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THE DYNAMICS OF LEUKOPENIA AND LEUKOCYTOSIS * †

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MANY features of the physiology of leukocytes are controversial. The origin of certain cells—for example, the monocyte and the plasma cell—is disputed. The functions of many of the cell species (e.g., the variously sized lymphocytes, the eosinophil, the basophil) are still conjectural, despite recent advances in cytochemistry. The lymphocyte has been implicated in such fundamental processes as immune globulin synthesis, antibody transport,[1] and the transmission of genetic material or information to proliferating tissues.[2] They have also been described as "pluripotential" cells, capable of differentiation into other hemic cells.[3]

In contrast to these less well defined and esoteric functions of other cell types, the granulocyte is clearly designed primarily for phagocytosis. Lymphocytopenia, eosinopenia or absence of monocytes from the peripheral blood is not associated with any obvious defect in body physiology directly attributable to the lowered blood concentration. Agranulocytosis, on the other hand, removes a major defense barrier against bacterial invasion.

The blood granulocyte is well defined from several aspects: morphology, site of origin, and function. In spite of these features which render it suitable for quantitative study, the granulocyte remains the object of much controversy as to its "life span," rate of production, etc. It is obvious that

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elucidation of disorders of granulocytopoiesis, such as granulocytic leukemia, leukemoid reactions, etc., must evolve from basic knowledge of the aforementioned type. The purpose of this paper is to review some of the more recent findings on the subject of granulocyte physiology, to attempt correlation of these findings into a workable concept, and to suggest their possible clinical significance.

Production of Granulocytes

In the normal human, granulocytopoiesis is confined to the marrow. Circulating cells of this lineage do not proliferate, as evidenced by their lack of desoxyribose nucleic acid (DNA) synthesis, mitosis, etc. It is well established that cell division does not occur among cells beyond the myelocyte stage; it would appear that cells which lack nucleoli are incapable of division. However, in situations associated with a greatly increased demand for granulocytes (e.g., acute bacterial infection), earlier forms may appear in the blood which show active DNA synthesis. This intramedullary localization of granulocyte production has permitted more detailed study of the movement of granulocytes from the marrow into the blood by labeling the DNA of the cells during DNA synthesis. The technics of isotopic DNA labeling with P^{32}- or C^{14}-tagged adenine or formate depend upon isolation of the leukocyte DNA in a highly purified state. Furthermore, granulocytes and lymphocytes must be separated in order to interpret the kinetic data. In spite of these technical handicaps, and in spite of the possibility of such complications as reutilization of the labeled DNA, these methods have provided valuable information. The more recent method of DNA labeling with tritiated thymidine, coupled with high resolution radioautography, has, in general, supported the findings with P^{32} or C^{14}.

The studies of Kline and Cliffton [4] and Ottesen [5] showed a curve of appearance and disappearance of DNA-labeled leukocytes which was characteristic. Ottesen, after correcting the curve for lymphocyte contribution and for the amount of P^{32} still available at a low concentration which would provide continuous DNA labeling, derived a curve as shown in figure 1. He interpreted the curve as indicating that there was a hold-up of granulocytes in the marrow for from five to six days, and that the circulating granulocytes have an "average age" of nine days. Kline and Cliffton estimated the granulocyte "life span" at about 13 days.

These data were in fair agreement with labeling experiments employing in vivo tagging with Cr^{51} and S^{35} cystine,[6, 7] ascribing a life span of about 13 days to the granulocyte after leaving the marrow. However, such estimates of a relatively long survival of granulocytes were in sharp contrast to the very short period which granulocytes labeled in vitro could be detected in the circulation in large numbers.[6, 8] Most experiments of this type provided an estimate of less than one hour. It has been the feeling of many workers in the field that these differences could be explained on the basis either of

cell trauma incident to the in vitro handling of the cells, with failure of these cells to circulate normally or of their temporary removal from the circulation and later reëntry. The general opinion has been that the in vivo labeling experiments, especially the DNA-tagging data, gave a more valid picture of granulocyte "turnover." However, the interpretation of this type of data has usually failed to take cognizance of certain factors which markedly influence the meaning of granulocyte DNA labeling.

