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Granulocytopenia

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GRANULOCYTOPENIA

SENIOR THESIS

By

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INTRODUCTION

Although there is reference in literature of the Nineteenth Century to syndromes similating the disease (granulocytopenia) as we know it today, it was not until the year 1922 that Schultz actually described his case as a disease entity and by so doing, stimulated the interest of the medical profession to further investigation. This preliminary investigation has resulted in unlimited publications on the various phases of granulocytopenia and, as with any recently recognized disease, has flooded the literature with numerous hypotheses as to the etiology and rationale of treatment, some of which are rather bizarre, other of which are very logical, but all of which are necessary steps in the clarification of such an uncertain disease. After reviewing the literature on the subject, it is quite apparent that the final word has not as yet been written but that the work of the last five years has seemingly accomplished the most toward that end.

In this paper an attempt will be made to correlate the various manifestations of the disease with special reference to etiology, pathology and treatment. No attempt is made in this paper to discuss the granulopenic syndrome under the various classifications that have been suggested because no classification has as yet been advanced which is satisfactory.

DEFINITION

Granulocytic cytopenia is a grave disease involving a number of disputed etiological factors and characterized by a marked reduction in total number of white cells with a complete or nearly complete reduction in the percentage of granulocytes, accompanied by aplastic, normal, or hyperplastic myeloid tissue. Following the peripheral granulopenia there may be any number of lesions or symptoms which might follow the removal from the body of such an important defense mechanism. The disease may be acute, recurrent, or chronic.

This definition is taken with modification from an article published in the Journal of The American Medical Association of 1933 by Regina C. Beck, M. D. (1)

HISTORY

As stated in THE JOURNAL (2), the first description of a condition similating granulocytic cytopenia was made by Turk in 1907. However Turk failed to distinguish his cases from the commoner leukopenia of overwhelming infection. This suggestion made by Turk ap-

parently did not stimulate sufficient interest for further study until 1922 when Werner Schultz (3) described a number of cases which revealed an almost complete absence of granular cells associated with a group of pathological findings and symptoms which he declared formed a clinical entity. It was not until the following year that Friedmann gave the name of agranulocytic angina to this syndrome described by Schultz. (4)

Although there is no reference to earlier description of a syndrome which can definitely be classed as granulocytic cytopenia. However there is no doubt that such a symptom complex was described before 1907. As early as 1857, Gubler described a gangrenous angina which he differentiated from diphtheria, and in 1865 Trousseau published a similar description. (5) Morrell Mackenzie (6) in 1880, in his "Manual of Diseases of the Throat and Nose", described a gangrene of the pharynx, distinguished it from diphtheria and scarlet fever, and called it "putrid sore throat". This term was used commonly for about twenty years thereafter.

Pepper (4) states, "It is further interesting to note that by the beginning of the new century the text-books of nose and throat diseases had begun to omit the heading "putrid sore throat", until by the time Schultz described the syndrome there was no description in the text-books which corresponded at all to the picture of

agranulocytic angina. In recent text-books, of course, this omission has been rectified by the description of the syndrome under its present name."

Since 1922 there has been a constant and increasing study of this disease. In 1927, Kastlin (7) collected reports of 43 cases and reported two more, with only three recoveries, a mortality of 93 per cent. Kastlin believed that the disease was not a clincial entity because of the variations in the cases reported. Blumer (8) in 1930 reported a case beginning with numerous boils that became large abscesses, the blood and the clinical course essentially the same as in the cases described by Schultz. Harkins (9) reported eight cases, four of which he considered to be agranulocytic angina and the other four of which he called granulocytopenia because of the anemia and hemorrhagic diathesis, although it answered Schultz's description otherwise. Farley (10) has collected reports of a series of cases following the administration of arsphenamine, which had an agranulocytic period following the therapy.

It is clear that there may be a variety of conditions associated with the low granulocyte count. Stocke (11) in 1930 divided the cases into three groups; one group answering the description of Schultz, a second showing the presence of anemia, and the third a tendency to hemorrhage.

Bacteriologic study has not as yet yielded anything definite. Friedmann isolated Bacillus Pyocyaneus from the blood stream once. (2) Lovett (12) found the same organism in the throat and determined that the isolated organism in the throat caused a relative lowering of the granulocyte count in rabbits. Dasse (13) found the organism in the throat in almost pure culture and confirmed Lovett's animal experiments.

Since Kastlin's report of forty-three cases in 1937, there has been a marked increase in the number of cases reported and in 1934 Madison and Squier (14) estimated that there were over five hundred cases on record.

In the last few years, along with the increasing incidence and increasing number of cases reported, there has been an unlimited amount of material written on the different phases of the disease and much progress has been made toward solving the etiology, as well as in the treatment of the disease.

NOMENCLATURE

Werner Schultz (3), in 1922 proposed the name agranulocytosis. The supply of hematologic terms is so abundant that there is little excuse of choosing such an ambiguous term. The term came into the nomenclature

no doubt, on account of its brevity. Schultz undoubtedly chose the word agranulocyte to describe "neutrophils without granulation" which he had seen in blood smears from cases of leukemia (1). Friedmann (15) being impressed by the usual severe localization of the process in the throat, suggested the name angina agranulocytica. This name was likewise unfortunate in that it implies that the granulocytopenia is a result of the angina rather than a syndrome of unknown etiology. It is now known that cases do rarely occur without angina. Baldridge and Needles (16) pointed out that if the derivation of agranulocytosis is assumed to be agranulocyteosis it would mean an increased number of these very special abnormal neutrophils. On the other hand, if the derivation is a-granulocyte-osis it would mean an absence of increase granulo cytes, or a normal count. They, therefore suggested the name Idiopathic neutropenia, thus making it analagous to idiopathic aplastic anemia and idiopathic thromboctopenia. Kracke (17) brought out the term granulocytopenia as more exactly expressing the actual condition existing in the disease. Boerner's (18) nomenclature is widely accepted and is consistent with that of Kracke's. His nomenclature describes both variations in numbers and percentages of white blood cells. It is as follows:

NEUTROPENIA--a decrease in neutrophils
LYMPHOPENIA--a decrease in lymphocytes
GRANULOPENIA--a decrease in granulocytes

The terms suggested is fitting to such a classification and expressive of the pathology. Many terms have been suggested, some of which are: (1) Mucositis necroticans agranulocytica, monocytic angina, sepsis with granulocytopenia, and agranulosis. Some of the better names that have been suggested are: idiopathic neutopenia by Baldridge and Needles (16) malignant neutropenia by Schilling (19), malignant (fatal) and benign (recovered) neutropenia by Rosenthal, granulopenia by Boerner (18), and granulocytopenia by Kracke. (17)

If a term were to be used which would most acurately coincide with the definition of the disease one would be forced to admit that granulocytopenia would be the most fitting term. It not only accurately describes the disease but also, by similarity of name, is suggestive of the misleading but more widely used terms of agranulocytosis and agranulocytic angina. For these reasons, this syndrome will hereafter be referred to as granulocytopenia.

CLASSIFICATION

When Schultz (3) first described his cases of "agranulocytic angina" he thought them to be a disease en-

tity and it is still regarded as such of some authors. (21) Schultz described only the rapidly fatal type and thought it to be a disease peculiar to women around forty who were approaching the menopause. However, since that time many excellent articles have appeared in the literature tending to prove that there are different phases of this malady, and that it is well to classify them under the primary and secondary types. Kracke (17), Roberts and Kracke (22), and likewise Piersol and Steinfield (23) have classified the different types of granulocytopenia in a most excellent manner. Roberts and Kracke classify them as follows:

1. Agranulocytic states due to chemical poisons, as benzene or arsenic. Agranulotoxicosis.

2. Agranulocytic states due to bacterial infection. Agranulosepsis.

3. Agranulocytic states due to irradiation, as after radium and x-ray. Agranuloradiation.

4. Agranulocytoxis, a disease entity, in which an unkown casue results in marrow, blood, and clinical onsets in the order named and characterized by single or recurrent acute attacks.

