Zeitschrift: Archives des sciences et compte rendu des séances de la Société
Herausgeber: Société de Physique et d'Histoire Naturelle de Genève
Band: 42 (1989)
Heft: 1: Archives des Sciences

Artikel: Polarity : from dipoles to biopolarizations. III. Addenda
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DOI: https://doi.org/10.5169/seals-740082

POLARITY

FROM DIPOLES TO BIOPOLARIZATIONS

III. ADDENDA

by

Gilbert Turian

Ce travail est la suite et le complément de celui intitulé POLARITY, paru en 1989 dans le volume 42, fascicule 1, des *Archives des Sciences*.

La numérotation des pages poursuit celle dudit travail et de l'addendum II. Nous conseillons donc à nos lecteurs de classer ce supplément à la fin du fascicule 1, vol. 42.

This paper supplements the review entitled POLARITY (*Archs. Sci.* 42, 1-323, 1989) and the addendum II (p. 325-397) published in 1990.

Société de Physique et d'Histoire naturelle
Genève 1991

ISSN 0252-9289

POLARITY

FROM DIPOLES TO BIOPOLARIZATIONS

III. ADDENDA

by

Gilbert TURIAN*

"La Polarité'' was first proposed in 1765 in the Encyclopédie by Diderot and d'Alembert to designate''la propriété qu'a l'aimant ou une aiguille aimantée de se diriger vers les pôles du monde'', one century before its first use in Biology by Allman (1864, see **I**).

The whole field of natural Polarity therefore covers the wide span recently surveyed (Turian, 1989-1990, **I** and **II**, updated in these **III**) from its physico-chemical fundaments to the multiple aspects of biopolarity. In this evolutionary perspective, Polarity was considered as the dual, directional principle of ''space-time arrow'' of Nature which, after having broken the original, neutral symmetry into the asymmetric couple of oppositely charged (+/-) subatomic electric particles of primeval matter, led through molecular and then macromolecular dipoles to the morphogenetic gradients of polarized and hierarchized biopatterns. As such, Polarity might thus be the answer to the old quest of the unifying principle behind the bewildering diversity of Nature, intuitively suggested by the Yin-Yang of oriental philosophies and rationally searched by the philosophers of ancient Greece.

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The electromagnetic forces involve the underlying attractions and repulsions of positively charged atomic nuclei and their surrounding negatively charged electrons. Their disturbance liberates radiation which emerges as quantum bundles of electrically neutral and massless photons. If there were electrically charged, positive and negatively charged photons, these could attract and form neutral clusters of light or ''photon-balls''. However, there is a still ambiguous possibility that ''there should exist new forms of matter such as ''glueballs'' which are similar in spirit to these imaginary photon-balls'' (Close, 1991).

Another couple of opposite electric charges is that of the positively charged proton and the negatively charged antiproton. Now, much is expected for further understanding of elementary particles from the smashing protons-antiprotons after their acceleration in the powerful particle accelerator Tevatron (Lederman, 1991).

Radioactive nuclear decay processes have many chemical consequences. The primary cause of the ensued ionization is the change of chemical identity, hence of the nuclear charge, undergone by the radioactive atom. Such a ''transmutation'' effect leads to the formation of monovalent cations by β^- decay and monovalent anions by β^+ decay or by electron-capture processes (Cacace, 1990).

2) *Electric dipoles*

The theory of electric polarization has been reviewed by Böttcher *et al.* from 1973 to 1978, and more recently by Blaive (1980). For this theory, the electric moment of a system of charges is a fundamental notion. According to Coulomb's law, the force between two point charges +e and -e evolves according to inverse square law. Generally, the polarization depends on the electric field strength. For example, surface charge density on a conducting sphere in a uniform field is axially asymmetric and this charge distribution can be solved by Laplace's equation (see Böttcher *et al.*, pp. 30-33, 1973). In Maxwell's electrostatic theory, matter is treated as a continuum and the vector fields are of importance to ascribe a dipole density to matter.

Electric dipole, quadrupole, and magnetic transition probabilities of ions isoelectronic to the first-row atoms have been reviewed by Cheng *et al.* (1979) and NMR spectra quadrupolar nuclei interpreted by Engstroem (1980). In aqueous solutions and biological systems, quadrupolar ions have been studied by NMR (Reimarsson, 1979) and chemical and biological agents detected by triple quadrupole mass spectrometry (Bauer, 1987). For nuclear quadrupole resonance spectroscopy, see Brown *et al.* (1983).

Giant electric and magnetic multipole resonances have been microscopically described by Sanchez-Dehesa (1977). Excitation of giant multipole resonances through inelastic scattering has been reviewed by Bertrand in 1976 and 1980 and giant multipole resonance experimentally recently studied in nuclei by Hakansson (1988).

Polarization asymmetries predicted by quantum chromodynamics, the ''grand unification'' of all particle forces, have been surveyed by Baldracchini *et al.* (1981).

Particles in QCD are known to be asymptotically free, that is at high energies quarks and gluons are weakly coupled, while at low energies they appear to be confined in hadrons - the nucleons protons and neutrons - and mesons (Olive, 1991).

3) *Polarized conductivity*

Unipolar high-frequency discharges and electronic processes in unipolar solid-state devices have been studied respectively by Trunecek (1965-67) and Dascalu (1977). Polarization and ''decomposition'' of copper and silver have been studied by Lehmann in 1975.

With the years, rectifier tubes have been replaced by barrier diodes and then the three-terminal transistor replaced the vacuum triode used for signal modulation or amplification. Physics of polarons and excitons in polar semiconductors and ionic cristals have been reviewed by Devreese and Peeters (1982). Field-effect and bipolar power transistor physics have been reviewed by Blicher (1981) and the bipolar junction transistor recently discussed by Neudeck (1989). For design and realization of bipolar transistors, see Ashburn (1988). A bipolar-compatible monolithic capacitive pressure sensor has been presented by Sandar (1980) and bipolar and MOS analog integrated circuit design has been studied by Grebene (1984). The fast advancing field of solid-state electronics which includes first the replacement of discrete circuit elements and the integration of many circuit elements onto hybrid ferromagnetic metal-semiconductors (iron/gallium arsenide as well as iron/zinc selenie) chips were recently surveyed by Prinz (1990).

According to the theory of Bardeen-Cooper-Schrieffer (BCS), low temperature superconductivity is a process in which conducting electrons somehow become ''pair-bonded'' into packets that slide through the superconductor's atomic lattice at low temperatures without the resistance encountered by single electrons. The reality of electron pairs has found support in magnetic flux measurements demonstrating that quantized units of flux - known as ''fluxons'' - ''are inversely proportional to twice the electronic charge in high-temperature superconductors'' (Hamilton, 1990).

Among the difficulties faced by this T_c superconductivity or BCS theory is that of a partial disorder that defies the classical periodic symmetry of solid-state physics. However, the theory is unaffected by scattering that breaks long-range translational order. Such symmetry breaking effects are ''in no way of essence to the fundamentals of the theory, so long as the relevant order parameter is nonzero in all directions'' (Schrieffer, 1991).

D. Magnetic polarization

1) *Cosmological level*

Related to the ''sun spot cycle'' (see Foukal, 1990, in **II**), sun spot pairs have been described as huge magnetic dipoles displaying an opposite orientation in the Northern Hemisphere to that in the Southern Hemisphere (Foukal, 1990).

Stellar genesis implicates powerful bipolar molecular outflows which remove circumstellar cloudy materials (Lada and Shu (1990).

Two of the most common cosmic defects with superstrings are the evolution of monopoles (see I.D.3) and texture. Nematic liquid crystals thought to be a fluid made of rodlike molecules have provided a model for their theoretical study on time and space scales at laboratory levels. Dynamical instability of texture has thus been unraveled by its decay into a monopole-antimonopole pair (Chuang *et al.*, 1991).

2) *Magnetic fields*

According to the so-called Ubbelohde effect (Robertson and Ubbelohde, 1939) the substitution of deuterium for hydrogen in hydrogen-bonded materials can lead to a change in the geometry of the hydrogen bonds. Using the new neutron diffraction technique, McMahon *et al.* (1990) demonstrate the effect of that substitution in KH_2PO_4. This prototypical hydrogen-bonded ferroelectric spontaneously acquires an electric dipole below a critical temperature. Two coupled subsystems, the proton tunnelling subunit, and the host lattice molecule have been considered in the determination of the process of proton ordering, and the development of polarization upon transition from the disordered to the ordered, ferroelectric state. Such proton-tunnelling units are embedded in molecular compounds such as ice (see II.B.1. in **I**) and biomolecules such as rhodopsin (see IV.B.b. in **I**) which thus examplify cooperative proton-tunnelling.

High-resolution solid-state NMR techniques were originally developed to enhance resolution by attenuation of dipolar couplings and other anisotropic interactions. Rotationally resonant magnetization exchange, a new nuclear NMR technique, has been applied by Creuzet *et al.* (1991) to the determination of the structure of membranar bacteriorhodopsin.

Magnetic fields have been modelled on a sphere with dipoles and quadrupoles by Knapp (1980) and magnetic dipole transitions studied in atomic and particle physics by Sucher (1978). There is a parallel, predicted by general relativity, between gravity and electromagnetism. According to this so-called gravitomagnetic effect, every electric charge has an electric field. A moving charge also generates a magnetic field, which influences other moving charges. As for the positively charged atomic nucleus, it is in motion, creating a magnetic field (see Appenzeller, 1990).

3) *Magnetic monopoles*

Following Monopole '83 (Stone, 1984) and a study of magnetic monopoles by Giacomelli (1984), the geometry and dynamics of magnetic monopoles have been reviewed by Atiyah and Hitchin (1988) and Horvathy (1988).

Magnetic monopoles are thought to be solitary poles, labeled north or south; unlike the two varieties of electric charge, positive and negative, which are often observed in isolation, magnetic poles seem to occur only in pairs ... ''Nature, it seems, abhors a

monopole'' ! (von Baeyer, 1990). However, Cabrera had obtained a positive result in 1982 which, unfortunately he has recently discarded (Cabrera, 1990).

Magnetic monopoles have been a long-standing problem for grand unified theories. Symmetry-breaking leads to the appearance of global monopoles which occur in abondance in liquid crystals (see I.D.l). The structure of monopoles and their apparent cylindrical but not spherical symmetry is now discussed in terms of the minimal energy solution which is cylindrically rather than spherically symmetric (Chuang *et al.*, 1991).

4) *Spin polarizations*

It is in 1945 that Purcell, Pound and Torrey detected the nuclear magnetic resonance (NMR) response of protons in paraffin and that Bloch, Hansen and Packard registered that of protons in water. Since then, advances in NMR spectroscopy have revolutionized chemical and biochemical analysis followed by medical diagnostics. Nuclear dipolar magnetic ordering, and heteronuclear dipolar couplings, total spin coherence, and bilinear rotation have been reviewed by Goldman (1977) and Garbow (1983) repectively.

Principles of dynamic nuclear polarization, chemically induced (Kaptein, 1975), have been reviewed by Abragam and Goldman (1978) and those of correlation and polarization reviewed by Crowe and Rudge (1988). Dynamic nuclear polarization in liquids and solids and nuclear pseudomagnetism in making polarized targets for high-energy experiments are among Abragam's (1989) most notable achievements.

E. Light polarization

Polarization is relevant for optical systems (Chipman, 1988, 1990) and induced polarization had been reviewed by Dodds (1976).

II. MOLECULAR DIPOLES AND CHIRALS

A. Electric dipole moments

Many neutral molecules are examples of charge systems with non-ideal electric dipole moments expressed in Debye units (see II.A in **I**), since in most types of molecules the centres of gravity of the positive and negative charge distribution do not coincide (Böttcher *et al.*, 1973).

Tables of experimental dipole moments can be consulted in McClellan (1963) and Exner (1975). Electron scattering by polar molecules has been studied by Itikawa (1978) and mechanical considerations given to elimination reactions over polar catalysts by Noller and Kladnig (1976). Polar dielectrics and their applications (Burfoot and Taylor, 1979), polar covalence (Sanderson, 1983), and preparative polar organic chemistry (Brandsma and Verkruijsse, 1987) have been reviewed.

The formation of a supramolecular crystal is the result of a repulsion between neighbouring domains, as it is the case for charged colloidal particles (Prost and Rondelez, 1991). As all the dipoles point in the same direction, each domain can be considered as a macrodipole that repels its neighbours (Andelman *et al.*, 1987; McConnell and Moy, 1988).

Atoms and molecules adsorbed on room-temperature surfaces can be manipulated by voltage pulse applied between the sample and probe tip of a scanning tunneling microscope. The adsorbed atoms (Cs, etc.) are induced to diffuse into the region beneath the tip ''by the action of the electric field gradient at the surface on the adsorbate dipole moment'' (Whitman *et al.*, 1991).

Surface dipole-dipole (Attard *et al.*, 1988) in their interplay with other forces (van der Waals, electrostatic, etc.) depend on interactions between membranes in a stack (Richetti *et al.*, 1990). The dynamic process of electronic energy transfer (DET) between donor and acceptor molecules in condensed phases is an important tool for probing the microstructure of spatially confined molecular systems. This DET mechanism, first introduced in 1948 by Förster, is a dipole-dipole-dominated reaction in which an electronic excitation initially localized on a donor, is resonantly transferred to an acceptor located at a given distance (Drake *et al.*, 1991).

