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MELANIN: THE ORGANIZING MOLECULE

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ABSTRACT

The hypothesis is advanced that (neuro)melanin (in conjunction with other pigment molecules such as the isopentenoids) functions as the major organizational molecule in living systems. Melanin is depicted as an organizational "trigger" capable of using established properties such as photon-(electron)-phonon conversions, free radical-redox mechanisms, ion exchange mechanisms, and semiconductive switching capabilities to direct energy to strategic molecular systems and sensitive hierarchies of protein enzyme cascades. Melanin is held capable of regulating a wide range of molecular interactions and metabolic processes primarily through its effective control of diverse covalent modifications.

To support the hypothesis, established and proposed properties of melanin are reviewed (including the possibility that (neuro)melanin is capable of self-synthesis). Two "melanocentric systems"--key molecular systems in which melanin plays a central if not controlling role--are examined: 1) the melanin-purine-pteridine (covalent modification) system and 2) the APUD (or diffuse neuroendocrine) system. Melanin's role in embryological organization and tissue repair/regeneration via sustained or direct current is considered in addition to its possible control of the major homeostatic regulatory systems--autonomic, neuroendocrine, and immunological.

INTRODUCTION

This article (together with a companion article on "Melanin and the Mind-Brain Problem" (32)) is the first published synthesis of extensive research into melanin and an integrative process theory of living systems. The major hypothesis advanced here is that melanin (in conjunction with other pigment/pigment-related molecules, such as the ubiquitous isopentenoid polymers) functions as the most significant organizational molecule in living systems through its effective in vivo control of the vital and diverse covalent modifications crucial for both physiological and psychological activity.

To organize a system is to arrange or form its elements into a coherent, functional whole. How such organization takes place within living systems such as the cell remains a central question of biological research (23, 537, 285, 220, 718, 499, 706, 707, 766, 767, 698, 750, 38, 146, 153, 221, 407, 555, 668, 756, 757, 761, 32). At the molecular level of cellular organization, nucleic acids have programming control

over the numerous dynamically responsive proteins. However, we propose here that melanin functionally organizes these original "raw" proteins which result following translation from the nucleic acids by controlling the subsequent post-translational covalent modifications (698, 750, 533, 99, 153, 221, 557, 273, 738, 628, 181, 251, 309) that change these "raw" proteins into "active" proteins. This protein activation in vivo occurs via melanin's directly and indirectly controlling the mechanisms of covalent modification, including peptide cleavage, phosphorylation, methylation, glycosylation, adenylation, uridylation, polyamination, acetylation, transsulfuration, etc. Our hypothesis is that melanin (and perhaps the isopentenoids) interact(s) closely with the nucleic acids (and perhaps the glycosaminoglycans) to form a "control axis" for living systems.

The hypothesis that melanin is the basic organizing molecule within in vivo systems can be supported by at least four major lines of research and argument. First are its remarkable set of properties as a unique biopolymer. In addition to being an extremely efficient light (photon)-absorbing molecule, exhibiting extraordinary photon-phonon[1] conversion processes (416, 418, 668), melanin transduces both acoustic and electric energy fields (169, 416, 415, 418, 170) and it can generate enough heat to effect metabolic processes (514, 416). In addition to responding functionally to both light and sound (and being abundant in both the eyes (770) and inner ears (321, 356), melanin and neuro-melanin (the form of melanin found in the central nervous system) is located in highly strategic functional regions of the central and peripheral nervous system (including the midbrain reticular formation, substantia nigra, and ventral tegmental area (580, 35, 64, 292, 293, 645, 341); the pontine reticular formation and locus coeruleus (580, 64, 35, 293); the autonomic and sensory ganglia (35, 219, 439, 406, 336); the glial cells (32, 626, 439, 189, 219, 334, 336, 444, 735); etc.). In vitro studies have shown that melanin functions as an amorphous semiconductor within physiological ranges of neuronal electrical potentials (415, 169, 170, 417, 512, 493). Electrotonic (graded potential) processing in neuronal systems (574, 576, 83, 597) may be effectively triggered by as little as one photon or by an auditory (phononic) input near that of mere Brownian motion (574, 576). Melanin's unique combination of photon-(electron)-phonon and electromagnetic semiconductive properties may serve in vivo to continuously regulate both the axonal action potentials as well as the glial-dendritic local circuit graded potentials, both of which are necessary for nervous system functioning (32, 561, 597, 83).

Furthermore, melanin can continuously produce and scavenge highly reactive free radicals (584, 157, 168, 567, 507), simultaneously oxidize one substance while reducing another (584, 390, 186, 187, 120) and function as a remarkable cation exchange polymer (able to bind and release a full range of strategically functional metal ions (584, 157, 398, 328, 508, 125)). An extended list of established and proposed properties of melanin appears later in this paper.

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[1] A phonon is a unit of vibrational or rotational energy, a quantum of an acoustic mode of thermal vibration (326). See discussion below under "Photoactive Pigment Molecules and Life."

The fact that melanin is the most primitive and universal pigment in living organisms, present since the inception of life (568, 309), would make its hypothesized organizational role particularly important. In searching for a basic organizational molecule, it would make sense to identify a primitive polymer which appears early in evolutionary process and which subsequently develops an impressive functional repertoire. As this paper will show, melanin/neuromelanin presents itself as a singular candidate for such a role.

Second, melanin seems the principle organizing molecule because of an impressive body of circumstantial evidence, especially because of its participation in what are described here as "melanocentric molecular systems." Two of these systems, analyzed below, are: 1) melanin's close connections (24, 25, 273) with the purines and pteridines and their functional derivatives, which regulate innumerable mechanisms of cellular behavioral control and signal transduction (628, 181, 411, 687, 251, 311, 177, 191, 625, 740, 497, 651), and 2) melanin's integral involvement in the APUD or diffuse neuroendocrine system (32, 482, 483, 484, 299). This APUD system can synthesize, store, and release both peptide hormones, which are crucial to such functions as memory, emotion, motivation, and trophic responses (32, 151, 702, 204, 768, 703, 704, 148, 149, 150, 85, 208, 676, 677, 320, 40, 378, 384, 193, 575, 454, 709, 147), and amine neurotransmitters[1] which are crucial to neuronal data transmission, sensory input and motor output (421, 400, 401, 277, 32).

(Neuro)melanin, which is itself primarily polymerized from tyrosine and tryptophan derivatives and such monoamine neurotransmitters as dopamine, norepinephrine, and serotonin (341, 705, 194, 551, 692, 693, 539, 479), appears to have the potential to bind, rearrange, polymerize and release virtually any molecular ring structure (564, 353, 539, 451, 341, 348, 349, 350, 169, 678, 31, 476, 629, 273). Melanin, using such internal capabilities, seems to function as an organizational "trigger". Sensitive hierarchies of strategically arranged cellular protein enzyme cascades, controlled by reversible covalent modifications (and in turn presumably by melanin), appear to provide the means for instantly activating and powerfully amplifying both the signal response to and catalytic potential necessary for diverse cellular organizational tasks (98, 630, 221, 698, 750, 153).

Third, during embryological development, melanin is present in every stage from the oocyte (225, 447, 542, 308) to the mature adult organism. In vertebrates, it grossly condenses during the embryonic development of the highly pigmented neural crest system (which also coincides with the formation of the neural tube) and disperses to many

[1] Both amino acid neurotransmitters (such as glutamate and GABA) and monoamine neurotransmitters (such as serotonin, dopamine and norepinephrine) are involved in neuronal data transmission, but the latter neurotransmitters serve a special regulatory role (32, 239, 240, 241, 151).

strategic homeostatic locations throughout the body (735, 279, 333, 334, 335, 336, 323, 444, 77).. Among the most notable of these are the central and peripheral nervous systems, the autonomic nervous system, and the disseminated yet intimately interconnected diffuse neuroendocrine system (the APUD system). This feat of embryological organization and development is apparently guided by an organizing flow of sustained (direct) current (38, 403, 282, 283, 375, 67) generated at the cellular level and first detected at the pigmented pole of the oocyte (447, 542). This sustained current is modulated by various mechanisms, accessible to control by melanin, that regulate ion flow and the electrotonic gap junctions connecting the embryonic cells (627, 376, 547, 42, 43, 352, 247, 256, 490, 388, 618, 619, 54, 685, 722). The fact that brain melanin (neuromelanin) increases with ascent up the phylogenetic ladder, reaching a culmination in man (372, 568, 176, 64, 580) gives additional support to the hypothesis that melanin is performing some as yet unrecognized major function within living systems (292, 293). The companion paper to this (32) postulates melanin to have evolved in its organizational capacity from that of regulating cell-tissue systems in lower organisms (through regulation of molecular covalent modifications) to developing a highly sophisticated central nervous system (CNS)-neuromelanin regulatory network in more advanced organisms, culminating in self-conscious cognitive mental capacity in humans.

Fourth, melanin may function as the primary molecular organizational agent in an evolutionary process that bridges the molecular, cellular, and embryological-neural systems levels. The presentation of an evolutionary process theory which we feel appears to integrate successfully our new understanding of melanin is, however, beyond the scope of these two introductory review articles. It should be noted here that what may be described as the Theory of Evolutionary Bioprocess (an extension of a more general process paradigm (756) developed by Arthur M. Young) gives both added theoretical support to the observations made in these papers and, more importantly, illuminates the theoretical issues that lie ahead in the future of melanin research.

Why Melanin Has Been Neglected

If melanin (in its proposed co-axial control-organization role with nucleic acids) is so strategically important, why hasn't it received more attention? Several reasons for this neglect suggest obstacles to acceptance of the melanin organizational hypothesis:

1) Melanin is an extremely stable molecule, highly resistant to digestion by most acids and bases (157, 539, 584, 660, 292), and even quite resistant to advanced techniques of analysis such as electron spin resonance, x-ray diffraction, and synchrotron radiation studies (584, 672, 673). This stability, which is remarkable for molecular structures, gives it a durability and permanence that ideally suits it for its hypothesized organizational role but which simultaneously renders it relatively inaccessible to analysis--making it a kind of molecular "black box". As a result, the synthesis and exact structure of melanin remain unknown. Even superficially illuminating: a) its heterogeneous molecular composition; b) its complex of multiple covalent,

ionic, (and possibly metallic) bonds; c) the gamut of metal ions it binds; d) the stable free radicals it contains; etc.--is extremely difficult without producing experimental artifacts (660). This hindrance to in vitro analysis has apparently discouraged many researchers from further effective study.

2) In vivo analysis of melanin's functioning is even more difficult. Disturbing melanin's subtle physio-chemical parameters will most likely disturb at least some of the intricate patterns which are responsible for its complex organizational properties. For example, the companion paper (32) claims that in vivo vertebrate neuromelanin functionally uses intricate and extensive systems such as: a) diffusely elaborated dendritic branching schemes, b) glycocalical-extracellular matrix modalities, c) intricately arborizing nonmyelinated monoaminergic trigger mechanisms, and d) extensive glial intercellular gap junctional communication networks. Such neuromelanin-related systems would be totally disrupted during all in vitro studies of melanin and at least partially disrupted during most in vivo studies. Also, some of the most strategic melanized areas (such as the brainstem melanin system) are extremely difficult to study in vivo because of their location deep within the brain and their intimate connections with surrounding brain systems.

