Special Article

Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

By William Dameshek

Of the various forms of leukemia, the chronic lymphocytic variety is, in many ways, of unusual interest. This is due not only to its considerable clinical diversity, but also to the frequent presence of abnormal immune manifestations, including both immunologic incompetence and autoimmune disorders. Since the lymphocyte may be called the "central" immunocyte, the manifestations of disturbed immunity are not unexpected; in fact, we have classified chronic lymphocytic leukemia as one of the "immunoproliferative disorders." As the disease progresses and the numbers of lymphocytes become enormously increased, both in the blood and the tissues, the various indications of both immunologic incompetence and of autoimmunity become more marked. Evidence has already been forthcoming that the small, "mature"-looking lymphocytes of the disease show indications of decreased functional capacity in vitro. The distinct possibility is therefore present that the indications of immunologic incompetence are due to the accumulation of immunologically incompetent lymphocytes.

Paradoxically, and of equal interest, are the many diverse manifestations of autoimmunity found in the disease, including hemolytic anemia, thrombocytopenic purpura, the Sjögren syndrome, and cold hemagglutinin disease. Greatly diminished immunologic capacity occurring simultaneously with autoimmune manifestations is reminiscent of the situation in agammaglobulinemia. Of further interest is the "triggering" action of large doses of x-rays or alkylating agents in inducing severe autoimmune disturbances. The present...
communication will discuss these and other manifestations of chronic lymphocytic leukemia and attempt to explain its many peculiar "complications" on the basis of a widespread immunologic incompetence of accumulated masses of small lymphocytes.

THE LYMPHOCYTE

The lymphocyte has been an enigmatic cell since it was first described as the "central particle of the blood with solid core" by William Hewson in the eighteenth century. Since this cell was found in the lymph, the thoracic duct and in the lymph nodes, as well as in the blood, it came to be called the "lymphocyte." It is to be noted that this is a "place" name rather than a morphologic term as with polymorphonuclear cell, monocyte, etc. First described wholly from its appearance as one of the "colorless cells" in unstained blood preparations, it was then studied fully in its varied appearances in stained preparations, and later, from its behavior in supravit preparations, both with and without phase microscopy. More recently, studies with cytochemical, ultramicroscopic, tissue culture and radioisotope technics have revealed important physiologic parameters.

Hewson suggested that the lymphocytes, so numerous in the lymph, were derived from both the thymus and the lymphoid tissues. He inferred a circulation from the thymus to lymphatic channels to thoracic duct to lymph nodes and then back again. Gowans, with the far more elegant technics and the sophistication of modern radiobiology, was able to prove this beyond question. Following the recent "rediscovery" of the thymus, concepts of lymphocytic derivation have had to be revised. Ehrlich, the "Father" of modern hematology, held that the lymphocyte was a cell sui generis, unconnected with the other blood cells such as the erythrocyte, the myelocyte, the megakaryocytes, etc. Two diametrically opposite views developed later: (1) The lymphocyte, like other blood cells, derived from a common ancestor, possibly Ferrata's hemohistioblast, which in turn differentiated into a set of "stem cells" that is, myeloblast, erythroblast, lymphoblast, etc. (2) The lymphocyte might actually be the progenitor of all blood cells and could itself become modified or be the progenitor of all the other blood cells.

As the polemics of blood derivation of Pappenheim's and Naegeli's days subsided, most workers thought in terms of stem cells; thus, derivation of lymphocytes from lymphoid tissue where the stem cells were surely present seemed logical enough. However, with the recent "rediscovery" of the thymus, and the parallel discovery of the bursa of Fabricius of the fowl as a thymic-like organ, attention was directed at these tissues, not only as sites of lymphocyte development, but also as organs which might direct the immune response. In the fowl, a reasonably sharp distinction could be made between the thymus, as an organ concerned with "cellular hypersensitivity," and the bursa of Fabricius, concerned chiefly with humoral antibody production. Good's group, working with both birds and mammals, accumulated evidence that the thymus was the source of one form of peripheral lymphocyte—that is, the collar of lymphocytes around the germinal follicles.
WILLIAM DAMESHEK

Fig. 1.—Lymphocytes from normal blood in tissue culture. Three days. Little, if any, change in cells. Wright-Giemsa stain. ×1200.

of lymphoid tissue—and that the bursa (or an analogous tissue in mammals) supplied cells for the germinal centers. Both Ackerman and Auerbach demonstrated that the small thymic cell (thymocyte) which had been thought for a long time to be a lymphocyte, albeit atypical, was indeed a lymphocyte, but of unusual derivation—that is, from epithelial tissue rather than from the mesenchyme. This revolutionary approach did not, however, rule out the possibility that blood lymphocytes might be derived from at least two sources—for example the thymus, and possibly the bursa or its analogue in the mammal. In turn, this brought up the possibility that all cells possessing the morphology of what is called "lymphocyte" were not necessarily the same physiologically; that is, they might react differently to similar stimuli.

