CONTROL OF CELL DIVISION BY THE ELECTRICAL VOLTAGE OF THE SURFACE MEMBRANE

Clarence D. Cone, Jr.

PRESENTATION TO

The Twelfth Annual Science Writers Seminar
American Cancer Society

San Antonio, Texas
20-25 March 1970

Molecular Biophysics Laboratory
Langley Research Center
National Aeronautics and Space Administration
Hampton, Virginia 23365

CONTROL OF CELL DIVISION BY THE ELECTRICAL VOLTAGE OF THE SURFACE MEMBRANE

Clarence D. Cone, Jr.
Molecular Biophysics Laboratory
Langley Research Center
National Aeronautics and Space Administration
Hampton, Virginia 23365

HIGHLIGHTS

This report announces two basic developments in cell division theory which may provide the basis for an increased understanding of cancer and new approaches to its control:

(1) A fundamental new theory, which proposes that the cellular ionic concentration pattern (caused by the electrical voltage which normally exists across the surface membrane) acts to exert precise control over division in body cells, has been developed and experimentally verified in tests with mammalian cells.

(2) This theory has provided, for the first time, an explanation of the functional connection between the two major pathological features of cancer (uncontrolled proliferation and metastasis) and implies that the basic functional aberrancy producing both of these conditions lies in an alteration of the molecular structure of the cell surface.

* * * *

ELECTRICAL INVOLVEMENT IN CELL DIVISION CONTROL

In the course of recent studies concerned with space radiation blockage of cell division, I became impressed with the fact that cells having large negative membrane voltages (E_m) seldom if ever divide (e.g. nerve and muscle) while cells with small negative E_m levels divide at maximum rates (e.g. cells dissociated from tissues in culture). I subsequently proposed the theory that the cellular ionic concentrations, which generate the E_m level (see Fig. 1), determine whether or not a cell will divide (ref. a). A comprehensive experimental test of this theory has recently been completed and has revealed that transmembrane ionic concentration differences (primarily those of sodium Na and potassium K) associated with the E_m of normal cells do indeed exert a powerful control over cell division, in full accord with the theory (ref. b). It was found, using rapidly dividing cells in culture and varying the intracellular ionic concentration of Na and K so as to simulate the range of E_m levels which normally exist in the body, that division was completely, but reversibly, blocked by highly negative E_m levels (-70 mV and beyond) while small negative levels (-10 mV) allowed maximum division rates to proceed. Most significantly, it was found that the blockage of division resulted from a prevention of synthesis of DNA, the fundamental genetic material of the cell. Since it is well established that, in the body, DNA synthesis is also naturally blocked in all cells which do not divide, the experimental results again imply that regulation of the cellular E_m levels in the various tissues of the body may constitute the fundamental mechanism by which cell division is normally controlled, as proposed in the theory.

Although the theory proposes a central mechanism for control of somatic (body) cell division which, if it proves to be generally valid, will provide a powerful new basis for research progress on many key biomedical problems

such as human conception, morphogenesis and birth defects, immunological response, somatic homeostasis, growth, differentiation and ageing, its implications for the cancer problem are particularly profound. In essence, it explains the fundamental source of the uncontrolled growth of malignancy, knowledge of which should lead to a number of new approaches to cancer control.

THE UNDERLYING MECHANISM OF CANCEROUS PROLIFERATION

The deadliness of cancer arises from two fundamental aberrancies characteristic of all malignant cells: (1) their uncontrolled proliferation and (2) their ability to metastasize and to invade normal surrounding tissues. Previously, there has been no known relationship between these two characteristics, although they always occur together. The foregoing theory and associated experimental observations on E_m-level control of cell division, however, imply that these two properties of cancer cells are intimately related, in the following manner. First, the theory predicts that the highly proliferative cancer cell should possess a much less negative E_m level than the homologous (same type) normal cell, which proliferates at a considerably slower rate; significantly, this decreased E_m level is precisely what has been found in all cases for a range of cancer forms. By way of example, in the cells of a malignant muscle tumor (myosarcoma) undergoing rapid growth, the E_m level was found to be only -10 mV, while in the adjacent normal (nondividing) muscle the E_m was -90 mV. Thus, the sustained proliferation of malignant cells appears to be due to the fact that they are permanently electrically depolarized and possess only a fraction of the E_m level of their normal counterparts.

