LYMPHOCYTES AND THEIR CELL MEMBRANES

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PREFACE

Analysis of the lymphocyte membrane has provided immunologists with new perspectives of the functions and interactions of lymphocytes. The demonstration of a large number of cell-surface markers has been of crucial importance for the identification and characterization of distinct lymphocyte subpopulations. This, in turn, has enabled a detailed analysis of the role of lymphocyte populations in different facets of the immune response. The participation of various receptors on the lymphocyte surface in the recognition of antigens and in lymphocyte triggering is slowly being unraveled.

In an intensive field of research, inevitably, the bewildering abundance of details does not always seem to fit into a coherent picture. While most of the present knowledge can be fitted into currently fashionable concepts, some observations may not be in line with what Weissman calls "common wisdom."

The papers included in the present volume are meant to serve two purposes. While on the one hand, they reflect current knowledge about the lymphocyte surface, on the other, they express prevailing doubts and uncertainties and point out areas requiring further research. The papers deal with such topics as methods for the analysis of the cell surface of lymphocyte populations, the differentiation pathways of lymphocytes, and the function of cell-surface receptors of lymphocytes.

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HISTOGENESIS OF B AND T LYMPHOCYTES

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The formation of the distinctive surface membrane of B and T lymphocytes is the end stage of developmental processes which seem, in some respects, to be fundamentally different when one compares the two cell types. In view of the importance now attached to these membranes, and to the respective roles of B and T cells in our current concepts of immune reactions, it is of interest to review briefly some of the basic facts about their kinetics and histogenesis, with special reference to the way in which lymphocytes with specific membrane receptors develop from precursor cells which do not appear to contain these receptors.

Different production pathways for B and T cells. Lymphocyte production in the bone marrow, a major source of B cells, occurs via what has been termed the short production pathway, in the course of which there are two to three mitoses (1). This contrasts with the long production pathway for lymphocytes in the thymus, in which T cell production involves about eight mitoses.

Before discussing this point further, it is important to emphasize at the outset that B cells are a heterogeneous group. As defined on the basis of the possession of an immunoglobulin coating, a certain amount of B cell production occurs in lymph nodes (C. Rosse, unpublished data), in some of which the production pathway has been estimated to involve six mitoses (2). However, the histogenesis of B cells in lymph nodes seems to be quite different from that in bone marrow (C. Rosse, unpublished data). Possibly, the marrow B lymphocytes are the so-called "virgin" B cells (3), while those in lymph nodes are the "memory" cells which take part in the secondary response and develop ultimately into plasma cells. The spleen, especially in the mouse, may be the site of production of both types of B cell. In addition, the possibility cannot be excluded that further subgroups of B cells may be identified. But despite all these considerations, it would nevertheless appear that in postnatal life the bone marrow is the major primary source of B cells. The following account will therefore be concerned essentially with the B cells which are being formed continually in large numbers in the bone marrow (1).

Association of B cell formation with hemopoiesis. Unlike that of T cells, B cell formation on a large scale is usually associated with hemopoietic activity. This appears to be true of fetal, as well as of postnatal, life. Stutman (4) reported that in the mouse, B cells—defined by surface Ig—could be derived from precursors in the yolk sac or the liver, even though the precursor cells themselves did not

contain detectable Ig light- or heavy-chains on their surface. Nossal and Pike (5) also favored the view that there was a multifocal origin of B cells in all the major sites of fetal hemopoiesis in the mouse, namely, in the liver, spleen and bone marrow, commencing three days before birth. Osmond and Nossal (6, 7) followed up this observation by a study of B cell formation in murine bone marrow after birth.

Of the various hemopoietic tissues, it is in the bone marrow that the histogenesis of B lymphocytes has been most fully investigated, and a precursor cell identified. In the case of fetal hemopoietic tissue, it is difficult to recognize a precursor cell for B lymphocytes in the yolk sac (8) or fetal liver (9), though a possible indication of such a precursor has been described in fetal liver in more recent studies (10, 11).

