MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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CHRONIC

GRANULOCYTIC

LEUKEMIA

(Chronic Myelogenous Leukemia)

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Case #1: [redacted] [redacted]

This 30 year old [redacted] was well approximately 6 months prior to his admission (1969) at which time he noted insidious but progressive development of ease of fatigue and loss of appetite with satiety associated with ingestion of small amounts of food. Over the 3 months prior to admission he noted night sweats, late afternoon fever to 100-101° F and weight loss of 20 pounds. He consulted his family physician because he felt a mass in his left upper abdomen.

On physical examination he was a well developed young man. The positive findings included a very large palpable spleen extending 12 cm beneath the left costal and 2 cm to the right of midline.

Laboratory study revealed a hemoglobin of 11.3 g%, hematocrit of 33 vol%. WBC was 308,000 with 4 segs, 29 bands, 12 metamyelocytes, 16 myelocytes, 3 progranulocytes and 2 myeloblasts (no Auer rods were seen), 5 eosinophils and 7 basophils (some of which had mixed granules). Platelets were 625,000. Red cells appeared normal. Uric acid was 9.3 mg%. Bone marrow aspiration and biopsy revealed a hypercellular marrow with an erythrocyte:granulocyte ratio of 1:500, with a marked shift to the left in granulocyte maturation.

Related study revealed a leukocyte alkaline phosphatase of 7 (normal 15-75) and peripheral blood granulocyte chromosomal analysis revealed evidence of the "Philadelphia" chromosome.

A diagnosis of Chronic Granulocytic Leukemia was made.

Course: The patient was placed on Myleran and supported with fluids and Allopurinol. After 3 months of oral Myleran therapy his WBC had declined to 15,000/mm^3 with normal differential, and his spleen was palpable 4 cm beneath the costal margin. Myleran dosage had been adjusted to WBC and when WBC was in 15-20,000 range it was maintained at dosage of 2 mg/d. By 5 months following initial diagnosis his WBC was 10,000 with a normal differential and his spleen was no longer palpable. All therapy was discontinued at that point.

Chronic Granulocytic Leukemia has commonly been defined as a neoplastic disease in which there is unrestrained proliferation of the granulocytes in the marrow with "infiltration" of these cells in excessive numbers in the peripheral blood, spleen and a variety of tissues. The term chronic was applied during the 19th century to indicate a duration of life after diagnosis longer than that for "acute" leukemia, sometimes defined as survival of 12 months. More recently it has been related to evidence that maturation of the granulocytic series is seen in chronic forms in contrast to a more singular and more primitive cell type in acute disease. Contemporary advances in the management of acute leukemia have led to a median survival well in excess of one year and for some forms of leukemia it approaches 3 years with evidence that a respectable cure rate will be seen.

In this light we will deal with selected issues raised by a diagnosis of Chronic Granulocytic Leukemia (CGL), one of the neoplastic diseases that has provided more important and specific biologic information in terms of etiologic mechanisms, clonal cellular derivation, and cytologic and biochemical markers than for any other neoplastic disease.

I. HISTORICAL PERSPECTIVE OF THE NATURAL HISTORY OF CGL:

1. Minot, G. R., T. E. Buckman and R. Isaacs. Chronic Myelogenous Leukemia. Age Incidence, Duration and Benefit Derived From Radiation. J.A.M.A. 82:1489, 1924.

Classical review of 166 "typical cases" which demonstrated:

1.) Peak incidence of disease ages 30-50.

2.) Average lapse of time from onset of symptoms to diagnosis: 1.4 years.

Average duration of survival from diagnosis to death: 1.6 years.

3.) Average duration of life from first symptom in patients untreated by any modality: 3.04 years.

Average duration of life from first symptom in those treated with radiotherapy: 3.5 years.

4.) Although the duration of survival was not affected by therapy, the "quality" of life (amount of useful life) was improved.

A numerical expression of the symptoms and signs classically described was provided from the Utah series:

SYMPTOMS AND SIGNS IN CGL

Symptoms at Diagnosis:	% Patients
Fatigue	83
Weight loss	61
Abdominal fullness	38
Ease of bruising or bleeding	35
Abdominal pain	33
Physical Findings:	
Splenomegaly	95
Hepatomegaly	48
Sternal tenderness	78
Purpura	27
Retinal hemorrhages	21
Fever	11
Palpable lymph nodes	64
Nodes > 1 cm in diameter	8

2. Wintrobe, M. M. Chronic Myelocytic Leukemia. In Clinical Hematology. Lea & Febiger, Philadelphia. 48:1500, 1974.

II. REGULATORY MECHANISMS OF GRANULOPOIESIS - ASPECTS OF GRANULOCYTE KINETICS:

A. Granulocyte Kinetic Data:

Although some unresolved differences exist (largely the result of the type of radiolabeled tracer utilized), enough solid data is available to provide a descriptive pattern of granulocyte pools and turnover:

Operational Terms and Data:

1. The peripheral blood granulocyte mass exists in two pools of approximately equal size in man (3-5):

a.) Circulating granulocyte pool (CGP)

b.) Marginal granulocyte pool (MGP) - marginated primarily in the post capillary venules.

