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This Week's Citation Classic

Moore G E, Gerner R E & Franklin H A. Culture of normal human leukocytes.
J. Amer. Med. Ass. **199**:519-24, 1967.
[Dept. Surgery, Roswell Park Memorial Institute, Buffalo, NY]

This paper describes establishment of continuous permanent normal lymphocyte cell lines derived from the peripheral blood which many 'basic' scientists said couldn't be done and was actually a malignant transformation. Culture medium RPMI 1640 was an evolution of over 1000 media designed for human cells. [The *SCI*® indicates that this paper has been cited over 390 times since 1967.]

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"I began cell culture in an attempt to grow cancer cells circulating in the blood in order to prove that such cells were viable even though only a few of them ever established metastases. It's the sort of research a surgeon can do between cases.

"The epic paper by Epstein and Barr[1] on the successful culture of Burkitt's lymphoma cells provoked a heated argument as to why normal lymphocytes and other bone marrow cells couldn't be established as cell lines. Other scientists had undoubtedly derived normal B-lymphocyte cell lines from bone marrow and leukemia blood but could not accept the theses: 1) that normal cells could be 'immortalized,' and 2) that cell lines from patients with leukemias and lymphomas could be other than malignant.

"The presence of an innocuous and perhaps useful passenger EB-virus in normal B-lymphocytes was and is a difficult concept for most scientists to accept despite the acceptance that sterility of the gut is detrimental.

"Once we established these B-lymphoid cell lines, we immediately attempted to grow cells from patients with genetic disorders, and unique malignant ceils, and to design a cel! plant for the growth of kilogram amounts of normal lymphoid cells for virus research and in the hope that they could be used for cancer therapy. We did grow about 90 kilograms of cells one year in a cell plant, and infused large amounts of cells in several volunteer patients with advanced malignant disease. This early attempt at cellular therapy for malignant disease was inhibited by our failure to increase the ratio of killer B-cells. The normalcy of the billions of infused cells was confirmed by subsequent freedom of any evidence of leukemia.

"I foresee a future in which we will culture and establish many normal functional human cells as cell lines. The dogma of the finite life of some cells may not be true of many other cells.

"The era of genetic and biochemical studies of bacteria is gradually being superseded by studies of mammalian (and human) cells. The lymphoid cell lines derived from a few drops of peripheral blood provide convenient means for screening and for comparative studies of those amazing sausages of information —the chromosomes. Intermediate methodology such as hybridomas and the growth of malignant cells will be replaced by the culture of functional normal cells as growth factors are identified. The production of interferon is a crude example of the future ability to produce in the laboratory specific hormones, proteins, enzymes, antigens, and antibodies from cultured cells. Special media without foreign protein will be used to grow large amounts of cells for cellular therapy —the replacement of erythroid and megakaryocyte precursors, islet cells for diabetics, autochthonous leukocytes to combat infection, skin cells to cover burns, and the culture of lymphoid cells to search out and destroy malignant cells.

"Our comments in this article are rarely quoted despite or because they proved to be quite accurate and now just 13 years later these studies are described in a grant critique as 'service functions!' "

1. Epstein M A & Barr Y M. Cultivation in vitro of human lymphoblasts from Burkitt's malignant lymphoma. *Lancet* **1**:252-3, 1964.