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

6. Pernicious anemia, terminal state.

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

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

9. Roseola infantilis.

10. Acute infectious diseases associated with or followed by leukopenia and rarely near agranulocytic states--typhus, typhoid, mumps, measles, malaria, influenza, dengue, phlebotomus fever, Eygptian splenomegaly, and certain pneumonias.

Piersol and Steinfield (23) believe that the syndrome described by Schultz merits the terms of primary granulopenia, and that instances without discoverable cause and corresponding to his original description should properly fit into this category. The term secondary granulopenia, they think, seems appropriate for the larger group of cases due to known causes. The term primary granulopenia therefore, seems to correspond favorably with number (4) or (Agranulocytosis) of Roberts and Kracke's classification. Piersol and Steinfield suggested the following classification:

PRIMARY GRANULOPENIA

1. Acute (Schultz)
2. Chronic (recurrent)

SECONDARY GRANULOPENIA

1. General infections
   Influenza
   Typhoid
   Some exanthemasa
   Sepsis, etc.
2. Focal infections.
3. Chemical (arsphenamine, benzene).
4. Irradiation (x-rays, radium).
5. Blood diseases (leukemia, spleenic disease, aplastic anemia, etc.).

Sachs (21) feels that the primary group should be divided into the acute, subacute, and chronic recurrent. He adds the subacute because two of his cases were subacute and not of a chronic recurring nature.

Rosenthal (20) in his classification made according to the clincial manisfestations and course, divided neutropenia into malignant (fatal) and benign (recovered) cases. Beck (1) suggests that it might be well to divide these into two main classes as follows: (1) primary benign and primary malignant neutropenia, in which the etiology is unknown; (2) secondary benign and secondary malignant neutropenia, the cases in which the etiologic agents are evident or in which one is dealing with examples of well recognized clinical entities.

Madison's classification is similar to that of Piersol and Steinfield except that he adds another subdivision to that of secondary granulopenias, namely, that of allergy. However he admits that the question of allergy is still far from settled insofar as its etiological roll is concerned.

From the above, it is quite evident how unsatisfactory attempts at a classification of this disease have been. The numerous classifications suggested all are based on an etiological basis and as the etiology of this disease is still quite obscure, is it not foolhardy to attempt to classify the disease on such a basis?

PHYSIOLOGY

Much of the accuracy in interpretation of the blood picture in disease is dependent upon an understanding of the underlying mechanism of hemopoesis. The many technics which have been developed for the study of the cells of the blood, together with data on cell origins and differentation obtained from embryologic and experimental investigations, now provide at least a working basis for the approach of the dyscrasias involving the hemopoetic system. There are very few pathological conditions with which the body has to deal, in which one, or more, of the types of cells represented in the circulating blood is not secondarily involved. That these circulating cellular elements may represent an important and powerful increment in the defense forces of the body is a fact attested by repeated observation. G. Lowell Gulland (25) looks forward to the time when the differential count will be more important than the auscultation of the heart.

Maximow(26) describes the granulocytes in the following manner. In contrast to the lymphocytes and monocytes, the granulocytes always contain granules elaborated in their protoplasm. These granules are the same in a given cell but vary in different species and in the different cells of the same species. Another gen-

eral characteristic of the mature granulocyte is the shape of its nucleus, it being lobated instead of constricted or spherical as in the monocyte and lmyphocyte. The granulocytes fall into three general groups designated as: (1) acidophil, (2) basophil, and (3) heterophil leucocytes. In the first the granules in the protoplasm are most often spherical or oval and are electively stained with acid dyes; in the second, they are of similar form, but stain electively with basic dyes; while in the third group the granules, although constant in particular species, differ as to form, size, and staining reaction according to species.

One of the striking properties of the leucocyte is amebism. This property is most prominent in the heterophils. The amebism probably explains in part why the leucocytes are not confined to the system of blood or lymph vessels, but may be found everywhere in the tissues. The leucocytes, in all probability perform their functions only when outside the vascular system. If these cells are needed in any place of the organism, they assemble rapidly in the blood vessels of the region and migrate into the tissues.

The phagocytic activity of the leucocyte is intimately connected with its amebism and as one would expect is most pronounced in the heterophils. Phagocytosis is of great biological importance as it is one of the means

by which the host destroys bacteria.

It has also been shown that the heterophil granulocytes contain proteolytic and oxidizing enzymes. The eosinophils display phagocytosis rarley if ever; however their granules give a marked oxidase reaction. The function of the baso phils and the chemical nature of their granules is unknown.

Roberts and Kracke (22) have found that the loss of the granulocytes from the body for seven days is incompatible with life. Granulocytes are one of the chief sources of immunity, and with their disintegration and release of ferments, they give much active daily immunity to the body. The heterophils are also thought to be the source of complement as well as the various immune bodies such as hemolysins, precipitins and bacteriolysins. (1)

The life span of the neutrophil in the blood stream has been shown to be approximately four days. (22) From this some idea can be obtained of the enormous numbers of granulocytes consumed daily by physiological degeneration.

The bone marrow throughout extra-uterine life is the natural source of erythrocytes, thrombocytes, and the three types of granulocytes. (27) The phagocytic macrophages (clasmatocytes), while always present in the marrow, are quite as regularly and normally found

in spleen, liver, and diffuse connective tissues of the body. However their size and ability to arise in situ throughout the body, as the need presents, tends to minimize their appearance in the circulation. (28) (29) Lymphocytes and monocytes, the remaining elements, which utilize the vascular bed as an avenue of distribution, develop in the lymph nodes, spleen, and in the more diffuse lymphoid and connective tissues of the body. Hence, hemopoesis in its broadest sense involves bone marrow, spleen, lymph nodes, connective tissue and the vascular and lymphatic systems. (27)

Confusion has existed, and still prevails, among hematologists relative to the origins and relationships of the cells of the blood. However it is agreed that all take their first beginning from the mesenchymal cells of the mesodermal layer in the embryo. But thereafter the theories and hypotheses diverge more or less radically; however the essential differences arise more in the interpretation and nomenclature than in opposing objective observations. In the usual hyperplastic red marrow, where blood cells are developing, it is difficult to distinguish the tissue landmarks, which separate and segregate the units comprising different cell strains. This difficulty has been obviated by certain investigators through a study of less complex areas, either experimentally produced (30) (31) or naturally occuring, as in the

zone between red and yellow marrow when hemopoesis is extending. (32) Under these conditions erythrogenesis has been observed to occur in foci separate and distinct from myelogenic centers and it is from this material that we have learned most about the relative location, distribution, and independent origin of erythrocytes and granulocytes. One of the principal dif ficulties to an unanimous agreement upon these intercellular relationships resides in the fact that the all of the cells of the blood continue to arise throughout life as primitive, immature elements incapable of performing their specific functions until after completion of a definite maturation cycle. Most of the criteria characteristic of the definitive cells, and which form the basis for morphological differentiation and classification, are elaborated during this maturation period. Hence, the earlier precursors of each strain of cells lack, in direct proportion to their immaturity, clear cut distinguishing features upon which hematologists can agree.

Maximow (33), in his studies, including both embryonic and adult tissues, was convinced of the hemocytogenic function of the "lymphocyte", in which exits solely to be played upon by the various forces of the body, with the corresponding cellular differentiation being a direct result of the need of the moment. Cunningham, Sabin, and Doan (34) conclude from their studies that a primitive stem cell for the white blood cells may be reco

recognized in the bone marrow, lymph nodes, spleen, and connective tissues. Fixed cells in the reticulum of these organs give rise by mitosis to a free primitive cell, the size of the small lymphocyte. During times of increased demand for myeloid or lymphoid elements these small round cells may be found increased in number in association with the more mature cells of the respective strains. Their studies differentiate this primitive stem cell from the lymphocyte, which they observed to develop into other definitive forms. Numerous authors have taken sides with either one or the other hypotheses. May it suffice to say, that our present information justifies both the position taken by those who have contended that the "lymphocyte-like" cells may differentiate into other specific definitive cell types, and those who have seen no evidence of such a transformation. Those who have used the super-avital and fixed techniques extensively together feel that the early precursors of the "lymphocyte cycle, the lymphoblasts, may be distinguished from the "primitive stem cell" of the whites and also from the myeloblast and monoblast. (34) They claim that the lymphoblasts have a relatively deeper basophilia, larger rod shaped mitochondria, and fewer nucleoli (one or two) than do the leucoblasts of the other two strains of white cells.