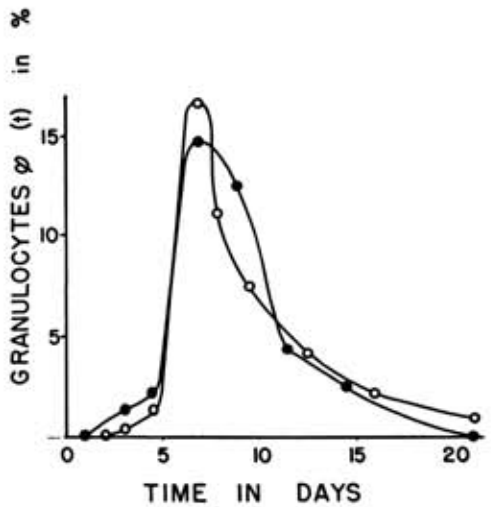

FIG. 1. The curve of appearance and disappearance of DNA-labeled granulocytes in the peripheral blood of two patients, as determined by Ottesen.[5] The curves have been corrected for the persistence of available P^{32}.

One of the assumptions which have been made is that a sample of the granulocytes in the peripheral blood provides an average age for all granulocytes in the peripheral blood and tissues, just as in the case of the red cell population. In order for this to be so, the granulocytes circulating in the blood must be in a state of free interchange with those in tissue extracellular spaces all over the body. It has been assumed by Ottesen [5] and others [2, 4] that the average granulocyte may leave the blood and reënter many times during its total life after leaving the marrow.

Another factor influencing data of this type is the extent to which the marrow mass of myeloid cells is labeled. As will be indicated later, it appears that this is the most important factor in shaping the course of blood granulocyte DNA labeling.

THE CIRCULATION OF GRANULOCYTES

There is abundant evidence that granulocytes are selectively sequestered in the capillary beds of certain organs, especially the lung, spleen and liver. The harboring of granulocytes in these areas is influenced by physical phenomena such as blood flow, vasoconstriction, ventilatory rate, exercise, etc.[9]

There are no definitive data as to how long granulocytes may remain in such capillary beds. It seems likely that this would vary greatly, depending upon a variety of factors. Obviously, these cells may either move through the capillary endothelium or be released back into the moving stream of blood. The studies of Ambrus and Ambrus [10] suggest that, in the case of the lung, there is a constant removal of granulocytes from the blood perfusing the lung unless the concentration of granulocytes in the perfusing blood is less than approximately 1,000 per mm.^{3} The removed cells appear in the alveoli and bronchial secretions, there being a constant attrition of granulocytes. When the perfusing blood is almost devoid of granulocytes (below 1,000 per mm.^{3}) there is a release of cells from the lung into the effluent blood. This repletion is short-lived, however, and is apparently related to cells harbored in the capillary network itself.

The numerical size of the granulocyte mass sequestered in various capillary beds is unknown. From leukopheresis experiments in dogs [11, 12] it was estimated that it approximately equaled the number freely circulating in the normal, steady state. In any event, the peripheral circulation of granulocytes may be envisioned as a freely circulating compartment and a capillary bed compartment. The cells in these two main compartments are, of course, readily exchangeable. The term "recirculation," as applied to granulocytes, is believed to denote the release of cells from capillary beds into the freely circulating blood, and not reëntry of cells from extravascular sites. There is no direct evidence that granulocytes in tissue spaces and in various body cavities and secretions reënter the blood in significant numbers. There is considerable evidence to the contrary, derived from leukopheresis experiments in normal and in irradiated animals.[11, 12] Furthermore, the induction of sterile peritoneal exudates in dogs failed to show an equilibrium between highly labeled cells entering the blood from the marrow and less highly labeled cells in the exudate over a period of seven hours.[13] For these reasons, the cells circulating in the blood are not believed to represent an average age of the entire mass of extramedullary granulocytes. This renders untenable the interpretation of DNA granulocyte labeling data in terms of cell survival time in blood and tissues.

The Marrow Granulocyte Reserve (MGR)

The normal marrow contains a volume of granulocytes no longer capable of division (i.e., beyond the myelocyte stage of maturation) which far exceeds the total number circulating at any one time. Donohue et al.[14] found marrow reserves of granulocytes and stab forms of about 20 times those in the circulation. Patt [15] estimates a ratio of marrow nonproliferating granulocytes to blood granulocytes at 26-to-one, and Osgood estimates 70-to-one.[16] This relationship is depicted in figure 2 and contrasted with the erythron, in which the number of mature red blood cells (reticulocytes and older) exceeds the marrow content of mature red blood cells by some 50 times.

