On the Nuclear Envelope[1]

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THE VAST SPECTRUM of genetically controlled cellular differentiations depends ultimately, according to our present concepts, upon the interchange of chemical substances between the genes and the cytoplasm. No ultra-long-range physical forces which might exert controlling influences through the chromosomal sheath or the nuclear envelope have been adequately demonstrated (*1*). In any discussion of nuclear function it therefore becomes necessary to consider the factors limiting the rate of movement and the nature of material diffusing between the substance of the chromosomes and the rest of the cell. Of central importance is the permeability of the nuclear envelope (karyotheca), which will be considered in the present paper.

It has been suggested that the nucleus possesses a semipermeable membrane and may exhibit osmotic properties (*2, 3*). If this is correct and if the membrane consists of the peripheral segments of chromosomal sheaths (*4*) possessing the same properties, then the genetic substance would appear to be permanently imprisoned behind a semipermeable barrier admitting only such substances as simple salts (*3, 5*), nucleotides (*3*), and certain dyes (*6*). Even without the experimental evidence to the contrary to be cited, such a conclusion is difficult to accept on purely theoretical grounds, since it does not appear possible that the complexities of genetic expression could be mediated entirely through simple salts and substances of comparatively low molecular weight (< 1000). It should be pointed out that the nuclear volume changes which previously had been considered to be evidence for osmotic behavior have been shown, in the case of the isolated rat liver nucleus, to be due to the effects of electrolytes on a predominantly anionic gel (*7*). Detailed studies have given no evidence of semipermeability.

The assumption that high-molecular-weight substances (gene products—presumably enzymes or nucleoproteins) may move from the site of their formation to other points within the nucleus to form a component of the nuclear sap or of the nucleoli, but may not diffuse across the karyotheca, only partially alleviates the difficulties, since only three mechanisms are then apparent for moving these substances to the cytoplasm across the nuclear membrane. The first of these, vacuolar or nucleolar extrusion through temporary openings in the nuclear envelope (*8*), may occur in special instances but has not received sufficiently wide demonstration to be considered as generally occurring. Except in the case of frog oocytes, the evidence has been obtained, for the most part, from the study of fixed and stained preparations, which are often difficult to interpret. The second mechanism, the release of gene products from the nucleus after the breakdown of the nuclear envelope during mitosis, deserves serious consideration.

If genetically important substances are received by the cytoplasm only during cell division, it is evident that the differentiated, nondividing cell lacks continuous nuclear direction. A number of observations suggests that this is not the case, chief of which is the well-known fact that most cellular differentiation occurs in cells which do not divide. Evidence for a high rate of nucleic acid synthesis in the nucleus of such a highly differentiated cell as the mammalian neuron has been found (*9*). Studies on the effects of enucleation in protozoa (*10*) and on regeneration in a variety of cells, especially *Stentor caeruleus* (*11*), provide very direct indication of active nuclear participation in complex synthetic activity. Here all available evidence shows that the nucleus alone is capable of directing the reconstruction of a complex three-dimensional structure complete with an integrated system of organelles. Further, the nuclear desoxyribonucleic acid (DNA) must be in a highly polymerized form to organize this process successfully (*12*). The most conclusive demonstration that the breakdown of the nuclear envelope is not a prerequisite for the release of gene products is based upon the well-known finding that the nuclear envelope in ciliates *never breaks down* but continues intact from one division to another. Similar envelope persistence during mitosis has been described in the *Tradescantia* stamen-hair cell (*13*). A number of other important evidences for nuclear-cytoplasmic interactions during interphase based on cytological studies have been carefully reviewed by Stern (*14*) and by Huskins and Steinitz (*14a*).