The evidence that there is active formation of B lymphocytes in the bone marrow does not in itself prejudge the answer to the question whether or not the bone marrow is the mammalian analog of the bursa of Fabricius. This view has gained facile acceptance, in part possibly because of the fortuitous accident that bone and bursa begin with the same letter. But whether or not the bone marrow is the mammalian representative of the bursa, the quantitative data on marrow lymphocyte production (12), together with the percentage data on B lymphocytes in the marrow (6, 7; C. Rosse, unpublished data), make it abundantly clear that the bone marrow is certainly the site of very large-scale production of B lymphocytes. The marrow transfusion experiments of Unanue et al. (13) also appear to implicate the bone marrow as a major source of B lymphocytes.

Histogenetic studies of bone marrow help to explain the close link between the production of lymphocytes and of other blood cells. It may well be the case that wherever there are primitive hemopoietic stem cells, there is also a potential for lymphocyte production (14–17).

B LYMPHOCYTE PRODUCTION PATHWAY IN BONE MARROW

Transitional (lymphoid) cells are the precursors of the small lymphocytes. In order to understand the origin of lymphocytes in bone marrow, one must briefly consider the hemopoietic stem cell compartment, the essentials of which are presented in Fig. 1. The stem cells are to be found among a group of cells which were designated "transitional," and they form a spectrum of cells ranging in size from cells as large as blast cells to cells just a little larger than small lymphocytes. When these cells were first illustrated (18), the name "transitional" was given to them on the basis of their morphology. They

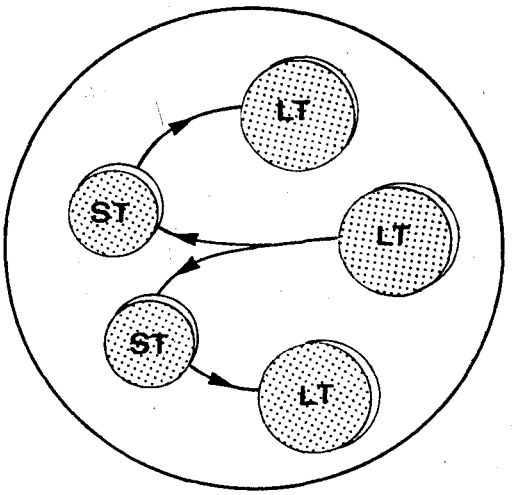

FIG. 1. Scheme of the stem cell compartment in bone marrow. The compartment consists of transitional cells of varying sizes, and is self-maintaining. Large transitional cells (LT) can divide to form small ones (ST), and these in turn can enlarge to become large transitional cells. Such a growth cycle in itself would merely result in a progressive increase in the number of transitional cells, but this does not usually occur, since cells are also leaving the compartment, as indicated in Fig. 2.

were then thought to be intermediate stages in the enlargement of small lymphocytes to form blast cells, and to be derived from small lymphocytes which had entered the marrow from the blood stream. Later work in the guinea pig (19), rat (20) and mouse (21, 22) showed that this interpretation was largely incorrect. Although we now know that the marrow lymphocytes are a heterogeneous population, most of them are a rapidly renewing cell group, with a turnover time of two to three days. This is the main lymphocyte population of the marrow throughout life, though it undergoes some age changes (21–25).

In addition to the large group of rapidly turning over cells, there is a smaller population of lymphocytes which persists in the marrow for a longer time after formation *in situ* (26), while some lymphocytes have been shown to enter the marrow from the blood stream (27–31). In the context of B cell formation, it appears to be the rapidly turning over small lymphocytes with which we are concerned.

Lymphocytes, then, are formed by the division of transitional cells, which are the essential precursors of B lymphocytes in the marrow. A full account of the transitional cell compartment, and of the way in which our understanding of their role has been modified and expanded, can be found elsewhere (12), together with the evidence that among the transitional cells are to be found the essential pluripotential hemopoietic stem cells.