(It might be mentioned at this point that the marrow reserve of platelets appears to be a volume about equal to that of the circulating platelet mass.)

The significance of this nonproliferating pool of marrow granulocytes in the response to an acute demand for increased numbers of these cells has been described previously.[12, 13] Movement of cells from the MGR into the blood accelerates immediately upon demand, and occurs whether or not granulocyte production is taking place in the proliferating tissue. In experiments in normal and irradiated dogs, it was evident that the speed and height of the leukocytosis following an acute, transient stimulus might be used to assess the status of the MGR.[17]

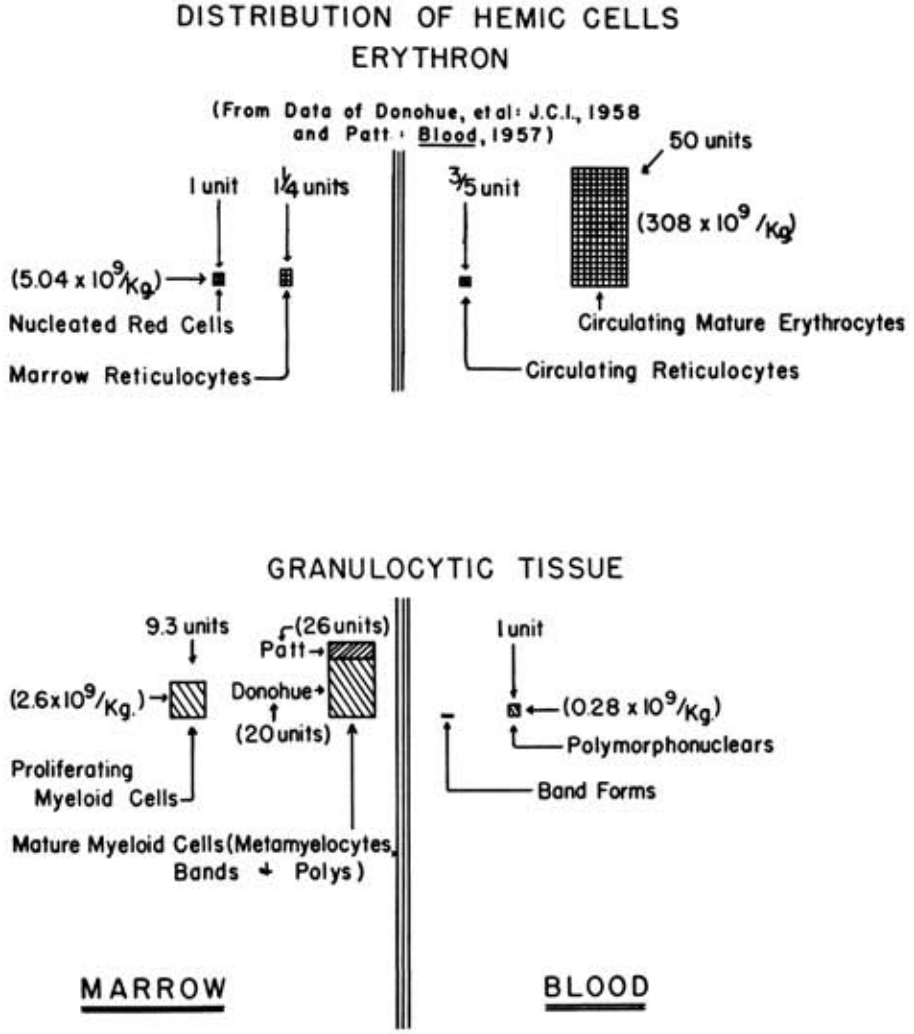

FIG. 2. Comparative sizes of the marrow content of erythroid and granulocytic cells to the blood compartment. Note that the unit values differ for the two series.

Since the approximate size of the marrow granulocyte mass is known (figure 2), and since the circulating granulocytes normally enter the blood from the marrow and not from other extravascular areas, the rate of entry of granulocytes into the blood can be calculated quite simply from the "turnover time" of the marrow granulocyte reserve. This is approximately five days. The number of cells entering the blood per hour in the 70-Kg. man will number in the range of 0.58×10^{10} to 1.0×10^{10}, depending upon what estimate of MGR size is employed. This volume of cells will be sufficient to replace those circulating (about 2×10^{10}) every two to four hours. If the size of the blood granulocyte mass is doubled to include those cells in the capillary beds, the blood granulocyte "turnover" would be about four to eight hours. As previously stated, this estimated rapid turnover of blood granulocytes in the steady state is an average value only, some cells probably remaining in capillary beds much longer than eight hours, and some passing through very quickly.

