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Neutropenia : an analysis of the risk factors for infection

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by

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ABSTRACT

The risk factors for infection were evaluated retrospectively in 107 neutropenic patients without underlying malignancy or cytotoxic drug therapy. Neutrophil count was an independent risk factor for infection, with the incidence of infection increasing as the neutrophil count decreased. The critical neutrophil count, below which the incidence of infection was significantly increased was $250/mm^3$, ($p < .001$). Eighty five percent of the ≤ 250 group entered with, or developed infection. Additional risk factors for infection included increased duration of neutropenia, age less than 1 year old, male sex, hypogammaglobulinemia, and recent antibiotic therapy. Fever was predictive of infection in 85% of cases.

The major consequence of infection was mortality, and the group with PMN's $\leq 250/mm^3$ had three times the mortality of all other subjects (10% vs. 3% respectively). Thus neutropenic patients with no other evidence of host impairment appear to be at greatest risk of infection when the neutrophil count drops below 250.

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INTRODUCTION

The role of the neutrophil in host defense, and the association between neutropenia and infection have been well documented (10,20). However, the bulk of the published studies have involved leukemic patients in whom neutropenia was only one manifestation of their generalized host impairment. In addition to cellular immaturity, the other factors that contributed to their increased risk for infection included malignancy and cytotoxic therapy (40,9). Most studies, including the classic study by Bodey (10), examined such groups of leukemic patients and discovered a definite predisposition to infection when the neutrophil count falls below 1000.

There are no published studies which directly relate the risk of infection in the neutropenic patient in whom there is no other obvious evidence of host impairment. This group of patients usually carries the diagnoses of idiopathic aplastic anemia or idiopathic neutropenia. With current studies suggesting the effectiveness of prophylactic modalities in preventing infections in the severely immuno-compromised host such as barrier reverse isolation and oral non-absorbable antibiotics (77,78), it has become increasingly important to recognize the critical granulocyte level at which the risk of infection is significantly increased. Furthermore, with the emergence of bone marrow transplantation as a therapeutic modality in some patients with marrow aplasia, an analysis of factors which predispose to infection

may provide some guiding principles to appropriately prepare these patients for transplantation before infection has developed (95,94).

With these considerations in mind, we have undertaken this retrospective clinical study to investigate the risk of infection in the neutropenic patient who does not harbor a hematologic malignancy and who is not receiving cytotoxic drug therapy.

The questions we attempted to answer in this study include:

1. How many neutropenic patients are seen at a University Hospital over a 10 year period, and what are the characteristics of this group?
2. What is the incidence of infection?
3. At what level of neutropenia is the risk of infection increased?
4. When do such infections occur?
5. What are the risk factors for infection?
6. What are the consequences of infection?
7. What is the survival of these patients in the hospital?
8. What are the risk factors for mortality?

THE NORMAL GRANULOCYTE LIFE CYCLE

In order to more fully appreciate the causes and consequences of neutropenia, a brief discussion of the life cycle of the granulocyte would be instructive. The term granulocyte is often loosely used to refer to neutrophils, but strictly speaking refers to eosinophils and basophils as well.

Granulocytes are normally produced in the bone marrow where they arise from precursor cells by a process of proliferation and maturation. The precursor cell in the bone marrow from which all the blood cells are believed to arise, is the pluripotent stem cell (32). A stem cell is a cell with two capabilities: the ability to replicate itself, and the ability to form more differentiated daughter cells. A pluripotent stem cell is one with the capacity to differentiate into more than one cell line, i.e., the erythrocyte, granulocyte, megakaryocyte, and monocyte series. In contrast, a unipotent stem cell can replicate itself, but can only differentiate along one pathway. For example, the myeloblast is a unipotent stem cell "committed" to the granulocyte pathway (commitment to neutrophilic, eosinophilic, or basophilic development occurs later at the promyelocyte stage of cell development). Many investigators believe that cells of the mononuclear-phagocyte series (monocytes and macrophages) share a common committed stem cell with the granulocytes (17) (See Figure 1).

The influences that determine the direction of differentiation of the granulocyte stem cells are not entirely clear. Relatively little is known about the mechanisms which regulate cellular differentiation from pluripotent to committed stem cells, however several factors are believed to be important. Pluripotent stem cells may "sense" the utilization of committed granulocytic stem cells, thereby signaling further differentiation in this direction. The stromal environment of the bone marrow or spleen may exert regulating influences on stem cells. These stromal elements have been referred to collectively as the hematopoietic inductive microenvironment.

In addition to the short range environmental influences mentioned above, many long range hormonal influences have been described. These stimulators of granulopoiesis have been called leukopoietins. The best documented leukopoietin is referred to as Colony Stimulating Activity (CSA). CSA is a 45,000 dalton glycoprotein derived from human urine, thought to stimulate granulopoiesis in a manner analogous to the effect of erythropoietin on red blood cell production. Serum and urine CSA preparations increase granulocyte production when injected into mice. Peripheral blood leukocytes form a potent source of human CSA, and the blood cell primarily responsible for its elaboration is the monocyte. The existence of the monocyte as the principal source of CSA is consistent with the evidence linking monocytes and granulocytes to a common committed stem cell. (See Figure 2)

Under the microenvironmental and hormonal influences mentioned above, the pluripotent stem cell develops into a committed stem cell, the myeloblast.

The myeloblast, with its active Golgi apparatus and endoplasmic reticulum develops into the promyelocyte with its primary (or azurophilic) granules. These granules contain myeloperoxidase, acid hydrolases, neutral proteases, cationic antibacterial proteins, and some of the cells' lysozyme. The myelocyte, the next stage of development, contains secondary (or specific) granules which contain lactoferrin, aminopeptidase, B_{12} binding protein, and most of the cellular lysozyme. The myelocyte has fewer mitochondria but has begun to acquire the unique oxygen metabolism that characterizes the mature polymorphonuclear leukocyte (PMN). Beyond the myelocyte stage, neutrophilic cells do not divide; instead their nuclear chromatin becomes condensed, the cell diminishes in size, and cytoplasmic glycogen accumulates. Approximately 8 to 14 days are required for a cell to move through the 4 to 6 cell divisions and complete maturation, from the myeloblast to a mature PMN. (See Figure 3)

The normal human neutrophil production rate is approximately 1.6×10^9 cells per kilogram per day (22). These cells remain within the marrow until their differentiation and maturation is completed. In contrast, monocytes are released into the circulation as immature cells, some of which can divide again after passing through the blood.

There are two large pools of granulocytes in the bone marrow, the mitotic or proliferative compartment, and the maturation-storage compartment (32). Myeloblasts, promyelocytes, and myelocytes are capable of replication, thus they constitute the mitotic compartment. Metamyelocytes, bands, and mature PMN's are nonreplicating and constitute the maturation and storage compartment. Studies have shown that the progression from

metamyelocyte to mature PMN is very orderly within this compartment, and have suggested a "first in, first out" pattern for cells leaving this compartment and entering the peripheral circulation (16). With the completion of maturation, the mature PMN's are stored in the bone marrow, and are referred to as the mature granulocyte reserve. This reserve usually contains more PMN's than are normally circulating in the blood. These mature neutrophils may be readily released by a number of stimuli, including stress, corticosteroids, and bacterial endotoxin. The final common pathway in release of neutrophils by the marrow is believed to be mediated by neutrophil releasing factor (29). This factor can be isolated from the plasma, and is felt to play an important role in regulating acute changes in the numbers of circulating neutrophils by affecting their release from the bone marrow. The average time sequence given for the stages of development in bone marrow include a 3 to 4 day period of intramedullary proliferative buildup, followed by a 5 to 7 day period of intramedullary maturation (17).

Under normal circumstances, granulocytes leaving the marrow are fully functional cells capable of chemotaxis, phagocytosis, endocytosis, degranulation, and bacterial killing. Granulocytes leaving the marrow storage compartment enter the blood, without significant reentry into the marrow, where they are approximately equally divided between cells freely circulating (circulating granulocyte pool, CGP) and those that are transiently and reversibly adherent to vascular endothelium (marginated granulocyte pool, MGP). Together, all the neutrophils in the vascular space constitute the total blood granulocyte pool, TBGP. Shifts between

the MGP and CGP occur readily in response to a variety of factors affecting blood flow in capillary beds or altering membrane properties of granulocytes or endothelium. For example, exercise, epinephrine, or stress cause a shift of cells from the MGP to the CGP.

After a variable period in the circulating or marginated pools, the cells migrate through the vascular endothelium into the tissues. Granulocytes do not reenter the circulation once they have entered the tissues; the flow of cells is unidirectional. The rate of disappearance of cells from the circulation has a half-time of about 6.5 hours. The exponential disappearance of cells from the blood suggests that they leave in a random manner (32). Thus granulocytes released from the marrow are as likely to leave the blood as are neutrophils that have been circulating for several hours.

The total number of cells released from the marrow per unit time may be increased by one or more of the following mechanisms:

1. maturation time may be shortened.
2. divisions may be skipped, and
3. release into the blood may occur prematurely.

Many abnormalities of granulocyte production, maturation, and distribution may be accompanied by release of immature granulocytes from the marrow. Immature granulocytes (normal or leukemic) show decreased motility, decreased chemotactic responsiveness, and decreased phagocytic and bactericidal functions. They also exhibit a longer lifespan in the circulation, and may reenter the blood and marrow from the tissues (17). This is in direct contrast with most abnormalities

of erythrocytes and platelets which, in general, shorten the lifespan of these cells. If the cells are very immature (myelocyte stage or earlier) they may divide again in the blood or tissues. Thus the basic principles of unidirectional kinetics characteristic of normal granulocyte production does not hold for immature or incompletely differentiated granulocytes (17).

The duration and precise activity of many neutrophils after they leave the circulation are poorly documented. The migration of granulocytes into areas of inflammation has been widely studied, but little is known of the fate of granulocytes in normal tissue. Granulocytes normally migrate into the lung, spleen, liver and oral cavity, and gastrointestinal tract. They may be lost from mucosal surfaces, die in the tissues or be sequestered by the reticuloendothelial system. Their average lifespan in the tissues is assumed to be several days (16).

In inflammation, the egress of granulocytes from the vascular space is facilitated by changes in the vascular endothelial permeability, as well as the formation of chemotactic factors at inflammatory sites (17). These chemotactic factors can include C3a, C5a, and C567 components of the complement system, low molecular weight substances released by bacteria, kallikrein, plasminogen activator, and transfer factor to name several. The normally random motility of the cells will be directed to move along an increasing concentration gradient of these factors to enable them to reach tissue sites of inflammation or infection. At the inflammatory site, phagocytosis is facilitated by humoral substances, opsonins, which have coated the surface of the foreign material to be ingested. Immunoglobulins

and complement are the best characterized opsonins, with complement playing the major role in phagocytosis of many bacteria by the deposition of C3b on the bacterial surface (67).

Phagocytosis stimulates numerous intracellular events including increased oxygen consumption, glycogenolysis, glucose oxidation via the hexose-monophosphate shunt, and the production of superoxide and hydrogen peroxide (43). Within the cell, phagocytized particles remain in a vacuole, and the contents of the secondary and then the primary granules are sequentially emptied into this vacuole. The vacuolar pH falls to about pH 6.0 favoring the activity of a variety of acid hydrolases (16). The neutrophil possesses a variety of bactericidal mechanisms giving it an "overkill" capacity. The best characterized bactericidal mechanism involves myeloperoxidase combining with hydrogen peroxide and a halide such as iodide or chloride (43). This system is also effective against viruses, fungi, and mycoplasma (16). The neutrophil usually degenerates after it digests the phagocytized material, and that, together with cellular debris and digested foreign matter form the pus that characterizes acute inflammation.

GRANULOCYTE DISORDERS

Granulocyte disorders can be classified into two main categories (43):

1. Quantitative abnormalities.
2. Qualitative abnormalities.

Qualitative abnormalities of granulocytes usually implies a normal number of improperly functioning granulocytes. These abnormalities can include defects of mobility and chemotaxis, bactericidal activity, or phagocytosis. They may occur in association with anomalies of nucleus and cytoplasm. Certain disease states have been known to cause, or be associated with qualitative defects in granulocyte function, including "Lazy Leukocyte" Syndrome (54), Chediak-Higashi Syndrome (8), and Chronic Granulomatous Disease (92,21,5), chronic alcoholism (13), SLE (88), rheumatoid arthritis (55), Diabetes mellitus (58) and uremia (86) (See Table 33).

Quantitative abnormalities of granulocytes refer to a reduced or increased number of normally functioning granulocytes, i.e., granulocytopenia or granulocytosis, respectively. Neutropenia refers specifically to an absolute reduction in peripheral neutrophils, and although technically imprecise, granulocytopenia has come to mean that as well.

The absolute number of circulating neutrophils is calculated as the product of the total leukocyte count and the percent of neutrophils in the differential leukocyte count. In the Western hemisphere, the

lower limit of normal in healthy adults is an absolute neutrophil count of about 1500-1600 per mm^3. There are some notable exceptions to this limit, and Yemenite Jews as well as Blacks in the U.S. and Africa often have a lower limit of normal. This is considered a benign variant (29).

In calculating the absolute neutrophil count, the assumption is made that the peripheral leukocyte counts are a reasonably accurate reflection of the total leukocyte pool, including the CGP, MGP, and marrow storage pool. Rapid temporary shifts from one compartment to another may invalidate the peripheral count as a reliable index of the blood granulocyte pool. For example, blood is sampled from the CGP, however if there is a sudden shift of granulocytes from the CGP to the MGP just prior to sampling, the peripheral counts would be low despite having no change in the total circulating leukocyte pool. Accordingly, the calculated absolute neutrophil count would be spuriously lower and therefore a poor indicator of the ability to generate an inflammatory response. This is one of many potential mechanisms by which cell counts may inaccurately reflect the total circulating neutrophils. Neutrophil counts may be spuriously low in electronic counters because of excessive leukocyte clumping (e.g., in the presence of certain paraproteins), because of a delay in counting, or excessive fragility of abnormal leukocytes (29).

Generally, neutropenia results either from diminished granulocyte production or from accelerated peripheral utilization, alone or in combination with one another (29). More specifically these mechanisms include:

A. Reduced delivery of mature granulocytes from the marrow to the peripheral blood pools (decreased effective granulopoiesis) as a consequence of:

1) decreased myeloid proliferation in the bone marrow (reduced granulopoiesis).
2) increased production of abnormal or ineffective granulocytes (increased ineffective granulopoiesis)
3) impaired release of granulocytes from the marrow storage compartment.

B. Increased utilization or loss of peripheral blood granulocytes due to:

1) accelerated diapedesis of mature granulocytes into tissues in response to:
   a) infection, or
   b) inflammation
2) reduced survival due to:
   a) a maturation defect
   b) a leukotoxic factor (e.g., antineutrophil antibodies),
   c) increased reticuloendothelial system activity (i.e., hypersplenism)
3) temporary or prolonged shifts into the marginal pool.

These alterations in granulocyte kinetics may be acute, chronic, intermittent or cyclic.

Finch has constructed a functional classification of neutropenias utilizing five major categories (29) (See Figure 4).

Type I or Reduced Granulopoiesis involves decreased myeloid proliferation: the number of granulocytes entering the peripheral blood (the effective granulopoiesis) from the marrow is inadequate to maintain a normal level, in the face of normal rates of egress from the peripheral circulation. In these situations marrow storage, marginal,and circulating granulocyte pools are reduced in size. Neutrophil mobilization at sites of inflammation is impaired. The total neutrophil turnover is reduced, but neutrophil survival is normal.

Type II or Increased Ineffective Granulopoiesis involves increased myeloid proliferation but the number of mature granulocytes entering the peripheral blood is reduced. The inability of mature granulocytes to leave the marrow may be due to an increase in the intramedullary death of myeloid precursors or because of a lack of the necessary stimulus for marrow release. As in Type I neutropenia, the MGP, CGP, and bone marrow pool are reduced. In addition, there is some evidence that in many of these conditions neutrophil survival is also shortened.

Type III or Reduced Granulocyte Survival involves the increased destruction or utilization of peripheral granulocytes. In this case, the increased peripheral utilization stimulates marrow granulopoiesis and an increased delivery of mature neutrophils to the blood (increased effective granulopoiesis). However, if the depletion rate exceeds the production rate, neutropenia develops. This condition may be due to leukotoxins, leukocyte antibodies, increased splenic sequestration, or increased leukophagocytosis by hyperfunctioning RES cells. Blood neutrophil survival is short, and the turnover rate is markedly increased.

When possible, removal of the factor responsible for the peripheral neutrophil destruction is usually followed by rapid resolution of the neutropenia with restoration of normal cell kinetics. However, in some cases, chronic peripheral destruction may eventually lead to bone marrow failure.

Type IV or Combination Granulocytopenia involves a combination of Type I or II, with Type III. Reduction in effective granulopoiesis is combined with a shortened neutrophil survival. This is the most common mechanism producing neutropenia.

Type V or Pseudoneutropenia is an apparent neutropenia due to reduction in the size of the CGP without change in the size of the total granulocyte pool. This usually results from a shift to the MGP. Leukocyte kinetics are normal.