The possibility that the lymphocytes of the blood and tissues, although identical morphologically, might be different physiologically has been broached recently by a number of observers. In fact, not only have differences been noted between thymic-derived and bursa-derived lymphocytes, but also the lymphocytes of peripheral tissues (Peyer's patches of the intestines, spleen, bone marrow, lymph nodes, etc.) have been stated to show variations.
The small lymphocyte is easily recognized as a round cell with a diameter usually of less than 10 μ, a nucleus containing densely-staining nuclear chromatin, surrounded by a thin rim of pale staining, nongranular cytoplasm. The cell may be functionally characterized as a nonphagocytic cell exhibiting a characteristic type of movement, in which a “foot process” is extended causing the cell to assume a shape reminiscent of a “hand mirror.” Small lymphocytes also display certain qualities which make them ideally adapted to function as immunologic cells. They have free access to all tissue compartments. They can normally be found in great numbers at sites of inflammation and antigenic invasion. They appear to be long-lived cells which may remain morphologically and metabolically unaltered for extended intervals. However, when exposed to the stimulus of foreign or “not-self” materials, they possess the capacity to enlarge and proliferate. Moreover, the memory of such an antigenic exposure appears to be retained indefinitely, and reexposure to the same antigen calls forth an accelerated as well as magnified proliferative response.

Proliferation in response to stimulation has recently been achieved in vitro. Phytohemagglutinin, an extract of the kidney bean, when added to tissue cultures of lymphocytes has been found to transform small, apparently “mature” lymphocytes into large “blast” cells showing all the features of primitivity. These “blast” cells then go on to DNA replication and mitosis. Profound alterations in RNA metabolism have been observed to occur very early following exposure to PHA, long before any morphologic changes can be detected. These findings have cast some light on the extraordinary ability of the small lymphocyte to remain dormant for prolonged periods and yet remain capable of reacting to appropriate stimuli. Extension of the in vitro studies with small lymphocytes has demonstrated that stimulus to proliferation has important immunologic implications. Thus, specific antigens have also been successful in stimulating in vitro lymphocyte proliferation when the donor of the lymphocytes had been previously sensitized to that antigen.

**The Response of the Lymphocyte to Antigenic Material**

Of the many advances that have taken place in the field of immunity during the past decade, none has been more significant than that of the growing appreciation of the cellular basis of the immune response. Whereas in previous years the reticuloendothelial system held first position, with the system of plasmocytes appearing of prime importance later, in the past five years or so the lymphoid system and the lymphocytes have assumed dominance in the immunoproliferative response. In fact, the lymphocyte is now generally conceded to be the central cell of the immune response. To be sure, the macrophages (histiocytes, reticulum cells, reticuloendothelial sys-

---

*This remarkable cell may be thought of as “hibernating,” often for lengthy periods, perhaps to awaken only in response to antigenic stimuli. As noted below, during “hibernation,” it may retain sufficient metabolic activity to keep it alive; when stimulated, a considerable increase in activity takes place, as indicated by the great increases in RNA and DNA, blast transformation, the development of mitoses, etc.*
tem) are of considerable importance, chiefly with respect to phagocytosis and probably digestion of foreign ("not-self") materials.\(^2\) Early in the immunoproliferative response, "mature" lymphocytes gather about the much larger macrophages and send out pseudopods to make contact with the histiocytic cytoplasm.\(^2\) Such pseudopods may remain in contact with the histiocyte for lengthy periods. During this period of prolonged contact, it is conceivable that antigens or biologic "information" are extracted from the macrophage. Following exposure to antigenic information, a remarkable series of events take place. The small and apparently mature lymphocyte expands in size, its block-like chromatin nucleus becomes finer, nucleoli appear, the cytoplasm develops basophilia; that is, a transformation from a supposedly mature cell to an obviously primitive one takes place.\(^2\) Whether this is "de-differentiation" or "de-repression," there is no question but that it occurs and that it may represent the important first step, after the histiocytic reaction, in immunity. The primitive-appearing transformed lymphocytes (variously called lymphoblast, hemocytoblast, large pyroninophilic blast cell, immunoblast)\(^2\) now undergo proliferation and differentiation with the formation of new large lymphocytes, which then mature to medium and small cells. It is

Fig. 2.—Lymphocytes from normal blood in tissue culture with added PHA. Striking "blast" transformation. Mitotic figure. Wright-Giemsa stain. \(\times\) 1200.
also possible that the immunoblast, either directly or through another precursor cell (plasmoblast?) differentiates into plasmocytes. In the humoral antibody response, a large number of plasmocytes develop; in the reaction of delayed hypersensitivity, on the other hand, a striking lymphocytosis is the rule.