Transitional cells form a self-maintaining compartment, in which large transitional cells divide to give rise to smaller ones, and these in turn can grow to form larger cells, as depicted in Fig. 1. This process of intrinsic proliferation would by itself merely result in a steady and progressive increase in the number of transitional cells, but this does not occur, for three main reasons. 1) The intrinsic proliferation of the compartment can apparently be either speeded up or slowed down, though we do not know how these changes are effected. 2) Cells may leave the compartment by developing basophilia and becoming blast cells. 3) Cells may also leave the compartment by dividing to form small lymphocytes (Fig. 2). The development of basophilia usually, though not invariably, seems to occur in the larger transitional cells.

The size of the transitional (lymphoid) cell compartment thus represents a very dynamic equilibrium between the intrinsic proliferation of the undifferentiated transitional cells, and their differentiation into

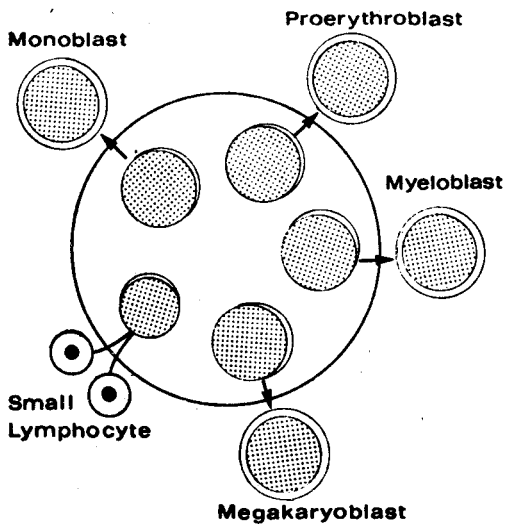

FIG. 2. Cells leave the stem cell compartment either by developing basophilia and becoming blast cells, or by dividing and giving rise to small lymphocytes. Most of the transitional cells which develop basophilia and form blast cells are differentiating into proerythroblasts or myeloblasts, while smaller numbers form monoblasts or megakaryoblasts. Small lymphocytes result from the division of the smaller transitional cells. Most, if not all, of these small lymphocytes are discharged from the marrow into the bloodstream. The size of the transitional cell compartment at any given time is the result of a dynamic equilibrium.

cells which leave the compartment (Fig. 2). In quantitative terms, the three main groups to which the transitional cells give rise are the erythrocytic, granulocytic and lymphocytic series; and the equilibrium can be upset by disturbance of any one of these three groups. Thus, an arrest of erythropoiesis, such as occurs in the bone marrow during posthypoxic polycythemia, is associated with a marked increase in lymphocytes and transitional cells (12). On the other hand, the combined stimulation of granulocyte and B lymphocyte production, observed after the administration of typhoid vaccine (G. Prindull, B. Prindull and J. M. Yoffey, unpublished data), places an unusually heavy load on the transitional cells, which are very significantly diminished.

In Fig. 2 a distinction is drawn between pale and basophilic transitional cells, but it must be emphasized that this is a distinction which is not always as clear-cut as Fig. 2 would imply (32). A high degree of basophilia is found in those transitional cells which are already committed to further differentiation and are becoming transformed into blast cells which, in turn, leave the compartment. The uncommitted pluripotential cells, on the other hand, are believed to be found, in all probability, among the pale transitional cells, which can remain in the G-0 phase for four days or more (33). Transitional cells with intermediate degrees of basophilia present difficulties both of classification and of interpretation (12).

Differing physical properties of lymphocytes and transitional cells. The morphological and labeling differences between transitional cells and small lymphocytes have been fully discussed elsewhere (12), and will not be considered in any detail. It should, however, be emphasized that there are important physical differences between transitional cells and small lymphocytes, and these differences are of value in studies of B lymphocyte production. Rosse (29) observed that *in vitro* the final division of transitional cells formed small lymphocytes, and noted that some time elapsed—about 6 hr—until the daughter cells acquired the morphology of typical small lymphocytes. Before this happened, the daughter cells underwent progressive condensation and shrinkage, during which time the nuclear chromatin gradually acquired the typically dense appearance (pachychromasia) of the fully formed small lymphocyte. Because of this final condensation, transitional cells are larger in size and lighter in buoyant density than the terminal small lymphocyte. Both these properties have been used in separating the small pachychromatic B lymphocytes from their transitional cell precursors.