The five functional classes above describe the general mechanisms of neutropenia. The causes of neutropenia include malignancy, drug reactions, industrial solvent exposure, allergic reactions, leukotoxin production, hypersplenism secondary to a number of conditions, vitamin deficiencies, sepsis, cancer chemotherapy (e.g., alkylating agents, antimetabolites, etc.), inflammation, and vasomotor changes, in addition to the idiopathic variety (29,35). The exact site or sites of granulocyte production and utilization that are affected by each of these etiologic agents in producing neutropenia are not fully characterized, and there is a great deal of conjecture on this. It is beyond the scope of this paper to deal with the various theories. Suffice it to say that most agents can affect various steps in granulocyte production or survival (See Figures 5 and 6).

NORMAL HOST DEFENSE

Normal host defense against microbial invasion can be divided into four systems:

1. Mucocutaneous barriers
2. The inflammatory response
3. The humoral immune system
4. The cellular immune system.

Modification of any one of these components may predispose the host to infection (35).

Mucocutaneous Barriers

The skin and mucous membranes serve as an interface between man and the internal and external microbial environments to which he is exposed. Each environment is inhabited by its own "normal flora" that varies by geographic location and body site. Four important elements of the mucocutaneous barrier system are exposure to non-indigenous flora, mechanical barriers to invasion, interbacterial inhibition, and secretory immunoglobulin A (IgA).

Invasion by microorganisms cannot occur without prior exposure. Schimpff et al., (79) in a study of leukemic patients, demonstrated that isolation of an offending organisms from serial surveillance cultures of various body sites preceded infection with that organism in 86% of cases. In almost half of these cases, the offending organism was not part of the patient's flora on admission; it had been acquired in the hospital.

Even prior exposure to an organism is usually insufficient for infection in the normal host, unless there is a breakdown of the mechanical barriers of skin and/or mucous membranes (35). This allows resident flora to become pathogenic.

Although the process by which normal flora can inhibit proliferation of one another or non-indigenous organisms on mucocutaneous surfaces is well documented, the mechanism is unknown (28).

Secretory IgA is known to be protective against viral infections that require mucosal penetration, and is believed to be involved in regulating bacterial invasion (68,97).

Inflammatory Response

The inflammatory response involves the delivery and normal function of inflammatory cells. These functions include generation of chemotactic factors, intact vascular supply capable of inflammatory cell transport, adequate numbers of normally functioning phagocytes (as described in the previous chapter, WBC Life Cycle), and opsonins. Various defects in the above mechanisms have been characterized and categorized into disease entities (e.g., Chediak-Higashi Syndrome, Lazy Leukocyte Syndrome, and Chronic Granulomatous Disease) all of which have increased incidence of infection (69,21,8,61,92).

Humoral Immune System

The humoral immune system involves B-type lymphocytes (B cells) and their elaboration of antibodies. IgG and IgM are the two major classes of antibodies whose two major functions include neutralization of organisms directly, and the opsonization of pathogenic organisms to facilitate

subsequent phagocytosis (67). The monocyte and the PMN have surface receptors for complement and the Fc portion of IgG. Thus, IgM must "fix" complement after opsonization in order to promote phagocytosis by the PMN or monocyte. In contrast, IgG can promote phagocytosis by opsonization directly or through complement fixation (68)

The role of the humoral immune system is well established in viral illness and in diseases due to the elaboration of bacterial toxins (e.g., diphtheria or tetanus). In these cases, antibodies directed against the viral organism or the bacterial toxin are correlated with resistance to infection (67). In other bacterial infections the role of this system is less well defined. The capsules, in encapsulated organisms, act to inhibit phagocytosis but their opsonization is essential for efficient phagocytosis. Accordingly, immunization with capsular antigen stimulates production of anti-capsular antibodies capable of opsonization and providing immunity. These capsulated organisms, including pneumococci, streptococci, meningococci, and H. influenza, are very common pathogens in hosts with hypogammaglobulinemia (31).

Gram negative enteric organisms have also caused infection more commonly in hypogammaglobulinemic patients (i.e., those with altered humoral immunity) and although the exact mechanism is not presently understood, recent studies suggest IgG opsonization (31).

In patients with hypogammaglobulinemia, encapsulated gram positive and gram negative enteric organisms are the primary pathogens because viruses are predominantly defended against by cellular immunity.

Cell Mediated Immunity

Cell mediated immunity (CMI) requires adequate numbers of T-type lymphocytes (T-cells) and macrophages capable of expressing delayed hypersensitivity. CMI is usually measured by the extent of induration to intradermal skin testing with "recall" antigens such as tuberculin, mumps, and trichophyton antigens. These "recall" antigens are antigenic substances to which the patient has already been exposed in the past, and should now be capable of expressing delayed hypersensitivity in response to its reintroduction.

The many functions of the T-cell include graft rejection, contact dermatitis, cooperation with B-cells for antibody synthesis to most antigens, suppression or regulation of other humoral or cellular immune responses, antitumor immunity, and defense against some infections (35). CMI is felt to be important in protection against infections caused by intracellular organisms. Intracellular residence, often within the monocyte, provides protection from the PMN's and humoral immune response. These organisms include Salmonella, Brucella, Mycobacteria, Candida, Cryptococcus, Aspergillus, Mucor, Toxoplasma, Pneumocystis and viruses (especially herpes viruses, vaccinia, and measles). Thus, impaired CMI would predispose the host to infection by any of the above organisms (31,46).

Consequences of Impaired Host Defense

Most pathogenic organisms are usually defended against by a specific system, or combination of systems, comprising the normal host defense. Infection by one of these organisms, thus implies a successful breach of one or more of the four systems of normal host defense. The following

classifications are generalizations and are not necessarily meant to be mutually exclusive.

Many microorganisms are highly susceptible to being killed by PMN's, and they rely heavily upon evasion of phagocytosis for their survival. The evasion of these extracellular pathogens is primarily due to the presence of surface factors which retard phagocytosis (25). Opsonins are necessary to overcome the antiphagocytic surface factors, thereby facilitating effective phagocytosis by the PMN (67). Since the presence of these microorganisms in tissues stimulates an outpouring of PMN's, they are known as pyogenic microorganisms. Infections due to pneumococci, streptococci, S. aureus, H. influenza, meningococcus, gonococcus, enteric gram negative rods, Yersinia pestis, nocardia, and disseminated fungi are those extracellular infections in which opsonins and PMN's are decisive in recovery (25).

There is another group of infections in which antibody may be decisive in prevention or in recovery, through a mechanism other than opsonization. This group includes diseases resulting from exotoxin production such as tetanus and diphtheria, and viral illness. Antibodies bind to the exotoxin thereby neutralizing its toxic effects (35). In viral illness, the antibody interacts with viral surface antigens thereby preventing viral attachment and host cell penetration.

Another category of etiologic agents produces infections in which humoral and cellular immunity, distinct from the acute inflammatory response, collaborate in host defense. This is a heterogeneous group of infecting microorganisms that may be extracellular or facultatively

intracellular and includes the following infections: syphillis, cryptococcosis, mucocutaneous candidiasis, salmonellosis, and listerosis (25).

The last group involves intracellular infections in which cell mediated immunity, CMI, is decisive in recovery, and humoral immune mechanisms play no protective role. The infecting organisms in this category include M. tuberculosis, M. leprae, Histoplasma capsulatum, Coccidioides immitis, and Brucella (67).

According to this classification, a defect in one of the four systems of normal host defense may predispose the host to infection by those organisms known to be defended against primarily by that system. However, theoretically, the risk of infection should be no greater in the other groups of microorganisms that are defended against by an intact host defense system (9). For example, a qualitative or quantitative defect in PMN's may significantly lower the defense to infection by the extracellular, pyogenic organisms, but it would not be anticipated to affect the risk of infection by agents known to be defended against by the humoral and cellular immune systems.

RATIONALE FOR STUDY

Neutrophils are essential to host defense. They assist primarily against bacterial and fungal infections (17). Any defects of neutrophil function, either qualitative or quantitative, might be expected to significantly alter host defense and thereby predispose the host to an increased risk of certain bacterial and fungal infections.

Patients with qualitative neutrophil defects and no other obvious signs of host impairment, such as those with Lazy Leukocyte Syndrome (54). Chediak-Higashi Syndrome (69,8,98), and Chronic Granulomatous Disease (21,49) have been shown to have increased incidence and severity of infection compared to the general population (61).

Prior studies of patients with quantitative neutrophil defects have also demonstrated an increased incidence and severity of infection compared to the general population (4,10,100). In fact, some studies have even demonstrated an inverse relationship between neutrophil count and incidence of infection (10). These studies, however, have invariably involved a patient population with underlying malignancy (especially leukemia), and one which has received cytotoxic drug therapy. The latter two conditions are known to affect all four systems of normal host defense, and thus these patients are at increased risk of infection for a number of reasons besides their neutropenia (30,36,100,85,46).

The mucocutaneous barriers are compromised and the risk of infection increased, by the mucosal changes induced by cytotoxic therapy in the

mouth, esophagus, colon, and rectum (9); the obstructive phenomena of tumor mass near the ureters, bronchi, or biliary tract (9); the damage to integumentary barriers caused by tumor, venipunctures, or decubiti (75); the iatrogenic procedures of venous or urinary catheterization (87); and the acquisition of new, often highly resistant pathogens from the hospital environment, notably Pseudomonas, S. aureus, and Aspergillus (79). All these factors interacting, in addition to the neutropenia itself, place the patient at a great risk of overwhelming infection.

The inflammatory response is also hampered by malignancy and its chemotherapy. Specifically, abnormal leukocyte function has been reported in both acute and chronic myelogenous leukemia, including decreased adhesiveness, phagocytosis, and microbicidal activity (57,60,70). Corticosteroids are known to impair the neutrophilic and monocytic inflammatory response, presumably due to decreased adhesiveness to the vascular endothelium (27). Radiation therapy has been reported to cause granulocyte dysfunction (7,91). In addition, many chemotherapeutic agents including vincristine (63), vinblastine (19), and colchicine (19,48) have been shown to alter normal neutrophilic chemotaxis, in vitro. All these potential defects in neutrophil function, coupled with a reduced number of circulating neutrophils found in any neutropenic state, could conceivably further increase the patient's risk of infection.

A derangement in the humoral immune system, usually manifest as hypogammaglobulinemia, is also found in some cancer patients (68,52). Hypogammaglobulinemia is an accompaniment of early disease in patients with multiple myeloma and chronic lymphocytic leukemia (9,52), both diseases of the B-cell system, while the acute leukemias, chronic myelogenous

leukemia, and solid tumors have been reported to have normal immunoglobulin levels (35,52). Chemotherapy (41), and radiation therapy (91, 56) may also depress antibody responses. Also, abnormalities of complement-mediated functions and of the third component of complement, C3, have been associated with increased susceptibility to infection (2). Thus a reduction in opsonins in an already neutropenic patient can increase the predisposition to infection (68,2,24,50,33), especially due to encapsulated gram positive cocci and enteric gram negative bacilli (25).

Finally, cell mediated immunity can be impaired to a clinically significant degree in some malignancies (36). The prototypic malignancy associated with cellular anergy is Hodgkin's Disease in which negative tests for CMI correlate with later stages of the disease (99,38). Similar observations have been made for patients with non-Hodgkin's lymphoma (38). In addition, corticosteroids have shown to be effective suppressors of CMI (27, 47). Some studies have demonstrated a relationship between depressed CMI and increased susceptibility to infection by intracellular bacteria, fungi, protozoa, and viruses (85,100)

In summary, no published study has examined the risk of infection in neutropenic patients without malignancy or cytotoxic therapy. Since both malignancy and its therapy have been shown to predispose the host to infection, it is difficult to ascertain the role that neutrophil count, alone, plays in infection. In this study we attempted to reduce other factors which may impair host defense against infection, and thereby concentrate more specifically on the risk of neutropenia only.

METHODS

I. Case Selection

This study was a ten year retrospective chart review involving all patients discharged from Yale-New Haven Hospital with the discharge diagnosis of aplastic anemia or neutropenia in the period from 1969-1978. These two filing categories included all patients with the discharge diagnosis of neutropenia of any cause during their hospitalization.

The patients' charts were pulled and then examined. The selection of patients for this review was based on the following criteria:

1) All patients had to have neutrophil counts of less than 1500 for at least two days.
2) The calculation of absolute neutrophil count was based on two or more consecutive CBC's (WBC count with differential) over a period exceeding two days.
3) The chart had to be complete for the entire hospitalization including a discharge summary, daily temperature chart, hematology lab results, and bacteriology lab results.
4) Patients were excluded from the study when other evidence of host impairment other than neutropenia was present, including:
   a. disseminated malignancy;
   b. cytotoxic drug therapy;
   c. corticosteroid therapy;
   d. active systemic diseases known to impair host defense such as:

(1) SLE

(2) Uremia/severe renal failure

(3) Rheumatoid arthritis

(4) Diabetes mellitus

(5) Chronic alcoholism

II. Definitions

Neutropenia - Neutropenia was defined as an absolute neutrophil count of less than 1500.

Infection - An infection was identified by the presence of any of the following:

1) a recognizable focus by physical examination.
2) positive bacterial cultures consistent with the clinical picture of the patient.
3) any positive blood culture with clinically significant organisms.
4) improvement in equivocal clinical findings temporally related to an appropriate, culture-based antibiotic regimen.
5) definitive radiologic findings consistent with infection.
6) positive biopsy findings.
7) positive autopsy results.

Community Acquired Infection - An infection documented by any of the above criteria, occurring at the time of admission or up to 48 hours following admission.

Nosocomial Infection - The development of the above criteria for infection 48 hours or more after admission into the hospital.

Febrile Episode - A significant febrile episode was defined as an oral or rectal temperature greater than 100°F, persisting at least 24 hours, and noted by the patient care staff to be clinically significant. Transient temperature elevations clearly due to the transfusion of blood products were not included in the study.

New Episode of Neutropenia - A new episode of neutropenia was defined as the onset of neutropenia at least 48 hours after the apparent resolution of a prior episode.

New Episode of Infection - A new episode of infection was defined as the recurrence of infection after the patient had been afebrile and without signs of infection for at least 72 hours or identification of a new pathogen in a patient who remained febrile on antibiotics.

Chronic Neutropenia - Any neutropenic episode lasting greater than 6 months, continuously. (The absolute neutrophil count may range anywhere between 0-1500/mm^3.

Acute Neutropenia - Any neutropenic episode resolving within 6 months of onset.

Incidence of Infection per 100 Hospital Days - The total number of new episodes of nosocomial infections occurring within 100 total patient days in the hospital.

Incidence of Infection per Hospital Admission - The total number of new episodes of nosocomial infection divided by the total number of hospital admissions.

Prevalence of Community Acquired Infection - The total number of community acquired infections divided by the total number of hospital admissions.

URI-Upper Respiratory Infection - Upper respiratory infection was defined to include the common viral URI, pharyngitis, sinusitis, otitis media and croup, alone or in combination with one another. The diagnosis was based on physical exam in the majority of cases.

LRI-Lower Respiratory Infection - Lower respiratory infection included pneumonia and bronchitis of any cause.

Skin Infection - A skin infection was a broad category defined to include wound infections, cellulitis, superficial abscess, bullae, and other skin lesions.

Anorectal Infection - Anorectal infections included anorectal abscesses, and infected fistulae.

UTI-Urinary Tract Infection - A urinary tract infection was defined to include cystitis, pyelonephritis, and bacteruria with greater than 10^5 pathogenic microorganisms obtained from a clean catch specimen.

Monocytosis - The upper limit of normal for monocyte level is considered 400-600 per mm^3 (29). Monocytosis was defined as greater than 400 monocytes per mm^3.

Immunoglobulin Levels - Immunoglobulin levels were measured by a radial immunodiffusion test. The age-corrected range of normal (in mg/100 ml) includes (53):

	IgG	IgM	IgA
Newborn	600-2000	0-30	<10
Children (6-8 years old)	450-1600	20-150	50-300
Adults (≥ 9 years old)	600-2000	20-250	60-400

Cell Mediated Immunity - CMI was assessed by the extent of induration to intradermal skin testing with recall antigens, including tuberculin, mumps, candida, and trichophyton (15). Normal CMI was defined as an area of induration at least 10 mm in diameter. Questionable CMI was defined as 5-10 mm of induration, and abnormal CMI was less than 5 mm.

Recent Antibiotic Treatment - In patients with normal renal and hepatic function, a subtherapeutic level of antibiotic was generally assumed to be reached by 48 hours after cessation of therapy. Recent antibiotic treatment was defined as any patient having received any antibiotic within 48 hours of time of infection.

III. Method of Chart Review

Each patient's chart with the discharge diagnosis of aplastic anemia or neutropenia was examined for the absolute neutrophil count throughout their hospitalization. Patients having less than 1500 absolute neutrophils for at least two days during the course of a hospitalization were considered eligible for the study, providing they exhibited no evidence of systemic disease or drug therapy known to cause serious host impairment (as outlined under Case Selection). Each qualifying hospitalization was then examined for the following: patient's age, sex, race, diagnosis, presumed etiology, hospitalization number during this 10 year period, WBC count with differential, absolute numbers of neutrophils and lymphocytes and monocytes, duration of neutropenia prior to admission, duration of neutropenia after admission, febrile episodes, temperature, infection site, episode of infection during this hospitalization, proof of infection, infection after how many hospital days, total number of hospital days, organism responsible for the infection, concurrent disease, survival, cause of death, recent antibiotics, catheterization prior to infection, duration of catheterization prior to infection, diagnostic procedures performed before infection, number of prior episodes of

neutropenia, immunoglobulin level, complement level, and degree of anergy.