During the course of the immune experience, with its intense antigen-induced metabolic changes, a series of proteins is produced, all of them having the capacity to react against the foreign material that has been introduced. It has been demonstrated that the protein first produced in large amounts is a macroglobulin, to be followed by increasing concentrations of $\gamma$-G globulin. When these have reached their maximal value, further production of $\gamma$-M is sharply reduced. The possibility of a "feedback" control of macroglobulin, which is perhaps "shut off" when $7S$ globulin reaches a certain level, has been raised. That $7S$ globulin is produced in the plasma cells—that is, cells having a well-differentiated ergastoplasm—is quite certain although not completely proved. It seems likely that the macroglobulins are produced by the lymphocytes of the large cell variety, and perhaps by immunoblasts as well.

The immunoproliferative response may be considered as a self-limited one in response to violation of the body's integrity by foreign material. During the peak of the reaction, there is an intense activity of lymphoid tissue, greatest in the area contiguous to the antigenic entrance, but eventually involving more central areas such as spleen, abdominal and thoracic lymph nodes, etc. With subsidence of the response, the immunoblasts diminish, the proliferating cells diminish, and the lymph nodes and other tissues return to their original status. In the wake of this response, a new type of cell is evidently present having the capacity of memory for the same antigen just previously encountered. The "memory cell" has yet to be defined. Is it one of the series of lymphocytes? If so, is it a blast form or a small lymphocyte? Since it must be a "committed" or "conditioned" cell, how does it differ physiologically, chemically, or in other ways from normal "uncommitted" lymphocytes? These are some, among the many, unanswered questions in the wake of the recent knowledge "explosion" in this field.

**Lymphocytosis**

The lymphocytes of the blood in the adult human comprise about 20 to 30 per cent of about 5000 to 10,000 leukocytes per cu. mm. In early childhood and in most domestic animals the absolute number of lymphocytes is much greater—that is, 50 to 70 per cent of 10,000 or more total leukocytes. Thus, in the adult the absolute number of lymphocytes varies from 1000 to 3000 per cu. mm., made up almost exclusively of small (mature) lymphocytes. A few medium and large lymphocytes may be present; these are characterized by a more abundant and lighter-colored cytoplasm, in which azure granules may be found. The nucleus in all of these lymphocytes is characterized by the presence of block-like masses of chromatin. Although nucleoli are not ordinarily demonstrated, occasional preparations which are understained or
otherwise imperfectly stained may show what appear to be nucleoli. Lymphoblasts are not ordinarily seen in peripheral blood, although occasionally typical cells of this type turn up in a careful scan.

During the first stage of a pyogenic infection, lymphocytes become greatly reduced in absolute fashion and continue to be present at low levels during the height of the polymorphonuclear response. However, with the onset of the first stage of convalescence, the monocytes become increased, and later a well-defined lymphocytosis occurs. At this time, “toxic” lymphocytes appear (Türk cells); they are distinctly larger than normal lymphocytes, with a dark-blue, fairly abundant cytoplasm and a larger, more oval nucleus of a more lacy character than in the small lymphocytes. The significance of these “atypical” lymphocytes has, until recently, not been generally suspected, although it seems clear from recent studies that they probably indicate the “sloughing off” into the blood of some of the lymphoid tissue cells participating in the early phases of the immunoproliferative response.26

The total absolute number of lymphocytes in the late stages of an acute pyogenic infection is not greatly increased, since the total leukocyte count may be low. On the other hand, in viral infections—for example, rubella, primary atypical pneumonia, poliomyelitis—an absolute increase in lymphocytes is usually present and many so-called atypical lymphocytes are found. Increases in serum proteins, chiefly in the cold hemagglutinins (macroglobulins) may occur; this is seen particularly in primary atypical pneumonia. However, the most striking hematologic and immunologic findings are found in infectious mononucleosis, in which there is marked lymphocytosis with the presence of many “abnormal” lymphocytes.

A chronic lymphocytosis of “mature” normal lymphocytes is occasionally seen in apparently normal individuals. Whether these and other conditions with well-defined relative lymphocytosis are of any significance is by no means clear. Such cases require further studies by all available technics, especially since it is clear that early cases of chronic lymphocytic leukemia may at first show only an absolute lymphocytosis of mature cells, with no objective physical manifestations. In such early cases the bone marrow usually shows a well-defined increase in lymphocytes.

