthusiastic about radiation therapy. Dameschek (10) treated twenty cases with improvement in seven, but a year later only two were living, giving a mortality rate of ninety percent. Therefore, I would say that a critical analysis of the results of radiation therapy does not seem to afford any very convincing evidence of its value.

Roberts and Kracke (16) believe that "sepsis and necrosis are the great hope of every patient with complete granulopenia". It seems to me that this hope is often fulfilled. These same authors, however, say that "there is death unless granulocytes reappear". The implication appears to be

that sepsis and necrosis in and by themselves stimulate the marrow to regeneration and thus restore the leukocytes to the peripheral circulation. It is difficult to prove otherwise but it certainly seems unlikely. That sepsis raises the white count in individuals with a normal marrow is no indication that it will do so in one whose bone marrow contains as far as white cells are concerned, only stem cells. Just how sepsis causes leukocytosis and a hyperplastic marrow in normal patients is not clear. There is no evidence, however, that it does so by stimulating the few pre-existent stem cells to maturation. The sepsis of agranulocytosis is admitted by all to be the result (not the cause) of leukopenia. Those authors with wide experience in the disease have seen cases in which the peripheral white count has risen co-incidentally with the development of abscesses. It does not follow that the abscess caused the hematological improvement. No one has suggested giving pyogenic organisms intramuscularly as a therapeutic agent. Many authors

report a white cell elevation coincidentally with the development of the outward and visible signs of sepsis and, if the peripheral blood be carefully followed, they report often, a sudden drop of leukocytes with abscess formation and to be followed again, in a few hours or days, by a prompt rise to the previous level or even higher level. According to Jackson and Parker (33) the bacteria have been present all along, but no white cells have been available. "Laudable" pus could not be formed; no "abscess" could develop. The return of bone marrow activity supplies these white cells and they have been immediately drawn to the sight of infection, thus temporarily depleting the supply in the peripheral circulation. Hence the transient fall in peripheral white count. Further investigation in this aspect of the disease reveals that agranulocytosis has developed in the presence of pre-existing and patent sepsis. Millmann and Furculo's (38) patient "was stricken in her second attack during a time when she was suffering from two abscesses in the gluteal region". This

would tend to indicate that in this case, at least, abscess formation which has been advocated as a method of treatment of agranulocytosis was of no benefit. Therefore, in this review of the literature, the evidence that sepsis and necrosis in cases of agranulocytosis bring about a regeneration of the marrow is not convincing.

Liver extract has been advocated by Foran (45). He injected the equivalent of one hundred grams of liver into the vein or muscle every eight to twelve hours until a definite rise of total white count had taken place. Four cases apparently true agranulocytosis were successfully treated. Coggeshall (46) injected six vials of liver extract (Lilly 343) intravenously each day. His cases failed to respond. Silver (29) treated a case of agranulocytosis due to dinitrophenol with liver without beneficial results. Bonsdorff (47) treated two cases with liver intravenously with recovery in both instances. However, his first case was evidently pernicious anemia. She had a red count of 528,00 per c.mm., a color index of 1.32 and a white count of 1,750. His second patient had extreme leukopenia, apparently due

to novarsenobenzol and bismuth. The withdrawal of these drugs may well have had as beneficial an effect as liver extract. Bonsdorff (47) implies that because the white cell count rises in pernicious anemia following liver therapy, it should rise in agranulocytosis. Yet the mechanism of leukopenia in pernicious anemia is not known. It may be that it is similar to that which produces the anemia in leukemia, namely a crowding out of one series of cells by an overgrowth of another. If this is so, liver therapy would raise the white count in pernicious anemia by an indirect rather than by a direct method. Therefore, summing up this phase of the treatment, we may say that some few cases have been successfully treated with liver extract, but the ultimate value of this drug at the present time cannot be estimated.

