MEDICAL GRAND ROUNDS

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CLINICAL EVALUATION OF THE LEUKOPENIC PATIENT

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I. INTRODUCTION.

The pathophysiologic mechanisms that produce the most clinically significant leukopenic states are those which affect granulopoiesis. These mechanisms result in a selective decrease in circulating granulocytes and, generally, the low total circulating white cell count (i.e. leukopenia) alerts the clinician either to a circumstance of decreased white cell production or of accelerated loss due to effective or ineffective utilization. To facilitate the application of the term leukopenia and/or neutropenia, the range of normal for the various white cells in the peripheral circulation is shown in Table 1. To effectively approach the leukopenic patient, the selective cell population involved must be identified. Because the major proportion of circulating white cells are granulocytes and because their modulation represents the major clinical issue, this review will primarily deal with the circumstance of neutropenia.

TABLE 1

LEUKOCYTE COUNT AND PERCENTAGES FOR VARIOUS CIRCULATING WHITE CELLS IN NORMAL ADULTS*

(CELLS X $10^3/\mu l$)

WHITE CELL TOTAL	NEUTROPHILS			LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS
	TOTAL	SEGS	BANDS				
7.4	4.4			2.5	0.3	0.2	0.04
(4.5-11.0)	1.8-7.7			(1.0-4.8)	(0.08)	(0-0.45)	(0.-0.2)
%	59	56	3	34	4	2.7	0.5

* From P.L. Altman and D.S. Dittmer: Blood and Other Body Fluids. Fed. Amer. Soc. for Exp. Biol., Wash. DC, 1961.

II. REGULATION OF GRANULOPOIESIS.

Granulocyte production rates in man are approximately $1.6X10^9$ cells per kg per day and, following a brief storage period in the marrow, the cells are released for a 6 to 7 hour half-life transit in the circulation. The fact that a reasonable steady state circulating granulocyte number is found in man bespeaks a finely modulated regulator system.

A. Granulopoietic Progenitor Cells:

The stem cell has two characteristics:

1. The ability to maintain itself by renewal.

2. The ability under appropriate inductive influences for differentiated daughter cells. The implicit concept of the stem cell is that it must survive; thus, the number of stem cells which differentiate is not greater than the number produced by division of the stem cells (1). Although we cannot identify the stem cell population, the classic studies of Till and McCulloch (2) provided, in the model of the heavily irradiated mouse, a technique for the recognition and quantification of hematopoietic stem cells:

> This model is based upon the observation that the ablation of hematopoietic tissues that results when a mouse is exposed to a potentially lethal dose of radiation can be circumvented by injection of syngeneic hematopoietic tissue (bone marrow, spleen or fetal liver cells). The animal will survive the lethal radiation and develop (3-4 weeks post-injection) splenomegaly. Depending upon the size of the hematopoietic inoculum, discrete nodules of recognizable hematopoietic cells will be found in the spleen, each colony arising from a single cell (3). This, so-called, Spleen Colony-Forming Unit: CFU-S has all of the characteristics of the hematopoietic stem cell.

Parenthetically, it should be noted that our knowledge of the stem cell pool is so modest that we overlook the fact that the spleen colony system is reliably reproducible only in the mouse in spite of extensive trials in other animals. Furthermore, studies of the kinetics of the system have shown that when a "seeded" spleen is subsequently suspended and injected into a second radiated mouse a "seeding factor" (f-number) can be determined which now appears to be approximately 8% (i.e. 8% of the injected colony-forming cells formed spleen colonies)(4). From this has come the functional expression of nomenclature:

CFC-S: the cell able to produce spleen colonies or the spleen colony forming cell.

CFU-S: is that CFC-S which actually lodges in the spleen and produces spleen colony forming units. Some of the characteristics of the hematopoietic stem cell population are shown in Table 2.

TABLE 2

CHARACTERISTICS OF CFU-S

1. PHYSICALLY SEPARABLE FROM CFU-C - THE CELL WHICH PRODUCES GRANULOCYTIC/MACROPHAGE COLONIES IN SOFT AGAR.
2. GREATEST CONCENTRATION IN THAT MARROW AT THE INTERFACE WITH BONE TREBULAR MATRIX.
3. DISTRIBUTION:
   - BONE MARROW < 95%
   - SPLEEN 2-4%
   - PERIPHERAL BLOOD ≃ 1%
4. ESTIMATED TOTAL BODY NUMBER 10^6.
5. CELL CYCLE TIME: 7 HRS.
6. CFC-S PRODUCTION: $2X10^5$ NEW PER DAY.
7. EACH CFC-S REPRODUCES ONCE EVERY 5 DAYS.
8. ESTIMATED: 200 DIVISIONS PER CFC-S IN MOUSE LIFE TIME.
9. OLD AGE OF DONOR DOES NOT AFFECT NUMBER OF CFU-S IN MARROW OR THEIR CAPACITY TO EXPAND.

An important step forward in studies of granulopoiesis was the development of in vitro culture systems (5,6) which supported proliferation and differentiation of granulocyte progenitor cells (CFU-C). The units (cells) are defined by their capacity to generate colonies of granulocytes, monocyte-macrophages, or both, in semi-solid culture systems. Some of the characteristics of this committed progenitor cell population are shown in Table 3. The recognition of such a committed cell population has made possible the study of some of the factors which regulate granulopoiesis.

TABLE 3

CHARACTERISTICS OF HUMAN CFU-C

1. A NON-ADHERENT CELL POPULATION.
2. MORPHOLOGICALLY:
   - LYMPHOCYTE-LIKE CELLS (9-11 μm).
   - NULL CELL FRACTION (BY: CYTOCHEMICAL
     CELL-SURFACE)
   - Ia - ANTIGEN POSITIVE.

B. HUMORAL REGULATION OF GRANULOPOIESIS:

The in vitro colony systems demonstrated that the support of growth required a diffusible non-cellular moiety, so-called colony stimulating factors (CSF). Even at very low concentrations (10^{-14}M), CSF will promote colony formation (7). It is clear that "CSF" represents many separate moieties, largely glycoproteins, some of which have a high degree of specificity for a single cell line (i.e. neutrophil granulopoiesis, eosinophil development, etc.). The in vitro biology of CSF has been extensively studied and defined particularly by the monumental studies of Metcalf and Moore (8). Among the in vitro observations that may have relevance to in vivo granulopoiesis are:

1.) CSF IS NOT SIMPLY AN INDUCING AGENT TO GRANULOPOIESIS; ITS PRESENCE IS REQUIRED THROUGHOUT THE STEPS OF PROLIFERATION AND DIFFERENTIATION.