**CHRONIC LYMPHOCYTIC LEUKEMIA**

In the past, we have defined chronic lymphocytic leukemia as a generalized, self-perpetuating neoplastic proliferation of lymphoid tissue, particularly of small lymphocytes.27 This definition may need some revision, as noted below. The many immunologic abnormalities, including reduced immunologic competency and the frequent presence of autoimmune disorders, the abnormal proliferation of small lymphocytes—one of the cells of the immunocyte complex—warrant inclusion of the disease among the immunoproliferative disorders (cf. below).

The frequent sibling cases, the not infrequent presence of lymphoproliferative disorders in two generations of the same family, and the occasional twin cases indicate a probable genetic fault, at least in some cases. The
relative rarity of the disease among Orientals may represent a further indication of this possibility. There is little evidence, at least at this time, of a viral etiology. Ionizing radiation does not seem to be of importance. On the other hand, the frequent indications of immunologic abnormality suggest an aberration of the immune apparatus, perhaps even fundamental to the disease. To speculate further, the combination of a possible genetic disturbance in association with the high frequency of autoimmune abnormalities suggest the possible inheritance of “forbidden” clones of immunocytes.

As with almost all chronic disorders, the course of the disease can be divided into several stages. For the “asymptomatic” variety, so commonly found in the older age group, Stage I is entirely asymptomatic and the only abnormality is the absolute increase in small lymphocytes, not only in the blood, but in the bone marrow. In Stage II, which may develop after a year or a decade, night sweats are common and there is usually generalized adenopathy, together with a variable degree of splenomegaly. The splenic and lymph node enlargement may go hand in hand, but not infrequently cases show marked splenomegaly with minimum or even no discernible lymphadenopathy, and vice-versa. In Stage III, the patient is increasingly symptomatic; he may show large masses of lymphoid tissue often felt intra-abdominally, as well as peripherally; and he may develop frequent infections. In Stage IV, bouts of fever, frequent infections, disturbances referable to various organs such as the nasal sinuses, the lungs, the skin, various autoimmune disorders and increasing anemia take place often in rapid succession; no sooner does one “complication” terminate than another seems to develop. Numerous keratoses of the skin, various forms of cancer, peculiar fungal infections, herpes zoster, neurologic disorders, and all manner of systemic manifestations occur, until eventually cachexia (“wasting”) and death supervene.

From the laboratory standpoint, the leukocyte count ordinarily rises steadily, reaching its highest levels (200,000 to 500,000) in the last stages. The differential formula, at first showing 60 to 80 per cent of mature lymphocytes, becomes increasingly and almost totally lymphocytic. Anemia, at first minimal, becomes increasingly marked in Stages III and IV and may become rapidly so in the presence of an autoimmune hemolytic state. The bone marrow, which may show a well-defined lymphocytosis early in the disease, eventually may become completely “packed” with lymphocytes, often making aspiration difficult.

However, of particular interest are the changes in the serum proteins, the immunologic aberrations, and the behavior of the lymphocytes in short-term culture with phytohemagglutinin and antigens. The gamma globulin component of the serum, frequently normal at the beginning of the illness, usually becomes progressively reduced, and toward the end is often extremely low. On the other hand, some cases show a striking increase in γ-G globulin and, in occasional cases, well-defined macroglobulinemia is encountered.

Many cases, probably at least 20 per cent, show at various times, either early in the disease or more frequently in its later manifestations, the in-
indications of autoimmunity; of these, hemolytic anemia is by far the most common, but ITP, vasculitis, thyroiditis, rheumatoid arthritis, the Mikulicz-Sjögren syndrome and even systemic lupus may be seen. At times, laboratory manifestations of these complicating disorders (for example, positive Coombs’ test, positive latex fixation test, etc.) can be found in the absence of overt clinical findings.

The manifestations of autoimmunity, which occur so commonly in chronic lymphocytic leukemia, are of unusual interest. If one examines the various immunoproliferative diseases as to cell type, it is readily seen that autoimmune disorders are far more common and far more abundant in the chronic lymphoproliferative type than in those associated with abnormal plasma cell or reticulum cell proliferations. Certainly autoimmunity, which is so common in the lymphoproliferative disorders, is unusual in myeloproliferative counterparts. What is also of great interest is the often sudden development, in a case of a previously “quiet” chronic lymphocytic leukemia, of a severe autoimmune manifestation following large dose ionizing radiation or drugs, or possibly a viral infection. This reaction, which we have alluded to as the "triggering" effect of various physical and chemical agents, is of considerable theoretical interest and will be discussed below.

