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POLARITY

FROM DIPOLES TO BIOPOLARIZATIONS

IV. 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 des addenda II et III. 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 addenda II (p. 325-397) and III (p. 399-467) published in 1990-1991.

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IV. ADDENDA

by

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We have theoretized in Addenda **III** (1991) that both intrinsic and genetically-acquired biopolarizing processes concour to confer their necessary directionality to the evolutionarily complexified and hierarchized morphogenetic processes. As such, Polarity was thus considered as "the directional arrow of biostructural Evolution". This evolutionary expression of Polarity will now be concretized by the proposal of a synoptic scale of polarization processes providing as Epilogue of these last Addenda a conceptual basis for further, deeper understanding of the fundamentals of Polarity.

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I. ATOMIC POLARIZATIONS

A+B. ORIGINS: FROM SYMMETRY TO SYMMETRY-BREAKING (ASYMMETRY)

Even though the ultimate goal of physics is a "theory of everything" that could explain all the forces of Nature, two basic partial theories have as yet attempted to describe the Universe: the Einstein's general theory of relativity explaining gravity as a function of curves in space and time, and quantum mechanics developed from Planck's quantum principle and Heisenberg's uncertainty principle. The grand unified theory (GUT) is a not too satisfactory attempt to incorporate the uncertainty principle into general relativity of quantum mechanics which implies that all particles don't have well-defined position and velocities but are represented by a wave. This wave/particle duality implies that particles have a property called spin and that there are two groups of particles, the matter particles with 1/2 spin such as the electron, and the force particles with integer spin 0, 1 and 2 such as the photon. Contrarily to the matter particles which have a different antiparticle, in the case of the force-carrying ones, the antiparticles are the same as the particles themselves (see Hawking, 1990).

In the speculative search of unification schemes involving higher dimensions, the key is now recognized as being the concept of *symmetry* (see also **III**, p. 400). There are various types of symmetry, from the simple rotational symmetry, through two-dimensional translational symmetry to the three separate symmetries known up to 1956 called C which means that the laws are the same for particles and antiparticles, the symmetry P which means that the laws are the same for any situation and its mirror image and the symmetry T which means the reversion of the direction of motion of all particles and antiparticles in time (see Hawking, 1990). It is classically known since A.E. Noether's work in 1918 that every symmetry of physical interactions implies a conservation law to which it corresponds. Among such conserved quantities in Nature, there is the electric charge to which and others can be attributed a symmetry (see Nambu, 1992 and chapter I.C.1).

As mentioned in Addenda **III**, according to Hunter (1991), "the final crack in the edifice of perfect symmetry was Lee and Yang suggestion (1956) that the charge-parity (CP) symmetry might be violated in the weak interactions". This mechanism has further been extended in 1967 by Sakharov to explain skewing the universe toward matter (**III**, p. 400 and **IV**.I.C.1). Recent scenarios for the origin of this matter asymmetry have been proposed by M. Dine and L. MacLerran which rely on a version of the inflationary model of cosmology (see Freedman, 1991). Otherwise, parity is known to be involved in two types of vectors: *axial* vectors (surface + sense of rotation) such as spin which are unchanged by reflection and therefore have even parity; *polar* vectors (length + direction) such as momentum which change sign on reflection and therefore have an odd parity. The product of a polar vector and an axial vector is called a pseudoscalar

and the processes involving it will not obey the law of parity (Ulbricht, 1959). Since, experimental results have been contradictory (Garay and Ahlgren-Beckendorf, 1990).

In the inflationary expansion of the post Big Bang cooling universe, the symmetry between strong and weak-electromagnetic forces would have be broken, quickly in the "old" (Guth), slowly in the "new" (Linde and others) chaotic inflationary models (see Hawking, 1990). *Symmetry-breaking* phase transitions early after the Big Bang could have led the Higgs field (see below) to multidirectionality in the universe.

When a quantum version of gravity will finally arise from the merger of Einstein's theory of relativity and quantum theory, it will prove to be asymmetrical (Penrose, 1989). If the Big Bang was itself a time asymmetric phenomenon, then we have further reason to consider polarity as the time-space evolutionary arrow (arrows of time see Hawking p. 152). Furthermore it has been proposed by Coweney and Highfield (1990 see **III**) that the theory of chaotic evolution (chaos, see chapter II) blows apart time-symmetric determinism.

Within the limits set by the incertainty principle, minimal nonuniformities would have then been amplified to progressively originate the ordered - and polarized - structures. Liquid crystals have recently been proposed by Yurke and Turok (see Flam, 1991) as providing such a real cosmic model of symmetry-breaking. The defects produced in liquid crystals are found to be closely analogous to those that may have arisen in the early universe and they appear where regions of differing molecular orientation meet (Spergel and Turok, 1992). The Higgs field is one of the possible processes that could break the symmetry between forces and particles. It indicates a direction in a comparable but more abstract sense than a magnetic field breaking the symmetry of space (see Spergel and Turok, 1992).

Supersymmetry posits an underlying symmetry - and thus interchangeability between particles that constitute matter and those that transmit force. A predicted consequence of supersymmetry is that all known elementary particles have unseen supersymmetric twins, sometimes called sparticles. This would unify the matter particles (spin 1/2 and 3/2) with the force carrying ones (spin 0, 1 and 2-graviton). Such concepts help to "discern deep communalities underlying nature's forces" (Witten in Horgan, 1991). Supersymmetry has been invoked (see **II**) as one of GUTs attempting to unit the three fundamental forces of nature that govern particle physics (Ross, 1984): quantum chromodynamics (QCD), the theory of the strong force that binds quarks together, and electroweak unification, "partial unification" of electromagnetism and the weak force. Such GUTs are not very satisfactory because they do not include gravity. "The main difficulty in finding a theory that unifies gravity with the other forces is that general relativity does not incorporate the uncertainty principle of quantum mechanics" (Hawking, 1990). A possible solution to this unification problem was the so-called "supergravity" which unifies the matter particles (spin 1/2 and 3/2) with the force-carrying particles (spin 0, 1 and 2 = graviton) into "superparticles" (Hawking, 1990). A set of "superparticles" might make the coupling constants converge at extremely high energies (Amaldi's current researches, see Hamilton, 1991). A window is expected to be

opened on the new supersymmetric world with the new accelerators and, indirectly, on the ultimate "theory of everything" to possibly unite the fundamental forces including gravity (Ross, 1991).

Complete unification scheme would thus require a reconciliation of the quantum theories and general relativity, the theory of gravity. However, as supersymmetry did not meet this goal, attempts were made to combine it with the newly developed *string* concept proposed to explain the strong force (see C) rather than by that of quantum chromodynamics (see above). A string is a one-dimensional vibrating loop which might be an electron if it vibrates at one frequency or a quark if it vibrates at another (see C.1). From that combination of concepts, Schwarz and others proposed in the 1970's the more ambitious *superstring* theory according to which just as stringlike particles could give rise to the strong force, so could "the vibrations of superstrings give rise to the mass-carrying particles and to all the forces acting on them - including gravity" (see Horgan, 1991). Thereby, the superstring theory necessarily involves gravity while holding according to one of his brilliant proponents, Edward Witten cited by Horgan (1991), that all physical phenomena - from quarks to quasars - would arise from multidimensionally wriggling strings.

C. Electric bipolarization

1) *Electric charges*

We have seen that a local symmetry is intimately connected with the basic forces of Nature (see A+B) and that electrically charged particles generate around themselves a field of force. In its turn, the electromagnetic field also exerts a force on the original charged particle (Newton's law of action-reaction). Consequently, the electric charge associated with a local symmetry (the electromagnetic force) is "both the source and the receiver of a field of force" (see Nambu, 1992).

The initial plasma of unbound quarks and gluons or "quark soup" (Fukugita and Hogan, 1991) cooling immediately after the Big Bang has preceded the transition to matter resulting from the containment of light quarks (up and down) into protons (+) attracting electrons (-) to build the first atom H and neutrons. Adjustment between both charges must have been extremely precise to meet the evolutionary constraints. Would the charges on the electron and proton have been a factor of three higher, the periodic table would end at the element boron! In other respects, would the charge on the electron have exceeded that on the proton by one part in 10^{18}, the overall electrical repulsion between a human and earth would equal the gravitational attraction and we would float off into space!... according to the dazzling statement of Wilkinson (1991).

The electromagnetic *attraction* between negatively charged electrons and positively charged protons has been pictured as being caused by the exchange of large numbers of virtual massless particles of spin 1, the photons. By contrast, the *repulsion* between two electrons would be due to the exchange of force-carrying photons (see Hawking, 1990).

In its attempts to solve the strong force, the original string theory regarded particles like the protons and the neutrons as waves on a string rather than only particulate quarks and gluons. The recently revised heterotic string theory proposes that the two charges +1 or -1 would result from a string deformation into knots, one (+) being perpendicular (up) to the string axis and the other (-) parallel (down) to it. It is the primordial positively charged knot which was baptised quark by Murray Gell-Mann in 1963 (see Hawking, 1990). As suggested by Bounias (1990), interactions between two differently or similarly oriented and electrically charged knots would thus prefigure respectively the *attractive* and *repulsive* phenomena described above.

2) *Electric dipoles*

Under the influence of an electric field, positive and negative charges will move in opposite directions. This asymmetric distribution of charges is said to have a dipole moment. Such electric dipole moment is the product of the charge and the resulting separation. It can also be induced by an alternating electric field with a local maximum produced by a focused laser beam (Chu, 1992). This dipole-force optical trapping of atoms complements those exerted by magnetic and electric fields.

Polarizability is then the constant of proportionality between this induced moment and the applied electric field. According to the simple, symmetric quark model, the neutron and proton electric polarizabilities would be equal. However, such a prediction could be contradicted by recent measurements revealing that the electric polarizability of the neutron to be larger than that of the proton (Holstein, 1991).

Charge density describes the distribution of electrons in a molecule. When partitioned among atoms and by numerical integration it permits to obtain atomic charges, dipoles, etc. (Wiberg *et al.*, 1991).

3) *Polarized conductivity*

Superconductivity is a striking macroscopic property that arises from the quantum nature of electrons (see **I-III**). A number of properties of the supraconductors cuprates and bismuthates have been precisely predicted from the local-density band theory. Thus, the so-called Fermi surfaces crossed by four low energy excitations or "quasiparticle" bands have been pictured with electron-like (-) and hole-like (+) charge carriers (Pickett *et al.*, 1992). Superconductivity has also been found in calcium-doped, symmetrical, so-called buckyballs of the C_{60} fullerene family (at 18 K in K_xC_{60}, Hebard *et al.*, 1991). This family has recently been expanded to include asymmetrical forms (see Koshland Jr., 1991).

Semiconductors are of direct concern for problems of bipolarity and modern computers with their electronic memories built from semiconductors such as silicon or germanium directly draw on that principle. The silicon is a *p*-type semiconductor which ordinarily does not harbor free electrons; the bit line is *n*-type silicon, a semiconductor that does harbor free electrons. In the alternative of a bit ("binary digit") or information

unit, the 0 corresponds to a charge by the electrons while the 1 is represented by the absence of electrons and therefore stored as the absence of charge. The 0's and 1's stored in a memory chip are therefore represented by the presence or absence of negative electric charge at sites in the silicon crystal.

In the crystalline lattice of the semiconductor, atoms are held together by electrons called valence electrons. These electrical properties of the 4-valence electrons silicon atom can be controlled by dopants such as the 5-valence electrons arsenic and phosphorus atoms providing an extra electron and therefore giving an *n*-type semiconductor. The 3-valence boron as impurity increases the conductivity by the introduction of "holes" - vacant sites into which electrons can move - thereby providing a *p*-type semiconductor by negative charge deficit. The electric charge in the chip can thus be conveyed by carriers of negative (electrons) or positive ("holes") charges (Meindl, 1987).

In *bipolar* transistors, contrarily to unipolar devices, both electrons and holes play an essential part. As part of modern electronic circuits, rectifiers are *p*- and *n*-types semiconductors in contact with one another and two such junctions placed back to back produce a bipolar transistor. First known to possess a rectifying action were copper in contact with cuprous oxide and selenium in contact with aluminium. When the transistor was invented in 1948 by Shockley, Bardeen and Brattain (see in **I**, I.C.3 and in Sze, 1991), the semiconductor insulating layer became known as the metal-oxide-silicon field-effect transistor, or MOSFET for short.