The data were analyzed using the computerized Statistical Analysis System (SAS) Package (39). All variables were cross tabulated using the Chi-Square Test for Association. Findings were considered significant if the probability (p-value) was less than or equal to .05, using a two tailed test (26).

RESULTS

I. The Study Population

Development of the Study Population

In the ten year period from 1969 through 1978 there were 816 admissions with the discharge diagnosis of neutropenia or aplastic anemia (See Table 1). Out of 816 admissions involving neutropenic episodes, only 188 admissions were eligible for the study; 23% eligibility. Only 145 of the 188 eligible charts were retrieved, giving a recovery rate of 77%. There were 157 episodes of neutropenia involving 145 admissions, in a total of 197 patients satisfying the criteria of the study.

Forty nine percent of the total neutropenic episodes (399 of 816) involved patients with malignancy, and were therefore ineligible for the study. The percentage of neutropenic episodes disqualified for other reasons included 7% having received cytotoxic drug therapy, 4% with chronic alcoholism, 3% with Diabetes mellitus, 2% with rheumatoid arthritis, 2% with SLE, and 1% with chronic renal failure and uremia. Overall, 70% of neutropenic episodes were ineligible.

Characteristics of the Study Population

The 107 patients in the study were composed of 57 males (53%), 50 females (47%), 85 whites (79%), and 22 nonwhites (21%).

For all episodes, the median age of eligible patients was 15 years old, with a range from newborn to 81 years old (See Table 2). This age distribution

varies markedly from that of the general patient population at Yale-New Haven Hospital (89).

The sex distribution included 101 males (64%) and 56 females (36%). The race distribution included 132 whites (84%) and 25 nonwhites (16%). Further defining the study population, we find that the whites are comprised of 68% males and 32% females while the nonwhites are 44% male and 56% female. Fifty seven percent of the study population is white male, 26% is white female, 9% is nonwhite female, and 7% is nonwhite male.

There were 8 different diagnoses assigned to the various members of the study population to describe their neutropenia. The breakdown was as follows: 39% neutropenia, 15% aplastic anemia, 12% congenital neutropenia, 12% leukopenia, 10% pancytopenia, 6% granulocytopenia, 4% agranulocytosis, and 2% cyclic neutropenia.

The etiology of the neutropenia was unknown in 55% of the episodes. Of the 45% of episodes with known etiology, 35% were secondary to a drug reaction, 21% were due to a congenital syndrome, 18% were presumed secondary to a viral illness, and the remaining 24% were due to immune reactions, solvent exposure, familial conditions, and hypersplenism (See Table 3). The viral infections presumed to be responsible for the resulting neutropenia were not included in the ensuing infection statistics.

Assuming the normal range of WBC counts to be 5,000-10,000, 73% of the patients were leukopenic as well as neutropenic during their episodes, and 8% had a leukocytosis (See Table 4).

The breakdown of the study population by neutrophil count reveals 38% of episodes occurred in patients with less than or equal to 250 PMN's,

13% in patients with 251-500 PMN's, 23% in patients with 501-1000 PMN's, and 26% in patients with 1001-1500 PMN's (See Table 5).

The median duration of neutropenia after hospitalization was 4 days. Sixty two percent of the neutropenic episodes resolved within 5 days, and 75% of the neutropenic episodes resolved within 8 days. Eighty three of the 107 patients, 78%, had an acute episode of neutropenia (defined as a neutropenia that resolved within 6 months of onset). Chronic neutropenia (defined as a neutropenia lasting longer than 6 months) was found in 22% (24 of 107) of patients. Further, 80% (126 of 157) of all neutropenic episodes involved patients with acute neutropenia, while 20% (31 of 157) involved patients with chronic neutropenia.

There was a significant association between the duration of neutropenia and age ($p = .012$). Acute neutropenic episodes were more common in the first two decades of life (See Table 37).

In general, most of the patients had an acute episode of neutropenia necessitating only one hospital admission. Only 19 of 107, or 18% of patients had more than one hospital admission for their neutropenia. In addition, only 5 of 107, or 5% of patients experienced more than one episode of infection during any one admission.

The outcome of the neutropenia among the 107 patients was as follows: Of the 83 patients admitted with an acute neutropenia, 62 resolved, 17 became permanent, and 4 died. Of the 24 patients admitted with chronic neutropenia, 19 continued, and 5 died.

For the entire study population, there was a total of 2033 days spent hospitalized, of which 1329 days were spent with neutrophil counts of less than 1500 (See Table 13).

Eighty seven of 157, or 55% of the episodes occurred in patients for the first time. Thirty five percent of the episodes occurred in patients having had at least 3 prior neutropenic episodes.

The total number of days hospitalized ranged from 1-180 days, with a median of 7 hospital days (See Table 6).

Only 15% of the patients developed neutropenia during hospitalization, while 85% of the patients were admitted with neutropenia.

II. Fever and Infection

Febrile Episodes

Eighty five of the 157 neutropenic episodes (54%) resulted in a febrile episode (See Table 10). The median temperature for those patients who became febrile was 101.8° Farenheit.

There was a statistically significant relationship between fever and infection ($p < .001$). Overall, 72 of the 85 febrile episodes were associated with a documented infection. Therefore fever was predictive of infection in 85% of cases. Fifty five of 72, or 66% of the afebrile episodes were not associated with an infection. This implies that 24% of afebrile episodes were still associated with infection. Thus, absence of fever as an indicator of absence of infection is less reliable (although still statistically significant) than presence of fever is of presence of infection. In other words, the sensitivity of fever as an indicator of infection was 81%, and its specificity was 81%.

We then divided the study population into two groups based on absolute neutrophil count. There was a statistically significant association ($p < .001$) between neutrophil count and febrile episodes, in

that episodes involving ≤250 neutrophils are more likely to be associated with febrile episodes than are episodes involving 251-1500 neutrophils. Furthermore, the statistically significant relationship between fever and infection remained for both groups of ≤250 and 251-1500 neutrophils. Forty seven of 60, or 78% of neutropenic episodes with ≤250 neutrophils developed febrile episodes. Forty four of the 47 febrile episodes had documented infections. Six of the 13 afebrile episodes were without infection. Thus, for patients with ≤250 neutrophils, fever was predictive of infection in 94% of cases, while absence of fever was predictive of absence of infection in only 46% of cases.

Thirty eight of 97, or 39% of neutropenic episodes with 251-1500 neutrophils developed febrile episodes. Twenty eight of the 38 febrile episodes had documented infections. Forty nine of the 59 afebrile episodes were without infection. Thus, for patients with 251-1500 neutrophils, fever was predictive of infection in 74% of cases, while absence of fever was predictive of absence of infection in 83% of cases. In other words, fever as an indicator of infection has a 86% sensitivity and 66% specificity in episodes involving ≤250 neutrophils, and a 74% sensitivity and 83% specificity in episodes involving 251-1500 neutrophils.

Infection Sites and Organisms

The sites of infection, broken down by organ systems reveals that 46% of infections involved the respiratory system, 14% involved the skin, 13% involved the gastrointestinal system, 13% involved septicemia without any known source, 8% involved the genitourinary system, 3% involved the

cardiovascular system, 3% involved the musculoskeletal system, and 2% involved miscellaneous sites (see Table 7).

Looking at more specific infection sites, the five major sites included 30% upper respiratory infections (URI), 15% lower respiratory infections (LRI), 13% skin infections, 7% anorectal infections, and 6% urinary tract infections (UTI). The remaining 29% of infections involved other sites (see Table 8).

Positive organisms were documented in 64% of the episodes of infection (57 of 89). The most frequent infecting organisms included, E. coli, Candida, Pseudomonas, S. aureus, Klebsiella, Enterococcus, and H. influenza, accounting for 23%, 14%, 12%, 12%, 9%, 5%, and 5% respectively of the documented organisms (see Table 9). Conversely, 70% (40 of 57) of the infections with documented organisms involved a "top five" organism.

The proof of infection was obtained in a variety of ways including positive wound cultures, blood cultures, physical exam, chest x-ray, gram stain, and specimen obtained through autopsy or biopsy. One third of all episodes of infection were confirmed by positive wound cultures. One fourth of all episodes of infection were confirmed by positive blood cultures, and one fourth by positive physical examination.

For a breakdown of infecting organism by infection site, refer to Table 30. Interestingly, S. aureus and Candida were only responsible for URI's and skin infections in this study. These two etiologic agents were responsible for all 7 URI's with documented organisms, and 5 of the 8 skin infections with documented organisms.

Examination of infection sites and organisms, when broken down by neutrophil count, provided some significant observations. Examining the organ systems involved with infection only a few significant differences exist between patients with ≤250 and 251-1500 neutrophils (see Table 25). Eighty two percent of infections involving the gastrointestinal system and 75% of infections involving the skin occurred in patients with ≤250 neutrophils. In addition, 8 of 11, or 73% of the cases of septicemia without documented source occurred in the ≤250 group.

In the 5 major infection sites, 75% of skin infections and 100% of anorectal infections occurred in patients with ≤250 neutrophils. In the three remaining major infection sites, there was a much more even distribution between the ≤250 and the 251-1500 groups (see Table 26).

The five major infection sites comprised 58% of all infections in the ≤250 group, 45% in the 251-500 group, 39% in the 501-1000 group, and 12% in the 1001-1500 group. Note the decreasing incidence of infection involving the five major sites as the neutrophil count increased. Overall, the five major infection sites comprised 58% (35 of 60) of the total infections in patients with ≤250 neutrophils, but only 29% (28 of 97) of the infections in the 251-1500 group. Thus, lower neutrophil counts were associated with an increased incidence of infection involving one of the five major sites ($p < .001$).

In patients with ≤250 neutrophils, a "top five" organism was responsible for the majority of documented infections as follows: 100% of Klebsiella infections (5 of 5), 86% of S. aureus infections (6 of 7), 71% of Pseudomonas infections (5 of 7), and 67% of E. coli infections (8 of 13). Only 38% of documented Candida infections occurred in patients with ≤250 neutrophils (see Table 27).

In the 57 infections with recoverable organisms, "top five" organisms were responsible for 75% of infections in the ≤250 group, and only 62% of infections in the 251-1500 group (p = .30). Overall, 53% of all infections in the ≤250 group were due to "top five" organisms, while only 38% of all infections in the 251-1500 group were due to these agents.

Another interesting statistic was the chance of recovering the infecting organism. For patients with ≤250 neutrophils, 71% of all infections had a recoverable and identifiable agent, while the remainder of patients with 251-1500 neutrophils had a recoverable and identifiable agent in 55% of the episodes of infection. Thus patients with ≤250 neutrophils had a slightly better chance of recovering their infecting organisms.

Incidence of Infection

Eighty nine of the 157 neutropenic episodes (57%) resulted in infection either prior to or after admission. These 89 infections occurred in only 57 patients, thus only 53% of the patients in the study developed infection. There were twice as many community acquired infections (59) as there were nosocomial infections. Overall, 19% of all the neutropenic episodes resulted in nosocomial infections, and 38% of all episodes resulted in community acquired infections.

Community Acquired Infection

A community acquired infection was recognized at the time of admission in 59 of the 145 admissions, giving an overall prevalence of 41% (see Table 12). In the large majority of these cases, infection was the cause of admission. Comparing the patient with neutrophil counts ≤250

and those with 251-1500, the respective incidence of community acquired infection per admission was 67% versus 27%, and this difference was statistically significant ($p<0.005$). The incidence of community acquired infection per admission in the $\leq$250 group was more than double that of all the other neutropenic patients.

Nosocomial Infection

Thirty of the 145 admissions were complicated by infection during hospitalization, giving an overall incidence of nosocomial infection per admission of 21% (see Table 12). The incidence of infection per admission in patients with $\leq$ 250 was 37% (18 of 49) as compared to an incidence of 13% (12 of 96) in patients with 251-1500 neutrophils. The incidence of nosocomial infection in the $\leq$250 group was significantly higher than that of all the other neutropenic patients ($p < .001$). It is also interesting to note that there were twice as many community acquired infections as there were nosocomial infections in the total study population.

There were 18 nosocomial infections acquired during the 536 days spent with neutrophil counts of $\leq$250 (see Table 13). There were 3 nosocomial infections acquired during the 130 days spent with neutrophil counts of 251-500, 7 nosocomial infections acquired during 409 days of 501-1000 neutrophils, and 2 nosocomial infections acquired during 254 days of 1001-1500 neutrophils. The incidence of nosocomial infection per 100 hospital days increased steadily with decrease in neutrophil count as follows: group 1001-1500 had 0.8 n/100 hospital days, group 501-1000 had 1.7 n/100

hospital days, group 251-500 had 2.3 n/100 hospital days, and group ≤250 had 3.4 n/100 hospital days. Evaluating these results in a broader, more relevant sense, the incidence of nosocomial infection for patients with ≤250 neutrophils was 3.4 n/100 hospital days while for patients with 251-1500 neutrophils the incidence was 1.5 n/100 hospital days. Thus, for patients with ≤250 neutrophils there was more than twice the incidence of nosocomial infection per 100 hospital days than there was among all other neutropenic patients.

III. Risk Factors for Infection

Neutrophil Count

For comparison, all episodes were divided into subgroups according to neutrophil count as follows: ≤250, 251-500, 501-1000, and 1001-1500. There was a statistically significant association between neutrophil count and infection ($p<0.001$). The overall incidence of infection, both community acquired and nosocomial, increased with decreasing neutrophil count (see Table 11). Fifty seven percent of all infections occurred in episodes with ≤250 neutrophils, while 15% occurred in the 251-500 group, 21% occurred in the 501-1000 group, and 7% occurred in the 1001-1500. group.The ≤250 group comprised only 38% of the population but managed to develop 57% of all infections while the combined group of 251-1500 comprised 62% of the population and developed only 43% of all infections ($p = 0.001$).

Further examination reveals that 51 of the 60 episodes with counts ≤250 developed infection, and 38 of the 97 episodes in the combined group with counts of 251-1500 developed infection. Thus 85% of all

neutropenic patients with counts of ≤250 entered with, or developed infection, while only 39% of all neutropenic patients with counts from 251-1500 were admitted with or developed infection, and this difference was also significant ($p \leq 0.001$).

Duration of Neutropenia

There was no significant difference in the incidence of infection between episodes of acute and chronic neutropenia (see Table 35). Sixty percent (76 of 126) of acute episodes of neutropenia resulted in an infection while 42% (13 of 31) of chronic episodes developed infections ($p = .064$). Even after controlling for neutrophil count, there was no significant difference between acute and chronic neutropenias. Further there was no significant difference in neutrophil distribution between acute and chronic episodes.

Nosocomial Duration of Neutropenia

In general, the longer the duration of neutropenia, the greater the incidence of infection. Since it is difficult to assess duration of neutropenia prior to admission, we cannot draw valid conclusions concerning community acquired infections and duration of neutropenia. In reference to nosocomial infections, patients with ≤250 and 251-500 neutrophils had increasing incidence of infections with increasing duration of neutropenia (see Table 14). For those patients with 501-1000 neutrophils, 100% of all infections developed within the first 14 days. No additional infections developed after that time period. Furthermore, of the patients with 1001-1500 neutrophils, 100% of all infections developed within the

first 5 days of hospitalization. In summary, increasing duration of neutropenia was associated with increasing incidence of infection in all patients with ≤500 neutrophils. While for patients with 501-1500 neutrophils, there was an increase in infection seen in association with increasing duration of neutropenia, up to 14 days following hospitalization, beyond which there was no increase.

Length of Hospitalization

Forty percent of all patients who developed nosocmial infections, did so within their first 5 days of hospitalization (see Table 14). Sixty three percent of the above patients developed their nosocomial infection within 14 days. Upon dividing the population according to neutrophil counts, we find that only 28% of the patients with ≤250 neutrophils who ultimately developed nosocomial infections, did so within the first 5 days of hospitalization. Interestingly, 58% of the patients with 251-1500 neutrophils who ultimately developed nosocomial infections, did so within the first 5 days. Examining the onset of infection within the first two weeks of hospitalization, we find that only 50% of the ≤250 group who ultimately developed nosocomial infection, did so within the first 14 days, while 83% of the 251-1500 group became infected within that time period. Even if we only count the first nosocomial infection in the course of a hospitalization and disregard the subsequent infections, only 38% of patients with ≤250 neutrophils developed their infection within the first 5 days, and 69% within 14 days.

Onset of Neutropenia

There was no significant difference in the incidence of infection between patients admitted with, or subsequently developed their neutropenia. Fifty nine percent (78 of 133) of patients admitted with neutropenia developed an infection, while 46% (11 of 24) of patients who subsequently developed neutropenia also developed an infection (see Table 39).