That immunity to bacteria, viruses, vaccinia, mosquito bites, and the like is often reduced or missing altogether has been demonstrated many times. Similarly, skin grafts may remain unrejected for an inordinately lengthy time. An insect bite may result in a violent, even fatal, reaction; a mosquito bite usually results in huge lesions. The application of virus vaccinia may result in a generalized, possibly fatal, disease. Herpes zoster is common and often of great severity; in some cases it may become generalized, showing the features of chicken pox. An apparently typical example of herpes simplex of the lip may result in a serious and widespread infection. The injection of known antigens has demonstrated a great reduction in humoral antibody production and, to a lesser extent, in cellular immune mechanisms. Thus, there are many indications that the disease is associated with immunologic incompetence. There is, furthermore, one striking laboratory finding which strongly suggests that the disease is due to the proliferation of a physiologically different, perhaps abnormal, immunologically incompetent lymphocyte. This is the definitely abnormal reaction of the lymphocyte to phytohemagglutinin.

The use of phytohemagglutinin for the study of the lymphocyte proliferation in short-term tissue culture may be credited as one of the more remarkable advances of recent years. At first used simply to agglutinate red blood cells and then separate them from leukocytes, phytohemagglutinin was later shown to be mitogenic; this remarkable finding was applied quickly to cytogenetic studies. Still later, in Nowell’s observations of chromosomes, note was taken of the transformation of apparently mature small lymphocytes to apparently immature cells under the influence of PHA. Further studies indicated not only striking changes in DNA and RNA synthesis, but also the actual production of immunoglobulins. Well-defined antigens such as
Fig. 3.—Lymphocytes from blood of chronic lymphocytic leukemia. Tissue culture 3 days. No indication of transformation. ×1200.

tuberculin and streptococcal products were shown to have effects identical with those of PHA, and later “mixing” experiments, using lymphocytes from different individuals in short-term tissue culture, demonstrated again the transforming capacity of allogeneic cells upon normal lymphocytes. Thus, the “stimulatory” effects of PHA seemed to coincide with the antigenic effects of known antigens and those of allogeneic cell types. The behavior of lymphocytes in short-term tissue culture began to be used as an in vitro model of the normal immunoproliferative reaction. When the lymphocytes of chronic lymphocytic leukemia were studied, a remarkable difference in the behavior of these cells to PHA and antigens was quickly apparent. Thus, the leukemic lymphocytes were largely nonresponsive to PHA. No transformation to blast forms at the end of three days was apparent. What is more, kinetic determinations, using specific labels (tritiated uridine; thymidine) for RNA and DNA demonstrated an altered pattern of RNA production, but no DNA production. These and other studies of the RNA-DNA responses indicated that at least a partial block in differentiation (de-differentiation) of the small lymphocytes of the disease was present.

The frequent occurrence of cancer in both the patient and close relatives of individuals with chronic lymphocytic leukemia is also of considerable
Fig. 4.—Lymphocytes from blood of chronic lymphocytic leucemia. Tissue culture with added PHA. Three days. No (or very little) indication of transformation. ×1200.

72 hour cultures

![Graph showing RNA and DNA production in lymphocyte cultures from normal and CLL cases](image)

Fig. 5.—The contrast in the production of RNA and DNA in 72-hour lymphocyte cultures from four normal cases as compared with four of CLL, all “stimulated” by identical amounts of PHA.
CHRONIC LYMPHOCYTIC LEUKEMIA

Table 1.—The Immunoproliferative Disorders

<table>
<thead>
<tr>
<th>Lymphoproliferative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious mononucleosis</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Lymphosarcomatosis</td>
</tr>
<tr>
<td>Macroglobulinemia</td>
</tr>
<tr>
<td>Heavy chain disease</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Plasmoproliferative</td>
</tr>
<tr>
<td>Multiple myeloma (including light chain disease)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Reticuloproliferative</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
</tr>
</tbody>
</table>

interest. The striking frequency of family cases of chronic lymphocytic leukemia, with numerous sibling cases, and occasional indications of disease in three generations suggest a genetic basis for the disease.4

DISCUSSION

The Immunoproliferative Disorders

I have recently proposed the concept of the “immunoproliferative disorders”1 as abnormalities of growth, usually of a generalized character, involving the cells of the immunocyte complex, and associated with abnormalities of the immune mechanism. Lymphoproliferative, plasmoproliferative and reticuloproliferative types may be discriminated. They are usually self-perpetuating, although self-limited disorders (for example, infectious mononucleosis) may also be found (Table 1). More recently, it has seemed logical to include under the broad heading of the immunoproliferative disorders not only those conditions with increased proliferation, but also those in which an abnormal, and perhaps even a diminished growth of immunocytes was present—that is, “immunodeficiency” disturbances.

