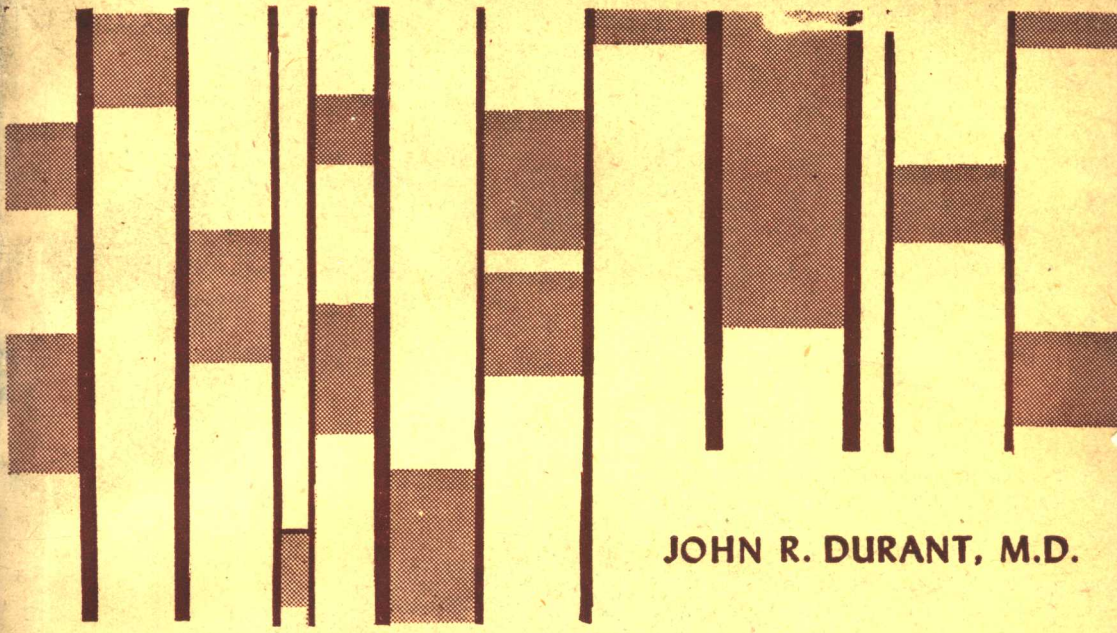

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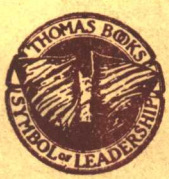
Chemistry, Pathophysiology and Treatment



THE CHRONIC LEUKEMIAS

Chemistry, Pathophysiology, and Treatment

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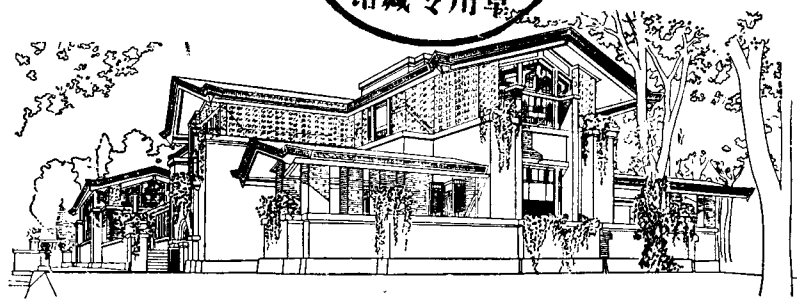

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EDITOR'S FOREWORD

OUR LIVING CHEMISTRY SERIES was conceived by Editor and Publisher to advance the newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspective of human disorders.

Dr. Durant and Dr. Smalley present the newer knowledge of chronic leukemia, the malignant neoplasms of the blood-forming organs, characterized by disorderly, purposeless proliferation of hemic cells with an overabundance of one type of white blood cell. Chronic myelocytic leukemia tends to be fairly homogeneous but chronic lymphocytic leukemia less homogeneous in the natural course of the disease, pattern of development, and rate of progress. Chronic from chronos for time implies no heightened expectations of longevity but leukemic manifestations with characteristic blood and marrow pictures. All signs and symptoms are directly attributable to the uncontrolled cellular proliferation that is little different from normal mature

granulocytes and lymphocytes in their growth and morphologic features, even though leukemic cells live to divide while normal cells are expendable. The slow rate of cell division and the gradual accumulation of an excessive body-burden of cells are apparently due to a defective system for removing them from circulation rather than to any overproduction.