2.) COLONY PRODUCTION DEPENDS UPON THE CONCENTRATION OF CSF RATHER THAN THE TOTAL AMOUNT.

3.) SINCE BOTH THE NUMBERS AND SIZE OF THE COLONIES ARE AFFECTED, CSF APPEARS TO HAVE A ROLE IN THE REGULATION OF HEMATOPOIESIS.

4.) HETEROGENEITY OF CELLULAR RESPONSIVENESS IS EVIDENT: SOME CELLS GROW WELL AT LOW CONCENTRATION OF CSF AND OTHERS REQUIRE HIGH CONCENTRATION.

5.) THE GROWING COLONIES THEMSELVES PRODUCE CSF. THUS, IN VITRO, COLONY CROWDING POTENTIATES COLONY GROWTH.

6.) REGARDLESS OF CSF CONCENTRATION, AN INITIAL LAG PHASE PRECEDES GROWTH.

7.) DIVIDING CELLS HAVE A CONTINUOUS NEED FOR CSF.

The translation of the extensive in vitro studies to an understanding of granulopoiesis in vivo has not been possible. Support for a role for CSF in granulopoiesis has been generated (7,8,9) by evidence of increased CSF in some patients with cancer and associated leukocytosis. It is clear that a major human source of CSF is the phagocytic-mononuclear cell (10). In spite of an extensive literature, no direct evidence exists to implicate CSF (now appropriately termed GM-CSF) as a physiologic regulator of granulopoiesis.

Inhibitors of granulopoiesis (cholones) have also been identified and studied, but their role in in vivo granulopoiesis is even less clear than that of CSF. For instance, agents which affect intracellular cAMP or cGMP levels and prostaglandins of the E Series have roles mutually antagonistic to CSF (7,9). Again, these are observations from complex in vitro systems making their translation to man difficult.

The concept of a negative feedback system for granulocyte production has been ascribed to many agents. The one granulocyte product with the greatest likelihood for a functional role in such an inhibitory mechanism is lactoferrin (11,12,13). Lactoferrin is found in mature granulocytes. When freed from cells, it can block the basal production of CSF by monocytes, thereby suggesting a modulating suppressive influence on granulopoiesis. In spite of extensive studies, the physiologic role of lactoferrin is uncertain. For instance, studies of lactoferrin turnover have been correlated with the data of measured granulocyte turnover; only 1% of granulocyte turnover could be correlated with the fractional catabolic rates of lactoferrin (12). Thus, our knowledge of the true physiologic regulators of granulopoiesis is clearly rudimentary.

III. KINETICS OF GRANULOCYTOPOIESIS.

A primary and major thrust of the Brookhaven National Laboratories under Eugene P. Cronkite, M.D., since World War II has been the examination of the dynamic relationships between production, distribution, survival and disappearance of granulocytes (14). These and related in vivo observations (15) have clarified the remarkable capacity for proliferation and amplification of the committed granulocyte pool. For instance, the ratio of CFU-C to the mature cell is approximately 1:170.

A variety of methods have been used to measure neutrophil kinetics in the peripheral blood, and these have recently been reviewed by Vincent (15) and are summarized in Table 4. The use of ^{3}H-Tdr provides the most perfect approach wherein isologous cells are labeled in the donor. DF^{32}P and ^{51}Cr studies are based upon the fate of autologous cells labeled in vitro. In general, DF^{32}P and ^{51}Cr overestimate the size of the marginal neutrophil pool (MNP). DF^{32}P underestimates the $T_{\frac{1}{2}}$ and ^{51}Cr overestimates the $T_{\frac{1}{2}}$.

TABLE 4

PUBLISHED NORMAL VALUES FOR NEUTROPHIL KINETICS
(Vincent, P.C. *Clin. Haematol.* 6:695, 1977)

Label		Blood neutrophil pools × 10^7/kg TBNP	CNP	MNP	$T_{\frac{1}{2}}$ (hours)	NTR × 10^7/kg/hr	Reference
$DF^{32}P$	Mean	70	31	39	6.7	6.8	(*a*)
	95% limits	14–160	11–46	0–85	4.0–10.0	2.1–14.2	
$DF^{32}P$	Mean	71	30	41	5.3	9.3	(*b*)
	± s.e.m.	12.0	2.2	9.5	0.5	1.0	
$DF^{32}P$	Mean	54	22	31	5.4	6.7	(*c*)
	± s.e.m.	10.1	2.7	9.7	0.6	0.9	
^3H	Mean	40	22	17	7.6	3.6	
	± s.e.m.	3.3	2.7	2.9	0.8	0.2	
^{51}Cr	Mean	51	24	27	16.1	2.2	(*d*)
	± s.e.m.	5.4	1.9	3.9	0.8	0.3	

*Peripheral blood studies; for abbreviations, see text.
(*a*) 109 subjects (TBNP, CNP, MNP) and 56 subjects ($T_{\frac{1}{2}}$, NTR): Cartwright, Athens and Wintrobe (1964).
(*b*) 10 subjects: Author's laboratory.
(*c*) 5 subjects in whom survival of isologous neutrophils labelled with ^{3}HTdR and autologous (2 cases) or isologous (3 cases) neutrophils labelled with $DF^{32}P$ were measured simultaneously: Dancey et al (1976). Pool sizes recalculated as cells × 10^7/kg, and turnover rates as cells × 10^7/kg/hr. Standard errors of the means (s.e.m.'s) calculated from original data.
(*d*) 7 subjects: Dresch, Najean and Bauchet (1975) (MNP, NTR and s.e.m.'s calculated from data).

Some of the other observations include the evidence that traffic of cells in the marrow compartment beyond the proliferative pool (myelocyte stage in the marrow) is on a "first-in", "first-out" basis. However, granulocytes in the circulation leave the blood randomly. In careful studies by the Brookhaven group (14) the exact fate of circulating granulocytes not responding to a chemotactic stimulus was examined. The exact site(s) of removal of granulocytes is not known. An attractive, albeit unproven, concept is that "unused" granulocytes are removed by the marrow where their products provide the negative feedback system noted above.

Studies of intramedullary granulocyte kinetics have been of interest because this compartment provides the basis for a more sustained responsive amplification of peripheral granulocytes. An increased flux through the mitotic pool (myeloblast → progranulocyte → myelocyte) can occur by shortening of transit time and increase of pool size. This is critical in calculating a granulocyte response, since it appears that some obligatory time is required for maturation between metamyelocyte and band neutrophil stage in order for these cells to function as the mature (segmented) cell with appropriate cytoplasmic machinery. The transit time through the maturation sequence is approximately 150 hours. Using ^{3}H-Tdr, some transit estimates are:

myelocyte → metamyelocyte	2-3 hrs.
myelocyte → band cell	36-48 hrs.
myelocyte → segmented neutrophil	48-72 hrs.