Since these cells are freely exchangeable between pools and both pools are functionally normal, the two pools can be considered a single kinetic unit.

2. Bone marrow, for kinetic considerations, can be divided into 3 compartments:

a.) Mitotic compartment (pool) - representing cells from stem cell through myelocyte stage (6).

b.) Maturation compartment (pool) - representing cells from myelocyte stage through mature P.M.N.'s.

c.) Storage compartment (pool) - mature granulocytes capable of release to circulation under appropriate "release" signal (7, 8).

(For kinetic analysis - the latter two pools often are expressed in literature as the post mitotic pool.)

KINETIC DATA

		Normal	CGL
1.	Granulocyte Turnover Rate (GTR) [Production Rate]	1.67 X 10^9/kg/d (3-5)	2-10 fold increased over normal (11)
2.	Marrow Granulocyte Reserve	2.7 X 10^{11}	-
3.	Effective Production Rate (12)	0.87 (± 0.13) X 10^9/kg/d	Not available
4.	Total Marrow Granulocyte Pool (12):	7.7 (± 1.2) X 10^9/kg	-
	Mitotic Pool -	2.11 (± 0.36)	-
	Post Mitotic Pool -	5.59 (± 0.9)	-
5.	Total Blood Granulocyte Pool:	61 X 10^7/kg	Increased 10-150 fold
	-Circulating Granulocyte pool	31	Normal 50:50 relationship
	-Marginal Granulocyte Pool	29	
6.	Circulating Granulocyte $T_{\frac{1}{2}}$	6.8 hrs. (range 4-10)	26 hrs. (prolonged 4-12 times)

Therapy in CGL results in a return of all altered kinetic values to <u>normal</u>.

B. Proliferative Characteristics and Capacity:

	Normal	CGL
1. Duration of DNA Synthesis (13)	10-15 hr	10-15 hr
2. Labeling Index of Proliferating Myeloid Marrow	23%	23%
3. Labeling Index of Spleen (14)	-	↑ LI which correlates with peripheral WBC
4. Proliferative Pattern (15) (after ^{3}H-Tdr label)	a) Low activity for 100 hrs b) Then single peak at 168 hrs	a) High level circulating activity b) Two peaks, one at 30-40 hours and a second at 120-144 hours. (The latter peak disappears in splenectomized patient.)
5. Labeling Pattern of Myeloblast Pool (16)	45-60	16.9 (a pattern similar to that of AGL)

Thus the observations of proliferative characteristics in CGL provide evidence of an important contribution to granulocyte mass from the spleen (24) and that the precursor pool (blasts) have features in common with acute leukemia.

C. Migration-Compartment Transit Data:

	Normal	CGL
1. Minimal Emergence Time (of Cell Labeled During Last Myelocyte Division)		
Normal Steady State	96-144 hrs	Same
With Stress (Infection)(9)	48 hrs	Same
2. Mean Transit Time Through Maturation Pool (Myelocyte → Blood)		
^{3}H-Tdr	6-9 d	Same
DF^{32}P	11 d (range 8-14)	
3. Ratio of Bands:Segs (↑ in bands indicates depletion of storage pool)	0.1 - 0.3	↑
4. Shift Leukocytosis Marginal → Circ. pool (exercise, paroxysmal tachycardia)	↑ to 20-25,000/m^{3}	Normal response
5. Sites of Granulocyte Loss	- saliva and urine - lungs, liver & spleen	?
6. Cell Egress to Tissues	One way route	Cells capable of returning (17) But poor egress of cells at myelocyte stage or younger (10, 18)

D. Regulatory Mechanisms for Granulopoiesis:

	Normal	CGL
1. Cyclic Oscillations (19, 20): Interval - Amplitude -	20 days (14-23 d) 2-4 fold granulocyte shift	Long Cycles (30-110 d) Large: May exceed 100,000/mm^3
2. Release Factor Leukocytosis-inducing factor	?	?
3. Colony Stimulating Factor (21) (granulopoietin)	?	?
4. Choline-Anticholine Inhibitory-Stimulatory Feedback Control (22)	Extracts of granulocyte (?) "Can" inhibit proliferation of granulopoietic cells.	?

However, all of the identifiable abnormalities disappear with therapeutic control of the disease (23). Each of the observations has been at varying times touted as a clue to therapeutic control, or to the primary physiologic derangement.