By contrast with the above electronic devices, the magnetic storage of binary data such as in floppy disks relies on a pattern of current reversals, reversing themselves the pattern of magnetization corresponding to a succession of 0's and 1's that constitute the individual bits of data (see Kryder, 1987 in **I** D.2).

D. Magnetic polarization

1) *Cosmological level*

The earth's magnetic field is reenforced by a self-perpetuating geodynamo process produced by a magnetic field itself induced by the electric current generated by the interaction of the earth's magnetic field with the conducting molten iron propelled through the earth's outer core. Every million years or so, the magnetic field reverses polarity (see Hoffman, 1988). The magnetic field at the core might be a simple dipole aligned with the earth's rotational axis, as suggested by the mostly blue color in the Northern and red in the Southern hemisphere of the earth's core-surface map (see Bloxham and Gubbins, 1989).

Among the alternative explanations proposed about the geomagnetic reversals of the poles there is the suggestion that the geodynamo generates less secular variations and nondipole field (Runcorn, 1992). An axial multipolar field could predominate rather than the classical dipolar pattern during the transitional interval (Bogue, 1991).

2) *Magnetic fields*

In the first computer memories, the "information-storage unit" was recorded as patterns of charge ("dots" or "dashes") produced by an electron beam at spots on the screen of the first televisions (Ridenour, 1955).

In the magnetic type of artificial memory system the units are tiny rings of ferrite magnetic materials called "cores". Like such magnetic cores which remember their magnetic history, a ferroelectric material such as barium titanate "remembers" the direction of an electric field applied to it. Ferromagnetic materials thus become polarized near magnetic fields while ferroelectrics become spontaneously polarized when exposed to an external electric field. Ferroelectrics remain polarized even when a field is removed. They can thus provide "the makings of nonvolatile computer memories, chalking up either a "1" or a "0", depending on how electric charges are distributed in the ferroelectric". The contents of such a ferroelectric memory can be switched by exposing the material to another electric field of the opposite polarity (Corcoran, 1991).

3. *Magnetic monopoles*

Following Cabrera's discard of his 1982 results (see **III**), a new monopole detection trap should soon be ready in a renewed attempt to get an unequivocal sighting of a solitary magnetic pole - a "north" without a "south" (Stone, 1991).

E. Light polarization

Sensitivity of vision to the polarization of light is widely spread among invertebrates and vertebrates. The double cone mosaic generates a "polarization contrast" neural image and a model referring to birefringence has been proposed (Cameron and Pugh, 1991 and ref. herein).

II. MOLECULAR DIPOLES AND CHIRALS

All molecules are in continuous random motion known as the Brownian movements which are a classical example of randomness studied by Albert Einstein in 1905 as due to the bombardment of dust particles by the surrounding water molecules in thermal motion. They are a classical example of randomness which gathers more information than it makes go away and thereby generates what it came to be called chaos (see Thom, 1972 in **III**).

The irregular oscillations of chaotic behaviour are scaled from the microscopic, thermal chaos to the macroscopic, non-equilibrium and turbulent chaos, between which are sandwiched Prigogine's dissipative structures (see Peacocke, 1983 in **III**). Chaotically moving molecules must be polarly ordered to contribute to a process such as the basic transport mechanism by diffusion in living things, a directional process which necessarily should act against chaos (see "antichaos", Kauffman, 1991 in VII). There is therefore order in chaos and randomness has an underlying geometric form (Crutchfield *et al.*, 1986). The question of what would such classical chaos do to quantum mechanics, first asked in 1917 by Einstein, has since been positively answered in the way that "symptoms of chaos enter even into the wave patterns associated with atomic energy levels" as imaged by the wave patterns of a highly excited hydrogen atom or Rydberg atom in a strong magnetic field (Gutzwiller, 1992, relevant references herein).

Chaos is exhibited by a wide variety of systems governed by nonlinear dynamic laws (Gleick, 1988). As best-studied chaotic chemical system, the Belousov-Zhabotinsky reaction based on the autocatalytic oxidative bromination of malonic acid (see Gray and Scott, 1990) has been described in terms of a set of differential equations containing only three variables (Györgyi and Field, 1992).

A. Dipole moments

1) *Electric polarizability*

Molecules of ferroelectric crystals are polar because of the dissymmetrical distribution of their + and - charges. Thus endowed with dipolar electric moment, they orient themselves spontaneously or under the influence of an electric field. Such polarization phenomena are displayed by crystals with hydrogen bonds (phosphates, sulfates, etc.) and by double oxides such as titanate (see **I, II**).

2) *Magnetic polarizability*

In a magnetic field, positive and negative charges move in opposite circular trajectories leading to a magnetic dipole moment. The constant of proportionality between the induced moment and the applied field is the magnetic polarizability β_M.

B. Mineral dipoles

1) *Dipolar water*

The conformation of biomolecules in a three-dimensional network of water and the regulation of the electrochemical potential across biomembranes have been reviewed (Vasilescu *et al.*, 1990).

Liquid water is symmetrical but, eventually, through its phase transition to ice crystals its symmetry is broken. Its strong, totally connected random tetrahedral network of hydrogen bonds should confer it rigidity rather than its familiar fluidity which can be ascribed to defects characterized geometrically by the presence of an extra, fifth molecule in the first coordination shell, or topologically by the presence of "bifurcated" hydrogen bonds (Sciortino *et al.*, 1991 and refer. herein).

From the experimental study of ice nucleation by bacterial proteins involving the freezing of water droplets on the hydrophobic surface of paired amino acids crystals, one chiral (D or L), the other racemic (D/L), emerged the following pattern: "in every pair the nonpolar crystal, where successive molecular layers are arranged so that the electric dipolar field cancel, is a less effective nucleator than the polar crystal, where the dipoles of successive layers reinforce" (McBride, 1992).

C. Organic dipoles

2) *Multiple molecules (polar chains)*

Polar multilayers of molecules can be formed by the well-known Langmuir-Blodgett procedure. The molecular orientation in solids has been obtained by a self-assembly strategy implicating the formation of polar dye multilayers either by a complex sequence of substitution reactions at Si and C atoms to form dye monolayers (Li *et al.*, 1990) or by a simple self-assembly procedure in which solid surfaces are joined by zirconium phosphate-phosphonate interlayers (Katz *et al.*, 1991).

Upon photoexcitation of a probe neutral molecule which contains two electron-rich donors and an electron-poor acceptor, charge separation occurs. A conformational change results from this fast intramolecular electron transfer described by Brouwer *et al.*, (1991) as "harpooning", a photoinduced process in which the charged centers are drawn together. The two opposite charges present within a single molecule would cause a profond increase in the molecular dipole moment.

D. Chiral molecules (Chirality)

Crucial molecules of life such as building blocks of DNA and proteins are chiral. Chiral symmetry is fundamentally a property of quark interactions on which is based polarizability (see chapter I.C.2). This handedness is slightly broken in Nature by the

small but finite quark masses (Holstein, 1991). Since introduction of the concept of antimatter by Dirac in 1928, antiatoms, the most suitable being antihydrogen results of the interaction of a positron and an antiproton (Hughes, 1991). Helical electrons do distinguish between molecules of opposite chirality (Garay and Ahlgren-Beckendorf, 1990) and an interdisciplinary treatment of chirality related to elementary particle physics has just been edited (Janoschek, 1991).

Chirality has been related to "cold prehistory of life" based on the phenomenon of molecular tunnelling (Goldanskii, 1979; Goldanskii and Kuzmin, 1991). Ulbricht (1959) had invoked the parity-violating weak interaction as the cause of biological homochirality (see chapter I). Morosov (1979) has then presented other hypotheses about the abiotic and the biotic origin of molecular asymmetry. As Pasteur (1884) and Wald (1957), he favored the hypothesis of a biological origin of chirality which assumed that "the very nascence and development of life ruined one type of the chirality of molecules". It would thus be by a process of spontaneous mirror symmetry-breaking that chiral purity resulted rather than from the gradual accumulation of an enantiomeric excess (Frank, 1953 in **I**; Morosov, 1979). This confirms that mirror-image chemistry of life is based on enantioselectivity.

III. MACROMOLECULAR POLARITIES

A. Free macromolecules

Both α-helical and β-sheet tertiary conformations of proteins involve intra- and inter-hydrogen (H) bonds and the specificity of base pairing in nucleic acids is also determined by H bonds.

1. Nucleics acids

a) Deoxyribonucleic acid (DNA)

DNA strands carry information encoded in the sequence of the H bonded bases, which can be considered as analogous to bits in a computer code.

a^1 *Structure*

The asymmetric location of base pairs in the B form of DNA (see **I**) creates a smaller minor groove and a larger major groove in the double helix. There are two major structural motifs, the helix-turn-helix and zinc finger and many DNA-binding proteins contain either of them (Schleif, 1988).

The double-DNA has been mimicked by self- assembly of the helices achieved in the presence of Cu^{+1} ions (Koert *et al.*, 1990). Many DNA-binding proteins recognize specific sites through small, discrete domains which reveal a variety of different designs folded to contact DNA base pairs in the major groove through hydrogen bonds, both direct and water-mediated, and non-polar van der Waals interactions (Harrison, 1991).

a^2 *Replication*

DNA and RNA are not the only possible replicators. Indeed, and as an aspect of self-organization in the perspective to unravel the origin of life, Rebek's (1992) recent test-tube replicators use as DNA itself H bonding as structural information. In Rebek's system, the product of pairing of an imide-ester and an adenine-containing amine is replicated by serving as template on which a new ester-amine pair lines up guided by H bonds. However, the holy grail remains to combine informational content with replication (Orgel, 1992).

Interestingly, the nucleoskeleton is implicated in the topology of replication (Cook, 1991). As for the current eucaryotic model of asymmetric DNA replication fork involving DNA polymerases for replication of both DNA strands according to the 5'-to-3' directionality rule, it is discussed by Hübscher and Thömmes (1992).

a^3 *Transcription*

Transcription factors interact with *cis*-acting control elements present in both nearby promotors and remote enhancers (Maire *et al.*, 1989). A protein-mediated joining of distant recombination sites at the enhancer has been termed the invertasome. This Hin protein "binds to two *cis*-acting recombination sites and catalyzes a site-specific DNA inversion reaction that regulates the expression of flagellin genes in *Salmonella*" (Heichman and Johnson, 1990). Little is known about the *trans*-active factors which control the *cis*-acting signals involved in the transcriptional activation of the interleukin (IL-2) gene. Cell type-specific *trans*-active proteins have been assayed in the *Xenopus* oocyte (Rungger *et al.*, 1990).

a^4 *Mutations*

H bonds are "ideal template forces for they are highly specific, unlike the van der Waals interactions" (Watson, 1970). Mistakes in such bonding during DNA replication lead to mutagenic replacement of a single base pair by another.

DNA strand asymmetry might be reflected in an inequality in the mutation rates of its two strands (Wu and Maeda, 1987, in Wu, 1991).

In polar mutants, ribosomes carrying nascent peptide chains are released as they encounter the nonsense codon in the messenger RNA of the mutated gene. This causes the mRNA distal to the mutation to remain "naked", i.e. not covered with ribosomes, a condition in which it seems to be highly susceptible to endonucleolytic attack (Hansen *et al.*, 1973 in **III**).

b) Ribonucleic acid (RNA)

Transfer RNAs (tRNAs) have a high net negative charge. A "hole" in the potential surface has been found in the anticodon region of the elongator tRNAs. Consequently, the anticodon region is the least negative, or conversely the most positive, region of the molecule. This may have implications in the ability of tRNAs to associate with other negatively charged macromolecules, in particular mRNA. This hole which is not found when simple Coulombic potentials are used is due "both to the structure of the elongator tRNA anticodon loops and to the different polarizabilities of the solvent and tRNA" (Sharp *et al.*, 1990).

Anti-sense RNA has been produced in a plasmid vector to study animal development (Rungger *et al.*, 1990). Self-splicing or catalytic introns have been assumed to fulfil protomotion of efficient *cis*- and *trans* splicing of RNA (Sharp, 1991). A short RNA molecule and six proteins are the components of the signal recognition particle (SRP) which helps proteins destined for export from the cell (Hann and Walter, 1991).

2. Proteins

Protein folding in vitro is a spontaneous process dictated primarily by the linear sequence of amino acids (Anfinsen, 1973). However, the problem of how a protein is folded in its tertiary structure cannot yet be predicted from its amino acid sequence. Preliminary structural assignments for the catalytic domain of protein kinases have been made by Benner and Gerloff (1990). The hydrophobic effect has been considered as the major factor in stabilizing such folded structures of globular proteins (Dill, 1990). Coiled coils formed by two or three α helices in parallel can be predicted from protein sequences (Lupas *et al.*, 1991).