Amplification can then result by an added mitosis at the myelocyte stage (effectively doubling the production rate) or shortening of the post-mitotic transit time (from 48 hours to 16 hours).

IV. REGULATION OF GRANULOCYTE RELEASE FROM THE MARROW.

Lichtman et al. (16) have extensively reviewed the four general factors that control marrow cell egress:

1. Marrow microenvironment: The organization and localization of hematopoietic cells in relation to the vascular channels of the marrow.

2. Maturation of hematopoietic cells so that cell surface characteristics (and nuclear factors) are "changed" to allow cellular translocation from their site of growth and maturation to the efferent vascular channels of the marrow.

3. Cell releasing factor: A chemical agent which may serve to "facilitate" egress of cells into the circulation.

4. Blood flow: Appropriate flow through marrow vascular channels to permit delivery of cells; the regulation of flow may reflect the role of vasoactive compounds or neural activity.

V. CLINICAL LABORATORY DIAGNOSTIC APPROACHES IN THE EVALUATION OF THE NEUTROPENIC PATIENT.

As one might expect, the characterization of pathophysiologic mechanisms and patterns of granulopoiesis has been extensively evaluated in the attempt to use the known physiologic parameters in a clinical approach to neutropenic states. The variety of laboratory tests available provide considerable insight into the biology of granulopoiesis and in selected circumstances provide an excellent diagnostic probe. These tests are outlined in Table 5.

TABLE 5

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
1.) SERIAL ABSOLUTE GRANULOCYTE COUNTS.	IDENTIFIES NEUTROPENIA & SEVERITY.	- CYCLIC NEUTROPENIA.	
2.) BONE MARROW EXAMINATION.	CELLULARITY & MORPHOLOGY.	- MEGALOBLASTOSIS. - INEFFECTIVE GRANULOPOIESIS. - HEMATOPOIETIC DYSPLASIA. - DYSGRANULOPOIESIS (CONGENITAL). - ARSENIC INTOXICATION.	DOES NOT PROVIDE KINETIC DATA.

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
3.) MURAMIDASE (SERUM/URINE) (17,18).	INCREASED GRANULOCYTE TURNOVER/ DESTRUCTION.	INEFFECTIVE GRANULOPOIESIS.	- DERIVED FROM MYELOPEROXIDASE-RICH PRECURSOR CELLS. - RELATIVELY INSENSITIVE. - POOR CORRELATION WITH KINETIC MEASUREMENTS.

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
4.) LACTOFERRIN-SERUM (18).	SIZE OF MATURE GRANULOCYTE POOL.	- CYCLIC NEUTROPENIA. - DRUG-INDUCED NEUTROPENIA.	CORRELATES WITH REGENERATING CELL POPULATIONS.
5.) LEUKOCYTE ALKALINE PHOSPHATASE (19,20).	MATURITY OF GRANULOCYTES (↑PRODUCTION WITH ↓-ING SCORE).	HEMATOPOIETIC DYSPLASIA.	- PROVIDES KINETIC PARAMETER, ALBEIT WEAK. - MARGINAL POOL HAS HIGHER VALUES THAN CIRC. POOL.

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
6.) VITAMIN B_{12}-B_{12} BINDING PROTEINS (TC I, III) (21).	- INDEX OF GRANULOCYTE POOL SIZE. - INCREASED GRANULOCYTE TURNOVER.	- MEGALOBLASTIC STATES. - INEFFECTIVE GRANULOPOIESIS.	REASONABLE CORRELATION OF TC WITH KINETIC STUDIES.
7.) LEUKOCYTE ANTIBODIES (23).	ANTIBODY-MEDIATED DESTRUCTION.	AUTOIMMUNE NEUTROPENIA.	SENSITIVITY & CLINICAL APPLICABILITY NOT CERTAIN.

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
8.) STIMULATION STUDIES		RESERVE POOL DEPLETION ASSOCIATED WITH:	TEDIOUS AND NONSPECIFIC.
a) EPINEPHRINE (24).	SIZE OF MARGINAL GRANULOCYTE POOL.	- INFECTION. - CHEMOTHERAPY. - DRUG-INDUCED DESTRUCTION.	
b) ENDOTOXIN (PIROMEN) (25).	MARROW RESERVE POOL.		
c) HYDROCORTISONE (26,27)	ADEQUACY OF MARROW RESERVE POOL.		

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
9.) IN VITRO CULTURE STUDIES			
a) CFU-C ASSAY (28,29,30)	EVALUATION OF COMMITTED GRANULOCYTE COMPARTMENT.	"CHRONIC IDIOPATHIC NEUTROPENIA"	THESE ARE STILL RESEARCH TOOLS WITH INCOMPLETE CLINICAL TRANSLATION.
b) CSF ASSAY (29,31)	EVALUATION OF STIMULATING FACTORS.		

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

	STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
10.)	GRANULOCYTE KINETIC STUDIES		OF QUESTIONABLE DIAGNOSTIC SPECIFICITY.	TEDIOUS, COSTLY AND GENERALLY LIMITED TO RESEARCH STUDIES.
	a) ^{3}H-Tdr	MEASURES PROLIFERATIVE CAPACITY OF MARROW.		
	b) DF^{32}P	EVALUATES CELL TURNOVER RATES.		
	c) ^{51}Cr	MEASURES CELL TURNOVER RATES.	CONGESTIVE SPLENOMEGALY.	
	d) ^{111}In (32)	GRANULOCYTE SURVIVAL STUDIES.	COMPLEMENT MEDIATED INCREASED DESTRUCTION.	

TABLE 5 *(Continued)*

CLINICAL-LABORATORY INVESTIGATIVE APPROACHES IN NEUTROPENIA

STUDY	DATA PROVIDED	DIAGNOSTIC SPECIFICITY	COMMENTS
11.) VASCULAR EGRESS STUDIES. - REBUCK SKIN WINDOW (33). - SKIN BLISTERS/ CHAMBERS (33).	EVALUATES NEUTROPHIL MOBILIZATION FROM CIRCULATION.	CHEMOTACTIC ASSOCIATED NEUTROPHIL LESIONS.	TEDIOUS, DIFFICULT TO INTERPRET.