Whereas the movement of granulocytes out of the blood is a random loss, the entry from the marrow and the turnover of the marrow granulocyte mass are an orderly process. The movement of labeled cells through the MGR into the blood imparts the characteristic form to the blood granulocyte DNA-P^{32} curve. Those granulocytes which first enter the blood from the labeled MGR are the most highly labeled cells because they are products of only one cycle of DNA synthesis and cell division after the time the isotope is given. The specific activity of the DNA-P^{32} becomes progressively diluted with each cell division. The MGR becomes labeled in a manner which reflects the mitotic activity of the proliferative compartment. The circulating granulocytes in the normal, steady state may be envisioned as the "top layer" of the granulocytic tissue in the marrow, i.e., cells which have passed through the various phases of maturation and are ready to be expended.

The disappearance of DNA-labeled granulocytes from the peripheral blood is a reflection of the turnover of the labeled MGR. Therefore, the rate of fall of the DNA-P^{32} curve is not significantly altered by acute fluctuations in the blood granulocyte concentration.[17] Indeed, the rate of disappearance of labeled cells is not much accelerated in patients with known pyogenic infection,[18] or in animals subjected to leukopheresis or peritonitis.[17] This is due primarily to the very large mass of labeled cells in the MGR in relation to the small size of the blood compartments.

The foregoing interpretation of the significance of the curve of blood granulocyte DNA labeling agrees well with the findings of others using tritiated thymidine.[3, 19] The work of Bond et al.[3] in a human receiving a large dose of this material displays a similar general curve, although the peak of labeling is earlier than with P^{32}. This difference must be reconciled, and may possibly be related to the clinical condition of the patient. It is

known that the presence of inflammation, for example, will accelerate the appearance in the blood of cells labeled in the marrow.[18]

On a theoretic basis, the MGR should be capable of maintaining the circulating granulocyte level for from five to six days after cessation of all myelopoiesis, as following a single exposure to massive whole-body irradiation. This agrees with the observations of Brown and Abbott on the change in leukocyte numbers following a single large exposure.[21] The rate at which granulocytopenia develops in this situation will also depend upon how much myelopoiesis remains, how soon recovery begins, and how rapidly granulocytes are being "utilized" in the periphery as a result of radiation sickness and damage to other tissues, such as the gut. In any event, the MGR is an important determinant of the time of onset of granulocytopenia and its severity. It would be expected that an individual whose reserves are already depressed, or a person suffering from an infection, would become leukopenic more rapidly than would a normal person exposed to a similar dosage.

If the fluctuations in freely circulating granulocyte number caused by alteration in the harboring and release of granulocytes by capillary beds are ignored, the blood granulocyte level depends upon the rate of entry and exit of granulocytes. Accordingly, granulocytopenia may be due to either a diminished rate of entry of cells or accelerated movement through the vascular compartments. Experiments with leukopheresis and peritoneal inflammation in dogs have shown that the blood level of granulocytes may not rise, or, indeed, may fall when granulocytes are "pulled" out of the circulation rapidly in spite of a greatly accelerated entry from the MGR. In subjects with a markedly increased peripheral utilization of granulocytes, as in "overwhelming" pyogenic infection, peripheral blood leukopenia may develop, indicating that the MGR has been depleted and is unable to keep pace with the demand. In situations of this type, the morphology of the peripheral blood and marrow indicates the depletion of mature granulocytes by the "left shift" and immaturity of the cells.

Clinical Evaluation of Marrow Granulocytic Reserves

Alterations in the circulating granulocyte levels should be interpreted in light of the relationship between the MGR and blood granulocytes. Some estimation of the adequacy of the MGR can be obtained by correlation of blood and marrow morphology with the granulocyte response to the intravenous injection of bacterial endotoxin. The agent which has been employed in this laboratory is a purified lipopolysaccharide from *Salmonella abortus suis*, Pyrexal.* This material has been used for its hematologic effects in Europe,[22, 23] and in doses of 0.1 to 0.2 γ causes very little in the way of systemic symptoms.

* We are indebted to Wander & Co. for supplying this material.