Chaperones stabilize unfolded or partially folded structures and seem to act as molecular detergents, primarily by preventing partially folded and unassembled protein subunits from aggregating and precipitating (Creighton, 1991; Gething and Sambrook, 1992). Heat-shock proteins play a role as molecular chaperones and so-called "protein chaotropes" might represent the trigger of the stress response (Welch, 1991).

The importance of polar substituants in the execution of organic synthesis has been surveyed by Tse-Lok Ho (1991) which emphasizes the use of the polarity of alternation rule as a framework for analysis.

6. Antigens-antibodies

The mechanism for their recognition involves not only hydrogen bonding, van der Waals contacts, salt bridges, and buried surface area but conformational changes in which peptide binding is replaced by an alternative hydrogen bond (Rini *et al.*, 1992).

7. Synthetic polymers

The principle of a light-harvesting "antenna" complex directing excitation to a semiconductor-based photosynthetic system has now been used to create a new type of solar cell (0'Regan and Grätzel, 1991).

B. Aggregates

1. Crystals and quasicrystals

By contrast with the disordered patterns of quasicrystals (three dimensional disordered structures, Shechtman *et al.*, 1984), crystals are arrays of molecules ordered through repetition of unit cells which enclose themselves a set of asymmetric units defined by the space group (see McPherson, 1989). They acquire isotropic heterogeneities during growth as a result of differences in surface structure. Sector zoning or anisotropic segregation of chemical elements (Mn^{2+}, Fe^{3+}, etc.) can be displayed by calcite crystals and associated with ordering and local reduction of symmetry (Dickson, 1991). However, the distinction between "crystals" and "quasicrystals" appears now artificial and might

have to be abolished as proposed by D. Mermin in a recent review book (DiVincenzo and Steinhardt, 1991).

Special attention will be devoted these next years to the so-called smart molecules which include piezoelectric ceramics, crystalline materials with electrical polarity (lead zirconium titanate, etc.) that quickly translate pressure or vibration into an electric current and vice versa. Otherwise, electrorheological fluids contain polarizable particles which can align themselves into filaments under the influence of an electric field thereby changing the material from a liquid to a near-solid (see Hoke, 1992).

IV. SUBCELLULAR POLARIZATIONS

B. Surface membranes

1. Primitive membranes

The self-assembly process of bilayer membranes involves complex interactions between amphiphilic molecules which have been mimicked by computer simulations. The two terms of the interactive model which involves hard-core *repulsion* between hydrophilic-hydrophobic spheres and anisotropic *attraction* between these particles can lead to assembly of a two-dimensional membrane (Drouffe *et al.*, 1991).

2. Plasma membrane

a) *Biochemical properties*

Water-soluble proteins often expose their polar and charged residues on the membrane surface, whereas apolar residues tend to occur in the interior (Perutz *et al.*, 1965 in **I**; Chothia, 1976 and others in Rees *et al.*, 1989). By contrast, the hydrophobic organization of membrane proteins is explained by models which use the hydrophobic transmembrane α-helix and an "inside out" pattern of more polar interior residues (Engelman and Zaccai, 1980 in Rees *et al.*, 1989).

The lipid bilayer of the plasma membrane is known to be asymmetrical (see Bretscher, 1973; Rothman and Lenard, 1977 in **III**) and this asymmetry might help to keep membrane proteins properly oriented in the bilayer. As for the highly asymmetric association of proteins with the membrane (Alberts *et al.*, 1983 in **I**; Singer, 1990 in **III**) it is of functional significance for the redistribution of mobile membrane proteins and cytoskeletal elements in biopolarizing processes (Poo, 1981 and Luther *et al.*, 1983 in Nuccitelli, 1988).

The anchoring of proteins to the lipid bilayer would be mediated by a phosphatidylinositol-glycan (PI-G)-specific phospholipase D (Scallon *et al.*, 1991). As recently found by many researchers (Hoffman, 1991a), the activity of many membrane-bound proteins needs prenylated lipid tags possibly to help directing them to the right cellular locations. This involves isoprenoid addition which thereby helps a protein such as Ras insert in membrane. Iterations of the positively charged lysine adjacent to the CAAX box would be essential to lead the protein to the plasma membrane.

The surface of the integral, outer membrane channel-forming, trimeric protein porin from Gram-negative bacteria displays polar and nonpolar aromatic side chains at the borderline between the polar and nonpolar parts of the membrane. Ca^{2+} sites can be predicted from electrostatic potential calculation (Weiss *et al.*, 1991).

b) *Structural polarity and recognition systems*

Dielectrophoresis denotes the motion of polarizable particles under the influence of a non uniform electric field (Pohl, 1978 and Zimmermann, 1982 in **I**; Schwan, 1989). It has allowed the determination of the critical frequency F_0 (the polarizability of a shell sphere minus that of the medium) which contains quantitative information on the electric parameters of the membrane of murine myeloma and *Neurospora crassa* slime cells (Marszalek *et al.*, 1991). Non-linear dielectric spectroscopy is a convenient mean to monitor the ability of living cells to transduce exogenous electric field energy (Woodward and Kell, 1990). Low-frequency fields can cause lateral movement of proteins in the plane of the membrane: appropriately charged proteins accumulate at a single pole under the influence of dc fields (Sowers and Hackenbrock, 1981) whilst ac fields cause their accumulation at both poles of spherical cells (Zimmermann and Vienken, 1982). There are many other reports in which very weak electromagnetic fields have been shown to elicit biological or biochemical responses (see Lin, 1989). Applied electric fields can cause a large asymmetry in the distribution of membrane particles on the cathode-facing sides of *Micrasterias* lobes (also see VI.C.c) oriented perpendicular to the fields (Brower and Giddings, 1980). Membrane permeability can be increased by electroporation of cells as reviewed by Lindsey and Jones (1990).

Among the many studies which have shown asymmetric changes in $[Ca^{2+}]$, that of Rooney *et al.* (1990) can be singled out as the first demonstration of oscillatory-Ca^{2+} waves caused by a localized hormone receptor/signal transduction system in a nonexcitable cell. Owing to functional polarization of the cell, the hormone-induced Ca^{2+} signals must originate from a limited membrane domain. The effector-target cell contact probably causes a directional delivery of signals into the effector cell. The transient intracellular polarization thereby established is manifested by the selective redistribution of cytoskeletal proteins and intracellular organelles (Podack and Kupfer, 1991).

c) *Energy transduction*

The plasma membrane H^+-ATPase generates an electric potential and pH gradient across the membrane by extruding protons from the cell; the energy bound in this electrochemical gradient is thought to be the driving force for solute carriers and channels that are responsible for nutrient uptake and maintenance of cell turgor (Palmgren, 1991). An auto-inhibitory domain in the C-terminus of the enzyme might interact with the catalytic site and/or a proton binding site (Palmgren *et al.*, 1990).

d) *Electric potentials*

Ion channels mediate the transmission of electric signals within and between cells of sensory organs. The functioning of several types of voltage-dependent ion channels involves a dual effect of membrane depolarization, first described for the sodium

conductance of the squid axon (see **I**.IV.B.e and also Hodgkin and Huxley, 1952). Such channels open upon depolarization in their activation phase and they spontaneously close, in their inactivation phase, even when the depolarization is maintained. Gating currents express electrically the conformation changes that lead to channel opening. Their measurement in the Shaker potassium channel of the *Drosophila* indicates that the charge on the voltage sensor of the channel is progressively immobilized by prolonged depolarizations (Bezanilla *et al.*, 1991). Neher and Sakmann (1992) have received the Nobel Prize for their patch clamp technique proposed in 1976 (see IV in **III**) to isolate ion channels from cell membranes. Voltage-gated K^+ channels have been reviewed by Miller (1991) and, in higher plant cells, Ca^{2+} channels have been shown to play a major role in such processes as bud formation and polar growth (Schroeder and Thuleau, 1991).

Mechanosensitive channels have been implicated in the regulation of many cell processes including the budding yeast (Gustin *et al.*, 1988). Such a type of channel has been found to transduce the membrane stress into a ionic influx which triggers differentiation of appressoria from the germling apices of *Uromyces* stopped in their polarity growth (Zhou *et al.*, 1991). Electric polarization microelectrode measurements have revealed an apical-basal potential difference in the fungal *Pilobolus* cells (Tarakanova *et al.*, 1991). Membrane potentials which are usually comprised between -60 and -70 mV in animals (see Meissner, 1976; Henquin and Meissner, 1984) exhibit a higher negative membrane potential, of the order of -200 mV (Sanders and Slayman, 1989), in fungi and plant cells.

Phototransduction in retinal rod cells results from a cascade of highly regulated chemical reactions implicating among others the G-protein-coupled receptor rhodopsin (see **I** V.B.5a and Palczewski and Benovic, 1991) that translate the light signal into a hyperpolarization of the cell plasma membrane. Illumination-induced transient hyperpolarization of the plasma membrane is followed by an intracellular acidification in *Trichoderma* (Gresik *et al.*, 1991).

Among the receptors of the central nervous system there are two main classes: ligand-gated ion channels such as the NMDA glutamate receptor recently cloned by Nakanishi's group (Moriyoshi *et al.*, 1991) and metabotropic receptors coupled with G-proteins.

e) *Action potentials*

The electrical properties and the voltage of the nerve cell membrane are determined by ion currents (see Hille, 1984 in **I**). Initiation and conduction of the neuronal action potential is due to voltage-sensitive Na^+ channels (see also d). Modulation of such channels in the brain by protein kinase C phosphorylation might have effects on signal transduction and synaptic transmission in the central nervous system (Numann *et al.*, 1991). Like the nerves, action potentials of algae such as *Chara* were accompanied by a sharp rise in membrane conductance (see Blatt, 1991). In the voltage-gated fluxes measured and simulated in *Acetabularia* the charge balance for the

transient Cl^- efflux, which frequently occurs during an action potential, can be accounted for by the observation of a corresponding release of Na^+ (Mummert and Gradmann, 1991).

Glucose-stimulated insulin secretion provokes B-cell electrical activity which follows an oscillatory pattern in membrane potential on which bursts of action potentials are superimposed (Henquin and Meissner, 1984).

Sensory cells convert different forms of energy to transmembrane potentials. Mechanosensory neurons in the marine mollusk *Aplysia* usually show marked action potential accomodation during prolonged depolarization (Klein *et al.*, 1986, in Walters *et al.*, 1991); axonal injury induces long-term changes in sensory neurons such as: decreased accomodation, decreased hyperpolarization (Walters *et al.*, 1991). Mahowald and Douglas (1991) have exploited the analogy between silicon devices and biological membranes to represent these different ion currents thus providing the voltage-dependent conductances. Complementary metal-oxide-semiconductor circuits have been used to represent the different ion currents thereby forming the silicon analog of a biological neuron.

f) *Synaptic membranes*

Nitric oxide (NO) is polarly transmitted through the neuronal synapse (Hoffman, 1991b). It can thus be considered as a "retrograde messenger" (Barinaga, 1991).

C. Endomembranar and vesicular systems

The secretory pathway targets proteins from the endoplasmic reticulum (ER) via the Golgi apparatus (G) and secretory vesicles to the plasma membrane (Fig. 1 in Reid, 1991). Three hydrophilic, soluble cytoplasmic proteins are required at different stages in vesicle transport (Aalto *et al.*, 1992): Sly1 between ER and Golgi, Sec1 between Golgi and the plasma membrane (Novick and Schekman, 1979), and Slp1 between Golgi and the vacuole. Reverse transport also occurs from Golgi to ER (Dean and Pelham, 1990). Molecular dissection of this pathway related to the Golgi model with a focus on transporting vesicles and their simple coat structure has been recently reviewed by Rothman and Orci (1992). Molecular signals allow the vectorial flow and filter selection of trafficking proteins travelling to the cell surface (Hopkins, 1992).

1. Endoplasmic reticulum

Intracellular trafficking of proteins is concerned with how polypeptides constituents of each cellular organelle and compartment are sorted and polarly delivered to their destinations as recently reviewed in a reference book edited by Steer and Hanover (1991).