Diagnosis of chronic leukemia is often easy, often difficult, often impossible but always a pathologist's diagnosis for the clinician's diagnosis is inferential embodying the doctor's total conception of the relationship between the patient as a person, the leukemia as a part of the patient, and the patient as a part of his world. The scientific clinician attacks the core of the problem to avoid being mousetrapped by tangential data. When the laboratory reports conflict with clinical judgment, the tests should be repeated before the clinical appraisal is discarded. The cells of chronic leukemia are so close to normal cells in biochemical characteristics that selective chemical eradication of the leukemic population is difficult. Effective elimination of chronic leukemia requires prevention of mutagenic events which produce leukemic cells and development of means for long-term repression of leukemic cell division, and/or outright destruction of these neoplastic cells in their sites of sequestration without excessive damage to vital normal cells. It requires considerable time to determine the virtues of a new form of chemotherapy and still longer to ascertain the harmful effects.

Complete remission is seldom induced in chronic lymphatic leukemia, and intensive chemotherapy cannot produce the dramatic results obtained in acute leukemia. Treatment during the course of the disease is doubtful except for specific indication such as anemia, thrombocytopenia, leukopenia secondary to gradual replacement of normal hematopoietic tissue; accumulation of toxic end products especially uric acid from breakdown of cells or other intercurrent disease. All treatment must be objective in the light of superimposed iatrogenic diseases which alter the clinical picture, pathology, and course. Indeed, postmortem findings may reveal none of the classical pathologic features for there may be bacteremias by organisms not usually pathogenic, fungemias by innocuous inhabitants of the skin,

marrow hypoplasia with fatal hemorrhages. It is getting more and more difficult to ascertain the nature of the edifice that has burnt down from a study of the ashes.

The problems of leukemia are always the same but the solutions differ with each era. Even the concept of leukemia varies with each discipline, a definition based on morphological features would not satisfy a geneticist, biochemist, biologist or clinician. We are dealing with a group of fatal diseases characterized by the accumulation of immature leukocytes, with paucity of platelets and rapid destruction of erythrocytes. The initiating, sustaining, compensatory mechanisms that are involved demand that the concept of the chronic leukemia in the future be on a broader basis rather than on one specific element. The authors unravel a host of fascinating problems, the solutions of which are necessary to clarify the nature of the neoplastic process. The try's the thing. Even if the endeavor does not lead to control of leukemia, it brings us nearer to the goal. Certainly, the logarithmic proliferation of current advances points the way to partial solutions; progress is slow, terribly slow, but nevertheless substantial in extending survival through improved treatment.

"It is not the talents we possess so much
As the use we make of them
That counts in the progress of medicine."

I. NEWTON KUGELMASS, M.D., PH.D., SCD., *Editor*

FOREWORD

THE LEUKEMIA-LYMPHOMA complex is an important neoplastic disease group that man shares with many animals, including chickens, mice, rats, cats, dogs, and cattle. In animal models, an RNA-type viral particle is assuming an increasingly pivotal role. In clinical studies, perforce limited to overt manifestations of the diseases, there has been emphasis upon the multifaceted pathophysiological manifestations. Eventually, the area between will be filled in by research defining key events in the reactions that will allow termination or reversal of the processes.

John R. Durant and Richard V. Smalley in this monograph have gathered and evaluated much of the complicated, diverse literature on the pathophysiology of chronic lymphocytic and granulocytic leukemia. The conviction of clinical medicine is that understanding of pathophysiologic features allows better management of the patient. This conviction is well supported by the increasingly rewarding, albeit still palliative, treatment available for patients with leukemia.

This monograph is a ready reference to much current clinical work on leukemia, by authors with wide experience in the clinic as well as in the laboratory. It will be useful to physicians confronted with the problems of supporting patients with leukemia. At the same time, the presentation includes numerous suggestions for further clinical tests and observations. As such, it should interest all practicing internists, as well as more academic students and their instructors.

