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INDEX PART I

THE ROLE OF THE LYMPHOCYTE IN HAEMOPOIESIS.

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The problem of the lymphocyte becomes progressively more complex and at the same time more intriguing. We are in possession of a number of assorted facts, which we are trying to fit together like the pieces of a jig-saw puzzle, but unfortunately there are still a number of gaps to be filled in.

The role of the lymphocyte in haemopoiesis has been for many years one of the most controversial problems in haematology. We ourselves now regard it as a pluripotential primitive cell, capable of developing in different ways according to its surroundings and the type of stimulus reaching it.

There appear to be three major sites of activity for the lymphocyte. One is in the bone marrow - and spleen in smaller animals - where its role is haemopoietic. A second is in some of the lymphoid tissues, where it is concerned with immune responses. A third is in the connective tissues, where in addition to immune responses, transformation into monocytes and various connective tissue cells may occur. In the blood the lymphocyte is merely en route from one region to another. Dr. Braunsteiner's work has centred largely on the lymphocyte in the connective tissues and on plasma cell formation (Braunsteiner, Fellinger & Pakesch 1953; Braunsteiner, Paerton & Thumb 1958). The work of Dr.Fichtelius has also touched on this, as well as on the movement of lymphocytes between different parts of the lymphomyeloid complex (1953; 1958).

WHY HAS THE LYMPHOCYTE PROBLEM BEEN SO CONTROVERSIAL?

It is interesting to examine the reasons for the controversy surrounding the lymphocyte. The first arises out of its pluripotential nature, as a result of which observers have concentrated on one of its functions and ignored the others. From a study of its immunological role one would not learn anything about its part in haemopoiesis, which can only be studied in the haemopoietic tissues. The second reason is that lymphocytes which look alike may in fact be quite different in their subsequent development. For example in those lymphoid tissues which are exposed to antigenic stimuli the lymphoid cells form antibody and follow the line of development leading to plasma cell formation. However, not all lymphoid tissues react in this way. Wiseman (1931) showed that after repeated injections of egg albumen the lymphoid tissues underwent hypertrophy, whereas the thymus did not. Similarly Bjorneboe, Gormsen & Lundqvist (1947) found no antibody in the thymus of hyperimmunised animals.

It might at first sight appear - as many indeed have concluded - that thymocytes and lymphocytes are fundamentally different. This is not so, however, for thymocytes in contact with antigen follow

the plasma cell line of development (Marshall & White 1961), can form antibody (Stoner & Hale 1955) and can reject heterologous cells (Bekkum & Vos 1957).

CONDITIONED AND UNCONDITIONED LYMPHOCYTES.

Phenomena of this kind have led us to the concept of "Conditioned" and "Unconditioned" lymphocytes. Whatever theory of antibody formation one may adopt, it involves some "conditioning", genetic or otherwise, of lymphoid cells exposed to antigen for the first time, in the so-called "primary" response (Leduc, Coons & Connolly 1955). Cells which have thus been conditioned, yet morphologically are still indistinguishable from other lymphoid cells, react to a further dose of antigen by rapid transformation into the plasma cell series, in the "secondary" response (Leduc, Coons & Connolly 1955; Nossal 1959). Lymphocytes which have not yet been conditioned retain their primitive character and are still capable of differentiating in directions other than antibody formation. Lymphocytes which have already been conditioned, though they still look like all other lymphocytes, have already lost their primitive character and are incapable of differentiation along any line other than antibody formation. Such lymphocytes, unless they are exposed to a secondary stimulus, cannot undergo any further development and presumably continue unchanged, both in the circulation and elsewhere, until they finally die. It is probably conditioned lymphocytes of this kind, formed in the later stages of an infection which is being overcome, which are responsible for a sustained post-infective lymphocytosis. It is possibly such conditioned lymphocytes which circulate aimlessly between blood and lymph. The unconditioned lymphocytes on the other hand would presumably spend only a short time in the blood and on leaving the blood could quickly become transformed.

It is conceivable that some of the discrepancies between the various tissue culture or transfusion experiments are dependent upon the origin of the lymphocytes employed and whether they have already been conditioned or not.

VARYING STEM CELL REQUIREMENTS.