In his search for electric dipole moments of the neutron, atoms and molecules, Hunter (1991) mentioned ''the first crack in the edifice of perfect symmetry'' resulting from Lee and Yang suggestion made in 1956 that the symmetry of parity ''might be violated in the weak interactions'', a suggestion soon confirmed in 1957 by the observation of an asymmetry in the β emission of polarized ^{60}cobalt by Wu *et al.*

B. Mineral dipoles

1) *Dipolar water*

Water is singular as a liquid because of its ability to form three-dimensional molecular networks, mutually hydrogen bonded (Wiggins, 1990). Its molecules are in a state of high energy if they fail to make the maximal number of hydrogen bonds possible either with one another or with solutes or surfaces (Finney, 1979 and 1982 (**II**); Wiggins, 1990). These new facts thus disprove Ling's (1962) association-induction hypothesis according to which water could be polarized in multilayers on protein surfaces. Wiggins' scheme of hydration of charged groups corresponds to a two-dimensional arrangement of water molecules round two negatively charged sites on a surface.

Biological processes implicate transient changes in active-site water structure that offer a simple mechanism for enzymes which perform chemical work. Synthesis of ATP, reaction of the Ca-ATPase are striking examples of the power of this newly described biological force which depends for its generation upon charged dipolar molecules and several other factors (Wiggins, 1990). It thus becomes more and more evident that the intracellular status of water is intimately connected with bioenergetics.

Freezing of water to ice is a most common example of symmetry-breaking phase transition. When the translational and rotational symmetry of the water is ''broken'', the system takes on the discrete symmetry of the ice crystal (Chuang *et al.*, 1991).

D. Chiral molecules

Chemical methods of asymmetric synthesis have been reviewed by Brown and Davies (1989). The molecular recognition process involves a combination of attractive forces (electrostatic or van der Waals) and steric repulsion. Differential biological effects of the two chiral forms of drugs such as thalidomide have also been again emphasized.

Chiral symmetry breaking has recently been demonstrated by autocatalysis and competition between L- and D- crystals of sodium chlorate (Kondepudi *et al.*, 1990). This revealing experiment, realized under polarized light, might help to understand how most of the molecules of life, including DNA, RNA, and proteins, came to exist preferentially in a right-handed or left-handed form. Asymmetric synthesis involves catalysts such as Cu and Fe for their reaction (Brown and Davies, 1989). Such controlled synthesis involving a novel titanium complex might even lead to the creation of three-dimensional structures (Brown, 1991).

The major non-histone component of the metaphase scaffold is topoisomerase II. In compact chromosomes the scaffolding is helically folded with sister chromatids having predominantly opposite helical handedness (Boy de la Tour and Laemmli,

1988). Considering the secondary structure of nucleic acids, Holliday (1990) shows that RNA molecules could exist in left- or right-handed forms. ''The sequences of bases in the stem and the side arms are the same, but the latter are inserted at different positions while retaining the same sequence polarity''. Only one or another of these asymmetric molecules might be transcribed from DNA and asymmetry could be lost or reversed by mutations. Such considerations are of relevance for the problem of RNA structures encoded by maternal DNA in the asymmetric coiling of snail shells (see VIII.3.e).

Studies of extraterrestrial amino acids have suggested that the characteristic ''handedness'' of biochemistry on Earth may ultimately have been determined by an asymmetry already existing in such compounds such as of L- and D-enantiomers of alanine which rotate the plane of polarization of light in opposite directions. The excess of the L-enantiomer was found to be indigenous (Murchison meteorite) rather than terrestrial contamination, suggesting that optically active materials ''were present in the early Solar system before life began'' (Engel *et al.*, 1990).

A symposium has been devoted to ''chirality and biological activity'' (Holmstedt et al., 1989).

III. MACROMOLECULAR POLARITIES

A. Free macromolecules

1a. Deoxyribonucleic acid (DNA)

DNA mobility and dynamics steady-state fluorescence polarization have been studied by Haerd (1986).

In the contact between DNA and binding proteins positively charged amino acids interact with DNA backbone or basis (Harrison and Aggarwal, 1990).

a^3 *Transcription*

Intracistronic polarity is the preferential expression of the promotor-proximal part of a gene as described in *Escherichia coli* (Hansen *et al.*, 1973). The reduced expression of promotor-distal parts of an operon relative to the promotor-proximal parts has been observed in many situations where translation is hindered. Exposition of *E. coli* cells to a nutritional downshift leads to the cessation of stable RNA accumulation. Following such downshift, a strong polarity was observed for the transcription of *lac*Z (Johnsen *et al.*, 1977) indicating that RNA polymerase runs away from the leading ribosomes in ppGpp synthetase mutants (Jensen and Pedersen, 1990).

2. Proteins

Helices in proteins are typically involved in multiple hydrogen-bonded, van der Waals, and electrostatic interactions. Constitutive amino acids have distinct conformational differences that lead to stabilization or destabilization of an α-helix (Fasman, 1989).

The α-helix dipole finds its origin in the dipoles of the single peptide units. Its formal charges lead to a dipole moment. Hydrogen bonds cause this polarization and thereby the peptide dipole moment of the α-helix. The field of a continous line dipole is equal to the field of a positive charge at the amino end and a negative charge at the carboxyl end. The helix dipole interacts with charged phosphate at N-termini and thus might be used in catalysis (Hol *et al.*, 1978).

Important for such helix stabilization are electrostatic interactions between charged side-chains and either another charged residue or the helical dipole (O'Neil and DeGrado, 1990). It is the arrangement of positive and negative charges along the helix which affect helix stability by an interaction between charges and the helix dipoles (Wada, 1976; Hol, 1985).

There are many models of protein folding (see Wetlaufer, 1990) possibly involving

structural constructs such as nucleation sites and flickering clusters, a term adopted in the field of water structure. Protein folding patterns require a compact structure and hydrogen bonds formed by buried polar groups. They necessitate the formation of α-helices or β-sheets which assemble to give the molecules their globular three-dimensional structures. The usual antiparallel packing (180°), rather than parallel manner (360°), of pieces of secondary structures that are adjacent in the protein sequence is one feature of chain topology (Chothia and Finkelstein, 1990).

Polarity (or lack of it) determines the nature and strength of interactions between amino acids in a protein and between the protein and water. The differences among amino acids stem from differences in their side chains namely, in shape, size and polarity. Shape and size affect the packing together of amino acids in the final molecule (Richards, 1991).

3'. Polyenes

These hydrocarbons are highly polarizable; that is electric field can induce substantial dipole moments (see also IV.D.3). Direct determinations of electro-optic parameters for these polyene chromophores by Stark effect spectroscopy have provided some quantitative basis in the evaluation of carotenoid band shifts under physiological conditions (Gottfried *et al.*, 1991). The centrosymmetric carotenoids in organic solvents show apparent dipole moment difference along with large changes in polarizability. Symmetry-breaking perturbations in solvents might be the reason for the apparent excited state dipole moment of these polyenic compounds (Liptay *et al.*, 1988).

5. Enzymes

Protein structure and enzyme function are the finely balanced end-products of weak interactions. Proteins are built on definable principles and enzymes use recognizable catalytic devices. In an extensive review, Hol (1985) proposed that the formal dipole associated with the classical α-helix modulates the properties of groups at the helix termini. The effects might be due to the electric field of α-helix dipole. From mechanistic and structural considerations on triosephosphate isomerase which imply polarity interactions, Knowles (1991) speculates that "the relatively large size of enzymes compared with most of their substrates may derive from the need for a matrix that positions their functional groups, focuses their helices and anchors the ends of their mobile loops".

In the process of lipase-catalyzed transesterification and esterification, polarity of every substrate must be obligatorily considered because of its ability to modify the water partition between the solid phase (enzyme) and the liquid phase (substrate and product) thereby leading to drastic changes in enzyme activity (Goldberg *et al.*, 1990).

6. Antigens-antibodies

Antibody-antigen interaction involves molecular recognition and its specificity is not only made by shape complementarity such as depressions on one surface field by protuberences from the other but by hydrogen bonding. Of particular relevance here is the directionality of the hydrogen bonds, necessitating a hydrogen bond receptor within a certain distance and within a certain solid angle of the hydrogen bond donor in order to form a strong bond. Antibody-antigen interfaces differ, with an average of about a dozen hydrogen bonds. The protein surface that is combining with the antibody has a significant content of polar residues (Davies *et al.*, 1990).

7. Synthetic polymers

Mixtures of deuterated and normal - protonated - polymers are chemically indistinguishable. However, above a certain molecular weight, symmetric mixtures of deuterated and protonated polybutadienes phase separate (Bates *et al.*, 1985), a universal phenomenon which is a consequence of the well-known reduction in carbon-hydrogen bond length that accompanies deuterium substitution in organic molecules. Such a decrease of the bond length reduces the bond polarizability, which is manifested as decreased segment polarizability (Bates, 1991).

The first step towards electronic devices with a polymer playing an active role was described in 1988 by Bloor and by Garnier *et al.* (1990) who report the construction of an all-organic transistor based on sexithienylene. Recombination of electrons and holes at the interface between emitter and transport layers produces an electroluminescence of high intensity. Among the possible mechanisms for electroluminescence, there are two possibilities, namely that of formation of negative and positive polarons would rather combine to form a neutral polaron exciton or that of electrons which would tunnel directly to the exciton levels (Bloor, 1991).

Characterization of electroluminescence in the conjugated polymer poly(*p*/phenylene vinylene) or PPV is also of interest to understand the fundamental excitations in this class of organic semiconductors. For such polymers, these excitations are polarons, either uncharged, as the polaron exciton, or charged, singly charged as the polaron, and doubly charged as the bipolaron (Fesser *et al.*, 1983). For electroluminescence, bipolarons, paired charges with low mobility, are very unlikely to be the charge carriers responsible for formation of polaron excitons. Therefore the charge carriers involved in the process are probably polarons (Burroughes *et al.*, 1990). This idea contrasts with the results from the previous optical work (Friend *et al.*, 1987) which suggest that bipolarons are the most stable quasiparticles responsible for the conductivity in PPV.

B. Aggregates

1. Crystals-quasicrystals

Contrarily to metal crystals, quasicrystals such as dodecahedral grains of aluminium, copper and iron melted together and cooled (Nelson, 1986, see **I**) cannot be

constructed from atoms in repeated unit cells. Laboratory produced quasicrystals conduct electricity rather poorly (Stephens and Goldman, 1991).

2. Viral assemblies

c) *Polar viral morphopoiesis*

DNA replication and regulated transcription in the development of bacteriophage T4 are closely connected (Epstein *et al.*, 1963). The enhancer of T4 late transcription is a break in the nontranscribed DNA strand to which the DNA polymerase accessory proteins bind. The noted preference of these polymerases for the nontranscribed strand point to a ''polarity'' for the placement of the nicked DNA template and present ''an interesting puzzle concerning one aspect of the mechanism of action of the DNA polymerase accessory proteins'' (Herendeen *et al.*, 1990). However, because of close coupling between recombination and replication in this phage development, there is no distinguishing relation polarities of late transcription and replication (Mosig, 1987).

IV. SUBCELLULAR POLARIZATIONS

B. Surface membranes

1. Primitive membranes

Polarization of synthetic membranes has been studied by Wijmans (1984).

2. Plasma membrane

a) *Biochemical properties*

The Singer's (1971) ''mosaic'' model has long been the main representation of membrane structure (see **I**, pp. 75-77). The observation that surface proteins and lipids tend to remain on the same membranar surface but are able to move laterally, has provided ground for the more recent ''fluid mosaic'' model of membrane structure in which proteins ''float upon a sea of lipids'' (Rothman and Lenard, 1977). The structure and insertion of integral proteins in membranes have recently been reviewed by Singer (1990).

b) *Structural polarity and recognition systems*

The electrochemical gradient across the membrane is negative inside (see d); it should prove favorable for hydrophobic sequences to insert with their positively charged ends inside (Yamane and Mizushima, 1988). However, according to the ''positive-inside rule'' of von Heijne (1986) the electrical polarization of membranes requires that hydrophobic sequences of proteins to orient themselves with the most positively charged end in the cytoplasm. According to Boyd and Beckwith (1990) ''membrane spanning stretches generally have a positive charge on the cytoplasmic side and few arginine or lysine residues in short extracellular domains''. Thus, charged amino acids play a role in the localization of secreted and membrane proteins. For instance, in bacteria a net dipole around the hydrophobic segment of the signal sequence may be important for this function. Topological models of membrane proteins could be derived from these new facts to explain why improper charge distribution around the signal sequence blocks secretion (Fig. 1 in Boyd and Beckwith, 1990).

Electromagnetic fields (EMF) have been incriminated in growth regulation for ''changing the pattern of charges on the surface of cell membrane so that the receptor is not in the best configuration to transmit its signal'' (Lubin cited by Pool, 1990). EMF exposure has also been reported to alter DNA synthesis (see also Pool, 1990) as well as calcium flow through the cell membrane which is important for the signaling process.

Second messenger waves implicated in cell signaling have many similarities to action potentials (IV.B.e) and to chemical waves in excitable media. According to

Meyer (1991), ''several types of chemical waves have been studied in systems that exhibit chemical reactions far from thermodynamic equilibrium''. This reviewer also questions ''How are diffusion and amplification related to the shape and the velocity of the wave ?'' A model amplifier is then described and mechanisms are postulated for both cAMP and calcium waves as being generated by diffusion and amplification of second messenger molecules in myocytes and oocytes.

