EDITORIAL

Leukemia and Auto-immunization—Some Possible Relationships

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DURING the past thirty years, the immunochemical studies of Landsteiner,1 Heidelberger,2 Haurovitz,3 Kabat4 and others have done much to clarify our understanding of antibodies and their in vitro reactions with antigens. In the work of these and many other investigators, the physical and chemical aspects of antibodies have been emphasized, sometimes to exclusion of all concern with their mode of origin. As a result, studies of the mechanism of antibody production at the cellular level have usually been relegated to the background, although a number of excellent reports dealing with this problem have appeared.5-7 All of them indicate the well defined cellular reaction that takes place during the immune response, which may indeed be considered as a specialized type of cellular proliferation. In some of its aspects,8 particularly in the case of “auto-immunization,” which once begun is often self-perpetuating, the immunologic reaction may be compared with the abnormal leukocytic proliferation of leukemia. It is the purpose of this speculative discussion to draw attention to some of these resemblances and the implications involved.

Antigenic substances have the remarkable property of stimulating the growth or proliferation of certain leukocytic tissues, notably those of the reticuloendothelial, lymphocytic, and plasmocytic systems. These “systems” are made up of groups of similar cells scattered throughout the entire body; they include primitive anlage cells variously termed lymphoblasts,9 hemocytoplasts,10 transitional cells,11 acute splenic tumor cells12 and reticular cells,13 as well as the more mature plasmocytes and lymphocytes. During the early phases of the immune response, reticulum cells and large, primitive cells in regional lymph nodes or spleen become greatly increased in number, and numerous mitotic figures are seen. Reticulum cells stimulated by the introduction of antigen appear to have the potential of developing into either plasma cells or lymphocytes by way of several intermediate forms. The direction of maturation may depend upon the nature of the antigen, its dose and route of administration.14 This “bivalent” type of cell development may be responsible for the continued controversy as to the relative merits of lymphoid and plasmocytic tissues as the prime sources of antibody production. Although the development of the primary immune response is a relatively sudden one,
this is even more striking in the secondary, or anamnestic, response, when there is an almost explosive proliferation of reticulum, lymphoid, and plasma cell types.

Accompanying these actively changing patterns which occur in the immunologic reaction, there occur increases in the nucleic acid content of the tissues (cells), and antibodies soon appear in the circulating plasma. The peak concentrations of circulating antibody and of cellular RNA coincide rather precisely with the peak of this proliferative activity.

Bursts of cell division similar to those seen in the immune response are by no means unique in mammalian tissues; in fact they represent some of the most common reactions to various external agents, such as trauma, infections, certain chemicals and hormones, and various physical factors. The polymorphonuclear response to pyogenic organisms may be cited as a prime example of cellular proliferation induced by infection. Such responses, it should be noted, are of a temporary or self-limited nature, and subside when the stimulus is removed. The temporary response of the antibody-producing tissues to a known antigen and the temporary cellular response of granulocytic tissues to diverse etiologic factors have these features in common: (1) They arise in response to a well defined agent, and (2) the cellular response is an acute and self-limited one. Once the agent has been disposed of, morphologic and biochemical indications of cellular activity subside and the tissues in question revert to their usual growth pattern. Both of these responses may therefore be classed as reactive. Although they are proliferative, the proliferation is a benign one, which becomes reversed when the offending agent is removed.

One important feature differentiating the self-limited immunologic response from the temporary polymorphonuclear response to a pyogenic infection is that the immunologic reaction may be said to leave a permanent “imprint” on the antibody-producing cells. As a result, when the same offending substance (antigen) is reintroduced, a marked, even explosive response takes place. Thus, the crucial point which distinguishes the growth pattern of the immune process from the other classes of cellular proliferation is the ability of antibody-forming cells to “remember” a previous antigenic stimulus. Several groups of experiments, including some from our own laboratory, seem to favor the view that antigen causes a specific, permanent and self-replicating change (genetic?) in the growth pattern of at least some groups of antibody-producing cells.

There is, however, one type of immunologic response, usually called autoimmunization, in which the response, once begun, continues and may in fact become permanent. Here, the abnormal protein (i.e., antibody) produced is directed against the individual’s own cells or tissues. Although according to Ehrlich’s dictum of the horror autotoxicus this type of response is inconceivable, it nevertheless appears to be responsible for a variety of conditions, including auto-immune hemolytic anemia, idiopathic thrombocytopenic purpura, acute vascular purpura, certain types of nephritis and thyroiditis, and presumably systemic lupus erythematosus. Whether or not the source of antigen can be found, there can be no question that antibody has
been produced, presumably by antibody-producing cells, and is present in the blood as a protein substance of gamma globulin type. This is ordinarily specific for a certain type of cell or tissue and may bring about profound physiologic and biochemical disturbances.

At the cellular level, auto-immunization may be said to represent an abnormal, self-replicating proliferation of cells producing an abnormal protein, which is usually harmful to the host. Since this process is a continuous one, it is fundamentally different from the benign, reactive, self-limited type of immunologic response. Does this therefore represent the formation of a new “race” of cells, genetically different, which continues to reproduce in an abnormal fashion and to produce abnormal protein?

