titioners as radiologists will be compelled to give opinions to which they are committed. Difficult x-rays will be submitted to computer scanning which will make up the radiologist's mind for him if he cannot do if for himself. The state will continue to nibble away at administrative and financial aspects of professional freedom. But it will not interfere with the basic person to person quality of the doctor-patient relationship. If it does it will ultimately incur litigation for malpractice.

For an indefinite period doctors in North America will be free to make a lot of money. With a few exceptions most are overpaid. The day is coming when a judgment will be made about the real worth of a doctor. However, when that day comes it will be appropriate for the doctor to ask, even if he cannot insist, that society apply similar criteria of worth to the activities of such highly overpaid, non-essential individuals as heavy weight boxers, ice hockey players, baseball pitchers, leading golf professionals, pop singers, disc jockeys and a few others it would not be difficult to name. A responsible society, like a responsible doctor, is only truly free when, in relation to the rights of all its citizens and with a sensible regard for its social priorities, it acts as it ought and not as it likes.

While the opinions in this lecture are my own I was particularly helped and stimulated by two books, namely "A History of Medicine" by Douglas Guthrie (Philadelphia, Lippincott, 1958) and "The Profession of Medicine" by Elliot Friedson (New York, Dodd, Mead, 1970).

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Light-chain disease (hypogammaglobulinemia and Bence Jones proteinuria) and sideroblastic anemia — preleukemic chronic granulocytic leukemia

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Preleukemia is an ill-defined disorder of hematologic cell function which occurs before the onset of overt malignancy. Study of the natural history of these premalignant syndromes and other proliferative disorders has suggested that there is an intimate relationship between disorders of various cell lines.[1-12]

This report describes a patient with hypogammaglobulinemia, Bence Jones proteinuria, sideroblastic anemia and neutropenia which had been present for three years; then chronic granulocytic leukemia developed. The preleukemic phase was suggestive of myeloma, but the later definitive disorder was in another cell line. The altered function in three cell lines during the preleukemic period indicated that the primary disorder was in a stem cell common to immunoglobulin-producing cells, erythrocytes, and granulocytes. Such naturally occurring syndromes support the concept of a multipotent stem cell, as suggested by studies in experimental animal systems.[13]

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Case report

A 77-year-old white man was admitted to hospital in March, 1964, for treatment of an inguinal hernia. He was otherwise well and physical examination disclosed no other abnormalities; however, the hemoglobin was 11.0 g.%, hematocrit 33%, and reticulocytes 1.3%. (In 1962, when he underwent prostatectomy in the same hospital, his hemoglobin was 14.7 g.% (Fig. 1)).

The blood smear showed marked anisocytosis and poikilocytosis with macrocytes and microcytes. Approximately 85% of the red cells had normal hemoglobin content and the remainder were hypochromic. There was no basophilic stippling. Details of hematologic findings are shown in Table I. A sternal bone-marrow aspirate yielded hypercellular particles and cell trails. It contained 14% neutrophils, 12% metamyelocytes, 5% myelocytes, 1% promyelocytes, 1% myeloblasts, 1% eosinophils, 14% lymphocytes, 5% juvenile forms, 1% monocytes, 9% plasma cells and 37% erythroid forms; the myeloid:erythroid ratio was 1.3:1. The erythroid series was hyperplastic and predominantly macronormoblastic, but nuclear maturation of some erythroblasts was slightly delayed; the myeloid series was hyperplastic but of normal morphology. Findings in an iliac marrow aspirate were similar, with 12% plasma cells. Marrow hemosiderin was increased[14] to 5+, and ringed sideroblasts were numerous. Serum folate measured 4.8 ng. per ml. and the serum vitamin B_{12} was 344 pg. per ml. Total serum protein was 5.4 g./100 ml, and electrophoresis showed 300 mg. gammaglobulin per 100 ml. (Table II, Fig. 2). The urine was positive for Bence Jones protein[15] and 24-hour urinary excretion of total protein was 1450 mg. Electrophoresis of the urine showed 95% of the urinary protein migrated as a sharply defined band in the gamma region (Fig. 3). Roentgenographic skeletal survey revealed no osteoporosis or osteolytic lesions.

During the next 33 months we saw the patient at regular intervals as an outpatient but prescribed no treatment. Findings in the peripheral blood and the levels of serum and urine proteins were unchanged during this period (Table II, Fig. 1) and in a second bone-marrow aspirate taken 20 months after the first.