For instance, the cyclic variation (oscillation) has led to much speculation concerning a controlling humoral factor (25). Great variability in the granulocyte patterns even before a diagnosis can be made makes most of the expressed views speculative.

Case #2: [redacted]

At age 22 this [redacted] male was admitted to [redacted] in 1961 with a RLL pneumonia. His Hb was 12.9 and hematocrit 43. WBC was 24,500 with 85% PMN's, 13% lymphs and 2 basophils. His WBC declined to but 14,500/mm^3 near the end of his hospital stay and he was seen by the Hematology Service. He had no physical findings, his leukocyte alkaline phosphatase was 98 and his marrow revealed [non-diagnostic] mild granulocytic hyperplasia. For unknown reasons, he was evaluated at the [redacted] in 1964 and had a normal CBC with WBC of 8000/mm^3. In [redacted] 1965, he was again admitted to [redacted] with bronchopneumonia. WBC was 41,000 and platelets were 580,000. LAP was elevated and marrow non-diagnostic. His WBC declined to 14,000/mm^3 by time of discharge, but he failed to return for serial evaluation. In [redacted], 1966 he was seen because of aching discomfort in joints. His spleen was palpable. His WBC was 87,000/mm^3, and he had a low L.A.P., a marrow compatible with Chronic Granulocytic Leukemia and the demonstration of the Ph^1 chromosome. A diagnosis of

CGL was made and he was begun on Myleran therapy. Two years after the initial diagnosis he had rapid development of "blast" transformation and died some 3 weeks after development of "blast" crisis.

The interpretation of the pre-diagnostic granulocytic peaks can only be speculative. Identified today - such a patient would have the benefit of search for all of the regulatory factors mentioned above.

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III. PATHOGENETIC OBSERVATIONS:

There are two unique features of CGL that make the disease a focal forum for epidemiologists:

A. Inducibility - Effect of Ionizing Radiation:

The induction of CGL by ionizing radiation (either by single or protracted courses) is established beyond all reasonable doubt. Although one can generate a wide bibliography extending from radiologists in days of old to current day "image intensifier workers", the solid data on radiation leukemogenesis is:

a.) Spondylitis Patients Treated With Radiation
- Where evidence suggests (26, 27) that 30-50 r doubles the incidence of leukemia in the exposed population.

b.) Japanese data on Hiroshima-Nagasaki survivors where incidence of CGL began to increase approximately 3 years after the bombs and peaked 6-7 years after the pulse like exposure (27, 28).

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B. The Philadelphia (Ph^1) Chromosome:

The exciting description in 1960 by Nowell and Hungerford of a chromosomal abnormality (an abnormally small chromosome) in 2 patients with Chronic Granulocytic Leukemia (30, 31), provided the first (and only) specific cancer-related chromosomal abnormality.

- Because defect is clearly different from that seen in Down's syndrome, the Ph^1 chromosome abnormality has been assigned to #22.

- Using the Q bonding technique (quinacrine mustard-fluorescence method), the "deletion" of the long arm of chromosome 22 is known to be a translocation usually to chromosome 9. In Ph^1 negative patients with CGL, extra chromosomal material not found, suggesting this is a translocation rather than an alteration in chromosome 9.

- Whatever causes the change, the hematopoietic cell affected must be a relatively undifferentiated stem cell, since the defect seen in granulocyte precursors is also seen in the megakaryocytes and the erythroid precursors, and recently reported in cultured fibroblasts.

- Except for rare (and very questionable)reports the Ph^1 chromosome is exclusively associated with CGL and is therefore a valuable diagnostic criteria.

- Approximately 80% of patients in whom a diagnosis of CGL is made (by other criteria) have the abnormality.

- The abnormality is clearly an acquired one, since in twins where one has CGL the other does not have the Ph^1; thus it is an acquired post zygotic defect.

- The abnormality may be acquired from either the maternal or paternal chromosome.

- The Ph^1 chromosome generally does not disappear from the marrow during conventional therapy.

- Evidence strongly supports a clonal origin for CGL.

- The clinical event of "blast" transformation is usually accompanied by other chromosomal changes such as aneuploidy (usually hyperploidy) and/or extra Ph^1 chromosomes.

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IV. LABORATORY CHARACTERIZATION:

A. Classical Characterization of CGL has included:

1. Peripheral Blood Findings:

- Elevated WBC: with all granulocyte stages represented in a continuous way (i.e. no hiatus). Arbitrarily usually less than 10% myeloblasts-progranulocytes. Usually associated with increased eosinophils and basophils.

- Anemia: of modest proportions with no distinctive features (36, 37).

- Platelets normal in most, but may be elevated in 1/3 of patients (38).

2. Bone Marrow:

- Hypercellular marrow, absent fat, and marked granulocytic predominance with peak at myelocyte stage of maturation.