The normal response of the granulocytes to such an agent is a sudden fall, followed by an increase to levels about twice base line.[17] The total increment in segmented granulocytes exceeds 2,400 per mm.^{3} in the normals thus far studied. It has been previously shown in dogs that a leukocytosis of this type involves the release of granulocytes from the MGR.[24] We have found this test of use in patients with leukopenia associated with Hodgkin's disease or other lymphomas requiring radiation or other myelotoxic therapy. However, it must be correlated with marrow and blood morphology to be of significance. Furthermore, in patients with complicating factors affecting the leukocyte level, such as massive splenomegaly, the test may be unreliable. The chief significance of the test is that, if a normal response is obtained, this is strong evidence that the marrow contains adequate reserves of granulocytes. The failure to develop leukocytosis after Pyrexal may or may not mean depletion of the MGR.

The Dilemma of Lymphocyte Kinetics

In spite of recent advances in technics of handling, labeling and following the course of lymphocytes, there remains considerable confusion as to the production, turnover and distribution of these cells. Undoubtedly, much of the apparent contradiction arises from the fact that the cells entering the blood from the lymphatic tissues are heterogeneous from a morphologic and physiologic standpoint. For example, Fichtelius [25] has shown that the distribution of lymphocytes in various tissues after labeling differs, depending upon whether the cells were obtained from the thymus or from the lymph nodes. Numerous investigators have observed that certain cells of larger size are actively synthesizing DNA as they enter the blood, and hence are proliferating in the lymph, blood and tissues after leaving the lymphatic tissue. These cells can be observed to divide while in the lymph and blood. The number and percentage of these proliferating cells in the lymph vary in different species.

It appears from these observations that lymphocytopoiesis, at least as carried on by these cells, is not confined to the lymphatic tissue. Is it possible that lymphocyte production may occur in any location where these large dividing cells lodge?

The majority of small lymphocytes are, like the circulating granulocyte, no longer capable of DNA synthesis or cell division. They are actively motile, and are believed to be important in protein synthesis and immunologic processes. Since the number of these cells entering the blood from the thoracic duct alone is sufficient to replace those circulating several times a day, it would appear that either the "turnover" of lymphocytes is quite rapid, or the total peripheral pool of lymphocytes is enormous, compared to the circulating number. Data from DNA labeling experiments in normal and leukemic humans have been interpreted as showing a very long "life span" for these cells, in the range of 100 to 300 days.

Gowans has presented evidence which may to some extent reconcile these apparent discrepancies. In rat experiments, his data suggest recirculation of lymphocytes between blood and lymph.[26, 27] If this can be shown to hold true in other species, then the high cellular output from the lymph may not be incompatible with a long-lived cell population.

The actual evidence for the small lymphocyte surviving for a long period of time after its initial entry into the blood rests primarily on the results from DNA-labeling experiments. As was pointed out for the granulocyte, the events occurring in the proliferating tissue appear to be the main determinants of the characteristics of the DNA-labeling curve.

From correlation of the DNA specific activity in lymph and blood, it would appear that there is no delay before DNA-labeled cells appear in the blood, as would be expected, since the large lymphocytes are actively elaborating DNA as they enter the blood. A sample of peripheral blood lymphocytes therefore contains a small percentage of proliferating cells and a larger percentage of "mature" or nonproliferating cells. The large proliferating lymphocytes appear to leave the circulation very quickly after entering.[28, 29] Experiments in this laboratory, employing reinfusion of autogenous thoracic duct lymphocytes, the DNA of which has been labeled by short-term incubation with tritiated thymidine, have shown that these cells, or their labeled progeny, may be detected in the circulating blood and marrow for two days after reinfusion in the dog. Whether these large cells lodge more selectively in certain tissues, such as the bone marrow or lymph nodes, is not known at present. Reappearance of cells in the thoracic duct lymph was not observed in these experiments. Furthermore, labeling of all thoracic duct lymphocytes (both the small variety and the larger proliferating cells) with P^{32} chromium phosphate has failed to show reëntry of these cells into the thoracic duct lymph over a two-day period. The reinfused tagged cells were viable insofar as the criteria of motility and vital staining may be relied upon. The reason for the discrepancy between these findings and those of Gowans, previously cited,[26, 27] is not entirely clear. Gowans' experiments more nearly approached physiologic conditions, and it may be that nonspecific effects of anesthesia, trauma, etc. prevented the recirculation of the labeled lymphocytes between blood and lymph in the dog experiments.