In 1930 Reznikoff (48) advocated the use of adenine sulphate (one of the breakdown products of Pentnucleotide) in the treatment of agranulocytosis and in 1933 Reznikoff (49) summarized the results in fifteen cases with eleven

recoveries. He also treated eight cases in which the diagnosis was doubtful with but one recovery and twelve cases complicating other diseases with two recoveries, and these were temporary. His conclusions in so far as pure agranulocytosis were concerned were conservatively optimistic.

In 1924 Jackson (50) definitely demonstrated the presence of pentose nucleotide in normal human blood. In as much as it has been shown by Doan, Zerfas, Warren, and Ames (51) in 1928, that such products could raise the peripheral white count in normal animals, Jackson (52) decided to try the effects of this substance, presumably a normal metabolite of the intact and healthy organism, in those conditions characterized by extreme leukopenia.

In 1931 he (52) reported the results of such therapy in twenty cases of extreme leukopenia or neutropenia with fourteen recoveries. In 1932 Jackson and Parker (53) reported an analysis of sixty-nine cases, including the original twenty. In the total series the mortality was only twenty-six percent.

Pentnucleotide (N.N.R.) may be given intramuscularly or intravenously. In the average case of agranulocytosis with a white count between 1,000 and 2,000 per c.mm., 10 cc. of Pentnucleotide are given intramuscularly two or preferably, three times a day until the white count has definitely risen and young neutrophils have appeared. This change usually occurs on or about the fifth day of treatment. 10 cc. are then given once a day until the white count has been normal for several days. Most authors advocate in those patients who are extremely sick and especially in those in which the total white count is below 1,000 40 cc. should be given a day until the white count has definitely risen and young neutrophils have appeared. 50 cc. may be given even more advantageously. The drug may also be administered intravenously well diluted in saline by the continuous drip method, the speed of injection by such that no untoward reactions occur. Usually fifty to one hundred drops may be given a minute when 20 cc. of pentnucleotide are diluted in 1,000 cc. of normal saline solution. The drug should be continued in large doses until the

white count has definitely risen and in somewhat smaller amounts until it has been normal for several days, further therapy with pentnucleotide is useless, (53).

Usually there are no untoward reactions of the patient to the drug. In some there is a transient sense of discomfort at the sight of the injection. In others, there may be precordial distress, dyspnea or nausea. Rarely are the symptoms alarming. If, however, they are sufficiently severe to upset the patient the individual dose may be reduced and the number of injections per day correspondingly increased. In this manner one can almost always give the required amount each day. It is useless, especially in severe cases, to give small doses. The drug should never be given to a patient with an anaphalactic history, nor to one with severe cardiac damage.

Doan (37) states that in favorable cases the first signs of improvement following pentnucleotide therapy are evidenced by the appearance of myelocytes in the blood stream. These cells may reach twenty

percent of the total white cells. According to most observers, this change usually occurs on or about the fourth day of therapy and corresponds in certain measure to the reticulocyte rise in pernicious anemia. Shortly thereafter, the temperature falls, the total white count rises and more mature neutrophils take the place of the immature cells.

In one series of one hundred and three patients reported that were treated in this way sixty-nine or sixty-seven percent recovered and are still alive (58). Four additional patients recovered from their initial attack but died in a subsequent relapse. Thus the mortality (thirty-three percent for the entire series) is considerably lower than that generally accepted for the untreated disease, and considerably lower than that for any comparable series treated by any other measures. Taussig and Schnoebelen (43), in three hundred and thirty collected cases give a mortality of seventy-six percent, and furthermore, they scored a recovery for each and every remission. The corrected mortality in their series would naturally be considerably higher. Brogsitter (2) in 1930 found a mor-

tality of seventy-seven percent in sixty-four cases. Fuld (54) in 1930 noted recovery in but twenty-three cases out of two hundred and forty-eight. A mortality of ninety-one percent. Uffenorde (40) found a mortality rate of seventy-seven percent in 1934. In 1934 Roberts and Kracke (39) stated "complete granulopenia is usually a fatal disease during the first or a later attack", and these authors say that they have not seen any of their recovered cases return to complete health. Rosenthal (55) reports ten cases with five recoveries.