Age

The younger patients in the study comprised the bulk of those who became infected (see Table 15). Twenty two of 89, or 25% of the total infections occurred in infants less than 1 year of age. Twenty three of 89, or 26% of the total infections occurred in children between the ages of 1-10 years old. Fifteen of 89, or 17% of the total infections occurred in children between the ages of 11-20 years old. The percentage of all infections found in each succeeding decade was as follows: 9% (8 of 89) in the 21-30 year olds, 0% (0 of 89) in the 31-40 year olds, 3% (3 of 89) in the 41-50 year olds, 7% (6 of 89) in the 51-60 year olds, and 13% (12 of 89) in the greater than 60 year olds. Recategorizing the ages into four groups including infants (less than 1 year of age), children (age 1-20), young adults (age 21-50),and old adults (age 51 and older), we found that 79% of all infants in the study became infected, 57% of children became infected, 39% of young adults became infected, and 53% of old adults became infected. Overall, 56% of all neutropenic episodes in this study resulted in infection. Thus, infants with their 79% infection rate were at a greater risk of infection than the general

study population, and young adults with their 39% infection rate were at a lesser risk of infection ($p = 0.029$).

Sex

As mentioned earlier, 64% of all the neutropenic episodes were in males (101 of 157), yet 76% of all the infections occurred in males. Sixty seven percent of all the neutropenic episodes in males resulted in infection, while only 38% of all episodes in females resulted in infection. Males are therefore at increased risk for infection compared to females ($p = .0003$). There were roughly twice as many males with neutropenic episodes than females, and the males were twice as likely to get infected (see Table 16).

Race

Whites comprised 84% of the study population (132 of 157) and they accounted for 87% of the infections (77 of 89). The number of whites who became infected versus those who escaped infection were roughly equal, 58% and 42% respectively. The same was true for the nonwhites with 48% getting infected and 52% escaping infection. Thus, there is no significant difference in risk of infection between whites and non-whites.

Catheter Use

Catheters were defined to include IV lines, heparin locks, Foley catheters, Penrose drains, hyperalimentation lines, tracheotomy tubes, or any other invasive conduits. Standard IV lines caused no increased

risk of infection at any time during their hospitalization. Hyperalimentation lines, Foley catheters, and heparin locks suggest an increased risk of infection, but the numbers were too small to be statistically significant (see Table 17).

Immunoglobulin Level

Immunoglobulin levels were quantitatived by radial immunodiffusion in only 45 of the 157 episodes of neutropenia (see Table 18). Patients with normal as well as increased levels of immunoglobulins (particularly IgG) experienced no protective effect from infection, as evidenced by their exactly equal breakdown between those with, versus those without infection. In contrast, 85% (11 of 13) of patients with decreased levels of immunoglobulins went on to develop infection. Thus there was a significant association between immunoglobulin levels and rate of infection, with decreased levels of immunoglobulins being associated with higher rates of infection ($p = 0.05$).

Monocyte Level

Since the upper limit of normal for monocyte level ranges from 400-600, we defined a monocytosis as greater than 400 monocytes. Of the 68 episodes that did not result in infection, 51% (35) had less than 400 monocytes and 49% (33) had greater than 400 (see Table 38). Of the 89 episodes that resulted in infection 54% (48) had less than 400 monocytes and 46% (41) had greater than 400. Thus a monocytosis was not protective against infection.

Complement Level

There were too few patients who had their complement levels documented to make any significant statement.

Delayed Hypersensitivity

Delayed hypersensitivity as defined by standard "recall" antigen skin testing was checked in too small a number of patients to make any significant statement.

Etiology of Neutropenia

The etiology of the neutropenia had no bearing on the risk of infection.

Recent Antibiotics

Thirty five of the 157 episodes occurred in patients who had received antibiotic therapy in the course of their hospitalization (see Table 34). In the patients who had not received any antibiotics, 48% escaped infection while 52% ultimately developed infection. This equal probability is what is expected. However, 74% of those patients who received antibiotic therapy developed infection within 48 hours of their last dose, while only 26% of them escaped infection. Thus recent antibiotic therapy in the neutropenic patients was not protective against infection, and in fact it seemed to increase the likelihood of infection ($p = .025$). It is important to note that the recent antibiotic therapy was usually a single drug and not the typical broad spectrum therapeutic regimen for neutropenic patients consisting of ticarcillin

(or other carbenicillin-type agent) and gentamicin (37,51,75,80). Ninety percent of the patients who received antibiotic therapy did so for therapeutic purposes. Ten percent of these patients received antibiotic therapy for infection prophylaxis, and 100% of this smaller group went on to develop infections. Thus prophylactic antibiotic treatment of neutropenic patients seemed to further increase their incidence of infection.

IV. Outcome of Neutropenia

Chronic vs. Acute Neutropenia

As discussed earlier, of the 83 patients admitted with an acute neutropenia, 62 resolved, 17 became permanent, and 4 died. Of the 24 patients admitted with chronic neutropenia, 19 continued, and 5 died.

Mortality

Nine patients did not survive their episode of neutropenia thereby producing an overall mortality rate of 6%.

V. Outcome of Infection

Mortality

The rate of infectious mortality was 9% (8 of 89). The cause of death was bacterial sepsis in 6 cases, fungal sepsis in 2 cases, and intracranial hemorrhage in 1 case. In other words, 89% of deaths in these neutropenic patients were due to sepsis (both fungal and bacterial), and specifically, 66% of deaths were due to bacterial sepsis.

VI. Risk Factors for Mortality

There was a significant association between mortality and infection ($p = .045$), and mortality was greatest in patients with infection (see Table 20). Even when controlled for neutrophil count, we still found that the greatest risk factor for mortality was infection. Examining the mortality among those who were infected we found that 75% of mortalities (6 of 8) involved patients with nosocomial infections, and 25% involved patients with community acquired infections (see Table 39). Nosocomial infections comprised only 34% (30 of 89) of all infections but 75% (6 of 8) of all mortalities from infection. Thus nosocomial infections were associated with an increased risk of mortality compared to community acquired infections ($p = .01$).

The association between neutrophil count and mortality did not achieve statistical significance (see Table 19). Patients with ≤ 250 neutrophils comprised 38% of the neutropenic episodes (60 of 157), and 67% of all mortality (6 of 9). Despite comprising only one-third of the population but two-thirds of the mortality, there was only a weak association between low neutrophil count and high mortality ($p = .07$). Further, when controlling for the presence of infection, neutrophil count was definitely not a significant risk factor for mortality. Overall, there was a 10% mortality rate in the ≤ 250 group (6 of 60), and only a 3% mortality rate in the 251-1500 group (3 of 97).

There was no significant association between duration of neutropenia (i.e., chronic vs. acute episodes) and mortality, although 7 of the 9 deaths involved patients with acute neutropenia (see Table 36).

The onset of neutropenia (i.e., admitted with vs. developed neutropenia) was not significantly associated with mortality, although 8 of the 9 deaths occurred in patients who were admitted with neutropenia.

The five most common infecting organisms identified in this study were E. coli, Candida, Pseudomonas, S.aureus, and Klebsiella (see Table 21). Seven of the 9 mortalities were due to overwhelming sepsis by one of these "top five" organisms including 2 by E. coli, 2 by Candida, 2 by Pseudomonas, and 1 by Klebsiella. Seventy-seven percent of all deaths, and 88% of deaths due to sepsis, were caused by a "top five" organism. However "top five" organisms were not associated with an increased risk of mortality ($p = .18$).

Males comprised 64% of the study population and females comprised 36%. In almost perfect concordance, 67% of mortalities involved males and 33% involved females. Thus, although males are at greater risk than females to become infected, they are at equal risk for mortality.

Eight of 132, or 6% of the white patients in the study did not survive their episode of neutropenia. One of 25, or 4% of the nonwhite patients in the study did not survive. There is no significant difference in survival between whites and nonwhites. It is interesting to note, however, that 21 of the 25 nonwhites were Black and they suffered no mortality.

Fifty five percent of the episodes in this study occurred in patients experiencing their first neutropenic episode, while 77% of the mortalities occurred in these patients. Upon directly comparing mortality versus number of prior neutropenic episodes we found that 45% of all deaths

(4 of 9) occurred in patients experiencing their first neutropenic episode, while 33% of all deaths (3 of 9) occurred in patients with chronic neutropenia (defined as 3 or more previous hospital admissions for neutropenia). Therefore, the number of prior episodes of neutropenia is no indication of risk for mortality.

Examining the mortality within each age group, broken down by neutrophil count, we found that the 1 infant death involved a patient with 251-1500 neutrophils, 4 of the 5 childhood deaths involved patients with ≤ 250 neutrophils, there were no deaths among the young adults, and 2 of the 3 old adult deaths involved patients with ≤ 250 neutrophils (see Table 32).

The breakdown of mortality by age group (see Table 22) reveals 1 death in the infants (age less than 1 year), 5 deaths in the children (age 1-20 years), 0 deaths in young adults (age 21-50 years), and 3 deaths in old adults (age 51 and older). The corresponding mortality rates for these groups are 4% in infants, 8% in children, 0% in young adults, and 10% in old adults. It is interesting to note that the greatest mortality rate for any one decade was 14.2% for children aged 11-20. Infants comprised 18% (28 of 157) of all episodes, 25% of all infections, and 11% (1 of 9) of all mortality in this study. Children comprised 43% (67 of 157) of all episodes, 43% of all infections, and 56% (5 of 9) of all mortality. Young adults comprised 18% (28 of 157) of all episodes, 12% of all infections, and 0% (0 of 9) of all mortality. Old adults comprised 21% (33 of 157) of all episodes, 20% of all infections,

and 33% (3 of 9) of all mortalitites. Although the numbers were too small to determine a significant association, the highest risk of mortality involved the old adults with their 10% mortality rate, and the lowest risk of mortality involved the young adults with their 0% mortality rate.

Six of 9, or 67% of all mortalities occurred in patients who had received recent antibiotic therapy (see Table 34). Ninety eight percent of all those who did not receive recent antibiotic therapy (119 of 122) survived their neutropenic episodes, while only 83% of those who did receive recent antibiotic therapy (29 of 35) survived. In other words, there was a 17% mortality among those who received recent therapy and only a 2% mortality among those who did not. Thus, recent antibiotic therapy was not protective against mortality and in fact, it was associated with an increased risk of mortality ($p = 0.001$). Therefore recent antibiotic therapy was a significant risk factor for mortality.

Eight of the 9 deaths, 89%, occurred in patients with $\leq$400 monocytes (see Table 38). The mortality rate was 10% (8 of 83) in patients with $>$400 monocytes, and only 1% (1 of 74) in patients with $\leq$400 monocytes. Thus, a monocytosis was associated with reduced mortality ($p = 0.025$).

The numbers were too small to make any comment about a significant association between mortality and the following potential risk factors: coexistent disease, ability to mount a febrile episode, immunoglobulin levels, complement levels, and cell mediated immunity.

Thirty three percent of deaths in this study occurred in patients with infections of one of the five major infections sites (LRI, URI,

skin, anorectum, and UTI), while 56% of deaths occurred in patients with infection of other less common sites, and 11% of deaths were not associated with sepsis (see Table 23). Although the five major infection sites comprised 71% of all infections, they only comprised 33% of all mortalities. The mortality rate was 5% (3 of 60) for patients with infection of one of the five major sites, and 17% (5 of 29) for patients with infection of other less common sites. Specifically, 5 of the 9 mortalities were due to septicemia without a documented source, and these 5 deaths comprised all of the infectious deaths not occurring in a major site. Therefore it was more correct to state that sepsis without a documented source was a significant risk factor for mortality compared to infection of any identifiable site ($p = 0.001$) and the rate of mortality in this group of patients was 42%.

VII. Miscellaneous Factors Related to Neutropenia

Duration of Hospitalization

For convenience, we divided total hospital days into three categories as follows: 1-7 days, 8-14 days, and ≥15 days. Overall, 49% of all the patients in the study were hospitalized for less than or equal to 7 days. Twenty eight percent of all the patients were hospitalized for greater than 2 weeks. However, 52% of the patients who were hospitalized for greater than 2 weeks had neutrophil counts of ≤250. Thus patients with neutrophil counts of ≤250 were at greater risk of longer hospitalization than other neutropenic patients ($p = 0.04$)(see Table 24).

Mean Values

In comparing the mean values between the sexes (see Table 28), males had a lower mean age (20 vs. 30 years old), higher WBC count (4,500 vs. 3,100 WBC's), fewer neutrophils (517 vs. 734 PMN's), nosocomial infection occurring at a later date (12 vs. 7 days after admission), equal temperatures during febrile episodes (102°F), longer hospital stays (22 vs. 13 days), and longer duration of neutropenia (20 vs. 8 days).

Infection Sites Versus Sex

Recall that 67% of all neutropenic episodes in males resulted in infection, while only 37% of neutropenic episodes in females resulted in infection. Eighty percent (32 of 40) of respiratory system infections, 82% (9 of 11) of gastrointestinal system infections, and 83% (10 of 12) of skin infections occurred in males. Thus males were at an increased risk of getting infections of the above three organ systems ($p = 0.0063$) (see Table 29).

Examining the five major sites of infection, males comprised 85% (11 of 13) of LRI's, 78% (21 of 27) of URI's, 83% (10 of 12) of skin infections, 100% (6 of 6) of anorectal infections, and 60% (3 of 5) of UTI's. Overall, 76% of all infections occurred in males. Thus males seemed to be at increased risk of LRI's and anorectal infections.

Neutrophil Count Versus Age

For the 89 episodes that culminated in infection, some generalizations can be made knowing the neutrophil count and the patient's age.

Twenty percent (18 of 89) of all infections occurred in infants with ≤250 neutrophils. Twenty percent (18 of 89) of all infections occurred in children with ≤250 neutrophils. Seventeen percent (15 of 89) of all infections occurred in adults (both young and old) with ≤250 neutrophils. Thus 57% of all infections involved patients of all ages with 250 neutrophils. Examining the various age groups, we found that 82% (18 of 22) of all infants who developed infection had ≤250 neutrophils, 47% (18 of 38) of all children who developed infection had ≤250 neutrophils, 55% (6 of 11) of young adults who developed infection had ≤250 neutrophils, and 50% (9 of 18) of old adults who developed infection had ≤250 neutrophils. Therefore for children, young adults, and old adults (i.e., all those patients 1 year old or older) the risk for developing infection was roughly equal whether they had ≤250 or 251-1500 neutrophils. However, for infants, neutrophil counts of ≤250 greatly increased their risk of infection (see Table 31).

DISCUSSION

I. Non-Neoplastic Causes of Neutropenia

Although malignancy and cytotoxic drug therapy are very common causes of neutropenia in a hospital population, there are many other etiologies as well. Non-neoplastic causes of neutropenia include drug reactions, industrial solvent exposure, allergic reactions, leukotoxin production, anti-neutrophil antibodies, hypersplenism, vitamin deficiencies, sepsis, inflammation, and vasomotor changes (29). There is also a substantial number of idiopathic neutropenias, many of which are chronic and/or familial. An analysis of the risk factors for infection in this subpopulation of neutropenic patients has been long overdue.

It was not surprising to see that 49% of the 816 admissions with neutropenia were due to malignancy over the ten year period from 1969 through 1978, considering the increasing incidence of cancer in the general population. There were 157 episodes of neutropenia eligible for this study, comprising a patient population that was 64% male, 84% white, with a median age of 15 years. This differs markedly from the general patient population at Yale-New Haven Hospital (89) which is comprised of more females than males, and having an average age between 50 and 60 years old. This disparity may reflect a very active pediatric hematology referral service, a predilection for non-neoplastic

neutropenia to occur in young white males, an increased incidence of malignancy in the older population, and/or the possibility of early deaths in the pediatric population. In addition, only 45% of the neutropenic episodes in our study had a known etiology, one third of which were presumed secondary to a drug reaction.

II. Types of Infection

The types of infection in this study coincided with the results of previous studies in neutropenic patients with underlying malignancy (10,84,76,35). Fifty four percent of all neutropenic patients, regardless of neutrophil count, ultimately developed an infection; 19% developed nosocomial, and 38% developed community acquired infections. The five major sites of infection included URI's (predominantly pharyngitis), LRI's (predominantly pneumonia), skin, anorectum, and urinary tract. The most frequent infecting organisms included E. coli, Candida, Pseudomonas, Klebsiella, and S. aureus.

In a recent study, Sickles et al., (84) examined the signs and symptoms of infection in granulocytopenic patient with less than 1,000 neutrophils per mm^3. The five most common types of localized infection were pharyngitis, skin infection, pneumonia, anorectal infections, and urinary tract infections (UTI's). Schimpff, in a related study (76), examined the diagnosis of infection in cancer patients and found that the major pathogenic organisms included E. coli, Pseudomonas, Klebsiella, S. aureus, Candida, and the hepatitis viruses. Over 80% of all infections involved the following six sites: lower respiratory tract, pharynx,

anorectal area, skin, urinary tract, and liver. Pneumonia was the most frequent cause of both serious infection and infectious death. In all patients, iatrogenic procedures and hospital acquisition of organisms are major predisposing factors to infection.

