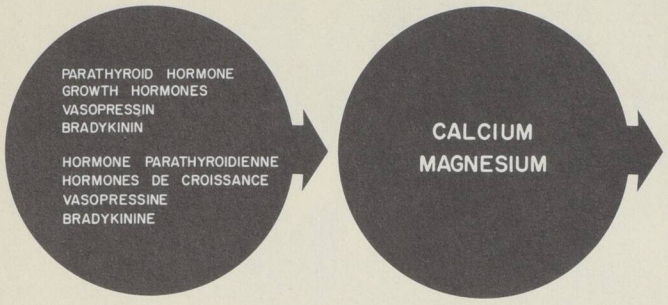
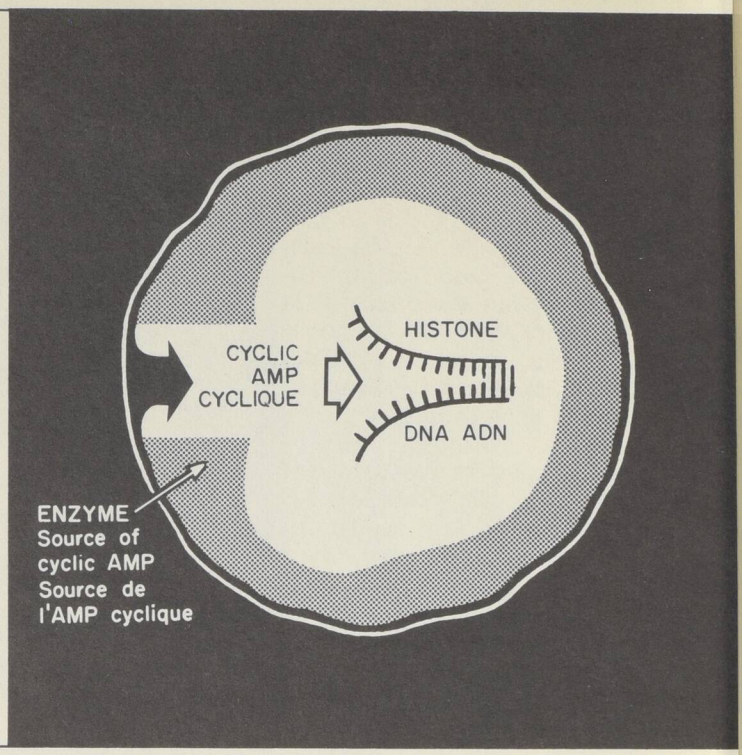
What initiates cell division? NRC's Dr. J. F. Whitfield and his research team suspect that the agent is cyclic AMP, located in the heart of the cell, which acts by stimulating the liberation of DNA from its union with histones. When this occurs, the liberated molecules become accessible to the DNA-synthetic machinery and DNA synthesis is initiated.





L'agent initiateur de la division cellulaire serait, de l'avis du Dr Whitfield et de son équipe, l'AMP-cyclique située au coeur même de la cellule. Cette substance rompt l'union entre les histones et l'ADN. Une fois libérée, celle-ci peut servir de modèle pour la synthèse de l'ADN qui commence peu après.

cyclic - AMP

The slides were dipped in a special photographic emulsion which was then exposed to the labelled cells for 48 hours. After developing, the film was fixed and dried and the cells under the emulsion were stained with a special nuclear stain. Under these conditions, the proportion of DNA-synthesizing cells which had incorporated the radioactive DNA constituent was strongly increased by cyclic AMP. The image showed clearly the distribution of the radioactive component in the cells producing DNA. Therefore it could be said that cyclic AMP was caught red-handed in the act of stimulating the initiation of DNA synthesis.

To sum up, it appears from this research that thymus and bone marrow cells progress into DNA synthesis immediately prior to proliferation in a process strictly regulated by cyclic AMP. The formation of cyclic AMP is in turn governed by several hormones and by calcium ions in the extracellular environment. It seems that the cyclic AMP might act by triggering a reaction which unlocks part of the DNA molecule from the clutches of various simple proteins (histones) within the cell nucleus. The liberated molecule then becomes accessible to the DNA synthetic machinery sparking DNA synthesis.

From a cellular point of view, both cancer and radiation sickness are diseases resulting from disturbances of cell proliferation. At one end of the scale, cell multiplication in uncontrollable fashion is responsible for the former; at the other, harmful radiation induces cell death and an over-all decrease in cells — the diminution of red and white blood cells is an early symptom. Fruitful approaches to therapy for both these illnesses may be forthcoming from these new findings.

Scientists elsewhere have recently shown that cells of an induced tumour have lost their sensitivity to hormones and that the activity of their cyclic AMP forming system is four or five times higher than that in normal cells. In the light of this evidence and the new findings of Dr. Whitfield's team, if a lymphatic cell should undergo some change (e.g., in its membranes) through which the hormones lose control of cyclic AMP formation, then the barrier which prevents the progression of cells into DNA synthesis would be removed — and the cell could then eventually flow freely into DNA synthesis and evenutally divide. Thus the cell and its progeny would multiply in an uncontrollable fashion and finally a tumour would form.

On the other side of the coin, cyclic AMP at very high levels, like ionizing radiations, causes a dissolution of the nuclear structure of thymus cells and thereby kills them. This change is due to a massive liberation of histones from their union with DNA and is simply a pathologically exaggerated version of the change which leads to stimulating cell reproduction. If excessive cyclic AMP production is responsible for radiation-induced cell death in the thymus and bone marrow, a compound such as imidazole which breaks down cyclic AMP should reduce cell death and thereby prevent the death of the irradiated animal. This idea was first conceived by Dr. R. H. Rixon of NRC's Radiation Physiology Section and then confirmed experimentally by the combined efforts of Dr. Rixon and Dr. P. V. Vittorio of the Defence Research Board. The therapeutic action of imidazole may prove to be very important on the practical plane and very intensive efforts are now being made to develop this approach.

A mystery over a century old may also have been solved through these investigations. Why does a wound hurt, redden and heal? For the last 120 years scientists have tried to identify the substance promoting the healing of wounds — the "wound hormone". Dr. Whitfield and his co-workers have found that a substance made up of a chain of amino-acids which is known to be rapidly released in all injured tissues, is also able to stimulate lymphoid cell proliferation by a cyclic AMP mediated stimulation of DNA synthesis. Aside from helping to unmask the wound hormone, this substance, bradykinin, will be of considerable importance to understanding the mechanism of tissue repair following injury. □