LEUKEMIA

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Preface

LEUKEMIA, like cancer and poliomyelitis, has been classed as one of the "dread diseases." Without doubt, it represents the most important single problem in hematology. In the United States alone it kills at least 10,000 annually, many of them bright, active children or intelligent men and women in their prime of life. Most statistics indicate that the disease is on the increase, particularly in the last three decades of life. Whether or not this is actually true or due simply to more case studies and better recognition, there can be no question regarding the seriousness of the problem and the necessity to cope with it by all available means.

There have been many thousands of articles written about leukemia but the paucity of books on the subject is amazing. Forkner's text of 1938 was encyclopedic in its scope and for many years remained almost the only central source. The enormous resurgence of interest in the disease, brought about in large measure by the possibility of achieving at least temporarily beneficial results with various chemicals, has led to a quest for more precise knowledge of the disease: its character, the nature of the leukemic cell, the pathophysiology of such features as the anemia, hyperuricemia, the hemorrhagic state, etc. Etiologic factors, previously unknown, have come to the surface, and today there is great talk of the viruses and much statistical evidence for the leukemogenic effects of ionizing radiation. The empirical nature of most of our therapy, even that with the newer antimetabolic and cytotoxic agents, and its eventually unsatisfactory characteristics, have naturally led to an increasing inquiry into the more fundamental aspects of cellular growth and proliferation.

What is leukemia? Is it a reactive disturbance, or is it neoplastic? Does it represent a cellular reaction to an infectious or other agent, or does a harmful mutation take place, leading to an abnormal type of unusually rapid leukocyte proliferation? The leukemic cell seems to have some rather characteristic features as we examine it, but when one tries to analyze it feature by feature, chemical by chemical, the apparent differences between normal and leukemic cells become less and less pronounced. Perhaps this is why, in treating leukemia, we are always limited by what the chemical or other agent does to the *normal* cells; the action upon both leukemic and normal cells is so much alike.

This work on leukemia is limited almost entirely to a consideration of *human* leukemia. Not that mouse leukemia and fowl leukemia are not important; they are of utmost importance, particularly from the investigational aspect. We present in this monograph a rather personal account, not only of our own interests in this field but of what we think the practitioner (internist, pediatrician, pathologist and clinical pathologist) may be interested in. The work is by no means encyclopedic nor is it a textbook, although sometimes, as in the clinical descriptions, it must partake of some of the features of the latter. There is probably more emphasis on certain aspects than on others, again an indication of our special fields of interest: etiologic agents, the myeloproliferative syndromes, therapy. Nevertheless, we believe that there is presented in these pages a fairly comprehensive picture of the present state of our knowledge (some might say

"ignorance") of leukemia. We realize full well that this is but an interim report and that perhaps in a short time, whether it be a year or a decade, a revolution in understanding and control of the disease may well take place. Actually, the fact that one has a difficult time in defining leukemia may in itself be somewhat hopeful. Since there is no complete certainty that the condition is malignant, nor even what "malignancy" is, it is altogether possible that leukemia may eventually turn out to be a deficiency state or an immunologic reaction or a response to an infectious agent. Again, what we learn from leukemia, with its readily available blood and tissue cells, should certainly be of considerable value in the understanding of neoplastic disease in general.

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William Dameshek
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Contents

I. Leukemia in the Past

LEUKEMIA, since its recognition as a distinctive disease, has had a history of little more than 100 years, and it is therefore a comparative newcomer among the major known scourges of humanity. It was first described almost simultaneously by two brilliant young men who, after applying their great gifts to a meticulous exploration of its features in the living and the dead, engaged at once in an almost venomous wrangle over the honor of having been the first to identify this fatal disease. Progress in the knowledge of leukemia has been fitful since these beginnings. It should be realized that at the time of its discovery very little was known about the composition, the origins and the functions of normal blood, nor were there any good methods available for investigating them. Each step forward had therefore to be preceded by an exploration of the normal. Where this lagged, speculation usurped the place of research and theory that of fact. Much of the literature of the first hundred years echoes with the clash of controversy which, lacking a basis of substantial facts, could only be dialectic and unproductive. It is regrettable but true that even today we do not possess the answers to many of the fundamental questions about the mechanism of normal hematopoiesis or the regulation of the blood elements. This fact largely explains our continuing ignorance of the causes of leukemia and of the means of subjugating it.