In another study by Schimpff et al., (79) the origin of infection in acute nonlymphocytic leukemia was examined to determine the significance of hospital acquisition of potential pathogens. Almost all infections in these patients arose from the patient's own resident flora, but in about half (47%) of the microbiologically documented infections the infecting organisms was hospital acquired. The most common infecting organisms were again Pseudomonas, Klebsiella, E. coli, S. aureus, and Candida. The predominant sites of infection remained lung, anorecturm, skin, pharynx, and urinary tract. As discussed in previous sections, reduced numbers of circulating neutrophils will cause impairment of both the inflammatory and humoral immune responses, thus the rate of infection, sites of infection, and infecting organisms in this study are all consistent with the critical role of the neutrophil in host defense (35,29,25).

III. Febrile Episodes

There is variable opinion as to the predictive value of fever for infection in granulocytopenic hosts. Rabb and Hoeprich (62) in a study of 90 leukemic patients found infection as the cause of fever in 70% of cases. Over 80% of febrile episodes were due to infection in leukemic patients in the studies of Boggs and Frei (12), Browder et al.,

(14) and Frei et al., (30). The study by Rodriguez et al., (66) of fever in all patients with neoplasm and neutropenia admitted to M.D. Anderson Hospital over an 18 month period, revealed that 145 of 203 episodes, or 71% of all fevers were ultimately attributable to infection. Closer examination of the Boggs and Frei study demonstrates a variability of the predictive value of fever depending on the type of malignancy. Among patients with acute leukemia, 60-70% of febrile episodes were due to infection, while in chronic lymphocytic leukemia it is virtually 100%, and only 25% in patients with lymphoma. Thus although the frequency with which fever is predictive of infection varies with tumor type, in general, roughly 70% of febrile episodes ultimately are due to infection.

In our study the presence of a febrile episode was highly correlated with the presence of infection. Fifty four percent of the neutropenic episodes resulted in febrile episodes, and 85% of the febrile episodes had a documented infection. Thus fever was predictive of infection in 85% of cases. The breakdown of this group by neutrophil count demonstrates a significant difference in the predictive value of fever as a sign of infection in the groups with less than and greater than 250 neutrophils. For patients with ≤ 250, fever is predictive of infection in 94% of cases, while in only 74% of cases in patients with 251-1500 neutrophils is fever predictive of infection. Our results of an 85% predictive value overall, and 94% for patients with ≤ 250 neutrophils are substantially higher than previous studies (66,84,76,62,12,14,30). This can be explained by the fact that virtually all these latter studies involved patients with malignancies, particularly leukemia and lymphoma, which are known to cause

fever in their own right, independent of infection (34). Thus many of these previous studies involved a small but significant number of patients with fever due to their malignancy, thereby decreasing the predictive value of fever. This study, by eliminating patients with underlying malignancy, has found fever to be very predictive of the presence of infection.

IV. Incidence of Infection

Many previous studies had indicated a relationship between granulocytopenia and the presence of infection, however Bodey's classic study in 1966 (10) was one of the first to examine the quantitative relationships between the degree and duration of leukopenia in patients with acute leukemia. He demonstrated that the presence of infection in patients with acute leukemia is related to the level of circulating granulocytes and lymphocytes, and the lower the level of these leukocytes, the greater the likelihood that infection will be present. This increasing incidence of infection was most marked in patients with less than 500 granulocytes/mm^3. Infection was present more often during relapse than during remission, at every leukocyte level, suggesting that other factors besides leukocyte level play a role in predisposing to infection.

The prevalence of all types of infection decreased with increasing levels of these leukocytes. At less than 100 granulocytes per mm^3, 53% of the patient days were spent with identified infection. The percentage of time spent with identified infection then decreased sharply with increasing granulocyte levels, and there was no further reduction at granulocyte levels above 1500/mm^3.

The incidence of infectious episodes also decreased with increasing levels of granulocytes and lymphocytes. With severe granulocytopenia of <100 granulocytes per mm^3, 43 episodes of infection were observed per 1,000 hospital days and this incidence dropped sharply with increasing granulocyte levels, with no further reduction occurring at levels of $>1500/mm^3$.

Furthermore the proportion of time spent with identified infections of all types decreased with increasing granulocyte and/or lymphocyte levels. Infection occurred most commonly when both granulocyte and lymphocyte levels were reduced. In addition the incidence of infection was greater in the presence of granulocytopenia alone than in the presence of lymphopenia alone.

In predicting risk of infection, a fall in granulocyte count carried a 12% risk of infection. However, if granulocytopenia was already present, a further fall in granulocyte level resulted in a 28% incidence of infection. Regardless of the magnitude of the fall, the risk is greater the lower the final granulocyte level, especially at levels ≤ 500 granulocytes/mm^3.

The most important factor in predicting risk of infection was the duration of granulocytopenia. Overall, any episode of granulocytopenia, regardless of its duration, had a 39% chance of resulting in infection. As the duration of granulocytopenia lengthened, the risk of infection increased. There was a 60% risk of developing infection if granulocytopenia persisted for 3 weeks, and a 100% risk for 12 weeks duration. In severely granulocytopenic patients with $<100/mm^3$, the risk increased to 100% by 3 weeks.

Schimpff, in a related study (76), examined the diagnosis of infection in cancer patients and concluded that the most important predisposing factor to infection in these patients is granulocytopenia, and both the frequency and severity of infection are inversely related to granulocyte level, especially below 500 neutrophils per mm^3.

To date, there have been no published studies of the quantitative relationship between circulating granulocytes and infection in neutropenic patients without underlying malignancy or cytotoxic therapy. Recall that Bodey's classic study involved leukemics, many of whom had received cytotoxic therapy. However a study at the Hospital of the University of Pennsylvania (45) examined granulocytopenia as an independent risk factor for infection in this subpopulation of neutropenic patients. Their unpublished results basically agree with Bodey's findings, with some modifications.

Over a ten year period, they reviewed 72 admissions with granulocyte counts of less than $1500/mm^3$ and satisfying the above criteria. The incidence of nosocomial infection per 100 hospital days did not change significantly until the granulocyte count fell below 250. The incidence of infection at that level of granulocytopenia was 4.7 per 100 hospital days. Patients with granulocyte counts greater than $250/mm^3$ were relatively infection free with an incidence of infection of only 0.8 per 100 hospital days. Furthermore, over the course of hospitalization, the overall prevalence of nosocomial infections was 45% in patients with $<250/mm^3$, and only 8% in patients with $250\text{-}1500/mm^3$.

In our study the overall incidence of infection, both community acquired and nosocomial, increased with decreasing neutrophil count.

The ≤250 group comprised 38% of the study population but managed to develop 57% of all infections. The combined group of 251-1500 comprised 62% of the population and developed only 43% of all infections. Furthermore, 85% of all neutropenic patients admitted with counts of ≤250 will enter with, or develop infection. In contrast, only 39% of all neutropenic patients with counts from 251-1500 will be admitted with, or develop infection.

The prevalence of community acquired infections increased with decreasing neutrophil count. The overall prevalence of community acquired infections was 41% of all admissions. The incidence of community acquired infection per admission in the ≤250 group was more than double that of all the other neutropenic patients (67% vs. 27%).

The overall incidence of nosocomial infection per admission was 21%. The incidence of infection in patients with ≤250 was 37%, as compared to an incidence of 13% in patients with 251-1500 neutrophils. The incidence of nosocomial infection per admission in the ≤250 group was roughly three times higher than that of all the other neutropenic patients. It is also interesting to note that there were twice as many community acquired infections as there were nosocomial infections in the total study population.

The results demonstrated a significant association between the incidence of nosocomial infections and neutrophil count. The incidence of nosocomial infection per 100 hospital days increased steadily with decreases in neutrophil count; for patients with ≤250 neutrophils, the

the incidence was 3.4/100 hospital days while for patients with 251-1500 neutrophils, the incidence was 1.5/100 hospital days. Thus, for patients with ≤250 neutrophils there was greater than twice the incidence of infection than there was among all other neutropenic patients.

Bodey's study in leukemic patients (10) revelaed an incidence of nosocomial infection of 43 per 1000 hospital days (i.e., 4.3 per 100 hospital days in severe neutropenia, while the unpublished results from the Hospital of the University of Pennsylvania (45) demonstrated an incidence of 4.7/100 hospital days, and our study showed an incidence of 3.4/100 hospital days. The striking similarity of these results may reflect the fact that neutropenia superceded all other risk factors for infection. These 3 studies involved three different hospitals, two different patient populations (leukemics and patients without malignancy) and three different time periods.

There could have been many possible explanations for differences between these three results. First, Bodey's incidence was derived for patients with <100 neutrophils, while ours was for <250 neutrophils. Considering the trend in our study of increasing incidence of infection with decreasing neutrophil count, we assume that had we isolated the 100 group, the incidence would have been substantially higher. Second, Bodey examined leukemic patients who are known to have compromised host defense for reasons other than just neutropenia (40,9,77,34). All four systems of host defense (as previously described) may be altered by leukemia and its cytotoxic therapy including mucocutaneous barriers, the inflammatory response, the humoral immune system, and the cellular immune system. Thus his population is at increased risk of infection

compared to ours, even with similar neutrophil counts. Third, Bodey's study was conducted from 1959-1963 and the University of Pennsylvania study spanned 1963-1972 while ours was from 1969-1978. The decades separating our studies saw a greater understanding of the risk of infection in neutropenic patients, and the adoption of various prophylactic measures to prevent infection including reverse isolation, laminar air flow rooms, oral non-absorbable antibiotics, better defined guidelines for the institution of empiric antibiotic therapy, strict handwashing, reduction in instrumentation, and even avoidance of fresh fruits and vegetables (29,77,78). These prophylactic measures might very well have contributed to a reduced incidence of nosocomial infection in our study, compared to the others, but evidently did not.

The overall rate of nosocomial infection at Yale-New Haven Hospital is approximately 3.7 per 100 discharges, very close to the mean rate for the 18 university hospitals in the National Nosocomial Infections Study (89). Our results, recomputed to compare with Yale's rate, revealed a nosocomial infection rate of 20.6 per 100 discharges for the total neutropenic study population. This broke down to a rate of 36.7 per 100 discharges for patients with $\leq$250 neutrophils, and only 12.5 per 100 discharges in patients with 251-1500 neutrophils. The incidence was higher in our study, and this confirmed the theory that neutropenic patients were at increased risk of infection compared to the general population, especially those with counts $\leq$250.

In general, the percentage of infections increased with increasing duration of neutropenia. Of our patients who developed nosocomial

infections, 40% did so within the first 5 days of hospitalization, and 63% did so within 14 days. Upon dividing the population, 28% of the patients with ≤250 neutrophils, developed their nosocomial infections within 5 days, and 50% did so within 14 days. This is below the percentages computer for the population as a whole. In contrast, of the patients with 251-1500 neutrophils, 58% developed their infection within 5 days, and 83% did so within 14 days. These results are very puzzling, for although we would expect to see an increasing percentage of patients developing infection as the duration of neutropenia increases, we would not expect to see the patients with greater numbers of neutrophils getting infected sooner. Evidently, there must have been other confounding variables exerting their influence on this analysis.

Dale et al., (23) conducted a study examining 29 patients with various forms of chronic neutropenia defined as prolonged reduction of blood neutrophil counts (for months to years) to less than 2,000 PMN's per mm^3 in patients with other blood cell counts being normal, without splenomegaly, and with no other ongoing disease process such as infection, inflammation, or malignancy, to which the neutropenia can be attributed. The results demonstrated elevated monocyte levels, elevated immunoglobulin levels, abundant myeloid precursors in the bone marrow but few mature PMN's, variable but consistently increased neutrophil counts in response to inducing agents (e.g., etiocholanolone, endotoxin, and hydrocortisone), diminished exudation of neutrophils in an acute inflammatory response but supernormal monocyte accumulation, normal urinary and serum levels of CSA, absence of antineutrophil antibodies, rare occurrence of life

threatening infections, no increase in frequency of infections compared to normal controls, and normal response to antibiotic therapy for infection. The only obvious abnormality in most of these patients with chronic neutropenia is a reduction in the ratio of mature to immature neutrophil precursors in the marrow, a "maturation arrest." The cause of the marrow defect is unknown in most cases.

Many studies, including Kyle and Linman's evaluation of chronic idiopathic neutropenia (44), Joyce and Bogg's study of hereditary autosomal dominant neutropenia (42), Rodin's study of infantile genetic agranulocytosis (65), and Cutting's review of familial benign chronic neutropenia (22) agree with Dale's findings. The consequences of neutropenia, both infection and mortality, are less severe for patients with chronic neutropenia than for patients with an acute neutropenia which occurs in idiopathiv acute drug reactions, myelotoxic drug induced granulocytopenias, leukemia, and aplastic anemia. There are several reasons for this difference. First, the latter series of conditions often involves multiple hematopoietic cell lines. Second, in many cases, mucosal and skin barriers are damaged by the underlying disease process. In addition, the monocytosis often seen in chronic neutropenia is not observed in these other conditions, and it is felt to exert a protective effect. Also, the inflammatory response as measured by the total number of cells responding, was much greater and closer to normal in patients with chronic neutropenia. Further, most patients with chronic neutropenia have some circulating neutrophils and a small but demonstrable marrow neutrophil

reserve And finally, these patients usually had normal function of other components of their host defense system (23).

In contrast to these previous studies of chronic neutropenia, we had no significant difference in the incidence of infection between patients with chronic and acute neutropenias. Furthermore, there was no significant difference in monocyte level between patients with acute and chronic neutropenias. One possible explanation for this discrepancy was that our group of "chronic" neutropenia was defined solely by the lack of resolution within 6 months, and thus any neutropenia of long duration was eligible. This included benign familial types of neutropenia as well as long standing neutropenia of acute onset (e.g., idiopathic drug reactions) and this latter group has been described as having a greater incidence of infection compared to the former (23). Also, our group of chronic patients did not consistently have elevated levels of monocytes and this factor might be important in protecting against infection in any patient.

From the preceding paragraphs, it is obvious that absolute neutrophil count is an independent risk factor for infection, with the risk of infection being increased as the neutrophil count is decreased. Likewise, the duration of neutropenia is an independent risk factor for infection, for the longer the duration of any level of neutropenia, the greater the risk of infection. However, we did not demonstrate any significant difference in incidence of infection between patients with acute and chronic neutropenias.

Many other risk factors were ascertained for infection in neutropenic patients. Infants (less than 1 year of age) with their 79% infection rate are at a greater risk of infection than the general study population, and young adults (aged 21-50) are at a lesser risk of infection. The increased risk seen in infants may be due to abnormalities of the humoral immune system. Newborns are usually not capable of significant antibody production, and the only immunoglobulin found in significant concentration in neonatal serum is maternal IgG which crossed the placenta. Later on, as infants, they might still be at increased risk of infection because despite increasing quantities of IgM and IgA, the physiologic nadir of IgG occurs at 3-6 months (53). Therefore, without an intact humoral system, the infant could be at even greater risk of infection when neutropenic. In addition, some of the infants in the study had congenital syndromes (e.g., Schwackman's Syndrome) which may have affected other aspects of host defense besides neutrophil count (71).

Sex was a positive risk factor in that males are at twice the risk of infection compared to females. There is no clear explanation for this phenomenon.

Race was not a significant risk factor. Whites and nonwhites had roughly equal rates of infection. Although Black Africans and Yemenite Jews are known to have higher incidences of benign chronic neutropenias than the rest of the world population (29), and these neutropenias do not predispose the hosts to increased incidence of infection, this fact evidently did not come into play in our analysis.

Standard IV lines caused no increased risk of infection. However hyperalimentation lines, Foley catheters, and heparin locks suggest an increased risk of infection but the numbers were too small to be statistically significant. These results are consistent with prior studies (28,73).

Immunoglobulin level was a positive risk factor for infection in that decreased levels significantly increased the host's risk of infection. This was consistent with the role that immunoglobulins play in the humoral and cell-mediated immune responses.

Monocyte level, in particular a monocytosis, has been reported to exert a protective effect against infection (29). Our results show that monocyte level is not a significant risk factor for infection, and monocytosis does not exert a protective effect against infection. Although monocytes are a phagocytic cell like the neutrophil, their rate of mobilization to sites of inflammation is relatively slow, and their phagocytic and bactericidal capacities are less than that of neutrophils (6).

Recent antibiotic therapy in these neutropenic patients was not protective of infection, and in fact it seemed to increase the likelihood of infection. At first glance, one might have expected antibiotic therapy to prevent infection. However, the therapy usually consisted of a single drug, and was not the recommended broad spectrum therapeutic regimen for neutropenic patients of ticarcillin (or other carbenicillin-type agent) and gentamicin (75,35). Ninety percent of the antibiotic

therapy was for treatment of an existing infection. Ten percent of the patients receiving antibiotic therapy did so for prophylactic treatment, and 100% of this group went on to develop subsequent infections. The increased incidence of infection in these treated patients may have been due to bacterial superinfection, fungal superinfection, or an initial choice of antibiotic to which the pathogenic organism was not sensitive (96). It is wise to consider the five most common infecting organisms in neutropenic patients when selecting an antibiotic regimen. In addition, there may be a bias in this result in that the patients who were sickest (i.e., the ones with the lowest neutrophil counts and greatest numbers of additional risk factors) were the ones most likely to get infected initially and need treatment. Despite this treatment, however, they remained at higher risk for subsequent infection.