In January, 1967, when he returned for review, he complained of tiredness and

Table I
Hematologic findings in peripheral blood

	March 1964	Jan. 1967
Hemoglobin (g./100 ml.)	11.0	7.9
Hematocrit (%)	33	33
Reticulocytes (%)	1.3	4.1
Total leukocytes (per c.mm.)	3800	145,000
Neutrophils (%)	26	30
Metamyelocytes (%)	4	30
Myelocytes (%)		12
Promyelocytes (%)		7
Myeloblasts (%)		2
Eosinophils (%)		5
Lymphocytes (%)	66	2

shortness of breath and looked ill and pale. The spleen was now palpable 3 cm., and the liver 1 cm., below the costal margin. The hemoglobin was decreased and reticulocytes had increased (Table I). The red cells varied in size and shape and there were many hypochromic forms. Total leukocytes had increased to 145,000 per c.mm. The leukocyte alkaline phosphatase score was 1 by the Kaplow technique.[16] Short-term marrow culture revealed the Philadelphia chromosome (Ph^1) in each karyotype examined.[17] The bone marrow was markedly hypercellular with an M:E ratio of 7.5:1 and 4+ hemosiderin, and the urine was positive for Bence Jones protein (Table II).

The patient received antileukemia therapy over the next few months and required blood transfusions (Fig. 1). Symptoms were exacerbated in October, 1967, when myeloblasts increased to 30% in the peripheral blood and to 40% in the marrow, and serum gamma globulins decreased further, to 100 mg./100 ml. (Fig. 4). Serum immunoglobulins were: IgG, 330 mg.%; IgA, 20 mg.%; IgM 12 mg.%. The paraprotein in the urine persisted (Fig. 5). There was a temporary response to 6-mercaptopurine, but the patient died in December, 1967. Necropsy revealed leukemic infiltration of the liver, spleen, bone marrow, lymph nodes, and brain.

Discussion

In this patient, the period before the development of overt leukemia was characterized by hypogammaglobulinemia, the excretion of large quantities of Bence Jones proteins (Lγ) in the urine, sideroblastic anemia and neutropenia. This phase, from the time of recognition to the development of overt malignancy, lasted 33 months. The hypogammaglobulinemia, the presence of large quantities of Bence Jones protein in the urine and increased plasma cells in the marrow, suggested that the patient had multiple myeloma: these laboratory features satisfy the myeloma diagnostic criteria of the Myeloma Task Force of the National Cancer Institute for patients who have a para-immunoglobulinopathy.[18] The disturbed function of the plasma cells resulted in decreased synthesis of immunoglobulins G, A and M, and excess light chain in the urine.

In addition to the slight plasmacytosis, the marrow had morphologic abnormalities in the erythroid series, with increased numbers of sideroblasts, many of them ringed, and delay in nuclear chromatin condensation in some erythroid precursors, not due to vitamin-B_{12} or folate deficiency. These morphologic abnormalities were associated with one recognized abnormality of function in the erythroid series — the inability to synthesize normal amounts of intracellular hemoglobin in one population of red cells. These abnormalities in the erythroid series could be related to the myeloma, since sideroblastic anemia has been observed in this disease.[19, 20]

During the period of observation this patient appeared to have a gammopathy with acquired sideroblastic anemia, and neutropenia with granulocytic hyperplasia was present in the marrow. Florid, typical chronic granulocytic leukemia developed subsequently. Thus for at least three years a disorder of the granulocytic cell line coexisted with abnormalities of the erythroid and immunoglobulin-synthesizing cells. Although disturbances in three cell lines could have been present simultaneously during this time, followed by accelerated proliferative capacity of one of the cell lines, it is probable that a stem cell was affected which is common to granulocytes and to immunoglobulin- and hemoglobin-synthesizing cells. The latter interpretation is supported by many "experiments of nature" that indicate coexisting autonomous proliferation of two cell lines, frequently with eventual predominance of one or the evolution of one proliferative cell line into another,[1-12] and experimental observations that apparent single clones contain colony-forming cells for erythroblasts, granulocytes, the thymus and lymph nodes.[13]

It has been apparent for many years that leukemia may be preceded by various hematologic abnormalities; in fact, this progression toward overt malignancy may be sufficiently consistent to warrant calling these

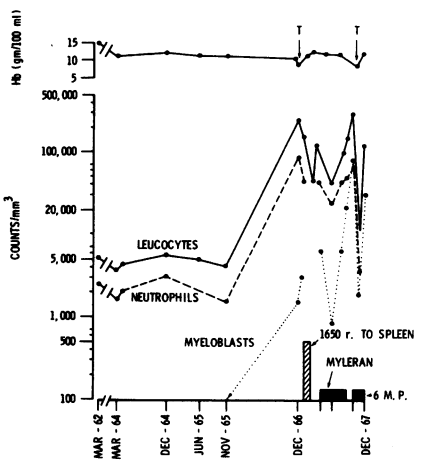

FIG. 1—Hematologic values when the patient was hematologically normal and during the preleukemic and leukemic phases. (T, transfusion; 6 M.P., 6-mercaptopurine.)