In no instance have we observed the appearance of the DNA label in other types of hemic cells after the reinfusion of lymphocytes labeled with tritiated thymidine. There would seem to be little doubt that these blood-borne proliferating cells arise in lymphoid tissue. They have been considered to be "pluripotential" or stem cells by some,[3, 31] but the actual demonstration of their differentiation into myeloid or erythroid elements remains for the future.

It would seem reasonable to assume that these proliferating lymphocytes are important in total lymphocytopoiesis, as has been suggested by others.[26, 30] In the dog, cells capable of DNA synthesis comprise about 15% of the

thoracic duct lymphocyte population. In previous experiments, the average number of cells entering the blood via the thoracic duct in a 20 to 25 Kg. dog was found to be 0.043×10^{10}, or 1.032×10^{10} in 24 hours.[28] The number of proliferating cells would therefore be about 1.55×10^{9} per 24 hours. Yoffey [31] estimates that at least two or three times as many lymphocytes enter the blood via other means than enter through the thoracic duct. Therefore, the total number of proliferating lymphocytes entering the blood per day would be between 3.1×10^{9} and 4.65×10^{9}.

It is of interest to compare the volume of proliferating lymphocytes entering the blood with the number of marrow erythroid progenitors. Patt [15] estimates that the dog marrow contains 6.7×10^{9} nucleated erythroid cells per kilogram. Since roughly half of these are capable of division, the dog's erythroid proliferative mass is 3.35×10^{9} cells per kilogram, or 67×10^{9} in a 20-Kg. dog.

From these rough calculations it would appear that enough dividing cells enter the blood from the lymph to equal the total erythroid proliferative mass every 12 to 22 days. This is a rather sizable "extralymphatic" mass of proliferating lymphatic tissue.

It may be argued that this large influx of dividing cells is more apparent than real because these cells are reëntering the lymph from the blood even while in the process of dividing. That this is not the case was shown by thoracic duct cannulation in dogs at varying time intervals after labeling the lymphocytes.[28] The sharp fall in thoracic duct lymphocyte DNA-specific activity after an early peak at eight to 12 hours is strong evidence against significant reëntry of these highly labeled cells into the lymph.

If one assumes that these proliferating cells, originating in lymphoid tissue, enter the blood for some good reason and do not promptly die, it seems reasonable to believe they may implant in certain areas of the body and continue to produce lymphocytes. It is conceivable that the rate of proliferation may vary, depending upon environmental conditions, vascularity, etc.

This concept of widespread lymphocytopoiesis at different rates of speed would agree well with the observed results of DNA labeling of lymphocytes, which indicate a very large proliferating mass of lymphoid tissue in relation to the small circulating mass of lymphocytes. The labeling of lymphocyte DNA in cases of chronic lymphatic leukemia receiving P^{32} therapy provides an opportunity to follow the labeling of lymphocytes under exaggerated circumstances. The curve follows a very erratic course in our hands, with multiple peaks suggesting the entry of labeled cells into the blood at different times. The very prolonged presence of some labeled cells in the circulation may well mean that the turnover by growth of certain segments of the total lymphopoietic tissue, and hence the rate of dilution of the DNA label, is very slow.

Just as in the case of the granulocyte, the disappearance of labeled cells

from the peripheral blood may have very little to do with the time the fully mature lymphocyte circulates in the blood and survives in the tissues. This aspect of the physiology of lymphocytes remains unsettled. In this regard it is of interest that lymphocytopenia is one of the earliest observable effects of whole-body irradiation, occurring before granulocytopenia. This is in spite of the purported long "life span" of the mature lymphocyte and its ability to recirculate between blood and lymph. It may be argued that irradiation distorts the architecture of the lymphatic organs to such an extent that recirculation cannot occur through the nodes. However, the actual numerical output from the thoracic duct lymph falls almost immediately after irradiation.[32] If the mature lymphocyte is a long-lived cell which recirculates between lymph and blood, it is difficult to understand why the number in both blood and lymph should fall so fast after irradiation. It is difficult to escape the opinion that the most important factor in maintaining normal numbers of lymphocytes in blood and lymph is a high rate of production, and that the mature cell is short-lived. Nevertheless, on the basis of existing knowledge, it is impossible to define the "life span" of the various types of lymphocytes.