The size difference made it possible to separate the transitional cells from the small lymphocytes by the technique of velocity sedimentation (34, 35). This technique was later applied (36) to obtain an enriched transitional cell ("B cell precursor") suspension whose maturation properties could then be readily studied.

B cell maturation. The formation of small lymphocytes in the marrow does not in itself constitute evidence of B cell formation. For this, one needs to demonstrate immunoglobulins on the cell surface, as well as to determine the actual source of the cells. The source, as already noted, is in the transitional cell group. As to the surface membrane, early observations on the nonspecific uptake of isotopically labeled protein by lymphocytes (37) were followed by more detailed studies of the binding of labeled anti-immunoglobulin sera (38–40).

Unanue et al. (13) drew particular attention to the bone marrow as a source of B cells. They reported that when adult mice were thymectomized, lethally irradiated, and transfused with bone marrow cells, they "showed a normal number of lymphocytes

with surface Ig, but were depleted of the Ig-negative lymphocytes." Basten et al. (41), noted that in murine bone marrow binding of anti-immunoglobulin serum could not be observed in the B cell precursors, i.e., the transitional cells, which they separated from the B cells by passing the cells through a specially designed column. They thus obtained enrichment of the precursor cells, which appeared to be colony-forming units —or in other words transitional cells (12)— which could give rise to the small lymphocyte B cells.

Lafleur et al. (36) removed B cells from a marrow suspension by velocity sedimentation (34, 35), and then injected the remainder of the suspension, containing the precursor cells, into lethally irradiated mice. They found that the precursor cells in the suspension differentiated into B lymphocytes, and they were thus able to establish a correlation between the two cell groups—"kinetic studies show that the precursor cells start producing detectable numbers of B cells within three days after transplantation; B cell activity then increases with a doubling time of 24 hr." All this, of course, again points to the transitional cells as the precursors of the small lymphocyte B cells. There are in fact no other cells in the marrow which can meet this situation. Lafleur et al. (36) confirmed previous observations that the precursor transitional cells were lighter than small lymphocytes (42). In addition, the precursor cells were present both in marrow and spleen, but not in lymph nodes. This, too, is a distribution characteristic for transitional cells in the mouse, in which species the spleen was first shown to be a source of pluripotential stem cells (43).

Osmond and Nossal (6, 7) combined labeling studies of surface immunoglobulins with kinetic studies of cell proliferation by means of tritiated thymidine. The initial immunoglobulin studies showed that, in adult mice, approximately half the marrow lymphocytes did not have surface immunoglobulin (44). This finding admits of several explanations, of which one is that there is a process of maturation of immunoglobulin-bearing cells from transitional (lymphoid) cells devoid of immunoglobulin. They postulated further that the transitional (lymphoid) cells form "subthreshold concentrations of surface immunoglobulin which immediately precede those cells with minimally detectable surface immunoglobulin." These findings suggested a continuous formation of Ig-bearing lymphocytes from non-Ig-bearing precursors (6, 7). If this were the case, the development of surface Ig would be the last stage in the maturation of a type of cell radically different from all the other main cell groups produced in the marrow, since all the other cells are postmitotic and without further growth potential, whereas the B lymphocyte is capable of further growth and development, though possibly of a limited nature.

Rosse (unpublished data) noted that in guinea pig marrow 30 to 40% of the small lymphocytes lacked surface Ig, and this figure is of the same order as that for the mouse (6). The question arises whether all these Ig-negative lymphocytes would eventually become Ig-positive, or whether a number of them would remain permanently Ig-negative, as has been suggested by Rosse (unpublished data). Rosse also developed the concept that a "sink" mechanism might be at work to get rid of surplus lymphocytes. Whether or not this is so, there is no doubt that the quantitative data on marrow lymphocyte production (1) point to a massive output of cells which seems to be inexplicable on the basis of our present knowledge.