B. Related Laboratory Observations:

- Hyperuricosuria and often hyperuricosemia - secondary to the increased cellular turnover (↑ production of uric acid). ↑ with chemotherapy (39).

- Hypercalcemia - usually associated with osseous lesions (40).

- Elevated serum lactic dehydrogenase, with normal granulocyte isozyme pattern (41).

C. Laboratory Observations with "Projected" Specificity and Attempted Clinical Implications:

- Histologic:

- Gaucher cells, first demonstrated by Albrecht (42) in 11 of 64 CGL patients, have now been shown ultrastructural characteristics in CGL that differ from the classical cerebroside in Gaucher's, suggesting these cells simply be called "storage cells" (43).

- Chromosomes: See above.

- Biochemical:

- Leukocyte alkaline phosphate (LAP): the decreased levels (both histochemical and biochemical methods) in CGL first quantitated in 1951 by Valentine and Beck (44).

- Normally: LAP activity increases with progressive myeloid maturation, with maximal activity in 3-4 lobed PMN's. When LAP is increased, all cells from myelocyte on have increased levels. Normal mature PMN's contain 2 chemically distinct types of granules, so-called azurophils and specific (45). Azurophils are produced in the promyelocytic stage of maturation and contain peroxidase and lysosomal hydrolases. Specific granules form later (myelocyte stage) and contain alkaline phosphatase and lack peroxidase (46).

- In CGL: decreased LAP in virtually all patients. The gene for LAP is not related to G-22 chromosome. A normal LAP in a known CGL should suggest some secondary stimulus (i.e. infection, etc). High LAP in CGL has been reported (47).

- In CGL both granules are found, and on EM some dyspoietic character of granules seen (46), and immunochemical studies reveal no abnormality of the enzyme, just decreased production (48).

- During remission, LAP activity often returns to normal, and has been considered by some a "favorable sign", representing a "normal clone".

- During Blast crisis, LAP almost always rises and the bone marrow, rather than the spleen, is the source of these cells (49).

- Other enzymes: A variety of enzymes involved in DNA synthesis (dihydrofolate reductase, thymidylate synthetase, etc.) have been increased (50), perhaps reflecting young cell pool and active DNA synthesis. Poorly studied are decreased levels of enzymes involved in thymidine metabolism (thymidine phosphorylase, deoxyribosyltransferase)(51).

- Muramidase: A hydrolytic enzyme with significant activity in granulocytes and monocytes. Serum levels and significant muramidasuria result from degradation of these cells (52) and afford a crude measure of granulocyte turnover.

- elevated serum and urine levels seen in CGL. Serum and urinary muramidase levels appear higher in Ph^1 negative CGL patients than in Ph^1 positive ones (53).

- Binding Protein:

- Vitamin B_{12} levels are increased 10-15 fold in CGL, due to increased amounts of Transcobalamin I (alpha globulin binder) and these (serum vitamin B_{12} and B_{12} binding capacity) can be used as a measure of granulocyte turnover. In remission, values fall, but not to normal, suggesting persistent ineffective granulopoiesis (54, 55).

- Gallium: Increased Gallium (^{67}Ga citrate) has been shown. May be useful for mass discrimination and/or kinetic analysis (56).

- Tissue Culture: Studies of in vitro cloning of bone marrow which results in the production of colonies of granulocyte elements have provided evidence (57-60) that:

- CGL is a clonal disease.

- that the leukemic cells are not "autonomous neoplastic cells" but are under some regulatory restraints and respond to regulatory control

- that leukemia is not a single-step transformation event.

Of considerably less value than originally predicted is a CGL line in tissue culture which has Ph^1 chromosome, no LAP or myeloperoxidase activity and has now been carried $3\frac{1}{2}$ years (61).

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V. THE CLINICAL "FORMS" OF CGL:

In a general way one can divide the patients into 3 broad groups. Not all accept such categorization and feel that only Ph^1 positive is CGL and all other "variants" are other diseases, i.e. acute myelomicrocytic leukemia or blast transformation of CGL.

CLINICAL PATTERNS OF CGL

	Ph^1 POSITIVE	Ph^1 NEGATIVE	DOUBLE Ph^1
Relative %	80%	15% (range 12-30%)	5% (3-10%)
Age (mean)	48 yr	66 yrs	Variable
Splenomegaly	++++	++++	Variable
Lymphadenopathy	Rare	Occurs	Primary feature with prominent peripheral adenopathy and/or hilar mass
Extramedullary masses	Rare	Rare	Common
WBC $<^{mean}_{(range)}$ X 10^3	126 (29-317)	58 (18-634)	Variable
Platelets X 10^3	330 (35-1,560)	157 (25-452)	-
Mitotic Index (N=25-28)	10.2/1000	6/1000	?
Serum Muramidase N= 7-14 µg/ml	17-33	60-228	-
Urine Muramidase N= < 2	0	30-800	-
Leukocyte Muramidase N= 90-320 µg/10^8	250-390	340-960	-
Survival (mean)	40 mos.	8 mos.	6 mos.