One of the rewards and pleasures of the passage of years is to see younger colleagues grow to full stature and assume positions that their potentials once only promised. It is my pleasure to see Dr. John R. Durant and Dr. Richard V. Smalley fulfill the promise of their rich potential, inherited and developed.

MICHAEL SHIMKIN

PREFACE

THIS SHORT MONOGRAPH on the two commonest forms of chronic leukemia is intended primarily for the practicing internist or generalist who desires to understand the abnormalities in pathophysiology which they will encounter in their patients with these diseases. It is hoped that they will, thereby, be better able to use the clinical and hematologic laboratories to help them in diagnosis and treatment. It is intended to provide a basis for understanding what highly trained and sophisticated hematologic consultants are talking about when various procedures (diagnostic, therapeutic, and experimental) are recommended. It also is intended to raise questions for the reader so that he will recognize that we treat this disease more on the basis of prejudice than on the basis of scientific data. The authors therefore suffer from the same disease of prejudice as others in their consideration of what constitutes therapy and its value.

We did not intend this monograph to be encyclopedic in its scope or bibliography, nor did we intend it to provide a critical evaluation of much of the latest information regarding nuances which interest the academician. Some of this sort of material is alluded to but only in the hope that it will aid understanding, especially about what is not known.

Finally, for those who are concerned with the rare and the curious, no mention is made of such unusual disorders as chronic monocytic leukemia, if indeed there is such a disease, or to other rare forms of possibly chronic leukemia, such as mastocytosis. For information regarding these questions, the reader is referred to well-known texts of hematology.

CONTENTS

THE CHRONIC LEUKEMIAS

PART I

CHRONIC LYMPHATIC LEUKEMIA

JOHN R. DURANT

Chapter 1

INTRODUCTION

In order to understand the clinical findings, pathogenesis, and treatment of chronic lymphatic leukemia it is necessary first to review normal immunologic defense mechanisms as well as the characteristics of the normal lymphocyte and its leukemic counterpart. This is so because abnormalities in the function of the lymphocyte, as seen in chronic lymphatic leukemia, are often measured in terms of disturbances in immunologic capacity which are due to the abnormal lymphocyte. Appropriate treatment of this disease depends upon the interpretation placed upon the meaning of these abnormalities. Unfortunately, a unifying concept to explain all facets of the disorder is not yet available.

IMMUNOLOGIC DEFENSE MECHANISMS

In general it may be said that there are two types of defense mechanisms. The first of these is the humoral one, mediated by circulating antibody. It has been of diagnostic and investigative use for many years. Recently more has been learned about the structure and function of the antibody molecule, greatly increasing the understanding of the nature of this system. In addition, much has been learned about the cellular and subcellular changes which accompany activity in the humoral antibody system. The other immunologic defense mechanism is that of delayed reactive hypersensitivity (DRH), traditionally measured by skin testing with antigens such as tuberculin. As with circulating antibody, there has been remarkable progress in elucidating the functioning of this system. The lymphocyte participates in both of these types of response. Whether the same lymphocyte can take part in only one or in both of these is not yet clear. Furthermore, there are those who contend that cell-bound immunity (DRH)

is merely humoral antibody so tightly bound to cells that it cannot be eluted.[1] It will become evident that the facts concerning chronic lymphatic leukemia and its immunologic abnormalities do not help to provide, at this moment, an answer to this problem.

Attempts at understanding the function of the lymphocyte now often center around various manipulations which interfere in one or both of the above systems. When changes are obtained, attempts have been made to correlate the changes in immunologic capacity with histologic changes observed in lymphoid organs. The results of these studies, both artificially contrived in the laboratory and noted as experiments of nature, have been exceedingly illuminating. They have not, however, settled the issue of whether there is one multipotential lymphocyte or a number of populations of lymphocytes with limited capabilities. What is clear, however, is that an understanding of these problems will greatly facilitate the clinician's understanding of the nature of a variety of lymphoproliferative diseases, including chronic lymphatic leukemia.

