had shown that two classes of substances could contribute to doubling the reproduction of lymphoid cells (and, as well, of bone marrow). The first comprised a variety of hormones, already known to regulate the growth and activity of tissues and organs. Growth hormone, oxytocin, vasopressin and prolactin came under this category. In fact, it was also shown that removal of the parathyroid hormone in a rat dropped the cell proliferation in the bone marrow and the thymus, a seat of lymphoid cells. When this same hormone was subsequently injected into the parathyroidless animal, cell production resumed at a much faster rate in bone marrow. From these results, a new, entirely unexpected and exceedingly important concept in mammalian physiology is emerging: the parathyroid hormone, universally considered to be used only to maintain normal calcium levels in blood, is also a principal regulator of cell proliferation in at least two major tissues of the body.

The second class of stimulants was discovered when, from hormones outside the cell, the research team focussed its attention on the cell wall and in particular on positively charged atoms of calcium and magnesium. On one hand, calcium was necessary for cell proliferation of lymphoid cells — the five hormones were powerless to stimulate cell reproduction in a calcium-free medium. On the other, it was found that both calcium and magnesium were themselves able to promote the increase of thymus cells. To cap these results, the evidence suggests that the various hormones previously mentioned as stimulating the initiation of cell reproduction all act in the same way, namely by assisting in bringing calcium into play.

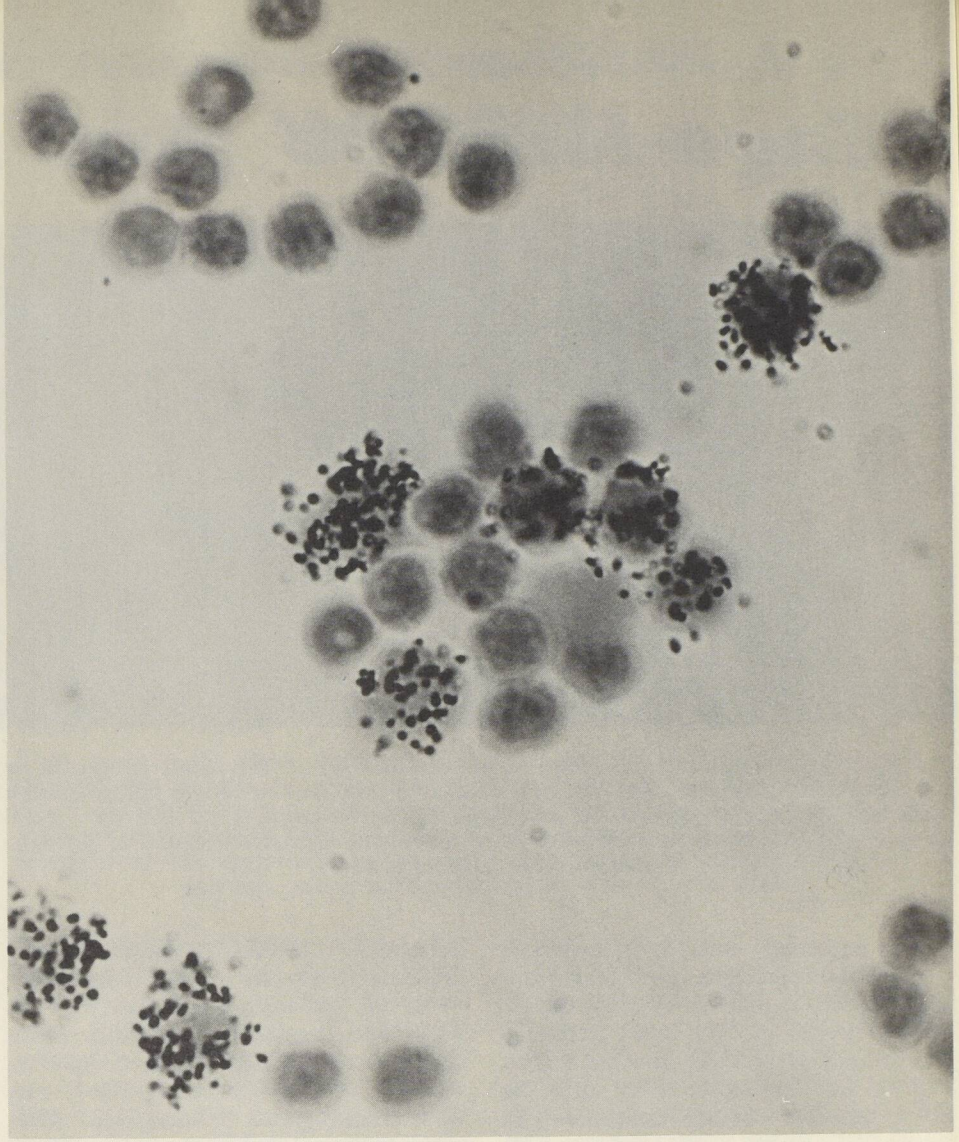
In early 1969, however, studies on this class of mediating substances led to an impasse when it was found that calcium (and magnesium) ions increased cell proliferation in the thymus by stimulating the cells to make deoxyribonucleic acid (DNA) thus breaking down the last barrier to cell reproduction. But how this was accomplished was an enigma: calcium is not known to be involved in any phase of DNA synthesis!

The hormones and divalent cations (atoms bearing two positive charges) must, Dr. Whitfield concluded, govern the formation of another substance located inside the cell, which gives the signal for DNA synthesis to proceed. What was this other substance, which may be the key to the control and regulation of cell proliferation?

The research group suspected it was a compound called adenosine 3′5′-monophosphate (cyclic AMP), which should act directly within the cell to increase proliferation. It was shown that the actions of growth hormone, parathyroid hormone, vasopressin and calcium are due to cyclic AMP and its subsequent activity. Moreover cyclic AMP at low concentrations was itself capable of doubling cell reproduction.

Evidence for this conclusion was ingeniously gathered. After cyclic AMP was introduced into the system, a substance called colchicine was used to stop the cell-splitting process at a distinctive intermediate stage (the metaphase) and thus permitted a much easier and more accurate enumeration of those cells undergoing proliferation as seen under the microscope.

That cyclic AMP triggers DNA synthesis in the cell and is the go-between for calcium and DNA was demonstrated by means of radioautographs. Cells suspended in a solution containing a radioactively labelled DNA constituent were exposed to cyclic AMP. After definite time periods, the cells were fixed, removed, washed and mounted on glass slides. →



Planted transmitters to spy on the cell. Radioautograph catches cyclic AMP in the act of triggering DNA synthesis in thymus cells (magnification: 2500 times). Dotted bursts are "beeps" of radioactive emissions from the cell.

Des "émetteurs" installés dans la cellule permettent de prendre l'AMP-cyclique sur le fait de déclencher la synthèse de l'ADN. Les points sur l'autoradiographie ci-dessus sont des "bips" d'émissions radioactives provenant de la cellule (grossissement: 2500).