Meetings

Information and Control Processes in Living Systems

Pathology and therapy of control mechanisms in living systems was the theme at the third of a projected series of conferences on information and control processes in living systems held in Pacific Palisades, California, 26 February–1 March 1967. Similar to other conferences in the series, the emphasis was on informal discussion of the present state of our knowledge and possible future directions of investigation rather than on formal presentation of recent research results.

Paul R. Gross (Massachusetts Institute of Technology) introduced the discussion of essential phenomena in the control of cellular growth and differentiation by defining the growth process as the uptake of molecules specific to the metabolism of the cell; cell differentiation involves a gamut of processes that establish structural and functional specificity in that cell. The technique of nuclear transplantation has been most useful for studying the question of whether all cells in a tissue possess the same genes. The differentiated nucleus can be transplanted into the cytoplasm of a zygote cell and the cell will develop normally; this result is taken as evidence for "genomic equivalence." Gross emphasized the characteristics of two fundamentally different classes of cells in the processes of growth and differentiation (namely, protokaryotes and eukaryotes). Protokaryotes such as bacteria and other unicellular forms were characterized as cells which do not have true chromosomes but do contain DNA, RNA, and protein. Therefore, their genomes are nondistributed. Eukaryotes comprise all other cells, characterized by true chromosomes. Consequently, they have a distributed or packaged genome.

Protokaryotes make their DNA over a large fraction of their life cycle. However, the average half-life for their messenger-RNA is only two minutes and appears to depend upon protein synthesis. In eukaryote cells messenger-RNA can have the same lifetime as the cell itself. As a measure of the difference between protokaryotes and eukaryotes, the fastest time in eukaryotes for the cycle of DNA synthesis in relation to the classic phases of mitotic division occurs in worm embryos and sea urchins; this cycle is 1000 times longer than in a bacterial cell such as *E. coli*. This different cycle rate can be attributed to differences in enzyme systems. Gross also considered the influence of environment on the developing cell. He reviewed the historical doctrines of "preformation" and "epigenesis" and related them to present-day knowledge of DNA-RNA control mechanisms.

Samuel Mc. McCann (University of Texas) described the intricate and heterogeneous hormonal and neurohumoral regulatory mechanisms in adult tissues. In particular, he explained the specific roles played by the follicle-stimulating hormone and the luteinizing hormone in the production of estrogen, prolactin, and progesterone. There appear to be at least two antagonistic brain centers controlling the luteinizing hormone, the suprachiasmatic region exhibiting a positive feedback control, and the median eminence exhibiting a negative feedback control. McCann described in detail the effects of manipulation of the portal circulation between the hypothalamus and the pituitary gland. This circulation provides an essential pathway for influences from the hypothalamus on the pituitary. As an example of the feedback effects mediated by the pituitary portal circulation, a median eminence lesion in the hypothalamus is followed in the rat by constant diestrus whereas a rostral hypothalamic lesion produces constant estrus.

The location of neurons in the hypothalamus acting as secretomotor cells was discussed by Barry A. Cross (University of Cambridge, England). He raised questions concerning the relationship of spike activity to neurosecretion in the same cell and whether secretor and neural fibers travel in parallel to the median eminence to interact with the portal circulation.

Charles H. Sawyer (University of California at Los Angeles) characterized the responsiveness of hypothalamic neurons to hormonal manipulation and to stimulation of the genital tract including the uterine cervix. Most responsive cells are located in the ventral lateral hypothalamus.

The genesis of the immune mechanisms in mammalian tissue was discussed by Gustav J. V. Nossal (University of Melbourne, Australia). He emphasized the role of the thymus in activating bone marrow cells into lymphoid cells. His discussion of the phenomenon of immunological memory raised one of the most interesting points of the conference. Cells which make antibodies apparently have the capability of capturing antigen at the surface. Antibodies are formed in juxta-membranal ribosomes, apparently without involvement of nuclear DNA-RNA mechanisms. This has been demonstrated by Nossal in reticular cells. In his view one cell at one time will make one type of antibody only.

This led to a discussion of the clonal selection theory developed by Nossal and Burnet in which selection requires recognition in order to fit the antigen on the outside of the cell to the antibody on the inside. Nossal next discussed the polycistronic theory of gene activation. In order that an antigen may activate a particular gene associated with immune response, it is necessary that the combined products of two genes be present simultaneously to initiate antibody production. Turning to the question of autoimmunity, Nossal suggested two explanations. This phenomenon may involve the release of hidden antigens which stimulate the normal immune system leading to the production of antibodies. Alternatively, trace stimulation by normal antigens may initiate a hyperactive immune response, leading in turn to a massive production of antibodies.

John A. Jacquez (University of Michigan) proposed a two-stage model of carcinogenesis. The initiation stage involves development of irreversible changes in tissue characteristics. This stage then is followed by promotion of the tumor as a second phase in the

cancer process. Jacquez then turned to the question of "dependent tumors" which require an endocrine factor to sustain them initially, but which thereafter become autonomous. The initiator is probably a virus and the endocrine dysfunction is a promoter. Jacquez concluded from the evidence accumulated from nuclear transplantation experiments that the basis for cancer is not exclusively genetic. He described the progression of cancer in terms of cell population genetics and ecology. The progression of the tumor involves cell growth, mutation, and selection. The selection mechanism usually favors the more malignant cell type and rarely leads to a cure of the tumor by regression.