Rosse (unpublished data) also found that a number of transitional cells had already begun to acquire immunoglobulin receptors,

confirming the earlier finding of Lafleur et al. (45), who had previously reported that a very small number (0.1%) of the "precursor B cells" took up fluoresceinlabeled anti-immunoglobulin serum. This is, in fact, in agreement with what has been observed with regard to the development of erythroid cells (12; C. Rosse, unpublished data), in which a small number of transitional cells may be seen to acquire hemoglobin.

Some general problems associated with the development of B lymphocytes. The formation of B lymphocytes from a pluripotential immunohemopoietic stem cell raises a number of intriguing biological problems. Is lymphocyte membrane immunoglobulin the end result of a process of active secretion? Is each lymphocyte capable of forming only its own specific immunoglobulin? How many different immunoglobulins are secreted? What is the differentiating stimulus which causes the stem cell to follow the pathway of lymphocyte differentiation rather than any other? Are B lymphocytes being constantly formed in numbers far in excess of normal requirements? It would be beyond the scope of the present article to deal with these and related problems at length, but in view of their fundamental importance, it is pertinent to mention some aspects briefly.

Is lymphocyte Ig actively secreted? When the surface immunoglobulin coat of B lymphocytes was first noted, the question was left open as to whether or not it was produced by these cells (39). However, it was soon accepted that the surface Ig of lymphocytes is endogenous (46–48). Loor et al. (48) suggested that there may be a continuous secretion of immunoglobulin by lymphocytes. This view accords with the findings of Harris et al. (49) who observed plaque-forming cells with typical lymphocytic nuclei, and cytoplasm with poorly developed endoplasmic reticulum but numerous polyribosomes.

One may perhaps at this point make a brief historical digression to draw attention to the writings of the great French histologist, Ranvier, who 100 years ago described the lymphocyte as "une glande mobile unicellulaire" (50). Little could he then have imagined that a century later, the secretions of this "mobile unicellular gland" should occupy such a focal point in biological research.

Monospecificity of lymphocyte immunoglobulins. The view that all the receptors on a given B cell are specific for the antigen which they bind (51) raises wider general issues of cell differentiation. If the concept of origin of B lymphocytes from pluripotential stem cells is correct, how does one stem cell give rise to a progeny with many different antigen receptors? Yung et al. (17) investigated the development of immune responses in lethally irradiated mice protected with fetal liver, and interpreted their data to indicate the development of a wide antigen-recognition spectrum from a single stem cell. This conclusion was thought to fit in well with the clonal selection theory, and the production of a cell population "with gradually diversifying antigen-recognition specificities," presumably by somatic mutation (52, 53). According to Yung et al., one stem cell, in the course of about 20 days, could give rise to a panel of lymphocytes capable of recognizing approximately 10,000 antigens. In fact, the only cells in the marrow capable of the rate of division needed to give rise to such a varied progeny of B lymphocytes are transitional cells. No other cells in the marrow can meet this growth requirement.

It is interesting to note that Trentin et al. (14) performed an essentially similar type of experiment to that of Yung et al. (17) except that in their experiments protection was conferred by suspensions of adult marrow. However, they interpreted their results

as evidence against the clonal selection theory, since they felt that the requisite mutation rate was far too rapid.

Whichever of these two interpretations is correct, we are still left with one fundamental problem. How do transitional cells give rise to comparatively uniform populations of other blood cells, such as erythrocytes and granulocytes, but such diverse populations as B lymphocytes? We have as yet no answer to this problem, nor for that matter have we any knowledge of the essential mechanisms for the control of B lymphocyte production as such, quite apart from the question of antigen-recognition diversity. We know, as yet, of no substance, comparable to erythropoietin in the field of red cell production, which could similarly influence B lymphocyte formation.