The inciting agent in most cases of auto-immunization is unknown, but in some there appears to be at least a temporal relationship between the onset of the auto-immune disease and viral infection27 (cf. the development of “ITP” after chicken pox or measles, or after vaccination for polio or Asiatic influenza). In others, as in the auto-immune hemolytic anemia of chronic lymphocytic leukemia, exposure to spray x-radiation or to alkylating agents may be followed by the sudden development of the anemia.28 It is possible that “antigen” as such may not be essential for the development of auto-immunization, but that various agents (virus, ionizing radiation, alkylating chemical) may induce an important modification in antibody-producing cells. This might result in a new “race” of cells, producing an abnormal protein active against certain of the host’s cells or tissues. If the hypothesis is accepted that auto-immunization represents at the cellular level the proliferation of a new group of metabolically different antibody-producing leukocytes, does this not resemble leukemic proliferation?

Leukemia may be considered as a generalized proliferation of one of the white cell-forming tissues, in which the proliferation is not only of an abnormal type, but having once been initiated, is continuous; it is furthermore “invasive” in most cases.40 Although it is possible to conceive of leukemia as a spontaneous mutation of certain leukocytes, occurring without reference to external stimuli, much evidence has been gathered in recent years to support the view that it represents a response to an external agent. The leukemogenic activities of ionizing radiation,29 of certain “carcinogenic” chemicals,30 and of viruses31 are now under extensive investigation, both in man and in the experimental animal. Suffice it to conclude from these studies that the evidence implicating radiation and viruses in animal leukemogenesis is substantial; in man, however, this evidence is still only circumstantial.

The auto-immune type of leukocytic reaction has many points of similarity with the leukemic process. In both, something seems to have occurred to change the growth habits of a group or groups of white cell tissues. In both, an abnormal proliferation may be initiated by a totally extraneous agent, such as ionizing radiation, chemical, or virus, which may conceivably induce the development of a new “race” of cells, possibly by enzyme deletion, leading to somatic mutation. In both, the proliferation, once begun, is self-replicating, and in both, the abnormal cellular tissue, whether leukemic or immunologic, may result in the formation of abnormal proteins. There are furthermore some
leukemic disorders in which immunologic or dysproteinemic abnormalities are simultaneously present; such disorders may conceivably offer important clues regarding both leukemic and auto-immunologic disease.

Multiple myeloma, which may be considered as a leukemic disorder of plasmocytes, is a generalized proliferation of these cells with all the features of malignancy or neoplasia, as we understand these terms in their classic sense. Histologically, there are both sheets of rapidly proliferating plasmocytes and nodules composed of the same type of cells. The disease is ordinarily distinguished by two features: a greatly increased growth of plasmocytes, usually of an abnormal type, and the presence in the serum of large quantities of an abnormal protein of the globulin variety. Studies of myeloma tissue and marrow\textsuperscript{32} and of mouse plasma cell neoplasm X5563\textsuperscript{33} have shown that this abnormal protein is a direct product of the tumor cells and is not synthesized elsewhere. Furthermore, its high concentration in the blood is due to a greatly increased rate of synthesis by these cells.\textsuperscript{34} Unlike other diseases in which diffuse hyperglobulinemia occurs, multiple myeloma is unique in that the massive increase of serum protein is due to the presence of a discrete, electrophoretically homogeneous globulin, usually of the gamma variety.\textsuperscript{35} Were it not the custom to consider this disease as a neoplasm, and were we faced today with a new disease in which the striking blood chemical finding was that of a high concentration of abnormal globulin, we might conclude that here basically was a disorder of abnormal globulin production, accompanied by plasmocytosis, and perhaps of an immunologic nature, although no effect against any specific cells or tissues by the abnormal globulin could be elicited. Perhaps multiple myeloma might be considered as \textit{both} a leukemic and an immunologic proliferation, in which an abnormal globulin is being produced.\textsuperscript{*}

One might speculate further that multiple myeloma is the end result of a series of repeated antigenic “insults” in which there have been so many responses to antigen that a continuous proliferation of antibody-producing cells (plasmocytes) eventually results with the ultimate development of invasive characteristics. Parenthetically, we have noted in some cases of multiple myeloma an unusually striking series of immunizations or of many infections over a period of years, long prior to eventual development of the disease.

Perhaps related to “multiple myeloma,” perhaps even more so to immunologic disease, is the disorder usually known as “macroglobulinemia.” First reports indicated that this condition was a chemical-serologic one in which the striking abnormality was a considerable increase in a heavy protein constituent, almost invariably found in the gamma globulin fraction. More recent studies indicate that there is present here an abnormal proliferative process of peculiar looking lymphocytes (“reticular lymphocytes”) which in all probability are producing the abnormal heavy protein.\textsuperscript{36} Since there has been as yet no complete agreement that this is a neoplastic proliferative dis-

\textsuperscript{*}It must be considered peculiar that the myeloma globulins, in contrast to those found in many cases of the lymphoproliferative disorders, have not as yet been found to have any immunologic specificity.
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order, it may be argued that this is a peculiar self-perpetuating disturbance of protein production, perhaps fundamentally immunologic, and resulting in an unusually high concentration of the heavy protein ordinarily found in certain auto-immune conditions. In any event, here is a classic example of the difficulties involved in distinguishing between immunologic proliferation on the one hand and leukemic proliferation on the other.