3) A related problem for analysis is that even minute quantities of melanin may still produce significant organizational effects. With cellular signal amplification enzyme cascade systems and electrotonic processing systems, only a very minute amount of functional melanin need be present to organize an entire cell or an entire neuronal system. Emphasis on the gross quantity of melanin has obscured the effectiveness of its organizational quality.

While this paper mainly discusses the observable properties of detectable cellular melanin, the possibility that melanin is significantly present in all cells and in all living organisms deserves careful attention. In those very few "amelanotic" organisms where melanin's presence is still unclear, several possible explanations for its non-detection may be offered. First, on some occasions, when melanin has been repeatedly said to be totally absent, different techniques for detection have found it to be present in abundance (292, 293). Second, the chemical properties of in vivo melanin may change with time (such as fetal vs. adult) as well as with circumstances, thus requiring different techniques for its detection during these different times and circumstances. Third, the minute quantities of melanin needed to provide its hypothesized trigger role within many cells could easily be overlooked without highly sophisticated micro-analytical techniques specifically designed for its detection. Finally, an intriguing and likely possibility is that melanin may exist within other cellular organelles, including the lysosomes and mitochondria as well as the melanosomes. Possibly melanin may "circulate" within the cell among such "organizational organelles" as the above as well as among the peroxisomes, the coated vesicles/receptosomes, and the secretory-synaptic vesicles. Such an "intracellular" transport mechanism would be analogous to the established "intra-organismic" transport of melanin

(723, 725), in hormone-like fashion, by white blood cells such as eosinophils (456, 458, 459), as well as by migratory mast cells (457, 458)--both having the capacity to synthesize and transport melanin. A related consideration is the dramatic intracellular transport of melanin granules to and from the cell center, which clearly happens within grossly melanized cells like the chromatophores (506, 573) and which possibly occurs within all cells in minute amounts. The melanosomes may be instantaneously transported from the centrosome (the cell center) to the peripheral plasma membrane (and vice-versa) via the cytoplasmic ground substance (506) and the cytoskeleton (the microtubules and microfilaments) (626, 420). If the proposed organellar transfer and/or synthesis of melanin does indeed occur, then it seems likely that melanin is present in varying amounts, as the need arises, in every region of every cell of every living organism. Functionally related molecules (such as isopentenoids, tetrapyrroles, lignins, etc.) in more primitive organisms (such as various plant cells) may organize in a manner similar to melanin.

4) General attitudes toward race may have inhibited melanin research, since melanin is the primary pigment responsible for one's skin color. Melanin (including neuromelanin) has perhaps been assumed to be only a passively acquired and thus minimally functional molecule. To downgrade the importance of melanin, however, is to overlook the significant differences between brain melanin (neuromelanin) and skin melanin properties (705). One's neuromelanin does not correlate clearly with one's skin melanin, in either known formative mechanisms, gross amounts, or major functions. While the internal molecular arrangements and diffuse interconnections of one's neuromelanin-monoamine network may vary uniquely with each individual (32), such variations in one's neuromelanin do not correlate (in any obvious way) with one's skin color (whether white, red, yellow, black, brown, or albino).

5) Perhaps the most significant reason for the relative inattention to (neuro)melanin has been the erroneous assumption that (neuro)melanin was simply a "waste product" of catecholamine metabolism (178, 35, 366). This single-function assumption/interpretation has lasted for years, not because of direct evidence, but because of circumstantial associations, such as the "excessive" accumulation of neuromelanin in neurons in old age and the possible atrophy of some of these neurons (366). However, a direct cause-effect relationship between these has not clearly been established. Furthermore, several alternative explanations could be offered even if the link between "excessive" melanin and neuronal atrophy is valid. For example, Sarnat and Netsky suggest that with advancing age, neuromelanin/lipofuscin's free radical/excited state electron-scavenging and detoxification properties are exhausted; they become overloaded with toxic free radicals, chemicals, etc.; and consequently the cells deteriorate because of the inability to deactivate these toxins (568). In other words, lipofuscin accumulation may be a heroic molecular attempt to salvage deteriorating cells.

Melanin most likely does serve a cytoprotective role (as well as a potentially cytotoxic role if "overloaded"). The role of neuromelanin in oxidation-reduction/free radical mechanisms would guarantee its

presence in regions of high metabolic activity (such as the brainstem sites of origin of all the catecholaminergic pathways). However, we contend that neuromelanin is located at the origin of the catecholaminergic pathways not primarily for cytoprotective reasons (although these certainly may be important) but, instead, to organize and control these pathways.

Fortunately, this question of whether melanin is simply a "breakdown polymer" of catecholamine metabolism may have been resolved experimentally by A.J. Kastin and Nobel laureate A.V. Schally of Tulane (292). They conclude that it is not. These noted researchers in neuroendocrinology have been meticulously investigating melanin, MSH (melanocyte-stimulating hormone),and MIF (MSH-inhibiting factor), along with other peptide hormones, for several years. They have carefully followed the appearance and subsequent concentration of both catecholamines and melanin in the developing rat brain. Their detailed analysis has demonstrated that the concentration of neuromelanin reaches a very stable adult level by 30 days of age, whereas the concentrations of the catecholamines dopamine and norepinephrine continue to increase from day 1 to day 60 or more. From this and other studies, Kastin and Schally conclude that neuromelanin is not just a "metabolic wastebasket" but, on the contrary, appears to have an important role in the functioning of the brain and nervous system (292). Furthermore, these researchers believe that the function(s) of neuromelanin are due to a "change in state" rather than a change in concentration (293). This is a highly significant point which cannot be emphasized enough and which should be kept in mind during the remainder of this paper. It will be analyzed in the companion paper (32).

The purpose of our review articles is to focus scientific attention on a relatively neglected but strategically significant area of research. Besides having many unique properties, most neuromelanin is located in the brain in a region that functions as a "gate" or "filter" system for all sensory input and all motor output, all emotional and motivational input and output, as well as a region that provides "conscious awareness" in general (35, 64, 580, 253, 729, 639, 640, 645, 32). Through its monoamine --glia electronic network, its known hypothalamic and autonomic nervous system connections, and its proposed diffuse neuroendocrine control, (neuro)melanin is in the ideal position to homeostatically regulate all self-organizing (autopoetic) systems (285, 706, 707, 295, 511, 766, 769, 553, 365, 374, 738, 746, 428, 430, 399, 353, 354, 239, 241, 190, 94, 4), such as the neuroendocrine system, the autonomic nervous system, the immunoregulatory system, etc. Accordingly, (neuro)melanin may be the key to the solution of a wide variety of disorders including "mental instability" (schizophrenia, manic-depression, etc.); autonomic, cardiovascular, and gastrointestinal disorders; and the various immunological disorders (allergic, infectious, autoimmune, and neoplastic).

The presentation here, while extensive, is preliminary. There is much we do not know about melanin: exactly how it is synthesized; what molecular forms or structures it takes; how it absorbs, stores, and uses photons (light quanta) as part of its organizational repertoire;

the exact nature of its relationship with key molecules like the purines and pteridines; what organizational functions the other pigment molecules and cellular organizational vehicles perform in relation to melanin; how melanin organizes itself in the evolutionary advance from molecular to cellular to embryological levels, etc. What is offered here is a concept new to bio-medical literature--that (neuro)-melanin may be the major organizing molecule in living systems, especially in advanced organisms with sophisticated neuroendocrine systems.

PHOTOACTIVE PIGMENT MOLECULES AND LIFE

Because the origin and maintenance of the process of "life" (i.e. negentropic organization) is inextricably connected with the photoactive pigment molecules (304, 232, 233), our analysis begins with a brief examination of these molecules. (Melanin appears to possess the most diverse functional properties of this group of light-absorbing molecules). Crucial electron transport and general energy flow systems invariably utilize molecules composed of light-absorbing conjugated planar configurations, which are responsible for these molecules' characteristic pigmentation properties as well as their unique oxidation-reduction properties (209, 481). (See Figure 1.)

Major photoactive molecules include: 1) the flavins such as FAD and FMN, 2) the tetrapyrroles (hemes, cytochromes, chlorophyll, vitamin B-12, catalases, peroxidases, etc.); 3) the isopentenoid lipids (carotenoid visual pigments, vitamins A,D,E, and K, cholesterol, steroids, etc.); 4) the purines and pteridines; 5) the phenolic → quinoid polymers (essentially melanin), and 6) various mixed derivatives or combinations such as the strategic molecule ubiquinone (which contains both a quinone ring and an isopentenoid chain) and lipofuscin (which may contain varying amounts of melanin, lipid pigments, and tetrapyrrole pigments). The tetrapyrroles (33, 361) and the isopentenoid polymers[1] (437, 382) have received considerable attention in the scientific literature, while melanin, and its functional significance, has been relatively neglected, for reasons noted above.

Of particular interest to this discussion are the photon-absorbing capabilities of melanin and the pigment molecules. Photons, packaged in discrete invariant "units" (light quanta or more precisely "quanta of action"), necessarily participate in all atomic and molecular interactions and changes in the physical universe.[2] The photon, as the

[1] The isopentenoid (isoprenoid) polymers are true polymers composed of a repeating 5-carbon monomeric unit which can be complexly varied in detail. See Nes and McKean (437, 382). Such polymers are postulated to interact closely with melanin through mechanisms that have yet to be determined.

[2] Arthur M. Young, in his comprehensive evolutionary process theory, outlined in The Reflexive Universe (756), has assigned a primary role to light quanta in the ongoing thrust of evolution. More specifically, Young's concern with the light-molecular interface has complemented this analysis of the functional significance of (neuro)melanin as an omnipresent organic information-processing molecule. Current physics/