When the ribosome becomes engaged with membrane proteins the entity is termed the translocon, and it catalyses the translocation of the nascent protein across the membrane into the lumen of ER. A ribonucleoprotein, signal recognition particle (SRP), functions in this targeting process (Walter and Lingappa, 1986, see **I**). A model for SRP's function has been proposed for yeast ER (Hann and Walter, 1991). Related to the problem of polarized translocation of proteins across membranes, the existence of a protein-conducting channel in the ER has been demonstrated by the use of electrophysiologic techniques (Simon and Blobel, 1991; Lingappa, 1991).

2. Golgi apparatus

Models accounting for donor-acceptor connections in inter-Golgi transport *in vitro* as well as the role of carrier vesicles in that polarized transport have been reviewed by Mellman and Simons (1992).

The fungal metabolite brefeldin A (BFA) can alter the distribution and flow of membrane through an interlocking membrane system (see **II** and Lippincott-Schwartz *et al.*, 1991). Polar transport from ER to the Golgi apparatus (G) has been inhibited by BFA in *Candida albicans* (Arioka *et al.*, 1991). From the G, proteins are involved in vesicular transport and membrane fusion (Waters *et al.*, 1991). In this ER-G transport, the integral membrane protein Sec12p is required for the formation of the transport vesicules generated from the ER (D'Enfert *et al.*, 1991).

Fusion of ER-derived vesicles targeting to G requires calcium and ATP (Rexach and Schekman, 1991). The ER-G traffic is regulated by a GTP-binding SAR1 protein localized to the early compartment of the yeast secretory pathway (Nishikawa and Nakano, 1991).

3. Intracellular vesicles

Receptor mediated endocytosis, well documented in animal cells, has now been reviewed in plants (Robinson and Hillmer, 1990). Evidence has been presented that constitutive exocytosis in yeast is insensitive to changes in cytosolic calcium levels and to voltage and ionic gradients changes across the plasma membrane (Lew and Simon, 1991).

Yeast plasma membrane secretory vesicles have been exploited as "an expression system for site-directed mutants of the [H+]ATPase" (Nakamoto et al., 1991). A GTP-driven mechanochemical enzyme, dynamin, is associated with vesicular traffic (van der Bliek and Meyerowitz, 1991). This nucleotide-sensitive microtubule-binding protein cross-links microtubules into highly ordered bundles, and appears to have a role in intermicrotubule sliding in vitro (Chen *et al.*, 1991).

D. Organelles

1. Lysosomes and microbodies (peroxisomes, etc.)

A peroxisomal targeting tripeptidic signal had been identified in a number of peroxisomal proteins (Gould *et al.*, 1989). The recent detection of the same mechanism

of polar translocation of proteins into glyoxysomes and glycosomes lends support to "a common evolutionary origin for these microbodies" (Keller *et al.*, 1991).

2. Mitochondria

The soluble form of the electron transport enzyme succinate dehydrogenase behaves as a diode gating electron flow in one direction only (Sucheta *et al.*, 1992).

3. Chloroplasts and phototransducing membranes

The hydrophobic organization of transmembrane regions of the photosynthetic reaction center from *Rhodobacter* (ex *Rhodopseudomonas*) *sphaeroides* has been studied by Rees *et al.*, (1989, see also IV.B.2). The polarity of the interior of the reaction center structure resembles that of soluble proteins and is "intermediate between protein surfaces exposed to aqueous solution and those exposed to hydrophobic cores of membranes" (Deisenhofer and Michel, 1991).

Long-lived photoinduced charge separation has been achieved and maintained in a redox, artificial photosynthetic system (Slama-Schwok *et al.*, 1992).

E. Cytoskeletal components

For a helpful book on these macromolecules, see Amos and Amos (1991).

1-2. Microfilaments (actin-myosin)

The dynamic filamentous structure of F-actin and the consensus reached on its three-dimensional atomic model (see **I**) have been reviewed (Bremer and Aebi, 1992). Phalloidin reduces the dissociation rate constants at both ends of actin filaments to near zero and also reduces the association rate constant at the barbed end by about 50% (Sampath and Pollard, 1991).

Dynamics and density of actin microfilaments and their turnover process in lamellipodia of locomoting cells have been accounted by a few models (Heath and Holifield, 1991) among which a first embodies a polarized array of actin filaments and another one of nucleation-release (Theriot and Mitchison, 1991). The force fluctuations in a single actin filament and the quantization of actin filament velocities have been described by Ishijima *et al.* (1991) and Uyeda *et al.* (1991).

"Myosin rods" have been studied in amoebae of *Dictyostelium discoideum* by immunoelectron microscopy (Yumura and Kitanishi-Yumura, 1990). The yeast cell type specific budding pattern is maintained by a myosin heavy chain gene (Rodriguez and Paterson, 1990). A myosin organization center would play a role in the determination of cell polarity in *Dictyostelium* (Fukui *et al.*, 1991) while a 110-kDa calmodulin complex identified in kidney microvilli shares with myosin the ability to associate with actin filaments to give them a defined polarity (Coluccio, 1991).

3. Microtubules-tubulins

Viewed from the outside, all protofilamentous subunits have the same orientation ("outside-out") and the same polarity ("polarity up", with two distinct ends, "plus" and "minus"). The intrinsic polarity of microtubules is the consequence of their formation from aligned asymmetric subunits. As a component of the spindle pole body, the newly discovered γ-tubulin first isolated from *Aspergillus nidulans* (Oakley *et al.*, 1990, see **III**) has been proposed to establish microtubule polarity *in vivo*. γ-tubulin genes have now been cloned and characterized from *Schizosaccharomyces pombe* and *Xenopus laevis* (Stearns *et al.*, 1991) as well as *Drosophila melanogaster* and *Homo sapiens* (Zheng *et al.*, 1991). Posttranslationally modified tubulins exhibit restricted subcellular distribution in polarized cells of developing *Artemia* (MacRae *et al.*, 1991).

When microtubules depolymerize *in vivo* up to a specific point, they either regrow along exactly the same path or abruptly reverse their directional growth (Schulze and Kirschner, 1988). Cytoplasmic components such as mitochondria might influence this directional process involving intramitochondrial chaperone proteins accounted by a new model for *in vivo* microtubule assembly (Gupta, 1990).

The dynamic instability of microtubules accounted by the GTP-cap model has been reviewed by Caplow (1992) and the role of microtubules in the orientation of plant cell wall cellulose microfibrils has been modellized by Emons *et al.* (1992).

4. Microtubule-associated "motor" proteins

This year has seen an explosion of new data about additional cytoplasmic microtubules motors. A novel kinesin, *unc-104* encoded, is a neuron-specific motor used for anterograde translocation *in vivo* of synaptic vesicles along axonal microtubules in the worm *C. elegans* (Hall and Hedgecock, 1991; see also VIII.2.a). The microtubule-based dyneins and kinesins were first thought to move in opposite directions along the asymmetric microtubules. The fact that the newly found kinesin-like motor, *ncd*, can move in the same directions as dynein raises the possibility that dyneins and kinesins have similar motor domains (McDonald *et al.*, 1990 and Walker *et al.*, 1990 in Goldstein and Vale, 1991). Using the fission-yeast with its bipolar intranuclear spindle, Hagan and Yanagida (1992) have proposed two models in which a spindle pole-body-associated, plus-end directing cut7 reorientates the microtubule arrays during spindle formation. Evidence has recently been obtained of another member of the kinesin family generating force toward the microtubule minus end, and that dynein may be either a bidirectional protein, or composed of closely related retrograde and anterograde isoforms (Bloom, 1992). However, motor proteins are not only microtubule-based as recently evidenced for unidirectional organelle movement in squid axoplasm shown to be ATP- and actin-dependent, and probably generated by a myosin-like motor (Kuznetsov *et al.*, 1992). This actin-based myosin motor uses the free energy of ATP hydrolysis to produce force or motion on a track which moves unidirectionally actin filaments. The polarity of the velocities was assayed *in vitro*

(Uyeda *et al.*, 1991) and determined such that the direction of the active movement is positive.

F. Nuclei and mitotic figures

Structural bipolarity is the fundamental property of mitosis. This polarity is not yet evident during the transition from prophase to metaphase. The movements of the centrioles at prophase, similar to those of the "polar plaques" in simpler organisms, are controlled by microtubules which are oriented in the spindle with their minus ends at the pole.

1. Interphasic and mitotic structures

Information complementary to that of Gerace and Burke (1988, see **I**) about the nuclear pore complex and its aqueous channels has been provided by Silver (1991) and cytosolic proteins which specifically bind nuclear location signals have been described as receptors for nuclear import (Adam and Gerace, 1991). Nuclear targeting signals allow selective entry of the acidic protein nucleoplasmin into the nuclear pore complex. Two interdependent basic domains have been identified in the nuclear targeting sequence (Robbins *et al.*, 1991). The bidirectional nature of this import-export exchange at the nuclear envelope is distinct from transport across the membranes of other organelles as reported in a recent meeting review (Nigg *et al.*, 1991).

The symmetry of the mitotic figure may exist without centrioles (Molè-Bajer, 1975, in Dustin, 1978) but these organites are "indicators of poorly understood factors which lead the cell to the bipolarity found at metaphase". As further stated by Dustin (1978) "mitosis is polarized, either by MTOC, by centrioles, or by unknown polar forces (as in higher plants)". The classical separation and migration of centrosomes to opposite poles on (or within) the nuclear envelope can be deviated to *multi*polar mitosis (Baltzer, 1908, in Czihak *et al.*, 1991). Such a deviation can be produced by mitotic inhibitors such as carbamates (urethane, etc., ref. in Dustin, 1978). Conversely, some special conditions such as colchicine poisoning (C-mitosis, see Dustin, 1978) provoke uni(mono)polar mitoses. The forces which must normally move bipolarly to position centrosomes, involving actin and microtubules (Euteneuer and Schliwa, 1985 see **I**; Schatten *et al.*, 1988), are someway disturbed. Microsurgical experiments designed by Maniotis and Schliwa (1991) have shown that animal cells never enter mitosis following removal of the centrosome. Centriole-free regenerated microtubule-organizing center (MTOC) regenerated in karyoplasts cannot partition and thus cannot generate the *intrinsic* bipolarity of the mitotic spindle. Intra-astral bidirectional motility – retrograde-anterograde – known to occur in animal cells (Rebhun, 1972; Bajer and Molè-Bajer, 1975 in **I**) has also been observed in fungal mitotic asters (Aist and Bayles, 1991). Models predict that a sliding mechanism operates between microtubules of opposite polarity to produce spindle elongation as observed by the occurrence of spaced bridges in amoebae of *Dictyostelium discoideum* (Jensen *et al.*, 1991).

At mitosis, spindle microtubules are assembled with a common polarity, the minus ends being embedded in pericentriolar material, the plus ends being free to grow into the cytoplasm. The way that this polarity is achieved starts only now to be understood. γ-tubulin has just been localized in the animal centrosome (Stearns *et al.*, 1991) and Zheng *et al.* (1991) also point to the role of this new tubulin on the side of α- β-tubulins in the establishment of this polarity in the microtubule organizing center.

2. Polewards chromosome movements

Chromosome-to-pole spindle forces involve complex molecular mechanisms (Koshland, 1991) and, in answer to the major question of the basis of their generation, it has recently been found that one of the best candidates for a "motor" for mitosis, cytoplasmic dynein (Salmon, 1989), is present at the kinetochore at least to meet the energy requirements for chromosome motion in prometaphase (Farr *et al.*, 1990; Steuer *et al.*, 1990). This finding shifts the emphasis on force generation within the chromosome from that of microtubule polymerization and depolymerization to a motor-dependent mechanism itself dependent upon the existence of a microtubule continuum (Snyder *et al.*, 1991a).

V. POLAR CELL MOVEMENTS

Cell motility, recently surveyed in a new book (Bray, 1992), involves a type of polarity which is largely an *extrinsic* consequence of structural and hence developmental polarity (chap. VII-VIII and synopsis in our Epilogue).

B. Cell movements

1. *Cilia-flagella*

The polar flagellar motor of *Vibrio alginolyticus* is known to be powered by the sodium-motive force (Chernyak *et al.*, 1983 and Tokuda *et al.*, 1988 in Atsumi *et al.*, 1992) as is also that of *Vibrio parahaemolyticus*, whereas its lateral flagellar motors are driven by the proton-motive force (Atsumi *et al.*, 1992).

3. *Amoeboid motion (transient polarity)*

The bipolar cellular organization of *Amoeba proteus* is stabilized by high external Ca^{2+} concentrations (~100 mM) which induce the polar propagation of Ca^{2+} waves from the uroid to the front region (Gollnick *et al.*, 1991).