Pentnucleotide (NNR) has been used with apparent success by many, (8), (9), (10), (26), (27), (38), (41), (56), (57), (58), (59), (60), (61), (62), and (63).

Zia and Forkner (64) have used it with considerable success in cases of agranulocytosis, complicating Kala-azar. They say, "It would appear that the administration of pentose nucleotide or purine basis offers by far the most satisfactory treatment, not only for agranulocytosis but also for the conditions of agranulocytosis, the result of pyogenic infection

or of chronic benzene poisoning".

Others have had less success, (47), (65), and (66). In not all of these cases was the diagnosis true agranulocytosis.

It is impossible at present to evaluate properly the true usefulness of the drug. It appears to be harmless, even over long periods of time. The mortality of those cases treated with it, seems to be definitely lowered than that in any comparable series treated by any other means. Certain confirmatory evidence is brought forward by the extramudullary myelopoiesis which may be brought about by its injection into animals and the uniformity with which hematological improvement occurs about the fifth day of treatment. The possibility of spontaneous remission must, however, always be born in mind and any individual case cannot be easily dismissed. Patients have received the drug in adequate amounts and recovered only to relapse again with complete therapeutic failure on the second attempt, (65). Patients have received the drug and failed to respond and then recovered

spontaneously, (57). However, the fact remains that no other therapeutic agent has been shown to be more efficient.

Zinniger (66) quoted above as being unenthusiastic about Pentnucleotide, used liver, iron, leukocytic extract, sodium nucleinate, adenine sulphate, and guanine with indifferent results. Silver (29) reports a patient with twenty percent neutrophils and ten percent monocytes that died in spite of liver extract therapy. Zinniger's (66) patient, who failed to respond to pentnucleotide; died two months later, having just "responded" to Addisin.

At present, it would seem that pentnucleotide, provided there are no untoward reactions, offers the best chance of recovery in a patient with agranulocytosis.

It stands to reason that intelligent bedside care, careful nursing, adequate nourishment, and fluids are all a necessary and obvious part of the treatment. The patient must be protected in so far as possible from infection, but to attempt to sterilize the ulcerated lesions by means of

antiseptics is fruitless. Such constant therapeutic nudging serves only to keep the patient awake when he should be resting, but frequent washings of the mouth and throat with soothing solutions may allay the pain, reduce the amount of secretion and make the patient in general more comfortable.

It has been suggested by Beck (15), Roberts and Kracke (39), that surgical intervention is contraindicated. However, in this review, I would say that most authors disagree and believe that such surgery should be undertaken as would be advised in a patient with normal blood.

It is certain that all drugs containing a benzene ring should be immediately and completely omitted. Madison and Squier (20) found one hundred percent in their six cases which continued to take amidopyrine or its allies.

In certain instances, edema of the throat may be so great that deglutition and even respiration may be difficult or impossible. Tracheotomy has been tried in such instances, but I believe most authors consider it of no avail.

SUMMARY

1. Whether agranulocytosis is to be regarded as a disease entity or a syndrome cannot as yet be dogmatically stated, but it is probable that such a disease entity does exist.

2. The etiology of the condition must for the present, remain uncertain. Amidopyrine and its allies, however, may and probably do have much to do with the development of certain cases.

3. The pathological changes in the bone marrow of agranulocytosis consist of a maturation arrest at the stem cell stage. Later in the course of the disease plasma cells and lymphocytes replaced, to a large extent, the previously existing stem cells.

4. Careful nursing and asepsis and intelligent general care of the patient are obviously essential and important parts of the treatment.

5. Pentneucleotide (NNR) intramuscularly or intravenously offers, at the present time, the best method of stimulating the bone marrow to recovery and the results following this therapy have been more satisfactory than those after any other type of treatment.

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