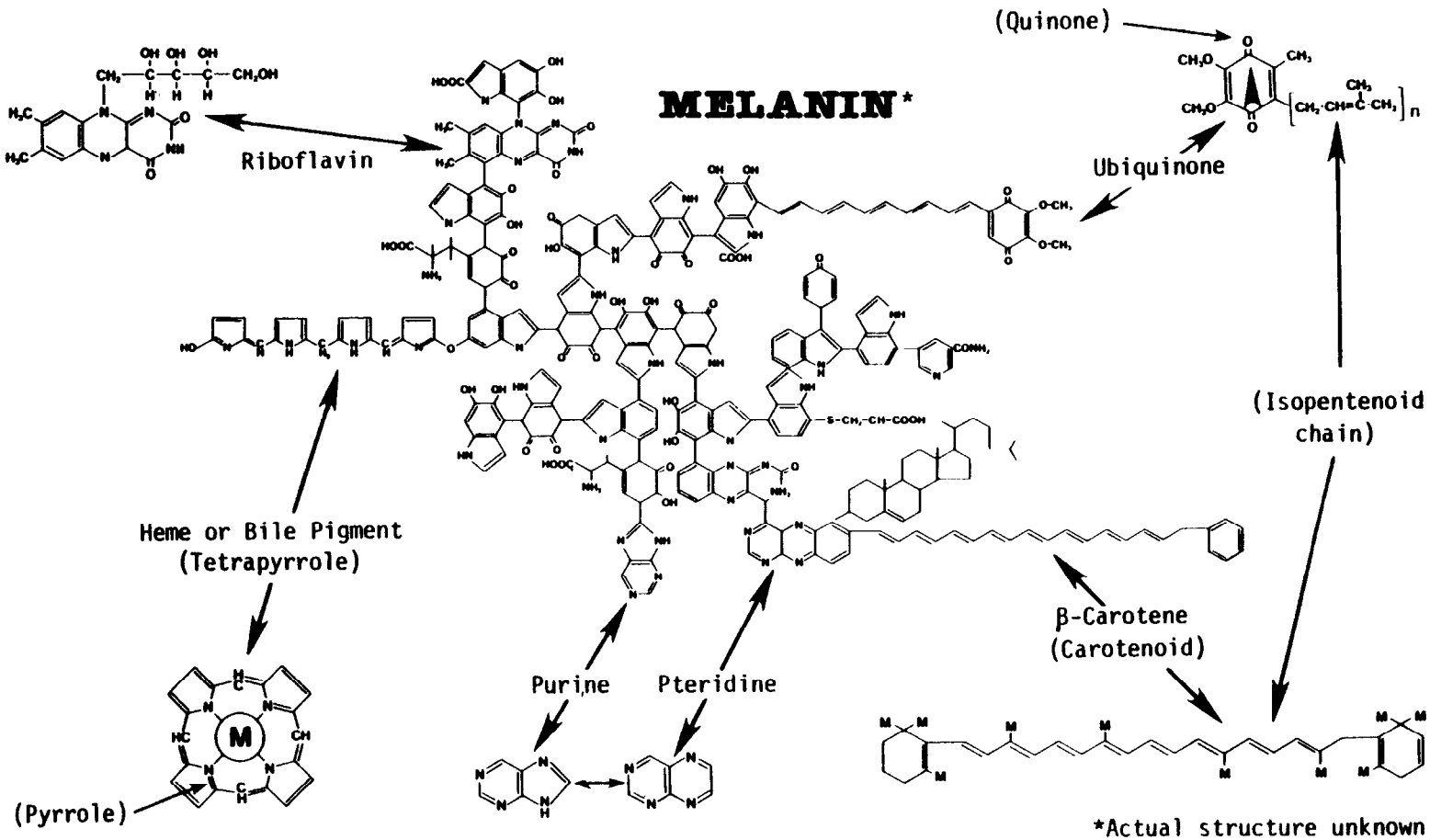

Fig. 1 Pigment Molecules (Some Abbreviated Examples)

primary "particle" of the electromagnetic field, has special relevance to living systems, as evidenced by the growing literature on electromagnetic fields and life (504, 5, 6, 7, 8, 9, 37, 38, 39, 282, 283, 407, 67).

In addition to their photon-absorbing properties, the photoactive pigment molecules all are located in areas of high functional metabolic activity. They are concentrated, for example, within the energy-producing-and-storing, oxidation-reduction pathways of the mitochondrial membranes. These pigment molecules (particularly melanin) are also generally found at all sites of free-radical production (wherever oxidation-reduction occurs and especially at sites of cellular and tissue damage), where they may function as free radical scavengers (157, 516, 424). Such molecules are also strategically located in regions of photic and acoustic activity (e.g. the skin, the inner ear, the iris and retinal pigment epithelium of the eye, etc.).

Among those researchers who have recognized the significance of melanin, McGinness and Proctor emphasize (416) that melanin is black because its absorbed light is not re-radiated, but is instead captured and converted into rotational and vibrational energy (i.e. heat). The relatively "featureless" spectrum of melanin, from the far ultraviolet spectrum through the visible and into the infra-red spectrum, means that such photon capture is available for any photon wavelength (and energy) between these spectral limits. Hence, melanin can be thought of as "black" over a larger range than just the visible spectrum.

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consciousness studies (712, 142, 62, 63, 510, 54, 202, 752, 207, 721, 61, 165, 505, 32) have opened up exciting new theoretical possibilities in regard to the "mind-brain" problem and meta-physics in general. In particular, these studies have emphasized the seemingly paradoxical "non-local" properties of the (massless, chargeless, spaceless, timeless) "quantum of action" (which, by a process called "pair creation", can actually create particles such as the proton and antiproton or the electron and positron).

For example, in a recent Nobel conference on "Mind in Nature," noted physicist J.A. Wheeler, in summarizing the mysterious properties of the photon in the famous split-beam experiment, succinctly states: "In other words, an elementary quantum phenomena is extended in space and time. It is non-localizable. Above all, it is untouchable, impenetrable, impalpable. For all we know, it may someday turn out to be the fundamental building unit of all that is, more basic even than particles or fields of force or space and time themselves" (753)

The epistemological and ontological priority of the "quantum of action" (the "non-local" unit of purposive action or teleological thrust) is already recognized and developed in Young's Theory of Evolutionary Process (and its more recent extensions in the life sciences). Furthermore, Young's process paradigm satisfactorily unites the teachings of the ancients (i.e., myths, religions, symbol systems) with the gamut of current transdisciplinary science and offers a solution not only to the ancient and contemporary philosophical dilemma of consciousness per se (756, 757, 758, 759, 760, 761) but also to the "interface" between consciousness, quantum physics, and biological systems (32).

Melanin, McGinness and Proctor suggest (416, 418, 513), provides the cell a means for converting excited-state or free radical energy into vibrational energy or heat, via photon-(electron)-phonon conversion processes.[1] The central hypothesis of this paper is that melanin effectively directs such transformed energy to neighboring molecules for metabolic organization. Such closely interacting molecules as, for example, 1) the metal ions, which are abundantly bound to (and released from) melanin, 2) the purines and pteridines, which may either bind with or interconvert to melanin, and 3) the various isopentenoids, omnipresent polymers with unusual organizational properties, may all perform at least some of their varied and coordinated functions by means of their effective assimilation of the transformed energy selectively released from melanin. This "trigger-like" release of energy[2] from

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[1] See Figure 2. Photons absorbed by melanin "kick" electrons into higher orbital or excited energy states. While the excited electrons can drop back down to a lower energy state (emitting photons in the process), in melanin's case, the excited state energy can instead be converted into molecular rotation or vibration (i.e. heat). McGinness's group has also presented evidence that melanin conversely may convert vibrational input (e.g. ultrasound) into excited-state energy. This group has provided a model which consolidates the observations that the cytoprotective and cytotoxic action of melanin involves both the photon-(electron)-phonon interaction and the oxidation-reduction capacity of the melanosome. Melanin contains both disassociable electrons and protons which can communication with the biological environment (493, 418). McGinness's group emphasizes that a redistribution of charge in the melanin structure (due to the absorption of photons, the binding of various exogenous drugs or endogenous molecules, pH change, etc.) will involve the surrounding bio-molecules. Such functional or structural modification of melanin can alter oxidation-reduction reactions, change the free radical-ESR signal, and modify electronic events (418, 298). These changes, in turn, may modify (neuro)melanin's precise regulation of the neuroendocrine system, enzymatic covalent modifications, etc.

[2] In his studies of the ontological significance of the photonic "quantum of action", Young has noted that the measure formula for action--["action" includes impulse, insight, decision]--is ML^2/T (M=mass, L=length/position, T=time). Action/Planck's constant/the "counted whole" comes in constant, invariant units; this "counted whole" of action contains and is greater than the "measured parts" (such as energy and time or momentum and position) that are derived from it, as consistent with Heisenberg's uncertainty principle (756, 761). Furthermore, Young points out: a) that angular momentum (i.e. rotation) has the same measure formula (ML^2/T) as action; b) that rotation per se, like action, is an absolute or invariant; c) that rotations or rhythmic cycles are omnipresent phenomena--(e.g. the unit spin of the photon, the angular momentum of particles, the resonating rings of cyclic molecules, the organizational rotation of the cellular centriole, the direct current of living organisms, the spin of the earth, the ultradian/circadian/lunar/solar rhythms, the angular momentum of the solar systems and the galaxies, and the recently discovered angular momentum of

melanin for activation of strategic molecules may be both 1) direct, such as with energy transfer from melanin to the resonating rings of contiguously associated molecules, and 2) indirect, such as emitting a piezoelectric signal throughout the cell via the centrosomal-microtubular apparatus (69, 573, 330).

Since melanin responds with conductivity changes to electric and acoustic fields as well as direct photic stimulation (416, 418, 169, 170, 668), it may use similar conversion mechanisms in processing all three sources of energy input. (See Figure 2.) Such a photon-(electron)-phonon coupling mechanism might explain the presence of melanin pigmentation in areas of the body not directly exposed to ambient light, such as the brainstem and inner ear.

THE SYNTHESIS AND STRUCTURE OF MELANIN

The most interesting of the photoactive pigment molecules, melanin has the most complex structure. Edelstein notes that "melanin" is frequently used as a catch-all term for all biological golden-brown to black organic substances that are polycyclic polymers of high molecular weight, insoluble in almost all solvents, and resistant to all but the severest acid or base digestion techniques (157). Although the exact synthesis and structure of melanin remain unknown because of its resistance to analysis, the most commonly proposed general mechanism for its formation is by phenolic oxidation into variations of quinoid structures which then autopolymerize (self-organize) into melanin (539, 514, 157, 660, 341, 705, 479). A wide range of pigments which closely interact with and/or interconvert to melanin incorporate these quinoid structures, including benzoquinones, napthoquinones, anthraquinones, polycyclic quinones, flavins, flavonoids, indigoids, phenoxazones, and especially the catechols, indoles, purines, and pteridines (539, 273, 194, 692, 693, 451). (Other ring structures, such as the pyrroles (705), have also been found in melanin.)

Basic Types of Melanin

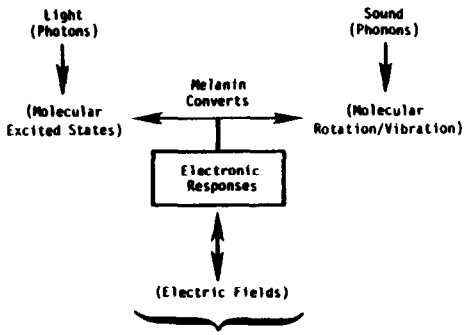
The eumelanins (black-brown) are generally considered primarily to be polymers of the oxidation products of the amino acid tyrosine which contain substantial amounts of indole (539, 514). The significance of tyrosine as the primary building block of eumelanin is that the three major catecholamine neurotransmitters--dopamine, norepinephrine (noradrenalin), and epinephrine (adrenalin)--all immediately

the universe itself); d) that rotational phase-timing is a key factor in the coordination of hierarchical systems (758, 756, 757).

(Neuro)melanin's abundant photon-capturing, resonating rings may have evolved phylogenetically and ontogenetically as a trigger-like molecular "phase-timing device," and this mechanism may account for the precision of its organizational capacities (such as precisely-timed neuroendocrine activation). See Winfree for a further explanation of the dynamics and significance of phase-timing (746, 747, 365, 374, 102, 572).

1. PHOTON-(ELECTRON)-PHONON CONVERSIONS

Melanin can convert the excited energy states of electrons (excited through photon absorption) into rotational and vibrational energy (i.e., heat). Conversely melanin may convert sound input into excited state energy. (A phonon is defined as a unit of vibrational or rotational energy, a quantum of an acoustical mode of thermal vibration.) Melanin responds to electric fields as well.