5. *Taxis*

a) *Chemotaxis*: Stimulation with the chemoattractant cAMP induces a transient membrane hyperpolarization which is consistent with the opening of potassium channels (van Duijn and Wang, 1990). Changes in internal [Ca^{2+}] during polarization and chemotaxis have been observed by imaging both calcium and eosinophil cell morphology: following chemotactic stimuli, the new leading edge had the lowest $[Ca^{2+}]_i$ (Brundage *et al.*, 1991).

Myosin modulates chemotaxis, posssibly by affecting cell polarity in the slime mold and a model for polarity generation has been proposed (Spudich, 1989). During chemotaxis of *Physarum polycephalum*, a two-layer coupled oscillator system composed of endoplasm and ectoplasm may play important roles for information integration (Miyake *et al.*, 1991).

Amoeboid chemotaxis of *Dictyostelium* involves a regulated increase in actin nucleation activity that is correlated with an increase in actin polymerization occurring seconds after chemotactic stimulation (Carson *et al.*, 1986 and Hall *et al.*, 1989, ref. in Sauterer *et al.*, 1991). An agonist-regulated capping protein, aginactin, has been isolated and characterized by Sauterer *et al.* (1991) that may regulate these changes in nucleation activity. Coronin, a newly isolated actin-binding protein of *D. discoideum* might be

implicated in the transmission of chemotactic signals from cAMP receptors in the amoebial plasma membrane (De Hostos *et al.*, 1991).

b) *Phototaxis:* Intracellular pH and ammonia might play a key role in the thermo- and phototaxis of migrating slugs of *D. discoideum* (van Duijn and Inouye, 1991).

c) *Galvanotaxis:* Motile cells frequently respond to imposed fields, and in most cases they migrate toward the negative pole or cathode (see Table 1, in Nuccitelli, 1988).

6. *Structural basis of directionality*

Cell polarization is generally microtubule-dependent essentially for long-range polarization (Vasiliev and Gelfand, 1976 in Gelfand and Bershadsky, 1991). However, there are examples in which polarization of the motile activity of the cultured cells per se may be achieved without microtubules (see Gelfand and Bershadsky, 1991).

VI. POLAR CELL GROWTH

Tropisms are biopolarizing processes which contribute to orient both growth and morphogenesis. Some of these processes such as galvanotropism and magnetotropic responses are more directly relevant to monopolar growth: fungal hyphae (A.b), pollen tubes (A.f), neurites (A.i), etc. Others such as gravi- and phototropisms are rather implicated in morphogenetic polarizations (tropic curvatures in higher plants, VIII.A.c[4]).

A. Monopolar

1. Outgrowth (emergence)

a[2] *Yeast budding*

The development of cell polarity in budding yeast involves virtually every aspect of cell biology. Two of its central challenges are the identification of interdependencies between the growth events and the determination of the primary inductive processes (Drubin, 1991). The asymmetry of yeast growth is also reflected in the rearrangement of many organelles (Baba *et al.*, 1989) and of the cytoskeleton (Barnes *et al.*, 1990) thereby polarly organizing the cytoplasm during projection formation ("shmoo" Fig. 18, in **I**) for the mating.

Genes responsible for cell polarity and the axis of cell division in *Saccharomyces cerevisiae* have now been identified as reviewed by Drubin (1991). Such patterns of oriented division involve a polarization of cell surface growth, bud sites being chosen in two distinct spatial patterns (see Hartwell, 1991): *axial* for a or α cells and *bipolar* for a/α cells. A model for bud site selection has consequently been proposed by Chant and Herskowitz (1991) which involves: (1) recognition of a morphogenetic landmark by certain *BUD* gene products; in the absence of *BUD* genes there is a random distribution of the bud sites around the yeast cells. (2) Recruitment of products (*CDC24* gene products) that restrict growth to the bud site; mutants defective in gene *CDC24* are unable to bud or establish cell polarity (Adams *et al.*, 1990 in **III**). (3) Recruitment of products such as actin filaments and secretion machinery necessary for bud growth itself. Moreover, it has been shown that *BUD5* interacts functionally with a gene, *BEM1*, that is required for bud formation (Chant *et al.*, 1991). As expressed by Chenevert *et al.* (1992) "Cell polarization requires that a cellular axis or cell-surface site be chosen and that the cytoskeleton be organized with respect to it". Their finding of the gene *BEM1* necessary for yeast cell polarization and whose product contains two SH3 domains provides such a link between the cytoskeleton and morphogenetic determinants on the cell surface.

Conditional-lethal actin mutants tend to enlarge uniformly instead of polarly localize their growth to a bud (Barnes *et al.*, 1990). Other mutants, lacking the Sac6 protein - a yeast fimbrin homologue - do not form normal actin structures and are also defective in morphogenesis (Adams *et al.*, 1991).

Yeast calmodulin was shown to be localized to sites of cell growth in *S. cerevisiae* but the fact the *cdc24* mutant which has a defect in bud assembly fails to exhibit polarized localization of calmodulin would indicate that the CDC24 gene product is responsible for controlling the polarity of calmodulin (Sun *et al.*, 1992).

The consequences on yeast budding of defects in F-actin structures, especially those resulting of mutations in the actin gene *ACT1* (Novick *et al.*, 1989), have been further reviewed by Solomon (1991). An act2 protein might have an important role in cytoskeletal reorganization during the yeast cell cycle (Schwob and Martin, 1992). The product of the gene *CDC11* and actin both localize to the budding site of yeast well in advance of bud emergence (Ford and Pringle, 1991). As for the vectorial transport of secretory vesicles to the site of bud yeast development, it might be mediated by the *MYO2* myosin gene along actin cables (Johnston *et al.*, 1991).

The polarized protein SPA2 (spindle pole antigen) is also known to accumulate at the sites of yeast vegetative buds and elongating "shmoo" buds (Snyder, 1989, see **II**). Now, G1 cells have been shown to contain a polarized distribution of both a SPA2 protein localized to a patch at the presumptive bud site of cells and a polarized distribution of actin spots in the same region (Snyder *et al.*, 1991b). In that case, the "cytokinesis tag" proposed by these authors would explain the localization process as a *non*-random positioning of bud sites in haploid cells. Rsr1p, a ras-like gene homologous to Krev-1, functions only in bud site selection and not in subsequent events of polarity establishment and bud formation (Ruggieri *et al.*, 1992).

Novel yeast genes can prevent spindle pole body duplication and lead to formation of a monopolar spindle (MPS1 and MPS2 genes) thereby causing monopolar mitosis (Winey *et al.*, 1991). When starved for nitrogen, RAS regulated a/α diploid cells of *S. cerevisiae* undergo a dimorphic transition (c) to pseudohyphal growth which requires a polar budding pattern by unipolar cell divisions (Gimeno *et al.*, 1992).

b) *Fungal germ tubes*

By contrast with axiation-needed microtubules, actin microfilaments are required for germ tube outgrowth from conidia of *Neurospora crassa* (Barja *et al.*, 1991a).

c) *Dimorphism*

Its controlling factors in *Mucor* have been reviewed by Orlowski (1991). In studies on polarization induction by electric fields in another Mucorale, *Mycotypha africana*, addition of calcium has been found to favour the M-form and to reduce the number of budding Y-germlings (Wittekindt *et al.*, 1989, 1990). In nutritional starvation, yeast cells can also undergo a dimorphic transition (see a^2) involving a Congo red-highly

stainable, β-glucan thickening of their intercellular walls (Turian, 1982, unpublished observations).

An alternative of the cell types, coccoid versus filamentous, is also examplified by certain algae, not only *Pleurococcus vulgaris* (see Sinnott, 1960 in **I**) but also by *Pleurastrum* species (Ettl, 1988).

2. Tip growth

b) *Fungal hyphae*

The tip acidification previously described (see **I**) has now also been probed by the quenched fluorescence of acridine orange in the apices of germ tubes outgrown from zoospores of *Saprolegnia parasitica* (Turian *et al.*, 1991). Ca^{2+} ions have also been assigned a role in the polarized apical extension of hyphae (see **I**) and their sequestration in mitochondria fronting the tip of germ tubes outgrowing from conidia of *Neurospora crassa* has been confirmed by chlorotetracycline (CTC) fluorescent probing (Barja and Turian, 1992). Such feature of the hyphal tip thus differs from previous observations on some pollen tubes (see Herth *et al.*, 1990). The absence of CTC fluorescence in the extreme hyphal tip where wall-vesicle membrane concentration and growth associated Ca^{2+} influxes are maxima have also been highlighted by Yuan and Heath (1991). Calcium has also been involved in the regulation of hyphal extension and branching in *Fusarium* species (Robson *et al.*, 1991) which show an increased branching in the presence of calmodulin antagonists as previously shown in *N. crassa* by Ortega Perez and Turian (1987).

The actin concentration detected at the hyphal tips and at the sites of septal formation suggests that "actin may play a central role in tip growth and hyphal wall formation" (Raudaskoski *et al.*, 1988, 1991; Jackson and Heath, 1989; Barja *et al.*, 1991b). Actin was cytochemically found to be most densely packed in the extreme apex of *Saprolegnia ferax*. Plastic changes in this actin cap and its disruption with cytochalasin E have led Jackson and Heath (1990) to propose a new theoretical model for apical growth complementing the debated ones previously proposed by Bartnicki-Garcia and Lippman (1972 in **I**) and Wessels *et al.* (1986 in **I**, 1988).

Exocytosis and apical growth may also be related as suggested by the restriction of glycoamylase secretion at the tips of growing hyphae (Wösten *et al.*, 1991). Temporal and spatial dynamic events intervening at appressorium formation in rusts are implied in the cessation of polarized tip growth and swelling of the hyphal apex (Kwon and Hoch, 1991).

Intracellular electric potential recordings in *N. crassa* hyphae have revealed a transfer of energy from proximal to apical cells (Potapova *et al.*, 1988). The galvanotropic response of growing hyphae was either mono- or bidirectional (longer hyphae) in an electric field (Gruler and Gow, 1990). Diffusion might be the mechanism

of bidirectional translocation of nutrients in mold hyphae (Olsson and Jennings, 1991). In the hyphal bundles of rhizomorphs of ectomycorrhizal basidiomycetes, translocation of solutes appears to be strongly polarized along concentration gradients towards sinks of various compounds (Cairney, 1992).

d) *Protonema (mosses)*

Chloronemal tip growth in *Funaria hygrometrica* is regulated by tip-localised H^+ secretion. From pH microelectrode measurements, Bittisnich and Williamson (1989) conclude that the "acid growth" hypothesis is applicable to tip growth in this moss.

e) *Prothallia (primary fern stage)*

Blue-light induces a mophological transition from a tip-growing filament to a planar prothallus (see Burgess, 1985 in **I**). Racusen *et al.* (1988) have shown that there is a rapid dissipation of both the longitudinally aligned electrical field and the tip-localized asymmetries in external cation distribution in blue-light, suggesting that "loss of electrical polarity in this tip growing cell may be an initial step in the chain of events which govern changes in cell shape".

f) *Pollen tubes*

Organelles in the subtip region of lily pollen tubes act as a sink for the calcium entering at the tip. The cytoplasmic gradient of calcium thus created, measured by microinjection of the indo-1 anion into pollen tubes by iontophoresis, is correlated with their growth (Rathore *et al.*, 1991). A distinct elevation of free intracellular calcium ion concentration has been measured at the extreme tip of actively growing *Lilium* pollen tubes by fluorescence ratiometric imaging (Miller *et al.*, 1992). Elevated levels of *membrane-bound* calcium had also been measured in lily pollen tube tip (Reiss and Nobiling, 1986) and the high $[Ca^{2+}]$ found with fura-2 at the same level is probably responsible for vesicle fusion at the tip (Obermeyer and Weisenseel, 1991).

g) *Root hairs*

The root hair membrane potential is depolarized by *Rhizobium meliloti* Nod factors (Ehrhardt *et al.*, 1992).

h) *Insect bristles*

Cell elongation determines the orientation of the axis of planar cell polarity which expresses itself as scales, hairs or bristles indicating thereby a supracellular tangential or "planar" tissue polarity (Nübler-Jung *et al.*, 1987), i.e. polarity in the plane of the cell sheet (Nübler-Jung and Mardini, 1990; Nübler-Jung and Eschbach, 1992, also see VII.C.6.b). Tissue polarity can be a manifestation of a gradient of cell adhesiveness

(Nardi and Kafatos, 1976), a gradient of a diffusible morphogen (Lawrence, 1966, 1970 in **I**; Stumpf, 1966), or direct cytoskeletal-plasma membrane connections between cells (Tucker, 1981, see also **I**). In this respect, the *Drosophila* tissue polarity gene *frizzled* (*fz*) is required to "coordinate the cytoskeletons of pupal epidermal cells so that a parallel array of cuticular hairs and bristles is produced" (Adler *et al.*, 1990).