Now, as to the source of this decreased E_m level, it is well established that the molecular character of the cell surface, which determines the nature

and degree of interaction and bonding with other cells, is intimately involved in determining the E_m level of normal cells. Thus, in normal tissue the surfaces of similar cells are highly compatible and tightly bonded by surface adhesion; the E_m level is quite negative and the rate of cell division is very small. Dissociation of normal tissue cells or loosening of their nutual bonding (say by enzyme treatment), results in a pronounced depolarization of the cells, however, followed by onset of greatly increased proliferation. It is highly significant, therefore, that in all forms of cancer, a prime characteristic of the malignant cells is their abnormal surface properties resulting in significantly reduced adhesiveness and surface bonding. The fundamental implication is that the primary, the really essential change which occurs when a normal cell becomes transformed to a malignant one consists in a basic functional alteration in the molecular architecture and specificity of the cell surface. This surface aberrancy accounts for both of the primary pathological features of cancer: the decreased adhesiveness of the cells, allowing them to invade and metastasize, while simultaneously producing the associated lowering of the E_m level which permits the unrestrained proliferation of malignancy. Since it is only through the molecular immunological specificity of the cell surface that like cells recognize one another and maintain functional tissue aggregations, the changes in surface molecular specificity which accompany malignant transformation produce what may be descriptively termed "molecular amnesia" of the surface; the malignant cells are thus unable to recognize and relate to their environment of normal and/or other malignant cells. In essence, the cells seem to "think" molecularly that they are in a semidissociated state approaching that of tissue culture.

In the present theory, any of the wide range of chemical, physical, or viral carcinogenic agents can be the trigger setting off the critical cellular disturbance which ultimately results in the functional alteration of the surface structure; the really important implication here, however, is that the theory specifically identifies the essential "malfunction" underlying malignant transformation, namely, the alteration of those pathways of cellular metabolism concerned with the synthesis and steric aggregation properties of the cell surface polymers. Obviously, if the malignant state is to be maintained, the biochemical pathways involved in producing the surface polymer aberrancy must be quite stable. It is easy to envision how permanent genetic mutations and lysogenic viruses can produce and maintain such a state, but perhaps of broader significance is the apparently natural tendency for cells maintained at small E_m levels for appreciable periods to redifferentiate metabolically so as to sustain the low E_m level, with corresponding surface immunological alterations. Thus, nearly all normal cells when maintained for appreciable periods in culture ultimately undergo malignant transformation. Also, of particular significance in regard to the role of the cell surface in malignancy, is the established fact that some viruses in bacterial cells cause very specific structural alterations in the cell surface polymers. In all probability, carcinogenic viruses in animal body cells also produce specific changes in the cell surface, since the coats of these viruses contain several constituents very similar to the cellular surface molecules. Thus, in summary, the present theory proposes that metabolically induced and stabilized surface polymer alterations play the central role in malignancy, these changes causing decreased surface adhesion and lowered E_m levels with attendant metastasis and active proliferation; the lowered E_m level then

feeds back to stabilize and sustain the very metabolic pathways which act to produce it. These and many associated aspects of electrical-metabolic involvement in cancer are discussed in reference c. (See Fig. 2.)

IMPLICATIONS FOR CANCER CONTROL

The implications of these concepts, if generally valid, for cancer control are significant, for attention is now focused on a very specific component of the cell (the surface complex) and on a very specific aspect of metabolism (that concerned with surface polymer production and assembly). The fundamental need is for a greatly increased understanding of the cell surface complex, particularly as regards the molecular mechanics of cellular adhesion and bonding and the detailed molecular mechanics of the E_m generation and level-determining processes. Since these two factors appear to be intimately related, an understanding of either could lead to new methods of attack on malignancy. For example, since a low E_m level appears to be the characteristic abnormality producing continuous division in cancer cells, chemical treatments which would act to raise the E_m level specifically of the aberrant cells would prevent tumor growth. Many agents are in fact known which affect E_m levels in varying degrees. Likewise, chemical treatments which would restore adhesion stability in transformed cells, either by direct surface reaction or through intermediate metabolic changes, would presumably block metastasis and division. Successful development of such treatments, however, would depend greatly upon a detailed knowledge of the forms of molecular alterations occurring in the surface polymers during transformation, and how these changes act to decrease adhesion and E_m level. Although elucidation of the precise metabolic pathway alterations which ultimately lead to surface aberrations in malignant cells would be