THE LONG PRODUCTION PATHWAY FOR T CELLS

In contrast with the short production pathway for B lymphocytes in the marrow, there are long production pathways in both lymph nodes and thymus. The earlier studies on the long production pathway were made soon after the introduction of tritiated thymidine as a tool for the labeling of dividing cells (54–57). The larger labeled cells at the beginning of the pathway undergo a number of divisions in fairly rapid succession, and there is thus an increasing number of cells with progressively diminishing cell size, until the small lymphocyte is reached. The repeated divisions of labeled cells result in a progressive and striking dilution of grain count (1, 56), somewhat more marked in the case of the thymus than in that of the lymph nodes. In the case of the thymus, it has been reported (56) that eight days after one i.p. injection of tritiated thymidine, virtually all the labeled thymic cells were small, and possessed only one or two grains, thus contrasting very forcibly with the much heavier labeling of B lymphocytes at the end of the short production pathway.

For a long time, the starting cell in the long production was thought, by most observers, to be a "reticulum" cell, and the number of mitoses from the reticulum cell to the final small lymphocyte (thymocyte) was estimated to be eight (58). Without going into too much detail on these two points, it should be noted that according to Caffrey et al. (59) the reticulum cell cannot be the start of the pathway, in which case the parent cell would be a lymphoblast or a "monocytoid" cell from the bone marrow (30). Furthermore, there may not always be exactly eight mitoses. Subject to considerations of this kind, the broad concept seems to be correct, namely, that there are several more mitoses in the long production pathway for T lymphocytes than in the short pathway for B cells.

Do many T cells die in situ, *and never leave the thymus?* Earlier work on lymphocyte production in the thymus, involving the use of radioisotopes such as tritiated thymidine, raised difficulties of interpretation because of the possibility of cell destruction and the reutilization of breakdown products. At one time it was suggested that most of the newly formed cells in the thymus died in that organ and never left it (60), but this view has not gained acceptance (61). All the quantitative data appear to indicate that there is massive production both of T lymphocytes in the thymus and of B lymphocytes in the bone marrow. Furthermore, from each of these organs there is a steady discharge of newly formed lymphocytes into the circulation.

Surface distinctions between B and T cells. The introduction of scanning electron microscopy has brought out interesting surface differences in structure between B and T cells. Notably, the surface of the B lymphocyte usually has a rough appearance, due

to the presence of many microvillous projections, while that of the T lymphocyte is much smoother, and exhibits a much smaller number of projections (62). We do not know to what extent the greater number of mitoses may be responsible for the smoother surface of the T lymphocyte as compared with the more villous surface of its B counterpart. It might help to decide this point if one could study the surface structure at the various stages of the long and short production pathways.

Do T cells leave the thymus at different stages of maturation? The greater number of mitoses in the course of the long production pathway opens up the possibility that an appreciable number of cells may leave the thymus at some of the earlier stages in the pathway, before the final small T cell is formed. At different stages of T cell maturation, these earlier cells could conceivably account for observations such as those of Cantor and Asofsky (63) or of Stobo and Paul (64), who distinguished two types of T cell. Cells which leave the thymus at earlier stages of maturation could presumably complete their maturation wherever they settle. It is possible, for example, that the $\theta+$ cells described in lymph nodes by Schlesinger and Yron (65) may fall into this category, although more information is needed on this point. Similar considerations would apply to T cells which migrate to the spleen.

FACTORS INFLUENCING B AND T LYMPHOCYTE PRODUCTION

Although it is obviously of great interest to know what factor or factors control the production of B and T lymphocytes, very little information is, in fact, available. However, we do know of some factors which may play some part in the control mechanism.