Cornelius A. Tobias (University of California, Berkeley) described the role of ionizing radiation and environmental factors in the production of abnormal growth. A radiation lesion acts as an initiator in the presence of "goal-seeking" promoters that relate to homeostatic balance in the tissue. Tobias discussed the sequence of phenomena in the production of ribosomal RNA, the suppression mediated by transfer RNA, the presence of regulators and operators, and finally, the role of the operon in the genetic apparatus. He described a scheme in which the DNA and RNA mechanisms are involved in a feedback loop that is statistical in operation and has different levels of action. He then used this model to indicate where breakdowns might occur leading to pathological control mechanisms.

George E. Stapleton (U.S. Atomic Energy Commission, Washington, D.C.) pointed out that the effect of irradiation is twofold. First, it inhibits macromolecular synthesis, and secondly, the process of cell division is modified. Minimum effects depend upon the status of the cell metabolically at the time of irradiation. It has been shown that the resistance of the cell to radiation depends on the amount and class of ribosomes present in the cell when radiation occurs.

Howard I. Adler (Oak Ridge National Laboratory) described an interesting mutant of *E. coli* which had lost the capacity to divide following small doses of ionizing radiation. These bacteria grow to approximately 200 times their normal length, but in other respects their DNA-RNA mechanisms appear normal. Mating occurs between them, but no progeny results. They are anucleate and thus without DNA, but possess RNA and protein. These bacteria can be reverted to a normal type by back mutation.

Endocrine control of reproductive mechanisms at three organizational levels—the hypothalamus, the hypophysis, and the ovaries—was discussed by Charles W. Lloyd (Worcester Foundation for Experimental Biology, Massachusetts). He pointed out that corticotropin and gonadotropin may be different in the circulating state from their condition in the target organ. This difference apparently relates to the removal of protein that coats the substances in the circulating condition. Lloyd noted that the technique of radioimmune bioassay has shown that previously held views on the sequence of hormone levels in the menstrual cycle are not strictly correct. The breakdown and blockage of endocrine control mechanisms was discussed in relation to hypergonadism and to the regulation of fertility by oral contraceptives.

Eugene Roberts (City of Hope Medical Center, Duarte, California) presented a series of models for correlative thinking about brain, behavior, and biochemistry. The effect of puromycin injections on memory processes in goldfish was discussed by Bernard W. Agranoff (University of Michigan).

The conference, chaired by W. Ross Adey (UCLA), was organized under the auspices of the Interdisciplinary Communications Program of the New York Academy of Sciences (Dr. Frank Fremont-Smith, director) and was supported by the National Aeronautics and Space Administration and the Smithsonian Institution. An edited transcript of the proceedings is scheduled for publication before next year's meeting. Aspects of innate versus learned behavior and the temporal patterning of control mechanisms in these behavioral processes will be the subject of next year's conference.

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Pi Complexes in Biological Systems

Pi-complexes have been implicated as intermediates in many chemical reactions and are involved in a number of important biological processes. To motivate interest and to demonstrate that π-interactions may well be the rule in biological systems and not the exceptions, the New York Academy of Sciences sponsored a discussion group that met on 28–29 March 1967 in New York City.

The opening sessions were devoted to a review of basic principles of π-interactions. The general theory of organic-organic π-complexes was summarized by S. P. McGlynn (Louisiana State University). Current theories of π-bonding in complexes of transition metals and organic compounds were covered by S. J. Lippard (Columbia University). Using the molecular orbital approach, with illustrations taken from various classes of organometallic complexes, he indicated that a major feature of these complexes is the "back-bonding" of accessible antibonding π-orbitals of the organic ligand which prevents the accumulation of an excess negative charge on the metal atom.

A. R. Lepley (Marshall University) discussed the electron-acceptor properties of indanetrione, a dehydration product of ninhydrin. This acceptor forms complexes with aromatic hydrocarbons and reacts with aldehydes, ketones, and amines via π-complex intermediates. Spectroscopic studies in various solvents yielded basic information concerning changes in transition energies and the nature of π-complexes. Evidence was presented for multiple complex formation.

Four papers on π-interactions in biological systems dealt with the question of the interaction of mutagenic and carcinogenic agents with nucleic acids. Isenberg (Oregon State University) discussed the solubilization of several aromatic hydrocarbons by DNA. Phenanthrene, pyrene, and benzo(*a*)-pyrene (but not coronene) are solubilized by DNA. The solubilization was ascribed to insertion of the hydrocarbon molecules between purine and pyrimidine base pairs of the nucleic acid and complex formation between the inserted hydrocarbons and the bases. In contrast to DNA, single-stranded polyadenylic acid did not solubilize these aromatic hydrocarbons.

The crystalline complexes formed by aromatic hydrocarbons or heterocyclics with purines are weak and dissociate in solution (B. L. Van Duuren, New York University Medical School). Both carcinogenic and noncarcinogenic hydrocarbons form such complexes. Also, both groups are solubilized by