Cadherins are newly identified Ca^{2+}-dependent cell-cell adhesion receptors. Their regulated expression controls cell polarity and tissue morphogenesis (Takeichi, 1991). The problem remains of how cadherin-bearing cell-cell junctions achieve a polarized distribution in cells (see VII.C.6b).

c) *Energy transduction and transport*

Mitchell's chemiosmotic hypothesis (see **I** and **II**) is still a challenge in bioenergetics (see in Anthony, 1988) and the important question arises from Kell (1988): ''Is the protonmotive force an energetically-significant intermediate in electron transport-driven phosphorylation?'' Kell's overview differs from many in bioenergetics by its conclusion that ''the proton motive force across energy coupling membranes catalysing electron transport-linked phosphorylation is energetically insignificant''. Such a conclusion is based on many arguments developed in Kell and Westerhoff (1985).

Intracellular pH measurements are important to assay transmembrane pH differences, proton exchanges catalyzed by the H^+ pump or by H^+ cotransport and, more generally, to appreciate cell activity (Kurkdjian and Guern, 1989). Measurements of redox activity at the plant plasmalemma leading to an estimation of proton fluxes have been reviewed by Rubinstein *et al.* (1990).

The system of *myo*-inositol transport in the bacterium *Klebsiella aerogenes* is by H^+-symport. The concentrative system of this molecule is bidirectional but is highly asymmetric. Energization of the membrane is essential to render the system asymmetrical as demonstrated by the abolition of the proton gradient in the presence of uncouplers (Deshusses and Reber, 1977). A periplasmic binding protein is involved in the process as also reported for mannitol transport in *Pseudomonas aeruginosa* (Eisenberg and Phibbs, 1982).

d) *Electric potentials*

The plasmamembrane Ca^{2+} pump, discovered 25 years ago by Schatzmann, is a model membrane protein for the study of ATP-driven cation transport as recently emphasized by Strehler (1991).

A special class of channel proteins is reponsible for the electrical activity of neurons. The structure of these voltage-gated channels spans 6 transmembrane helices from the NH_2 (+) to COOH (-) poles. Recent experiments (Yool and Schwarz, 1991; Hartmann *et al.*, 1991) involving site-directed mutagenesis identify the pore region (P)

as the pore-forming sequence. They demonstrate that P is critically involved in ions permeation and selectivity (potassium ions can pass through while sodium ions are excluded). The recording of ions currents from biological membranes has been revolutionized by the highly sensitive electrophysiological, patch-clamp technique (Neher and Sakmann, 1976). In mature plant cells, the two membranes - plasmic and vacuolar - are positioned in series. Their current rectifications are in opposition upon depolarization (ref. in Hedrich and Schroeder, 1989). Therefore as reported for gap junctions (see p. 414), ''bipolar gating phenomena may be found when ion currents through both membrane are recorded in series''.

Depolarization of membrane potential is not only provoked by rise in Ca^{2+} concentration (ref. in **I** and, Tsien and Tsien, 1990). Uptake of K^+ also depolarizes the cells, suggesting that it is accompanied by the influx of a positive charge (Bakker and Harold, 1980).

Hyperpolarization of the cell membrane of *Saccharomyces cerevisiae* can be caused by metabolic substrates such as glucose or ethanol (van de Mortel et al., 1988). The glucose-induced hyperpolarization activates Ca^{2+} influx by reducing the negative membrane potential below a threshold value (Eilam and Othman, 1990). There are also indications that the transient hyperpolarization of the yeast cell membrane by glucose is caused by opening of specific K^+ channels (Borst-Pauwels *et al.*, 1988). In hyperpolarized algal cells, inward K^+ current rectifies the membrane polarization as found (Sokolic and Yurin, 1986).

Among the channels contributing to ion (I) transport through the plasma membrane, the I_K+ out channels allowing K^+ efflux become activated by depolarization of the membrane potential. The observed depolarization can be provoked by the addition of K^+ to the extracellular medium of *Neurospora* (Rodriguez-Navarro *et al.*, 1986).

Changes in circular dichroism suggest ''a decrease in α-helicity and increase in β-structure with the membrane potential positive inside and vice versa when the potential was positive on the outerside of membrane vesicles from where alamethicin was inserted into the membrane''. These alamethicin channels therefore depend upon electric field (Brumfeld and Miller, 1990).

Channel-like analogues in icosahedral viruses, called ''channelogs'', encompass structures with narrow regions analogous to selectivity filters which can be lined by negative or positive dipoles. The source of the impermeable barrier is the repulsive ion-charge interactions, largely due to the parallel orientation of the helix pentamers. This ''helix dipole'' effect (Hol *et al.*, 1978) was verified by Langevin energy profiles calculations (Eisenman and Alvarez, 1991). The concentrations of permeant species can be modified by interactions with ionizable, dipolar, and hydrophobic groups. Helix dipoles can thus cause a sterically open structure to be impermeable to ions (Eisenman and Alvarez, 1991).

The single channel conductance and ion selectivity of the membrane channels are controlled by pH. Thus, the large voltage-dependent channels formed in planar lipid

layers by botulinum, tetanus and diphtheria toxins are pH-gated. Channel formation was shown to be optimal when the protein-containing *cis*-side of the plasma bilayer is at low pH (4.5) and the opposite, *trans*-side is at physiological pH (7.0). A pH gradient would therefore enhance formation of channels which could function as tunnel proteins (Hoch and Finkelstein, 1985).

Blue light and intracellular pH induce changes in the electric membrane potential of hyphae of the fungus *Phycomyces blakesleeanus*. The induced hyperpolarization is mediated by the parallely induced rate of acidification in the medium (Weiss and Weisenseel, 1990).

Movement of nutrients across the bacterial plasma membrane is by no means *uni*directional. Bacteria are known to export and secrete antibiotics, iron-sequestering siderophores, toxic byproducts. For instance, ''protein must ''know'' where it is destined to go''. Such a polarized process ''implies the existence of targeting and localization (stop transfer) signals within the protein structure'' (Pugsley and Schwartz, 1985).

In symbiotic associations, such as in vesicular-arbuscular endomycorrhizas, the host plasmalemma apparently retains its normal function of *bi*-directional nutrient transfer whereas in pathogenic relationships this transfer is *mono*-directional. There should occur some type of depolarization of the electrical potential difference associated with H^+-ATPase activity across the host-fungus membrane interface (Gianinazzi-Pearson *et al.*, 1991). It remains to understand how changes of the membrane potential ($\Delta\Psi$) decide of the monopolar or bipolar directionality of the nutrient transport (Smith and Smith, 1989).

e) *Action potentials*

The organization of the top three outer layers of the retina - photoreceptors, horizontal cells and bipolar cells - has been modellized to build a silicon chip (Mahowald and Mead, 1991). However, ''biological computation must be very different from its digital counterpart'': in the human retina, bipolar cells transmit a signal corresponding to the ratio of the signals from rods and horizontal cells through the ganglion cells while, in the silicon retina bipolar cell, circuitry amplifies the difference between the signal from the photoreceptor and the local average.

Depolarizing bipolar retinal neurons can be hyperpolarized by the neurotransmitter glutamate which supresses their cGMP-activated conductance (Nawy and Jahr, 1990). Bipolar cells isolated from the salamander retina are thought to be the hyperpolarizing or off-center bipolar cells. In such cells permeation of calcium ions occurs through non-*N*-methyl-D-aspartate - glutamate channels (Gilbertson *et al.*, 1991).

Stimulation of olfactory neurons developed an inward current when stimulated with odorants. The resulting depolarization can be sufficient to induce action potentials, as recently achieved by tight-seal patch-clamp recordings of frog olfactory cilia (Kleene and Gesteland, 1991).

f) *Synaptic membranes*

Synapsins, proteins interacting with synaptic vesicles and targeted in nerve terminals (Huttner *et al.*, 1983, see **I**; De Camilli *et al.*, 1990) appear in development during synaptogenesis. Synapsin is a filamentous protein which is thought to link synaptic vesicles and actin as shown in quick-freeze electron micrographs of nerve terminals. From these recent results (Han *et al.*, 1991), a model of synapse formation is proposed.

C. Endomembranar and vesicular systems

1. Endoplasmic reticulum

Intrinsic membrane proteins are inserted vectorially into the endoplasmic reticular membrane during or immediately after biosynthesis. Such asymmetric insertion provides a functional model for the small-intestinal Na^+, D-glucose cotransporter. In that gated transport agency, the substrate binding sites are more easily accessible from the cytosolic pole, the negatively charged mobile pole being a part of the Na^+ binding site (Semenza *et al.*, 1985).

The biphasic process of protein transport across the endoplasmic reticulum (ER) membrane comprises (1) an initiation of targeting cycle, and (2) the actual transfer of the polypeptide chain through the membrane. The question remains to know if this last process occurs through a translocation tunnel. According to one model (Rapoport, 1990 and **I** pp. 95-97), polypeptides are transported through a hydrophilic or amphiphilic tunnel that is assembled from transmembrane proteins.

The import of secretory protein precursors into the ER of *Saccharomyces cerevisiae* requires components such as a polypeptide (p) coded by the gene *SEC62*. This *SEC62p* spans ''a ER membrane twice, displaying hydrophilic amino- and carboxy-terminal domains towards the cytosol'' (Deshaies and Schekman, 1990).

2. Golgi apparatus

Proteins imported from the endoplasmic reticulum are polarly transported across the Golgi stack before secretion or storage in vacuoles. According to the endomembrane flow theory, in their polar progression, the cisternae of the dictyosomes would be formed consecutively at the *cis*-face and, after maturation steps, would be lost at the *trans*-face during the formation of secretory vesicles (see Steer, 1991). The alternative ''Rothman model'' suggests that individual cisternae are static and that transported molecules are successively passed from one cisterna to the next in vesicle shuttles (Rothman, 1985).

Monovalent cations are involved in the mechanism of Golgi secretion by animal cells as shown by blocking export of cell wall matrix polysaccharides from pea cells by the H^+- and K^+ exchanging ionophore, nigericin. The associated requirement of an

acidic internal pH in the cisternae might be explained by an osmotic model (Griffing and Ray, 1985). Another ionophore, monensin, is known to disturb the polarized traffic from the Golgi (see **I**, p. 99 and Tartakoff, 1983). Lipid traffic has further been studied by Pagano (1990) using his fluorescent marker microscopic technique.

3. Intracellular vesicles

Endocrine and exocrine secretory processes mediated by endocrine and exocrine vesicles respectively are directionally inverse shuttling operations. These shuttles involve a special class of lipid-rich, proton-poor membranes that appear to use an inwardly directed H^+-translocase ATPase activity operative for pH-dependent sorting of transported molecules (Castle *et al.*, 1987).

Within polarized epithelial cells (see VII.C.6b), the export traffic can be directed to a distinct plasmalemmal domain which distinguishes exocrine from endocrine secretion and import traffic can be directed transcellularly.

Exocytosis is a membrane process, which requires calcium and ATP as shown by membrane-bound chromaffin granules which store secretory products of the adrenal medulla cells and release their contents (catecholamines) to the cell exterior. Such release is triggered on cell depolarization by acetylcholine or by certain concentrations of K^+-ions; Ca^{2+} channels then open up and an increase in Ca^{2+} influx follows to reach its critical level of intracellular concentration. If exocytosis is a true contractile event involving cytoskeleton proteins (actin, α-actinin, myosin) and their regulatory ones, ''a sliding filament mechanism similar to that found in muscle would operate in chromaffin cells'' (Trifaró and Fournier, 1987). The intracellular Ca^{2+}-concentration reached during stimulation would activate calmodulin-dependent processes and phosphorylation of myosin light chains, a condition required for chromaffin cell myosin-ATPase actin activation and formation of bipolar myosin filaments (Trifaró *et al.*, 1985).

In an attempt to explain the exocytotic fusion of membranes of secretory vesicles with plasma membranes, Pollard *et al.* (1987) have proposed a novel ''hydrophobic bridge'' hypothesis for how synexin, a new calcium-binding protein, both drives and directs the fusion process. Conformational changes of the protein in the presence of calcium would expose its hydrophobic domains and shield its charged and neutral domains.

The cells make use of ionic gradients across the plasma membrane for signaling purposes, as in the propagation of the action potentials in excitable cells (see IV.B.2e), and for doing osmotic work, as in Na^+-dependent transport systems in epithelial cells (see VII.C.6b) and in the process of acidification of vesicles and other intracellular organelles. Moving of H^+ ions from the cytoplasm to the vesicle lumen by the ATP-driven H^+ pump has two consequences (Rudnick, 1987): the vesicle lumen becomes acidic and also positively charged with respect to the cytoplasm. For net H^+-pumping to occur, counter ion movement (anion influx or cation efflux) must dissipate the transmembrane potential.

Membranes of neuroendocrine secretory vesicles contain a H^+-translocating ATPase responsible for the generation and maintenance of the electrochemical proton gradient, ΔpH inside acidic, and transmembrane potential, $\Delta\Psi$ inside positive. This electrochemical proton gradient serves as the driving force for the intravesicular accumulation of compounds such as the biogenic amines inside the chromaffin granules (Johnson *et al.*, 1987). Synaptic vesicles and vesicles of the *Torpedo* electric organ also show ATP driven proton pump acidification (Stadler, 1987).

D. Organelles

2. Mitochondria

Direct evidence for an active role of microtubules in moving mitochondria in Spongillid pinocytes has recently been obtained (Weissenfels *et al.*, 1990).

3. Chloroplasts and phototransducing membranes

In photosynthetic systems, carotenoids serve the dual fonctions of light harvesting and photoprotection. Moreover, shifts in their absorption spectra are used to measure transmembrane potentials and the electrogenicity of charge separation steps. Such polyenes are highly polarizable, that is, electric fields can induce substantial dipole moments. Measurements of the seemingly anomalous dependence of carotenoid band shifts on transmembrane potential have revealed the production of large protein-induced dipoles for a symmetric carotenoid in the photosynthetic antenna complex of *Rhodobacter sphaeroides* (Gottfried *et al.*, 1991).