The third possible mechanism for the movement of macromolecular gene products to the cytoplasm in the presence of a semipermeable membrane involves the formation of the membrane from the gene products themselves. These would be presumed to accumulate at the nuclear-cytoplasmic interface, and to dissolve gradually on the cytoplasmic side. Certain regulatory properties are inherent in such a system. Excess nuclear synthesis would result in the formation of a thick membrane, tending to slow down the diffusion of low-molecular-weight substrate compounds into the nucleus until cytoplasmic solution of the envelope material again thinned the membrane. At any

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one instant such an envelope could be impermeable to its own constituent macromolecules, yet still be serving as a mechanism for their transportation. The chief advantage of this theory is the simple explanation it provides for the breakdown of the envelope during cell division, to wit, cessation of nuclear synthetic activity coupled with continued cytoplasmic solution resulting automatically in envelope disappearance. While this theory deserves further experimental consideration, there is at present little evidence to support it. Studies on the stability of the nuclear envelopes of isolated nuclei and on isolated nuclear envelope preparations carried out in this laboratory suggest, on the contrary, that they are very stable structures permeable to macromolecules.

Evidence for complex nuclear-cytoplasmic interactions during interphase, occurrence of nuclear envelopes which persist during cell division, and difficulties encountered in attempting to explain the movements of gene products to the cytoplasm in the presence of a semipermeable membrane all support the generalization advanced here that genetically important (determining) substances move from the genes to the cytoplasm *through the nuclear envelope*. The nature and physical size of such substances then become the central problem. In the preceding discussion it has been assumed that these molecules have the general dimensions of soluble cytoplasmic proteins or nucleoproteins. While it is difficult to prove experimentally that nuclear control is *not* mediated through organic compounds of relatively low molecular weight (*15*) (< 1000), numerous studies of the effects of thousands of synthetic substances and drugs on living cells have produced little evidence that any known compound is "genomimetic." For the present it can only be considered as most probable that the cytoplasmic expression of nuclear control (differentiation, regeneration, etc.), which involves the synthesis of an almost countless number of specific proteins throughout the estimated one million or so species comprising the plant and animal kingdoms, is mediated principally through the movement of macromolecules having the size characteristics of enzymes, structural proteins, and certain nucleoproteins.

Nuclear Permeability

Evidence from several sources indicates that substances of high molecular weight ($> 15{,}000$) may pass through the nuclear envelope. Macromolecules possessing a higher anionic charge density than nucleic acids (heparin, sulfated polymanuronic acid, etc.) have been observed to enter isolated rat liver cell nuclei and to displace very highly polymerized DNA, which then passes rapidly out *through* the nuclear envelope without producing apparent changes in its structure (*15a*). Phosphatases are bound by isolated nuclei and are readily displaced by a number of proteins, including protamine (*16*). Recent work in this laboratory on the effects of nucleases on freshly isolated unfixed rat liver cell nuclei (*17*) has shown that these enzymes penetrate such nuclei rapidly and produce characteristic effects in a surprisingly short time (*ca.* 30 seconds for ribonuclease and 1 to 4 minutes for desoxyribonuclease). Evidence for the penetration of isolated nuclei by bovine serum albumin, partially hydrolyzed gelatin (*18*) and hemoglobin has also been found. Nuclei isolated from a number of sources have been observed to lose protein rather easily (*19*). While these observations all support the view that the nuclear envelope is permeable to large macromolecules, it should be emphasized that results obtained with isolated nuclei must be interpreted with caution.

Evidence for the penetration of the nucleus by macromolecules in the intact cell comes from several independent sources. Antigens injected into whole animals have been subsequently demonstrated in tissue nuclei (*20*). The extensive work of Caspersson and his co-workers, indicating that nucleoproteins or nucleic acids are synthesized in the nucleolus and subsequently move to the cytoplasm (*9, 21*), has received considerable confirmation from studies involving the use of radioactive tracers (*22*). Jeener and Szafarz state that ribonucleic acid (RNA) moves from the nucleus to the cytoplasm in the form of macromolecules which do not sediment at $60{,}000 \times g$, and are therefore smaller than the microsomes (*23*). Suggestive as these observations are, the unequivocal demonstration that *normal* macromolecular constituents of the cell readily cross the membrane in both directions is still lacking. Studies employing isotope techniques to demonstrate first the rapid synthesis of nucleolar RNA and second its subsequent movement to the cytoplasm assume that the RNA showing isotope incorporation is the same in both instances, and do not rule out entirely the possibility that the tag has actually moved across the nuclear-cytoplasmic interface as a component of a relatively small molecule.

