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On the intravascular development of erythrocytes in the bone marrow of the adult pigeon.

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The observations of Maximow[1] and Danchakoff[2] in fixed tissue, and of Sabin[3] in the living blastoderm, have demonstrated that the red blood cells differentiate intravascularly in the embryo. Maximow and others have contended that the adult bone marrow differs from the embryological vascular areas in the method of producing red cells. They believe that, in adult marrow, the erythrocytes develops in extravascular clumps, the mature cells later making their way into the bloodstream. This has been so generally accepted that most recent workers have concentrated on attempting to determine the mechanism whereby the adult erythrocytes obtain entrance to the circulation.

In studies on the vascular pattern of the pigeon's marrow with an hypolasia induced experimentally by starvation, an extensive system of intersinusoidal, collapsed capillaries lined by an embryological type of endothelium was observed for the first time.[4] These capillaries, evidently, are not normally patent to the circulating blood as are the transition capillaries which connect arterioles and venous sinuses. The cellular elements in the hypoplastic marrow are reduced to three types: fat cells, reticular cells, and endothelial cells; and the depleted cellular structure of the marrow is replaced by an increase of fat deposit.

The hypoplastic marrow of the starved animal recovers rapidly upon the resumption of an ordinary diet thus providing a simple physiological method of experimental control without

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1 Maximow, A., *Arch. f. mikr. Anat.*, 1909, lxxiii.

2 Danchakoff, W., *Arch. f. mikr. Anat.*, 1909, lxxiii, 117.

3 Sabin, F. R., *Contributions to Embryology*, 1920, ix, 213, Carnegie Inst. of Washington, Publ. 272.

4 Doan, C. A., *Contributions to Embryology*, 1922, xiv, 27, Carnegie Inst. of Washington, Publ. 277.

the introduction of any complicating factors. When feeding is resumed and observations are made at varying intervals thereafter, it is possible to secure a series of marrows of various degrees of complexity, as normal cellularity is approached. An analysis of each stage, from the simple depleted to the normally cellular state, enables a clarity of interpretation and understanding of the normal process of blood-cell formation and development hitherto unknown. The phenomena revealed by this series have proved highly suggestive.

Forty-eight hours after the resumption of feeding in an animal with a previously induced hypoplasia, a most remarkable change in the appearance of the marrow is to be seen. The excessive deposit of fat has very largely disappeared. This is evidenced by a marked stellate appearance of the shrinking fat cells, with the fat therein divided into many various sized globules, in contrast to the hypoplastic state where it was deposited as one homogeneous mass in the large fat cells. In this stage the fat cells simulate clasmatocytes in appearance, and are most numerous along the outsides of the blood vessels. There is in addition to this a most striking proliferation of endothelium. Because of the prominence of the strands of endothelial cells, their distribution is very readily appreciated. There remains no doubt in this stage that the inter-sinusoidal channels which in injected hypoplastic marrow are seen surrounding the fat cells, are true endothelial capillaries, for the proliferated endothelium follows precisely and accurately their pericellular, intersinusoidal outline. The picture described is not that seen in a few isolated areas, but it is a transformation in which the entire marrow substance participates. Here and there are to be seen a few young red blood cells, all intravascular, and in contact with the swollen endothelial cells of a collapsed capillary. In the extravascular parenchymal spaces there is to be seen an occasional so-called "reticular cell' in the process of mitotic division. The "reticular cells" of the hypoplastic state are large irregular pentagonal or hexagonal cells with faintly staining eosinophilic cytoplasm, and round vesicular nuclei; simulating in appearance primitive mesenchyme.

In the marrows analysed after seventy-eight hours of stimulation most of the fat deposit has entirely disappeared, and only a few vacuolated cells remain. There is still more extensive proliferation of the capillary endothelium than at forty-eight

hours and a veritable honey-comb design is outlined by the vessels, a small number only of which seem to be completely open to the circulation. There are very many developing red blood-cells, all within strands of endothelium. In some places it appears almost as though the endothelium were being actually replaced by a strand of developing red blood-cells, though the regularity and continuity of outline is nowhere broken. There are numerous small groups of from five to eight young granulocytes in various stages of development, all located extravascularly in the parenchyma. Succeeding stages increase the complexity of the picture. However, insofar as we have been able to observe, the red blood-cells have appeared only intravascularly, and the white blood-cells extravascularly. No analyses of hyperplastic marrows have as yet been attempted.

124 (2084)

On the intravascular development of erythrocytes in the bone marrow of the adult rabbit.

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Bone marrow has been one of the most difficult tissues to understand because it has proved so hard to reduce it to a sufficiently simple state for analysis. The older methods, consisting chiefly in classification of cell types, have led to the almost universal acceptance of the monophyletic theory, and in general to the conclusion that the developing red blood cells are formed in parenchymal spaces outside the vascular system, hence differing from the manner of development found in the embryo. Since it has been accepted that the red cells develop extravascularly, it has been obviously necessary to determine their mode of entry into the circulation. The two principal explanations offered have been: (1) That the endothelial lining of the vascular bed was incomplete, as in the spleen, and consequently the young cells could be forced through these openings; and