Age. Age is one of the factors which seems likely to be involved. Involutionary changes in the thymus with increasing age—after the pubertal growth peak—have long been known. However, the age changes in the transitional (lymphoid) cell and lymphocyte population of bone marrow are not so generally appreciated. In the latter half of fetal life, human fetal marrow has a high percentage of transitional cells and lymphocytes (66). Both in man and in animals, these cells may increase even further during the immediate postnatal period. They remain above the adult level throughout the growth period, and then undergo a steady fall, although they are always present (1, 12, 21–25). A more detailed account of age changes in bone marrow and thymus has been given elsewhere (1, 12).

Access of proteins to developing B and T cells. Another factor whose significance we are not yet able to assess is the extent to which proteins in the circulation obtain access to and influence the development of B and T cells. The sinusoidal endothelium of bone marrow is freely permeable to protein molecules, and even to particulate matter (1). Proteins in the bloodstream traverse the sinusoidal endothelium very rapidly, enter the marrow parenchyma and come into close contact with its cells. They can however, also pass through the endothelium in the reverse direction, with equal speed and facility, to reenter the bloodstream. It is for this reason that there is no need for lymphatics in the marrow to return extravascular protein to the circulation (1, 67).

In the case of the thymus the existence of a "blood-thymus" barrier has been postulated by a number of workers (1). Although the barrier is only a partial one, it undoubtedly exists. Clark (68) injected mice i.v. with iodinated bovine and human serum albumin, as well as with colloidal iron, ferritin, and trypan blue. He was unable to detect either colloidal iron or bovine serum

albumin in the thymic parenchyma, at times ranging from 15 min to 48 hr after administration. He could, however, identify the other substances, although they were "less concentrated in the thymic parenchyma than in other lymphoid organs."

The obvious question which arises is whether the variation in access of proteins to the developing cells might conceivably be one of the factors determining the different lines of development of B and T cells. Here, for the moment, we can only speculate, and then try to submit our speculations to experimental analysis. In some instances, small amounts of undigested protein can be shown to be absorbed from the lumen of the intestine (1). There may be a link with the process of "subinfection," a concept put forward in the early days of pathology [as, for example, by Adami (69)], when it was suggested that there could be a continuous absorption into the blood stream of small amounts of antigenic material, mainly through the intestinal mucosa. It is conceivable that a few molecules of foreign protein, upon reaching the marrow, would come into contact with some uncommitted transitional cells and channel them into immunoglobulin synthesis. However plausible such a speculation might appear, it does not fit in with some of the facts. As already noted (66), the bone marrow in the human fetus is particularly rich in transitional cells and lymphocytes, at a time when exposure to antigenic material would appear to be minimal. Yet B cells are apparently being formed at virtually the same rate as in postnatal life, when the antigenic exposure is much greater. The percentage of B cells in the blood of adults (70) is of the same order as that in cord blood (71). If the percentage of B cells in the blood is a reliable criterion for assessing B cell production, this would imply that the formation of B cells occurs, to a large extent, independently of antigenic stimulation. It may well be, as Rosse (unpublished data) suggests, that the formation of lymphocytes in the marrow is one way of maintaining some degree of constant turnover in the stem cell compartment. It is now generally accepted (12, 72) that in the normal steady state a certain proportion of cells in the stem cell compartment is constantly turning over. Lymphocytes would then be produced when stem cells are no longer differentiating into any of the other blood cells, constituting what Rosse describes as a "sink" mechanism.

SUMMARY

There are striking differences in the histogenesis of B and T cells. 1) The formation of B lymphocytes seems to be closely associated with that of other blood cells, whereas the formation of T cells is not. 2) In postnatal life, the bone marrow is a major site for the formation of B cells, while T cells are produced mainly in the thymus. 3) B cells are formed in a short production pathway, consisting of two or three mitoses, whereas T cells are formed in a long production pathway, consisting of about eight mitoses. 4) The starting point for the short production pathway is a large transitional cell. The long production pathway starts with a reticulum cell, a large lymphoblast or a cell which has been termed "monocytoid." 5) Plasma proteins have ready access to the cells of the short production pathway in bone marrow, but because of the blood-thymus barrier are not as readily accessible to the tissues involved in T cell formation in the long production pathway in the thymus.

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