The extent of these studies and their modest diagnostic specificity have resulted in their limited use, particularly those which are complex and expensive. For instance, theoretically, granulocyte kinetics should provide a powerful tool in the dissection of a clinical case of neutropenia, since the contributions of decreased production, shortened neutrophil survival and excessive margination can be determined. In fact, most pathophysiologic mechanisms produce combinations of these effects making the resultant measurements descriptive rather than diagnostic or predictive.

The most recent surge of laboratory interest in the characterization of the neutropenic stage has come from selected cases where an immunologic mechanism appears relevant. The recent recognition of "autoimmune neutropenia" has led to a profusion of tests (23) to identify and characterize these antibodies as shown in Table 6.

TABLE 6

STUDIES OF GRANULOCYTE ANTIBODIES

GRANULOCYTE AGGLUTINATION (34).

GRANULOCYTOTOXICITY (35).

IMMUNOFLUORESCENCE (36).

OPSONIC ASSAY (37).

ANTIBODY-DEPENDENT LYMPHOCYTE MEDIATED GRANULOCYTOTOXICITY (38).

STAPHYLOCOCCAL PROTEIN A NEUTROPHIL ANTIBODY ASSAY (39,40).

Finally, we will not review those studies which help provide a specific diagnosis in clinical circumstances in which the neutropenia is merely part of a more significant and evident disease process (e.g. sucrose hemolysis or Ham test in paroxysmal nocturnal hemoglobinuria; immunologic studies in congenital a- and dysglobulinemias; etc.).

In summary, application of all of the studies in a variety of clinical settings has resulted in continued confidence in the examination of the bone marrow as the single most valuable test in the evaluation of the neutropenic patient.

VI. ISSUES IN CONGENITAL NEUTROPENIC STATES.

Congenital neutropenia was extensively defined by Kostmann (41) in 1956. Since that time a variety of reports have described other patterns of congenital neutropenias. Table 7 lists a few of these, largely descriptive contributions (42-47). The mechanisms for these rare congenital lesions have been related to an altered marrow microenvironment with related chromosomal changes, a genetic mechanism with a specific HLA pattern or a "marrow factor capable of suppressing normal myelopoiesis (43). Fortunately, these congenital lesions are rare and so unlikely to reach the age of relevance to us, that the internist can leave them to the nosologic talents of the pediatricians.

TABLE 7

SOME CONGENITAL NEUTROPENIC STATES

HEREDITARY NEUTROPENIA (KOSTMANN SYNDROME).	AUTOSOMAL RECESSIVE.	PROFOUND NEUTROPENIA; CHROMOSOME ABNORMALITIES.
FAMILIAL BENIGN NEUTROPENIA (GÄNSSLEN SYNDROME).	AUTOSOMAL RECESSIVE.	BENIGN CLINICAL COURSE.
FAMILIAL SEVERE NEUTROPENIA (HITZIG SYNDROME).	AUTOSOMAL DOMINANT.	PROFOUND NEUTROPENIA.
RETICULAR DYSGENESIS.	UNCERTAIN.	THYMIC APLASIA; ABSENT GRANULOCYTE PRECURSORS.
DYSGRANULOPOIESIS.	UNCERTAIN.	

VII. CLINICAL CHARACTERIZATION OF NEUTROPENIC STATES.

In approaching a granulocytopenic patient, it would be helpful to apply the lessons learned from the model of erythropoietic lesions where sequelae of altered production (e.g. reticulocytopenia) or increased destruction (e.g. membrane changes) provide evidence by changes in the peripheral blood. For the red cell, even minor nuances of altered production (e.g. defects in hemoglobin synthesis resulting in microcytosis or defects in nuclear synthesis resulting in macrocytosis) are frequently recognizable by examination of the blood. Unfortunately, similar parameters do not exist to assist in the differential diagnosis of leukopenic states. This lack led to the pursuit of a variety of in vitro studies (e.g. cell culture approaches) to attempt to provide meaningful physiologic classification of the neutropenias. To date, all of these diagnostic aids have provided only limited assistance to the clinician who must depend heavily upon clinical descriptive data for help in diagnosis of the neutropenic lesion.

A. Neutropenias Manifest in Childhood - Lifelong.

1. Benign Familial Neutropenia:

Probably the most common form of neutropenia in the world is benign familial neutropenia. This was first noted by Huber in 1939 (47) and extensively defined by Glansslen in 1941 (48), and series have since often carried their eponyms. It has often been called "African" neutropenia because of significant incidence among black Africans (49). However, it has also been extensively described among black Americans (50, 50a), West Indians (51) and Yemenite Jews (52,53). The extent of these studies does not reflect clinical significance of the lesion, but rather the consideration that it represented a genetic contribution that could be used to follow anthropologic issues.

a. Clinical Features: A mild neutropenic state, absolute neutrophil counts generally above 500/µl (usually 800-2000). No increased incidence of infections nor related clinical diseases. Transmitted as an autosomal dominant trait (48). Clearly most common in those with African heritage.

b. Other Laboratory Features: Increased monocytes and/or eosinophils usually present. The findings may lead to an inappropriate diagnostic consideration of the primary hematopoietic dysplastic state.

c. Studies of Pathophysiologic Mechanisms of Neutropenia:

1.) Normal bone marrow cellularity and maturation of granulocytes.

2.) Normal in vitro growth of marrow; normal granulocyte kinetics (54).

3.) To date, no studies have been done to implicate ineffective granulopoiesis (i.e. changes in muramidase, B_{12} binding proteins, serum uric acid, urinary beta aminoisobutyric acid, etc.). Nevertheless, the lesion has been considered due to altered marrow release of granulocytes (54).

d. Comments: This is a non disease. The patients are healthy.

The potential genetic population contributions have been extensively pursued. A lack of common haplotypes after an extensive study of HLA antigens in population groups has ruled out a simple genetic contribution from the Africans (to the Yemenite Jews, for instance) and has led to the view that the changes in the various populations were not related, but due to a "mutation" (53).

2. Pancreatic Insufficiency Associated with Neutropenia:

In 1964, Frank Oski (55) and coworkers described the unusual finding of defective exocrine function of the pancreas and lifelong neutropenia.

a. Clinical Features: Clinically manifest during the first decade of life with clinical findings (steatorrhea, recurrent infections) similar to fibrocystic disease. Hereditary, but not sex-linked. Mild diabetes common.

b. Other Laboratory Features: Neutrophil counts generally in the range of 300-500/µl. Sweat test is negative. Decreased exocrine function is a constant finding. Increased fecal fat (56).

c. Studies of Pathophysiologic Mechanisms: Patients are capable of mounting a granulocyte response to infection. Bone marrow is hyperplastic with predominant granulocytic hyperplasia. The most interesting feature has been the recognition of a leukotoxin, a circulating γ globulin cytotoxic for granulocytes (57), suggesting that the mechanism here is one of pure increased peripheral destruction of granulocytes.

d. Comments: No further definitive characterization of these findings has been done. The recognition of a circulating "cytotoxin" (57) has renewed implications in light of our growing knowledge of immune granulocytopenias.