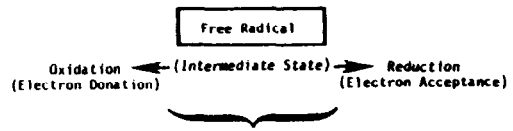
Photon-(electron)-phonon conversions involved in production of:

Free radicals,
Heat,
Semiconductive responses,
Diverse forms of energy output directed to trigger and sustain various metabolic/organizational processes.

MELANIN

2. FREE RADICAL-REDOX MECHANISMS

Melanin scavenges, binds, and releases free radicals (molecules with highly reactive unpaired electrons). Melanin can also produce free radicals through constituents like quinones/semiquinones.



Redox mechanisms necessary for:

Ionization
Covalent modifications
Cellular energy storage and release
etc.

3. ION EXCHANGE MECHANISMS

Melanin, through polyanionic attraction, binds and releases the full range of metal ions.

Metal ion binding release pivotally involved in:

Enzyme activation/deactivation
Peptide activation/deactivation
Cellular membrane regulation
Secretory processes,
etc.

Fig. 2 Basic Mechanisms of Melanin Regulation

derive from tyrosine. Each of these catecholamine neurotransmitters polymerizes into melanin, both naturally and artificially (194, 341). The other major monoamine neurotransmitter (in addition to these three catecholamines) is the indoleamine, serotonin (derived from the amino acid tryptophan), which polymerizes to melanin via NADPH-dependent mechanisms (692). The pineal hormone melatonin and its derivatives, such as 6-hydroxymelatonin (an indoleamine), also can polymerize into melanin (693). To summarize, various catecholamines and indoleamines of profound physiological neuroendocrine significance, are precursors of melanin.(See Figure 3.)

The diversely colored phaeomelanins (red, yellow, green, blue, violet, etc.) are melanins which have been modified primarily by the introduction of sulfur (via transsulfuration by thiols such as cysteine and gluthathione) into strategic locations of the melanin structure (539, 514). In fact, melanin and the thiol molecules closely and significantly interact (514, 106).

Melanin thus either incorporates or could incorporate a wide variety of ringed molecular constituents during its synthesis as well as during its diverse functional states. Its apparent ability to reversibly bind and release other key functional molecules (such as the purines and pteridines, riboflavin, etc.) is a significant mechanism for melanin's proposed cellular organizational control and will be further developed in this paper. Regardless of the specific constituents it may incorporate, melanin may be defined as a heterogeneous polycyclic polymer containing several types of important bond linkages (e.g. carbon-carbon, carbon-nitrogen, peroxide, ether, etc. (390)). Further insights into the structure and function of melanin appear in reviews by Riley, Edelstein, Lerner, Sealy et al, and Altschule and Hegedus (539, 157, 341, 15, 16, 479).

Mechanisms for Melanin Synthesis

The in vivo synthesis of melanin from the multiple constituents just noted largely remains a mystery. Closely examining the possible mechanisms for forming vertebrate melanin is important, however, for several reasons:

1) If (neuro)melanin is the organizing molecule of living systems, greater understanding of where and how it is produced in the body may further illuminate its functioning.

2) Rather than (neuro)melanin being formed by a single uniform enzyme, tyrosinase, as is commonly assumed, evidence points to multiple pathways for its synthesis. The richer variety of synthetic mechanisms both deepens the melanin mystery and provides clues to possible answers to it.

3) The most important reason for reviewing melanogenesis, however, is that a closer examination of its synthetic mechanisms suggests that (neuro)melanin may actually be capable of self-synthesis.

(Neuro)melanin's potentially diverse quantum states and its numerous organizational properties, together with its potential self-organizational (autopoetic) capacity (particularly within strategic bio-organizational regions, such as the diverse sites of neuroendocrine

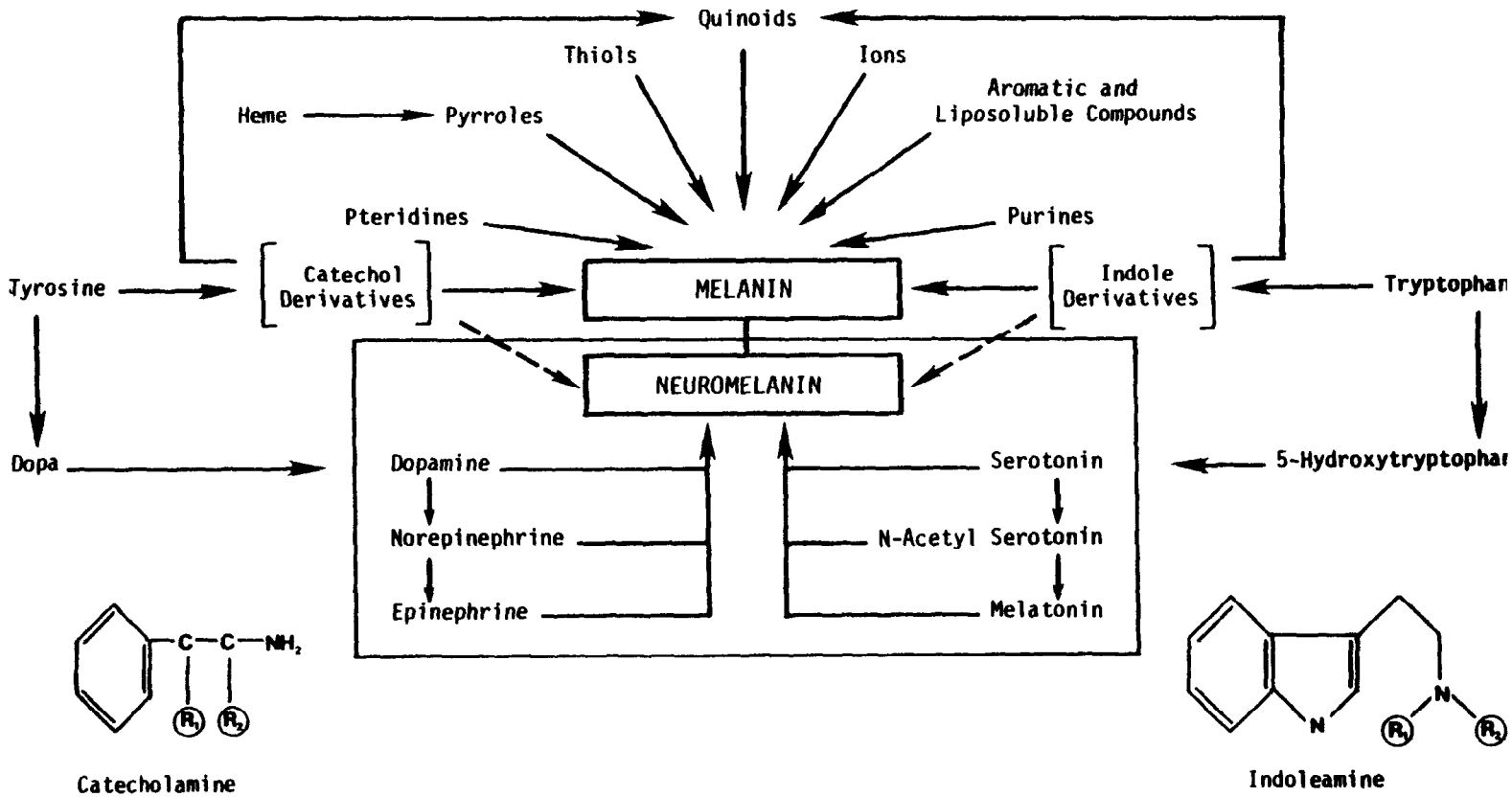


Fig. 3 Major Constituents of Melanin/Neuromelanin

functioning) could offer life scientists basic answers to the long-sought mysteries of "life", "mind", and bio-organization in general. In other words, elucidating (neuro)melanin's proposed in vivo self-synthesis (and related autopoetic capacities) in particular could further clarify self-organizational systems in general.[1] With the potential significance of such self-synthesis in mind, let us look at some of the synthetic mechanisms most frequently proposed for the construction of the melanin polymer for further understanding of its functioning.

Most, if not all, of the neural crest-derived melanin such as that found in the skin, is thought to be formed via the enigmatic copper-containing enzyme tyrosinase (228, 188, 724, 514, 539). Most (but not all) current melanin researchers think this enzyme is capable of catalyzing two reactions:

1) the rate-limiting hydroxylation of tyrosine to form dihydroxyphenylalanine (DOPA), and
2) the dehydrogenation (oxidation) of a series of diphenols, including DOPA, cyclo-DOPA, and dihydroxyindole.

However, several significant findings make this simple version of the tyrosinase-mediated synthesis of melanin questionable:
1) Different post-translational control systems activate the different melanogenic systems which tyrosinase supposedly mediates, as Eppig and Hearing point out[2] (162). These various post-translational modifications may have significant implications for the self-synthesis of melanin, because melanin itself may regulate such covalent modifications.
2) Pawalek et al (479), studying mouse melanoma cells, have isolated 3 factors which appear to control melanin synthesis in these cells: a) dopachrome conversion factor, which accelerates the conversion of dopachrome to 5,6-dihydroxyindole; b) 5,6-dihydroxindole conversion factor, which catalyzes the conversion of 5,6-dihydroxyindole to melanin and is active only when cells are exposed to melanotropin (MSH); and c) 5,6-dihydroxyindole blocking factor, which restricts melanogenesis of 5,6-dihydroxyindole. This third factor appears to protect cells from the cytotoxic effects of melanin precursors, and it is removed when the cells are exposed to MSH. These researchers note that the discovery of these 3 factors indicates that regulation of the melanin biosynthetic pathway is more complex than previously

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[1] Self-organizational systems offer potential new insights into bio-organization, and such systems have been extensively reviewed by Varela, Maturana, Prigogine, Katchalsky, Jantsch, Eigen, Schuster, Haken, Zeleny, etc. (706, 707, 511, 295, 285, 220, 766, 767, 718, 438). Mathematical and quantum chemical speculations/interpretations of (neuro)melanin's proposed quantum-linked self-synthetic/organizational abilities are beyond the scope of this article, however.

[2] For example, Riley notes that glycosylation may be a significant covalent modification involved in tyrosinase functioning (539).

supposed. The molecular structure of these factors and the means for regulating them remain to be illuminated, as does the mechanism(s) for inactivating tyrosinase (585, 681).

3) Okun claims that the supposedly multi-functional enzyme "tyrosinase" is actually a dopa oxidase unable to hydroxylate tyrosine "under any conditions" (497, 232, 595). Okun's group has steadfastly maintained for several years that the heme-containing enzyme peroxidase (an apparently common unrecognized "contaminant" in melanogenic studies) is the actual enzyme which hydroxylates tyrosine, with dopa acting as a cofactor. Many studies by Okun's group with such cells as leukocytes and mast cells, etc. strongly suggest that peroxidase can form melanin (456, 458, 459, 460, 461). Nevertheless, the "tyrosinase vs peroxidase" debate regarding the hydroxylation of tyrosine has yet to be resolved.