E. Cytoskeletal components

They are the actin microfilaments and the tubulin microtubules, on one hand, and the myosin, kinesin, dynein and dynamin microfilamentous ''motor'' proteins which are mechanochemical nucleotide triphosphates (ATPases), on the other hand (see new § E 4.). Such microtubule motors have not yet been identified in plants. As a cause of microtubule movements within the phragmoplast, tubulin might be incorporated at the interdigitating + ends and could move through microtubules by flux or minus-end assembly might also be involved (Lloyd, 1991). According to Asada et al. (1991) the equatorial region of the phragmoplast would be associated with a mechanochemical enzyme that generates the force for microtubule translocation by hydrolysing GTP.

Microtubules and neurofilaments (intermediate filaments, see new § E 5) are major elements of the neuronal cytoskeleton. However, contrarily to microtubules, neurofilaments are composed of an antiparallel array of subunits which may not be polar filaments and therefore could not support directed movement of organelles.

Cytoskeleton of the *Drosophila* fly has been extensively reviewed in 1990 by Fyrberg and Goldstein.

1. Microfilaments-actin

Actin filaments (F-actin) are important components of the cell cytoskeleton where they are often involved in transport processes. The actin monomer (G-actin) has been originally isolated by Straub (1942). Isolated F-actin filaments are suitable for three-dimensional reconstruction (Aebi *et al.*, 1986b). The atomic structure of their monomer complexed with the enzyme DNase I as well as an atomic model for the structure of the filament, a helical polymer of actin subunits have been recently unraveled by Holmes *et al.* (1990) and Kabsch *et al.* (1990).

The association between types of filaments and plasma membrane specializations first seemed to respond to a general rule. Thus, single actin microfilaments have been described as uniformly polarized at their attachment, with arrowheads (- ends) pointing away from the plasma membrane (Ishikawa, 1979). In other words, ''cables of actin consist of bundles of microfilaments all with the same polarity, i.e. with the barbed end (+) anchored in the membrane'' (Fulton, 1984, see **I**). However, at odds with this directionality there are reports of actin filaments anchored at their pointed end to cell membranes (Stossel *et al.*, 1985, see **I**, pp. 114-115).

According to a recently proposed working model (Schwartz and Luna, 1988), based on geometric considerations and observations from equilibrium binding studies, membrane-bound actin nuclei initially assemble with both barbed and pointed ends free (Shariff and Luna, 1990).

Within a bundle, actin microfilaments are arranged according to two types with respect to the polarity: uni- and bidirectional arrangements. According to such dual directionality, the bundle can be attached to the plasma membrane in side-to-membrane association and only with one end, if any end-to-membrane association exists (Ishikawa, 1979).

Enzymes are associated with an F-actin microfilament, leaving in the interstices of the Porter microtrabecular lattice (see **I**) a solution containing ions and some metabolites, but no proteins. Most of charged residues (more negative than positive) of actin must be in contact with water, so that, according to Clegg's model (1984), the F-actin filament is a highly charged, high-molecular-weight polyelectrolyte. As such it must generate special kinds of water structure involving a counterion adjacent to each charged group. In the electric balance, the ''couple'' H_3O^+ and OH^- compensates the deficit in diffusible inorganic ions (Wiggins, 1990).

2. Microfilaments-myosin

The myosin motors are force-generating enzymes (ATPases) which move toward the barbed (or plus) end of the actin filament (see Fig. 13 in **I**). In their bidirectional movement, myosin filaments can translocate actin filaments both toward and away from

their central bare zone. This illustrates the polarity of such sliding filaments (Sellers and Kachar, 1990).

3. Microtubules-tubulins

In microtubules, tubulin subunits are arranged in tandem composing a complex helical array (Vallee and Shpetner, 1990). Therefore, "the polar properties of microtubules on the supramolecular level are based on the polar properties of the tubulin subunits" (Mandelkow *et al.*, 1987). Evidence for the asymmetric shape of the tubulin molecule came mainly from image processing of electron micrographs of negatively stained microtubules or related polymorphic tubulin assemblies. Axial polarity was observed along protofilaments (up/down) siddedness (left/right) and radial asymmetry (inside/outside). Each subunit, and the microtubule as a whole, has therefore an inherent or intrinsic polarity.

Polarity was first deduced from this highly organized array of microtubules that make up the ciliary and flagellar axoneme (Borisy, 1978). These microtubules all have the same orientation with the end proximal to the cell body designated as "-" and the distal end as "+". This is what occurs in axons with their "anterograde" (away from the cell body) and "retrograde" (toward the cell body) directional transport of organelles. Such movements are therefore toward the + and - ends of the axonal microtubules, respectively. By contrast, neuronal dendrites contain microtubules of *mixed* polarity (Burton, 1988; Baas *et al.*, 1988), which "raises perplexing questions regarding the expected behavior of dendritic organelles" (Vallee and Shpetner, 1990).

As in the actin microfilaments, the inherent or intrinsic polarity (Huxley, 1963, Amos and Klug, 1974 in **I**) is reflected in the asymmetric addition of subunits at the two ends of the polymer (Haimo, 1989; see **I** and **II**).

Many factors regulate microtubule assembly and organization in the cytoplasm among which are the thermodynamic polarity of the microtubules themselves, their number, the presence and number of nucleating sites and the concentration of tubulin (Kirschner and Mitchison, 1986).

For measuring the polarity of cytoplasmic microtubules two methods have been developed (see Linck, 1989): 1) flagellar dynein reassociation with non-flagellar microtubules (Haimo *et al.*, 1979 in **I**); 2) brain tubulin assembly onto existing microtubules, forming curved arcs or hooks in cross section (Heidemann and McIntosh, 1980 in **I**).

The fundamental structural polarity of microtubules derives from the head-to-tail organization of α- and β-tubulin heterodimers in the profilament lattice constituting the wall of the tubule. "This polarity is made apparent on a larger scale by the polarized grouping of such accessory structures as the radial spokes on ciliary and flagellar tubules and by the different rates at which tubulin assembles and disassembles at the two ends of a tubule" (ref. in Gibbons, 1989).

In plants, the orientation of microtubules is transverse across the long axis of the stem, and perhaps might be causely related to the orientation of the cellulose microfibrils that give structural integrity to the cell wall. Shortly after growth begins to slacken, the horizontal orientation of microtubules rapidly changes toward longitudinal positioning in the pea stem (Laskowski, 1990). Cellulose microfibrils are also reoriented during cell elongation to a longitudinal orientation. Such a parallel orientation to the long stem axis provides longitudinal strength to its mature cells.

4. Microtubule-associated "motor" proteins

There are three classes of microtubule-associated motor proteins to power intracellular movements. Relative to the intrinsic structural polarity of the microtubule, dynein produces movements toward the minus end (Vallee and Shpetner, 1990), while kinesin generates movements toward the plus end (Vale *et al.*, 1985, in **I**), and dynamin bundles microtubules and causes them to slide relative to one another (Shpetner and Vallee, 1989, in **II**). The polarity of movement of the recently found kinesin-like *ndc* protein of *Drosophila* is also minus end directed (McDonald *et al.*, 1990).

The microtubule-associated mechanochemical enzymes or "motor" proteins kinesin and dynein contain a specialized enzymatic domain that hydrolyzes ATP and uses the derived chemical energy to produce force and movement along a cytoskeletal polymer. With kinesin and myosin adenosine triphosphatases (ATPases), dynein represents one of the three general classes of ATPase that couple energy derived from the hydrolysis of ATP to the movement of cellular components along stable tracks of either microtubules (dynein, kinesin) or actin filaments (myosin) (see Warner, 1989). The recently discovered dynamin (Shpetner and Vallee, 1989) has a microtubule-activated ATPase activity. This mechanochemical ATPase mediates sliding between microtubules and its properties are distinct from those of the other two proteins. Indeed, its molecular cloning has recently revealed homology with a new family of GTP-binding proteins (Obar *et al.*, 1990). By contrast, dynein and kinesin provide locomotive forces along cytoplasmic microtubules, but by analogy to a railroad, the microtubules themselves are far more than simple, inert tracks (Linck, 1989). Dynein can bind to axonemes or to nonaxonemal microtubules thereby revealing their intrinsic structural polarity.

Movement of the motor along the polymer is unidirectional, which is "a consequence of the inherent asymmetry of the polymer and the motor" (Vale and Goldstein, 1990). These microtubule motors are either plus-end directed (kinesin) or minus-end directed (dynein). Dynein (22S and 14S) extracted from axonemes of *Tetrahymena* produces force in the direction of the minus-end predicted from the outer doublet sliding experiments of Sale and Satir (1977). This direction is opposite to that of kinesin-induced movement along a microtubule (see Vale and Toyoshima, 1989).

Microtubles and associated molecular protein motors are also known to mediate the movement of pigment granules (chromatophores) in cytomatrix protein (Weissenfels

et al., 1990) and other-surrounded cell compartments (Couchman and Rees, 1982; Schroer *et al.*, 1988).

5. Intermediate filaments

There is ample evidence that microtubules and microfilaments are of importance for the onset of cell polarity and generation of cell movements, while the function of intermediate filaments remains elusive (Traub, 1985). Some of their subunit proteins have a specificity for binding to DNA rather than to RNA intermediate filaments and could thus be involved in signal transduction from the plasma membrane or cytoplasm to the nucleus. In fact the nuclear lamina is a meshwork of intermediate-type filaments lining the nucleoplasmic surface of the inner nuclear membrane (see Aebi *et al.*, 1986a).

F. Nuclei and mitotic figures

1. Interphasic and mitotic structures

The development of a bipolar spindle is an essential prerequisite for the segregation of chromosomes during mitosis (Mazia, 1961 and Nicklas, 1971 in Borisy, 1978) and the polar functions of the spindle reflect the polarities of the microtubules originating from the centrosomes and the chromosomes (Subirana, 1968 and McIntosh *et al.*, 1969 in Borisy, 1978). "Given that microtubules possess intrinsic molecular polarity (see IV.E.3), there are two ways in which they might be oriented relative to a nucleation site and therefore four possible polarity relations for the microtubules of opposite centrosomes and chromosomes" (McIntosh, 1977 in Borisy, 1978). There is not yet a readily interpretable indicator (morphological marker) for microtubules polarity such as heavy meromyosin in the case of actin filaments (Huxley, 1963, see **I**; Ishikawa *et al.*, 1969). For cytoplasmic microtubules, their intrinsic polarity is therefore reflected in their direction of growth. Their elongation *in vitro* is known to be a biased-polar process (Allen and Borisy, 1974, see **I**; other ref. in Borisy, 1978) in which the tubulin dimers are added at the ends of the tubule (see IV.E.3).

In the model for cytokinesis proposed by Pollard *et al.* (1990), actin filaments of the cellular isotropic gel are attached by their barbed ends to the plasma membrane (see also E.1) and cross-linked by alpha-actinin and other proteins preexisting in the cortex. Myosin II assembled into bipolar filaments also interacts with actin filaments thereby activating the cleavage process. Actomyosin is also involved in the organization of mitosis. In *Dictyostelium amoebae*, specific accumulation of myosin I

might occur in the polar amoebal lamellipodia and be related to apparent ''axial relaxation'' (Fukui, 1990).

The mitotic spindle in higher plants is typically anastral (without polar bodies) but some cell types possess the potential to develop asters. With the exception of certain algae, plant spindles are also acentriolar. The preprophase band is a unique feature of cell division in such non-algal plants (Pickett-Heaps and Northcote, 1966). By late preprophase, microtubules appear around the nucleus of the fern *Athyrium filix-femina* in a preferred orientation establishing division polarity before the onset of prophase. Thus ''the polar ''caps'' of microtubules concomitantly appear as an additional element re-enforcing the axial polarity'' (Jenni *et al.*, 1990).

The organization of microtubules into arrays such as the mitotic spindle is choreographed by structures known as microtubule organizing centres (see **I**, pp. 126-128). A particularly well-studied centre, the spindle pole body of the budding yeast *S. cerevisiae* has now been isolated by Rout and Kilmartin (1990). This should provide an attractive model to study the ability of the pole body to assemble microtubules and a tool for its still unknown biochemistry.

It has been proposed by Oakley *et al.* (1990) that γ-tubulin attaches microtubules to the spindle pole body, nucleates microtubule assembly, and establishes microtubule polarity *in vivo*. A microtubule-severing protein has now been identified in *Xenopus* egg extracts (Vale, 1991). This factor may be involved in disassembling the interphase microtubule network prior to constructing the mitotic spindle.

2. Polewards chromosome movement

There are three types of spindle microtubules, kinetochore microtubules, central spindle microtubules, and astral microtubules. They originate from a spindle pole, the centrosome, and are oriented with their minus ends at the poles, plus ends out. There are two known motive forces on chromosomes: polewards movements transmitted via the kinetochores, and forces away from the poles, the polar ejection forces transmitted to chromatin. Carpenter (1991) concludes that the balance between the polar wind, pole-directed kinetochore forces, and bonding by interchromosomal microtubules can explain all known interactions within the process of distributive segregation involved in mitosis.

A model for the dynamics of chromosome movement has been proposed by Palmer *et al.* (1989) founded on the analysis by digital imaging microscopy of DNA nuclear movement in live cells of the budding yeast *Saccharomyces cerevisiae*. The mechanism of these movements and their induction have been studied in certain cell deficient cycle mutants (cdc), and the axis defined by the segregating genomes found to rotate relative to the cell surface. Quite recently, two different microtubule-based motor activities with opposite polarities have been unraveled in kinetochores by video microscopy (Hyman and Mitchison, 1991).