It seems likely that the first accurate description of a case of leukemia was given in 1827 by Velpeau.[37] His patient, a 63 year old florist and seller of lemonade, "who had abandoned himself to the abuse of spirituous liquor and of women without, however, becoming syphilitic," fell ill in 1825 with a pronounced swelling of the abdomen, fever and weakness, and symptoms caused by urinary stones. He died soon after admission to hospital and at autopsy was found to have an enormous liver and spleen, the latter weighing ten pounds. The blood was thick, "like gruel, . . . resembling in consistency and color the yeast of red wine . . . . One might have asked if it were not rather laudable pus, mixed with blackish coloring matter, than blood." It was in fact the peculiar character of the blood, as seen post-mortem, which first attracted the attention of all the early observers of leukemia. Thus Barth,[2] in 1839, was so interested in the autopsy findings in one of his patients that he submitted the blood to microscopic examination. This was carried out by Donné, who reported that more than half of the blood consisted of "mucous globules" which could not be distinguished from pus corpuscles. It appears that Donné[10] was the first to examine the blood of another leukemic patient during life; it was so full of colorless corpuscles that at first he thought it was pus.

In spite of these and other early observations, leukemia was not recognized as a definite entity until its description in 1845 by Bennett[4] in Scotland and by Virchow[38] in Germany. The independent publication, within one month of each other, of two cases of the same new disease, was less remarkable than the fact that each observation came from the pen of a man who was to become a leader in his own field, Bennett in physiology and Virchow in pathology. In each of the two cases it was the post-mortem appearance of the blood which first gave the

hint that an unusual condition was present. In Virchow's patient the blood vessels contained a "yellowish-white almost greenish mass." Microscopically it consisted "besides very few red blood corpuscles . . . . of the same colorless or white bodies which also occur in normal blood, namely small, not quite regular protein molecules, larger, granular, fat containing, non-nucleated corpuscles and granular cells with one rounded, horseshoe-shaped or trefoil-like or several hollowed-out distinct nuclei." The relation between red and colorless corpuscles was about the reverse of the normal one, so that Virchow coined the term "White Blood" (*Weisses Blut*) to describe the condition. The spleen weighed 7 lbs. 12 oz. in Bennett's case and measured nearly a foot in length in Virchow's patient. Thus, while the findings were similar, the two authors interpreted them in a different fashion: Bennett as "suppuration of the blood," Virchow, much more cautiously, as probably not "pyemic". A few months later[39] (August 1846), having reconsidered not only his own case but also those published by Bennett,[4] Craigie,[8] and Fuller,[18] Virchow took a much more definite attitude against the pyemic theory of leukemia, pointing out that there was no evidence of local suppuration which could have spread to the blood, that "pus" corpuscles were identical with the colorless bodies normally occurring in the blood, and that in leukemia (still called "White Blood") there was merely an increase in the normal number of these latter cells. Such an increase was also shown by Fuller[18] who examined the blood three times during life in his patient and found on each occasion, "in addition to the natural blood-corpuscles, a very large proportion of abnormal, granular, colorless globules." (Craigie[8] observed his case several years before those of Bennett and Virchow but did not realize its significance until he watched Bennett's autopsy of his own first patient. Both Craigie and Bennett thereupon reported their cases as instances of the same disease in the same number of the *Edinburgh Medical and Surgical Journal*. Fuller was apparently not cognizant of Bennett's and Virchow's papers when he presented his case at a meeting of the London Medico-Chirurgical Society in June 1846.)

Following these early publications further cases were reported in rapid succession both by the two chief protagonists of the new disorder and by lesser figures, so that by 1852 Bennett could publish a monograph on "Leucocythaemia"[5] in which he described 37 cases which were by then known. Of these 17 had been diagnosed during life by means of blood examinations, and at least one had been followed for eighteen months, during which time the colorless corpuscles had been constantly increased. Meanwhile Virchow introduced the term "Leukemia" in 1847[40] and published a series of brilliant studies on the nature of the disease, which he summarized in 1856[41] in a paper of great interest and importance.

Virchow started by asserting that the colorless corpuscles are always present in normal blood and are increased after digestion, in pregnancy, and in most inflammatory conditions. Such an increase is not by itself a disease and must be distinguished from leukemia which is a definite pathologic state characterized not only by an increase in colorless corpuscles but also by a decrease in the number of red cells and dependent on changes in certain organs. There are in fact two kinds of leukemia, the first—"splenic" or "lienal"—associated with a

swelling of the spleen, the second—"lymphatic"—with tumefaction of the lymph nodes and the presence in the blood of colorless corpuscles resembling those which are ordinarily seen in the lymph nodes. Moreover, the changes in the organs precede those in the blood, for there are cases in which enlargement of lymph nodes or spleen may be found months or years before changes develop in the blood. Pathologically, the lesions in both spleen and nodes are a hyperplasia of normal elements, and both the liver and kidney may be infiltrated with the cells present in the blood, although such foci are probably formed locally rather than from cells which have wandered out of the blood stream. Virchow did not know the reason for these changes which he thought were not inflammatory, although they might be accompanied by inflammatory lesions of the skin or mucous membranes; the latter were however likely to be a consequence rather than the cause of the blood and visceral changes.