The major consequence of infection in neutropenic patients was mortality. The mortality rate was 6% among all neutropenic patients (9 of 157), and 9% among infected patients (8 of 89). Eighty nine percent of all deaths were due to sepsis (both fungal and bacterial), and specifically, 66% of deaths were due to bacterial sepsis.

Infection was the major risk factor for mortality in these neutropenic patients, even when controlled for neutrophil count. In addition, nosocomial infections were associated with an increased risk of mortality compared to community acquired infections. The latter result is not surprising considering the high rate of colonization of patients with nosocomial organisms (79), and the known virulence and antibiotic

resistance of these organisms compared to the normal resident flora of nonhospitalized patients (28).

Age was correlated with risk of mortality. The highest mortality rate for any single decade was 14% in the 11-20 year old bracket. Yet examining our four arbitrarily defined age groups, we found the highest risk of mortality involved the old adults with their 10% mortality rate, and the lowest risk of mortality involved the young adults with 0% mortality. Older patients are often debilitated hosts for other reasons beside neutropenia (9) and this may explain their increased risk of mortality. There is no clearcut explanation for the relatively low risk of infection and low risk of mortality in young adults.

The association between neutrophil count and mortality was not quite statistically significant ($p = .07$). After controlling for the presence of infection, there was still not a significant association between neutrophil count and mortality ($p = .08$). This was an interesting finding because patients with lower neutrophil counts were more likely to get infected, and infection was a significant risk factor for mortality. However, low neutrophil counts, by themselves, did not seem to be a significant risk factor for mortality.

Recent antibiotic therapy was a significant risk factor for mortality. Sixty seven percent of all mortalities occurred in patients who had received recent therapy. The mortality rate was 17% among those who received recent antibiotics, and only 2% among those who did not. As discussed earlier, possible explanations for this increased risk of

infection and mortality include poor antibiotic choice, superinfections, resistant organisms, and the possibility of already having selected out a high risk subgroup of patients.

Monocyte level was also a significant risk factor for mortality. Eighty nine percent of all mortalities occurred in patients with ≤ 400 monocytes. The mortality rate was 10% in patients with ≤ 400 monocytes, and only 1% in patients with a monocytosis of > 400. Thus although a monocytosis was not protective against infection, it was protective against mortality. One can theorize that since monocytes are less efficient than neutrophils in host defense, they cannot necessarily prevent infection, but they can prevent infection from overwhelming the host.

Infection site was determined to be a significant risk factor for mortality. The five major infection sites comprised 71% of all infections, but only 33% of all mortalities. Sepsis without a documented source comprised 13% of all infections, but 56% of all deaths. The mortality rate was 5% for infection of one of the five major sites, and a staggering 45% for septicemia without a source. Therefore septicemia without a documented source was a significant risk factor for mortality compared to infection of any identifiable site. These results concur with the findings of Bodey (9) that 65% of fatal infections in leukemia, and 53% of fatal infections in lymphoma patients are due to disseminated infection or sepsis.

All other potential risk factors for mortality were not determined to be significant. These non-significant factors included onset of

neutropenia (admitted with vs. developed neutropenia), duration of neutropenia (acute vs. chronic), age, sex, race, number of prior neutropenic episodes, and ability to mount a febrile response.

In general, because the actual number of mortalities was small (9 patients), many of the determinations for significant associations could not be performed, and others might have changed, had there been a few more mortalities.

CONCLUSION

The value of a retrospective study of this type is that it might assist in predicting who is at risk of infection, and when, in the neutropenic population with no other obvious source of host impairment bsides reduced numbers of circulating neutrophils. A better understanding of the risks for infection should enable one to institute more successful therapy aimed at a specific subgroup of this population. The most significant risk of infection and its attendant mortality occurred when neutrophil counts fell below 250, regardless of whether the neutropenia was of relatively acute onset or had been present for over 6 months. Another significant risk factor for infection, particularly when neutrophil counts fell below 250, was increasing duration of hospitalization, especially beyond 14 days. This subgroup of patients might benefit most from measures to prevent infection.

Infection in neutropenic patients often does not present with the classic signs and symptoms, so one must be alert to a few diagnostic clues. In accordance with previous studies (74,84) only erythema and local pain or tenderness were present in most infected patients regardless of site of infection or neutrophil count, while other physical findings were often absent. Radiologic imaging and microbiologic cultures were mainstays of our diagnostic modalities. In addition, our study found fever to be an extremely reliable indicator of the

presence of infection. In 85% of all our patients, and 94% of patients with neutrophil counts below 250, fever was predictive of infection. Thus, fever, erythema, and local tenderness were very reliable clues to the presence of infection in neutropenic patients, and might prompt a thorough search for the source and responsible organisms, as well as commencement of aggressive therapy.

Management of infection presently includes four major modalities: barrier reverse isolation, antibiotics, WBC transfusions, and bone marrow transplantation. The use of these modalities, both prophylactically and therapeutically, is the subject of much current investigation.

Readily available preventive measures include reverse isolation (77), strict handwashing (90) elimination of fresh fruits and vegetables from the diet (83), and in some institutions, laminar air flow units (78). There is good reason to believe that these measures could be useful in our patients.

Prophylactic antibiotic regimens have been reported to be successful in leukemics. Oral non-absorbable antibiotics (ONA's) have effectively decreased the incidence of infection by suppressing gut flora (59). Since 3 of the 5 most common infecting agents in our study were gram negative rods, the prospect of the use of ONA's is particularly exciting. Trimethoprim-sulfamethoxazole has been reported to reduce the incidence of infection by Pneumocystis carnii (106). There were too little data in our study to make a highly definitive or absolute statement, but in the one subgroup that received prophylaxis, there was

a 100% infection rate. The leukemic regimens might not be applicable and they have not been studied systematically in our patients. In addition, our limited data raises the question of whether antibiotic prophylaxis, in general, is effective.

There is very limited data on WBC transfusions for infection prophylaxis. In at least one study, prophylactic granulocyte transfusions were effective in preventing infection in bone marrow transplantation recipients, albeit under rigidly controlled conditions employing single donors (101). In another study in which random donors were used, no benefit to prophylaxis with leukocyte transfusions was observed (108). No data is available on the use of this treatment in patients with neutropenia due to the etiologies reported in our study either prophylactically or therapeutically, and is an area for future investigation.

There have been several studies documenting effective therapeutic modalities for infection in cancer patients, many of whom were also granulocytopenic. Antibiotics have been the mainstay of therapy. A number of studies (37,51,80) have demonstrated the effectiveness of empiric carbenicillin and gentamicin in the treatment of presumed infection in granulocytopenic cancer patients. The sites of infection and infecting organisms are surprisingly similar in leukemics and our neutropenic patients. The most common sites of infection in both groups include upper respiratory tract, lower respiratory tract, skin, urinary tract, and anorectum (30, 84). The most common infecting organisms in both groups include E. coli, Pseudomonas, Klebsiella, S. aureus and Candida (48,84). Because of these similarities, it seems reasonable

to consider the use of empiric carbenicillin and gentamicin therapy in our patients, although no definitive study has yet been done.

Investigation of granulocyte transfusions in the therapy of infection in granulocytopenic patients has revealed its efficacy for certain subsets of the leukemic population. In neutropenic patients with documented septicemia, granulocyte transfusions have definitely been shown to improve survival (103,104,108). The contribution of granulocyte transfusions to survival in infections not accompanied by septicemia or infections with nonbacterial organisms is not clear (102). It is also recommended for improved survival that these patients have a reasonable expectation of recovering some of their bone marrow function so that the decision to initiate granulocyte transfusions also be based on whether the patient is expected to recover from his neutropenia, and whether, with recovery, his survival will be measurably improved (105). There were too few patients in our study who received WBC transfusions to be able to note any benefit. In addition it would be a difficult area for investigation due to the low frequency of occurrence and the heterogeneous etiologies for the neutropenia. However, there are lessons to be learned from the leukemics which might somehow be applicable to our population.

The ultimate form of infection management is to attempt a "permanent" correction of the neutropenic state. Some studies have documented partial correction of neutropenia on every other day prednisone therapy (27). More recently, bone marrow transplantation has been investigated as the ultimate "cure" for refractory neutropenia. In patients

with acute leukemia, marrow transplantation from an identical twin donor has been associated with complete remission rates approximating 90% (107,94,95). Some progress is being made toward resolution of the problems of transplantation biology, especially in better understanding the major histocompatibility complex (95). The subset of patients suffering from chronic myeloid hypoplasia due to any of the etiologies identified in our study, might be expected to have a favorable response to marrow transplantation since their marrow resembles the barren, hypoplastic marrow observed in the leukemic following administration of cytotoxic chemotherapy (prior to their transplant). This might be an exciting area for future investigation since our study demonstrated the critical role that neutrophils play in host defense, and a modality that can restore normal marrow function is the surest way to protect against infection.

APPENDIX

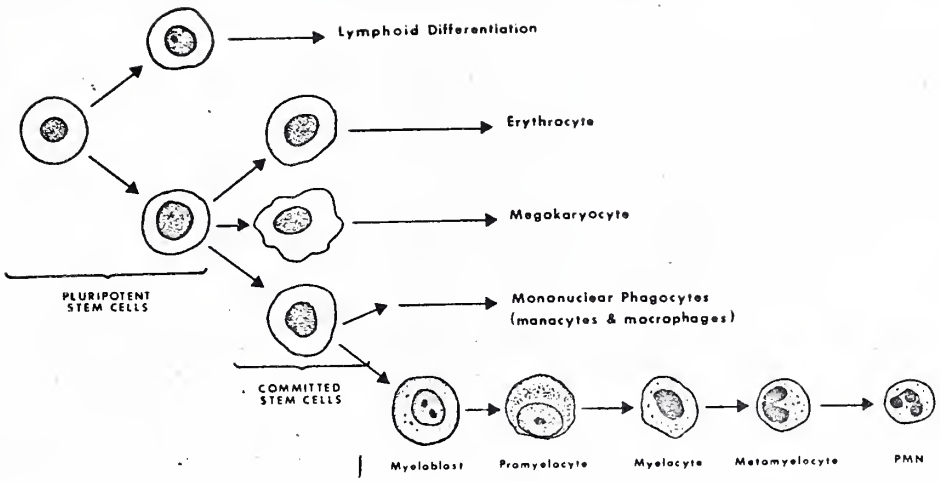

Figure 1. Scheme of stem cell differentiation and granulopoietic maturation.

From: W.J. Williams et al., Hematology (New York: McGraw-Hill, 1977), p. 700.

Figure 1. Scheme of stem cell differentiation and physiological maturation.

From: W.J. Williams et al., Hematology (New York: McGraw-Hill, 1977), p. 700.

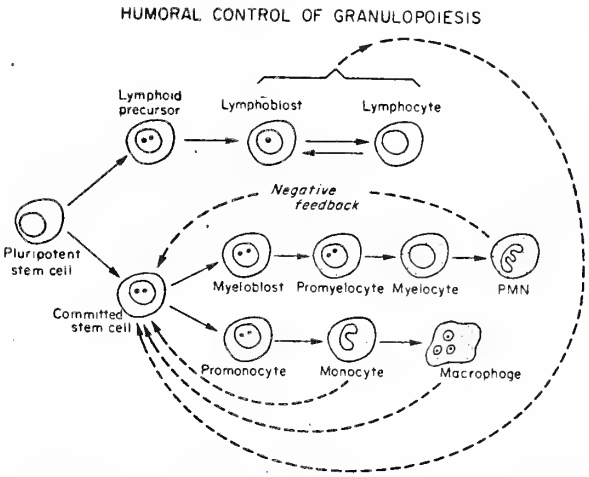

Figure 2. Tentative scheme of humoral regulation of granulopoiesis. Arrows from the monocyte, macrophage, and lymphocyte undergoing blastogenesis indicate stimulation (positive feedback) of the committed stem cells via colony-stimulating activity. Arrow from the mature granulocyte (PMN) represents negative feedback or inhibition of granulopoiesis at the stem cell level.

From: W.J. Williams et al., Hematology (New York: McGraw-Hill, 1977), p. 701.

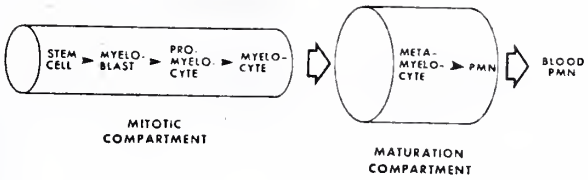

Figure 3. The bone marrow compartment is usually divided into the mitotic, or proliferating compartment and the maturation and storage compartment. The mitotic compartment consists of granulocytes through the myelocyte stage of development; the maturation and storage compartment consists of metamyelocytes and mature PMN neutrophils.

From: Cline, The White Cell, Harvard University Press, Cambridge, Mass., 1975.

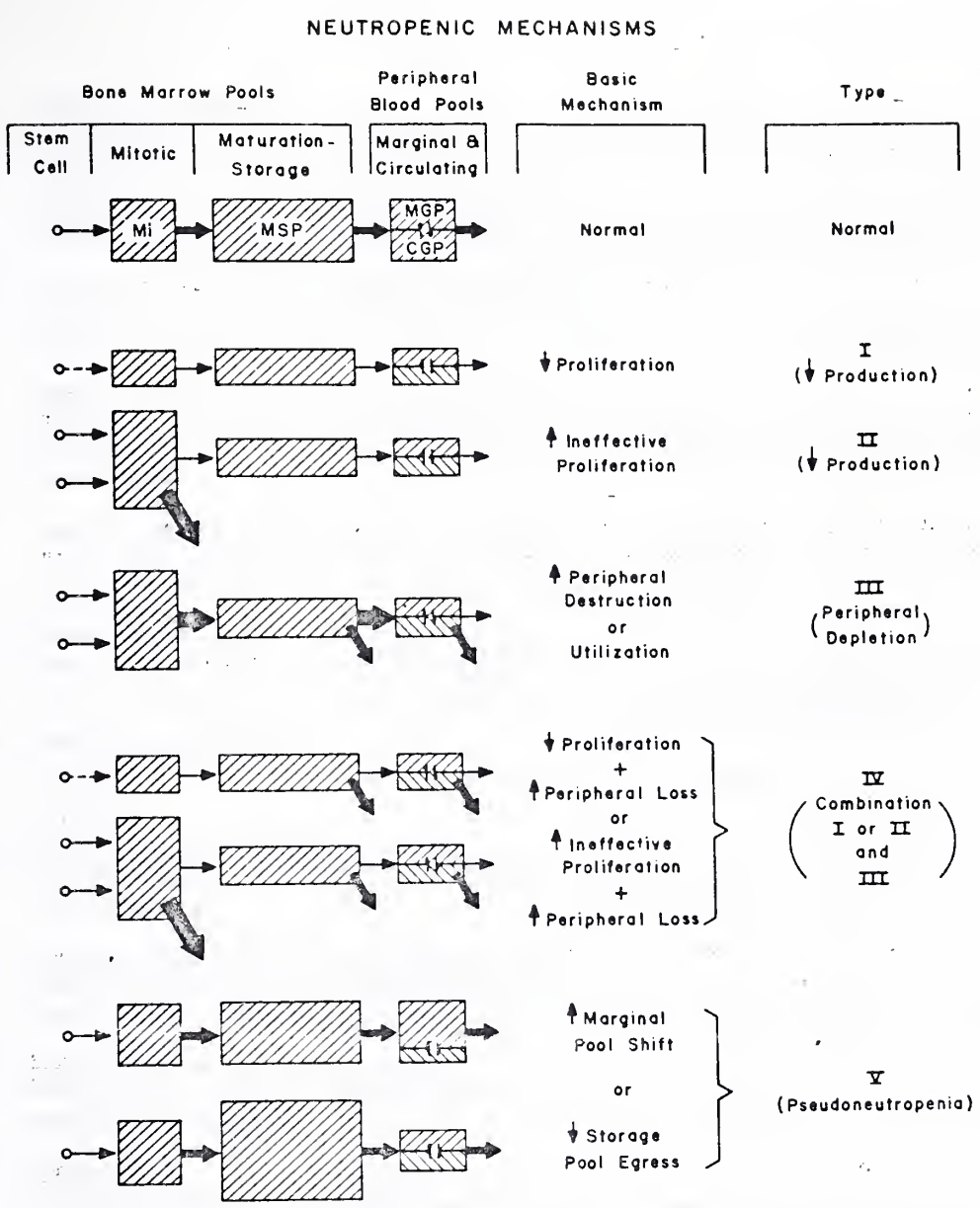

Figure 4. The types of neutropenia refer to those described in Figure 5. The size of each granulocyte pool [stem cell, mitotic (Mi), maturation and storage pool (MSP), marginal granulocyte pool (MGP) and circulating granulocyte pool (CGP)]is schematically represented by the size of each cross-hatched area. The rate of cell flow into and out of each compartment is proportional to the size of the arrow.

From: W.J. Williams, et al., Hematology (New York: McGraw-Hill, 1977) p. 719.