Case #3: [redacted]

19 year old NM [redacted] who presented 4/70 with a 2 month history of progressive ease of fatigue and some decreased athletic performance. On physical examination he had 1-2 cm nodes in both axillae and femoral regions and spleen palpable 6 cm beneath the LCM. WBC was 190,000. Treated with Myleran and gained a complete remission. While a student at [redacted] he developed a rapidly increasing right cervical mass, and he returned to [redacted]/71. He had generalized lymphadenopathy (1-2 cm nodes) involving axillary, epitrochlear and femoral areas. Spleen and liver were not enlarged. Peripheral blood and marrow were normal. Biopsy of neck revealed a "myeloblastic tumor" (chloroma). He was treated with radiotherapy to the neck. He remained stable until [redacted]/71 when increasing lymphadenopathy and hip pain led to increased therapy with Myleran. He was stable until [redacted]/71 when he developed a second large mass in right axilla. Aspiration biopsy also revealed chloroma. Although he did not have peripheral hematologic or marrow evidence of "blast transformation" he was Rx with Cytoxan, Prednisone and Vincristine with good resolution of most of his generalized lymphadenopathy. [redacted]/72 he began to have recurrent fever and episodes of pneumonia and progressive evidence of tissue infiltration and he died [redacted]/72. Chromosomal analysis on the first chloroma revealed Double Ph^1 chromosomes.

Other "variants" have been described:

A. XO, Ph^1 Positive CGL (66) - now at least 12 cases have been described; all have a long and benign course. All males and the missing chromosome in the Ph^1 positive cells now proven to be the Y chromosome.

B. Myelofibrosis: may be seen at any stage of disease. As more biopsies being done in CGL it is evident that focal fibrosis common. Often do not have classical morphologic changes; marrow frequently difficult to obtain and anemia may be more severe than expected (67).

In addition, a variety of clinical presentations appear to relate to Blast transformation or metamorphosis:

VI. BLAST CELL CRISIS OR METAMORPHOSIS:

In the majority (60-75%) of patients with CGL, the "natural history" of the disease is associated with a clear change in the character of the disease, often very dramatic in onset and progression - so-called "Blast Cell Crisis or Transformation" but probably better expressed in the terms of Gunz as Metamorphosis, because the blast cell change is only one finding during this change.

A. Clinical Findings - Heralding or Associated with Transformation (68-74):

1. Symptoms/Signs:

a) Unexplained weight loss

b) Unexplained fever (and/or night sweats)

c) Evidence of bleeding - clearly most common event

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d) Rapid enlargement of spleen (or liver)

e) Appearance of extra-myeloid tumors (chloroma - myeloblastic tumors):
neurologic symptoms - perineural and epidural myeloblastomas
lymph node enlargement - nodal and mediastinal chloromas
arthritis - diffuse cellular infiltrate
bone pain - osteolytic myeloblastic tumors
cardiopulmonary symptoms - pericardial and/or myocardial diffuse cellular infiltration
skin lesions - infiltrative or nodular myeloblastic proliferation
(Other rare sites include liver, breast)

2. Laboratory Features:

a) Rapidly worsening anemia

b) Progressive thrombocytopenia (rarely thrombocytosis)

c) Progressive increase in circulating myeloblasts and progranulocytes (? > 30%) and hiatus

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d) Advent of myelofibrosis

e) Marked increase in leukocyte alkaline phosphatase

f) Numerous chromosomal abnormalities (aneuploidy, etc.) in addition to Ph^1 change

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g) Shortened doubling time of the immature granulocytes in the circulation

B. "Natural" History of CGL in Metamorphosis:

- median duration of survival about 9 weeks

[One of the clinical diagnostic criteria had been failure to respond to therapy. Reasonable clinical remissions were first demonstrated by James T. Wheeler, M. D. of Dallas in 1966 to Vincristine and steroids (75); similar data was recently published by N. I. H. group (76).]

C. What is Metamorphosis?

? Blast Crisis of CGL

? Acute Transformation of a Preleukemic Lesion (CGL)

? Lymphoblastic Leukemic Conversion of CGL

Preleukemic Concept:

The Scandinavian workers (Pedersen and Killman) have provided data to support their concept that CGL is in fact a pre-leukemic lesion and that the metamorphosis is the true leukemic process (77, 78):

- Normal histologic findings in CGL; light and E. M. changes in the transformed state

- In CGL myeloblasts (like normal) are PAS and Sudan negative with no peroxidase activity; in transformed state all are positive

- Change in generation time and mitotic index with transformation

- Development of karyotypic abnormalities

Lymphoblastic Conversion Concept:

Boggs (79) has summarized the cogent clinical arguments in favor of considering at least some cases of transformation to be Lymphoblastic Conversions:

- Morphologic similarity to lymphoblasts

- Clinical responses to Vincristine and Prednisone (like ALL)

Laboratory support for this concept has come from the unfolding Terminal Deoxyribonucleotidyl Transferase Story:

Terminal deoxyribonucleotidyl transferase (TdT) catalyzes the polymerization of deoxyribonucleotide triphosphates, producing elongation of the polydeoxyribonucleotide chains without template instruction. The enzyme was originally found in calf thymus and has been proposed as an effector of immunologic diversity (specificity). Recently, the enzyme was demonstrated in leukemic cells from patients with classical acute lymphocytic leukemia, and the uniqueness of the enzyme's localization has led to the suggestion that these ALL's were of thymocyte origin (80).

Recent evidence from two groups (81, 82) has shown high levels of the TdT in the "blast" cells from some patients with classical "blast transformation of CGL". It is of interest that Ph^1 chromosomes had been seen in these cases. Thus, the proposal has been raised:

- that in the blast transformation it is thymic derived lymphoblasts rather than myeloblasts which proliferate, or, if you will, a lymphoblastic conversion of CGL.

The above must be considered a "preliminary possibility" since TdT activity (albeit at low level) has now been demonstrated in normal marrow and in acute granulocytic leukemia peripheral blood (83).

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Case #4: [redacted] [redacted]

37 year old NM who was first admitted [redacted]/73 because of a history of malaise and weakness of 4 months duration and abdominal fullness of 2 months duration. Physical examination revealed decreased auditory acuity on left, bilateral retinal hemorrhages (Roth spots) and massive splenomegaly.

Hemoglobin was 15 g, hematocrit 43 vol%. His WBC was 516,000 and platelets 212,500. Uric acid was 6. Ph^1 chromosome positive. LAP 0.

He was treated with Cytoxan and Cytosine Arabinoside (Ara-C), fluids and alkalinization. He achieved good control of his disease and refused to return for follow-up care.

He was readmitted [redacted]/74 after a 24 hour history of nausea, vomiting and a sudden episode of unconsciousness. In EOR he was unresponsive and decorticate, had normal vital signs and no fever. Pupils were dilated and fixed. Evidence of a melanotic stool. His hemoglobin was 10.5 g/hematocrit 32. WBC 541,000 and platelets 47,000. He expired shortly after arrival.

At autopsy: Classical leukostatic lesions of small vessels in CNS, heart and lungs.

VII. OTHER "COMPLICATIONS" OF CGL:

Survival and direction and mode of therapy must consider two other major risks beside the above issues:

A. Sequelae of Intravascular Leukocyte Thrombi:

Such leukostatic lesions (leukocyte thrombi or aggregates) are usually considered in Acute Leukemia, but in Vanderbilt series (84) they were found in 36% of patients with CGL. Predominant sites: CNS and lung.

CNS Symptoms: Confusion and/or somnolence most common

Cardiopulmonary Symptoms: Dyspnea most prominent

Relationships:
- seen in all patients with WBC > 200,000/mm^3
- seen in 50% with WBC 50-200,000/mm^3
- virtually none with counts below 50,000

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B. Bleeding:

Second only to metamorphosis as cause of death. Results from therapy, ? progression of disease, development of platelet functional defect, or such transformation.

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VIII. THERAPY IN CGL:

A. Current Survival Data:

Median survival of virtually all series of patients ranges from the median survival data of untreated patients recorded by Minot et al. (1) of 36 months to the results compiled by the use of very contemporary modes of therapy (62, 87-96).

	Number of Patients	Median Survival (months)
Other Early Data:		
Wintrobe Study (88)	259	37
Tivey Review 1925-'51 (89)	1090	32
Recent Data - Various Rx:		
Roswell Park Series (62)	28	40
USAF Series (90)	99	41
British Research Council (91)	102	41
Dameshek Series (92)	35	approx 36
New York Memorial Series (93)	178	31
NIH Series (94)	40	45
French Series (95)	187	approx 36
Dallas [Baylor-SWMS](96)	159	39

However, median survival data is only crude reflection because early deaths are seen in approximately 15% of patients (thereby providing a "selected" population to above referral hospitals) and because long survivors (about 15%) break out at far end of curve (97).