B. Cyclic Neutropenia.

Human cyclic neutropenia is a rare but distinctive lesion characterized by regular oscillations in blood neutrophil counts (58). Since the first clinical description by Leale in 1910 (59), the rhythmic oscillation, generally with a 21-day periodicity, has generated an inordinate interest because it was felt that this lesion held the true secrets concerning the control of granulopoiesis. A very important chapter in the history of this lesion occurred with the recognition by Lund and coworkers in 1967 that the grey collie dog had cycles of neutropenia (60). Other studies (61,62) demonstrated that the episodes of neutropenia were associated with 11-13 day cycles of reticulocytosis, monocytosis and thrombocytosis. These findings have generally been felt consistent with a primary defect in the multipotent stem cell, sometimes expressed as a "syndrome of recurring marrow failure".

a. Clinical Features: The clinical onset has been described at all ages (63,64) with uncertain hereditary pattern. The cyclic episodes of neutropenia are usually accompanied by recurrent illness characterized by malaise, fever, aphthous stomatitis and cervical adenopathy (58). The NIH studies (58) suggest the clinical expression is beginning with a 1-3 day period during which the patient is "listless" and "irritable", and it is at this time that the neutrophil counts decline, rapidly reaching their nadir. The second phase (also lasting 1-3 days) is associated with aphthous ulcers and tender cervical lymphadenopathy; temperature elevations, if they occur, are highest at that time. The third phase is one of recovery (usually taking 1-2 days); recovery does not occur until the neutrophil count in the circulation recovers.

b. Laboratory Features: The neutropenia is episodic, varying from 15-35 days, with little variation in any given patient (64a), 85% of the reported cases have cycles of 20-22 days (58). Neutrophil counts typically fall to zero; usually remaining below 200/µl for at least 3-5 days.

Monocyte cycling, equal but reciprocal to the neutrophil cycle, is common. In some patients, cycling of platelets and reticulocytes (like in the grey collie dog) also is seen.

Bone marrow examination during the neutropenic periods consistently show increased cellularity, with a shift to the left of granulocyte precursors. This, so-called, "maturation arrest" reflects only the absence of mature forms. Parenthetically, and not surprising, these findings have resulted in the diagnosis of leukemia in some cases (65).

c. Studies of Pathophysiologic Mechanisms: The grey collie dog has served as a remarkable model of this lesion in the pursuit of regulatory mechanisms of granulopoiesis. Thus, the cyclic "lesion" was proven to be a marrow (myelopoietic) one by the ability to eliminate it by bone marrow transplantation (66), or induce it by similar means (67). A variety of humoral factors have been investigated. Yang et al. (68) have shown an inverse relationship between neutrophil count and CSF. Although erythropoietin levels also cycle (69), marrow engraftment fails to affect this cyclic pattern (70), making a " -poietin" mechanism unlikely. Studies have shown that the clonal growth of granulocytic (CFU-C) and erythroid precursors (CFU-E) is also cyclic, with the peak colony activity at the nadir of the neutropenia (71). Jones et al. (72) have just shown that adherent marrow cells grown in vitro as underlayers to normal canine non-adherent marrow cells provide evidence that an intrinsic defect in these adherent cells exists with their having the ability to affect normal cells in a cyclic pattern.

d. Comments: Lithium carbonate has been shown to abrogate the recurrent episodes of neutropenia in the canine model (73). It appears to do so by directly effecting the differentiation and proliferation of CFU-C, resulting in a "normalization" of the proportion of CFU-C entering committed granulocyte production (74).

Notwithstanding, models of perturbations of granulopoiesis in cyclic neutropenia continue to be proposed to explain the altered granulopoiesis; one recent mathematical model (75) projects the view that an overly active feedback control mechanism is the pathophysiologic basis of cyclic neutropenia.

To further confound the clinical issues in man, not only have a wide variety of therapeutic adventures (steroids, androgens, estrogens, vaccines and splenectomy) been tried with variable success (76), but, in most, the lesion spontaneously disappears in 5-20 years.

C. Neutropenias Manifest in Adulthood - Acute.

In 1968, Kaplow and Goffinet (77) described sudden leukopenia developing early in hemodialysis. It was transient, the counts spontaneously returning to normal in spite of continuation of the procedure. Originally considered due to sequestration on dialyzer membrane, the studies of Jacob and his coworkers (78-82) defined the actual pathophysiology of the lesion and opened a new chapter in the characterization of accelerated granulocyte destruction. These studies demonstrated that the granulocytes were aggregated and sequestered, primarily in the lungs, because complement activation (primarily via the alternative pathway) occurred when plasma contacted the cellophane membrane of the dialyzer.

The recognition of the importance of the effect of the complement fragment (C $5a_{desarg}$) in the aggregation and adherence of circulating granulocytes has been further extended to provide evidence that the transient nature of the leukopenia is due to selective down-regulation of cellular (granulocyte) response to C $5a_{desarg}$ [which is actually constantly produced during the entire course of hemodialysis](83). That other "chemical" intermediates also are potential pathophysiologic causes of acute granulocytopenic episodes has now been well documented (84). Thus, recent studies have shown that arachidonate metabolic derivatives (particularly 5,12-dihydroxy-6,8,10,14-eicosatetraenoic acid) may be the actual mediators of the neutropenia not only produced by C 5a, but also by other mediators such as platelet activating factor (PAF), a phospholipid produced during certain circumstances of anaphylaxis (84,85) or N-formyl-methionyl-leucyl-phenylalanine (FMLP), an analogue product of growing bacteria (84,86). These findings provide evidence that intermediate metabolic and biologic products are, heretofore unrecognized, important mediators of neutropenic episodes.

D. Neutropenias Manifest in Adulthood - Chronic.

In approaching the more frequent problem, that of "chronic" neutropenia with onset in adulthood, potential "environmental" issues can be considered early in the clinical evaluation.

1. Non-Ionizing Electromagnetic Radiation:

In general, radiation exposure classically produces a lymphopenic type of leukopenia until reasonably high exposure rates occur. A new form of exposure has now begun to provide a different clinical picture than expected.

Exposure to non-ionizing electromagnetic radiation (NEMR) extends from industrial use of radar and high frequency radiowaves, through commercial use of video display terminals and related microwave equipment to "unusual" exposure to microwave radiation as experienced by United States Embassy personnel in Moscow between 1953 and 1976.