Melanin could regulate peroxidase, and hence its own synthesis, in several ways. The photon-(electron)-phonon, free radical-redox, and ion exchange properties of melanin may all help regulate the heme core of peroxidase. Melanin's ion exchange capacities (584, 56), for example, may be involved in synthesizing and activating peroxidase. Melanin may control the pivotal metal ion within the heme core of peroxidase (which is crucial for its functioning). Furthermore, metal ions are known to regulate the synthetic metabolism of heme (361), and thus the core of peroxidase. Melanin could very well selectively provide these metal ions (56). In addition, a close connection exists between melanin and the sulfhydryl groups of glutathione (514, 106), and between the sulfhydryl groups of glutathione and the ability of metal ions to affect the synthesis of the enzymes which produce heme (361). Several other potential mechanisms for melanin's control of peroxidase are also available, but what about the availability of peroxide?

The key molecule peroxide and its frequent associates, the oxygen free radicals, are apparently prevalent molecules. These active molecules appear to "fuel" the autopolymerization of melanin (168, 567, 584). Hydrogen peroxide may be provided by monoamine oxidase (MAO), nicotinamideadenine dinucleotide (NADH) oxidase, or flavoprotein enzyme reactions (705), all of which have apparent functional associations with melanin. (Both peroxide and peroxidase are found within areas of high neuromelanin content in the brain (705, 604)).

4) In addition to tyrosinase and peroxidase, another enzyme, monoamine oxidase (MAO), could be a means for synthesizing (neuro)-melanin (705). MAO oxidatively deaminates various catecholamines and indoleamines into their respective aldehydes, which can then polymerize and form melanins in vitro. Advanced vertebrate brain mitochondrial preparations containing MAO have clearly been demonstrated to synthesize melanin. However, most researchers feel that MAO does not provide the major means for (neuro)melanin synthesis since MAO is a mitochondrial enzyme whereas (neuro)melanin appears to be synthesized primarily in lysosomes/melanosomes. On the other hand, the mitochondria may simply synthesize smaller amounts of functional melanin than the melanosomes. The intriguing connections between the mitochondria and melanin deserve further careful study.

5) Albinos[1] which supposedly have a tyrosinase deficiency and thus deficient eye and skin melanin, nevertheless have a normal amount of melanin (neuromelanin) within their brain (178). All attempts to detect "tyrosinase" within the brain have failed (705). The absence of tyrosinase, along with a normal amount of brain melanin in albinos, has effectively invalidated the previous assumption that tyrosinase alone was responsible for the synthesis of melanin.

6) Metals such as ferric and cupric ions oxidize catechol derivatives (in the presence of hydrogen peroxide), leading to the formation of melanins. Partially metabolized heme compounds also can oxidize catechols. These nonenzymatic reactions are called pseudoperoxidation and the agents are called pseudoperoxidases (705).

Oster and Oster (467) have shown that copper ions free in solution may duplicate the oxidative activity of tyrosinase (which contains copper as its active component). Their experiments show that a necessary condition for oxidizing tyrosine is that cupric ions (oxidized copper ions) be reduced to cuprous ions. The cuprous ions, in turn, are readily oxidized by molecular oxygen, producing hydroxyl free radicals, which can then immediately react with tyrosine to produce dopachrome, leading to autopolymerization and melanin formation. Melanin, which contains an abundance of copper ions (125, 508, 584, 328), as well as a highly functional redox system (584, 390, 186, 187) could be the electron donor (for reducing cupric to cuprous ions) necessary for hydroxyl radical formation. In addition, either hydrogen peroxide or DOPA could provide this latter function (457). Melanin may not only enhance the hydroxyl radical oxidation of tyrosine, but (by its hydroxyl radical-scavenging properties) it may also inhibit the hydroxyl radical oxidation of tyrosine. The above findings suggest that (neuro)-melanin's free radical, redox, and ion exchange mechanisms may be intimately involved in regulating its own synthesis.

Whereas Okun postulates that melanogenesis requires two separate enzymes, a peroxidase for oxidizing tyrosine to DOPA, and a DOPA oxidase for subsequently oxidizing DOPA, Oster and Oster suggest that a single copper-containing enzyme would serve both these functions. They conclude that copper ions[2] simulate not only tyrosinase activity but also the activity of peroxidase, of DOPA oxidase, and of catalase. In

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[1] The variable diminished pigment formation in both albinism and vitiligo (and the associated brainstem, neuroendocrine, hematopoetic and autoimmune disorders) remains a complex mystery, which has been only partially resolved (731, 340, 748, 119, 180, 50, 203, 246, 408, 57, 12).

[2] The APUD or diffuse neuroendocrine system, suggested in this paper to be regulated by melanin, produces both monoamine neurotransmitters and peptide hormones. Among the latter molecules are the opiate hormones (the endorphins and enkephalins). The reader should note here that opiate hormone receptor function may be modulated via an oxidation-reduction mechanism involving simply a complex of oxidized glutathione and copper ions (368). Presence of melanin (and lipofuscin) within

fact, an enzyme may not be required at all for synthesizing melanin, as melanin itself contains both the copper ions and the free radical-redox properties necessary for the non-enzymatic synthesis of melanin. Rodgers and Curzon (551) found no evidence of enzymatic activity during the uptake of C^{14}-labelled melanin precursors by human brain in vitro and concluded that brain melanin synthesis may be largely a non-enzymatic activity.

Possible Self-directed Synthesis of Neuromelanin

Though the regulatory mechanisms for tyrosinase (or peroxidase/pseudoperoxidase)-mediated peripheral melanogenesis remain unresolved, the mechanisms for neuromelanin formation remain even further from resolution. Though tyrosinase is apparently not involved in neuromelanin formation, several conceivable mechanisms for neuromelanin's self-synthesis have been pointed out above. Further research illuminating neuromelanin's potential self synthesis/organization may complement the mechanisms just mentioned and focus our attention on neuromelanin's dynamic role in the "mind-brain" problem.

First, the location of neuromelanin in different regions of the brain correlates with neuromelanin's predominant monoaminergic composition. For example, dopamine is the major constituent of the neuromelanin in the heavily melanized substantia nigra of the midbrain (130); norepinephrine is the major constituent of the neuromelanin in the locus coeruleus of the pons (360, 580); and serotonin may soon be shown to be the major constituent of the neuromelanin in the diffuse brainstem raphe system (692, 73). The variable molecular combinations (ratios) of monoamine neurotransmitter precursors constituting the functionally distinct neuromelanin molecules throughout the interconnected brainstem melanin system remain to be determined, but it is likely that each neuromelanin molecule (like each person's "mind") is structurally and functionally unique. Furthermore, the abundant pigment, lipofuscin, is variably concentrated through the brain (73, 74) and contains significant amounts of melanin. The intriguing suggestion that lipofuscin is located throughout the brain as a functional storage depository capable of interconversion to neuromelanin (568) has yet to be explored. (The possibility that neuropeptides involved in emotion, motivation, and memory may function as a result of their interaction with neuromelanin/lipofuscin will be explored in the companion paper (32)).

Second, the rate-limiting enzyme in the synthesis of all the catecholamines (dopamine, norepinephrine, and epinephrine) is tyrosine hydroxylase (105, 41, 430); whereas, the rate-limiting enzyme for indoleamine (serotonin) synthesis is tryptophan hydroxylase (105, 41, 430). Both of these rate-limiting enzymes essential for the monoamine

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the regions of opiate hormone receptor binding and melanin's intimate relationship with both glutathione and copper ions suggest a potentially simple and effective means for melanin's proposed regulation of at least one type of peptide hormone function.

neurotransmitters (which are the basic "monomers" of the neuromelanin polymer) are controlled via the pteridine cofactor, tetrahydrobiopterin (41, 430, 179, 354). (Pteridine and its intimate relationship with melanin will be considered in more detail subsequently.)

Third, tyrosine hydroxylase, and hence catecholamine synthesis, has recently been shown in vitro to be activated by melanin itself (428), via melanin's regulation of the pteridine cofactor (and possibly via melanin's polyanionic properties). This discovery further opens the door for considering melanin as a self-organizing (autopoetic) polymer/system (661, 365, 374, 553, 353, 94, 190, 518, 4, 399, 652, 738, 430) similar to other "cooperative" or "nonequilibrium" systems (767, 285).

If a similar control by melanin of catecholamine neurotransmitter synthesis can be demonstrated in vivo, as it has in vitro, then neuromelanin may very well: 1) play an essential role in regulating the metabolism of the brain's catecholamine (as well as possibly the indoleamine) neurotransmitters (102, 365, 374), with their well-known physico-mental regulatory functions, and 2) regulate its own synthetic autopolymerization, by mechanisms such as those previously described. (See Figure 4.) In addition to its proposed self-formation (by internal molecular rearrangements and oxidative polymerization from the monoamine neurotransmitters), neuromelanin's in vivo autopolymerization and internal self-organization may directly correlate with the evolving embryonic and developmental maturation of certain strategically functional brain systems.[1] Some of these possibilities will be explored in

[1] One such speculation potentially connecting neuromelanin and mental maturation concerns eye movements (419, 528, 662, 644). Stevens has presented studies correlating rapid eye movements (R.E.M.) and blink rates with photic modulation of predominantly red wavelength light (filtered through the closed eyelids) which is transmitted from the ganglion cells of the lateral retina, via the accessory optic tract, to a nucleus between the highly melanized substantia nigra and ventral tegmental area of the midbrain (644, 643, 642, 762, 116, 662). She proposes: 1) that lateral eye movements (both REM's and blinking) participate in linking the environmental light/dark cycle to the circadian excitability of the melanized mesolimbic catecholamine system (644, 662, 65, 762) and 2) that abnormalities of lateral eye movements (which are apparently associated with schizophrenia and bipolar affective disorders) suggest a fundamental disturbance in the regulation of this ancient light-modulated (and melanin-laden) neuroendocrine axis located at the top of the brainstem (291, 224, 764, 245, 357, 227, 122, 608, 572, 495, 427, 252, 662). This melanized regulatory region is at the cross-roads of the nigrostriatal and mesolimbic dopaminergic systems, a region involved not only in schizophrenia and manic-depression but also in the integration of sensory input, motor output, emotion, motivation, eye movements, etc. (639, 640, 645, 253, 729). There is accumulating evidence that a periodic and/or phasic organization is involved with eye movements (331, 635, 314, 315, 126, 666, 102, 365, 374). The appearance of REM abnormalities in infants has been recently shown to be a good early indicator of abnormalities in the infant's

the companion paper, "Melanin and the Mind-Brain Problem" (32).