Neither hypothesis may be considered as mutually excluding the other, but rather the difference seems to be a question of interpreting just where, if at all, specificity begins and reversible dedifferentiation becomes impossible.

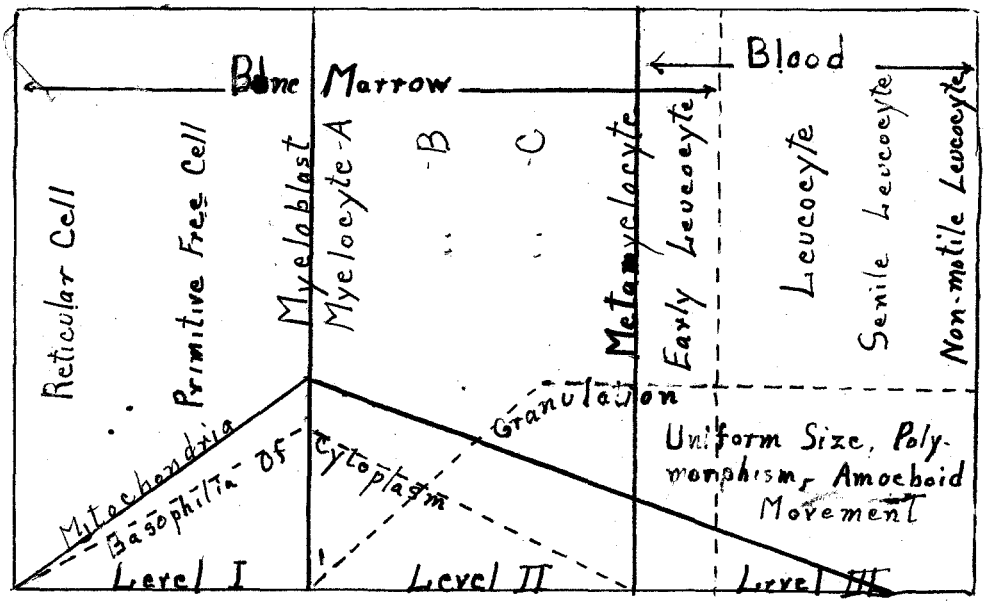


Diagram Of Maturation Of Granulocytes

The above diagram by Sabin (35) expresses very completely certain criteria in the maturation process of the granulocyte. On this chart maturation is represented as a series of varying factors, constantly changing. In some levels, the factors may increase together, in others, some may increase while others decrease.

Sabin gives the following explanation of the chart. Level I is best studied in a completely aplastic adult

bone marrow from which active marrow is readily and quickly regenerated. (31) In such a quiescent marrow, only three types of cells can be seen: fat, endothelium, and reticulum. Of these three, the fat is but accessory to blood formation. Evidence indicates that the red cells regenerate from the endothelium, while the white cells regenerate from the reticulum.

The reticular cells are easily found because they are the only cells lying between the fat cells along the reticular framework. The nuclie have so little chromatin as to make them scarcely more basophilic than the cytoplasm. These cells are probably as close to primitive embryonic mensenchyme as occurs in the adult animal. Mallory (36) describes the reticular cells as a type less differentiated than the fibroblast but also says they may differentiate into a fibroblast. These reticular cells were described by Cunningham and others (37) as to there characteristics and relation to the origin of the white blood cells. These cells can always be found in bone marrow, lymph glands, and spleen, and have been reported along the blood vessels in connective and brain tissues, and nervous tissues in general. (38) In regenerating marrow, this primitive reticular cell, with repeated divisions, gives rise to a primitive free cell. In this process, a few mitochondria are elaborated in the cytoplasm and basophilia gradually develops. (37)

Finally, as the basophilia of the cytoplasma and the numbers of the mitochondria reach a maximum the cell becomes a myeloblast. It is this small primitive free cell which has caused so much confusion in hematology because of its similarity morphologically to the small mature lymphocyte.

The classification of the myelocytes, Level II, by the number of granules was introduced by Cunningham, Sabin, Austrian, and Doan. (39) Myelocyte type A is derived from the myeloblast. It is of maximum basophilia and mitochondria but contains a minimum of granulation. Type B represents the stage during which granulation is increasing, while Type C is the stage at which granulation reaches its maximum. The conventional classification of Level II is promylocyte and myelocyte depending on the changing chemistry of the granules. At the end of Level II basophilia and cell division ceases while amoeboid activity is initiated. The cell first showing amoeboid movement is termed a metamyelocyte.

The third level, marking the end of maturation, is characterized by cells of approximately uniform size and content of specific granulation. These factors mean functional maturity. The nuclei fragment, but cell division has ceased. The leucocytes become more mature in the circulating blood and finally pass into the Arneth pattern involving muclear changes and finally in-

to the non-motile, fragile forms.

Granulopoesis occurs in the more vascular areas and develops around the patent sinuses and moves toward their borders as the cells become more mature; in contrast to the red cells which develop in the area of the closed sinuses, the more mature cells moving toward the center of the sinusoid.

With the concept in mind that bone marrow as an organ is the place where two types of cells are made, that it holds a large store of each strain almost ready for delivery, and that its store of immature forms is small in numbers, but of exceedingly high potentiality toward multiplication, growth, and maturation, the question of the mechanism whereby a normal structure in both the marrow and blood is maintained becomes the major problem of hematology.

Doan (40) and others have shown that whatever controls the proportion of collapsed capillaries to open sinuses is an important factor in the regulation of the proportion of red cells to myeloid elements in the marrow, the ratio being directly proportional. This mechanism, they claim, involves both vasomoter a nd chemical control. Doan and Zerfas (41) give the following myeloid--erythroid ratios: 80:5, 80:4, and 71:13. Sabin (35) after analyzing the works of Krogh, Hooker, Richards,

Rich and others, states that it is not clear what part the vasomoter nerves and what part chemical stimulation of the local endothelium plays in collapsing the sinuses.

Besides the factors controlling the mechanism of maturation, one must also consider the mechanism of delivery of the cells to the circulation. Sabin (35) finds that for admission of cells into the circulation two structures are involved: the endothelial walls of the sinuses, and the blood cells themselves. The granulocytes, as maturation progresses tend to become massed against the capillary wall and eventually bend it inward until finally the tense membrane ruptures between two endothelial cells. The number of leucocytes in the blood is dependent upon two factors: first, the rate of maturation, and secondly, the rate of delivery into the blood. Sabin (35) calls the second factor, a chemotactic factor (C) while the former she designates as a maturation factor (M). Doan and others (40) have adminstered inactivated typhoid bacilli to a rabbit and followed the blood through the stages of leucocytosis. The marrow was finally found entirely depleted of myelocytes C and B and reduced to a low level of amyelocytes A and myeloblasts. Sabin (35) expresses their results as a condition due to a chemotactic factor minus a maturation element. This concept of leucocytosis and leucopenia postulates the infecting organism as introducing both a chemotactic and a maturation factor when leucocytosis results and chemotactic factor alone when a leucopenia follows a temporary leucocytosis.

An important contribution on the subject of chemotaxis was introduced in 1928 by Doan, Zerfas, Warren and Ames (42) in a study of the effect of large doses of mucleic acid. Their studies of the bone marrow showed clearly a chemotactic effect of the nucleic acid, with the massing of leucocytes 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 then found that the granulocytes could be called from the marrow by the split products of nucleic acid, adenine and guanine nucleotide. From this they conclude that nucleic acid and its derivatives are important physiological factors in the chemotactic action, and that the showers of non-motile, fragile leucocytes in the circulating blood may give a rythmic discharge of such products into the circulation and so be responsible for the rythmic discharge of leucocytes from the bone marrow which actually occurs normally.