In *Drosophila*, the genes *Notch* and *scabrous* participate to the specification of position-dependent cell fate of ommatidial founder cells and the formation of epidermal bristles in the adult epidermis (Hafen and Basler, 1991).

The interactions between the segment polarity genes have been analysed in order to unravel the different ways in which they contribute to epidermal patterning. The expression patterns of some of the segment polarity genes such as *wingless* and *engrailed* are spatially restricted (Hidalgo, 1991). There are similarities between these genes and those responsible for the dorso-ventral axiation (see VIII.B.2).

i) *Animal neurites*

The neuronal cytoskeleton has been recently reviewed (Burgoyne, 1991). The axonal cytoskeleton had been considered as a static complex travelling down the axon (Lasek and Black, 1988 in **II**), a view challenged by others (ref. in Okabe and Hirokawa, 1990). Recent results of analyses of the turnover of fluorescently labelled tubulin and actin in the axon of cultured neurons favor that view that these cytoskeletal filaments are dynamic structures that continue to assemble along the length of the axon (Okabe and Hirokawa, 1990).

The binding of microtubules-associated proteins (tau, etc.) to the microtubules might contribute to their stability in mature neurites. Consequently, tau antisense oligonucleotides can inhibit neurite polarity (Caceres and Kosik, 1990 in **II**).

Microtubule sliding has been reported to mediate axon elongation and tubulin transport (Cleveland and Hoffman, 1991). This sliding and slow axonal transport are powered by a common motor and by a molecule with the same polarity as microtubules such as dynein. However, Bloom's review (1992) points out to the new predictions emerging from the kinesin/dynein model for bidirectional transport (see IV.E.4). Otherwise, new evidence (Kuznetsov *et al.*, 1992, see IV.E.4) supports the hypothesis that both actin-based (actomyosin-like mechanism) and microtubule-based motility systems are associated with each other to produce and regulate the movement of organelles in axoplam.

The functional polarity of nerve cells requires targeting of microtubular components which are asymmetrically distributed. There is a known difference in the polarity of the microtubules in the axon and the dendrites (Black and Bass, 1989). In the axon, the polar orientation of microtubules is uniform with assembly ends (+) pointing away from the cell body whereas in dendrites microtubules are mixed with both (+) and (-) ends pointing away from the cell body. It remains to know "how the neuron selectively directs the specific mRNA into its dendrites and axon and whether microtubules are involved in this process" (Ginzburg, 1991). Additional factors, independent of microtubule polarity orientation, might also contribute to the targeting mechanism. It was indeed shown that

the synaptic terminals are deprived of neurofilaments or microtubules (Lasek and Hoffman, 1976) and that their disaggregation would be due either to a higher calcium ion concentration (Lasek and Hoffman, 1976) or the action of a calcium-activated protease (Roots, 1983). A possible role of proteases secreted by the growth cones in neurite polar advancement has again been suggested (Pittman *et al.*, 1989 in Bixby and Harris, 1991). During axonal elongation, microtubule translocation is the principal means of tubulin transport (Reinsch *et al.*, 1991). However, the mechanism of such transport and the location of polymer assembly are presently unknown.

A review on functions of nerve growth cones at the tips of elongating axons and dendrites (Cypher and Letourneau, 1992) cites two monographs about them (Burgoyne, 1991; Letourneau *et al.*, 1991). Growth cones can distinguish one group of neurons from another. This guidance ability is called selective fasciculation mediated by fasciclin II, a member of the immunoglobulin superfamily. This molecular model confirms in *Drosophila* "the existence of functional labels on specific axon pathways in the developing nervous system" (Grenningloh *et al.*, 1991).

The "neuroblast identity gene" *prospero* (*pros*) regulates other neuronal precursor genes and encodes a nuclear protein which is essential for the axonal outgrowth and pathfinding of central and peripheral neurons (Vaessin *et al.*, 1991).

The synergistic action of three known cell surface molecules (L1, N-cadherin and integrin) and additional unidentified components concour to the polarized elongation of peripheral axons (Bixby *et al.*, 1989; Rathjen, 1991). In the regulation of axonal growth by gradients of chemotropic molecules intervene many proteins among which cell adhesion molecules ("neurite outgrowth promoting molecules", see Bixby and Harris, 1991). Spatial gradients of axon guiding molecules would provide positional and directional cues for retinal ganglion cell axons growing within the optic tectum (Baier and Bonhoeffer, 1992).

The orienting role of electric fields and the galvanotropic response of nerve cells as well as the problem of their "normal regeneration which utilizes the electric field as part of the signaling process to attract neurites to the regenerating region" have been reviewed by Nuccitelli (1988). Of interest was the observation by McCaig (1986) that the electric field can influence neurite morphology by creating a cell asymmetry only after neurite outgrowth.

By combining neurophysiological principles with silicon engineering, Mahowald and Douglas (1991) have produced an analogue integrated circuit with the functional characteristics of real nerve cells (see also IV.B.2.e). For their "neuromime" they have built a silicon microchip circuit that mimics the electrical polarized behaviour of real nerve cells (Andreou, 1991).

B. Bipolar growth

a) *Bacterial elongation*

A FtsZ protein has been found to self-assemble as a ring structure at the future division site of the cell of *Escherichia coli* (Bi and Lutkenhaus, 1991). As tentative

model to explain the central ring's localization (homobipolarity), it has been proposed that the cell poles at old sites can compete with the medial cell site (Begg and Donachie, 1977 in **I**, and 1985).

C. Multipolar

c) *Desmidial algae (multiradiate pattern)*

As already mentioned (Brower and Giddings, 1980, also in **I**) the lobes of *Micrasterias* exhibit galvanotropism toward the cathode while those growing toward the anode tend to be shorter (Brower and McIntosh, 1980).

VII. POLARIZED CELL DIFFERENTIATIONS

The internal polarizing processes involved in the orderly phenomenon of cell differentiation require the concourse of the counter-forces of *antichaos* to polarly reorganize the systems disordered by the randomizing, nonlinear forces of deterministic *chaos*. Preeminent among these antichaos forces would then be the polarizing ones. In this antichaos struggle toward polarly ordered self-organization, differentiation of the cells is assisted by the coordinated behaviour of their genomic system which "acts like a complex parallel-processing computer, or network, in which genes regulate one another's activity either directly or through their products" (Kauffman, 1991). Computer models based on the algebric systems of random Boolean networks have first been proposed by Kauffman in attempts to understand the complexification features of cells differentiating into their dissimilar patterns of genetic activity. In these mathematical models, the behaviour of each gene is considered as a simple binary - on or off - variable and each combination of binary element activities constitutes one network "state" in which it will respond to combinations of signals. It is a transient flipping of a binary element to its opposite state of activity which may push the network into a different basin of attraction and therefore a new state cycle of network behaviour (Kauffman, 1991).

Mechanisms by which cell differentiation is initiated are both asymmetric cell division and cell interactions. The problem of asymmetric division concerns many types of differentiating cells (see VIII.A.2.b., *Volvox* patterns, B.2.i., mouse epithelia) and spatial aspects of cytokinesis beginning with the establishment of division polarity have been reviewed by Wick (1991). The previously described examples of asymmetric cell division in invertebrate embryo development (Davidson, 1986 in **I**) have now been completed by Gurdon (1992) and, concerning their mechanisms, Horvitz and Herskowitz (1992) have attempted to answer the following questions: "what causes a mother cell to be polar? How do initially identical sister cells become different? And in each case, how do initial differences in sister cells lead to their ultimately distinct fates?" The *asymmetry* during embryogenesis is established as a response to signals which are transformed into different positional fates under the controls of the complex genetic system of homeotic selector genes (reviewed by McGinnis and Krumlauf, 1992; St Johnston and Nüsslein-Volhard, 1992). However, their understanding "does not itself account for *how* cells adopt the correct spatial relationship to each other" (Gurdon, 1992).

Molecular probes have allowed to follow the establishment of "fields" and the emergence of properties such as boundaries, gradients, polarity and generation of cell diversity in terms of molecules and mechanisms. However, the concepts these words convey still elude explanations in terms of molecular mechanisms (Ingham and Martinez Arias, 1992).

The fundamental polarizing role of the cytoskeleton in cell differentiation has been emphasized by Pollard and Goldman (1992). In this respect, we have now found that actin microfilaments and dots are selectively accumulated in the differentiating female gametangia of the aquatic fungi *Allomyces*, whichever their positioning - apical-subapical - on the reproductive hyphae (Turian *et al.*, 1992). Suggestion that such high actin content of female organs might be related to their richness in RNA (Turian, 1963 in **I**) rejoins Singer's (1992) speculation of an actin involvement in the setting of apical-basal polarity by an asymmetric exit of mRNA through the nuclear pores.

C. Apico-basal differentiations

3a) *Algal eggs (rhizoid-thallic poles)*

Endogenously-produced ionic currents and gradients are thought to be fundamental to polarity (Nuccitelli, 1983 in **I**, 1988). Around germinating zygotes of *Pelvetia*, Gibbon and Kropf (1991) have measured extracellular pH gradients which contrarily to ATP-produced ionic currents (Harold, 1986, Gow, 1989 in **I** and **III**, respectively), would be generated from polarly distributed mitochondria and thus might play a subtle role in polarized growth.

In developing zygotes of *Fucus*, the process of polar axis stabilization (or fixation) following that of its formation involves both components of the cytoskeleton and the extracellular matrix, a structural complex postulated to stabilize membrane asymmetries generated as a result of axis-forming vectors (Quatrano *et al.*, 1991). It is the polar axis which is labile and can be easily and repeatedly reoriented by imposing a unilateral light gradient from a different direction (Quatrano, 1978 in **I**).

6. *Higher animal cells*

a) *Eggs (animal-vegetal poles)*

The importance of the cytoskeleton for embryo polarity has been reviewed by Elinson (1990). It has been considered how a polarized network is constructed and how useful are the activation steps for contraction of actin in developing eggs.

a^3 *Insects*

As reviewed by Gurdon (1992), the polarity of the egg of *Drosophila* is determined by the relative position of the oocyte to its nurse cells within the ovary; the nurse cells contribute gene products coded by *bicoid* which controls monopolar anterior development, *nanos* which controls posterior development, *torso* which controls bipolar, terminal developments of the egg, and other genes. Such developments rely on prelocalized positional determinants present within the cytoplasm of the newly laid egg (Frohnhöfer and Nüsslein-Volhard, 1986 in **I**). These maternal materials are localized to

the anterior and posterior poles of the egg, and St Johnston and Nüsslein-Volhard (1992) have further described how, on the molecular level, the four maternal signals concour to establish positional information in this embryo.

Oskar has been found to organize the germ plasm of the *Drosophila* oocyte and to be colocalized with *nanos*, suggesting that *oskar* directs localization of the posterior determinant *nanos* (Ephrussi *et al.*, 1991). *Oskar* mRNA has been localized to the posterior pole of the *Drosophila* oocyte (Kim-Ha et al., 1991). The posterior group gene *staufen* also codes for a protein which is one of the first molecules to localize to the posterior pole of the oocyte, in the polar granules, perhaps in association with *oskar* RNA (St Johnston *et al.*, 1991).

a5 *Amphibians*

The animal-vegetal, future anterior-posterior bipolar axis of their egg is determined by the relative position of the nucleus and an asymmetric creating accumulation of mitochondria in the oocyte (Heasman *et al.*, 1984 in Gurdon, 1992). A nucleotide localization signal would direct RNA localization to the vegetal pole (Mowry and Melton, 1992).

b) *Epithelia (apical-basolateral poles)*

The polarity of epithelial cells is manifested at many levels of organization and mechanisms by which they generate and maintain cell surface asymmetry are still largely unknown (Gumbiner, 1990). An important role in the sorting process of the two - apical versus basolateral - domains is suggested by differential blocking of the apical delivery of secretion enzymes by the microtubule-active drug nocodazole (Eilers *et al.*, 1989). A role had also been ascribed by Achler et al. (1989) to microtubules (MTs) in polarized delivery of apical membrane proteins to the brush border of the intestinal epithelium using colchicine- and vinblastine-induced depolymerization of MTs. Microtubule disruption by colchicine or nocodazole impairs the transport of proteins to the apical pole of rat hepatocytes (Durand-Schneider *et al.*, 1991). A role for the uniformly aligned microtubules has also been ascribed in maintenance and generation of polarity in enterocytes (Drenckhahn, 1992).

How proteins finally residing on the apical or basolateral surfaces are sorted from each other? Polarity trafficking signals are effective in that process (Hopkins, 1991). Contrary to current models, basolateral transport in MDCK cells (see **I**) has now been found to occur not only by "default" but to depend on one or more cytoplasmic domain determinants (Hunziker *et al.*, 1991). Nevertheless, many membrane proteins can reach the apical surface in the absence of this determinant.

A 14-residue sequence of the cytoplasmic domain proximal to the membrane-spanning segment has been found (Casanova *et al.*, 1991) to contain an autonomous signal, which specifies sorting from the trans-Golgi network to the basolateral surface, a process previously postulated to occur by "default" (see above).

Development and maintenance of cell surface polarity is fundamental for proper epithelial cell function and proteins are asymmetrically distributed in such polarized cells (Simons and Wandinger-Ness, 1990). The basolateral *versus* apical sorting of plasma membrane proteins has been studied by polarized Caco-2 monolayers and a model proposed for the sorting of apical and basolateral membrane proteins and their transcytotic pathway in intestinal epithelial cells (Matter *et al.*, 1990). Interesting "molecular cross talks" between epithelial cells and pathogenic microorganisms have been further discussed in a recent meeting summarized by Wick *et al.* (1991).

Epithelial cells often display - perpendicular to their apico-basal polarity - a second polarity axis within the plane of the cell sheet. This planar cell polarity expresses itself as scales, hairs or bristles whith point tangentially with respect to the epithelium. A supracellular tangential tissue polarity is thus produced by the uniform orientation of cell structures (Nübler-Jung and Eschbach, 1992).

GPI (glycosyl phosphatidylinositol)-anchored isoforms of N-CAM (calcium-independent neural cell adhesion molecule) are targeted to different surfaces of polarized epithelial cells (Powell *et al.*, 1991). Several signals have recently been identified that control the sorting of plasma membrane proteins among which the GPI anchor for their apical targeting (Bomsel and Mostov, 1991). Many additional references about polarized sorting are provided by this last review.

Preferential retention of active Na^+, K^+-ATPase in the basal-lateral membrane domain and selective inactivation and loss from the apical membrane domain would be the mechanism by which cell surface distributions of membrane proteins are regulated in polarized MDCK cells (Hammerton *et al.*, 1991). These last cells lack membrane-cytoskeletal complexes contrarily to other polarized epithelial cells with different distributions of the ATPase in which the same subunits are localized in the apical membrane (see Gundersen *et al.*, 1991). The normal renal tubule polarized location of Na^+-K^+-ATPase in basolateral membranes has been shown by immunolocalization studies (Wilson *et al.*, 1991) to be completely reversed to apical, luminal plasma membranes of autosomal dominant polycystic kidney disease (ADPKD). Such a polarity mislocation is due to an intracellular sorting defect specific for the ATPase pump.

Field potentials across the lingual epithelium modulate taste reception, the functional unit of which includes receptor cells that contain apical Na^+ channels and basolateral sodium pumps connected functionally in series. Chloride provides a shunting that compensates the electropositive field potential due to the transcellular and paracellular transport of Na^+ (Ye *et al.*, 1991). The electropositive potential created could act as a hyperpolarizing field potential depressing the receptor potential of the taste cells (Harper, 1987 and Elliott and Simon, 1990 in Ye *et al.*, 1991).

VIII. MORPHOGENETIC POLARIZATIONS

Applied electric fields can impose their own polarity on developing cells and organisms (Lund, 1947 in **I**; Nuccitelli, 1988). However, and even though there are many examples of morphogenetic implications of endogenous ion currents generated by bioelectric fields (see **I-III**), caution should be exercised about "an obligatory connection between morphogenesis and bioelectric fields or transcellular ion currents" (Harold, 1986 in **I**).

A. Plants

1. *Embryonic polarity*

The apical-basal polarity of the embryo with the shoot and the root meristems located at opposite poles of the main body axis are controlled by patterning genes and their still unknown products (Jürgens *et al.*, 1991). The identified genes act very early in plant embryogenesis. Among these early events, formation of tissues does not require apical-basal polarity. Thus, pattern formation along the axis of polarity and formation of the radial pattern are two separate processes. As for the apical-basal axis it would be initially partitioned into three apical-central-basal regions (Mayer *et al.*, 1991). This early partitioning of the axis bears some superficial resemblance to similar events in the *Drosophila* segmentation process where the gap genes are involved in the initial regionalization of the anterior-posterior axis (see VIII.B.1.g).

Abnormal polarities have been further studied in higher plants and defects have been noticed in the apical-basal pattern before the heart stage of cruciferous embryogenesis (Meyerowitz, 1991). Nine genes have been found to affect three different aspects of the body organization in the *Arabidopsis* embryo: apical-basal pattern in the axial polarity, radial pattern, and shape (Mayer *et al.* 1991).

2. *Organismic polarities*

a) *Mushrooms*

They grow upwards but "how do they know which way is up?" Unfortunately, no gravity-sensing apparatus has yet been identified in fungi. However, perception and response to gravity have been studied: differential elongation of the stipe growth zone was shown to drive gravitropic reorientation of disoriented fruiting bodies (Moore, 1991a); when such cultures of *Coprinus cinereus* were rotated on a clinostat, they aborted at the primordial stage (Moore, 1991b). Curvature experiments with explanted

fruiting bodies of *Flammulina velutipes* demonstrated a restricted localization of the graviperceptive region in the connective area of pileus and stipe of the fruiting body (Kern et al., 1991). Grafting experiments in a *F. velutipes* have shown that the polarity of translocation in the elongating stipe is reversible (Gruen, 1991).

Cytoskeletal elements may be involved in fungal graviresponse (Monzer *et al.*, 1992) as also suggested in moss protonema (c^4). Mitochondria might also be involved in the perception and transduction of the gravitational stimulus (Block and Briegleb, 1989). Future space missions providing microgravity conditions should further answer pending questions about graviperception.

b) *Colonial algae*

A central role has been ascribed to the basal body apparatus, and particularly its microtubular rootlets, in the control of asymmetric divisions that pattern the *Volvox* embryo (Kirk *et al.*, 1991).

c) *Green plants*

According to Sachs' recent review (1991a), there is a positive feedback relation between cell polarization and the transport of auxin: "polarity determines oriented auxin transport while transport itself induces both new and continued polarization". However, polarity could not be specified only by differences in the concentrations of "morphogens" involved in the early establishment of their "prepatterns" (Wolpert, 1971 (**I**), 1989 (**III**), Meinhardt, 1982 (**I**). In his recent book, Sachs (1991b) has proposed an hypothesis of "epigenetic selection" in which decisions on cell fate depend on dynamic prepatterns.

c^4 *Polar auxin transport and tropic curvatures*

Polarly transported indole acetic acid (IAA) is assumed to play an important role in vascular differentiation (see Aloni, 1988) and initiation of lateral roots (see **I**). Elongation growth is correlated with free IAA in etiolated lupin hypocotyls (Sánchez-Bravo *et al.*, 1991). It should now be further confirmed the existence of an IAA gradient between the transporting and the growth competent cells. Polar transport of auxin has also been involved in other growth processes such as phototropic curvature (Firn and Digby, 1980; Baskin *et al.*, 1986).

Gravity is one of the most important formative factors for plants and, among its tropistic effects, there are the modifications of symmetry from radial to dorsiventral or vice and versa (Sinnott, 1960 in **I**). As suggested by space-flight experiments, the orientation of root growth is directed by gravity while that of shoot is guided by both gravity and light. As gravitropic responses to these space-flights, there are cytological abnormalities indicating a disturbance in the mitotic process (Halstead and Dutcher, 1987). These effects of microgravity on mitotic index and root orientation could not be

simulated by clinorotation (Legué *et al.*, 1992). In gravitropically responding moss protonema, microtubules accumulate at the lower flanks of the tip cells (Schwuchow *et al.*, in Herth *et al.*, 1990).

c^5 *Flowering shoots*

Homeotic changes have been further investigated in floral organs (Coen and Meyerowitz, 1991). The expression pattern of the *Arabidopsis* genes is in part established by regulatory interaction between these genes (Drews *et al.*, 1991). In their attempt to integrate molecular data in genetically grounded models of development, Veit *et al.* (1991) have strategically considered floral development in maize. Among its known mutants, pistil-like structures develop anthers in ear of silky.

B. Animals

In his approach to the old problem of tissue polarity, Waddington (1941 in 1962, see **I**) had advocated the stretching role of attachment bodies and desmosomes at the ends of cells lined up in the anterior-posterior direction of gastrulating amphibian embryos. This interesting suggestion still remains unfortunately speculative. A related problem is the anteriorization of the cylindrical nervous tube which is a crucial event of developing embryos.

In these addenda **IV**, the three possible biopolar axiations will be presented in their developmental sequence (1-3) rather than in their more difficult to define sequential, mono- to triaxial, hierarchized patterns (**I** to **III**). Of the three geometric axes of a vertebrate body, i.e. anterior-posterior, dorsal-ventral and left-right, the formation of this last, displayed in heart and liver development, is still the least understood (Oppenheimer, 1974 in Yost, 1992 and other ref. in **III-IV** VIII.3).

Three pattern-forming sets of genes are necessary and sufficient for the specification of 1) the anterio-posterior (A/P) axis: the anterior system (A), responsible for the segmented region of head and thorax, the posterior system (P) which determines the segmented abdomen, and the terminal system (T) which determines the nonsegmented acron and telson; 2) the dorso-ventral (D/V) axis is determined independently of that of the A/P axis (Nüsslein-Volhard *et al.*, 1987 in **I**; St Johnston and Nüsslein-Volhard, 1992; Lawrence, 1992); 3) the bilateral, left-right or handedness axis. Lipshitz (1991) has further reviewed axis specification in the *Drosophila* embryo and has considered that "three genetic hierarchies control cell-fate specification in largely distinct regions of the antero-posterior axis of the embryo, whereas a single hierarchy specificies dorso-ventral cell-fates". A link between dorso-ventral and anterio-posterior patterning has also been suggested by studies of certain genes (*capu* and *spir*) in *Drosophila* (Manseau and Schüpbach, 1989).

Growth factor and homeobox genes have been implicated in the establishment of positional identity in the embryonic body axes (Melton, 1991 in **III**). Specific effects of

morphogens such as retinoic acid (RA and see 1 . k) on anterior-posterior and dorso-ventral positional identity have been demonstrated in regenerating limbs of vertebrates (Stocum, 1991). Changes in the localization of homeobox proteins can be induced by RA in the anterior-posterior axis of *Xenopus laevis* embryos (López and Carrasco, 1992). Concerning the diffusible signalling molecule RA, there are opinions that it is "a poor candidate for a morphogen" (Williams and Hogan, 1991, see also Slack in III) even though there is some evidence to suggest that RA may direct several different developmental processes (1 . k).

1. Anterior-posterior (A/P) polar axiation (monoaxial patterns)

Homeobox genes are an ubiquitous feature of polarity in multicellular organisms and the first gene complexes which control anterior-posterior polarity might have evolved from the level of primitive animals such as rotifers and flatworms. In both invertebrates and vertebrates, homeobox gene clusters on a chromosome are arranged in a precise order and read polarly from left to right; therefore, on the linear DNA molecule "left genes" are expressed in posterior body part and "right genes" closer to the head (D. Duboule and R. Krumlauf in De Robertis *et al.*, 1990, see **III**).

In a recent EMBO Workshop, aimed to unravel the mechanism of action of the homeodomain at the level of its interaction with DNA, it has been highlighted that in the conformational foldings of the α-helices of homeodomain proteins, specific interactions might be mediated by H_2O, "given the strong angle or orientation dependence of H bonds" (Riddihough, 1992).

Members of conserved *Antennapedia*-class homeobox gene clusters (HOM-C) are thought to give specific body regions their identities (Gehring, 1987 see **I**; Kenyon and Wang, 1991). HOM-C genes especially *mab-5* can not only direct region-specific patterns of cell division and differentiation but can also act with migrating cells to program region specific migratory behaviour (Salser and Kenyon, 1992).

a) *Mycetozoa (slime molds)*

The *Dictyostelium* slug is a regulative structure, in which extracellular signals act to direct a polarized cellular differentiation. Positively and negatively acting signals regulate its stalk cell and anterior-like cell differentiation (Ceccarelli *et al.*, 1991). Cell transplantation experiments have shown that "when posterior prestalk cells are transplanted to the prespore zone, respecification of sorting preference is suspended until the cells return to the prestalk zone" and "anterior-prestalk cells acquire posterior-prestalk sorting preferences" (Buehl and MacWilliams, 1991).

c) *Hydrozoa*

Head and foot factors have been involved in the establishment and maintenance of polarity in hydra. The foot regeneration deficiency of a strain of *Hydra oligactis* was shown to be due to a drastically reduced foot activator (Hoffmeister, 1991).

d) *Worms*

The axis of *Caenorhabditis elegans* embryos results of the specific rotational movement of the pair of centrosomes and nucleus (Hyman and White, 1987). Perturbation experiments of the centrosome movement by a laser support this positioning model possibly involving dynamic microtubules (Hyman, 1989). It has recently been found that the order of homeobox genes along the chromosomes of the nematode *C. elegans* corresponds to the order of expression domains along the anterior-posterior axis of the animal (Bürglin *et al.*, 1991).

g) *Insects*

Determination of polarity along the longitudinal axis is carried out by the maternal genes (Nüsslein-Volhard *et al.*, 1987 in **I**; Reid, 1990) while the polarized distribution of their gene products leads to the regional expression of the zygotic gap genes (Ingham, 1988 in **I**). In the anterior system, *bcd* interacts with *hb* while in the posterior morphogen system, *nos* does not seem to interact directly with the posterior gap gene *knirps* (Pankratz *et al.*, 1992).

Maternal regulatory systems function to position a transcription factor asymmetrically thereby contributing primarily to define the longitudinal, anterior-posterior axis. Graded activity of the posterior morphogen determinant *nos* controls the transcripts of the *hb* maternal gene and hence abdominal pattern (Wharton and Struhl, 1991). *Nos* gene has been isolated and molecularly characterized and its RNA shown to be functionally equivalent to the morphogenetic activity found in the posterior pole of the *Drosophila* embryo (Wang and Lehmann, 1991). It has also been suggested (Brönner and Jäckle, 1991) that it is by repression of central gap genes that the terminal gap genes *huckebein* (*hkb*) and *tailless* (*tll*) possibly functioning in the posterior pole region of the *Drosophila* embryo prevent its metamerization.

An interesting case is presented by the early *Drosophila* embryo which is a syncytium that permits the intermixing of regulatory factors by diffusion. The choice in cell fate might involve a slight asymmetry in the concentrations or activities of regulatory factors inherited by daughter cells and setting up on-off patterns in gene expression such as that of segmentation even *skipped* (*eve*) of the strip 2 element (Stanojevic *et al.*, 1991).

k) *Birds*

Retinoic acid has the same effect as the polarizing region of the limb bud when placed at its anterior margin: mirror-image duplicated limbs with additional digits

results (Tickle *et al.*, 1982, 1985). Some authors have cautioned that the role of retinoic acid as an endogenous morphogen is still speculative (see Brockes, 1990, 1991 and **III**). For a review about homeobox genes as possible targets for regulation by retinoic acid and their possible encoding of positional values in chick limb buds, see Tickle (1991).

Morphogens are diffusible substances that can form a concentration gradient across an embryonic field (Wolpert, 1969 in I). The controversy about them is continuing (Newman - Slack in *Nature* 354: 26, 1991) ... "We have" (see Slack in **I**) or "may not have" (Slack in **III**) them. However, we now have some candidate morphogens, the retinoids and some candidate primary response elements, the Hox-4 genes (Izpisùa-Belmonte *et al.*, 1991 in **III**; Stocum, 1991) which probably encode positional information (Tickle *et al.*, 1975).

The concept of the Hox complex is a colinearity between the arrangement of the genes along the chromosomes and the spatial extent of their expression domains: 3'-located homeobox genes with *anterior* expression boundaries, *posteriorly* restricted expression for 5'-positions within a Hox complex (Dollé *et al.*, 1991). For further information about polarized molecular models for limb development, especially how "*Hox* genes and the anterior-posterior axis interact", see Tabin (1991), and Stocum (1991) for problems of polarized regeneration.

2. Dorso-ventral (D/V) axiation (Biaxial patterns)

A single set of genes determining an asymmetric distribution of their products is responsible for that pattern (Nüsslein-Volhard *et al.*, 1987 and Govin and Steward, 1991, cited in Casanova, 1991).

d) *Insects*

d^1 *Egg-embryo patterns*

Laser ablation of the oocyte nucleus has shown its requirement for dorso-ventral patterning of the *Drosophila* embryo (Montell *et al.*, 1991).

As now summarized by Stein and Nüsslein-Volhard (1992), twelve maternal effect genes (the dorsal group and *cactus*) are required for the establishment of the embryonic dorsal-ventral axis in the *Drosophila* embryo so successfully analyzed by the genetic approach (Nüsslein-Volhard and Wieschaus, 1980 in **I**; Nüsslein-Volhard, 1991). The ventral formation of a ligand for the *Toll* receptor defines this type of embryonic polarity within the perivitelline compartment. The polarity along the embryonic dorsal-ventral axis is initiated by an extracellular signal, with the dorsal gene *Toll* (*Tl*) product which plays the role of a receptor (Stein *et al.*, 1991). They propose that "the polarizing activity, normally present at the ventral side of the egg is a ligand for the *Toll* receptor". In both the dorsal (*Tl*) and the terminal (*tor*) systems, an evenly distributed membrane protein has been identified and it has been suggested that a ligand for *tor* is expressed (Stein *et al.*, 1991).

d[2] *Wing patterns*

Segment polarity genes appear to be involved in intrasegmental patterning as suggested by their mutations which alter discrete regions within each segment of the *Drosophila* larva (Ingham, 1990). For instance, in *wingless* (*wg*) larvae the denticles which cover the naked cuticle are oriented towards the midline of each apparent segment (Rijsewijk *et al.*, 1987; also see Ingham *et al.*, 1988 in **I**), whereas in the *ptc* (patched)-*wg* double mutant this loss of polarity cues with respect of *wg* larvae could be explained by the epistasis of *wg* over *ptc* (Hidalgo, 1991).

Unrestricted expression of the gene *ptc* which encodes a transmembrane protein allows a normal segment polarity (Sampedro and Guerrero, 1991). Positional signalling in the cellularized *Drosophila* embryo requires cell interactions expressing the homeodomain protein *engrailed* and the secreted glycoprotein encoded by *wingless*. The receptor for this signal might be the *patched* protein itself (Ingham *et al.*, 1991 and ref. herein).

The generation of dorso-ventral polarity in the early embryo of *D. melanogaster* relies upon the expression of 12 maternal-effect genes termed the dorsal group (Gay and Keith, 1991). In the set of maternal genes which define the D/V pattern, the "dorsal group" acts only on the polarity of the embryo and the gene *dorsal* encodes a nuclear protein acting as a morphogen (Nüsslein-Volhard and Roth, 1989). The other maternally genes act to set up the gradient of this protein in the correct orientation (Roth *et al.*, 1989). Sequence-specific expression of *twist*, a zygotic gene required for differentiation of mesoderm along the D/V axis, is transactivated by the dorsal gene product (Thisse *et al.*, 1991). All these "smart genes" that through elaborate chemical messengers control polarized differentiation and morphogenesis are being further deciphered (see Beardsley, 1991).

f) *Amphibians*

In early embryogenesis, the fibroblast growth factor (FGF) signalling pathway plays an important control in the formation of the posterior and lateral mesoderm (Amaya *et al.*, 1991).

Results obtained by Sokol *et al.* (1991) show that microinjected synthetic mRNA (Wnt oncogenic type) can induce a new and complete dorsal axis. However, injection of Xwnt-8 mRNA can also rescue the development of a dorsally complete anterior-posterior axis in UV-irradiated ventralized *Xenopus* embryos (Smith and Harland, 1991). Cells were thus led to act as a Nieuwkoop center (the vegetal-inducing component of normal dorsal axis formation).

i) *Mammals*

Microtubules play a role in the asymmetrical, epithelial cell divisions (see VII) and the onset of cell polarity during mouse early embryogenesis (Maro *et al.*, 1991).

3. Bilateral asymmetry or L/R handedness (triaxial patterns)

This 3rd component of the axial biopatterns complements the two other polar axiations of most advanced organisms, from the worms to the human beings even though it is already "prototyped" in helical bacteria and many protozoa in which it is superposed on their usual anterior-posterior axis according to a biaxial type of pattern. In vertebrates such as *Xenopus laevis* gastrulae, the left-right asymmetry is regulated by a fibronectin-rich extracellular matrix (Yost, 1992).

The question asked by Wolpert and others of why there are left-right asymmetries in organisms from bacteria to vertebrates has been summarized in the proceedings of a recent Ciba Foundation Symposium edited by Bock and Marsh (1991). The central problem remains of how three-dimensional structure, determined by primary structure, is determined by the asymmetry of basic monomers. "An epistemological gap exists in embryology between understanding structures that arise from cellular self-assembly and understanding those that require higher levels of causation" as commented by Slack (1992).

EPILOGUE

Polarity has been considered as "the directional arrow of Evolution" leading from the primordial, *intrinsic* electro-bipolarity born in the abiotic phase and amplified in the prebiotic phase through the electro-structural polarity of macromolecules, to the induced, newly called *extrinsic* biopolarizations achieved in the biotic phase (see Addenda **III**).

In this evolutionary view of Polarity, the advent of progressively complexified developmental polarities, capable of overstepping elementary self-assembly processes, has been achieved by the *take-over* of a positional genetic information increasingly competent in its gradiential expression of morphogenetic molecules. However, in this genetic take-over, the intrinsic electrical bipolarity could be conserved through its fruitful exploitation of the unique dipolar and vectorial electrostatic proprieties of hydrogen bonding, prototyped in the H_2O network, developed in the first biomolecules and the intra- or inter-molecular H bonds of α-helical - β-sheet proteins respectively, and finally amplified in the informational base sequence of DNA coding for the most complex polar bioaxiations. Endowed with both electro-structural and informational polarity contents, the H bonding can thus be considered as the unifying principle of continuity in the evolutive complexification of Polarity from its intrinsic, physico-chemical fundamentals to its extrinsic, genetically-controlled but epigenetically, environmentally-modulated polar bioaxiations as sequentially summarized in the following synopsis:

Scale of Polarity complexity

1) electrical (-magnetic) bipolarity:
   a) subatomic asymmetries (+/- electric charges, N/S magnetic poles),
   b) atomic (H), molecular inorganic (H_2O, etc.) and organic (amino acids, etc.) dipoles, and H electrostatic bonds;

2) electrical-structural bipolarity:
   a) informational (nucleic acids),
   b) translational macromolecules (polypeptides - proteins, etc.);

3) structural bipolarity:
   a) cytoskeleton (actin, myosin, tubulins),
   b) viral self-assemblies.

4) physical-chemostructural polarizations:
   a) physical effectors (light-induced charge separation, etc.);
   b) chemostructural effectors (crystals → light polarization, semi-superconductors → electric fields).

5) electrical-structural pericellular biopolarizations:
   a) transversal ("perpendicular") through
      plasma and organellar membrane (a^1) conformations,
      (a^2) energy transduction and (a^3) electric potentials;
   b) tangential ("planar") along
      (b^1) apical-basolateral, epithelial and
      (b^2) longitudinal, axonal membranes (action potentials);

6) structural-functional intracellular biopolarizations:
   a) monopolar (a^1) molecular intermembranar targetings,
      (a^2) vesicular traffics and (a^3) energetic motors;
   b) bipolar (b^1) homo-symmetric mitoses,
      (b^2) hetero-asymmetric cell divisions;

7) genetical-developmental biopolarities:
   a) apical (a^1) monopolar and (a^2) bipolar growth patterns;
   b) axial (b^1) anterior-posterior, (b^2) dorsal-ventral,
      (b^3) bilateral (chiral) differentiation patterns;

8) environmental polar movements:
   a) cellular tactisms (chemo-, photo-, etc.)
   b) organismic tropisms (chemo-, photo-, gravi-, galvano-, polaro-).

From now on, we expect to use this first integrating frame to further select "New Trends in Polarity" from the ground-line of the encyclopedic information assembled since 1989 in our Survey and its Addenda.

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