Case #5: [redacted] [redacted]

At age 28, this [redacted] presented [redacted] 1962 with progressive (40 lb) weight loss, recurrent daily fever and night sweats; he had a very large spleen and bilateral "thigh masses". WBC was 355,000 and Hb 9.8. He was treated with Myleran and by 6 weeks of therapy his WBC was 114,000 and Hb 10.4. By [redacted] 1963 he had a normal WBC and absent spleen. Myleran was stopped and in August 1964 he had recurrent splenomegaly, WBC of 22,000 ("all blasts") and Hb 8.4 g. He was told he would "probably die" by LMD. Re-Rx with Myleran led to another remission. He did well until 1969, when recurrence led to consideration of "Blast Transformation". Myleran therapy resulted in another remission. In September of 1974 he presented with recurrence of fever, night sweats and weight loss, spleen tip palpable at LCM. WBC was 31,300/mm^3, Hb 10.5 and Hct 33 vol%. LAP was 6. Patient initially treated with Myleran, with partial remission. In [redacted] 1975 he was begun on VCR and Prednisone for CGL in metamorphosis.

Such cases have led many to search for "prognostic signs" in CGL. In general terms, the unfavorable signs are those identified with Transformation (98).

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B. Modes of Therapy:

1. Splenic Irradiation - essentially abandoned as sole mode of therapy because of evidence it is clearly inferior to Myleran (91 as well as 90). However, Clarkson et al. (93) and others (95) demonstrate it is effective as part of a Rx program.

- In addition, kinetic studies by Clarkson (13) have documented that an important percentage of the primitive cell population had its origin in spleen in CGL.

Irradiation yields:
- Regression of spleen size
- Suppression of circulating cells (all series)
- "Normalization" of marrow

Mechanism of Marrow Effect:
a) ? Destroy peripheral production pool: however, splenectomy fails to do same thing
b) ? Interrupts peripheral blood to marrow cycle in CGL (17), by killing those in spleen and altering microenvironment for maturation of subsequent generations of cells (99).
c) ? Production of a humoral factor that affects granulopoiesis and/or circulating granulocytes (100).

Indications:
Part of Combination Rx Program
Selected Circumstance Where Drugs Cannot be Used
Localized Splenic Symptoms

2. Alkylating Agents - have become the classical mode of therapy. Busulfan (Myleran) is the "accepted drug of choice" (18, 101).

- individual daily dose appears more important, relative to toxicity, than total dose

- fall in leukocyte count is a reliable indicator of response

- WBC may increase during first 2-3 weeks of therapy

- Usual dose for onset of Rx is 4 to 6 mg/d. There is virtually no advantage to larger doses. Follow weekly.

- Dosage decreased as WBC declines

- Myleran discontinued when WBC around 15,000/mm^3, since count will continue to fall for 4-6 more weeks

- A fall in platelet count during therapy when WBC still significantly elevated represents a serious problem in management. Continued Myleran therapy has resulted in irreversible marrow aplasia.

- Re-treatment instituted when WBC rises to $\frac{1}{2}$ of initial diagnostic level or to 50,000/mm^3 whichever is lowest.

- No data supports chronic low dosage therapy to be better than such intermittent therapy.

Complications of Myleran Therapy:

a) Marrow aplasia and persistent thrombocytopenia (18, 101)

b) Marrow (myelo) fibrosis (101, 102)

c) Gonadal suppression (102)

d) Hyperpigmentation ("Pseudo-Addisonian") syndrome (103)

e) Interstitial pulmonary fibrosis (104, 105)

f) Cytologic dysplasia of respiratory and vaginal epithelium (106)

g) Cataracts (106)

h) Pituitary insufficiency (107, 108)

i) Endocardial fibrosis (109)

It has been used during pregnancy; effect on fetus not clear (granulocyte mass apparently not disturbed, effect on gonadal function unknown). (110, 111)

Although specificity for the efficacy of Myleran has been popularized by Rundles (112), it is clear that other alkylating agents, like melphalan, are effective (113) and from above list of problems plus the survival data other agents have reasonably been sought.

One attractive recent addition is DBM - Dibromomannitol (1,6 dibromo-1,6 dideoxy-D-mannitol), a brominated sugar alcohol. Mechanism of action uncertain, but probably by alkylation.

- dosage 250 mg/M^2/d orally X 3 days;
  then 150 mg/M^2/d until response.
- No evidence that it offers any advantage over Myleran.
  In one series of 122 patients, median survival was 43 months (114), not unlike U. S. experience (94), where survival was same for both.

3. Ribotide Reductase Inhibitor - Hydroxyurea:

Cell cycle-phase-specific agent which interferes with ribotide reduction to deoxyribotide in pyrimidine biosynthesis (115).