Type I	*Reduced granulocytopoiesis* Characterized by marrow myeloid hypoplasia. There is reduction in both total and effective granulocytopoiesis
Type Ia	*Predictable (chemotherapy) drug-induced granulocytopenia* Reactions are slow in onset and are dose-dependent. Damage to stem cells and proliferating myeloid cells is incurred through a variety of mechanisms (alkylating agents, antibiotics, etc.).
Type Ib	*Idiosyncratic (chemotherapy) drug-induced granulocytopenia* Reactions are slow in onset and dose-dependent, but there is wide variation in individual susceptibility (e.g., phenothiazide derivatives).
Type Ic	*Idiosyncratic (hypersensitivity) drug-induced granulocytopenias* Reactions are of variable time in onset and usually are dose-independent. The mechanism of granulocytopoiesis interruption is unknown. Reactions may be *acute*, lasting from days to weeks or *chronic*, lasting from months to years.
Type II	*Increased ineffective granulocytopoiesis* Increased intramedullary destruction of granulocytes results in increased total but diminished effective granulocytopoiesis. The marrow is characterized by myeloid hyperplasia.
Type IIa	*Predictable (ineffective) drug-induced granulocytopenia* Reactions are slow in onset and are dose-dependent, with wide individual susceptibility. Frequently the marrow is megaloblastic due to folic acid deficiency (e.g., methotrexate, diphenylhydantoin).
Type III	*Reduced granulocyte survival* Granulocytopenia is due to increased granulocyte destruction or utilization (e.g., sepsis, hypersplenism, antibody).
Type IIIa	*Idiosyncratic (drug-hapten-antibody) granulocytopenia* Reactions usually are extremely rapid in onset and are dose-independent in sensitized persons (e.g., aminopyrine).
Type IV	*Combination (Type I or II and Type III) granulocytopenia* Diminished effective granulocytopoiesis combined with increased peripheral destruction or utilization may result in severe neutropenia (e.g., sepsis, antibody).
Type IVa	*Drug-induced (combination) granulocytopenia* Drug-activated antibody may accelerate peripheral granulocyte survival and eventually cause marrow myeloid damage (e.g., aminopyrine).
Type V	*Pseudoneutropenia* Total granulocyte pool is of normal size, but apparent granulocytopenia is due to shift of granulocytes from the circulating to the marginal pool.
Type Va	*Drug-induced pseudoneutropenia* Reactions usually are secondary to vasomotor changes (e.g., histamine).

*Note that a small letter following a Roman numeral designates the subgroup class of drug-induced granulocytopenia.

Figure 5. Functional classification of granulocytopenic disorders.*

From: W.J. Williams, et al., Hematology (New York: McGraw-Hill, 1977) p. 720.

Drug	Possible mechanism(s)
ANALGESICS	
Aminopyrine (Pyramidon)	IIIa
Antipyrine (Phenanzone)	Ic
Cinchophen	Ic
Paracetamol	Ib
Dipyrone (Metamizol)	IIIa
ANTIBIOTICS	
Ampicillin (Polycillin, Penbritin)	Ic
Carbenicillin	Ib
Cephalothin (Keflin, Keflex)	IIIa
Chloramphenicol	Ia, Ib, Ic, IIa
Fumagillin	Ic
Gentamicin (Garamicin)	—
Griseofulvin (Fulvicin)	Ib
Isoniazid (INH)	Ib, Ic
Lincomycin	—
Methicillin (Staphcillin)	—
Nafcillin	—
Metronidazole	Ic
Nitrofuradantoin (Furadantin)	Ic
Novobiocin (Albamycin)	Ib
Oxophenarsine	Ib, Ic
Phethenylate (phenyl PAS)	Ib
PAS (paraminosalicylic acid)	Ib, IIIa
Penicillin	Ic, IIIa
Rifampin	Ia
Ristocetin	Ia, Ib
Streptomycin	Ib, IIIa
Thiacetazone (Tibione)	Ib
ANTICONVULSANTS	
Diphenylhydantoin (Dilantin)	Ib, IIa
Ethosuximide (Simantin)	Ib
Mephenytoin (Mesantoin)	—
Primidone (Mysoline)	IIa
Trimethadione (Tridione)	Ib
ANTIHISTAMINES	
Ethylene diamene	Ib
Metaphenylene (Diatrin)	Ib
Thenalidine (Sandostene)	Ib
Pyribenzamine	Ib
ANTI-INFLAMMATORY AGENTS	
Gold salts	Ic, IIIa
Indomethacin (Indocin)	—
Oxyphenbutazone (Tandearil)	—
Phenylbutazone (Butazolidin)	Ib, Ic, IIIa
ANTIMALARIALS	
Amodiaquine	—
Dapsone	—
Hydroxychloroquine (Plaquenil)	Ib
Plasmochin	—
Quinine	—
Pyrimethamine (Daraprim)	IIa
ANTITHYROID	
Carbimazole	Ib, Ic
Methimazole (Tapazole)	Ib
Methyl thiouracil (Methiacil)	Ib, IIIa
Propyl thiouracil	Ib, Ic, IIIa
Thiouracil	Ib
CARDIOVASCULAR AGENTS	
Dioxide	Ib, Ic
Procainamide (Pronestyl)	Ib, Ic
Quinidine	Ic
Methyl dopa (Aldomet)	Ic
Propanalol	Ic, IIIa
DIURETICS	
Acetazolamide (Diamox)	Ic
Chlorthalidone (Hygroton)	Ic
Chlorthiazide (Diuril)	Ic
Ethacrynic acid	Ic
Hydrochlorthiazide (Hydrodiuril)	Ic
Mercurials (Mercuhydrin, etc.)	Ic, IIIa
HYPOGLYCEMIC AGENTS	
Chloropropamide (Diabinese)	Ic, IIIa
Tolbutamide (Orinase)	—
PHENOTHIAZINES	
Chlorpromazine (Thorazine)	Ib, IIIa
Mepazine (Pacatol, Pecazine)	Ib
Methotrimeprazine	Ib
Methylpromazine	Ib
Prochlorperazine (Compazine)	Ib
Promazine (Sparine)	Ib
Thoridizine (Mellaril)	Ib
Triflupromazine (Mepazine)	Ib
Trimepazine	Ib
SEDATIVES AND NEUROPHARMACOLOGIC AGENTS	
Chlordiazepoxide (Librium)	—
Desimipramine	—
Diazepan (Valium)	—
Imipramine	Ib
Levo Dopa	Ib
Meprobamate (Miltown, Equanil)	—
SULFONAMIDE ANTIBIOTICS	
Salicylazosulfapyridine (Azulfadine)	Ic, IIIa
Sulfachlorpyridazine	
Sulfacrysoidine	Ib
Sulfadimethoxide (Madribon)	Ic, IIIa
Sulfaguanidine	Ic
Sulfamethoxydiazine	Ic
Sulfamethoxypyridazine (Kynex)	Ic, IIIa
Sulfanilamide	Ib, Ic
Sulfapyridine (Dapsone)	Ic, IIIa
Sulfasalazine	Ib, Ic
Sulfisoxazole (Gantrisin)	Ib, Ic
Sulfathiazole	Ib, Ic
MISCELLANEOUS	
Allopurinol (Zyloprim)	IIc
Benzene	Ia, Ic
DDT (Chlorophenothane)	—
Dinitrophenol	Ib, Ic
Ethanol	Ia, IIa
Nitrous oxide	Ia
Penicillamine	Ib, Ic
Phenindione (Hedulin)	Ic
Dextran	Va
Histamine	Va
Iron oxide	Va

Figure 6. Classification of common (idiosyncratic) drug-induced granulocytopenias

From: W.J. Williams, et al., Hematology (New York: McGraw-Hill, 1977), pp. 732,733.

Table 1

Chart Retrieval
1969-1978

No. of potential discharges with diagnosis of:		
aplastic anemia	373	
neutropenia	443	
	816	
Total No. of discharges with neutropenia		816
No. of discharges disqualified for:		
malignancy	399	
cytotoxic drugs	60	
SLE	13	
diabetes mellitus	20	
rheumatoid arthritis	18	
uremia/renal failure	8	
alcoholism	32	
misdiagnosed	78	
	628	
Total No. of ineligible discharges		628
Total No. of eligible discharges		188
minus No. of lost charts		- 43
Total No. of discharges		145
involving: 107 patients		
145 admissions		
157 episodes		

Table 2

Age Distribution

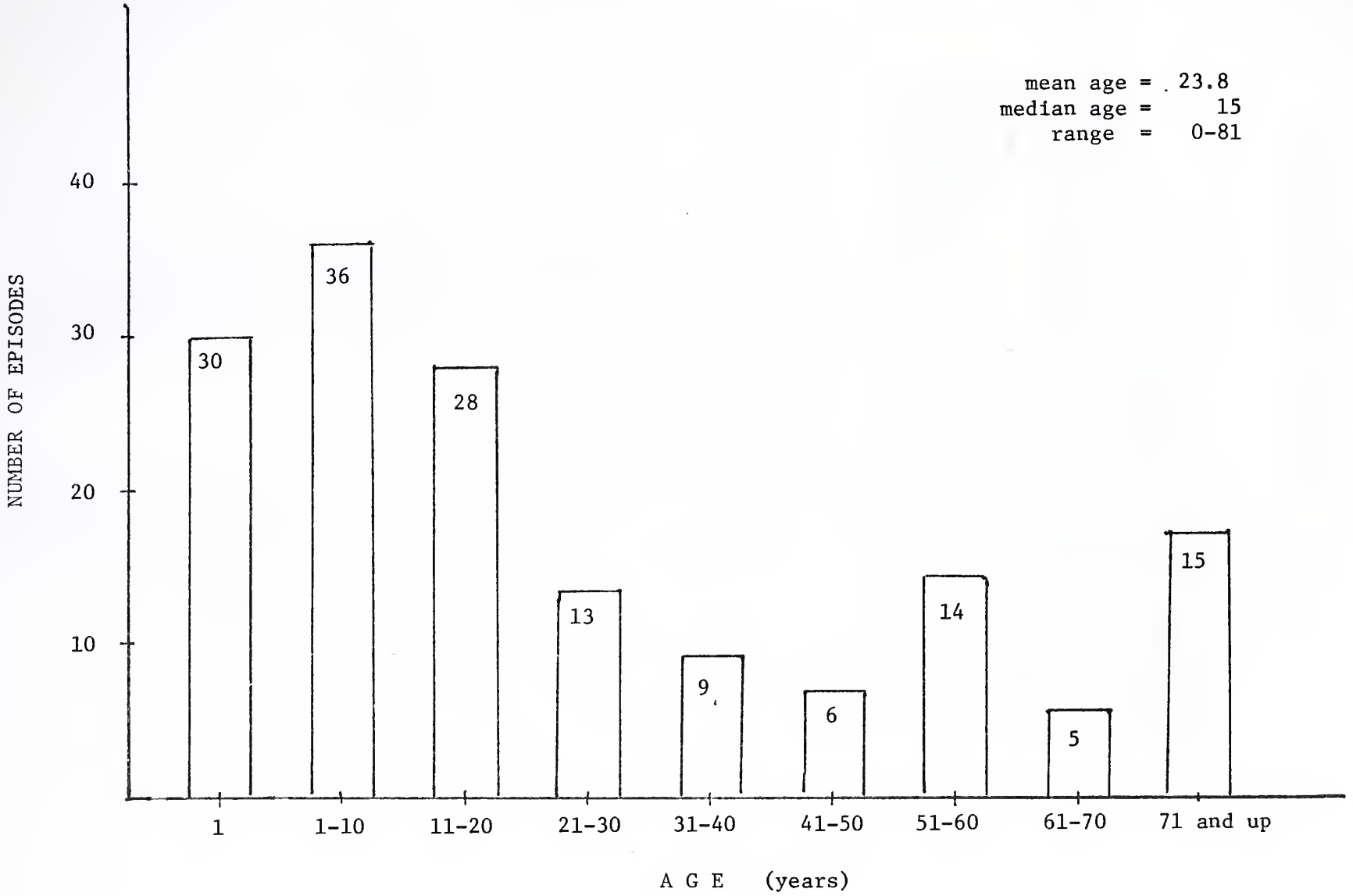

Table 3

Etiology of the Neutropenia

		Frequency	% of Total	% of Known Etiologies
	unknown	86	55	-
secondary to:	drugs	25	16	35
	congenital syndrome	15	10	21
	virus	13	8	18
	immune	6	4	8
	solvents	5	3	7
	familial	3	2	4
	?preleukemia	3	2	4
	hypersplenism	1	1	1