Many of the instances cited as demonstrating the permeability of the nuclear envelope also demonstrate the ease with which large molecules may diffuse through the substance of the nucleus. The rapid effects of ribonuclease on the nucleolus, and the fact that dissolution of the interior by desoxyribonuclease takes place evenly throughout the body of the nucleus and not from the edge inward (*17*), suggest that the chromosomal material exists in the interphase mammalian somatic cell as an open gelwork. The almost free diffusion of proteins in similar gels is well known.

Recently it has been suggested that rat liver nuclei isolated in a sucrose-$CaCl_2$ mixture may have a protein-impermeable membrane, since a higher protein-DNA ratio was observed than is found, for instance, with citric acid (*24*). It was further suggested that loss of enzymes after disintegration with ultrasonic vibrations also demonstrated that the membrane was impermeable. It should be pointed out, however, that DNA has repeatedly been shown to combine with a wide variety of proteins while in a highly polymerized state (*16, 25*) but not when depolymerized. It would

be expected that the intranuclear DNA would hold a considerable amount of protein in rather loose combination. Since ultrasonic waves, which were used to destroy the nuclear envelope, depolymerize DNA with surprising rapidity (*26*), one would expect nuclear protein to be solubilized by this treatment. These experiments cannot be considered to bear directly on the protein permeability or impermeability of the nuclear envelope.

Numerous studies have been made of the distribution of substances between various isolated cell components and fractions (*27*). The interpretation of these is difficult and will be discussed at length elsewhere. Following the pioneering work of Dounce (*28*) on nuclear enzymes, Lang (*29*) demonstrated that glycolysis occurs in the nucleus. Glycolytic enzymes have also been demonstrated in nuclei prepared by the method of Behrens by Stern and Mirsky (*30*). Since the glycolytic system is characteristic of what we shall here term the *soluble continuous phase* (*31*), it would be expected to permeate the nucleus.

It should be emphasized that the existence of a permeable nuclear envelope does *not* imply uniform distribution of a great number of enzymes between nucleus and cytoplasm, since these may be expected to be adsorbed in varying degrees on particulate constituents.

The Structure of the Envelope

The substance of the nuclear envelope has been considered to be composed chiefly of basic proteins (*32*) with associated lipid (*33*), which, in fixed preparations, constitutes a "perinuclear layer" (*34*). Recent electron microscope studies on isolated envelope material from amphibian oocytes and amebae suggest the presence of at least two components or layers, one a continuous sheet, the other regularly perforate (*35*). Preliminary studies on mammalian somatic nuclei have not revealed the presence of similar perforate structures (*36*). It should be noted that all observations so far reported appear to have been made on air-dried material, the interpretation of which is equivocal, since resultant surface tension effects have been shown to cause extreme alterations in biological materials (*37*).

Observations on the effects of a number of solutions on nuclei isolated from rat liver and studied in the unfixed state have suggested that the envelope in this instance also is composed of two components, one a structural layer consisting either of a meshwork of fibrils or of a fine porous sheet (*18*). The extreme elasticity (*7*) favors the meshwork hypothesis. Associated with it is a second mobile component which is presumed to be rich in phospholipid. Normally, the mobile component is believed to be associated with the structural component in such a manner as to leave open the pores or interstices. Alterations in the composition of the medium (*18*) appear to cause the mobile component to move to the surface of the envelope and give rise to a continuous, protein-impermeable sheet. This sheet may even lift off the nuclear surface to form either blebs or free-floating spheres. Bleb formation by the mobile component is easily reversible and may be demonstrated in isolated nuclear envelopes prepared by a combination of enzymatic digestion and treatment with nonionic media. A highly schematic diagram of the formation of blebs is shown in Fig. 1.