Very limited data is available on studies in humans. The greatest experience has been accrued by the Russians, and the data they have made available has been summarized by Smialowicz (87). In man, there is clear evidence that exposure results in leukopenia which is primarily a neutropenia associated with a relative lymphocytosis; findings very different than that recorded with ionizing radiation. The difficulty in evaluating the seriousness of these findings is in part related to the paucity of data concerning the microwave frequency, intensity and duration of exposure, all critical features in the animal observations. Current evidence suggests that this may be one of our "new clinical states" of the future. Clearly, we have little data regarding the pathophysiologic mechanism of neutropenia.

2. Nutritional Mechanisms of Neutropenia:

Nutritional factors have been implicated as a mechanism for neutropenia. In general, these have been recognized in three general settings:

A. Malnutrition:

Malnutrition is known to produce neutropenia. Extensive studies of mechanisms have not been done (88). Peripheral neutrophil counts can be less than 400/µl and hypocellular marrows are seen. Two

mechanisms have been used to explain these findings. A corollary to protein malnutrition producing reduced erythropoietin production has been drawn to "explain" reduction of all " -poietins" with resultant lack of appropriate stimulus for entry of cells into the committed maturation compartment (89). This has been used to explain the slow repair (sometimes many weeks) after institution of nutritional repair. A second mechanism is that of trace metal deprivation. Thus, copper deficiency has long been associated with neutropenia (90). Although we now know that the mechanism in copper deficiency is actually related to a defect in DNA synthesis, our current knowledge of the critical trace metal requirements for hematopoiesis has provided adequate explanation for a failure of stem cell function (91).

B. Anorexia Nervosa:

A special form of malnutrition, that of anorexia nervosa, has been more extensively studied (92,93), because of the rarity of infections in these patients in spite of profound low granulocyte counts. Bone marrow examinations have demonstrated hypocellular marrows, but with a relative mature granulocyte hyperplasia. In addition, studies of marrow granulocyte reserves (with steroid stimulation tests) have demonstrated normal reserves in spite of the overall hypoplastic marrow (93). This capacity may explain the ability of patients with anorexia nervosa to generate a granulocyte response to infections. The pathophysiologic basis for the differences between starvation and anorexia nervosa is unknown. One consideration is that in starvation the diet is deficient in vitamins and proteins as well as in calories; whereas, in anorexia nervosa the deprivation is that of carbohydrates and calories, since the protein intake is adequate and true vitamin deficiency rare (93). The mechanism for the neutropenia in anorexia is not explained by these differences; the laboratory findings suggest a defect in granulocyte release.

C. Megaloblastic States:

Megaloblastic states, regardless of their etiology, commonly have an associated neutropenia (94). Since the peripheral neutropenia is seen after other classical findings of megaloblastosis, the diagnosis is quite simple. The pathophysiologic mechanism for the neutropenia has been shown to be due to ineffective granulopoiesis, wherein the normal intramedullary death of granulocytes (probably 15-20%) is remarkably increased (95). That appropriate therapy of the megaloblastic state results in very prompt repair (3-5 days) of the neutropenia (94,96) is in keeping with ineffective granulopoiesis secondary to a defect in DNA synthesis.

3. Neutropenia in Infectious Disease:

In general, the neutropenia in infections is of the acute and transient type. The increased incidence of infections in the neutropenic patient sometimes makes the primary basis difficult to identify (i.e. the infection causing the granulocytopenia). Finch (76) has provided a recent extensive review of neutropenia in infections. Although one might expect these types of neutropenia to be better understood in terms of their mechanisms, in fact, virtually all of the data is descriptive. Table 8 provides some of the available descriptive data for neutropenias associated with infections. Probably the limited spectrum of infections and the presence of other circulating cells provide the clinician with the best initial clue to the likelihood that the infection caused the neutropenia.

4. Neutropenia Secondary to Drugs:

Neutropenias ascribed to drugs represent a problem in differential diagnosis and mechanism. Apparently, virtually any drug can cause neutropenia (97). In response to the common clinical circumstance where the patient has been exposed to several agents, re-challenge trials were used in days of old; the potential serious morbidity of such a maneuver has essentially eliminated it as an approach (98) Current practice has instead attempted to exploit in vitro tests (98-100) to identify the offending agent.

a. Clinical Features: Drug-induced neutropenia generally has an explosive or abrupt onset, and the patient presents with a sudden illness characterized by fever, malaise and, at times, evidence of a focal site of infection. Although the onset of the drug-associated neutropenia generally occurs within a few days to a few weeks of instituting the drug, the evidence of a variable time of occurrence (months to years) is clear.

b. Laboratory Studies: In addition to the neutropenia, an absolute lymphopenia is common. Changes in red cells and/or platelets, by contrast, pose the likelihood of a major cytotoxic injury to the early progenitor compartment. Three broad types of marrow changes have been seen in patients with drug induced neutropenia:

1.) Hypocellular marrow with a major loss of granulocyte precursors: generally indicates toxicity to the stem cells and early committed compartment. Any of the cancer chemotherapeutic agents fit well in inducing this type of injury.

TABLE 8

FINDINGS IN NEUTROPENIA ASSOCIATED WITH INFECTIONS

TYPE OF INFECTION	ONSET OF NEUTROPENIA	PRESENCE OF OTHER CIRCULATING CELLS	MARROW		DURATION OF NEUTROPENIA	EVIDENCE OF INCREASED PERIPHERAL UTILIZATION
			CELLULARITY	GRANULOPOIESIS		
BACTERIAL, ESPECIALLY: - TYPHOID. - BRUCELLOSIS.	PRIOR TO SYMPTOMS.	↑ MONOCYTES.	NORMAL TO ↓	↓	7-10 DAYS.	NO.
VIRAL, ESPECIALLY: - INF. MONO. - INF. HEPATITIS. RICKETTSIAL.	AT ONSET OF SYMPTOMS.	↑ ACTIVATED LYMPHOCYTES.	NORMAL.	↓ c̄ LYMPHO-RETICULAR HYPERPLASIA.	3-7 DAYS.	YES. EARLY IN THE COURSE OF INFECTIONS.
INF. GRANULOMATOUS DISEASE, ESPECIALLY: - MYCOBACTERIA. - HISTOPLASMOSIS.	EARLY IN COURSE OF INFECTION.	↑ MONOCYTES	NORMAL TO HYPO-PLASTIC.	NORMAL; GRANULOMA MAY BE SEEN.	DAYS TO WEEKS.	?