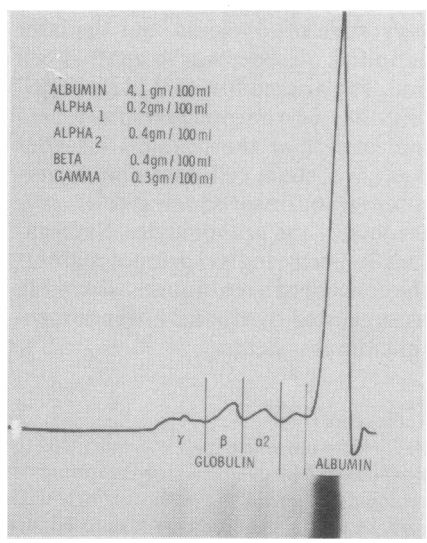

FIG. 2—Initial (1964) paper electrophoresis and densitometer tracing of serum proteins during preleukemic period, showing hypogammaglobulinemia.

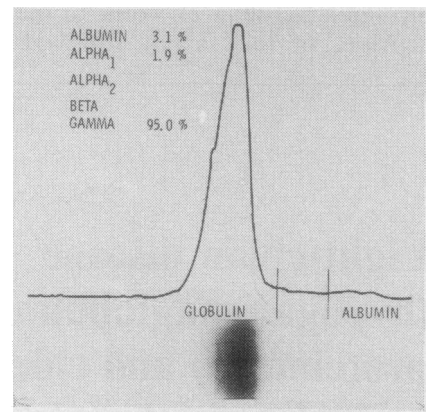

FIG. 3—Paper electrophoresis of urine protein during preleukemic phase, showing a single paraprotein.

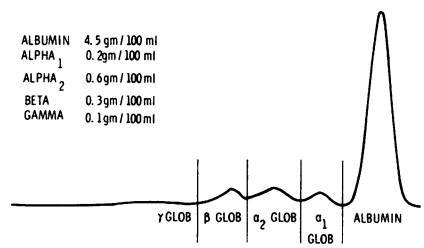

FIG. 4—Cellulose acetate electrophoresis of serum during leukemic phase.

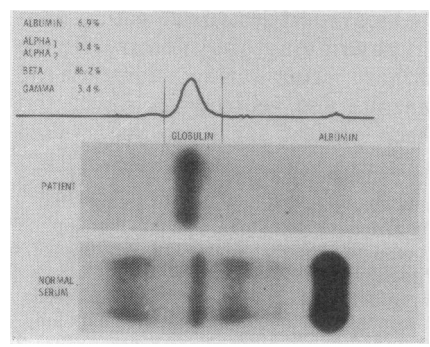

FIG. 5—Cellulose acetate electrophoresis of urine during leukemic phase, showing a homogenous protein.

syndromes preleukemias. Rowley, Blaisdell and Jacobson[21] classified preleukemia into three general categories — aplastic, proliferative, and dysplastic — and suggested that the first two might be termed "potentially malignant" and the third "premalignant". There are several reports of leukemia following aplastic anemia,[9, 21] and it is known that proliferative syndromes such as ^{32}P-treated polycythemia rubra vera, thrombocythemia or myeloma may terminate in leukemia.[10, 22, 23]

The most characteristic pattern of preleukemia is pancytopenia of the peripheral blood and hypercellularity of the marrow.[24-29] When the patient with preleukemia is first seen the most striking abnormality may be in another cell line — for example, erythroid or immunoglobulin-producing cells. Dacie *et al.*[30] described seven cases of "refractory normoblastic anemia": the patients had anemia with low reticulocyte counts, hyperplastic marrow, and abnormal sideroblasts, with neutropenia and thrombocytopenia in some. Similar cases have terminated in overt leukemia.[7, 11] It was reported recently that there is a defect in platelet membranes and granulocytes[31] and in red cells in paroxysmal nocturnal hemoglobinuria and that this disease also may terminate in acute leukemia.[32-34]

Since overt leukemia may develop in patients with a monoclonal gammopathy, the latter may sometimes be classified as a functional dysplastic preleukemic syndrome. Stoop *et al.*[35] described a patient with monoclonal IgG whose urine contained *lambda* light chains and in whom lymphoblastic leukemia ultimately developed. Monoclonal gammopathies have been reported associated with erythremic myelosis[36] and chronic granulocytic leukemia[12, 37, 38] also. Thus, monoclonal gammopathies may be associated with both myeloproliferative and lymphoproliferative disorders. In our patient there was dysplasia of both morphology and function, involving lymphoid, granulocytic, and erythroid cell lines, suggesting that hypogammaglobulinemia and increased urinary light chains, in addition to monoclonal gammopathy and sideroblastic anemia, may indicate the dysplastic preleukemic state.