Summary and Conclusions

Certain aspects of the physiology of granulocyte and lymphocyte production and circulation have been presented. In normal human granulocyte physiology the maturing cell spends a period of about five days in the "marrow granulocyte reserve" (MGR). The cells in the MGR are products of the proliferating myeloid tissue, and the relative sizes of these marrow "compartments" have been calculated by others. The MGR contains a volume of maturing cells some 20 to 25 times the number estimated in the circulating blood.

DNA-labeling experiments, combined with leukopheresis and other methods of inducing leukopenia and leukocytosis, have shown that granulocytes circulate freely for variable but brief periods, and may be sequestered in various capillary beds for most of their intravascular life. The average time spent in the circulation appears to be between four and eight hours. Once the granulocytes leave the vascular system entirely and migrate into tissue spaces, they do not appear to reënter the circulation in significant numbers.

The MGR is the most important factor in the development of an acute leukocytosis as induced by leukopheresis, intravenous bacterial endotoxin and experimental peritonitis. The adequacy of the MGR can usually be assessed by correlation of blood and marrow morphology with the granulocytic response to a purified bacterial lipopolysaccharide, Pyrexal. The response to Pyrexal has been studied in a variety of clinical states, and has been found to be of use in patients undergoing therapy with myelotoxic agents. A normal response is strong evidence for adequate marrow granulocytic reserves. However, the failure to develop a leukocytosis in the

normal range must be interpreted in the light of other clinical findings, since it may be due to accelerated removal of cells peripherally, rather than to depletion of the MGR.

The physiology of lymphocytes is as yet poorly understood. Present evidence suggests that lymphocytopoiesis may take place in a variety of tissues as well as in lymph nodes, lymph and blood. It is pointed out that the isotopic data previously interpreted as showing a very long survival time for the mature lymphocyte may actually reflect the very slow turnover by growth of the large mass of lymphocytopoietic tissue.

SUMMARIO IN INTERLINGUA

Es presentate certe aspectos del physiologia del production e circulation de granulocytos e lymphocytos. In le physiologia normal del granulocytos human, le cellula maturante passa un periodo de circa cinque dies in le "reserva granulocytic del medulla" (RGM). Le cellulas in le RGM es productos del proliferante tissu myeloide. Le dimensiones relative de iste "compartimentos" medullari ha essite calculate per altere autores. Le RGM contine un numero de cellulas maturante equal a circa 20 o 25 vices le numero estimate de cellulas in le circulation.

Experimentos con marcation de acido disoxyribonucleic, combinate con leucopherese e altere methodos pro inducer leucopenia e leucocytosis, ha monstrate que granulocytos circula liberemente durante variabile periodos de tempore, e que illos pote esser sequestrate in varie capillaturas durante le plus grande parte de lor vita intravascular. Le duration medie de lor sojorno in le circulation pare esser inter quatro e octo horas. Post que le granulocytos ha quitate le systema vascular e ha migrate a in spatios tissular, il pare que illos non re-entra in le circulation in numeros significative.

Le RGM es le factor le plus importante in le disveloppamento del leucocytosis que es inducite per leucopherese, per endotoxina bacterial intravenose, e per peritonitis experimental. Il es usualmente possibile evalutar le adequatia del RGM per correlationar le morphologia de sanguine e medulla con le responsa granulocytic de un purificate lipopolysaccharido, Pyrexal. Le responsa a Pyrexal ha essite studiate in un varietate de statos clinic. Illo se ha provate de valor in le caso de patientes subjicite al therapia con agentes myelotoxic. Un responsa normal es un forte indication pro le adequatia del RGM. Tamen, quando leucocytosis non se disveloppa intra le mesuras normal, iste facto debe esser interpretate in le lumine de altere observationes clinic, proque il es possibile que le causa es un accelerate elimination peripheric de granulocytos e non un depletion del RGM.

Le physiologia del lymphocytos es pauco comprehendite a iste tempore. Le datos currentemente disponibile suggere que lymphocytopoiese pote occurrer in un varietate de tissus e non solmente in le nodos lymphatic, le lympha, e le sanguine. Es signalate que le datos de isotopia que esseva previemente interpretate como prova de un longissime superviventia del lymphocytos matur reflecte forsan plus tosto le lentissime processo metabolico-crescential del grande massa de tissu lymphocytopoietic.

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