The radial microtubule array emanating from the centrosome is one of the important controlling elements in cell form and polarity. "Since kinesin would be expected to move objects to the periphery of the cell on those microtubules, it could be very useful in building and maintaining polar distributions of materials within cells" (Sheetz *et al.*, 1987). For further information about kinesin and dynein implications as motor molecules in chromosome movements, see Carpenter (1991).

V. POLAR CELL MOVEMENTS

A. Cytoplasmic movements

Rotational cytoplasmic streaming has been widely accepted as being caused by active shearing at interface between the moving endoplasm and the stationary ectoplasm (Kamiya, 1981, see **I**). Microtubule bundles are indispensable for such cytoplasmic streaming in the Characean cells (see Williamson, 1975 in **I**; Nagai and Hayama, 1979).

Directionality of streaming in amoeboid cells is ensued by the polarity of actin filaments and interaction between the mechanochemical electric field and the electric dipoles built by the movement of protons along the filaments "may cause the turning over of the filaments, giving rise to shuttle-streaming and to oscillations of the electric polarization" (Tirosh *et al.*, 1979, *not* 1980 as in **I**).

B. Cell Movements

1. *Cilia-flagella*

The flagellum of *Allomyces* zoospores has an intrinsic polarity when it beats perpendicularly to the long axis of the rhizoplast (Aliaga and Pommerville, 1990).

3. *Amoeboid motion (transient polarity)*

A possible mechanism of motion in *Amoeba* which involves repolarization by two types of K^+ channels of the cell depolarized by the influx of Ca^{2+} through both mechano-sensitive and voltage-gated Ca^{2+} channels has been proposed by Franciolini (1990). In this model, entering calcium binds to the contractile filaments, conferring movement on the *Amoeba*.

4. *Amoeba-flagellate reversible transformation*

In this transition process, well-studied in the life cycle of the slime mold *Physarum*, the amoeba becomes a different cell type and displays polarity while developing a new organelle, the flagellum (Sauer, 1982). Microtubules have been recognized as the major structural components of this amoeba-flagellate transformation (Sauer and Pierron, 1983).

The transition from flagellates to amoeba cells involves disintegration of flagellate-specific microfilamentous structures. A cold treatment or the artificial elevation of intracellular Ca^{2+} concentration disintegrates flagellate-specific microfilamentous cytoskeleton and induces amoeba specific microfilamentous cytoskeleton (Uyeda and Furuya, 1990).

The numerous insights into the role of Ca^{2+} in cell shape changes of *Naegleria* (see **I**, pp. 138-139), and in the yin-yang alteration of actin-based and tubulin-based cell motility in the amoeba-flagellate *Naegleria* have been recently updated by Fulton (1990).

5. *Taxis:*

a) *Chemotaxis*

When growing on the surface of rotting tree bark, the plasmodium of the slime mold *Physarum polycephalum* looks like a fan and is polarized because of its chemotactically-directed search for food in contrast to well-fed laboratory cultures (Sauer and Pierron, 1983). Reversible polymerization cycles of actin (G $\leftrightarrows$ F forms) accompany the shuttles of ecto-endoplasms and are thus involved in rhythmic contractions of the plasmodium.

Polarization is the degree to which a neutrophil leukocyte forms a pseudopod or adopts motile or ''polarized morphology'' (Wilkinson, 1990). In the presence of chemoattractants, all leukocytes can respond by chemotaxis (directional locomotion) and chemokinesis (change in cell speed). As first event, chemotaxis is a change in morphology from a spherical shape to an anteroposterior polarity. According to Wilkinson (1990) ''the same shape change occurs both in isotropic attractant concentrations and in gradients. Any theory of gradient detection must explain how cells in isotropic attractant concentrations adopt a head-tail polarity''. Intrinsic cellular mechanisms would determine polarization and locomotion, while chemotaxis and chemokinesis would be determined statistically by the nature of cells' environment (Wilkinson, 1990).

Polarization and adhesiveness of neutrophils are affected by globulin factors in plasma. Induction of this polarization appears to be linked to promotion of adhesiveness (Bignold *et al.*, 1990).

Large, rapid increases in actin polymerization and in the amounts of actin associated with the cytoskeleton are part of cellular responses to chemotactic and phagocytic factors. Actin appears to be actively recruited to plasma membrane sites, including the anterior ends of locomoting cells, phagocytic cups, and adherens junctions (for review, see Shariff and Luna, 1990).

Chemotactic factors are reported to trigger the formation of new actin nucleation sites with free barbed ends, i.e., the increased actin polymerization during chemotaxis is inhibited by the barbed-end capping agent, cytochalasin D (Shariff and Luna, 1990). The intracellular location of these actin nucleation sites is unknown. The identification of an actin-binding protein (ABP-50) as elongation factor (1a) and its association with the cytoskeleton has been found to be regulated during chemotaxis of Dictyostelium (Yang *et al.*, 1990).

In signal transduction during cyclic-AMP induced chemotaxis in the cellular slime mold *Dictyostelium discoideum* the plama membrane potential plays a possible role. From experiments involving measurements of cyclic GMP and cyclic AMP responses in

cells with a depolarized membrane potential, it was concluded that ''membrane-potential-regulated processes, such as voltage-gated ion channels, do not play an essential role in chemotaxis in *D. discoideum*'' (van Duijn *et al.*, 1990). *Dictyostelium* amoebae translocating in buffer are elongate and, by the addition of cyclic AMP, exhibit expansion zones primarily at their anterior end. Filamentous, F-actin is primarily localized in anterior pseudopodia. In such conditions, the pattern of microtubules organization is unaffected (Wessels *et al.*, 1989). In cultured fibroblasts, selectively stabilized microtubules are oriented toward the direction of cell migration. Such remodelling of microtubular arrays suggests that ''selective stabilization of microtubules is an early event in the generation of cellular asymmetry'' (Gundersen and Bulinski, 1988).

b) *Phototaxis*

In their review of photomorphogenesis in lower green plants, Wada and Kadota (1989) have tabulated orienting phenomena that are dependent upon blue-light absorbing pigment(s) such as polarotropism and hyperpolarization in ferns and mosses. They mentioned the fact that dipole moment theory of red-light-absorbing form of phytochrome spirally arranged in the cell surface plays a role in chloroplast photo-orientation in the green alga *Mougeotia* (Haupt and Bock, 1962).

6. *Structural basis for directionality*

The underlying polarity of the microtubules determines the directionality of force transmission by both orienting the attached force generators and influencing the direction of microtubule assembly and disassembly (Linck, 1989 and **I**). Microtubule-dependent events such as mitosis (IV. F) and motility are coupled to such assembly and disassembly processes (see **I**). In flagella the polarity of assembly was first observed *in vitro* by experiments showing that ''brain tubulin assembles preferentially onto the distal or plus ends of basal bodies and axonemal A-tubules and to a lesser extent onto the proximal or minus ends'' (ref. in **I** and Linck, 1989).

Among important forces responsible for cellular movements there are electric forces and mechanical torsional movements. Tropomyosin would interact by its polar side chains in the possible torsional processes during Ca^{2+}-activation. This would lead to a rotation of the tropomyosin coiled-coils, as demonstrated with a molecular model (Jarosch, 1979).

The ruffling movement of L cells on a glass substratum was analyzed by time-lapse cinemicroscopy. The ruffling movement could be stopped and the leading edge retracted in the presence of cytochalasin B. The ruffling processes changed to pseudopodia-like structures when colchicine was added to the culture medium. Finally ''the cell changed from a fan-like shape to a circular one, loosing its polarity'' (Ohnishi, 1979).

Fish (teleost) chromatophores are capable of rapid pigment transport and possess a finalized intracellular organization, the cytomatrix (Bikle *et al.*, 1966). This granule-moving matrix also implicates mitochondria, nucleus and plasma membrane and is connected with the pigment transport system (Green, 1968). A model for matrix-microtubule interaction has been constructed by McNiven and Porter (1984) using a modification of the technique of Heidemann and McIntosh (1980, see **I**) to determine the direction - clockwise or counterclockwise - of microtubule hooks as probes for arm microtubules polarity (McIntosh and Euteneuer, 1984, see **I**). In summary, the dynamic matrix in chromatophores requires "energy for expansion, is controlled by Ca^{++}, is non-actomyosin dependent and requires microtubules for support and direction" (McNiven and Porter, 1984).

VI. POLAR CELL GROWTH

A. MONOPOLAR

1. OUTGROWTH (EMERGENCE)

a^2 *Yeast budding*

Budding in the yeast *Saccharomyces cerevisiae* involves a polarized deposition of new cell surface material that correlates with a highly asymmetric deposition of the actin cytoskeleton. In cell cycle deficient mutants, this cell-surface deposition is delocalized and found to be associated with a loss of asymmetry (?) of the actin cytoskeleton (Adams *et al.*, 1990). In the control of the budding direction of CDC mutants of *Saccharomyces cerevisiae* it has been shown by Matsuoka *et al.* (1988) that it is the stage after spindle pole body duplication which is effective for that directionality using an electric stimulus.

The events associated with budding and those of the nuclear cycle thus represent two independent pathways within the cell cycle. These new results are supported by the fact that temperature sensitive mutant cells (CDC42 and 43) arrest as large unbudded cells when grown at restrictive temperature while events associated with the nuclear cycle (DNA replication and formation-elongation of mitotic spindle) continue. The mutant CDC42 which is involved in the development of yeast cell polarity has been molecularly characterized (Johnson and Pringle, 1990). Some of its proteins have been found to show similarities to *ras* proteins and some of these similarities were more pronounced in the regions that have been implicated in GTP binding and hydrolysis, thereby suggesting membrane and/or microtubules involvement in CDC42 function. The CDC43 gene product also involved in establishing cell polarity during the yeast-division cycle has recently been isolated and its sequence analyzed (Johnson *et al.*, 1990).

b^1 *Fungal germ tubes*

In a study of the inductive signal to shift from polarized germ tube growth to non-polarized appressorial growth in *Metarhizium anisopliae*, St Leger *et al.* (1990) found "no evidence for a gradient of Ca^{2+} in the spore which could establish the initial polarity. Calmodulin, however, was localized at the poles of the conidia, near the site of germ-tube emergence".

b^2 *Algal eggs*

Polarization of the zygote in Fucoid algae leads to its asymmetric cleavage on germination (see **I**). The equal first division of the zygote corresponds to its asymmetric

cleavage. This cytological process is preceded by a polarization of the initially spherical cell which can be equated to the symmetry-breaking defined by Prigogine's school (Prigogine and Stengers, 1984). It involves polarization of the whole cell, from its peripheral wall to its cytoplasmic content along an antero (thallus)- posterior (rhizoid) axis of polarity. The polarizing role of light and external ionic gradients has already been emphasized (see **I** and **II**). It should be noted that Kropf's (1989) experiments with fluorescent chelators have not supported an interaction between these two inductors.

c) *Dimorphism*

pH appears to control the dimorphic choice between sexual process, namely macrocyst formation and asexual development, namely sorocarp formation (Iijima and Maeda, 1990).

2. Tip growth

Its processes have been recently reviewed not only in fungal but also in plant cells (Heath, 1990).

b) *Fungal hyphae*

In 1982, Koch has developed a formula to account for the shape of the apex of hypha and allowing ''the calculation of the rate of synthesis at a point on the tip from its distance from the axis and the slope of the tip at that point''. Koch considered the growing hyphal tip as ''analogous to a molten glass bubble blown under special conditions''.

Apical growth in fungi and other developmental processes in yeasts and algae have recently been shown to illustrate the diversity of vectorial physiology and of the forms it generates (Harold, 1990). In such processes, according to Turian and Favre (1990), ''the primary polarity signal in a relatively isotropic structure such as the conidium of *Neurospora* would be endogenously endorsed by a few uncoupled mitochondria strategically positioned by microtubules to enforce, by protons from their dissipative gradient, electrical depolarization of a local site of the plasmalemma, thereby selected as the genetically determined single outgrowth site''. By contrast, germinated conidia of *Monilia fructigena* are bipolarly determined (Turian, 1985, see **I**). The local lowering of pH would be an acid activation signal for phospholipase expected to hydrolyse phospholipids to unsaturated agents uncoupling frontal mitochondria, thereby lowering their ATP productivity and favoring inward leakage of H^+ with the electrical loops entering into the elongating hyphal tips. Moreover, phospholipase activation would act as a secondary signal for production of inositol 1,4,5-trisphosphate-mobilizing Ca^{2+} from its endomembrane store and thus concour to set a concentration gradient of calcium ions in the hyphal apices (Turian and Favre, 1990). Concerning this problem of apical growth it

must be pointed out that recent results from Harold's group disprove any obligatory connection between inward current and hyphal outgrowing processes. Consequently the hypothesis that electric currents localize hyphal growth has become questionable and in need of a reassessment (Cho *et al.*, 1991a). This leaves open our above and previous suggestions of an internal control of this process (Turian, 1983, see **I**).