2.) Cellular marrow with shift to left in granulocytic mass in marrow, scanty numbers of mature cells (i.e. reduction in reserve pool). This has been termed "maturation arrest" in the older literature because of the increased numbers of myeloid cells in the absence of mature granulocytes. This pattern is commonly seen where an immunologic mechanism (leukoagglutinin) for destruction is recognized.

3.) Hypercellular marrow with granulocytic hyperplasia. These findings are seen in infections where there is increased peripheral utilization, and also characterize the common form of the "phenothiazine" lesion.

c. Pathophysiologic Mechanisms: Several pathophysiologic mechanisms for the drug-induced neutropenias have been recognized. Unfortunately, for most cases the actual mechanism is unknown; certainly, the molecular mechanisms of injury are not known for any of the lesions.

1.) Direct Cellular Injury: Direct cytotoxic injury of cells in the dividing pool: In a predictive manner, virtually all of the anti-neoplastic agents will produce destruction of the stem cell and committed granulocyte precursor pool, with resultant marrow hypoplasia. Well defined drug dose-response curves for most of these agents exist. Generally, 7-14 days after the elimination of the offending agent, a wave of granulopoiesis can be seen and neutrophil recovery begins. For many drugs not clearly anti-neoplastic in type (e.g. chloramphenicol, cimetidine), a "cytotoxic" injury to granulocyte progenitor cells can be seen at very high doses (101,102); even laetrile has been so implicated (103).

2.) Drug Synergism to Produce Toxic Effect: Considerable interest has developed to try and characterize circumstances in which a single drug (or therapy program) having toxic potential, when associated with a second, otherwise relatively benign, agent results in neutropenia. Attempts to use these to characterize mechanisms and sites of injury are presently quite active. Some of these are: 1.) Cimetidine with immunosuppressive drugs (101,102); 2.) Allopurinol compounding starvation (103,104). 2)Levamisole compounding cytoreductive agents (105,106) Bactrim compounding immunosuppressive drugs (106).

3.) Immunologic Mediated Injury: Several immunologic mechanisms of neutropenia have been described, but most focus upon production of antibodies to the drug or drug cell membrane conjugates (97). Aminopyrine was the classical prototype of this type of reaction. Although the use of the immune mediated destruction mechanism is attractive, the actual documentation of antibody mediated injury has been uncommon. Phenylbutazone, a variety of psychotropic drugs (107) and anti-inflammatory agents have been implicated. In general, such immune

destruction results in injury to the mature granulocyte population (i.e. the granulocytes in the peripheral blood and marginal reserve of the marrow), thereby providing a marrow often described as "maturation arrest". To further confuse things, leukoagglutinins which are not drug-activated have been identified in the sera from a variety of patients having been given many different drugs (96).

For some drugs the "immunologic" aspects are confusing. Thus, Pisciotta (109) has shown that the agranulocytosis occurring with propylthiouracil is associated with the appearance of anti-granulocyte, complement dependent, IgM antibodies which disappear within 4-5 days of stopping the drug. Other studies have shown that sera from such patients profoundly affects hexose monophosphate shunt function in granulocytes (109).

4.) "Idiosyncratic" Drug Injury: Two forms of such reactions have been described, one in which cytotoxicity appears to be the primary clinical complex (the phenothiazine reaction being the prototype) and the other in which a "hypersensitivity" reaction (particularly the sulfa drugs) is seen. In neither form do we have any meaningful understanding of the mechanisms involved.

Finally, these attempts at categorization fail when one seeks to characterize some other uncommon, but considered, clinical circumstances of neutropenia, such as those seen with chronic alcohol exposure (110).

5. Neutropenia Secondary to Immune Mechanisms:

Although "immune" mechanisms as the basis for neutropenia have been very attractive and frequently reported, few reports have stood critical analysis. Indeed, their interpretation is difficult due to a variety of technical problems which at least include lack of reliability of leukagglutination tests, the propensity of plasma proteins (including immunoglobulins) to adhere non-specifically to surface neutrophils, and the general lack of characterization of allo- versus autoantibody status (97). Of the two forms of immune mediated neutropenia recognized, clearly the isoimmune type is best established.

A. Isoimmune Neutropenia:

Over the past two decades, Lalezari and coworkers (111-114) have provided the clinical and laboratory characterization of this lesion. By classical definition, it is a transient neutropenia seen in the first few weeks of life. Cutaneous infections serve as the diagnostic clue. The total white count often is normal, but no granulocytes are present; the neutropenia persists 2-17 weeks (median 7 weeks), after which counts slowly return to normal. Bone marrow examination reveals granulocytic hyperplasia with [same, variable] decrease in the marrow reserve pool (111-114).

The mother, of course, is normal. The lesion is the result of development of maternal antibody to fetal neutrophil antigens during gestation (97,114). Neutrophil leucoagglutinating antibodies have been seen in both the maternal and fetal serum, and the antibodies react with the neutrophils of the patient, the father and some siblings, but not with those of the mother. The antibody, an IgG, crosses the placenta and interacts with the mature neutrophils of the infant (114). It is of interest that these leukoagglutinins are common in multiparous pregnant women, yet isoimmune neutropenia appears uncommon. It has been suggested that this paradox is due to the requirement for antibodies to neutrophil-specific antigens for the lesion; whereas, the leukoagglutinin assays actually identify antibodies to a variety of tissue antigens (e.g. HLA, etc.) which are shared but not unique to neutrophils (114).

That an adult counterpart may exist has been speculated, particularly in this era of component therapy repair. One relevant parallel appears in a case of post-transfusion purpura (115) where neutropenia was seen.

B. Autoimmune Neutropenia:

More difficult to characterize with certainty are a large number of case descriptions of "auto-immune" neutropenias. In general, although women are in slight numerical predominance, no specific clinical features define these cases. The "immune" mechanisms extend from cases in which leukoagglutinins were found (93,116,117), to those with clear evidence of a cytotoxic antibody (118), to those with abnormal T cell function and/or immunoglobulin abnormalities (119-123), and even include the implication that a mixed cryoglobulin may produce injury to the progenitor cell compartment (124).

The correct biological characterization of the "auto-immune" type of neutropenia will require future dissection.

6. Neutropenia Due to Congestive Splenomegaly: "Primary Splenic Neutropenia".

In 1942, Wiseman and Doan (125) described 5 patients with neutropenia (without an evident cause), splenomegaly, generalized hyperplasia of the marrow, who had "complete repair" with splenectomy. Clinically, these patients were called "primary" but all had other cellular elements involved, and the clinical picture was that of congestive splenomegaly. It seems quite likely that this, now extinct, lesion really was simply classical congestive splenomegaly (i.e. hypersplenism), particularly in the setting of a connective tissue disease, supporting accelerated removal as the probable mechanism.