However, of the maturation factor there is but little known. The physiological maturation factors for white cells are not known, but Sabin (35) has postulated that those bacteria that produce a sustained leucocytosis introduce such a factor for they produce an increased division, growth, and maturing of the less mature myelocytes in the marrow far beyond normal counts. Novy

and Eppler (43) consider that the maturation factor comes from altered body protiens and not from factors introduced into the body from the outside.

Certainly the modern aspect of the problem involves a shift in emphasis from the morphological study to the investigation of the chemical maturation factors. These chemical factors should be sought in bacteria known to affect blood cells, in certain organ extracts, as well as in specific dietary factors, some of which may be vitamines. Such a knowledge of these chemical factors should unravel the conditions which underlie abnormal changes in mechanism, for example, granulocytopenia.

ETIOLOGY

Since the first report of Schultz (3) in Germany thirteen years ago and the report of Lovett (44) in the United States but eleven years ago, cases of granulocytopenia reported have been constantly on the increase until in 1934 Kracke and Parker (45) collected reports of 473 cases from the American and Canadian literature. With this increasing frequence, many investigators have directed their efforts toward the solution of the etiologic factors. The following presents a review of the work which has been done in this field.

GEOGRAPHIC DISTRIBUTION: Parker and Kracke (45) have collected from literature reports of 473 cases from 1922 to 1932 inclusive. They report an increasing number of cases each year probably because of the larger number of cases and its more widespread recognition. During this same period there have been reported some 350 cases in Germany, 100 cases in France and but 6 cases in England. Dennis, in a personal communication with Kracke (45) reported 2 cases observed in Beirut, Syria and states the physicians from Palestine and Eygpt had seen cases. The rarity of the disease in England is significant and will be referred to later. Granulopenia seems to occur chiefly in the United States and Germany.

AGE, SEX, and RACE: Fitz-Hugh and Comroe (46) in a series of 18 cases find the average age to be 48.1 years, the youngest 19 and the oldest 78. Madison and Quier (14) in a series of 14 cases, the youngest 22 and the oldest 80, give an average age of 51 years. Kracke and Parker (45), from their report of 473 cases, find the average age to be between 40 and 50. These authors find that the disease occurs in a ratio of two females to one male. Kracke (45) reports only 8 colored cases to 465 whites. None of the authors report any seasonal variations.

OCCUPATION: Parker and Kracke (45) make the following statement: "It is a striking fact that granulopenia is more prevalent among physicians and their relatives,

nurses, hospital employees, and medical students than in any other group of people. Based on the 1930 population census of the United Sates, it occurs 50 times more frequently in physicians than in teachers." Madison and Squier (14), Stelhorn and Amolsch (47), Harkins (9), and Conner and associates at the Mayo Clinic (48) and others who have made a study of the disease (46), have all madethe remarkable observation that many of the patients were members of the medical or allied professions, or were relatives or friends of physicians. These men have also repeatedly called attention to the fact that this disease occurs for the most part in the better class of our people.

BACTERIA: Lovett (44) in 1924, 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. Windham (49), Keeney (50), and others have made similar observations. These findings have led many to suspect it as an etiologic factor but up to the present time efforts to reproduce the disease in laboratory animals with it, has been unsuccessful.

Kracke and Parker (45), from their report of 473 cases, find 74 of the cases to have positive blood cultures. Among the infecting organism were 26 different

types, which illustrates the wide variety of infecting organisms. Fried and Dameshek (5), reported the experimental production of granulocytopenia in rabbits by the intravenous injection of Salmonella Suipestifer. However they failed to produce a sustained and prolonged depression of the leucocyte count but only a temporary depression, which has well been demonstrated to follow the injection of any killed organisms or other matter in a finely divided state . (23)

There are many reports in 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 this work has been unsuccessful. Piersol and Steinfield (23), injected intravenously into rabbits inactivated cultures, Berkefeld filtrates, and supernatant fluids of cultures of many organisms and failed to reproduce the condition. They called attention also, to the fact that a temporary leucopenia may be produced by the injection of peptones and a large number of other protiens.

Since the works of Ruedeger (52) in 1905, Nakayama (53) in 1920, and Gay and Oram (54) in 1931, it has been known that continued absorption of toxins from sites of focal infections has the property of destoying white blood cells, particularly granulocytes. To this toxin they gave the name of leuccidin. Dennis (55), was par-

ticularly impressed by their findings and in 1923 reported a series of experiments in rabbits which show great promise. From Dennis' study of other cases reported in literature, he learned that the bacteria most often present were Streptococci and Staphlococci. He felt that if viable cultures of such organisms could be enclosed in a membrane which would permit egress of only the soluble products of bacterial metabolism, leucocidins, that experimental agranulocytosis could be induced. He brought about this condition by injecting a living eighteen hour culture of organisms into parchment capsules and sealing the punctures with celloidin. After a thorough soaking in 70 percent alcohol, these capsules were introduced into the abdominal cavities of twenty rabbits, through small incision made under aseptic conditions. Two rabbits received capsules of sterile broth as controls and were entirely negative. Staphlococcus aureus, Streptococci hemolyticus, Streptococci viridins, and B. proteus asiaticus were separately used, all producing granulopenia. Strep. viridins produced, in two animals, a syndrome practically identical with acute clinical granulocytopenia, terminating fatally. From this, Dennis suggests that granulocytopenia in man is due to the action of leucocidin rather than a specific microorganism.

The injection of dead bacteria in the course of vaccination has been suggested as a possible cause. Bromberg and Murphy (56), Kracke (57), and others have

reported typical c ases following typhoid vaccination. However, these cases had received considerable previous medication.

GLANDULAR DYSFUNCTION: The influence of the endocrine glands on the output of both granulocytes and erythrocytes has been studied considerably and has long been suspected. Jaffe (58), studied a patient with generalized infiltration of lymphadenoma which included invasion and destruction of the adrenal cortex with the patient finally dying with a typical granulopenia. He infers from this that the granulopenia was due to a cortical adrenal insufficiency. Britton and Corey (59), have reported that adrenal insufficiency in cats resulted in a marked degree of neutropenia with the return of the granulocytic level to normal following the administration of cortico-adrenal extract. They did not however produce the typical granulopenic syndrome. Kunde and others (60) have noted the production of hypoplastic and aplastic bone marrow in thyroidectomized rabbits. Hubble (60) postulates that bone marrow depression may be caused by a pituitary basophilic insufficiency, and he states th t there is much evidence to indicate that granulopenia may be caused by cortico-adrenal dysfunction. Evidence accumulated indicates that the ductless glands may play a part in the etiology, however, this concept will have to await further confirmation.

RADIATION: Excessive exposure to radiation has been suspected as a possible etiologic factor although it is sometimes used in minute quantities in the treatment of the disease. (45)

ALLERGY: A few authors believe that granulocytopenia may be a form of allergy in which the bone marrow is the point of least resistance. Shilling (19) produced a blood picture similar to that of granulocytopenia experimentally in anaphylaxis, so that he thinks it may be an anaphylactic reaction instead of an individual disease. The cases of Bromberg and Murphy (56), as well as Kracke (57), who received typhoid vaccine, have already been mentioned. It is possible these cases may have resulted from an overwhelming reaction to foreign protein in a sensitive subject, however it is interesting to note that in all these cases there had been previous drug therapy.