Our own investigations into the haemopoietic role of the lymphocyte have been based mainly upon the quantitative study of guinea pig bone marrow (Yoffey 1960), and more recently upon the study of human foetal marrow (Yoffey & Thomas 1961). These studies, while pointing to the lymphocyte as a stem cell, indicate (a) that it is not an exclusive stem cell, and (b) that its role as a stem cell is subject to considerable variation. It varies markedly in different species. Thus it is much more in evidence in the smaller laboratory animals such as the mouse, rat or guinea pig than it is in dog or man. Secondly, even in one and the same species there are marked differences with age, and therefore changing stem cell needs. As quantitative data accumulate we are beginning to appreciate more clearly the reasons for these variations.

Thus in the case of the red cells it now seems to be agreed

(Yoffey 1957; Erslev 1959; Alpen & Cranmore 1959) that they are formed by maturation from stem cells which are in constant need of replenishment. In the course of this maturation, about 2 mitoses occur in the dog (Alpen & Cranmore 1959), and presumbly also the smaller laboratory animals.

Since new red cells in the adult are required essentially to replace those worn out, then other things being equal the life of the circulating red cell would determine the number of stem cells. The guinea pig with a red cell life of 80 days (Everett & Yoffey 1959) or 65 days (Gronroos 1960) would need one and a half to twice as many stem cells as man, with a red cell life of 120 days.

Further there is evidence which suggests that in man it takes 4-5 days for the stem cell to become the mature erythrocyte, as against 2-3 days in the smaller animals. If in the guinea pig 2 mitoses occur between the stem cell and the mature erythrocyte, then one stem cell gives rise to four mature cells. If in man, with a 4-5 day maturation period, we assume three mitoses instead of two, then 1 stem cell = 8 mature erythrocytes.

Considerations of this nature, while not too precise, do seem to indicate a definite need for more stem cells in the marrow of smaller animals than in man. When we look for a marrow cell present in appreciably greater numbers the only one which we seem able to find is the small lymphocyte.

THE STEM CELL PROBLEM IN THE FOETUS.

Though we have as yet no quantitative data on the bone marrow of the human foetus, it is clear from the progressive increase in the numbers of circulating red cells that the demand for stem cells must be enormous. The bone marrow alone is unable to supply the need for new red cells, and as is well known the liver is involved throughout the greater part of embryonic life. Haemopoiesis in the liver is in fact almost exclusively erythropoietic (Thomas, Russell & Yoffey 1960). As far as our own material is concerned the appearances seem to fit in best with the view of Toldt & Zuckerkandl (1875), that the liver cells themselves become transformed into haemocytoblasts. We have found no evidence to support Maximow's (1927) concept of the origin of hepatic haemocytoblasts from invading mesenchemal cells.

The composition of human foetal marrow is strikingly like that of guinea pig marrow (fig.1), and markedly different from that of adult human marrow, in its much richer content of lymphocytes and transitional cells (Yoffey, Thomas, et al. 1961).

LYMPHOCYTIC MARROW REACTIONS.

Finally we have observed changes in the marrow lymphocytes where the production of granulocytes or erythrocytes has been stimulated experimentally. Following sublethal irradiation, there is a great

accumulation of lymphocytes in the marrow before erythropoiesis and granulopoiesis get under way (Harris 1956). In the response to hypoxia more especially secondary hypoxia (Moffatt et al 1961) there is likewise a great increase in marrow lymphocytes preceding increased erythropoiesis, and at the same time a marked increase in transitional lymphocytes. If the lymphocyte is not here functioning as a stem cell two questions need to be answered:- (a) What is the purpose of the lymphocyte accumulation? (b) What other stem cell is present in the increased numbers required?

CONCLUSION.

In conclusion, our work seems to indicate that the small lymphocyte in bone marrow is capable of acting as a stem cell. The extent to which it does so is subject to considerable variation. It is especially prominent when there is a great demand for stem cells.

BIBLIOGRAPHY.

Alpen, E.L. & Cranmore, D. (1959) Observations on the regulation of erythropoiesis and on cellular dynamics by Fe^{59} autoradiography. The Kinetics of Cellular Proliferation. Ed. F.Stohlman, Jr. Grune & Stratton, N.Y. and London, p.290-300.

Bekkum, D.W.van & Vos, O. (1957) Immunological aspects of homo- and heterologous bone marrow transplantation in irradiated animals. J. Cell. Comp. Physiol., 50, Suppl.1, (Symposium on Antibodies) p.139-156.

Bjorneboe, M., Formsen, H. & Lundqvist, F. (1947) Further experimental studies on the role of the plasma cells as antibody producers. J. Immunol., 55, 121-129.

Braunsteiner, H., Fellinger,K. & Pakesch,F. (1953) Demonstration of a cytoplasmic structure in plasma cells. Blood, 8, 916-922.

Braunsteiner,H., Paerton, J. & Thumb, N. (1958) Studies on lymphatic function. Blood, 13, 417-426.

Erslev, A.J.(1959) The effect of anemic anoxia on the cellular development of nucleated red cells. Blood, 14, 386-398.

Everett, N.B. & Yoffey, J.M. (1959) Life of guinea pig circulating erythrocyte and its relation to erythrocyte population of bone marrow. Proc. Soc. Exp. Biol. Med., 101, 318-319.

Fichtelius,K-E. (1953) On the fate of the lymphocyte. Acta Anat. Suppl., 19, 1-78.

Fichtelius, K-E. (1958) A difference between lymph nodal and thymic lymphocytes shown by transfusion of labelled cells.
Acta Anat., 32, 114-125.

Gronroos,P. (1960) The life span of guinea pig red cells estimated by the use of $^{51}Na_2CrO_4$
Austr. J. Sci., 23, 195-196.

Harris, P.F. (1956) Quantitative examination of bone marrow in guinea-pigs after gamma irradiation.
Brit. Med. J., ii, 1032-1035.

Leduc, E.H., Coons, A.H. & Connolly,J.M.(1955) Studies on antibody production. II. The primary and secondary responses in popliteal lymph node of the rabbit.
J. Exp. Med., 102, 61-72.

Marshall, A.H.E. & White, R.G. (1961) Experimental thymic lesions resembling those of myasthenia gravis.
Lancet, i, 1030-31.

Maximow, A. (1927) Bindegewebe und blutbildende Gewebe.
in: Hanb.d.mikroskop. Anat.des menschen,Bd.II,Teil I. Ed. by W.v.Mollendorf. Julius Springer,Berlin,p.232-583.

Moffatt, D.J.,Rosse,C., Sutherland,I.H. & Yoffey,J.M. (1961) The effect of hypoxia on guinea-pig bone marrow.
J. Physiol., 157, 48-49P.

Nossal,G.J.V. (1959) Antibody production by single cells: II.The difference between primary and secondary response.
B.J.Exp. Path., 40, 118-124.

Stoner, R.D. & Hale,W.M.(1955) Antibody production by thymus and Peyer's patches intraocular transplants.(Mice).
J. Immunol., 75, 203-208.

Thomas, D.Brynmor, Russell,P.M. & Yoffey,J.M.(1960) Pattern of haemopoiesis in the foetal liver.
Nature, Lond., 187, 878-877.

Thomas, D.Brynmor & Yoffey,J.M. (1961) Developmentsl changes in human foetal blood.
J. Physiol., 157, 49-50P.

Toldt,C.& Zuckerkandl,E. (1875)
Sitzunger.d.K.Akad.d.Wiss,Wien,72, abt.3, 241.

Wiseman,B.K.(1931) The induction of lymphocytosis and lymphatic hyperplasia by means of parenterally administered protein.
J. Exp. Med., 53, 499-510.

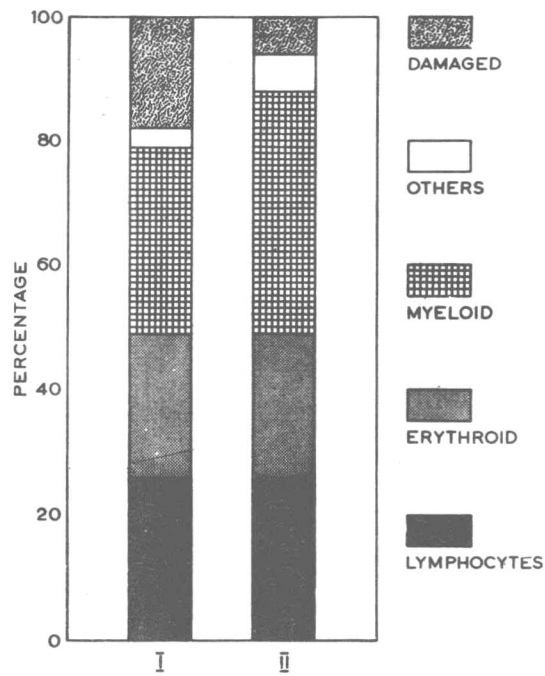
Yoffey, J.M. (1957) Cellular equilibria in the blood and blood-forming tissues.
Homeostatic Mechanisms. Brookhaven Symposia in Biology, No.10, 1-30.

Yoffey, J.M. (1960) Quantitative Cellular Haematology.
Charles C Thomas,Springfield, Illinois,U.S.A.

Yoffey, J.M. & Thomas, D.Brynmor (1961) The development of the bone marrow in the human foetus.
J. Anat., (in the press).

Yoffey, J.M., Thomas, D.Brynmor, Rosse,C., Moffatt,D.J. & Sutherland, C.H. (1961) Non-immunological functions of the lymphocyte.
Ciba Found. Symp. "Biological Activity of the Leucocyte." (in the press).

MAIN GROUPS OF NUCLEATED CELLS IN BONE MARROW OF HUMAN FOETUS AND GUINEA PIG.



I HUMAN FOETUS, FEMORAL MARROW.
Thomas & Yoffey (1961) unpublished data.

II GUINEA PIG (400gm.)
From Harris & Harris (1956), quoted by Yoffey (1957).

Fig.1. The human data are the average values for 30 human foetuses ranging in age from 13-26 weeks, obtained immediately after delivery by abdominal hysterotomy.

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THE LIFE-SPAN AND RECIRCULATION OF LYMPHOCYTES.

KARL-ERIK FICHTELIUS

The life-span of a lymphocyte is here defined as the time from the birth of a lymphocyte at mitosis to the death of the lymphocyte or its next mitosis. The life span defined in this way is at the most a matter of a few days for the immature lymphocytes, among which many mitoses are seen. It is the life span of the mature lymphocytes, identical with the small lymphocytes (18), which is controversial and about which I am going to speak.

The average time a lymphocyte spends in the blood is at the most a matter of hours as shown by cannulation of the thoracic duct. This time, the blood span, gives no information about the life span. A greater interest in this connection has the age of the lymphocytes in the blood, that is the time from their birth at mitosis until they are found in the blood. According to Ottesen (30), blood lymphocytes in man form two groups, one with a mean age of 3-4 days (comprising 11 -22% of the lymphocytes) and the other with a mean age of 100-200 days (comprising 78-89%). In his experiments the lymphocytes were labeled during their formation by incorporation of radioactive phosphorus into deoxyribonucleic acid (DNA). According to Ottesen, this DNA remains in the cells throughout their lifetime. To explain the high age of blood lymphocytes based upon DNA turnover (8,20,21,29) Hamilton (20,21) has put forward a hypothesis concerning specific reutilization by lymphocytes of large fragments of nucleic acid or nucleoprotein molecules from progenitor lymphocytes. This reutilization hypothesis may still be said to be far from proved. But the only alternative is to accept a total life span of 200 days or more for many blood lymphocytes.

The problem of the life span of lymphocytes is of course intimately connected with the problem of a large scale recirculation of lymphocytes from the blood to lymph and back to blood. The investigations of Gowans (19) have convinced many hematologists of the existence of such a large

scale recirculation. The low output of lymphocytes, which resulted from prolonged drainage of lymph from a thoracic duct fistula in rat, could be restored to a normal level by intravenous transfusion of lymphocytes. Experiments with tritiated thymidine showed that this increase in output was not due to the formation of new lymphocytes in the recipient rat. Further experiments with tritiated thymidine showed that the number of new lymphocytes formed each day in a rat amounts to only a small fraction of normal output of lymphocytes from the thoracic duct. The results of Gowans' experiments can, however, all be explained by a specific reutilization of lymphocyte DNA at the formation of new lymphocytes.

Fichtelius and Diderholm (15) suggested that the recirculation of lymphocytes is derected to a larger extent via the liver and liver lymph than via other possible routes. Autoradiography revealed that fewer lymphocytes can be traced to the mesenteric node than to the hepatic node after transfusion of P^{32} labeled thymus or lymph node lymphocytes. Experiments with tritiated thymidine indicated that there is a larger accumulation of labeled recirculating lymphocytes in the hepatic node than in the mesenteric nodes (17). Comparison between lymphocytes in postglandular hepatic lymph and intestinal lymph showed a higher incidence of old lymphocytes in hepatic lymph: there were fewer lymphocytes synthesizing DNA and fewer lymphocytes with high numbers of mitochondria in this lymph (3). This result accords with the hypothesis of a more extensive recirculation of lymphocytes via the liver lymphatics than via other possible routes.

The most important question at present in our understanding of lymphocyte life span and recirculation is, as far as I can see, whether reutilization of lymphocyte DNA does or does not occur at the formation of new lymphocytes. The morphologic and biochemical basis for the reutilization hypothesis has already been discussed (20,21,23,31,33,34). A further argument in favour of the hypothesis has been added by Bryant (4). Isologous lymphoid cells labeled in vitro with thymidine H^3 were transfused to recipient mice having regenerating liver. A wide difference was observed in mean silver grains of labeled transfused cells and many of the labeled recipient lymphoid cells. A calculation showed that the weakly labeled recipient lymphocytes would have to pass through a mini-

mum of six divisions within the 48 hours after their transfusion to account for their derivation from the transfused cells. While this is not impossible it is unlikely in view of the fact that the weakly labeled recipient lymphocytes showed a complete range of sizes, with the larger cells predominant, rather than the smaller cells one might expect after the minimal six divisions. Bryant concluded that the DNA of the transfused cells was probably reutilized in the recipient by lymphoid cells. The possible reutilization of lymphocyte DNA at the formation of other cells than lymphocytes has been studied at our lab in Uppsala and these experiments will be briefly described.

A relatively small fraction of the lymphocyte population in mice was labeled with four daily injections of thymidine H^3 (16). Three days later, when free thymidine was presumably non-detectable, a wound was made on the mice, and after an additional five days, when there was a marked accumulation of lymphocytes in the wound, the animals were sacrificed and the wound and symmetrically located skin as control were examined autoradiographically. It was shown that there were more labelled "round cells" in the wound than in control skin, and that the additional label of the "round cells" was brought to the wound from outside- probably via nucleated cells. In addition, it was shown that the labeling of fibroblasts and epidermal cells was higher in the wound than in control skin.

Our experiment did not indicate whether mononuclear blood cells transform into fibroblasts or epidermal cells in the wound, or whether DNA of these cells (perhaps including granulocytes) was reutilized on some level for the purpose of fibroblast or epidermal cell formation in the wound. Fibroblasts are at least partly hematogenous in origin and are very likely formed by direct transformation from lymphocytes or monocytes. Epidermal cells, on the other hand, seem unlikely to derive directly from lymphocytes or monocytes. The transformation from lymphocytes has been claimed by Andrew and Andrew (2), but their work has been criticized by Andreasen (1) who described lymphocytes degenerating in epidermis and concluded that epidermis is one of the disposal areas for lymphocytes(see also 14).The high labeling of epidermal cells in the wound can be most readely interpreted as a reutilization of blood leukocyte DNA.

We have tried to confirm and extend our observations on a possible DNA reutilization in recent investigations. A relatively small fraction of the lymphocyte population in recipient CBA mice was labeled with three daily injections of thymidine H^3 (11). Two days later, when free thymidine was presumably no longer detectable, the animals recieved an isograft and a homograft from a C_{57}BL donor. At 7 days post-operation the animals were sacrificed and the grafts, with the surrounding skin, were examined autoradiographically. Although the results are not yet complete, very few epidermal cells in either homografts or isografts appeared as labeled. The epidermal cells which are labeled, however, have localizations of silver grains directly over their nuclei, indicating that the activity is not derived only from the general body pool of tritiated metabolites.

In a third experiment (4) mice were injected with tritiated thymidine at 6 hours after surgical partial hepatectomy and sacrificed at either 10 hours, 3 days or 15 days post-operation. Imprints of residual livers were examined with autoradiographs. At 10 hours only very infrequent labeling of liver cell nuclei was observed. At 3 days or 15 days a majority of parenchymal cell nuclei and 30 to 40 percent of reticuloendothelial nuclei were labeled. Silver grain counts over labeled liver cell nuclei were slightly reduced in the interval between 3 and 15 days, but the total detectable labeled DNA in the liver was unchanged at a level 75 times that in the 10 hour livers. This accession of labeled DNA in cells of regenerating liver over several days is very likely due to a reutilization by proliferating liver cells of the labeled DNA contained in blood leukocytes.

The interpretation of these experiments, postulating a reutilization of leukocyte DNA by cells of regenerating epidermis and liver, should be viewed with some caution until labeled DNA precursor availability in the range of a few days after labeled thymidine injection has been given definitive study. Recent years have seen many in vivo studies of DNA synthesis and cell proliferation kinetics utilizing labeled thymidine, which assumed as their basis that labeled DNA precursor was available for only a few hours (9,24).

We have not yet reliably demonstrated that the lymphocyte is the