This paper contains in a rudimentary form many of the views on the pathology of leukemia which are still held today. It is all the more remarkable as there was extremely little knowledge at the time it was written concerning the sites and mechanisms of hematopoiesis, and the functions and fate of the blood cells. The general view on the origin of the red blood cell was still that put forward by Hewson in the eighteenth century: that is that red cells are formed from the colorless corpuscles in the blood itself. Thus Bennett (1852)[5] suggested that the red cell was the "liberated nucleus of the colorless cell." Colorless corpuscles were thought to be formed in the "lymphatic glands," including the spleen, thymus, thyroid, suprarenals and pineal body, whence they entered the blood. They were probably produced "in an organic fluid, by the production of molecules, the successive development and aggregation of which constitute the higher formations." Later the blood corpuscles are dissolved in the liquor sanguinis and "with the effete matter absorbed from the tissues constitute the blood fibrin." Virchow himself, like many others, had at first accepted the transformation of colorless into colored corpuscles in the circulating blood, and had explained leukemia as a retardation in this process, with the production of increased numbers of white and of decreased quantities of red cells. By 1856,[42] however, he had abandoned this view and now regarded the white corpuscles as "simple, non-specific cells" which are not transformed into red corpuscles once they have left the sites at which they themselves are produced; they are rather "a relatively superfluous part of the blood, a sort of superfluous excess." The transformation of lymph corpuscles into red cells does however take place in the spleen and lymph nodes; but once they have reached the blood stream "their specific metamorphosis into colored corpuscles becomes impossible." They circulate for a brief while and then perish.

We may summarize this first phase of research on leukemia by saying that within twelve years of its recognition, the two chief varieties of chronic leukemia, as well as the acute form (Friedreich, 1857)[17] had been described, and the main clinical and pathologic features tabulated. Owing to the exceedingly crude hematologic methods then available it was possible to make only the most superficial examination of the leukocytes themselves, and though it was realized that there was more than one variety of these cells, they could not be characterized morphologically or traced back to the sites of their formation.

It had however been acknowledged even by those who, like Bennett, had originally regarded leukemia as the result of a special kind of inflammation, that the changes in the blood were not caused by an admixture of pus, but probably by a proliferation of those white corpuscles which are a normal constituent of the blood. The primary changes in the disease were now sought in the "lymphatic organs" rather than in the blood itself.

It is a significant sidelight on human vanity that in the face of the overwhelming evidence which pointed to leukemia as a distinct and in many ways remarkable disease, there were still loud voices which denied its very existence. At a discussion held in Paris in 1855, one physician (Cahen)[6] exclaimed: "Leukemia has no special causes, special symptoms, particular anatomic lesions or specific treatment, and I thus conclude that it does not exist as a distinct malady," while another (Barthez)[3] added: "There are enough diseases without inventing any new ones."

The thirty years which followed the publication of Virchow's great paper brought little significant progress. They were a time of consolidation of existing knowledge, although one notable addition to it was Neumann's[24] demonstration that the bone marrow was an important site for the formation of blood corpuscles in health and disease. His studies originated from the observation (1870) of abnormal marrow appearances at the autopsy of a man who had died from obvious "splenic" leukemia. The marrow was not red like that of normal people but "dirty yellow-greenish" like pus. Neumann thought that such changes might well be common in leukemia, and that they had probably not been previously described because nobody had looked for them. He surmised that there might in fact be a "myelogenous" leukemia, in addition to the splenic and lymphatic forms, and proceeded to prove this suspicion in a number of publications which he summarized in an extensive article, in 1878.[25] He was by then certain that the marrow normally formed colorless corpuscles and delivered them to the blood. Whether such corpuslces were transformed into colored ones, as had been generally assumed, appeared rather doubtful to Neumann, for he could show that the immediate precursors of the red cells were nucleated red cells which he found regularly in the marrow, and sometimes also in leukemic blood. If a transformation of white to red cells did occur, he reasoned, leukemia could be caused either by an overproduction of the former, or by a failure of their transformation to the latter; but if red cells were formed independently of the white ones, then there must also be a disturbance in their production in the marrow in order to account for their diminution in leukemic blood.