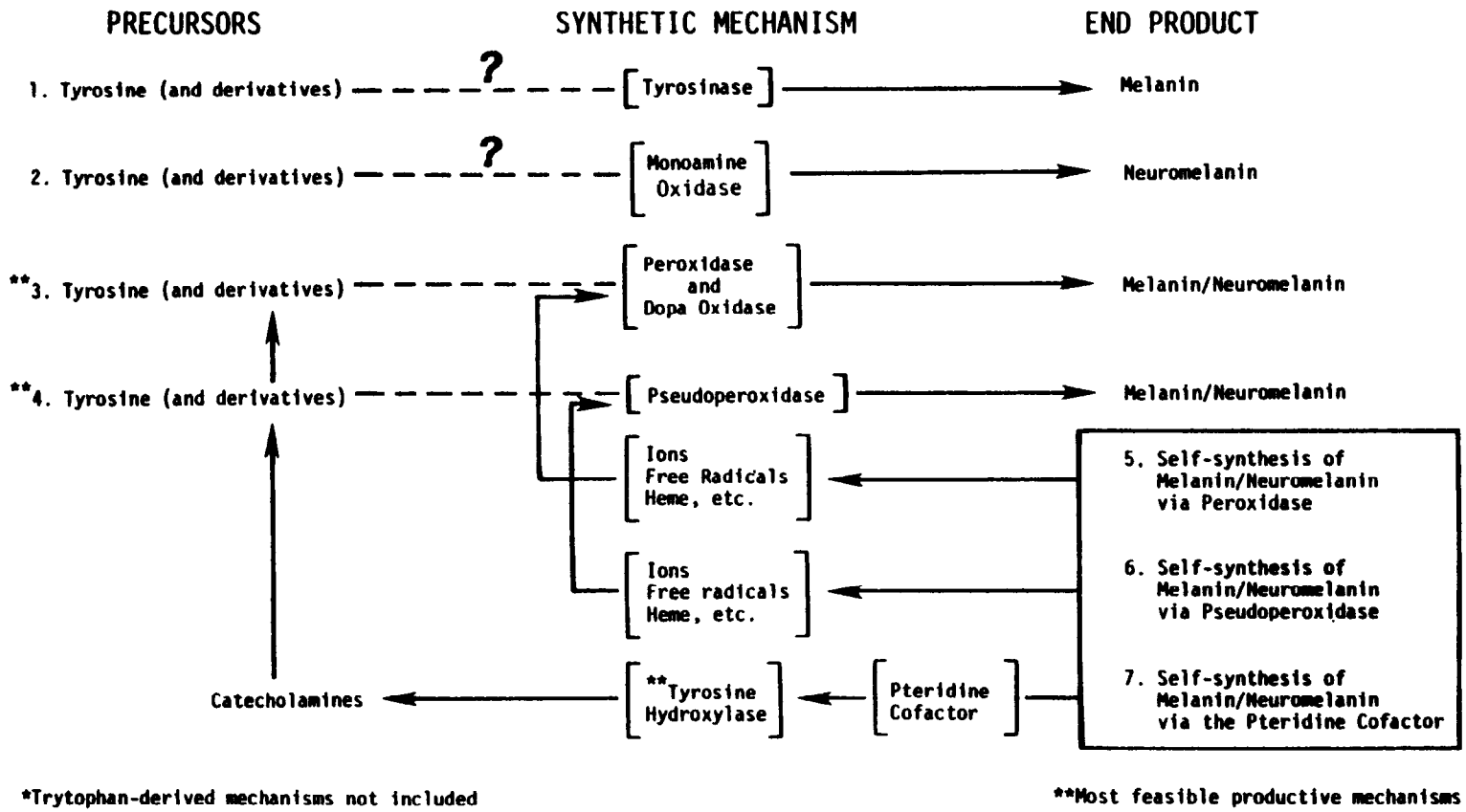
In summary, we suggest that neuromelanin is a self-organizing biopolymer which can organize, as well as derive itself from, the monoamine neurotransmitters. Since neuromelanin is a heterogeneous polymer with the potential to autopolymerize and internally rearrange its catecholamine and indoleamine neurotransmitter constituents to form unique functional configurations of neuromelanin (as well as to synthesize and release these neurotransmitters discriminately throughout the brain),[1] we may tentatively hypothesize that each individual's unique mental capacity (i.e. one's "mind") is directly correlated with his/her unique melanin-monoamine configurations and interconnections. Melanin's other organizational properties certainly tend to support such a significant organizational role. The next sections of this paper will examine these properties.

future mind/brain maturation (36). The timing of gross accumulation of human brainstem melanin appears to correlate with mental maturation/organization, increasing at age 3-4 and usually decreasing in old age, as does memory (366, 501, 35). In addition, neuromelanin is located at the brain site of: 1) control of eye movements, 2) input of modulated impulses via the accessory optic tract from the lateral retina, as well as from the cortex, 3) integration of sensation, movement, emotion, memory, motivation, etc. (64, 580, 645, 48, 35, 526, 565, 32). It follows that eye movements per se, whether they occur during blinking, dreaming, thinking, memory retrieval, etc. (even with blindness) may provide a self organizational means for the qualitative (and quantitative)maturation of both one's neuromelanin system and one's "mental" organizational/integration (122, 419, 528, 526, 662).

A considerable amount of research indicates that dreaming (and its concomitant REM's) is involved in establishing long term memory (470, 288, 59, 60, 61, 160, 332, 413, 419, 217). The slow-wave sleep preceding REM sleep triggers growth hormone release, protein synthesis, and other factors involved in glycocalyx/cell surface dynamics, etc. (32, 155, 663, 638, 385, 732, 594, 749, 566, 201, 196). Melatonin, as the proposed releasing agent for pineal vasotocin and perhaps pituitary vasopressin (which is involved in memory consolidation), may be involved in these functions (480, 337, 132, 92, 53, 478, 557, 384). Furthermore, not only is neuromelanin potentially related to eye movements and mental organization/memory consolidation, but neuromelanin dynamics have been proposed to explain the direct correlation between iris pigmentation and reaction time (322, 222, 173). Such correlations between neuromelanin and physico-mental organization will be further developed in the companion paper (32).

[1] The companion paper, "Melanin and the Mind-Brain Problem" (32) will examine in more depth the neuroanatomical and functional significance of the brainstem melanin system and its strategic monoaminergic connections. These highly significant monoamine neurotransmitters originate in the heavily melanized neurons of the brainstem melanin system, are released throughout the brain from the varicosities of these ubiquitously arborizing non-myelinated brainstem axonal projections as well as from their dendrites, and apparently modulate the diffuse neuroglial system and its organizational direct current.

Four currently hypothesized mechanisms for melanin/neuromelanin. Also shown are three hypothesized mechanisms for self-synthesis of melanin/neuromelanin developed in this paper.



*Trytophan-derived mechanisms not included

**Most feasible productive mechanisms

Fig. 4 Synthesis of Tyrosine-Derived* Melanin/Neuromelanin

ESTABLISHED PROPERTIES OF MELANIN

A list of some of the more significant established properties of melanin follows (see Table 1):

1) Melanin is an ancient pigment which was present at the inception of "life" and which appears to have a nearly ubiquitous distribution within and among living organisms (568, 390, 724, 514).

2) Melanin is a heterogeneous polymer, composed of varying amounts of different ringed precursors (primarily tyrosine and tyroptophan derivatives), which maintains ionic, covalent, (and probably metallic) bonding arrangements, thus providing, for each individual melanin molecule, a potential uniqueness (390, 584, 481, 660, 157).

3) Brain melanin (neuromelanin) increases with ascent up the phylogenetic ladder, reaching a peak concentration in man (64, 568). Moreover, it is invariably found in strategic highly functional loci of the brain (64, 568, 35, 580, 639, 645).

4) Melanin exhibits an extreme stability, both in vivo and in vitro (481, 157, 292).

5) Melanin is an exceptional cation exchange polymer, able to bind and release the gamut of metal ions (584, 508, 328, 125, 398, 157).

6) Melanin exhibits extraordinary binding properties for aromatic and lipid-soluble compounds (564, 348, 349, 350, 327, 451, 678, 31, 476, 629).

7) Melanin continuously produces functionally active free radicals and, in addition, is a scavenger of free radicals (584, 157, 168, 567).

8) Melanin is a remarkable oxidation-reduction polymer, able to simultaneously oxidize one substance while reducing another (186, 187, 584, 390).

9) Melanin has been shown in vitro to have semi-conductive properties and to respond to photic, acoustic, and electrical stimulation (415, 169, 170, 512, 507).

10) Melanin is synthesized in leukocytes and mast cells (456, 457, 458, 459, 724) and therefore may be transported by the bloodstream in a hormone-like fashion throughout the body, having variable access to every cell as needed (723).

A brief expansion on these established properties should provide a clearer picture of melanin's potential role in living organisms.

1) Melanin is the most primitive and universal pigment in living organisms, e.g. being abundantly found in primitive organisms such as fungi as well as advanced primates (568, 390). Furthermore, within each living organism, melanin appears to be located in major functional sites. For example, in vertebrates, melanin is not only present in the skin, eyes, ears, central and peripheral nervous systems, and the diffuse neuroendocrine loci (e.g. pineal, pituitary, thyroid, thymus, parathy-

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The neuromelanin-(monoamine)-neuroglia system with its electrotonic (analog) trophic/supportive, and neuroendocrine-regulating properties is proposed to organize and control synaptic (graded potential) dynamics and consequently the activation of neuronal (digital) action potentials.

ESTABLISHED PROPERTIES

1. The most primitive and universal pigment in living organisms, present at the inception of life, and having a potentially ubiquitous distribution across the plant and animal kingdoms.
2. A heterogeneous polymer with multiple constituents and types of bonds.
3. Neuromelanin increases with phylogenetic ascent, reaching a peak in man.
4. Extreme *in vitro* and *in vivo* stability and highly resistant to experimental analysis.
5. Functions as a remarkable cation exchange polymer.
6. Exhibits extraordinary binding of aromatic and lipid-soluble compounds.
7. Possesses exceptional oxidation-reduction properties.
8. Scavenges, releases, converts, and produces free radicals and maintains a stable free radical signal.
9. Has semiconductive properties with physiological responses to photic, acoustic, and electrical stimulation.
10. Synthesized in leukocytes and mast cells and transported throughout the body in hormone-like fashion.

PROPOSED PROPERTIES

1. As an amorphous semiconductor, may regulate neuronal firing.
2. May function as an organic superconductor at room temperature.
3. As a melanosome, may store and release energy in a manner similar to mitochondria.
4. May direct embryological tissue differentiation as well as tissue regeneration.
5. May direct mast cell functioning.
6. May direct homeostatic regulation of neuroendocrine functioning, immune response, tissue repair/regeneration, and the autonomic nervous system.
7. May play both a cytoprotective and a cytotoxic role through its photon-phonon and free radical properties and its strong binding of lipid-soluble molecules.
8. May regulate enzyme and membrane activity via its control of metal ions functioning as cofactors or activators.
9. May regulate the various vitamins and cofactors involved in metabolism.

Table I Properties of Melanin

roid, adrenal, carotid body, etc.) but is also abundantly present in the viscera, including the heart, the liver, the arteries, the muscles, the gastrointestinal tract, the gonads, etc. (724, 16, 333, 334, 335, 336). To reiterate, melanin (and/or its functionally related pigment allies) appears to be ubiquitously present in living organisms and most likely in all cells, in varying amounts (see the Introduction). Therefore, melanin could be expected to serve some important function solely on the basis of its pervasive presence among living organisms.

2) Melanin is a "heterogeneous"[1] polymer, i.e. its component molecules may vary considerably in type, amount, and structural arrangement (660, 390, 157, 539). Various tyrosine and tryptophan derivatives appear to be the most common constituents of the melanin biopolymer, but other aromatic and lipo-soluble molecules may be incorporated into melanin in vitro and in vivo (564, 157). These primarily ringed molecules can be reversibly or irreversibly bound to melanin by mechanisms yet unknown. Furthermore, each melanin molecule contains a variable number of diverse metal ions and free radicals (584). Finally, its multiple types of ionic and covalent bonding arrangements guarantee that each molecule of melanin is unique (206).