CHEMOTACITIC AND MATURATION FACTORS: It has been previously mentioned that two different processes must be considered concerning the mechanism to maintain production and destruction of granulocytes at a constant level(35): (1) the mechanism of delivery of cells to the circulation and (2) the mechanism of maturation. Fitz-Hugh and Krumbnaar (62), from autopsy study of the bone marrow are of the opinion that there may be a definite hyperplasia up to the myelocytic level but that

maturation ceases at that point. Rosenthal (65) and Kracke (64) have independently reported cases in which there was a definite hyperplastic bone marrow at sternal puncture at a time when there was a peripheral neutropenia. Beck's conception of such casis is as follows: In typical cases of malignant neutropenia with myeloid aplasia, the part of the bone marrow that manufactures the granular leukocytes, level I, has ceased to function, or nearly so. The life of the granular cells of the blood stream being but from 3 to 5 days, when level II and III are exhausted, the granulocytes of the blood stream will totally disappear in from 3 to 5 days thereafter. There is little evidence that the granulocytes are abnormally destroyed in the blood stream. The bulk of the evidence points to the fact that the primary lesion, so far as is known is the granulopoetic area of the bone marrow, and that this condition precedes the clinical symptoms and local infections. She reasons that the primary lesion is not in the bone marrow but in the organ or tissue which give rise to the substance (maturation factor) that keeps the granulocytes to a normal blood level or keeps the destruction and production at a constant level. She points out that the text book picture of pernicious anemia can very aptly be substituted for that of malignant neutropenia and as a ma-

turation factor for erythropoesis has been found, so it remains but to find the maturation factor for granulocytes. She suggests that a chemical analysis of bacteria known to produce a leucocytosis might lead to a solution but that it seems more logical to search within the body for the particular organ extract regulating granulopoesis.

The other group of patients showing peripheral neutropenia with slight hypoplasia, normal, moderate, or marked hyperplasia of the myeloid tissue, she considers as due to a lack of the chemotactic factor. The cells may be growing and maturing but are not being called to the circulating blood. The normal stimulus for calling the granulocytes from the marrow to the circulating bood has been shown by experimental work (42) to be the liberated products (nucliec acid, adenine, guanine, and etc), from disentegrating granulocytes in the blood stream. This theory, she points out, could account for failures in the treatment of patients with nucleotides who clinically were similar to those who recovered under such treatment. If the maturation factor is absent, a chemotactic factor would be of little value.

CHEMICALS: It has long been known that various chemicals will depress the bone marrow function, resulting in partial or complete inhibition of one or all cel-

lular types. Farley (10) gives Labbe and Langlois the credit for describing the first case of depression of the bone marrow function following the use of arsphenamine. This was in 1919, just nine years after the introduction of salvarsan and neosalvarsan by Ehrlich. Since that date, up to and including 1929, Farley collected 39 such cases from literature. Of these, 23 patients died and 16 recovered. The symptons varied from those of purpura hemorrhagica to those of severe aplastic anemia, and malignant neutropenia, depending on whether the principal effect was on the granulopoetic, megakaryopoetic, or erythropoetic tissues or on all of these combined. Farley summarizes his cases in saying that it seems likely that the direct cause is the disintegration, in vivo, of the arsphenamines so that a benzol-like action takes place, and suggests that the rarity of occurrence may be explained on a preceding weakness of the hemopoetic apparatus of the individual.

Selling (65) in 1910 reported three cases of benzene poisoning, characterized by granulocytopenia and complicated by purpura and hemmorhages, in girls working in a rubber factory. One of these girls had quit her work long before, which illustrates the delayed and cumulative effects of the chemical. In 1916 Selling (66), experimented with benzene by subcutaneous injections into rabbits and demonstrated the production of

leukopenia without an erythropenia. Since 1910, benzene poisoning has become a fairly well recognized syndrome to the medical profession with numerous reports of cases. These cases for the most part show a depression of more than one of the bone marrow functions. In 1932 Kracke (67) was able toproduce a selective activity on the granulopoetic tissues without disturbing the erythroctic and thrombocytic elements.

There have been numerous cases reported from France following the injections of certain preparations of gold. (45)

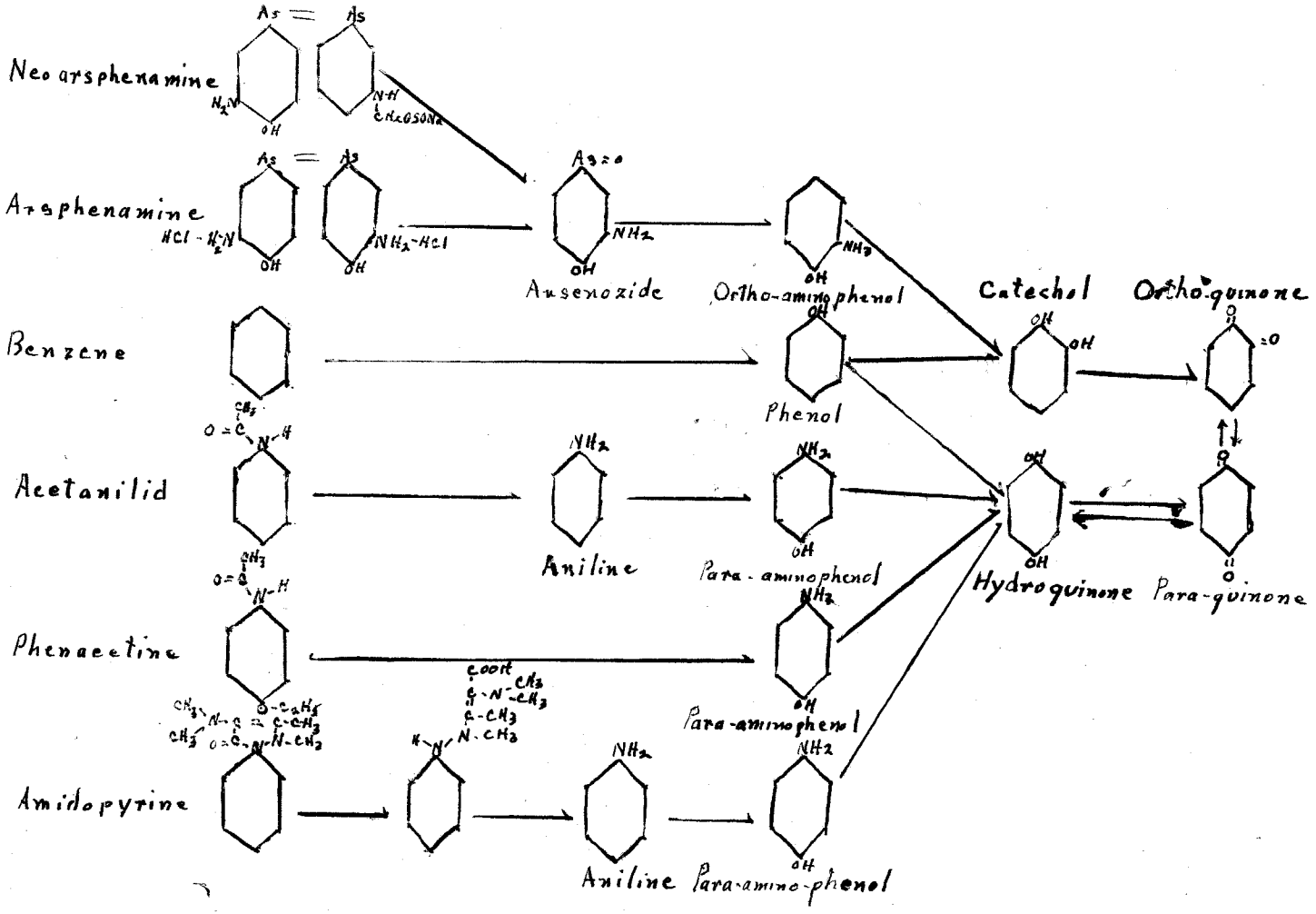
The fact that typical granulopenia can be produced by gold preparations, by arsphenamine, and by coal tar derivities (to be substantiated later), all of which contain a bonzene ring is evidence that all of these substances must have some common factor which manifests a selective activity on the granulopoetic tissue. In following this hypothesis it may be well to outline briefly the works of Kracke and Parker (45), in which they studied the relation of drug therapy to granulopenia.

From reports to a questionaire, they gathered that there exists almost a direct proportion between the incidence of granulopenia and the incidence of usage of drugs containing the benzamine (benzene amide group) group, ie., 3 out of 4 nurses or 3 out of 5 physicians but only 1 out of 4 laymen and 1 out of 8 negroes will

select a coal tar drug for use as an analgesic. They feel that the prevalence of the disease in the United States and Germany parallels the usage of coal tar drugs, while in England these drugs are used but little. These drugs have been introduced only in the last ten or twelve year period which corresponds to the period of granulopenia.