Gowers (1879),[19] in a masterly monograph on leukemia, took this argument a step further by pointing out that the anemia in leukemia might theoretically be caused either by a diminished formation of red cells, or by their excessive destruction. He inclined to the view that the former mechanism was the main cause, although increased destruction might also play a part. It is of interest that this fundamental question has even now not been finally solved (cf Chapter IX).

Although Gowers accepted Neumann's views on the role of the marrow in normal and leukemic hematopoiesis, he still regarded it as less important than that of the spleen and the lymph nodes, and subdivided leukemia into "splenic

leukocythaemia" and "lymphadenosis." Very significantly he equated the latter term with "Hodgkin's disease" and thus foreshadowed an era of prolonged confusion about the diseases of the lymphatic tissues and their interrelations. Gowers believed that the increase in the number of white cells which occurred in "splenic" leukemia was only a symptom accompanying the primary changes in the blood-forming organs, and that it need not be present before the diagnosis of leukemia could be established. He thus anticipated the much later recognition of the subleukemic or aleukemic forms of leukemia which could only follow after new methods had permitted a separation of the various types of normal and abnormal leukocytes.

We now enter upon a period of uncertain groping for new truths during which time efforts were made to define especially the features of the acute leukemias, and the position of all leukemias in the wider field of those diseases which affect the hematopoietic organs. Into this period, which extended well into the twentieth century, falls Ehrlich's discovery of staining methods which, for the first time, made it possible to see the cellular details of the various forms of leukocytes and to describe accurately the cytologic features of the leukemias. It required considerable time, however, before the new techniques could be assessed and assimilated and before it was feasible to trace securely the connections between the many different cell forms whose bewildering array now stood revealed. In the meantime Ehrlich's stains probably added to rather than relieved the difficulties of classifying the leukemias.

During the late nineteenth and the early twentieth centuries hematologists conjured with a host of new terms like pseudoleukemia, leukosarcoma, chloroma, lymphosarcoma, myelosis, myeloma, and various combinations. Many of these were ill defined at the time of their first appearance, and definitions had to be altered in the light of accumulating clinical or pathologic experience, generally under the pressure of attacks by rival schools of physicians. Presently the same term would be used in a variety of different ways by its proponents as well as its antagonists, until it might eventually become attached to conditions far removed from those to which it was originally intended to apply. Only a very brief account of this disturbed period need be given here, and even this would be unnecessary but for the facts that faint echoes of these old battles are still heard today, and some of the terms have survived to give useful descriptions of more precisely defined hematologic conditions.

A characteristic example of the metamorphosis and eventual disappearance of a hematologic neologism is "pseudoleukemia," which still appeared in official classifications of leukemia as late as 1938, although it had long since been discarded by serious students of the subject. This term was first used by Cohnheim[7] in 1865 to describe a disease which, to judge by its account, was undoubtedly an example of acute leukemia. The patient, who died four months after the onset of his illness, showed all the clinical and pathologic features of a rapidly progressive leukemia, but neither during life nor at autopsy was it possible to show an increase in the number of the white blood corpuscles. It should be realized that at the time no actual blood counts could be made, and that only the relative proportions of red and white cells could be approximately determined, without attempts at "differential" counting. Hence "pseudoleukemia" in effect de-

scribed any condition associated with splenomegaly or lymphadenopathy in which there was no gross increase in the number of the leukocytes, and which could not be otherwise diagnosed. The term was obviously a convenient one, and there is no doubt that many cases of tuberculosis and other infections, as well as Hodgkin's disease, neoplasms and non-leukemic hematologic abnormalities were at one time or another included in the group of "pseudoleukemias." Following the introduction of staining methods attempts were made to define the condition more narrowly, a "relative" lymphocytosis becoming now an additional requirement (Pinkus).[27] By 1912 doubts about the existence of pseudoleukemia as a separate entity had grown so pronounced that even those who defended the usefulness of the term (Fraenkel;[16] Sternberg[33]) appeared to be uncertain about the sense in which it was to be used. It was finally buried in 1918 by Symmers[35] who demanded that it "be discarded as a misleading and inappropriate designation" and suggested "that the lesion so named should be included among the lymphosarcomas;" a classification which would certainly be entirely inappropriate for Cohnheim's original case.