- dose 50 mg/kg/d in two divided doses until WBC reaches 10-15,000

- median survival essentially that for alkylating agents (116)

4. Other Therapeutic Studies:

a. Other Drugs:

Besides the agents above, virtually all chemotherapeutic agents shown to produce marrow suppression have been used with modest success (117) - No evidence exists to support an advantage over above drugs.

b. Extracorporeal Irradiation of Blood:

- irradiation via an A-V shunt: 500 rads delivered via each transit dose. Provides decline in peripheral circulating WBC and decrease in spleen size; no complete remissions and rapid return (weeks) to pre-therapy status (118, 119).

c. Leukopheresis:

- IBM cell separator has been used as primary mode therapy. Results in a significant decline in WBC (mean 80%), but fall in platelets as well (mean 54%). Does not result in complete remissions, requires 2-5 runs per week, and does not delay metamorphosis ("Blast Transformation"). (120, 121)

5. Splenectomy:

Splenectomy was utilized as a mode of therapy prior to era of radiotherapy. Surgical morbidity was in excess of 25% and until recent years no indications for splenectomy were accepted short of splenic rupture. In recent years splenectomy has been used for:

a) Myleran Induced Thrombocytopenia (due to decreased production): In 6 patients so treated platelets rose and were sustained in 5, permitting continued therapy (122).

- In Dallas, this has been managed by use of Cytoxan with a rise in platelet value and yet progressive control of WBC and spleen size (123).

b) As Therapy for Blast Transformation: In the face of Clarkson data (17), one could "hope" for a response; of 15 patients so treated at Roswell Park, 2 reverted to stable chronic stage (124). Little supportive data.

c) As "Preventive Therapy" for Metamorphosis:

This study was begun by M. R. C. Leukemia Unit 9 years ago. Two other groups have used similar approaches and reported, during this interval, that:

- Villegrief, France (125): 18/43 CGL patients agreed to splenectomy. 3 post-op deaths. Median survival 43 months, compared to 37 months for the non splenectomized (remainder of therapy not unusual).

- N. Y. Memorial Study (126): Specific goals were: Could Ph^1 chromosome be irradiated; was metamorphosis delayed. Concept that previous Rx failures might have been due to prolonged therapy with non-cycle active drugs so that normal stem had been destroyed and could not normally repopulate.

Study began in 1970, 21 patients now evaluable:

Rx: - Initial radiotherapy to spleen using 25 rads 3 X/wk (↑ to 100 slowly) to a complete remission. Median dose required 900 rads (600-2000 rads)
- Elective splenectomy when in remission
- Post operative therapy: Ara-C and Thioguanine as acute granulocytic leukemia

Results: 8/21 patients have lost their Ph^1 chromosome: No conversions to date in this group
5/21 have had blast transformation post splenectomy at 4, 8, 12, 13 and 29 months, with 4 deaths

- M. R. C. Study (127):

Basis:
- English review that patients with prolonged survival have only "slight" splenomegaly at diagnosis (126)
- Hematologic remissions in some splenectomized patients (124)
- Spleen known to contain Ph^1 positive cells (24)
- Proliferative activity of immature granulocytes in spleen differs from that in the marrow (14, 23)

26 patients studied, all Ph^1 positive, 15 men and 11 women. Ages 16-64 yrs. Low LAP in 18, normal in 5.

- Busulfan Rx to remission, especially reduction of platelet count to less than 200,000/mm^3.

Results:

- WBC rose to 3-6 times pre-operative level reaching peak 24-48 hours post-op and returning to pre-splenectomy level by 72 hours.

- LAP rose to 5-10 times pre-op level within 72 hours and remained up for weeks to months.

- Platelet count rose slowly over next 7-10 days to peak, generally 4-6 times pre-op level, and remaining for weeks to months.

- Effect on survival:

21 of 26 still alive: 2 died of unrelated causes and 3 of CGL in metamorphosis. In addition 2 others are alive but in stage of metamorphosis. Comparison with control MRC study indicates that instead of 5, there should have been 12 cases of metamorphosis in the follow-up period available.

6. Combination Therapy:

A number of studies have employed multiple drug therapy. The possibility of non-cycle active agent injury to normal stem cells in marrow limiting recovery in the manner seen in acute leukemia has extended such trials (126). The most extensive combination on study by M. R. C. (128) is TRAMPCO(L):

TRAMPCO(L) REGIMEN

Drug	Dose	Route	Duration
Thioguanine	100 mg/M^2/d	oral	3-5 days
Rubedi omycin (Daunorubusen)	40 mg/M^2	I.V.	Day 1 only
Ara-C	100 mg/M^2/d	I.V.-push	3-5 days
Methotrexate	7.5 mg/M^2/d	I.V.-push	3-5 days
Prednisolone	200 mg/d	oral	Days 1 to 5
Cyclophosphamide	100 mg/M^2/d	I.V.	3-5 days
Oncovin (Vincristine)	2 mg	I.V.	Day 1 only
L-Asparaginase	8000 U/M^2/d	I.V.	Day 1 to 28

Results: 5/9 patients had improvement: 4 with survival of plus 3, 8, 12 and 14½ months.

IX. PROSPECTS FOR CONTROL:

- ? Regulatory controls of granulopoiesis (129, 130)

- ? Eradication of Leukemic Clone

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