3) Neuromelanin within neurons and glia is concentrated in strategic locations of the brainstem (32, 35, 64, 580, 73) which (together with monoaminergic axonal and dendritic extensions) allow for the "gating" of all sensory and motor input and output as well as all emotional and motivational input and output (32, 422, 639, 645, 378, 384). This increases the probability that neuromelanin functions as an integrative "trigger molecule" for regulating the monoamines and neuroglia during physico-mental processing. The in vitro evidence for melanin's actual activation of catecholamine synthesis (428, 430) as well as the highly efficient in vivo compensatory functional response of severely damaged catecholaminergic neurons (652, 211, 4) originating in the grossly melanin-laden regions of the brainstem, further supports a highly significant organizational role for neuromelanin.

4) The extreme chemical stability (481, 157) of melanins (as well as the similar stability of the isopentenoid polymers) has allowed them to persist as "chemical fossils." Melanocytes have been demonstrated in the remains of a 150 million year old ichthyosaurus, in mammoth skin, and in an equally ancient squid (133, 723). In more recent times, melanin has been abundantly found in human mummies (133, 517).

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[1] Melanin's "heterogeneous" composition (in vitro assumed to be similar to in vivo) has frequently been assumed to be "randomly" acquired and thus its functional significance has been accordingly depreciated. Such assumptions may be entirely erroneous for several reasons, including: 1) the absence of conclusive knowledge of (neuro)melanin's composition or synthetic pathways, in vitro as well as in vivo (not to mention whether or not such syntheses are random or non-random) and 2) the advantage of a "heterogeneous" molecule in the role of a "mental" organizational trigger molecule.

In addition to melanin's resistance to in vitro degradation techniques, the same stability is found in vivo. Kastin, Schally, et al (292, 293) have convincingly demonstrated that the amount of brain melanin found in rats either at birth or maturity is not altered by: a) removal of the pituitary, pineal, adrenal gland, thyroid gland, testes, or ovaries; b) exposure to constant illumination or darkness; or c) daily injection of either melanocyte-stimulating hormone (MSH), MSH-inhibiting factor (MIF), or melatonin.[1]

5) As an extraordinary cation exchange polymer, melanin has the capacity to accumulate all types of metal ions in vitro and in vivo (584, 508, 328, 125, 398, 157). The in vitro cation affinity of melanin seems to increase with the atomic weight of the cation (508). Melanin has been found to contain abundant transitional metals which have numerous physiological roles (584, 28). It contains a particularly high quantity of zinc (539, 398). (See Proposed Properties of Melanin, #8, for a discussion of some possible major functional regulatory roles of melanin's binding/release of zinc ions.) Metal ions (of particular type and amount) activate enzymes, and many enzymes cannot function without specific metal ion cofactors/activators (28, 391, 496, 51, 524, 271, 152). Therefore, any molecule with the ability to selectively control the strategic binding and release of metal ions (56) could control the activation of key enzymes and therefore control cellular metabolism in general. In vitro studies have established that melanin can bind metal ions as effectively as the well-known heavy metal chelator, EDTA (584). However, melanin's in vivo interactions with metal ions have yet to be examined.

6) Melanin has an extraordinary affinity for binding aromatic and liposoluble compounds and for maintaining this binding for an extremely long time (564, 348, 349, 350, 327, 451, 157, 678, 31, 476, 629). For example, it binds strategic vitamins (such as riboflavin (451)); universal metabolic cofactor/precursors (such as the purines and pteridines (451, 273, 24, 25)); innumerable consciousness-influencing drugs (such as the amphetamines, cocaine, the psychedelic hallucinogens and the neuroleptics (564, 678, 348, 349, 350, 31, 327)). Of particular interest is melanin's strong binding of neuroleptics, the commonly used antischizophrenic drugs (phenothiazines, butyrophenones, etc.) which are used to "stabilize" the schizophrenic process. In addition, melanin binds to (and is derived from) the ring-containing monoamine neurotransmitters. Furthermore, the "active sites" of most (and possibly all) peptide hormones are their aromatic residues (562), which are therefore potential sites for interaction with melanin.[2]

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[1] Such remarkably stability may perhaps weaken only during such non-equilibrium (dissipative) states as are seen with an aberrant monoamine metabolism, giving rise to "rheomelanin", a soluble ("unstable") melanin with membrane-disruptive properties, which is postulated by some researchers to be involved in the etiology of schizophrenia (15, 699, 700, 230, 231).

[2] The psychopharmacology of the neuroglia, the proposed major recep-

7) Electron spin resonance (ESR) studies have shown melanin to produce a stable free radical signal (and thus stable free radical activity) under all known conditions (584). The quinoid structures within melanin may form and maintain free radicals by means of electron resonance stabilization among their semiquinone and hydroquinone components (157, 584). Free radicals are metabolically important in a) oxidation-reduction reactions (see below), b) chain reactions and polymerizations, c) photochemical reactions, d) molecular/cellular damage and repair mechanisms, etc. (157, 424, 516, 584). A ubiquitous organic regulator of free radicals would therefore be inestimably valuable in all electron transfer systems (535). In vitro melanin interacts with all free radicals studied but especially with the oxygen radicals (the superoxide and hydroxyl free radicals) (168, 567, 584). Sealy, et al (584) have reviewed the literature pertaining to ESR-free radical studies of melanin and note that introducing zinc and hydroxide ions into melanin significantly increases free radical concentration. Free radical intensity also increases with increase in pH and with exposure to visible light.

Sarna, et al (567) have studied the interaction of melanin with oxygen and note that melanin significantly utilizes oxygen. They show that the consumption of oxygen in vitro varies with changes in pH, light, temperature, and the type of melanin. Furthermore, these researchers suggest that this oxygen consumption is related to the redox reactions of melanin (such as the oxidation of NADH and the reduction of oxygen to the highly reactive superoxide anion). However, the in vivo reactions of melanin and free radicals remain unexplored.[1]

tor sites of the neuromelanin-monoamine system, has been reviewed by Henn (239, 240, 241, 32, 701, 344).

[1]The theoretical possibilities involving the reactions between in vivo melanin and free radicals (especially oxygen radicals) are essentially unlimited. For example, Oberley, et al (449, 450) have presented a case for the vital association of the oxygen products superoxide and hydrogen peroxide (as well as the superoxide dismutase enzymes) and their connections with the cyclic nucleotides in regulating cell division in normal and transformed cells. Melanin would be an ideal in vivo candidate for such a vital regulatory role since (via free radical interactions) it is functionally closely involved with a) these oxygen products, b) the cyclic nucleotides, and most likely with c) the superoxide dismutase enzymes. (Melanin may regulate these enzymes via its regulation of the zinc, copper, and manganese metal ions which are necessary for their activation). Melanin synthesis (autopolymerization) may actually be "fueled" by oxygen (and its radicals) as evidenced, for example, by the rapid melanin pigmentation of a freshly bitten (and thus aerated) apple or the gross melanin deposition noted in humans exposed to too much oxygen (oxygen toxicity) (16). The brainstem melanin system (32) is involved in the regulation of breathing and therefore oxygen uptake, oxygen free radical accumulation, and, consequently, melanin-free radical dynamics (including melanin autopolymerization). Controlled breathing techniques (e.g. hatha and kundalini yoga) may effect (neuro)melanin and its postulated neuroendocrine phase-timing regulation.

8) Melanin is an oxidation-reduction polymer (584, 390, 186, 187, 157, 120). This follows from its free radical interactions. As Edelstein points out, any electron transport pathway (such as the flavin-ubiquinone-cytochrome redox system, which produces ATP in the mitochondria) can produce free radicals (157). Although most oxidations of organic molecules are bivalent, they probably proceed by two univalent steps whose intermediate state may be a free radical. (See Figure 2.) Redox studies of melanin have shown that it can simultaneously oxidize one substance while reducing another substance (186, 187, 390). For example, in vitro melanin oxidizes NADH to NAD while it concomitantly reduces molecular oxygen (O_2) to hydrogen peroxide (H_2O_2). (Both natural and synthetic in vitro melanins contain considerable water (298, 169, 584), whose potential in vivo significance remains unclear, especially in regard to melanin's free radical-redox functions and its various semiconductive properties.)

9) Melanin has in vitro semiconductive properties and responds to photic, acoustic, and electrical stimulation (415, 169, 170, 512, 417). For example, McGinness has shown that in vitro melanin responds dramatically to a carefully applied electrical field by abruptly changing its electromagnetic conductivity at a specific level of electrical input (415, 169). This in vitro response depends upon the hydration and upon the temperature of the melanin (169). The conductivity change exhibits both threshold and memory switching properties. Melanin's tenacious absorptive interactions with other molecules is highly significant because such binding can produce a conductivity change in melanin of as much as 10 orders of magnitude (169). This mechanism for potential neuro-modulation suggests new interpretations for neuromelanin's role(s) in the functioning of the brain.

The known semiconducting properties of melanin include: a) the ability to threshold and to memory switch, b) photo-conductivity, and c) piezoelectric responses (170). Recently a significant correlation between pH changes and melanin's semiconduction properties has been discovered. Specifically, during the "on" state, in vitro melanin develops a pH gradient[1] proportional to the product of the current X the duration of current. Reversing the current for an equal time cancels this pH gradient (170).

10) Leukocytes (particularly eosinophils) and tissue mast cells contain peroxidase and synthesize melanin (456, 457, 458, 459). Therefore, the eosinophils in the bloodstream have the potential to deliver melanin in a "hormone-like" fashion to any cell throughout the body within a matter of seconds. Wasserman, indeed, considers melanin to be a type of hormone (similar to the well-known isopentenoid hormones--the steroids) which may be transported by leukocytes in the blood to areas of need (723). Wasserman's "skin window" research demonstrates the

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[1] Such a connection between melanin's semiconductive properties and intracellular pH changes has potential functional implications in the (postulated) melanin-regulated, pH-sensitive, gap junctional-mediated direct current (analog) nervous system (to be discussed later).

vascular transport of melanin (725) to sites of tissue injury or inflammation (where significant numbers of free radicals are produced).

Wasserman stresses that an intercellular transport of melanin takes place in sponges, coelenterates, and flat-worms, even in the absence of a vascular system (723). This finding is theoretically significant because it indicates that the circulation of melanin is phylogenetically much older than the circulation of blood. The demonstrated vascular/intercellular circulation of melanin (along with the hypothesized organellar/intracellular circulation mentioned previously) allow for varying amounts of melanin to circulate to important organizational tissue regions as well as to organizational sites within every cell, as needed.

PROPOSED PROPERTIES OF MELANIN

Although the established properties of melanin alone should provide researchers with enough incentive to re-examine its in vivo functions, the expanding list of proposed properties of melanin would appear to open up new vistas in integrative theoretical biology. A selected list of the more significant proposed properties of melanin follows:

1) Neuromelanin is an amorphous semiconductor which may regulate neuronal firing by its ability to act as a bistable switch at physiological neuronal potentials (512).

2) Melanin (along with the nucleic acids) may be an organic superconductor at room or body temperature (108).

3) The melanin granule (melanosome) membrane may store energy as the mitrochondria do and release it to a highly specialized membrane system in cells (157).

4) Melanin and the isopentenoids, in conjunction with the glycosaminoglycans and nucleic acids, may be responsible for directing the normal embryological (and adult regenerative) pluripotential differentiation of tissue.

