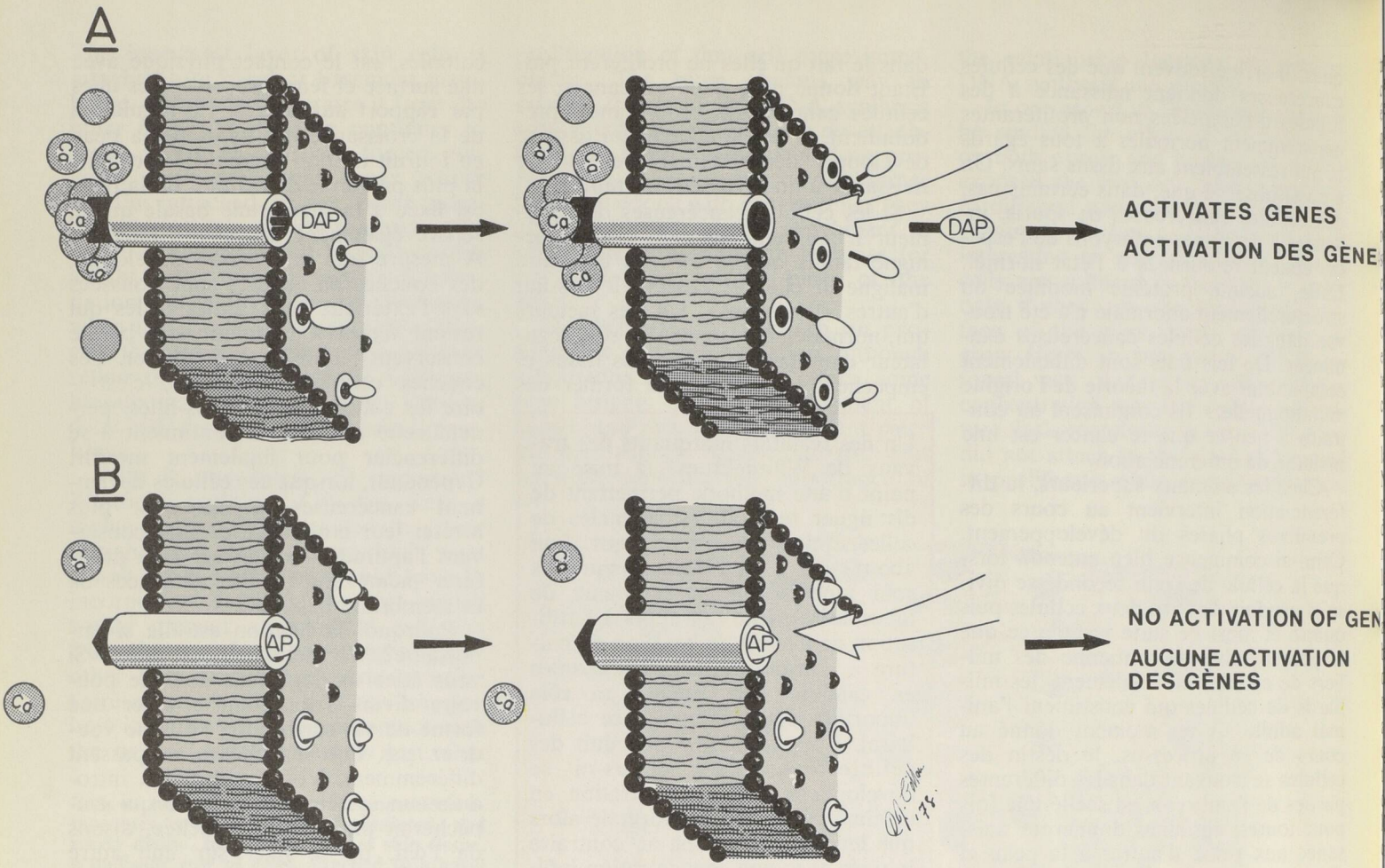

David Gillan, NRC/CNRC

A schematic diagram which attempts to explain the relationship between contact of the cell's outer membrane with a surface and DNA synthesis (and therefore cell duplication). The drawing (A) represents a section through the membrane of a cell showing its double layer characteristics, the cylindrical attachment device which is maintained in its functional state by calcium (Ca) and the DNA activator protein, DAP, located on the inside of the membrane. At some point in the cell's normal proliferation process a signal (represented by the arrow) causes the release of DAP, which activates the genes leading to cell duplication. In the experimental condition (B), when calcium is removed from the nutrient medium, normal cells do not attach to a surface, and cease to grow. One explanation is that the reduced calcium concentration outside the cell has some effect on the attachment device in a manner which prevents the release of DAP from its site.

In the cancerous state this connection between attachment and DAP (and thus DNA synthesis) is somehow lost or altered. DAP is no longer controlled by attachment and DNA synthesis remains permanently "on".

Représentation schématique visant à expliquer le rapport existant entre le contact de la membrane externe de la cellule avec une surface et la synthèse de l'ADN (et, par conséquent, la réplication cellulaire). Le dessin «A» représente une vue en coupe de la membrane d'une cellule montrant les caractéristiques de sa couche double, le dispositif de fixation cylindrique qui est maintenu en état de fonctionnement par le calcium (Ca) et la protéine d'activation de l'ADN, PA, située sur la face interne de la membrane. Au cours du processus de prolifération cellulaire normal, un signal (représenté par la flèche) provoque la libération de la PA qui active les gènes et permet la réplication cellulaire. Dans les conditions expérimentales «B», lorsque le calcium est retiré du milieu de culture les cellules normales ne se fixent pas à une surface et cessent de se développer. On peut expliquer cela par le fait que la réduction de la concentration en calcium à l'extérieur de la cellule affecte le dispositif de fixation de telle sorte qu'elle empêche la PA de quitter son site.

Dans l'état cancéreux, ce rapport entre la fixation et la PA et, partant, la synthèse de l'ADN, est d'une manière ou d'une autre perdu ou modifié. La PA n'est plus régulée par la fixation et le mécanisme de synthèse de l'ADN est «activé» en permanence.

completely unaffected by a similar drop in calcium. We do know that cessation of growth is not due to a change in the level of calcium inside normal cells because the internal concentration remains the same. On the basis of this kind of information we proposed that the outer membranes of normal cells have structures which anchor them to a surface, and further, that calcium helps to maintain this structure in the proper form or shape required for attachment and its function as the trigger for initiating DNA synthesis (at the appropriate moment in the proliferation process). Obviously, if the calcium level is in some way reduced or the cell wanders away from its normal site, as frequently happens in many tissues, it will be unable to initiate DNA synthesis and multiply in an inappropriate place. In cancer cells, on the other hand, these structures may be absent, functionless, or somehow overridden so that the starting switch for DNA synthesis is locked permanently (or quasi-permanently) in the "on" position. Thus, the "fail-safe" system has itself failed and the cancer cell has acquired the deadly ability to colonize new and unusual places in the body, or as in the laboratory situation, multiply even when suspended in liquid medium. The loss of calcium dependence is of no consequence to cancer cells because the extracellular calcium level in patients is usually normal. However, this change signals the failure of the "fail-safe" system and thereby provides an easy assessment of a cell's cancer-producing potential. This test could prove useful for the identification of cancer-producing chemicals."

As in most cases of scientific study which attempt to explain diseases at the molecular or biochemical level, final anwers will become apparent only when the nature of growth and function of normal cells is fully understood. Only then will scientists be able, by comparison, to discern the missing links which cause the disease state. □

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