The lymphoproliferative disorders exhibit a considerable diversity, perhaps because the lymphocyte, in its reaction to antigenic contact, goes through a continuous series of striking transformations—that is, small lymphocyte to blast form to large, medium and small lymphocyte. “Transitional” forms which are difficult to classify may be seen along the way. Included among the lymphoproliferative disorders are many diverse conditions. Infectious mononucleosis stands as the prototype of the acute self-limited proliferation of lymphocytes. Chronic lymphocytic leukemia, “macroglobulinemia,” and “heavy chain” disease are to be discriminated. Also included in this category is lymphosarcoma, whether localized or generalized, and in one or another of its variations. There are, in addition, conditions in which there is a complete lack of lymphocytes (alymphocytosis, “Swiss” type of agammaglobulinemia), conditions characterized by probable maturation arrest or disturbed “feedback” mechanism from 7S to 19S globulin production (“macroglobulinemia”) or by the continued production and probable accumulation of a special type of small lymphocyte (chronic lymphocytic leukemia).
What is more, the possibility that the lymphocyte may be the precursor of the plasma cells in the immune reaction may involve it in many peculiar “mixed” proliferations, in which hypergammaglobulinemia is a feature. In any event, a variety of immunologic aberrations are found, including hyper γ-G globulinemia; hyper-γ-M globulinemia (macroglobulinemia), hypogammaglobulinemia, the development of autoantibodies and of autoimmune disorders and the presence of reduced cellular hypersensitivity.

As we have pointed out in previous publications, the immunologic reaction is fundamentally a cellular one involving a special group of cells of which the lymphocyte is central. It is conceivable that an abnormal or aberrant immunologic reaction might at first comprise a small clone of abnormal lymphocytes eventually resulting in a detectable immunologic or protein abnormality. As the “forbidden” clone continued to be stimulated by self-antigens, its expansion from a more or less occult phase to an overt one with large masses of lymphoid tissue could take place. What should be emphasized is that the abnormal self-perpetuating autoimmune state and the leukemic one might be fundamentally the same, the leukemic state comprising possibly a quantitatively massive clone as compared with the relatively small “forbidden” clone needed to produce an autoimmune manifestation. Thus, these two conditions could be considered as different expressions of the same fundamental self-perpetuating, but faulty, immunologic mechanism. Leukemia or “lymphoma”—as applied to the disorders of reticulum cells, lymphocytes, or plasma cells—could be the clinical designation of a greatly expanded, aberrant immunologic proliferation. Of the various lymphoproliferative disorders, chronic lymphocytic leukemia is by far the most common, at least in the Western world.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is an abnormal, generalized, self-perpetuating proliferation of small lymphocytes. Although the disease is usually detected rather late in life, it is conceivable that it may have begun years, possibly many years, previously. Since there are indications of an inherited disorder, at least in some cases, it is even conceivable that it might be congenital. The continued increase in lymphocytes of a similar type year after year suggest an increased proliferation of these cells, but a number of studies, including very low levels of RNA synthesis, and the failure to detect evidence of increased DNA replication and mitotic activity suggest that accumulation of poorly reactive lymphocytes, rather than increased proliferation, may be fundamental to the disease. It is likely that the lifespan of the small lymphocytes of the disorder may be considerably lengthened with the consequence that they remain and accumulate in lymph nodes, spleen, bone marrow, liver and blood.

It has been demonstrated that the small lymphocytes of chronic lymphocytic leukemia are metabolically abnormal; that is, they do not respond to phytohemagglutinin or antigens. As Quaglino and Hayhoe have shown, their cytochemical reaction to PAS is also abnormal, suggesting a disturbance
This idea has already been expressed by Gorman and by Marmont.47

Fig. 6.—Hypothetical model of the “life” of lymphocytes as compared with those of CLL. It is suggested that the normal lymphocytes respond to every “passing” antigen, while the leukemic cells are nonresponsive. One may speculate that the nonreactive lymphocytes, living an “indolent” life, have a long survival time, thus gaining an ecologic advantage and eventually accumulating in large masses.

of glycogen metabolism. The in vitro behavior of the leukemic lymphocytes may well equate with their in vivo functioning. Thus, if a lymphocyte is unable to transform in vitro in response to PHA, it may not transform in vivo in response to antigen. Conceivably, this ineffective cell would not enter into the pool of constantly transforming lymphocytes and would thus live a very quiet life (hibernation?). The leukemic lymphocytes, unable to react to various antigenic agents, might well possess distinct ecologic advantage and thus gradually occupy all the available “niches” in lymphoid and other tissues, eventually replacing the metabolically and immunologically more active, normal lymphocyte of shorter lifespan.* As this happens, immunologic competency would gradually become increasingly reduced, finally leading to a state seen in terminal phases of the disease when there is a condition of almost complete immunologic paralysis.