The clinician is well aware of the means of studying antibody responsiveness. For many years he has employed a rise in the titer of circulating antibody as a criterion of recent infection. More recently he has used a measurable antibody response to immunization as a measure of a competent immunologic mechanism in patients suspected of being deficient in immunoglobulin synthesis. On the other hand, the clinician's ability to study DRH has been limited by a paucity of good methods applicable to this problem. As noted, he has used the tuberculin test as an indication of past or present contact with *Mycobacterium tuberculosis,* but a positive skin test does not indicate whether or not active infection is present. Furthermore, the absence of such a response may indicate either that no infection has ever occurred or that the individual's ability to recognize the organism as foreign is deficient. Since many patients now have never had actual contact with *M. tuberculosis,* this test cannot be relied upon as an adequate screen for competency in the system of DRH. A single antigen to which everyone has been exposed and should be reactive against is not known for this system.

Many house officers are accustomed to overcoming this problem with a battery of skin tests. In the past those for histoplasmosis, coccidioidomycosis, and blastomycosis were often employed for this purpose. Unfortunately, true contact with these is, except for certain geographic areas, less likely than with tuberculosis. Thus, this battery of skin tests often fails to give a true picture of the ability to generate a delayed type of response. More recently other antigens have been employed more successfully. Mumps is a very common self-limited disease with which most people have had contact and to which a delayed type of skin response develops. Results of this skin test cannot be totally relied upon, however, because as many as 20 percent of those with a positive clinical history and an antibody titer against mumps have a negative skin test.[2] *Candida albicans* is almost universally a part of the environment. It too produces skin responses of the delayed type and has recently come into common use as one of the screening antigens for DRH. As a matter of fact, a battery of skin tests now employed as a screening procedure includes tuberculin, mumps, and *Candida*. As a first line of diagnostic effort, this is probably quite satisfactory, for most people can be expected, if normal, to respond to at least one of these. Nevertheless, although a negative response to all of these very likely means anergy, a loss of DRH, it is not conclusive. More precise methods have been developed to help solve this problem.

It is possible to attempt to induce a positive skin test of the delayed type by inoculation of various substances into previously unsensitized subjects. This offers the advantage of testing responsiveness at the moment to a new antigen. There are a number of chemicals available for this purpose. One of the most popular is 2,4-dinitrochlorobenzene. Another is picryl chloride.[3] Keyhole limpet hemocyanin[4] has also been used and is of particular value because an antibody response to this substance also occurs. Patients to be tested to one of these substances are usually given a control skin test in order to prove initial nonresponsiveness. After such is determined, the chemical is introduced intracutaneously, and the patient is skin tested again after about six weeks. Should sensitization fail to occur, it is necessary to repeat

the inoculation several more times in order to be certain of the patient's inability to respond. BCG vaccination can also be used for this purpose, although there may be some who have reservations about exposing potential immunologic cripples to a live agent even as innocuous as BCG. This method of skin testing, regardless of the antigen employed, requires the cooperation of the patient, is difficult to quantitate, and if the antigen is not carefully selected, runs the potential risk of creating sensitivity to a substance which might at some remote time be unknowingly encountered with disastrous results.

DRH can also be assessed *in vivo* by means of a test of homograft rejection. Most individuals will accept for a period of about two weeks a skin graft, for instance, from a donor with whom they have not had previous antigenic contact. The graft will then be rejected, sloughing off with a characteristic histologic reaction of round-cell infiltration followed by necrosis in the graft and the appearance of large pyroninophilic cells in the regional lymph nodes draining the area of the graft. A second graft from the same donor will evoke a similar reaction which will occur more quickly and violently and which is known as the second-set reaction. This type of response has been shown to depend upon the same factors as the tuberculin test and is apparently little influenced by the presence of circulating antibody.[5] For the purposes of testing immunologic capacity this method again offers the disadvantages of requiring considerable time and the cooperation of the patient and a donor. An *in vitro* assessment of this function would be a distinct advance.

Recently two methods which may help to solve the problem have been developed and are currently being widely investigated and employed. The first of these depends upon the transformation of lymphocytes grown in tissue culture into immature forms. This phenomenon will occur when the cells in question encounter certain chemicals or an antigen to which they are sensitive. The development of this method is of considerable interest. In 1960, Dr. Peter Nowell of the University of Pennsylvania noted that phytohemagglutinin was a strong mitogenic agent and could induce apparently resting lymphocytes to undergo a series of morphologic changes followed by mitosis[6] (see Fig. I-1). This