Table 4

Distribution of WBC Counts

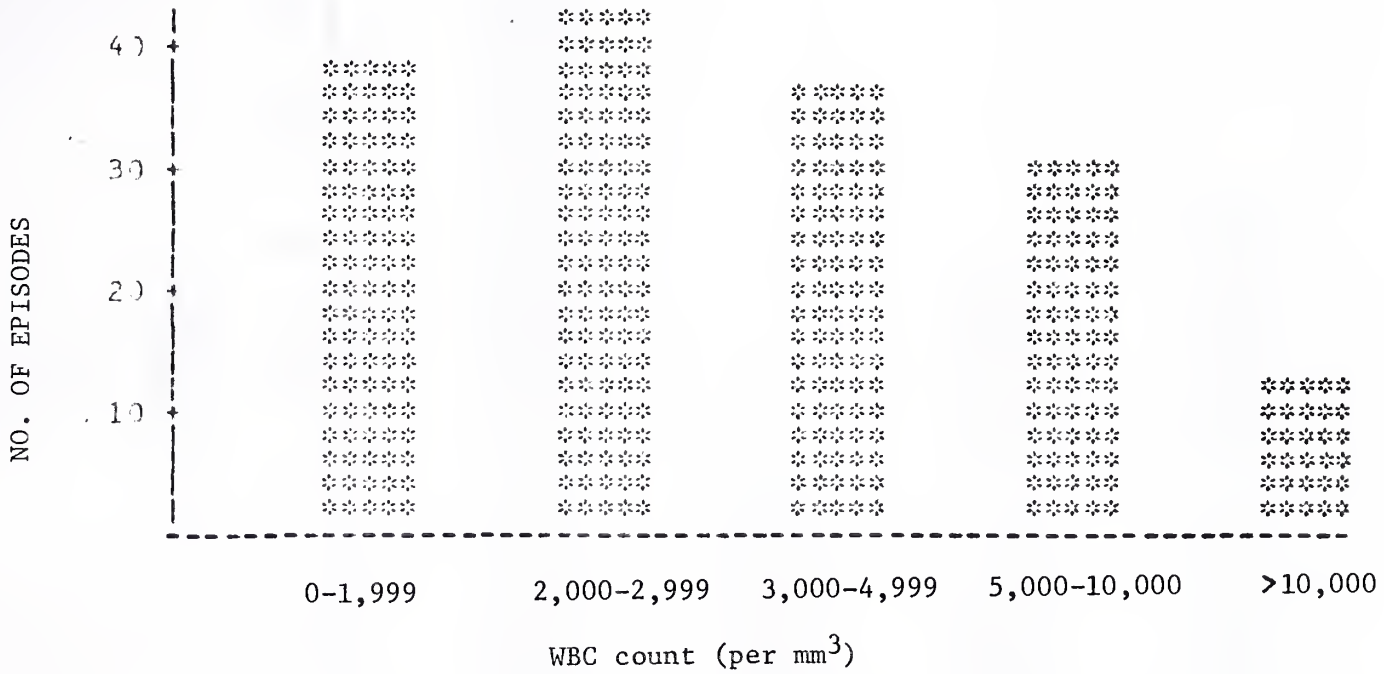

Table 5

Distribution of Neutrophil Counts

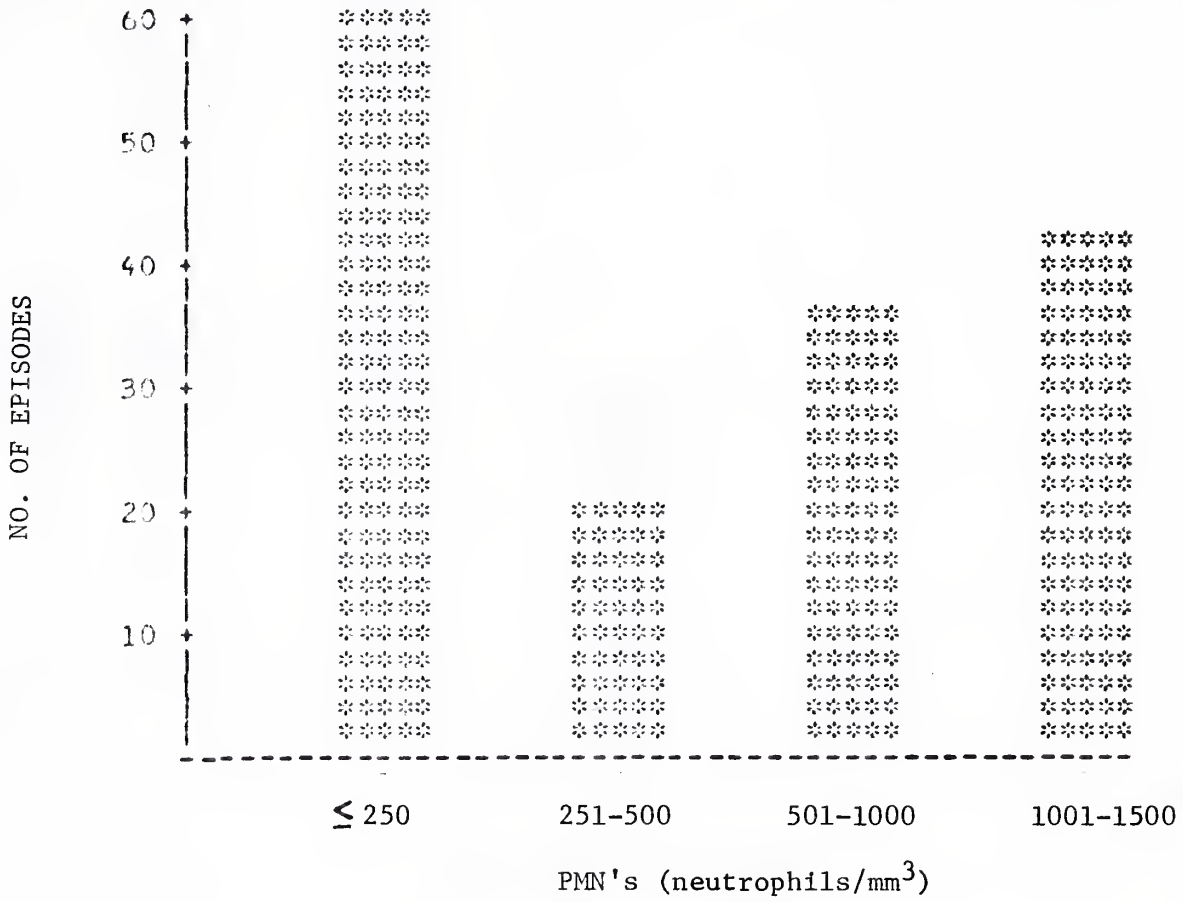

Table 6

Distribution of Total Days Hospitalized

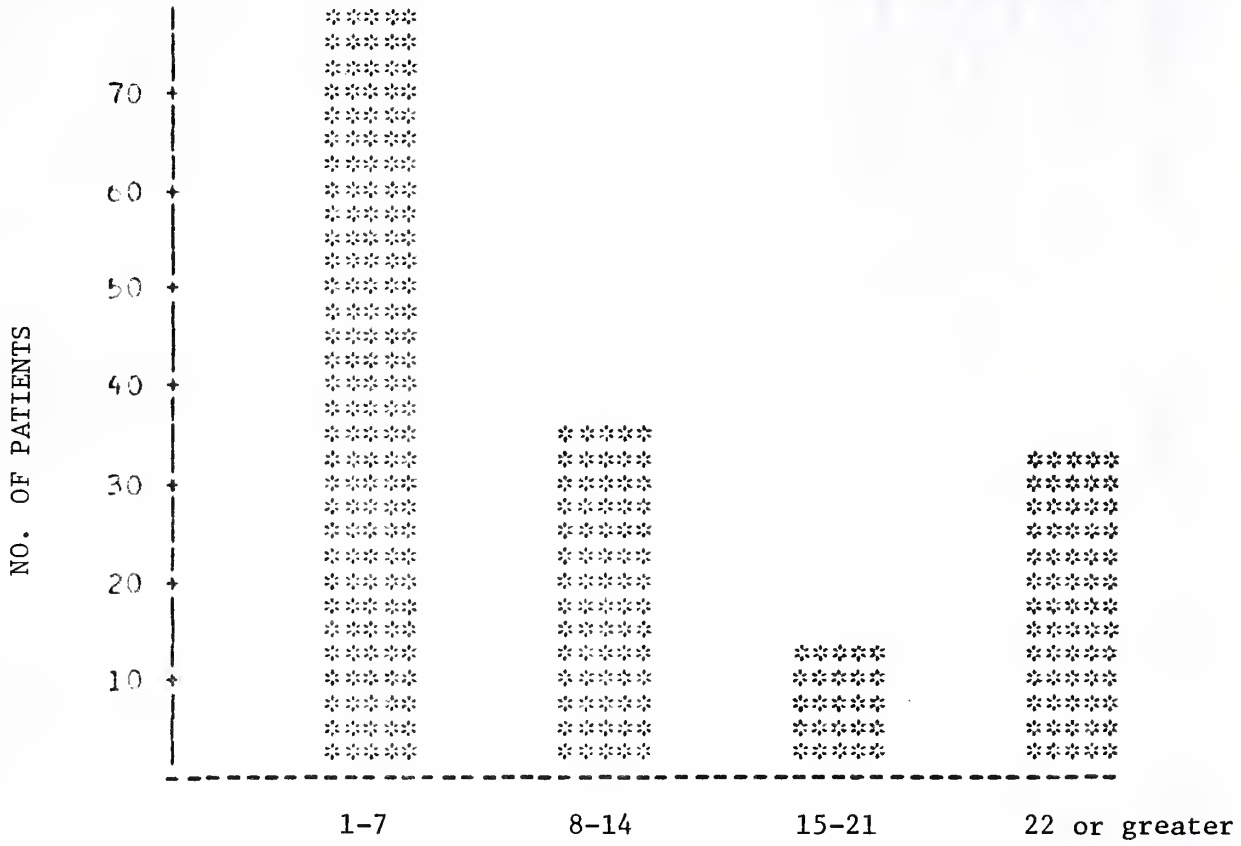

Table 7

Infection of Various Systems

System Involved	Frequency	% of Total	% of Those Infected
no infection	68	43	x
respiratory (resp.)	40	25	46
skin	12	8	14
gastrointestinal (GI)	11	7	13
septicemia without source	11	7	13
genitourinary (GU)	7	4	8
cardiovascular (CVS)	3	2	3
musculoskeletal (MS)	3	2	3
miscellaneous	2	1	2

Table 8

Infection of Various Sites

Site	Frequency	% of Those Infected
lower respiratory tract (LRI)	13	15
upper respiratory tract (URI)	27	30
skin	12	13
anorectum	6	7
urinary tract (UTI)	5	6
others	26	29

Table 9

Breakdown of Infecting Organisms
in Patients With Infection

Organism	Frequency	% of Those With Documented Organism
no organism	32	X
E. coli	13	23
Candida	8	14
Pseudomonas	7	12
S. aureus	7	12
Klebsiella	5	9
Enterococcus	3	5
H. influenza	3	5
B-strep	3	5
others	8	14

Table 10

Is fever predictive of infection?

	FEVER: NO	FEVER: YES
no infection	55	13
positive infection	17	72

$p < .001$

Broken down by neutrophil count

≤250:

	FEVER: NO	FEVER: YES
no infection	6	3
positive infection	7	44

$p < .001$

251-1500:

	FEVER: NO	FEVER: YES
no infection	49	10
positive infection	10	28

$p < .001$

Table 11

Incidence of Infection as a Function of Neutrophil Count

Neutrophils:	No Infection	Positive Infection	Total No. of Episodes	Infected Episodes as Percent of Total
≤ 250	9	51	60	85%
251-500	7	13	20	65%
500-1000	17	19	36	53%
1001-1500	35	6	41	14%

Table 12

Prevalence of Infection

Granulocyte Count	No. of Admissions	No. of Admissions With Community Acquired Infections	% of Admissions With Community Acquired Infections	No. of Admissions With Nosocomial Infections	% of Admissions With Nosocomial Infections
≤250	49	33	67%	18	37%
251 - 500	19	10	53%	3	16%
501 -1000	36	12	33%	7	19%
1001 -1500	41	4	10%	2	5%

Table 13

Relationship Between Granulocyte Count and Infection

Granulocyte Count	No. of Admissions	No. of Episodes	Total Hospital Days	Total Days of Neutropenia	No. of Community Acquired Infections	No. of Nosocomial Infections	Incidence of Nosocomial Infections per 100 Hospital Days*
250	49	60	823	536	33	18	3.4
251-500	19	20	325	130	10	3	2.3
501-1000	36	36	455	409	12	7	1.7
1001-1500	41	41	430	254	4	2	0.8

*Incidence of nosocomial infections per 100 hospital days with a given level of neutropenia.

Table 14

The Occurrence of Infection During Hospitalization

Neutrophil count (per mm^3)	Infection After "n" Hospital Days			
	0-5	6-14	15-21	≥ 22
≤ 250	5	4	0	9
251-500	1	0	0	2
501-1000	4	3	0	0
1001-1500	2	0	0	2

Table 15

Incidence of Infection Related to Age

	Age (in years)							
	<1	1-10	11-20	21-30	31-40	41-50	51-60	>60
no infection	6	16	13	7	7	3	7	9
positive infection	22	23	15	8	0	3	6	12
% of total infected	79	59	54	53	0	100	46	57

Table 16

Incidence of Infection Vs. Sex

	MALE	FEMALE
no infection	33	35
positive infection	68	21
% with infection	67%	38%

$p = .0003$

Table 17

Do Catheters Increase the Risk of Infection?

	No Catheter	IV	Hyperal. Line	Tracheo-stomy	Foley Cath.	Heparin Lock	Penrose Drain
no infection	44	21	0	1	0	0	1
positive infection	68	12	5	0	2	2	0
% infected	61	36	100	0	100	100	0

Table 18

Relationship of Immunoglobulin Levels to Infection

Immunoglobulin Level	No Infection	Positive Infection	% Infected
decreased	2	11	85%
normal	11	10	48%
increased	6	5	45%

$p = .025$

Table 19

Comparison of Survival by Neutrophil Count

Neutrophils:	Survival NO	Survival YES	% Mortality
≤ 250	6	54	10%
251-1500	3	94	3%

p = .08

Table 20

Does Infection Increase Risk of Mortality?

	DIED	SURVIVED	% Mortality
no infection	1	67	1.5%
positive infection	8	81	9.0%

$p = 0.446$

Table 21

Organisms Responsible for Mortality

	ORGANISM					
	E. coli	Candida	Pseudo-monas	S. aureus	Klebsiella	Others
Survival No	2	2	2	0	1	1
Survival Yes	11	6	5	7	4	16
% mortality	15.3	25	28.5	0	20	6.2

(Based on the 57 episodes of infection with documented organism).

Table 22

Breakdown of Survival by Age

Survival	AGE (in years)							
	<1	1-10	11-20	21-30	31-40	41-50	51-60	>60
NO	1	1	4	0	0	0	1	2
YES	27	38	24	15	7	6	12	19
% mortality	3.5	2.3	14.2	0	0	0	7.6	9.5

NO	1	1	4	0	0	0	1	2
YES	27	38	24	13	7	6	12	32
% Mortality	3.5	2.3	14.3	0	0	0	7.6	5.9

Table 23

Breakdown of Survival by Infection Site

Survival	LRI	URI	Skin	Anorectum	UTI	Septicemia Without a Source	Others
NO	1	0	1	1	0	5	1
YES	12	27	11	5	5	7	81
% mortality	7.6	0	8.3	16.6	0	41.6	1.2

Table 24

Breakdown of Total Hospital Days by Neutrophil Count

	Total Hospital Days		
Neutrophils:	1-7	8-14	≥15
≤250	25	12	23
251-500	9	8	3
501-1000	22	4	10
1001-1500	21	12	8

Table 25

Breakdown of Infected Systems by Neutrophil Count

Neutrophils:	No Infection	SYSTEM Resp.	CVS	GI	GU	Skin	MS	Sepsis	Miscellaneous
≤250	9	20	1	9	2	9	1	8	1
251-500	7	5	2	0	1	2	0	3	0
501-1000	17	11	0	2	3	1	1	0	1
1001-1500	35	4	0	0	1	0	1	0	0

Table 26

Breakdown of the Five Major Infection Sites by Neutrophil Count

Neutrophils:	Infection Site				
	LRI	URI	Skin	Anorectum	UTI
≤250	6	12	9	6	2
251-500	2	5	2	0	0
501-1000	2	9	1	0	2
1001-1500	3	1	0	0	1

Table 27

Frequency of Infecting Organism Broken Down by Neutrophil Count

Neutrophils:	E. coli	Candida	Pseudo-monas	S. aureus	Klebsiella	Others
≤250	8	3	5	6	5	9
251-500	0	2	2	0	0	4
501-1000	4	2	0	0	0	3
1001-1500	1	1	0	1	0	1

Table 28

Mean Values for Each Sex

	MALE	FEMALE
age	20	30
WBC count	4,500	3,100
PMN count	517	734
infection after "n" hospital days	12	7
temperature (when febrile)	102.0	102.4
total hospital days	22	13
duration of neutropenia	20	8

Table 29

Breakdown of Infected System by Sex

	No Site	Resp.	CVS	GI	GU	Skin	MS	Sepsis	Miscellaneous
Male	33	32	3	9	3	10	3	6	2
Female	35	8	0	2	4	2	0	5	0

Table 30

Breakdown of Infecting Organism by Infection Site

Organism:	Infection Site				
	LRI	URI	Skin	Anorectum	UTI
E. coli	2	0	2	2	3
Candida	0	2	3	0	0
Pseudomonas	0	5	2	0	0
S. aureus	1	0	0	1	0
Klebsiella	1	0	1	1	1

Table 31

For Patients with a Documented Infection,

the Breakdown of Age by Neutrophil Count

	AGE (in years)							
Neutrophils:	<1	1-10	11-20	21-30	31-40	41-50	51-60	>60
≤250	18	9	9	3	0	3	3	6
251-500	1	9	0	1	0	0	2	0
501-1000	2	5	4	4	0	0	0	4
1001-1500	1	0	2	0	0	0	1	2

Table 32

For Those Who Did Not Survive, the Breakdown of Neutrophil Count by Age

Neutrophils:	AGE (in years)							
	< 1	1-10	11-20	21-30	31-40	41-50	51-60	>60
≤ 250	0	1	3	0	0	0	1	1
251-500	1	0	0	0	0	0	0	0
501-1000	0	0	0	0	0	0	0	1
1001-1500	0	0	1	0	0	0	0	0

Table 33

Nature of Defects of Leukocyte Function

Function	Defect	Clinical Condition
1. Delivery		
a) production and destruction	↓number of mature cells	neutropenias leukemias
b) adhesion	↓adhesiveness at inflammatory site	anti-inflammatory drugs alcohol
c) chemotaxis	↓cellular responses	Chediak-Higashi Syndrome Lazy Leukocyte Syndrome actin deficiency serum inhibitors rheumatoid arthritis diabetes mellitus
	↓production of chemotactic factors	depletion of complement (C3) C3 deficiency C3 hypercatabolism SLE
		serum inhibitors Hodgkin's Disease uremia cirrhosis
. Attachment and Ingestion	↓phagocytosis	cellular immaturity hyperosmolarity acidosis uremia actin deficiency
	↓humoral function (i.e., opsonization)	antibody deficiency complement deficiency
		defective opsonic activity sickle-cell anemia SLE cirrhosis
. Intracellular killing	↓oxygen dependent mechanisms	Chronic Granulomatous Disease Chediak-Higashi Syndrome hypoxia G6PD deficiency myeloperoxidase deficiency
	↓non-oxygen dependent mechanisms	Chediak-Higashi Syndrome miscellaneous defects

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Adapted from:

R.K. Root and M.G. Farquhar: "Defects of PMN leukocyte function." (Clinical Correlations, Yale University School of Medicine, 1976).

Table 34

Risks of Recent Antibiotic Therapy

1) Risk of Infection:

	Recent Antibiotics: NO	Recent Antibiotics: YES
No infection	59	9
Positive infection	63	26

p = .025

2) Risk of Mortality:

		Recent Antibiotics: NO	Recent Antibiotics: YES
Survived	NO	3	6
	YES	119	29

p = .005

Table 35

Incidence of Infection Broken Down by

Duration of Neutropenia

For all patients:

Duration of Neutropenia	No Infection	Positive Infection
Acute	50	76
Chronic	18	13

$p = .064$

For Patients with 250 neutrophils/mm^3:

Duration of Neutropenia	No Infection	Positive Infection
Acute	6	45
Chronic	3	6

$p = .10$

For Patients with 251-1500 neutrophils/mm^3:

Duration of Neutropenia	No Infection	Positive Infection
Acute	44	31
Chronic	15	7

$p = .45$

Table 36

Survival Broken Down by Duration of Neutropenia

For all patients:

Duration of Neutropenia	Survival: No	Survival: Yes
Acute	7	119
Chronic	2	29

$p \cong .8$

For patients with ≤ 250 neutrophils/mm^3

Duration of Neutropenia	Survival: No	Survival: Yes
Acute	6	45
Chronic	0	9

$p = .35$

For patients with 251-1500 neutrophils/mm^3:

Duration Neutropenia	Survival: No	Survival: Yes
Acute	1	74
Chronic	2	20

$p = .06$

Table 37

Duration of Neutropenia Broken Down by Age

Duration of Neutropenia	AGE (IN YEARS)							
	<1	1-10	11-20	21-30	31-40	41-50	51-60	>60
Acute	28	26	23	14	4	6	10	15
Chronic	0	13	1	1	3	0	3	6

$p = .012$

Table 38

Breakdown of Infection by Monocyte Level

	Monocyte Level ≤400	Monocyte Level >400
No infection	23	27
Positive infection	40	36

p = .55

Breakdown of Mortality by Monocyte Level

Survival	≤ 400	>400
No	8	1
Yes	75	73

p = .025

Table 39

Risk of Mortality vs. Type of Infection

Type of infection:	Survival	
	NO	YES
Community acquired	2	57
nosocomial	6	24

$p = .01$

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