The fundamental reason for the possible proliferation and accumulation of the immunologically incompetent lymphocytes of chronic lymphocytic leukemia is by no means clear. Conceivably, they could represent an inherited “forbidden” clone, which by its gradual expansion leads to the disease. Alternatively, it is conceivable that the “abnormal” lymphocyte is in reality a normal constituent of the normally heterogeneous population of small lymphocytes of the blood and lymphoid tissues. In this connection, Gorman47 has hypothesized that immunologically incompetent (I.I.) lymphocytes may be quite normal, and, in fact, may constitute the cells concerned with maintenance of immunologic tolerance to specific antigens.

Other possibilities exist: (1) That the lymphocyte of CLL is actually a neoplastic cell, perhaps having a deleted antigen or an enzymatic defect, sufficient to make it abnormal but without interfering with the perpetuation of its kind. Thus it could proliferate in its own way, gradually displacing the
normal population of lymphocytes. (2) That it is a normal constituent of
the heterogeneous lymphocyte population, but that an aberration in a con-
trol mechanism of the progenitors of these cells has taken place. (3) If
different lymphocytes are derived from thymus, the bursa of Fabricius or
its possible analogue in the mammal, or perhaps from other tissues such as
the marrow, it is conceivable that the lymphocytes derived from these
sources differ both antigenically and metabolically. Some evidence for such
antigenic differences has already been obtained. (4) It is also conceivable
that one or another of these various origin-areas for lymphocytes normally
becomes involuted at a given age—for example, the thymus at puberty. The
possibility is present that such a tissue, instead of becoming “shut off” at
puberty, might continue to function and thus add lymphocytes throughout
life; these might be immunologically incompetent. That the cells of the
thymus are, at least within the thymus, immunologically incompetent has
been demonstrated repeatedly. There is, furthermore, some work to indicate
that thymic lymphocytes do not respond to PHA. Good and his colleagues
would explain the possible role of the thymus in chronic leukemia in a dif-
ferent fashion: The thymus controls the “collar” of lymphocytes around
the germinal follicles; if this control is lost in some manner, an abnormal
proliferation of these cells takes place, eventually resulting in the disease.

The frequent presence of autoimmune disorders and the sudden appear-
ances of autoimmunity in response to intensive radiation or large-dose cyto-
toxic agents seem at first glance to be at variance with the idea that chronic
lymphocytic leukemia is a condition of immunologic incompetence. We may
cite, however, the analogy with agammaglobulinemia, in which autoimmune
hemolytic anemia and other autoimmune disorders occur. For both conditions,
it is possible that the greatly reduced number of cells possessing immunologic
competence would allow the development of new abnormal clones of
lymphocytes, possessing the capacity of reacting with self-antigens. The
greatly increased frequency of cancer in patients with chronic lymphocytic
leukemia4 could also be explained on this basis. As several observers have
speculated, one of the chief functions of the lymphoid system is not to de-
stroy kidney or other grafts, but to exert a “surveillance” function and, if
aberrant clones of mutated cells are “observed,” to destroy them. In the
chronic imuno-incompetent situations, as in chronic lymphocytic leukemia
and agammaglobulinemia, one might therefore expect a higher incidence of
autoimmune disease and of neoplasia. A possibly related phenomenon is
the “triggering” effect in chronic lymphocytic leukemia of ionizing radiation
or of large doses of alkylating agents in the induction of severe autoimmune
disease. Under these circumstances, new abnormal clones of lymphocytes
having the capacity of reacting with self-antigens might develop. To be sure,
alternative possibilities are present, including our previous speculation that
a state of presumed tolerance existing between the leukemic “graft” and the
“host” patient might be abrogated by radiation or chemical agent, thus re-
resulting in a “graft vs. host” reaction.