The nature of preleukemia and of the disturbance that causes dysplasia of cellular function and morphology is unknown. In our patient the disturbance(s) in several cell lines (erythroid, myeloid, and immunoglobulin-producing) were profound by the time overt malignancy could be recognized in one. The search for a "key" metabolic change that may endow a cell with malignant characteristics has resulted in the documentation of several biochemical abnormalities in the malignant cell, including the depression of many enzymes that catalyze the normal catabolism of metabolic substrates. Few biochemical studies have been made of preleukemic cells; however, decreases in glucose-6-phosphatase,[27] heme synthetase[39, 40] and adenosine diphosphate[10] have been reported, and it is thought that the decreased zinc content of marrow cells in preleukemia may reflect decreased enzymes that have zinc as the prosthetic group.[27]

Although knowledge of the preleukemic state might provide valuable insight into the nature of leukemia, the documentation of biochemical changes is not yet sufficient to enable us to trace the evolution of this malignancy. However, Morris and associates[41-42] have developed an improved experimental model — "minimal-deviation tumors" — for studying the initial subtle changes in malignancy, and their findings appear to have some relevance to the preleukemic state. With this model, hepatomas have been induced with chemical carcinogens in rodents: the tumors are highly differentiated and their cells resemble normal liver cells in most respects but have malignant characteristics. The first detectable biochemical change is a failure in feedback inhibition of enzyme activity or in repression of enzyme synthesis, and failure in the induction of enzyme synthesis.[41-44] The biochemical pathways become relatively fixed and do not increase or decrease activity to maintain homeostasis, resulting in an accumulated excess of the products of some reactions and depletion of others without influencing the reaction rates. These metabolic events are assumed to result from changes induced in DNA molecules which code for regulatory proteins. Changes can be induced in DNA by various carcinogens, including viral, radioactive and chemical agents, and one change in DNA (abnormal numbers of chromosomes) has been observed in three of 15 potentially leukemic syndromes.[21] Futhermore, abnormal chromosome morphology is associated with leukemia. However, morphologic changes in chromosomes are gross compared with the postulated changes in individual DNA molecules.

An intriguing question is whether altered DNA is the sole explanation for malignancy, or whether DNA function is further disturbed by the altered cellular metabolism — autocatalyzing, as it were, its own plunge into malignancy. The latter possibility is purely speculative; but if such catalysis did occur, and could be detected at an early stage, it might be amenable to therapeutic intervention. The answer may not be known until changes observed in minimal-deviation tumours can be duplicated at the molecular level in a cell-free system.

Table II
Serum and urine proteins

	1964	1965	1967			
	Apr.	Nov.	Jan.	Apr.	Oct.	Nov.
Serum proteins (g./100 ml.)						
Albumin	4.6	4.5		3.9	4.5	3.8
α Globulin	0.8	0.6		0.7	0.8	0.7
β Globulin	0.6	0.7		0.5	0.3	0.4
γ Globulin	0.4	0.4		0.2	0.1	0.2
Serum immunoglobulins (mg./100 ml.)						
IgG (normal range, 650-1600)			680		330	300
IgA (normal range, 80-400)			31		20	19
IgM (normal range, 60-225)			19		12	14
Total urinary proteins (mg./24 hr.)	1450	1904	935			1163
Urine proteins						
Albumin (%)	3.1	trace				6.9
Globulin (%)	96.9					93.0
Bence Jones	+	+	+	+	+ (not done)	

The clinical findings in our patient provide some evidence of altered metabolic control in the preleukemic phase: the plasma cells synthesized predominantly light chains instead of intact immunoglobulin molecules; erythroid cells could not synthesize normal amounts of intracellular hemoglobin, and defective erythrocytes were released; normal maturation of granulocytes was impaired; and at least one intracellular enzyme was decreased. Frank, clinically recognizable malignancy was merely the last mile on a long road of cellular intrigue and mystery.

We are grateful to the Editorial Service to the Faculty of Medicine for assistance in preparing this paper for publication.

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