It is there opinion that it is not the direct action of benzene that produces the depressant action upon the bone marrow, but the action of one of the oxidation products of benzene. In support of this contention, they injected rabbits subcutaneously with mixtures of equal parts benzene and olive oil and upon analysis 18 hours later found only traces of benzene but considerable phenol and catechol. Control animals showed these substances to be absent. Furthermore, the bone marrow of the injected animals was analyzed and showed the presence of both phenol and catechol but no trace of benzene. Control animals were negative in this case also.

The oxidation of hydoquinone or catechol to paraquinone and orthoquinone respectively can easily be carried out both in vivo and in vitro. In vitro the reaction is activated by the enzyme phenolase which is present in the leucocyte. This progressive oxidation is illustrated on the accompanying chart beginning with the original substance, benzene.



Possible Oxidation Reactions of the "Benzamine Drops" and of Benzene

Oxidation beyond this point would break the ring and so reduce the serious toxic action. The relation of coal tar derivities to granulopenia has previously been mentioned. These drugs all have substituted amine groups on the benzene ring which make them primary amines and are designated as "benzamine drugs". The benzamine drugs include neoarsphenamine, arsphenamine, acetanilid, phenacetine, and amidopyrine. There structual formula can be studied from the chart. The amine group sets these benzamine drugs apart from other coal tar derivaties, such as aspirin which do not have such a group, because of the much greater ease under which oxidation can occur. Kracke and Parker have worked out the possible oxidation products of the benzamine drugs in an attempt to arrive at an end-product common to all. The reactions are logical and sound chemically but highly theoretical physiologically in that they have not been proved to occur in vivo. The progressive oxidation products of these compounds are illustrated on the accompanying chart. The oxidation of phenacetine and acetanilid to para-amino-phenol has been established in vivo.

Voegtlin (68) has well established that arsphenamine or neoarsphenamine, when administered intravenously, is readily decomposed by breakage of the double bond with the resulting formation of two molecules of arsenoxide. Kracke and Parker theorizes on their further oxidation.

Kracke and Parker have been able to produce mild and severe grades of granulopenia experimentally by use of the oxidation products in only an occasional animal. However, they amend this fact by saying that one must remember that not all laboratory animals have an inferior bone marrow and the same situation may exist in the rabbit as in the human, namely, only an occasional human being develops granulopenia while many thousand of individuals have taken benzamine drugs indiscriminately and have shown no depression of the bone marrow.

And so one may conclude that the etiology of granlocytopenia is still unknown. But that there has been much promising work done in the past few years, the most outstanding of which includes Dennis' work on leucidins, Beck's work on the maturation and chemotactic factors, and last but probably the most important, that of Kracke and Parker on the benzamine drugs.

PATHOLOGY

The pathology of the 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 pathognomonic 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. From smears of the 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 must be based. Custer(69), Peabody (70), and Jackson and Parker (71) have all expressed this same opinion. Finally, the normal variations of cellularity from bone to bone must be recognized so that one will not make the mistake of pronouncing the bone marrow "aplastic" from an examination of the tibia alone. (71)

Roberts and Kracke (72) say that there is an unanimity of opinion that the essential pathology of granulocytopenia is a marked and practically complete hypoplasia of the myelocytic tissues. In one of their cases, sternal puncture and smear showed a marrow entirely devoid of granular cells of any type, including even myeloblasts. Dodd and Wilkinson (73) state that the bone marrow is aplastic, but their case was a colored girl of eleven years with hereditary syphilis who after treatment with sulpharsphenamine developed extreme leukopenia. This condition could hardly be called true idiopathic granulocytopenia. Schultz often thought that the marrow might be aplastic. However, Leon (74) who described the marrow in Schultz's cases, merely says that there were neither mature neutrophils nor m

myelocytes to be found and that the femur was partly red, partly fatty. In the case under consideration, only the tibia or mid femur was examined so is it any wonder that the histological picture of the disease is regarded as confusing.

Jaffe (75) found a bone marrow rather more cellular than normal with signs of marked degeneration in the granules of the myelocytes. He believed the majority of the white cells to be myelocytes with a moderate or considerable number of plasma cells and lymphocytes. Megakaryocytes found in normal or increased numbers. Fitz-Hugh and Krumbhaar (62) as well as Jackson and Parker (71), postulate a maturation arrest at the stem cell stage with the added possibility of an end stage which might be regarded as aplastic.

Jackson and Parker (71), after an examination of the marrow from twenty-five cases dying in various stages of what seemed clinically and hematologically to be classical agranulocytosis, make the following generalizations. They found the marrow of the vertebrae, ribs, sternum and mid femur essentially the same. The degree of cellularity was usually normal. Rarely the femur remained fatty as in the normal adult. They thought that in such instances death occurred too soon for the marrow activity to spread peripherally. In some sternal and vertebral marrows, particularly in patients dying later in the disease, a

certain amount ofhypoplasia 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 they think this fact to be of minor importance. They found little or no disturbance in the red cell series. Erythroblats, normoblasts and nucleated red cells occurred in normal or slightly increased numbers and showed no abnormal features. The megakaryocytes aslo were found in the usual numbers and histologically appeared perfectly normal. Rotter (76) and Jaffe (75) agree with the latter. However Roberts and Kracke (72) are of the opinion that the hemorrhagic tendency which they regard as a very common sympton of the disease may be traced to a marrow disfunction involving megakaryocytes and a decrease of platelet formation.

Jackson and Parker report that the most marked bone marrow changes naturally occurred in the cells of the granular series. No mature granulocytes either neutrophils or eosinophils, were found in any marrow, nor were there any true myelocytes. Very rarely they report a promyelocyte. Practically every cell belonging to the granular series was a stem cell. Occasionally, in patients dead from pulmonary embolus, sepsis, or some other complication they found myelocytes, metamyelocytes, and young neutrophils in profusion throughout the bone marrow which was

generally hyperplastic. But in those cases which, at the time of death, showed extreme leulopenia and granulopenia, only stem cells, plasma cells or lymphocytes were found. Fitz-Hugh and Krumbhaar (62) contrue this fact to evidence a maturation arrest rather than a failure of delivery of cells into the blood stream. Jackson and Parker agree with this theory. The parent cells were often seen in active mitosis but further maturation was denied.

In those patients who survived the ravages of infection for a considerable period (eight to twenty days) the bone marrow picture was somewhat different. It was then found to be relatively hypoplastic. Gradually as the diease progressed the stem cells dimished 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 these cells constituted virtually the only white cells in the marrow. Rotter (76) is in agreeance with the above findings. Pepper (77) and Jaffe (75) stress the degenerative changes occurring in the marrow. However other authors (71) are of the opinion that when such changes occur they are the result of bacterial invasion of the bone marrow itself.

Beck (1) states that infection of the bone marrow in benign and malignant neutropenia has never been demonstrated except in terminal septicemia. However she admits

that the work along this line has not been exhaustive and further research may show this to be a great factor, especially in fulminating cases.

The reaction in the spleen Beck (1) found to depend on the predominance of toxic or septic symptoms. In cases observed at autopsy, a splenic tumor, partly of splenic character, was disclosed in some cases. Enlargement of the spleen in some cases she states as due to a great increase in the reticulo-end-thelial cells, which outnumber the lymphoid cells. The lymph follicles are not prominent on the cut surface. Microscopically, the sinuses are filled with erythrocytes, proliferating reticulo-endothelial cells and lymphoid cells. The liver, Beck says, may be somewhat enlarged and show cloudly swelling. Microscopically, some cases have shown fatty degeneration, and occasionally small multiple foci of necrosis. There is an increase in Kupffer's cells, There are bile casts in the bile capillaries and bile pigment in the hepatic cells. Sometimes there are interstitial lymphatic infiltrations.

Hueper and Garrison (78) describe the pathologic-changes in the lymph nodes as follows: The submaxillary, cervical, peribronchial and mesenteric lymph nodes are in general enlarged and they sometimes contain hemorrhages. Microscopic examination reveals atrophy of the lymph follicles; there are no young lymphocytes in the germinal

centers, only mature lymphocytes being present. There is a proliferation of the reticulo-endothelial cells.