Some ideas as to the best form of therapy for chronic lymphocytic leu-
CHRONIC LYMPHOCYTIC LEUKEMIA

581

LYMPHOID MASSES & SPLEEN

PREON/SONE

Fig. 7.—Semidiagramatic chart showing the effects of large dose prednisone therapy in CLL. Note the quick reduction in size of spleen (lymphoid masses are not shown), the initial rise in leukocyte count, due largely to lysed lymphocytes, then followed by their gradual reduction.

leukemia might well be gleaned from the above considerations. Conceivably, the use of large doses of x-ray therapy or of alkylating agents could do more harm than good. We have counselled that no therapy is often far better and certainly less potentially harmful than some therapy, particularly if large doses of potent agents such as ionizing radiation or alkylating agents are to be used. On the other hand, with the use of large dose corticosteroids (prednisone, 50 to 150 mg. daily), the lymphomatous masses usually "melt away" quickly, often within a matter of days. Simultaneously, the blood leukocyte count rises to far higher than the usual values, with the presence of numerous so-called "smudge" cells (partially destroyed lymphocytes). After a peak is reached in 2 to 4 weeks, there is then a gradual reduction in the leukocyte and lymphocyte counts to below their usual previous values. These findings may indicate that accumulated leukemic lymphocytes are lysed to some extent by the prednisone, and then disengaged from their pool within lymphoid tissue to a blood pool, which then is gradually reduced as the disgorged cells are removed from the circulation. Disposal of this extra pool of cells in the blood may take several weeks or months. Eventually, the leukocyte counts may reach normal values, but this may require the additional use of small doses of such "gentle" alkylating agents as chlorambucil or cyclophosphamide. These drugs are particularly important as the dose of corticosteroids is being reduced, since without them, the lymphoid masses and the concentration of lymphocytes in the blood quickly become greatly increased. Theoretically, one could perhaps "empty" completely the pool of abnormal lymphocytes in the lymphoid masses by the continued use

From www.bloodjournal.org by guest on November 13, 2017. For personal use only.
of corticosteroids, and then destroy them, both in the tissues and in the blood, by cytotoxic agents. In line with this concept would be the possible use of Cronkite’s method of extracorporeal radiation of the patient’s blood from a cobalt source.52

SUMMARY

Chronic lymphocytic leukemia, far from being simply a very chronic, very dull disease, has many facets which may help to illuminate the pathogenesis of a variety of immunologic aberrations. It appears likely that this is an accumulative disease of lymphocytes rather than one which is due to rapid proliferation, as was originally thought. The abnormal lymphocytes of the disease—with their various indications of metabolic but, more particularly, immunologic incompetency and their reduced ability to transform with both PNA and antigenic stimulation—eventually accumulate in large masses throughout the body. In the course of time, a host of disorders develop, including reduced immunity of both humoral and cellular varieties, autoimmunity, and extreme reactions to viruses and insects, numerous infections and wasting, finally leading to death. A striking response to corticosteroids is characteristic of the disease. On the other hand, large doses of x-ray or alkylating agents may result in violent and often fatal autoimmune reactions. Many future studies are indicated to demonstrate the nature of the metabolic defect in the lymphocyte and its pathogenesis, whether genetic or on some other basis. The possibility of modifying the tendency of the abnormal lymphocyte to accumulate, perhaps with the judicious use of corticosteroids, in association with other methods deserves intensive study.

ACKNOWLEDGMENTS

I am indebted to many individuals for their help in the preparation of this manuscript: Dr. Arnold Rubin for his instruction in the specialized knowledge of the lymphocyte, particularly in tissue culture and in lymphocyte RNA and DNA kinetics; Dr. Lung T Yam for his excellent photomicography of lymphocytes from tissue cultures, with and without PHA; Dr. Klaus Havemann, for his data on RNA and DNA kinetics in CLL lymphocytes; Dr. Shaul Kochwa for his many courtesies; Dr. Henry M. Stratton for his many years of friendship and collaboration; and finally to the Australian group of hematologists, notable Drs. Robert Walsh, W. B. Pitney and Carl deCruchey, for making this lecture possible.

REFERENCES


CHRONIC LYMPHOCYTIC LEUKEMIA


30. Rosenthal, M. C., Pisciotta, A. V., Konninos, Z. D., Goldenberg, H., and Dameshek, W.: The autoimmune he-
Dameshek, W., and Gunz, F.: See ref. 27.
35. Dameshek, W., and Gunz, F.: See ref. 27.
42. Baim, B., Vas, M. R., and Lowenstein, L.: The development of large immu-
Gunz, F.: Personal communication. Based on statistical studies of leukemia in New Zealand.
45. Dameshek, W., and Gunz, F.: See ref. 27.
50. Good, R. A.: Cf. ref. 11.
52. Cronkite, E.: Personal communication.
Special Article: Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

WILLIAM DAMESHEK

Updated information and services can be found at:
http://www.bloodjournal.org/content/29/4/566.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml