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This Week's Citation Classic®

Volkman A & Gowans J L. The origin of macrophages from bone marrow in the rat. *Brit J Exp Pathol.* 46.62-70, 1965.
[Medical Research Council Cellular Immunology Research Unit, Sir William Dunn School of Pathology, Oxford University, England]

The source of the dividing precursors of blood monocytes and adherent immigrant macrophages was sought in the rat using glass cover-slips applied to superficial abrasions or inserted subcutaneously It was concluded that the bone marrow is the major source of the macrophages that emigrate from the blood into foci of acute, non-bacterial inflammation [The *SCI*® indicates that this paper has been cited in over 385 publications since 1965]

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I developed a keen interest in the origins of macrophages and in the inflammatory exudate while I was still a medical student. A widely held view at that time was that blood lymphocytes, in response to an inflammatory stimulus, migrated into tissues, hypertrophied, and "transformed into macrophages." Methods for demonstrating this phenomenon had not deviated since the turn of the century from the sampling of inflammatory foci at intervals. Employing one such method, I found it left room for subjective interpretations. The evidence for this belief was said, nevertheless, to be overwhelming, particularly by its proponents. Highly objective observations of individual monocytes that emigrated from venules and developed into macrophages *in vivo*, although reported as early as 1939 by Ebert and Florey,[1] were largely ignored.

In the summer of 1961, I was able to resume the study of this problem at the Sir William Dunn School of Pathology in Oxford University. By then, the powerful and objective methods of isotopic labeling of cells and autoradiography had become available and were being employed by James L. Gowans, now Sir James L. Gowans, in his classic studies of the traffic of lymphocytes and their functions in immunological processes.[2] Although the day of the macrophage had not yet arrived in the world of immunology, Lord Florey was still interested in the problem of its origins; he and Gowans indulged me. Almost a year was consumed in establishing methods and developing models but then results came quickly. Studies of autoradiographs of macrophages harvested from sites of inflammation in rats injected at earlier intervals with tritiated thymidine (^{3}HTdR) showed these abundantly labeled cells to have a cytokinetic identity that made them unique as a class. They were distinct from pre-existing macrophages in tissues and serous cavities, on the one hand, and from major subclasses of lymphocytes, on the other. Only the blood monocytes could have given rise to the immigrant macrophages. The search for a source of these monocytes and macrophages involved a series of transfers of labeled cell populations, organ extirpations, and cell tracing in unilaterally labeled parabiotic rats. Lymphocytes from the thoracic duct and lymphoid tissues yielded consistently negative results. Since exceedingly few monocytes and macrophages incorporated ^{3}HTdR directly, we knew that we were seeking a very actively dividing precursor. Bone marrow proved to be far and away the best source of such cells both in cell-transfer experiments and in autorepopulation studies in lethally irradiated rats whose limb bones had been shielded from x-rays with lead. By April 1963, we had established the origin of monocytes and migratory macrophages from actively dividing precursors in the bone marrow in rats. Studies by others in a wide variety of mammalian species have established the universality of this observation.

The intellectual climate in Gowans's laboratory, his demands for precision of thought and high levels of laboratory skills, Florey's challenging and incisive comments, and the unique milieu of Oxford all contributed to the success of the investigations. It was a special time in a special place; I am very pleased that the work I did there has received recognition.

1. **Ebert R H & Florey H W.** The extravascular development of the monocyte observed *in vivo* *Brit J Exp Pathol* 20 342-56, 1939 (Cited 155 times since 1955)
2 **Gowans J L.** The fate of parental strain small lymphocytes in F_1 hybrid rats *Ann NY Acad Sci* 99 432-55, 1962 (Cited 360 times)