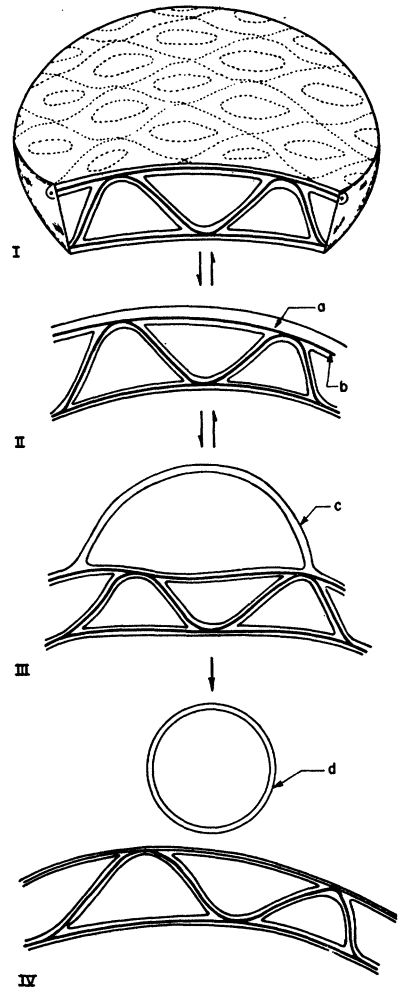

FIG. 1. Schematic diagram of nuclear envelope composed of a meshwork of fibrils coated with lipid material. Stage I shows portion of envelope as it appears to be in the freshly isolated nucleus. In stages II–IV the mobile lipid component (a) moves from the protein fibrils (b) to the surface to form a continuous sheet which may rise off to form blebs (c) or free floating spheres (d). Stages I–III are reversible.

The two-component system proposed provides a mechanism for altering the permeability of the envelope, possibly in a cyclical manner. Histological studies often show the nuclear envelope to disappear unevenly during cell division, whereas observations on living grasshopper neuroblasts show it to disappear very suddenly and completely (*38*). Since efforts to fix the blebs formed on the surface of mammalian nuclei have not been successful (*36*), it is probable

that the envelope seen in histological preparations is composed chiefly of the structural component. During cell division this component is believed to dissolve, leaving behind the mobile component as a thin continuous sheet which, like a soap bubble, may lose its structure throughout its entire circumference very suddenly. Phospholipid vacuoles resembling the dissolving membrane have been described by Bungenberg de Jong (*39*).

Envelope Dissolution at Prophase

Little experimental data is available on the mechanism of the breakdown or dissolution of the envelope during cell division. Lettré has considered that nucleic acids present in the envelope during interphase prevent proteolytic enzymes from acting on this structure (*40*). Movement of nucleic acid to the chromosomes during prophase is thought to leave the envelope proteins unprotected and subject to digestion. It has been proposed by Heilbrunn and Wilbur (*41*) and by Goldstein (*42*) that calcium, released from the cortex of *Nereis* or *Chaetopterus* eggs, activates a proteolytic enzyme of a type demonstrated by Gross (*43*). The ready digestibility of the envelope by proteolytic enzymes has been recently demonstrated in this laboratory (*17*). Such enzymes attack the DNA-nucleoprotein even more readily, however. The work of Monné and of Baud (*44*) suggests the possibility that surface-active substances may be involved in envelope breakdown. On the basis of studies on the stability of nuclei in homogenates, the author prefers to conclude that the structural component of the karyotheca is not digested in the usual sense, but becomes a part of the mitotic apparatus, returning to its former position at the nuclear-cytoplasmic interface at the end of division. The probable role of the envelope in mitosis has been stressed by Schrader (*45*).