enormously complex, a shortcut to the problem may, ironically, be provided by certain of the carcinogenic viruses themselves. Several of these possess only four or five genes at most; thus, knowing now what to look for, it should be possible to determine which genes are producing what surface aberrations and even to map the associated metabolic alterations which take place in the course of malig nt transformation. Once the specific surface aberrations are identified by this technique, they can then be looked for in other forms of carcinogenesis, and chemical countermeasures to their malfunctive properties developed.

REFERENCES

a. Cone, C. D., Jr.: Electroosmotic Interactions Accompanying Mitosis Initiation in Sarcoma Cells In Vitro. N.Y.A.S. Transactions 31 (4):404. 1969.

b. Cone, C. D., Jr.; and Tongier, M., Jr.: Control of Somatic Cell Mitosis by Simulated Changes in the Transmembrane Potential Level. NASA Publication (L-7126). 1970.

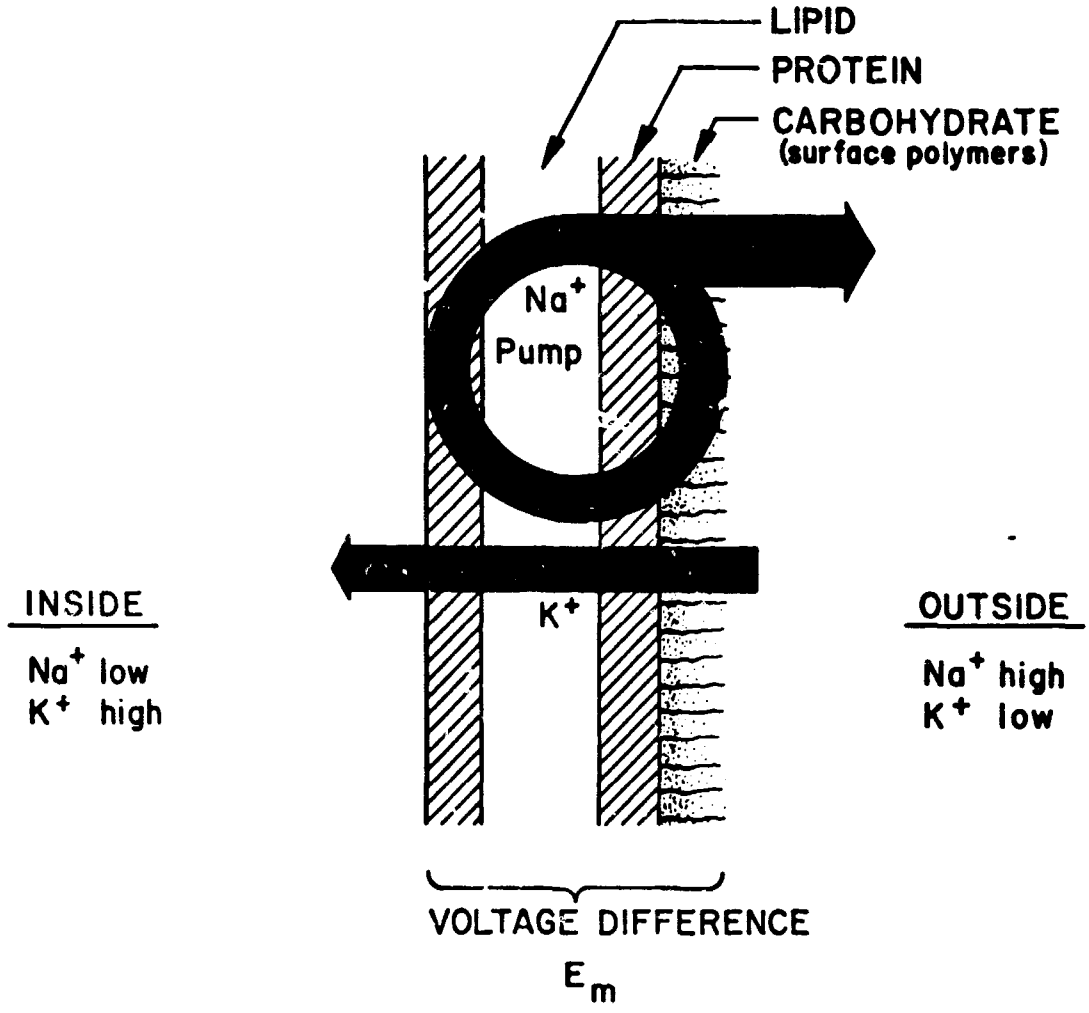
c. Cone, C. D., Jr.: Variation of the Transmembrane Potential Level as a Basic Mechanism of Mitosis Control. NASA Publication (L-7164). 1970.