Wild type hyphae of *Neurospora crassa* grown in the presence of the calcium-channel blocker verapamil, unlike untreated controls, do not show Ca^{2+} in their hyphal tips and display an enhanced branching of their hyphae. This hyperbranching mycelial pattern could be corrected by the addition of Ca^{2+}. Two morphological hyperbranched mutants, ''frost'' and ''spray'', failed to demonstrate Ca^{2+} in hyphal tips and could also be corrected to normal branching in the presence of exogenous Ca^{2+} (Dicker and Turian, 1990). These new results support our previous finding of the inverse H^+/Ca^{2+} gradients in the hyphal apex of *N. crassa* (Turian *et al.*, 1985, see **I**). In their controlling role of polar growth, exogenous Ca^{2+} ions would enter through the tips by antiport with the H^+ ions effluxed from subapical mitochondria thereby uncoupled by the Ca^{2+} that they sequester (Turian, 1979, see **I**). This would thus provide an autoregulative system (flip flop mechanism ?) of polarity maintenance.

The ''Spitzenkörper'' which is an aggregate of apical vesicles is centrally positioned at the extreme hyphal apex of septomycetous (not ''Streptomycetous'' as wrongly spelled p. 164 in **I**) fungi. Its disruption by a demethylase inhibitor, cyproconazole, leads to an inhibition of apical extension of the hyphal cell (Roberson and Fuller, 1990).

The hyphae in expanding mushrooms of the *Agaricus* type have been shown to grow by diffuse extension over their whole wall surface (Mol and Wessels, 1990) in contrast to the prevalent apical elongation occurring in colonizing substrate hyphae.

The architecture of the actin and tubulin cytoskeletons of the oomycete fungus *Phytophthora infestans* might be involved in the maintenance of the spatial organization of its hyphal protoplast (Temperli *et al.*, 1990).

c) *Algal rhizoids and filaments*

An abundance of endoplasmic reticulum and Golgi vesicles aggregated into a spherical apical body or ''Spitzenkörper'' have been observed in the tip of fast growing *Chara* rhizoids (Bartnik and Sievers, 1988).

A negative apico-basal gradient has been demonstrated by the fluorescence of chlorotetracycline, a calcium chelator in the growing phase of *Acetabularia* (Reiss and Herth, 1979). This calcium gradient correlates with electrical polarity in growing cells: the apex is hyperpolarized and action potentials due to a chloride pump arise from it (Gradmann, 1976; 1989 in **II**) until the cap is initiated. Calmodulin fluorescence followed the same negative apico-basal gradient as calcium (Cotton and Vanden Driessche, 1987 in Vanden Driessche, 1990). A light sensitive, transcellular current has been detected along the regenerated enucleated posterior stalk of A. *mediterranea* (Novak and Sironval, 1976).

d) *Protonema (mosses)*

In protonemal tip growth of the moss *Physcomitrella patens* microtubules impose polarity and directionality upon expansion while F-actin is necessary for outgrowth (Doonan *et al.*, 1988) as also found in fungi (Turian *et al.*, 1985; Yokoyama *et al.*, 1990).

f) *Pollen tubes*

Shortly before their germination, pollen grains show a precise spatial and temporal organization of actin (Tiwari and Polito, 1988) which has microfilamentous arrays preferentially accumulated beneath germination apertures. Cytochalasin D treatments indicate that an uninterrupted progression of actin organization is essential for pollen germination (Tiwari and Polito, 1990a).

An actomyosin is involved in the transport of organelles and also of larger inclusions in pollen tubes (Heslop-Harrison and Heslop-Harrison, 1989). A concentration of small microtubules, forming a collar at the base of the tube protruding from a germinating pear pollen grain, has been detected by Tiwari and Polito (1990b).

Ca^{2+} appears to play a fundamental role in establishing the dominance of apical growth in pollen tubes (Picton and Steer, 1982, 1983) as it does in fungi (ref. in **I**; St Leger *et al.*, 1990).

i) *Animal neurites*

Fast axoplasmic transport within the squid giant axon provides an excellent model system for viewing directly the bidirectional vesicle transport along "transport filaments" (Allen *et al.*, 1982). Sequential examination in the light and electron microscope revealed that a "transport filament" was a single microtubule without associated actin (Schnapp *et al.*, 1985). An assay system using centrosomal microtubule arrays was used to determine the direction of kinesin movement relative to microtubule polarity, which is defined by the direction of preferred microtubule polymerization (Vale *et al.*, 1985). Within axons the polarity of microtubules is such that the plus (+) ends are oriented toward the synapse (Burton and Paige, 1981; Heidemann *et al.*, 1981). The minus (-) end motile factor (dynein) would be responsible for moving organelles in the retrograde direction, whereas organelle movements in the anterograde direction from the cell body to the synapse would be driven by kinesin (see IV.E.3 in **I**).

Microtubules are polarly oriented in the axons and dendrites in hippocampal neurons. In axons, they are uniformly oriented with respect to polarity: (+) ends are directed away from the cell body toward the growth cone, in sharp contrast with the nonuniform orientation of microtubules in the mid-region of the dendrites. However, at distance within 15 μm of the growth cone, microtubule polarity orientation is similar in both dendrites and axons (Baas *et al.*, 1988).

The neurons in the isthmo-optic brain nucleus are already polarized during the early chick embryogenesis and most neurons near the border of the nucleus already have inwardly polarized dendrites (Clarke and Caranzano, 1985). Dendritic geometry and its modulation in the developing brain involves an early target removal which eliminates a retrograde signal that normally enhances dendritic polarization. In this work on arborization of dendrites and its possible control by the axonal target region, Blaser *et al.* (1990) propose an ''index of polarization'' defined as the ratio between the ''length of polarization'', which is a measure of dendritic polarization, on the square root of the area covered by the dendrites.

In the developing neural tube the flow plate would act as an intrinsic organizer to establish pattern and polarity in this system (Hirano *et al.*, 1991).

j) *Capillary vessels*

Normally well-polarized capillary-like tubes can be recovered from the spherical hemiangioma, aberrant morphogenetic behavior of endothelial cells by neutralization of excess proteolytic activity by exogeneously added serine protease inhibitors (Montesano *et al.*, 1990). The local gradient of angiogenetic rounding of endothelial cells (neovascularization) can be inhibited by antibiotics (Ingber *et al.*, 1990).

In coupled endothelial cells, the electric signal of hyperpolarizing substances can be preferentially directed by the endothelium along the longitudinal axis of arteries (Bény and Gribi, 1989).

B. Bipolar growth

b) *Yeast elongation*

A protein kinase (*kin1*) mutant of the fission yeast grows as spheres on enriched medium in contrast to the wild type cells, which grow as rods. The gene *kin1*-positive is therefore important for growth polarity in *Schizosaccharomyces pombe* (Levin and Bishop, 1990). As in *S. pombe*, F-actin was found in *S. japonicus* to be concentrated as "dots" at the growing poles of interphase cells (Alfa and Hyams, 1990).

e) *Algal cells elongation*

The response of round *Euglena gracilis* cells to Ca^{2+} channel blockers in the early part of their light cycle suggested that the process of gradual cell elongation produced was the result of an uncoupling from the biological clock (Lonergan, 1990). *Euglena* cells have been studied by the detergent-extracted cell model which has been adapted by Lonergan (1990) to the study of microtubule repolymerization.

f) *Higher plant elongating cells*

The acid growth theory of auxin action has been recently reexamined by Böttger's group who concluded from their experiments using a computer-controlled pH-stat that "'the acid growth theory correctly describes incidents taking place in the early phases of auxin-induced growth'' (Lüthen *et al.*, 1990).

VII. POLARIZED CELL DIFFERENTIATION

In symmetrically cleaving cells at their cytokinesis, a "contractile ring" is formed by the circumferential concentration of cortical actin and myosin-II filaments (Schroeder, 1972; Pollard *et al.*, 1990, see also IV.E.1.). By contrast, asymmetric, differentiating cleavage is mediated by a "contractile arc" which contains bundles of actin filaments of opposite polarities oriented parallely to the long axis of the cleavage-furrow (Mabuchi *et al.*, 1988).

Cytokinesis in diatoms involves a cleavage furrow rather than a cell plate and a band (preprophase) of microtubules coalesces circumferentially around the cell before the onset of mitosis (Wordeman and Cande, 1990).

Deviation from symmetric division occurs at female meiosis where the three unused chromosome complements are discarded in small cells called polar bodies. These bodies result from an unequal cell division generally attributed to the localization of the meiotic apparatus at the animal pole of the egg. Recently, however, polar body formation studied in the egg of the freshwater oligochaete *Tubifex attai* has been attributed to the reorganization of the cortical actin (Shimizu, 1990).

Embryonic mitosis also creates two different cell types which are placed in their appropriate position by the orientation of their division planes. For example, "in grasshopper embryos neuronal stem cells not only divide asymmetrically to give a nerve cell precursor (which is small) and a new stem cell (which is large), but also divide in a precise orientation so that the nerve cell precursor comes to lie internal to the more superficially located stem cell. Continued polarized divisions of the stem cell produce an ordered series of neuronal precursors, with the first born being the most internal. This polarity appears to influence the ordered structure of the nervous system since each neuronal precursor gives rise to different types of neuronal cells" (Doe and Goodman, 1985, O'Farrell *et al.*, 1989).

Factors inducing unequal cytokinesis have also been studied in grasshopper neuroblasts and found to be caused by the eccentric location of the spindle which maintains a definite polarity in dividing cells (Kawamura and Yamashiki, 1990).

A. Intercalary differentiations

1. *Bacterial endospores*

A novel mechanism of cell division has recently been described in a gram-negative bacterial rod by Mohn *et al.* (1990). Its polar growth occurs with a collar which girdles each cell.

3. *Fungal zoospores*

In the aquatic fungi Chytridiomycetes, the monoflagellate zoospores emerged from sporangia (see **I**, VII.B.1.a[2]) have an inherent structural polarity with regard to the apico-basal sequence: ribosomal nuclear cap - nucleus - nucleolus - rhizoplast - flagellum. The highly polarized zoospore of species of *Blastocladiella* shows a single, basally positioned mitochondrion (Cantino *et al.*, 1963) and that of species *Allomyces* a large kinetosome-associated basal mitochondrion sorted from the other ones (Fuller and Olson, 1971; Aliaga and Pommerville, 1990). In the other aquatic fungi Oomycetes, the zoospores of *Saprolegnia* are biflagellate and diplanetic, namely they sequentially change from the piriform to the reniform type. These last, symmetrical secondary zoospores display an asymmetrical arrangement of microtubules (Holloway and Heath, 1977): ''given the asymmetry of flagella themselves (whiplash versus Flimmer) some asymmetry in the microtubular root system might be anticipated''.

C. Apico-basal differentiations - heterobipolar axiation

1. *Caulobacterial cells (flagellate-stalk poles)*

Differentiation in Caulobacteria is high-lighted by an asymmetric cell division producing two different cell types, a motile swarmer cell and a slightly larger, nonmotile stalked cell (see **I**, Fig. 25); this cell cycle is subtly regulated (Newton and Ohta, 1990).

In a further study of the assembly of the two major polar organelles of *Caulobacter crescentus*, the flagellum and the stalk, Driks *et al.* (1990) have identified a polar particle (10-nm) as a new structural feature at the flagellate and the tip of the stalk. The characteristic asymmetry of the *Caulobacter* cell appears to be disrupted in mutants (*flbT*) in which the polar particle is absent at the flagellar pole.

4. *Cryptogamic spores (rhizoid-thallic poles)*

Signals controlling polar development of moss protonema and fern prothallia have been reviewed by Jaenicke (1991) who mentioned the fact that growing chloronemata of *Funaria hygrometrica* can be converted by indole acetic acid (IAA) into budding caulonemata by inducing an asymmetric division in this moss grown on agar at low light (Bhatla and Bopp, 1985).

5. *Higher plants cells*

b) *Epidermal cells*

Mechanoreceptor cells from the trigger hair of *Dionaea muscipula* Ellis are characterized by concentrically ordered cisternae of endoplasmic reticulum which occupy both basal and apical cell poles (Buchen *et al.*, 1983). To elucidate the

development of this polarity, electron microscopic examinations of these hairs were conducted at successive stages of differentiation (Casser *et al.*, 1985).

6. *Higher animal cells*

a^2 *Molluscs and Worms*

Embryonic development from the fertilized egg of the nematode *Caenorhabditis elegans* begins with series of *unequal* cell divisions that give rise to six founder cells (Wood, 1988; Riddle and Georgi, 1990).

a^3 *Insects*

Antimicrotubule chemicals such as colchicine or nocodazole disrupt cytoplasmic streaming within the late stages-oocyte of *Drosophila* and also lead to an abnormally positioned oocyte nucleus (Gutzeit, 1986a). Conversely, the antimicrofilaments cytochalasin B and D interfere with streaming from nurse cell to oocyte (Gutzeit, 1986b). Actin may thus be required for movement into the oocyte while microtubules may be necessary for proper placement within the oocyte.

a^5 *Amphibians*

The eggs of *Xenopus laevis* have been used as a model system to investigate the role of polarity in amphibian development. The presence of an animal/vegetal polarity within the *Xenopus* egg plasma membrane has been demonstrated with certain lipid probes which appear to partition into the plasma membrane and indicate the existence of lipidic microdomains when they recover upon photobleaching (Dictus *et al.*, 1984).

Xenopus oocytes have a high density of cholinergic (muscarinic) receptors clustered around the animal pole (Kusano *et al.*, 1982). Activation of these receptors generates inositol triphosphate (IP_3) which then releases calcium, which opens chloride channels (Oron *et al.*, 1985). The function of these calcium-activated chloride channels is unclear but, according to Berridge (1987), ''they could be responsible for the current that is known to enter the animal pole and that might be responsible for establishing the anterior-posterior axis that controls early development''. The same author has further suggested that, in the polar transduction of their message toward the cell center, IP_3 and diacylglycerol mediate the action of mitogenic factors e.g. fertilization and growth factors.

Following their experiements using anti-cytoskeletal agents, Yisraeli *et al.* (1989) proposed a model for the localization of Vg1 mRNA in which ''translocation of the message to the vegetal cortex is achieved via cytoplasmic microtubules and the anchoring of the message at the cortex involves cortical microfilaments''. Polarity of the surface and cortex of the amphibian egg has been studied from fertilization to first cleavage (Stewartsavage *et al.*, 1991).

b) *Epithelia (apical-basolateral poles)*

Epithelial cells display a structural and functional polarization implicating the division of their plasmalemma into apical and basolateral domains. The generation of this polarity has been unravelled by the discovery that animal enveloped viruses mature in a polarized fashion in infected epithelial cells, namely that, during infection a viral protein goes to the basolateral surface of the polarized cell (Rodriguez-Boulan and Sabatini, 1978 and ref. in **I**). Epithelial polarity in the presumptive myocardium can be demonstrated by polarized release of enveloped viruses in the embryonic chick heart (Peng *et al.*, 1990). Viruses have been shown to sort vectorially in either apical (influenza) or basolateral (vesicular stomatitis) membrane surfaces in monolayers of polarized kidney cells. There are stage-dependent differences in polarized budding of these two viruses.

Generation and maintenance of steep electrochemical gradients in transporting epithelia depend upon the compartmentalization of surface enzymes, ion, and metabolite transporting systems into the apical and basolateral domains of the plasma membrane (Rodriguez-Boulan, 1983). During biogenesis of epithelial cell polarity there occurs an intracellular sorting and vectorial exocytosis of an apical membrane glycoprotein (Misek *et al.*, 1984). Analogs of erythrocyte ankyrin have recently been found to be confined to the basolateral plasma membrane of transporting epithelia, neurons and photoreceptors (Drenckhahn and Bennett, 1987).

In the known asymmetric cell surface distribution of ionic pumps in epithelial cells (see **I**), the major driving force for the transepithelial transport of ions is the sodium pump. This Na^+, K^+-ATPase pump controls among many cellular functions, intracellular pH, free calcium concentration and membrane potential (Rossier *et al.*, 1987; see also IV.B.2d).

The meeting process in a cell-free assay that measures the fusion of apically and basolaterally derived endocytic vesicles with late endosomes requires the presence of polymerized microtubules, and also depends on the mechanochemical motors kinesin and cytoplasmic dynein (Bomsel *et al.*, 1990). Since microtubules in unpolarized cells radiate from the perinuclear region, where late endosomes are clustered, with their plus ends directed toward the cell periphery, Bomsel *et al.* (1990) suggest that "the centripetal movement of endosomes is expected to occur in a retrograde direction", involving a dynein-like activity (Vale, 1987 (**I**), see IV.E4).

The development of the polarized epithelial cell phenotype and the role of tight junctions in apical/basolateral membrane polarity has been reviewed by Rodriguez-Boulan and Nelson (1989), Cereijido *et al.* (1989) and Wandinger-Ness and Simons (1990). They all emphasize that the question of how epithelial cells generate and maintain this high degree of cell polarity remains still largely unknown. Recently, Watson *et al.* (1990) have used Na^+, K^+-ATPase as a marker to explore the factors governing apical/basolateral polarity during differentiation of mouse trophectoderm. They conclude that cell adhesion mediated by the protein uvomorulin (E-cadherin) is involved in spatially restricting the expression of the catalytic subunit of ATPase.

This subunit shifted from the basolateral to the apical plasma membrane when fully developed blastocysts were treated with cytochalasins. These findings of Watson *et al.* (1990) suggest "a primary role for the apical plasma membrane in the process of polarization, and implies that tight junctions are a manifestation of polarity that serve to maintain the separation between apical and basolateral markers".

Cadherin-bearing junctions (see IV.B.2b) are generally localized at the apical portions of cells (Rodriguez-Boulan and Nelson, 1989). The transfection of a fibroblast line with E (epithelial)-cadherin cDNA causes the polarized distribution of Na^+, K^+ adenosine triphosphatase, suggesting a function for the cadherin system in the establishment of cell polarity (McNeill *et al.*, 1990).

There is a lack of knowledge about spatial distribution of Ca^{2+} signal and of the Ca^{2+}-dependent ion channels in the secreting epithelial cells (Marty, 1987 in Kasai and Augustine, 1990). It has been found a polarization of $[Ca^{2+}]_i$ elevation and ion channel activation which suggested to Kasai and Augustine (1990) that this comprises a novel "push-pull" mechanism for unidirectional Cl^- secretion.

Dotti and Simons (1990) have suggested that neurons and epithelial cells sort viral glycoproteins in a similar manner. A recent report (Dotti *et al.*, 1991) of the polarized sorting of a glycolipid-anchored protein proposes that the mechanism of sorting of surface components may therefore be similar in neurons and epithelial cells. Both proteins and lipids must be segregated and transported differentially to the apical and basolateral surfaces. Lipids are known to be asymmetrically distributed among the various cellular organelles. Glycosphingolipids are preferentially enriched in the apical membrane. Glycosylation appears important for generating this polarized distribution. In the involvement of glycolipids in protein sorting, glycosyl-phosphatidyl-inositol acts as a "dominant" apical targeting signal (Lisanti and Rodriguez-Boulan, 1990).

VIII. MORPHOGENETIC POLARIZATIONS

A. PLANTS

1. *Embryonic polarity*

The origin and perception of positional information in plant embryos, and the temporal and spatial expression of their genes have been recently reviewed by Racusen and Schiavone (1990). They feature that ''the spatial distribution of certain gene products is correlated with changes in morphology''.

The gradient of a chemical mediator and its associated transcellular electric fields (Nuccitelli, 1988; also **I**) arise from the diffusion of substances from different regions of an organism. Electric fields have been monitored around plant embryos (Brawley *et al.*, 1984; Rathore *et al.*, 1988). The associated electric currents in carrot embryos appear to be most sensitive to changes in external concentrations of Ca^{2+} and H^{+} with expected consequences on the cytoskeletal assembly. ''The presence of electric fields implies an asymmetric distribution or activation of ion transporters in the membranes of participating cells'' (Racusen and Schiavone, 1990).

Blockage, or removal of the auxin supply (see also c^4) from the apical end of the somatic embryos of carrot promoted rapid elongation in the basal, root portion (Schiavone, 1988).

A recent study of the distribution of membrane-bound calcium has suggested that calmodulin was displaced to one or the other apical poles of developing carrot embryos. Proembryonic masses, showing an unexplained propensity for acting as sites of embryo formation in culture, exhibited a polarized distribution of calmodulin (Timmers *et al.*, 1989).

2. *Organismic polarities*

c^2 *Vegetative shoots*

Plants display polar growth: the primary axis of the shoot elongates by the addition of new structure at one pole, therefore structures located at the base of the shoot formed later are located in more apical positions. Such polar developmental pattern or heteroblasty ''makes it extremely difficult to distinguish temporal, spatial and quantitative factors in shoot development'' (Poethig, 1990).

In experimentally-induced (deficient nutrition), asymmetrically budding plantlets of the Composaceae *Bidens pilosus*, the transport of messages involved in the storage of the symmetry-breaking information is associated with the induction of a wave of electric depolarization (Desbiez and Thellier, 1990).

A polarity has been detected in light-induced unrolled grass leaves. ''The top end of the basal section of a divided leaf unrolls more than the base end of the distal section'' (Virgin, 1990).

c^4 *Polar auxin transport and tropic curvatures*

The structural polarity of statocytes from roots of *Lepidium sativum* is converted to a physical stratification of organelles by apically-directed centrifugation of the whole plantlet (Sievers and Heyder-Caspers, 1983). After return of the roots to normal gravitational force, the integrity of the distal cells pole and their underlying endoplasmic reticulum complex is reestablished. Direction of the earth gravity vector does not influence the recovery of the normal cell polarity. Therefore, perception of gravity is inevitably correlated with the integrity of statocytes (Wendt and Sievers, 1985).

A gradient of auxin along the longitudinal axis has been suggested by the demonstration of polar transport of this hormone in embryonic hypocotyls of *Pinus* (Greenwood and Goldsmith, 1970) and in similarly prepared hypocotyls of bean and sycamore (Fry and Wangermann, 1976). More recently, Schiavone (1988) explored the developmental significance of polar auxin transport in somatic embryos of carrot by auxin donor-block experiments.

Gravistimulation changes the pattern of electric current surrounding the root tip and alters membrane potentials within the root cap (Behrens *et al.*, 1985). The pattern of current flow around a vertically oriented root of *Lepidium* has been reported to change from symmetrical upon gravistimulation to asymmetrical.

Electrotropism or galvanotropism, modification of the direction of growth of certain plants or organs by an applied electric field has been reported in fungi (McGillivray and Gow, 1986) and other plants such as maize roots which curve toward the positive electrode or anode (Ishikawa and Evans, 1990a). These last authors also reported that, unlike gravitropism, electrotropism does not depend upon the root cap. Gravistimulation also induces hyperpolarization of intracellular potentials along the upperside of the elongation zone and depolarization in cells along the lower side of the elongation zone. This suggests to Ishikawa and Evans (1990b) ''the possibility that differential growth may be linked to membrane potential changes in both gravitropism and electrotropism''.

Gravity detection can be indirectly evidenced within the root tip and this induces the movement of a growth-modifying signal from the tip toward the elongation zone. There is good evidence that auxin IAA mediates gravitropism (ref. in Evans, 1991). Bandurski *et al.* (1984) had suggested that auxin asymmetric redistribution toward the lower side of the organ may develop by gravi-induced differential release of free IAA from its esterified form and thereby would cause the growth asymmetry. The classical Cholodny-Went hypothesis of gravitropism has recently been reassessed on criteria of interaction of modulation of hormone sensitivity of the gravity receptor and effector redistribution (Evans, 1991).

There is also an asymmetrical distribution of ions, already described for Ca^{2+} (see **I**, p. 237), which involves K^+ ions. Thus, in twining shoots of *Phaseolus vulgaris* maximal concentration in potassium has been correlated with maximum of curvature, suggesting that differential distribution of this ion and lateral polarity is directly connected with circumnutation of shoots in volubile plants (Badot *et al.*, 1990).

c^5 *Flowering shoots*

Among the recently investigated changes in the markers of flower induction there are thickening and chemical modification, possibly involving amphipathic molecules, of plasma membranes (Greppin *et al.*, 1990).

Homeotic genes in plants can provide insights into the underlying molecular regulatory mechanisms of flower development. However, unlike in animals, morphogenetic processes in plants cannot easily be related to maternally determined positional information. It has recently been shown that different gradients of diffusible factors and cellular receptors sensing them induce alternative pathways in the developing flower primordia of *Antirrhinum* (Sommer *et al.*, 1990; Schwarz-Sommer *et al.*, 1990).

Homeotic mutations affect the position of the four concentric whorls of the floral organs of *Arabidopsis* (Bowman *et al.*, 1989). The homeotic gene *agamous* "probably encodes a transcription factor that regulates genes determing stamen and carpel development in wild-type flowers" (Yanofsky *et al.*, 1990).

B. Animals

The unfertilized egg has only one axis of developmental polarity, the animal-vegetal (A/V) axis. A dorsal protein and perhaps other gene products are then involved in polarizing the egg in the dorsal-ventral (D/V) axis. A recent review by Melton (1991) underlines important gaps in our knowledge of such polar pattern formation.

"We may not have a morphogen"!... such is the surprising announcement recently made by Brockes (1991) which contradicts a previous statement (Slack, 1987b, in **I** p. 240). Brockes cites the findings of Noji *et al.* (1991) according to which "retinoic acid (RA) induces polarizing activity but is unlikely to be a morphogen in the chick limb bud" and those of Wanek *et al.* (1991) which suggest that "the graded response to exogenous RA may reflect variation in the number of adjacent cells induced to become polarizing cells".

As the effects of maternal mutations that affect a somatic cell fate directly are still unknown, the present interpretation of spatial determination in the early development of animals fits with Wall's "This Side Up" title of his recent (1990) book that the egg contains little developmental information other than instructions needed to specify the poles of the embryo.

1. Monoaxial patterns

a) *Mycetozoa (slime molds)*

Much evidence supports the hypothesis that cytoplasmic pH may be an essential regulator of the choice to differentiate the pseudoplasmodial slug of *Dictyostelium discoideum* in either the prestalk or prespore pathway (see **I**). No gradient of intracellular pH along the anterior to posterior axis of the slug was detected (Furukawa *et al.*, 1990).

Prestalk gene expression in this slime mold induced by the differentiation-inducing factor (DIF), or by conditions that decrease intracellular pH (pH_i), is facilitated but not mediated by cytoplasmic acidification (Wang *et al.*, 1990).

New roles in the early development of *Dictyostelium* have recently been ascribed to the chlorinated molecules of DIF. Among those effects, transient inhibition by DIF-I of cAMP oscillations and cAMP relay during spiked oscillations and transient decrease in cellular cGMP levels in cells taken before oscillation start (Wurster and Kay, 1990). Such efects could possibly affect cytoskeletal organization of the developing slime mold.

c) *Hydrozoa*

Two types of head activator receptors have been characterized on *Hydra* cells (Neubauer *et al.*, 1991).

2. Biaxial patterns

Animal eggs are divided into two parts, a dark animal pole (future tadpole) and a lighter, larger, vegetal pole (yolk supply). In such regionally differentiated eggs, it has been suspected that the cytoskeleton confers its form to the egg by the protein vimentin as suggested by disturbances of the early cleavage pattern which result from knocking out vimentin by blocking its messenger RNA (Wylie's experiments, see Cherfas, 1990).