On the Function of the Envelope

The available information supports the view that the nuclear envelope is a porous structure, generally permeable to macromolecules, yet containing within itself a mechanism for markedly altering its own permeability. *The point at which this system is poised may well vary during the life of the cell,* but on the basis of the evidence presented, it is believed to be shifted toward high permeability in somatic cells generally. Germinal vesicles, which accumulate considerable material within their envelopes, may well be shifted to the other extreme. The exclusion of cytoplasmic particulates from contact with the chromatin may be the key to the peculiar structure of the envelope, since desoxyribonuclease, which readily attacks DNA in isolated nuclei, is generally bound to cytoplasmic particulates (*46*). Several authors, following Mazia's original work (*46, 47*) have inferred that this nuclease plays some role in DNA synthesis. It appears more probable, in the absence of any demonstrable synthetic activity by this enzyme, that it serves to destroy DNA which has become loosened from an organized nuclear gel, and which cannot be allowed to survive in the cytoplasm. According to Painter (*48*), thousands of chromosomes are poured into the cytoplasm of developing oocytes by surrounding cells. This material becomes sufficiently depolymerized to be Feulgen-negative, but may well persist as polynucleotides. Schultz (*49*) has recently suggested that this phenomenon may account for the unexpectedly high DNA values obtained by gross analytical techniques (*50*). The necessity for mechanisms which will isolate and destroy products of defective synthesis or of accident at many levels of organization has been well pointed out by Crane (*51*). The nuclear envelope may well be part of such a system.

It is difficult to conceive of effective nuclear control of complex cytoplasmic processes, especially in cell regeneration, without the transfer of information (substances) from the cytoplasm back to the nucleus. Such a transfer would be analogous to the "feedback" principle stressed by Wiener (*52*). The simplest controlling feed-back system applicable here is the one inherent in an equilibrium state where the product concentration controls the reaction rate. If the continuous soluble phase of the cell includes, as suggested here, the soluble proteins and nucleoproteins of the cytoplasm, then these substances may be considered to be in equilibrium with the genetic material itself. Alterations in the composition of the continuous soluble phase would then result in compensatory nuclear activity.

In conclusion, it must be said that information on the structure and function of nuclear components is still very meager. It is hoped that the results and concepts reviewed here will serve to stimulate greater interest in this difficult field.

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William Herbert Hobbs: 1864–1953

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WILLIAM HERBERT HOBBS was born on July 2, 1864, in Worcester, Mass., the son of Horace Hobbs and Mary Paine Parker Hobbs. The death of his mother the next year was followed within another year by the arrival of a stepmother. To his father and stepmother he owed much of his character, personality, and habits. At the age of 18 he had shot up from a small, anemic boy to his adult stature of 5 feet 10½ inches, with no more constitution and proportionally no more flesh. In spite of these handicaps he became a wiry, energetic, intensely vital man, who was able to round out a life of 88½ years, passing away in Ann Arbor, Mich., January 1, 1953.

Dr. Hobbs gave some attention to his lineage and wrote that his ancestors settled in the vicinity of Worcester, Mass., during 1620–1671. He traced every line he could find—155 in all—and learned that they came from the British Isles and all bore British surnames, giving him a pure British-American ancestry, of which he was proud.

In a scholar's biographical sketch, life can be divided into academic periods. For Dr. Hobbs there were four: 25 years of study in America and Europe culminating, though not ending, with his doctorate at The Johns Hopkins University in 1888; 16 years at the University of Wisconsin as a teacher of mineralogy and petrology; 28 years building up a strong department of geology at the University of Michigan from a one-man department with 131 students to a ten-man department with 1035 students; and 18½ years after retirement. A full year for European study separated the two University appointments.

The story can also be told in terms of his major interests: drawing and mathematics from childhood to the year 1886–7, when his attention was transferred