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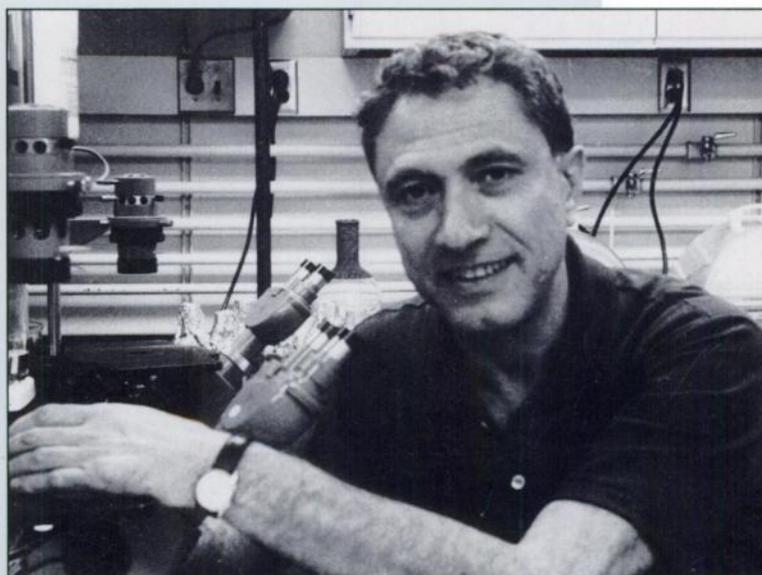


# Cancer Research

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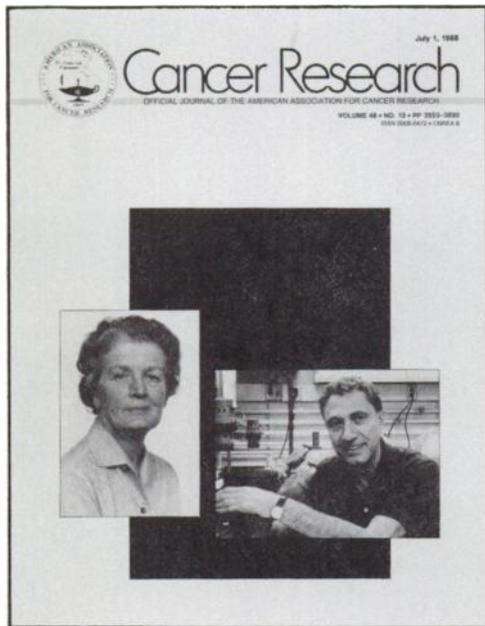
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# COVER LEGEND

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Since its formulation in 1951 the concept of the cell cycle has had a considerable impact on biology and medicine. This impact derives from two fundamental discoveries that are the keystones of the cell cycle concept: (a) the duplication of genetic material occurs only during a discrete, well defined period of the cell interphase, now called the S phase; and (b) the cells that make up the tissues of higher animals can be classified into three distinct populations, *i.e.*, continuously dividing cells, nondividing cells, and resting cells that do not divide but can still be induced to divide if an appropriate stimulus is applied.

The first discovery was originally made by Alma Howard and S. R. Pelc. Working with roots of *Vicia faba* they demonstrated that DNA synthesis occurred in interphase and was temporally separated from mitosis by gaps, which they called  $G_1$  and  $G_2$  for gap 1 and gap 2 (Exp. Cell Res., 2: 178–187, 1951). This concept developed slowly at first but with the advent, in 1958, of [ $^3\text{H}$ ]thymidine and high resolution autoradiography (W. L. Hughes *et al.*, Proc. Natl. Acad. Sci. USA, 44: 476–483, 1958), it rapidly was applied to cells of higher animals and quickly codified into clearly defined relationships. Those definitions are still alive today and the cell cycle is still defined as the interval between the midpoint of mitosis in a cell and the midpoint of the subsequent mitosis in one or both

daughter cells. The terms  $G_1$  and  $G_2$  are still used to signify the interval between mitosis and the beginning of S phase, and the interval between the termination of S phase and the beginning of mitosis. The term  $G_0$  was introduced about the same time by L. G. Lajtha (Physiol. Rev., 37: 50–65, 1957) to indicate cells that had temporarily exited from the cell cycle but were still capable of reentering under proper circumstances. This definition of  $G_0$  distinguished these nondividing cells from those committed to differentiation, which leave the cell cycle and are destined to die without further divisions.

These early studies branched in two directions. One of these developed into the very active field of cell kinetics which, through the pioneer studies of Mortimer Mendelsohn and Renato Baserga, compared the kinetics of growth of cancer cells and normal cells. Their work flourished around 1962 and was summarized in a review by Baserga in *Cancer Research* (25: 581–595, 1965). The kinetics of the cell cycle is still an active field; although applications in cancer therapy have not been as successful as first hoped, they still are used and certain possibilities still have not been exploited fully.

The development of the cell cycle toward the biochemical and molecular basis of proliferation in animal cells has been much more successful. Baserga and Michael Lieberman, at the University of Pittsburgh [now at the Fox Chase Cancer Center], were the first to introduce the concept of a biochemical basis of the cell cycle [review by R. Baserga (Cell Tissue Kinet. 1: 167–191, 1968)]. Since then the biochemistry of the cell cycle has swept forward into cell biology and molecular biology. Arthur B. Pardee at Harvard University and Baserga were the first to apply new techniques of molecular biology to the cell cycle. The cell cycle model now extends into bodies of knowledge ranging from virology to oncogenes and growth factors.

The cell cycle and its implications for cancer have been subjects of intensive study and numerous conferences. Despite the elaborate models now encountered and the vast contributions of molecular biology, virology, cell biology, and other fields, the cell cycle still remains focused on the simple concept of a DNA synthesis phase as a central stage of cell proliferation first suggested by Howard and Pelc in 1951.

Photographs are courtesy of Dr. Brian Lord and Dr. Baserga, who also assisted in preparation of the legend.

Sidney Weinhouse