Additional conditions bearing on this interesting problem, which becomes more provocative as one tries to analyze it, may be cited. Thus the serum of some patients contains typical “myeloma” proteins, and yet examination of the tissues shows a considerable infiltration with lymphoid rather than plasma cells. The hazy borderline between plasma cells and lymphocytes is thus breached by these interesting patients. It is well known that immunologic abnormalities are found in a substantial number of patients with chronic lymphocytic leukemia. About 20 per cent of the patients with this disease develop auto-immune hemolytic anemia some time during their course. These cases stand in striking contrast to patients with chronic granulocytic leukemia, in which auto-immune hemolytic anemia is rare. A self-limited lymphoproliferative disorder which is probably caused by a virus, that is, infectious mononucleosis, is also associated with the formation, in almost every case, of a peculiar antibody against sheep erythrocytes, i.e., the heterophile antibody. In all probability this is produced by the abnormal lymphocytic proliferation, and without reference to specific antigen (sheep, horse red cell, etc.). What is more, occasional cases of infectious mononucleosis are also associated with auto-immune hemolytic anemia or idiopathic thrombocytopenic purpura. It is apparent that abnormal proliferations of lymphoid cells, whether benign or malignant, are commonly associated with the production of abnormal globulins, and that some of these globulins are harmful to specific cells or tissues, i.e., are antibodies.

It is evident that several types of lymphoproliferative disease and of plasmacytosis may be associated with the production of abnormal globulins and with the development of various types of immunologic responses; it remains to be proved whether aberrant immunologic responses when continued or repeated on numerous occasions may eventually give rise to what are called neoplastic proliferations.

One further clue bearing on the problem of the leukocytic proliferations of the immune response and leukemia resides in consideration of the action of certain chemical agents on both these states. The action of antimetabolites, such as aminopterin and 6-mercaptopurine (6-MP), on leukemic proliferations is well known; the ultimate effects induced by these agents are probably on nucleic acid metabolism. In addition, a number of workers have recently demonstrated that various antimetabolites, especially those interfering with nucleic acid metabolism, have profound effects on antibody

*The definition of “antibody” as a specific substance which can be produced only through the mediation of “antigen” may be debated. There are substances with all the physical, chemical, and immunologic criteria of antibodies in which antigen seems to have played little if any part in their development.
synthesis. Thus, it was shown that 8-azaguanine not only interfered with the production of red cell agglutinins in mice,\textsuperscript{41} but that it diminished the in vitro uptake of amino acids by antibody-synthesizing cells.\textsuperscript{42} In our laboratory, it was shown that 6-MP completely blocked the formation of antibody against purified protein antigens in rabbits.\textsuperscript{43} Uphoff demonstrated that amethopterin prevented the development of the homologous bone marrow reaction, a disorder now universally accepted as a tissue antigen-antibody reaction.\textsuperscript{44} Deoxypyridoxine has been shown to prevent red cell agglutinin formation in rats\textsuperscript{45} and also has been found to prevent the rejection of homologous skin grafts by these animals.\textsuperscript{46} All of these agents have a certain degree of usefulness in the treatment of leukemia, especially 6-MP and amethopterin. In addition to these drugs, other agents have been studied whose antitumor activity roughly parallels their anti-immune activity. The best known of these are x-radiation, nitrogen mustard and the corticosteroids. The remarkable effects of the corticosteroids, particularly when given in massive dosage in both acute leukemia\textsuperscript{47} and chronic lymphoproliferative disorders,\textsuperscript{48} almost surely indicates that they are, at least in "pharmacologic" dosage, "antiproliferative" or "antimetabolic" agents. In the experimental animal, they have been shown to be not only lymphocytolytic\textsuperscript{49} but also to reduce antibody production.\textsuperscript{50} Whether the dual action of these various substances, i.e., on leukemic and immunologic proliferations, is merely a coincidence, or whether it is a nonspecific effect on any rapidly proliferating tissue, or whether some close metabolic similarities, which are revealed by these agents, exist between tumor formation and antibody formation remains to be determined. It seems unlikely that these observations are due to chance. Furthermore, if the anti-immune activity of radiation and 6-MP were due exclusively to their anti-proliferative activity, then a depressant effect on antibody formation might be expected during the secondary response, since one of the main features of this reaction is cellular proliferation. This, however, is not the case,\textsuperscript{51} and the time of administration of 6-MP and radiation\textsuperscript{52} with respect to antigen administration is an important factor in determining their anti-immune action. The third possibility, namely that tumor cells, particularly neoplastic leukocytes and antibody-forming cells, are close metabolic relatives and that their similarities are brought out by their reaction to ionizing radiation, antimetabolites, and the corticosteroids, is susceptible to laboratory analysis. Perhaps work on this point will provide a fruitful, albeit roundabout, approach to a better understanding of leukemia.

REFERENCES

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