SYMPTOMS

A great many patients give a history of weakness or lack of vitality for varying periods before the onset of the condition, especially in the chronic recurring cases. Some patients state that there was a lack of energy for years and a marked weakness for a few weeks or months before the onset of the acute symptoms. On the other hand, neutropenia occurs in some patients who have always been well and who were active physically and mentally until the sudden onset. (1)

Beck (1) says that the usual mode of onset is marked by fever, chill and sore throat, which may be sudden or gradual. To these may be added headache, marked palpitation with a tumultus heart beat, general aching, drowsiness and occasionally delirium. Some patients are nauseated and vomit, and, as a rule, there is dysphagia. There is an offensive, fetid odor to the breath, and the tongue is often heavily coated.

The patients are wilted 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. Jaundice is rare in typical cases. 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. Beck states that there is evidence that just mere lack of neutrophils will cause such symptoms as fever, weakness, inertia and mental and physical collapse. Roberts and Krack (72) found that complaints of weakness, exhaustion and fatigue were twice as frequent in the neutropenic patients as in those showing a normal white cell count. Furthermore, they found that the severity of the symptoms paralleled to a remarkable extent the degree of neutropenia found. The fulminating cases are rapid in progress, with a 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 group usually correspond to the fatal group of cases as far as the early symptoms are concerned.

Jackson and Parker (71) point out that the fever has nothing characteristic about it and most authors agree with this. As a general rule the temperature reaches a maximum of 103° or 104° F. Rarely it may rise to 106° or even 107° F. In some patients only a very moderate hyperpyrexia is the rule. A steady, high, unremitting temperature is of extremely grave prognostic import.

The local lesions seen in benign and malignant neutropenia 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, soft palate, lips, pharynx and buccal mucous surface. More rarely the nose, uterus, vagina, rectum, anus and skin are invovled. 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.

Owing to the absence of neutrophils there is none of the usual inflammatory reactions about the ulcerations. But a peculiar brawny edema may be most extensive and in the throat constitutes a grave menace to the patient's life. This edema, as stressed by Jackson and Parker (71) may be so great and so extensive as to preclude the possibility of swallowing and render breathing well-nigh impossible

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. Gangrene and consequent sloughing may occur: this is particularly dangerous event when it occurs in the gastro-intestinal tract. Two patients in the series of Jackson and Parker (71) died from rupture of a necrotic intestine. In one the blood picture had already become normal too late, however, to be of avail.

The classical clinical description given above is a-

greed upon by most authors some of which are Beck (1), Jackson and Parker (71), Jackson H. Jr., (79) Baldridge and Needles (16), Kastlin (7), Doan (80), and Fitz-Hugh and Comroe (46).

In a series of 103 cases reported by Jackson and Parker they found the following blood counts. (71) The white count was rarely as high as 2500 per cmm. and is often 1000 or less. Frequently it is in the hundreds. Thirty had white counts less than 500, twenty-eight had white counts between 500 and 1000, thirty-eight had white counts between 1000 and 2000, and only seven had white counts of between 2000 and 3000. Neutropenia of an extreme grade was the rule. Only seven of their cases showed neutrophils of over 5 per cent at the height of the disease. Eosinophils were rather consistently absent. Such neutrophils as remained were old and often degenerated. The majority of the white cells present were lymphocytes, for the most part of the adult type.

Most authorities agree that in the true disease there is little or no material alteration of the red blood cell picture, or any notable diminution of the platelets. (7), (76), (81), (82), (71). Aubertin and Levy (83) find, on the other hand, a constant thrombopenia and Roberts and Kracke (84) believe that the platelets are markedly reduced. Most authors point out that such cases of reported thrombopenias are to be regarded as an indication that some other disease, notably aplastic anemia or acute leukemia, is under consideration.

DIAGNOSIS

Neutropenia must be diagnosed early if the mortality is to be reduced. There should be more critical cytologic examinations of the blood, as there is much evidence in the literature that the neutropenia precedes 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 usually ill from several days to several weeks, or perhaps months, before the acute stage in many cases. The symptoms and blood picture are as characteristic as those occurring in pernicious anemia in most typical cases. The symptoms and blood picture have already been referred to and will not be repeated at this time. The rule should be to follow up each case of continued fever with frequent leukocyte and differential counts. If angina and fever are both absent and there only weakness, malaise, and drawsiness, a frequent leukocyte and differential count should be made. The diagnosis is made on the low total count and the neutropenia. Burcky (5) goes so far as to say that the diagnosis of agranulocytosis can be definitely made only when the white blood count is greatly reduced, usually below 1000 cells per cubic millimeter, and when the granulocytes are either completely absent or found in very small numbers, and usually abnormal in character. The presence of such

symptoms as great prostration, necrotic mucous membrane ulcerations, and high fever, he says, are very important corroboratory findings.

PROGNOSIS

The prognosis of agranulocytsis is extremely grave", states Burcky (5) in an article published in 1935. He points out that before the use of the present theraphy (nucleotides), the mortality ranged between 80 and 90 per cent for first attack with recurrences the usual thing, nearly always terminating fatally. Kastlin (7) in 1927 gave the mortality as 95 per cent.

Harkins (9) in 1931, reviewing the cases in literature, obtained a mortality of 82 per cent. In the same year, Rosenthal 63 reported a mortality of 46.2 per cent in a series of twelve "malignant" and fourteen "benign" cases. The same year Taussig and Schnoebelen (87) in a review of 328 cases found a mortality of 75 per cent in cases without special therapy and miscellaneous forms of treatment; 63 per cent with transfusion; and 53 per cent with Roentgen treatment. With the introduction of nucleotide therapy the prognosis has become more favorable. Jackson and Parker (71) in 1935 report a mortality of 33 per cent in a series of 103 cases receiving such treatment. In cases presumably due to drug therapy, the

mortality is nearly 100 per cent with the continued use of the drug in question. (14)

It is evident that with the loss of immunity to bacteria, the loss of strength, the prostration of the mental function, the rising fever and the quick sepsis, that death is inevitable unless a new crop of granulocytes is quickly restored to the blood stream. This becomes more difficult as the total white count and granulocyte count falls. The more favorable prognosis since 1927 can undoubtedly be attributed to two factors: first, the earlier diagnosis of the disease, and secondly, the use of nucleotides as a therepeutic measure. The increaseing use of blood counts should cause the mortality rate to continue to decrease.

TREATMENT

The treatment of any disease, the pathogenesis and nature of which is uncertain, is at best unsatisfactory and more so when that condition may be easily confused with other pathological entities of a probable different fundamental nature. Many measures have been advocated to combat granulocytopenia. None is apparently specific. Almost 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 leucocytes removes one of the body's greatest defenses against infection. Without bone marrow recovery, there can be no cure.

NON-SPECIFIC THERAPY. The injection of sterile milk, turpentine, reticulin, metaphen, and formic acid, in conceded by almost everybody to be useless. Doan (80) in 1932, found a mortality of 74 per cent in 178 patients receiving such treatment. 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 granulocytopenia where there are no neutrophils in the bone marrow to call forth. The probable effect of such treatment in normal patients is chemotactic and not an increase production of white cells. Doan (80) compiled mortality statistics on a large group of patients which received various types of treatment. His figures are as follows:

THERAPY	CASES	DEATHS	MORTALITY %
Untreated	Many	Many	90
Miscellaneous therapeutic measures	178	133	74
Arsphenamine	33	24	72
Blood Transfusion	33	34	64
Irradiation	64	34	53
Nucleotide	44	11	25

The three most efficacious methods of treatment as

gathered from these statistics would be blood transfusion, irradiation and nucleotides. Doan suggests that these three therapeutic measures must have some common factor which is the active principle. He supposes that nucleotide is this specific principle and explains its presence in the following manner: In blood transfusions, nucleotide is introduced in small quantities in solution (85) and formed by disentegration of white cells. In irradiation, he supposes that autogenous nucleotide is liberated by the destruction of intact myeloid focii. With this hypothesis in mind let us review these more specific treatments of granulocytopenia.