7. Neutropenia in Association With Connective Tissue Disease Lesions: "Felty's Syndrome":

Since the description by Felty in 1924 of an association between leukopenia, splenomegaly and chronic arthritis (126), a massive literature has developed describing every conceivable alteration in granulocyte progenitor activity, granulocyte kinetics, potential pathophysiologic mechanisms and therapeutic maneuvers and responses. In Felty's revisited by Spivak, a review of 72 patients from Hopkins was compared with Felty's original 5 cases, thereby providing a picture of the heterogeneity of the lesion (127). Some of the enormous variations in findings in cases of Felty's are shown in Table 9.

Many of the findings noted in groups of patients with Felty's syndrome are also seen in other connective tissue disorders (136-138).

The profound neutropenia and not uncommon incidence of infections have led to extensive therapeutic trials in patients with Felty's. Splenectomy has been a time-honored approach, and recent evidence that it results in a decline in serum granulocyte binding IgG has added further support to this approach (139). That splenectomy has limited value has been seen in virtually all series; only approximately one-half of the patients sustain clinical improvement. The experience with splenectomy has further demonstrated the lack of knowledge of the pathophysiologic mechanisms involved.

It is quite clear that the asymptomatic patient (regardless of the granulocyte number) requires no therapy. Two considered alternates in the symptomatic patient (prior to splenectomy) include attempts to treat with "anti-inflammatory agents" (i.e. gold or penicillamine), as reported by Hurd and Ziff and coworkers (140,141); or, by attempts to expand the granulocyte mass with lithium therapy (130). Until the mechanisms are better understood, it is unlikely that our therapeutic adventures will be any more specific, nor are they likely to be very much more effective than they have been in the earlier era.

TABLE 9

FEATURES OF FELTY'S

A. CLINICAL FEATURES: PREDOMINANCE OF WOMEN (> 2:).
DURATION OF ARTHRITIS (MEAN 14 YRS).
SPLENOMEGALY (90%).

B. HEMATOLOGIC FEATURES: NEUTROPENIA (80%)
ANEMIA (90%)
THROMBOCYTOPENIA (40%)
USUALLY HYPER CELLULAR BONE MARROW.

C. OTHER LAB FEATURES: LE CELLS (18%)
ANA (63%)
RHEUMATOID FACTOR (94%)
" >1:1280 (60%)

D. FINDINGS RELATIVE TO WBC'S:

1. NEUTROPENIA IS FREQUENTLY CYCLIC (128).
2. GRANULOPOIESIS: ↓ PROGENITOR PROLIFERATION (129).
↓ CSF (130).
3. NEUTROPHIL KINETICS: ↑ GRANULOCYTE MARGINATION (131)
4. SEROLOGIC FINDINGS: REDUCED C3 (127)
↑ NEUTROPHIL-BOUND IgG IN 60% OF CASES (132).
↑ SERUM IgG NEUTROPHIL-BINDING ACTIVITY IN >50% OF CASES (132)
5. NEUTROPHIL FUNCTION: IMPAIRED BACTERICIDAL ACTIVITY (133).
IMPAIRED CHEMOTAXIS (134).
IMPAIRED MIGRATION [SKIN WINDOW](135).

8. Chronic Idiopathic Neutropenia:

Second only to Felty's, probably the most extensively studied lesion and least well understood is that called "chronic [benign] idiopathic neutropenia" (140-149). This entity is largely seen in women and the duration of neutropenia may be decades, although by definition it is not life-long. The clinical symptom complex that characterizes these patients contrasts sharply with the pattern of infections seen in other neutropenic patients (145). Life-threatening infections are very rare and the more typical issue is that of mild recurrent, but troublesome, upper respiratory infections, otitis, minor skin infections and rare episodes of pneumonia. The laboratory findings in this lesion are shown in Table 10.

TABLE 10

CHRONIC IDIOPATHIC NEUTROPENIA
LABORATORY OBSERVATIONS

BONE MARROW:	CELLULAR; ABUNDANT GRANULOCYTE PRECURSORS; DECREASED MARROW GRANULOCYTE RESERVE.
KINETIC STUDIES:	DECREASED MITOTIC COMPARTMENT (ESP. WHEN RELATED TO PERIPHERAL GRANULOCYTE MASS).
	REDUCED SIZE AND VARIABLE RESPONSE (TO STIMULI) OF MARROW RESERVE COMPARTMENT.
PROGENITOR ACTIVITY:	REDUCED CSF ACTIVITY.
OTHER FINDINGS:	REDUCED SKIN WINDOW RESPONSE.
	IMMUNE COMPLEXES REPORTED.

In long term followup (144,145), some patients have spontaneous disappearance of the lesion (145). In spite of aneuploidy seen on chromosomal analysis in some patients (144), leukemic transformation does not occur.

Although the lesion continues to be "idiopathic", the data suggests a mechanism can be defined. A common description is that of "ineffective granulopoiesis" (142-145), but the classical features of increased intramedullary death are lacking. The more appropriate "kinetic" pattern is the failure to recognize and/or respond to the peripheral neutropenia. The decreased levels of CSF described by Greenberg and coworkers (143) suggests this lesion is truly a "hypoproliferative" one, not unlike that expressed by the erythron in the presence of decreased erythropoietin activity.

Almost no investigator has found the need to treat such patients because of their relative lack of symptoms. Alternate-day steroids have been studied at the NIH and shown to increase the neutrophil count (145). Whether that is "therapy" for the patient or the physician viewing the counts is not clear; nevertheless, it is not a recommended approach (145).

9. Other Lesions With Neutropenia:

A variety of uncommon clinical lesions are associated with neutropenia as part of other, more complex, lesions, generally involving multiple cellular elements. These extend, for instance, from the congenital lesion myelokathexis (150) to the acquired lesion oft termed pre-leukemia or hematopoietic dysplasia. The other diagnostic features of such lesions permit the clinician early elimination of the focus upon the "neutropenic" aspects; these, therefore, will not be herein reviewed.

VIII. THERAPY.

Depending upon the "acute" nature of the neutropenic state and presence of secondary complications (primarily infections), several therapeutic approaches have been variably exploited. These include "protective isolation"(151), nutritional support (152) and treatment of [existent] infections (153-155). Specific therapy has focused upon attempts to increase the granulocyte mass, particularly with lithium carbonate (156-160) or to provide transient support in the form of granulocyte transfusions (161-164). Obviously, the most effective approach to the neutropenic patient is to identify and treat the basic pathophysiologic mechanism.

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