Of much greater importance than pseudoleukemia was the problem of the lymphosarcomas and their relation to leukemia. The name lymphosarcoma was first used by Kundrat[22] in 1893 for a primary affection of the lymph nodes or mucous membranes which sooner or later spread to neighboring structures in the fashion of some malignant diseases and, starting from one part of the lymphatic system, progressed by gradual stages to involve succeeding groups of lymph nodes. Kundrat thought it possible to distinguish this disease from leukemia by virtue of its greater local invasiveness, much less widespread generalized manifestations and absence of a leukemic blood picture. He believed that it was not a cancer and advanced chiefly, if not entirely, by lymphatic rather than by hematogenous channels.

The term lymphosarcoma as used by Kundrat soon became accepted as denoting the nodular and usually rapidly fatal affections of the lymph nodes, either regional or generalized, which occurred in the absence of a leukemic blood picture. It was not long, however, before Türk[36] recognized that there were close connections between lymphosarcoma and leukemia, for many leukemias had little if any increase in the normal number of lymphocytes in the blood, and the clinical features of both conditions were very similar. In a remarkably farsighted paper (1903) Türk[36] grouped together the lymphatic leukemias, both chronic and acute, and the lymphosarcomata in one system of "lymphomatoses," stating that this included benign (chronic lymphocytic leukemia), acute—either benign or malignant—(acute leukemia, chloroma), and chronic malignant (lymphosarcoma) forms, which differed from each other in only two ways: by the degree of proliferative activity and local invasiveness of the lymphoid cells; and by the presence or absence of blood invasion. Moreover there might be transitions between the various "lymphomatoses," though Türk thought that these were rare. Symmers,[35] some years later, went one step further by actually including lymphocytic leukemia among the lymphosarcomata.

It is obvious that Türk's classification of the "lymphomatoses," though differing from present-day views in some details, is fundamentally in harmony with all that is now known of the interrelationship of the various diseases of

the lymphatic system. It is all the more regrettable that his important theory became almost at once overshadowed by Sternberg's promotion of a new concept of what he called "leukosarcoma." Because in this monograph we are using this term as a generic one for leukocytic neoplasms, and in a sense that is quite different from Sternberg's and that of others, the development of the term is discussed rather fully here.

Sternberg (1904,[31] 1905[32]) separated cases of "lymphatic leukemia" into two groups: The first showed the usual leukemic features and an infiltration with small lymphocytes of all those organs which normally contained lymphocytes; the second, which he termed "leukosarcoma," also presented lesions of organs which were ordinarily free of lymphocytes. Many of the lesions were "tumorous," and showed large and often atypical lymphocytes, both in the tumors and in the blood. The most characteristic of such lesions, according to Sternberg, were mediastinal and arose either from the thymus or the mediastinal lymph nodes, spreading among the great vessels and sometimes enveloping the heart. Blood changes were always present but tended to be minimal, i.e., seen only with careful study of a well-prepared and stained blood smear. In the second of his first two papers on the subject,[32] Sternberg discussed the relation of chloroma to the new syndrome, realizing that the two conditions might produce very similar appearances. He solved the problem by renaming chloroma as "chloromyelosarcoma," inventing a corresponding "chlorolymphosarcoma" and including both among his "leukosarcomata."

The definition of Sternberg's new disease clearly cut across the lines of that of several of the leukemias, as well as of Kundrat's lymphosarcoma. His first group of cases certainly included some of acute granulocytic leukemia, as he later acknowledged (1916).[34] It was in fact questionable from the first if the condition "leukosarcoma" could actually be distinguished from either the leukemias or the lymphosarcomas, and such authors as Naegeli[13] and von Domarus[9] maintained very soon that this was merely a special type of leukemia. It was left to Sternberg's supporters like Paltauf[26] to attempt a more precise definition of "leukosarcoma" and especially its separation from acute leukemia. In spite of their efforts, the term began soon to assume a meaning practically synonymous with lymphosarcoma, and to be applied especially to cases with pronounced mediastinal involvement (Weber;[43] Weber and Wolf[44]). The distinction from lymphocytic leukemia became gradually less and less clearcut, so much so that Flashman and Leopold[14] in 1929 were able to return once more to a classification which was practically identical with that advanced by Türk more than 25 years earlier. These authors suggested a hierarchy of "lymphoid hyperplasias" extending from the most benign group of chronic lymphocytic leukemias to the most malignant lymphosarcomata, via an intermediate group of "leukosarcomata" which they considered as more or less localized primary and invasive lymphoid tumors accompanied by a leukemic blood picture. More recently, the term "leukosarcoma" became increasingly vague, used by some authors (Isaacs)[21a] synonymously with "lymphosarcoma" to designate certain cases of leukemia or lymphosarcoma in which the peripheral blood showed large, atypical, and definitely abnormal primitive lymphocytes, usually with indented or peculiarly shaped nuclei.