TRANSFUSION. Transfusion of blood has been endorsed by many authors among which have been Hueber (86), Peper (77), Fitz-Hugh and Comroe (46), and Taussig (87). Without question recoveries have followed blood transfusions but aside from this there is no evidence that transfusions have a stimulating effect upon the bone marrow. Jackson and Parker (71), even go so far as to state that it is not an uncommon experience to find the peripheral white blood count lower after transfusion than before. They state that the mortality in their series was the same for the group receiving both transfusions and pentnucleotide and for these receiving only pentnucleotide.

In the last three or four years the enthusiasm of the efficacy of blood transfusions has been lost in the greater enthusiasm for pentnucleotides (71), (88), (89), (5).

X-RAY. Stimulating doses of X-ray have been advocated by many (89), (87), (90), (91). Friedmann and Elkeles treated 43 cases with irradiation with a mortality of 82 per cent. Taussig and Schroebelen had a mortality of 50 per cent in four cases. Licklerstein treated 20 cases with improvement in seven but a year later only two were alive--a mortality of 90 per cent. Heuber (86) enthusiastically recommends radiation. Reznikoff (92) has expressed the idea and Jackson and Parker agree (71), that even small doses of X-ray tend to depress the marro w and they point out that four or five days must elapse before the effects of any maturation element can be detected in the peripheral blood. It is usually claimed by advocates of radiation that favorable changes occur within a few hours. When such changes occur Jackson and Parker attribute the rise as spontaneous, or, if actually due to radiation, to a redistribution phenomenon rather than a maturation factor. Like transfusion, X-ray therapy has come to be disapproved in the last few years.

LIVER EXTRACT. Liver extract has been advocated by many, Foran (93), injected the equivalent of 100 grams

of liver into the veins or muscel every 8 to 12 hours until a definite rise in the white count had taken place. Four cases were apparently successfully treated. However, Coggeshall's (94) case failed to respond to six vials of liver extract intravenously each day. Four of the patients in Jackson and Parker's (71) series received liver extract as well as pentnucleotide yet all died. Silver (95) treated a case apparently due to dinitrophenol without benificial results. Bonsdorff (96) treated two cases with liver extract with recovery in both instances. However Parker (71) points out that one case was probably a pernicious anemia and the other due to novarsenobenzol and bismuth which when removed may have been of considerable prognostic importance. Walker (97) states that the value of liver therapy is doubtful because it is not known definitely if it has a stimulating effect upon granulopoesis. However he thinks it does no harm, and in cases of anemia is beneficial.

NUCLEOTIDES. "The history of this remedy goes back to the days of frequent sepsis and 'laudable' pus", says Walker. (97) Pus was easily obtained in those early days, and from it nucleic acid was prepared, being so called because it was believed to be chiefly derived from the nuclei of leucocytes and other cells. Later it was

found that nucleic acids occur in combination with various protiens in the form of nucleoprotiens. By a process of hydrolysis the purine bases adenine and guanine were isolated, and derived from these products was pentose nucleotide, found to exist chiefly in the nuclei of living cells. In 1924 Jackson (85) definitely demonstrated the presence of pentose nucleotide in normal human blood.

In 1930 Reznikoff (98) advocated the use of adenine sulphate in the treatment of granulocytopenia. In 1933 (99) he 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 only temporary. His conclusions were conservatively optomistic. The treatment with adenine sulphate consists of dissolving one gram of the salt by boiling two or three minutes in 30 to 40 cc of normal saline solution, allowing to cool slightly, filtering through a small adapter containing cotton to filter out all undissolved crystals, and injecting intravenously while still warm (105° to 110°F.). This dose is to be used three times a day for at least three days. (5) The drug is non-toxic, gives no disagreeable reaction, and may be used in the presence of myocardial disease.

Inasmuch as it had been shown by Doan, Zerfas, Warren

and Ames (42) in 1928, that pentose nucleotide could definitely raise the peripheral white count in normal animals, Jackson and his co-workers (100) decided to try the effect of this substance in those conditions characterized by extreme leukopenia. In 1931 they reported the results of such therapy in twenty cases of granulocytopenia with fourteen recoveries. In 1932 they (101) reported on 69 cases treated with pentose nucleotide (including the original twenty) with a total mortality of 26 per cent. Since 1932 Jackson and Parker (71) have added 34 cases to this series making a total of 103 cases with a mortality of 33 per cent. Only those cases treated for less than 48 hours or those which died of some entirely unrelated disease were excluded. They have followed all these cases to date (1935), including all deaths in their mortality figures.

Pentose nucleotide was introduced as "Nucleotide K 96", but is now marketed under the trade name of "Pentnucleotide". It is obtainable in 10cc. rubber-stoppered vials, each containing the equivalent of 0.7 grams of the solid material. In the average case of granulocytopenia with a white count between 1000 and 2000 per c.mm., 0.7 gram is given intramuscularly two, or preferrably, 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.

o.7 grams is then given daily until the white count has been normal for several days. In cases which are extremely sick, and especially in those in which the total white count is below 1000, 40 cc. should b e given daily until the white count has definitely risen and young neutrophils are present. Fifty 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 being such that no untoward reaction occurs. Usually 50 to 100 drops may be given per minute when 20 cc. are diluted in 100 cc. of normal saline solution. The drug should be continued in larger doses until the white count has definitely risen and in somewhat smaller amounts until it has been normal for several days. If there has been no response in ten days, most authors consider further therapy useless.

Fitz-Hugh and associates (46) report a reaction of alarming character but do not state whether the drug was given intramuscularly or intravenously. They also say that one of their patients reacted violently with fever up to 104 degrees with each intramuscular dose but tolerated the same dose intravenously without reaction. In some, there is a transient sense of discomfort at the site of injection. In others there may be precordial distress, dyspnea and nausea. Very rarely are the symptoms

alarming. If however they are sufficiently severe symptoms to upset the patient, Jackson and Parker (71) suggest that smaller doses of the drug be given at more frequent intervals until the required amount is given daily. They also point out that the drug should never be given to an anaphylactic individual nor to one with severe cardiac damage.

Doan (80) points out that the first sign of a favorable reaction to pentnucleotide is evidenced by the appearance of myelocytes in the blood stream. These cells may reach twenty per cent of the total white cells. This change, he says, usually occurs about the fourth day following treatment and corresponds in some measure to the reticulocytic 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.

Pentnucleotide has been used successfully by many and at present is the treatment advocated by most authors. (102), (103), (104), (105), (106), (107), (109), (93).

GENERAL CARE. It stands to reason that intelligent bedside care, careful nursing, adequate nourishment, and fluids are all a necessary and obvious parts of the treatment. The patient must be protected in so far as possible, from infection. But attempts to sterilize the ulcerated

lesions is detrimental. Frequent washings of the mouth and throat with soothing solutions may allay pain and make the patient more comfortable.

It had been suggested by some (Walker (97), Beck (1), Roberts and Kracke (109), that surgical intervention is contra-indicated. Lintz, Thompson, Jackson and Parker (71), however, do not agree with this. They advise any immediate surgery as would be done in a patient with a normal blood count.

CONCLUSION

An attempt has been made in this paper to review the literature on granulocytopenia and compile this information in more or less of a textbook fashion. A review of the physiology of granulopoesis and pathological conditions occurring in granulocytopenia was given in order to gain a more accurate understanding of possible etiological factors and the validity of each treatment presented.

From this study, the following facts seem to be of primary importance: Whether granulocytopenia 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. The etiology of the disease is as yet uncertain, however those particular drugs

containing the benzamine nucleus undoubtedly do have much to do with the development of certain cases. The pathological changes in the bone marrow consists of a maturation arrest at the stem cell stage. Effective specific treatment is as yet largely limited to the use of nuclleotides. The more favorable mortality in the past yew years has more or less paralleled the more rapid diagnosis of the disease and the introduction of the use of nucleotides in the treatment. Until the nature, etiology and pathology of granulocytosis is unequivocally placed upon a sound basis, the diagnosis, treatment and prognosis of the condition will remain little changed.

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