In the sea cucumber (*Holothuria leucospilota*) oocyte, there are two visible structures which serve as markers for the main animal/vegetal (A/V) axis (Maruyama, 1990): the polar cytoplasmic protrusion at its presumptive animal pole which, at maturation, migrates as germinal vesicle to the pole where it breaks down into a pair of asters; a clear spot of special cytoplasm near the cell surface opposite the presumptive animal pole.

a) *Worms*

The soil nematode *Caenorhabditis elegans* has been proposed by Sydney Brenner in 1965 as a model system for studying how an animal's genes specify its development and behavior (see the "Book of the Worm", Wood, 1988; Riddle and Georgi, 1990).

Key attributes include: "small size (1 mm in length), a simple anatomy, the adult hermaphrodite has 959 somatic nuclei and the adult male has 1031, a transparency for microscopic observation of internal structures, ease of laboratory cultivation, suitability for high resolution genetic analysis, and small genome size (10^8 DNA base pairs)". Among genes that control the development of this worm there are temporal (heterochronic), and spatial (homeotic) ones.

The body plan of the *C. elegans* adult, typical for nematodes, shows a few left-right asymmetries, but the majority of tissues themselves are arranged with bilateral symmetry (White, 1988). By contrast, the embryo exhibits some left-right asymmetries with generally invariant handedness (however, possible reversal of handedness see VIII.3.d). Therefore the left-right embryonic axis must have a consistent polarity (Wood, 1991) "whose origins and subsequent effects on development are not understood" (Brown and Wolpert, 1990).

Dorso-ventral polarity is of morphogenetic importance and had been studied in regeneration processes in *Nereis* (Boilly and Boilly-Marer, 1972). Recently, it has been shown that positional information according to Wolpert (1969, see **I**) may be changed during regeneration of the nerve cord in that annelid (Boilly *et al.*, 1990).

The influence of head and tail grafts on axial polarity in regeneration of the freshwater plathelminth *Planaria* has been further studied by Kurabuchi and Kishida (1990).

d) *Insects*

d^1 *Egg-embryo patterns*

Homeotic genes are involved in the conversion of positional information in the egg into the specific expression of the genes needed for differentiation of the various body segments (Gehring, 1987, see **I**). The homeotic gene products are DNA-binding proteins which contain a sequence known as the homeobox that is conserved in evolution. They also have regulatory capabilities and there is a need for identification of the subordinate target genes in order to understand specification of individual segmental pathways of development. According to Gould *et al.* (1990) the genes encoding the 35 and 48 transcripts are good candidates for target genes directly regulated by the homeotic gene ultrabithorax which encodes homeodomain-containing transcription factors that determine segmental identity in *Drosophila.*

The segment-polarity genes act coordinately by means of local cellular interactions to assign and maintain an identity for each cell in the segment, and to establish segment boundaries. Unique among these genes so far characterized, the *zeste-white*3 gene encodes proteins that have homology to serine-threonine protein kinases (Siegfried *et al.*, 1990).

Segmental polarity and identity in the abdomen of *Drosophila* do not depend on the relative concentration of posterior pole plasm activity but rather on the position of

gap gene expression (Lehmann and Frohnhöfer, 1989). In the initiation of segment polarity, periodic patterns of pair-rule gene are expressed in response to gap gene products. By the end of the fourteenth nuclear division cycle, ''the stripes of the pair-rule gene *even-skipped* (*eve*) sharpen and polarize, a process that is essential for the precisely localized expression of segment-polarity genes'' (Warrior and Levine, 1990).

There is a hierarchy of regulation among the three segmentation gene classes active in embryonic development of *Drosophila*: the gap, pair-rule, and segment-polarity genes. Such regulation intervenes in the transition from the early pair-rule to the segment-polarity pattern of expression. During primordial segmentation, there is a two-step conversion of the initial analogue specification of position along the anteroposterior axis into a digital code specified by combinations of active segment-polarity and homeotic genes (Baumgartner and Noll, 1991). Two segment-polarity genes represent the *gooseberry* locus (Bopp *et al.*, 1986) which, according to recent results of the Noll's group, specifies the orientation of the larval segments and consists of two transcription units encoding proteins.

A gradient in the *bicoid* (*bcd*) protein is known to specify a position in the anterior region. The bicoid homeodomain protein morphogen would act by an interaction of its recognition helix with DNA (Hanes and Brent, 1991). The correct formation of a gradient of the *bicoid* protein requires the localization of *bcd* RNA to the anterior pole of the egg of *Drosophila*. However, the mutation in maternal-effect genes lead to an almost uniform distribution of *bcd* RNA in the early embryo (St Johnston *et al.*, 1989).

In addition, experiments resulting in alteration of the normal expression of homeobox genes support the hypothesis that these genes function in patterning. They subdivide the embryo along the head-to-tail axis into morphogenetic fields each of which contains a ''gradient-field'' of information for specifying an organ (De Robertis *et al.*, 1990).

f) *Amphibians*

The sperm entrance point determines the embryonic axes and therefore the animal/vegetal polarity of the amphibian egg (Nieuwkoop, 1977 and Gerhart *et al.*, 1981, in **I**).

Like other amphibian eggs, that of *Xenopus* transforms its polarized cylindrical symmetry into bilateral symmetry within the first cell cycle after fertilization by a microtubule-mediated process which involves cortical cytoplasmic rotation (Gerhart *et al.*, 1989, in **I**).

A so-called ''molecule of the moment'' (Slack, 1991), activin has recently been uncovered by three research groups and shown to be an inducer of mesoderm polar axiation (vegetalizing factor ?) in the early *Xenopus* embryo. An activin A homologue elicits dorso-anterior tissues as a graded response characteristic of classically postulated morphogens (Green and Smith, 1990).

The anteriorizing effect of a new peptide growth factor can be overriden by both retinoic acid and a homeodomain protein (Cho *et al.*, 1991b).

h) *Birds*

Regional differentiation of the chick neural epithelium along the anteroposterior (A/P) axis is apparent at the neural plate stage while the differentiation of cell types along the dorsoventral (D/V) axis of the neural tube occurred later. Yamada *et al.* (1991) provide evidence that the pattern of cell differentiation along this D/V axis is regulated by polarizing signals derived from the notochord and floor plate. This polarizing activity might be mediated by retinoic acid, an endogenous ''morphogen'' (?) also involved in the establishment of axial polarity in the developing chick limb.

In a further study of the specification of position in chick wing development, it has been shown that the putative endogenous morphogen, retinoic acid, induces *de novo* transcription of the homeobox *Hox-4* genes (Izpisúa-Belmonte *et al.*, 1991). The primary morphogenetic signal provided by homeobox genes might thus be translated into a "complex network of positional information".

Patterning in the limb does not always depend on a positional signal (Wolpert, 1990). STOP, GO, STAY and POSITION are signals which play a role in such developments and pigment patterns associated with feather germs.

i) *Mammals*

How cells in the developing embryo ''know'' what structures to become? Molecules called morphogens - literally ''shape-givers'' - might play this specifying role by spreading across the embryo in a concentration gradient. The transplantation of a polarizing region from a donor to a host chick limb bud induces on that last one a second polarizing region causing the growth of extradigits. In 1987, Thaller and Eichele have shown that the morphogenetic role is assumed by retinoic acid (see **I**, p. 240 and 265) and many recent publications have suggested that this compound and other derivatives of vitamin A have also a shaping role on the developing mammalian embryo (Hoffman, 1990). Thus, human homeobox genes belonging to the complex of HOX loci are differentially activated by retinoic acid in embryonal carcinoma cells (Stornaiuolo *et al.*, 1990).

3. Triaxial patterns

d) *Worms*

In *Caenorhabditis elegans* bilateral asymmetry becomes evident between 4- and 6-cell stages. Left-right polarity cannot be fixed until after dorsal-ventral polarity is established between the 2- and 3-cell stages (Priess and Thomson, 1987). The worm exhibits left-right asymmetries at all developmental stages. Reversal of this embryonic handedness by micromanipulation (6-cell stage) resulted in mirror-image in otherwise

normally developed, fertile animals with all the usual left-right asymmetries reversed (Wood, 1991).

e) *Molluscs*

The direction of coiling of the shell of snails such as *Limnaea* is one of the best known examples of asymmetry known to be inherited maternally (Sturtevant, 1923, see **I**). Molecular determinants are probably involved in such asymmetry in development (Brown and Wolpert, 1990). However, Galloway (1990b) recently pointed out that this is unlikely because the structure of individual proteins is either right- or left-handed and that gene mutation could not readily produce a change in handedness. Moreover, Galloway states that the primary structure of nucleic acid cannot be ambidextrous. However, and more recently, Holliday (1990) disagrees with that last remark (see II.D). Parallely to other work by Galloway (1990a, see **II**) concerned with the role of microtubules in the right-handedness in *Limnaea*, Holliday (1989) suggested that secondary and tertiary RNA structures, encoded by maternal DNA, may be important cytoplasmic determinants in the egg and developing embryo of this snail.

EPILOGUE

Electric bipolarity originated from the separation of the first opposite electric charges of negative electrons and positive positrons from neutral energetic photons. However, such symmetry was then broken and this original electric charge parity violated with the "overpowering" of matter over antimatter. Electric symmetry of matter was recovered with the advent of another positive partner for the electron resulting from the confinement of quarks into a unit of positive electric charge, namely the proton. The symmetry of charge thus recovered was however paralleled by an asymmetry of mass, the proton being 1840 x heavier than its negative counterpart, the electron. It is this event which can be considered as crucial as it gave birth to the primordial atom, hydrogen (H), and thereby the prototype of the electric atomic and then molecular dipoles by further complexification from the biogenic H_2O toward the most sophisticated biopolarized structures spanning the evolutionary ladder.

All primordial polarities can be considered as passive or *intrinsic* to matter, from the intra-atomic mass disparity between the electron and the proton to the inter-atomic organization of the molecules as well as macromolecules. In contrast, active or *acquired* biopolarities are the result of polarization processes such as they intervene by energetically-driven charge separation in the cellular membranes which then exhibit an electric bipolarity. Similarly, they are also active polarization processes those which break the symmetrical content of initially homogeneous cells and thereby lead them to the classical example of bipolarly axiated spores and eggs of plants and animals. In short, passive polarities and active polarizations have in common the mediation of a symmetry-breaking process but differ in the fact that this asymmetry is established once for all in the first case while it must be re-created each time in the second case for every new polarization. It is at this level that symmetry-breaking processes associated with the dissipative structures described by Prigogine's school might be implicated. Such symmetry-breaking instabilities arising by a bifurcation mechanism are a most important property of those dissipative structures arising in far-from equilibrium conditions and are thus implicated in the onset of polarity.

We can then address the important question: can we extrapolate from *electric* to *biostructural* polarities involving gradiential distribution of morphogens? These questions can be tentatively answered by the two extreme points of view expressed by developmental biologists and summarized by Meinhardt (1982, in **I**):

1) Driesch's (1899) assumed that the overall orientation of the dorso-ventral (D-V) axis of a sea urchin egg results from the alignment of individual polar elements arranged like the dipoles of a magnet (see same comments about plants by Sinnott (1960 in **I**). Similarly, Harrison (1921) attributed the origin of overall polarity to the superposition of many small polar, proteinaceous structures. Meinhardt also considered (p. 37) as a biological fact that "most tissues have an *intrinsic* asymmetry, a polarity". On the basis

of reversal experiments of D-V orientation, he thus contended that ''such polarity proper would exist in many tissues in which it would occur as a very stable graded property which orients a generating activator maximum according to the internal polarity'' (see 3 Figs in Meinhardt, 1982, in **I**).

2) From Slack's (1976, in **I**) graft experiments on the antero-posterior (A-P) organization of amphibian limbs, Meinhardt also admitted that there is strong evidence that ''polarity does *not* result from many polar substructures but from the slope of graded distributions of morphogenetic substances''. Many of these so-called morphogens have now been detected and characterized (see retinoids, p. 443, 447).

Recent knowledge of the polar structures of the two ubiquitous self-assembling protein systems present as pools within the ground plasm, the tubulin and the actomyosin systems, contributes to bridge the gap between these two points of view, electric-structural (1) and gradiential diffusion of morphogens (2). The establishment of a cell polarity can thus be traced back to polarity of its molecular units, such as the tubulin heterodimer and the F-actin molecules interconnected by bipolar myosin-aggregates. Microtubules are the cytoskeletal elements actively determining biopolarizing processes through the active mechanical mediation of motor proteins such as dynein and kinesin (see IV.E.4) while actin microfilaments function as electric cables through ionic tunneling processes (see **I**, 1989) and confer polarity through their directional assembly processes controlled by positional DNA.

Positional information has been suggested to play a central role in developmental pattern formation and has recently been revisited by its proponent, Wolpert (1989), who distinguishes a positional signal from an inductive interaction because ''the former specifies multiple states, confers polarity, and can act over a long range; a gradient in a diffusible morphogen is just one way of specifying position''. As directional polarities of cytoskeletal microfibrillar proteins must also be coded by positional sequences of the double-stranded DNA as suspected in the process of bipolar axiation of our *Allomyces* model (see **I**), we can then suggest that the DNA controlled polar orientation of morphogenetic gradients is primarily mediated by the polar positioning of protein filamentous structures endowed with *dual*, electric-structural polarizability.

We are indebted to Faculty colleagues for useful discussions, to the Committee of the ''Société de Physique et d'Histoire Naturelle'' for financial support, and to Ariane Fehr for expertise in manuscript preparation.

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