BIOGRAPHICAL SKETCH

Clarence D. Cone, Jr.

Clarence D. Cone, Jr. (38) is Head of the Molecular Biophysics Laboratory at the NASA Langley Research Center in Hampton, Virginia. Basically a chemical engineer, he also has a Master's degree in aeronautical engineering and some years ago completed studies for the Ph. D. in biophysics. His present research at NASA is concerned with elucidation of the mechanisms by which ionizing space radiations damage human cells. His research studies in cancer *per se* have been carried out on a personal interest basis.

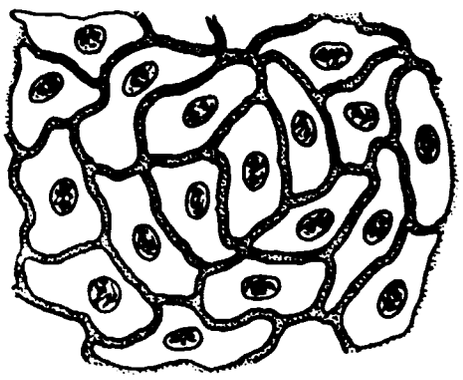
In addition to his molecular level studies in cellular biophysics, he has engaged in research on various aspects of avian biophysics and natural aerodynamics, particularly the aerodynamic theory of soaring and flapping birdflight of which he is an international authority. His early studies of vulture soaring in Georgia led to discovery of the thermal "vortex-shell" convection which was subsequently applied to development of the first mathematical description of the velocity field within the mushroom cloud of atmospheric nuclear explosions.



Each normal cell of the human body possesses a surprising degree of negative electrical charge produced by active pumping of positive sodium ions out of the cell. This removal of sodium ions generates a substantial electrical voltage (E_m) across the surface membrane; this voltage can be accurately measured by inserting ultramicro electrodes into the cell, and serves as a convenient indication of the degree to which the ionic concentrations, primarily those of sodium (Na^+) and potassium (K^+), differ between the inside and outside of the cell.

Figure 1

ESSENTIAL MECHANISM OF CANCEROUS GROWTH
BASIC ROLE OF THE CELL SURFACE



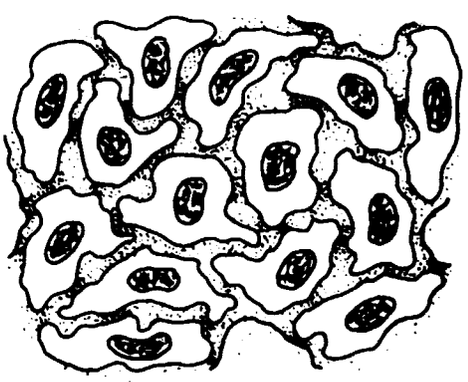
NORMAL CELLS

Cell surface bonding strong; cells immobile
E_m level high; division rate very low

Malignant transformation by

Physical
Chemical
Viral
} Carcinogens

alters cell surface polymers



MALIGNANT CELLS

Surface bonding very weak; cells are mobile, invading normal tissue and metastasizing

E_m level decreased, division proceeds unchecked

Figure 2