5) The (melanin-laden) pigment granules and the (glycosaminoglycan-laden) metachromatic granules of mast cells closely interact (457) and may be responsible for the potentially highly significant functions of the mast cell.

6) Melanin (via transport within leukocytes and mast cells, as well as by its normal presence in the autonomic nervous system, perineural cells, diffuse neuroendocrine loci, skin, etc.) may be a molecular "homeostatic regulator," directing such stabilization/re-stabilization phenomena as the immune response, tissue repair/regeneration, and autonomic homeostasis.

7) Melanin appears to play a cytoprotective role (by its binding of harmful aromatic and liposoluble drugs, as well as its scavenging of potentially harmful free radicals), but it may also exhibit cytotoxic properties (if "overloaded" with these toxic substances) (418, 157). More importantly, melanin may effectively utilize these potentially cytoprotective/cytotoxic photon-(electron)-phonon and free radical-redox mechanisms for energy production/utilization (including the production and strategic release of "heat" for metabolic processes).

8) Melanin may regulate numerous enzymatic activations and membrane functions by its control (binding and release) of metal ions.

9) Melanin may regulate the major vitamins and other molecular cofactors necessary for producing and utilizing energy in living systems.

As with the established properties of melanin, a closer look at these proposed properties may stimulate further research into the in vitro, and ultimately the in vivo, properties of melanin.

1) McGinness and Proctor have proposed that melanin is an amorphous semiconductor (415) which may effectively act as a regulatory inhibitor of neuronal depolarization by its ability to act as a "bistable switch" within physiological ranges of electrical potentials (512, 493). Power (in the form of electrical current) is needed to switch melanin to the "on" (i.e. highly conductive) state and to maintain it in this state. Electrical potentials much greater than those required to switch melanin in vitro ($\sim$ 300 V/cm) are available near a depolarizing axon, and neuromelanin may concentrate at the axon hillock (176). The power which is required to switch these melanin granules "on" (conductive) could inhibit or selectively facilitate axonal membrane depolarization in the vicinity of neuromelanin particles in the brain, the inner ear, and the eye (512).

The giant neurons of Aplysia hyperpolarize (becoming less conductive) in response to light, and these neurons have hence been studied as model photoreceptors (238). Upon receiving light, pigment granules within the neuron change their substructure from globular particles to membrane-like lamellae (resembling lysosomes, which they most likely are). This light-induced pigment granule/lysosome transformation occurs with the release of the calcium ions necessary to initiate the events leading to the neuronal membrane hyperpolarization (238, 79).

A sophisticated investigation into neuromelanin's variable conductivity roles is greatly needed to begin to understand now neuromelanin functions in the brain. However, regardless of the impressive conductivity phenomena demonstrated with in vitro melanin,[1] in vivo neuromelanin may have vastly different photic, acoustic, and electric responses. For example, in vivo neuromelanin (with its postulated intricately-arranged monoaminergic-astroglial connections) (32) may respond to minute electro-magnetic changes in its vicinity and accordingly trigger significant neuronal and glial responses (by electrotonic processing (574, 576) and/or other mechanisms).

2) Cope has proposed that melanin (and the nucleic acids) may function as a superconductor at room temperature (108). He has shown discontinuities in the effects of high magnetic fields upon the micro-

[1] Unfortunately, most studies of melanin have been performed in vitro with artificially produced melanin or compressed melanoma melanin, neither of which may represent the actual functional state of normal in vivo melanin. Furthermore, no conductivity studies have yet been performed on in vitro neuromelanin. Significant in vivo studies on tyrosinase-produced melanin as well as neuromelanin are essentially non-existant.

wave conductivities of both melanin and the nucleic acids at room temperature. Cope claims that these discontinuities: a) show behavior analogous to that of Barkhausen noise (which is observed during the penetration of magnetic flux into type 2 superconducting metals) and b) correlate with theory and previous experimental findings regarding superconduction in organic materials and biological systems (109, 110, 111). Cope concludes that his research findings suggest that both hydrated nucleic acids and dry (non-hydrated) melanin[1] possess superconductive properties at room temperature (108). He uses natural melanin as well as synthetic melanin (the latter theoretically containing no ions) to support this proposal. This proposal has yet to be verified, but for melanin and nucleic acids to possess physiological superconductive properties in vivo could revolutionize the life sciences, especially in regard to a direct superconductive interaction between the nucleic acids and melanin. (Melanin granules[2] usually occupy a strategic perinuclear position within the cell which might facilitate a melanin-nucleic acid superconductive communication in vivo.)

3) Because of studies by Demopoulous (541) which indicate significant ATP generation by melanin granules (comparable to ATP generation by mitochondria),[3] Edelstein (157) suggests that the melanin granule

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[1]Since McGinness (169) has demonstrated an increase in semiconduction with in vitro melanin following an increase in hydration (i.e. "wet" melanin) and since Cope (108) claims to have demonstrated possible superconduction in "dry" melanin in vitro, perhaps the presence and absence of water may change the type of conductivity manifested by in vivo melanin (107, 298). Peptide hormones such as vasopressin, oxytocin, etc. which are involved with memory, emotion, and motivation, as well as the complex regulation of water and ions, may functionally intermediate between hydrated/non-hydrated nucleic acids and hydrated/non-hydrated melanin.)

[2]Recognizing that living organisms may respond to weak magnetic fields (e.g. 0.1 to 1.0 gauss) and that only superconductive detection systems are likely to have sufficient sensitivity to achieve such detection in any obvious manner, Cope (112) has calculated the minimum anatomical size necessary for such a response. He calculates that biological magnetodetectors would be of the size of melanin granules, mitochondria, and retinal rods. Pineal and autonomic cells respond to weak magnetic fields, with the former responding to a weak (earth-strength) magnetic field by a significant change in electrical activity (589). Melanin is abundantly present in both the pineal gland and the sympatho-adrenergic system and may be involved in the pineal's light-activated circadian-function. Furthermore, electric field stimulation of the pineal gland, with its glial pinealocytes, causes a copious release of cyclic GMP (765), melanin's free radical-associated molecular companion.

[3]In regard to a functional association between melanin and mitochondria, several observations should be noted. For example, Woods, Burk, and Hunter, in contrast to most researchers, have proposed that melanin granules represent modified mitochondria that have acquired

(mature melanosome) membrane could produce and store energy as ATP (by a method similar to the mitochondria) and then release it to a highly specialized membrane system in cells. The effects of such an additional energy production/release system upon cellular functioning would be of obvious importance.

4) The melanin-laden neural crest cells are pluripotential that is, capable of conversion into many different tissue-cellular types (279, 444, 333, 334, 335, 336, 735, 170, 272, 477). The melanin-laden retinal pigment epithelium (derived from the neural tube/central nervous system) is also pluripotential, having been shown, for example, to convert into bone, muscle, lens, retina, and even an optic nerve (163, 115). Possibly melanin is the crucial guiding factor responsible for these pluripotential properties (and for embryological differentiations in general) via several mechanisms including its interactions with the nuclear nucleic acids and with the cell surface glycosaminoglycans.

The migratory pattern and differentiation of neural crest cells depends upon the type and amount of various glycosaminoglycans in the extracellular matrix (ECM)[1] through which the neural crest cells migrate (144, 500, 617, 306, 77). Melanin, via its interactions with the isopentenoids, may be responsible for regulating the formation/composition of the glycocalyx/extracellular matrix (ECM). The section on "The Glycoproteins/Glycosaminoglycans and the Glycocalyx" notes that the

melanin during the course of a specialized ontogeny (754). Though this hypothesis is questionable, melanin does appear to be present in at least some (if not all) mitochondria, and it has been postulated that mitochondrial monoamine oxidase (MAO) may be involved in melanin synthesis, as catecholamines have been shown to be converted to melanin by mitochondrial MAO in vitro (705). The mysterious electron-dense matrix granules of mitochondria, in addition to containing phospholipoprotein components, may be a site for melanin accumulation, in small but effective quantities. In addition, perhaps the melanin located within the neural crest-derived autonomic ganglia participates in arranging the remarkably organized spatial patterns (whose function is unknown) of large numbers of mitochondria noted in human autonomic ganglia by electron microscopy (234). Such patterns may be involved in "cooperative" electromagnetic "windowing" responses (7,8, 38, 39).

[1] In a review (440, 441) of the dynamics of the brain cell microenvironment, Nicholson lists some possible functions (originally formulated by Ellisman and Margolis) of the glycosaminoglycans and glycoproteins of the extracellular matrix, pertaining both to embryological development and normal functioning. These include: 1) recognition and adhesion properties, 2) ionic buffering, 3) modulation of ionic fluxes (particularly at the nodes of Ranvier), 4) control of local molecular mobility, and 5) regulation of synaptic function (i.e. modulation of the local ionic environment in the vicinity of the synapse as well as the binding, storage, and release of the neurotransmitter amines.)

isopentenoids, in at least some instances, carry the glycoprotein/glycosaminoglycan components of the glycocalyx/ECM from inside the cell through the plasma membrane, and into their respective positions outside the plasma membrane, forming the glycocalyx (719, 403, 140, 141, 751, 226). The glycocalyx becomes a part of the extracellular matrix, forms the cell surface receptors, and apparently has "dominion" over the functioning of the cell by its "recognition-activation" properties (32, 44, 441, 442, 363, 113, 367, 392, 609, 570, 546, 5, 6, 7, 339, 274). The ECM surrounding the migratory neural crest cells is itself functionally modified (organized) by the neural crest cells as they migrate (500, 144, 617, 77). This modification may be effected by the melanin-isopentenoid organizational mechanism just mentioned, which subsequently allows the glycocalical/ECM to activate the various specific tissue differentiations that occur in these pluripotential cells. If Reid and Charlson's hypothesis of a simultaneous formation of glycocalical glycoproteins/glycosaminoglycans and functional glycocalical DNA (530) is correct, (see "The Glycoproteins/Glycosaminoglycans and the Glycocalyx"), then melanin (in conjunction with the isopentenoid carriers) may indeed organize the glycoproteins /GAG's of the glycocalyx as well as regulating the formation of the cell surface DNA. One major function of this proposed simultaneous synthesis is possibly to link the continuously changing extracellular (environmental) glycocalical "recognition-activation" properties with the intracellular (genetic) nuclear "potential" of the cell, determining how the cell will ultimately differentiate into one specific cell type from among its vast genetic choices. Therefore, the melanin-isopentenoid "organizational system" may well maintain a continuous feedback loop with the glycocalical glycoproteins, glycosaminoglycans, and nucleic acids. The glycocalyx, in turn, may maintain a link with the nuclear nucleic acids by means of the glycocalical nucleic acids (and/or nuclear glycosaminoglycans). In other words, during cellular differentiation, input from the glycocalyx/ECM may selectively "activate" and/or modify the "potential" pathways for cell development (represented by the "genetic memory" of the nuclear nucleic acids). The "organizational vesicles"[1] (containing melanin and isopentenoids) may, in turn, organize the component glycoproteins/glycosaminoglycans of the glycocalyx/ECM (with their "recognition-activation" property). For a further discussion see Figures 6, 8, and 10 and "Cellular Process".

The embryological melanin system, including the neural crest system, appears to have the potential capability of organizing all tissues.

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[1] A close interaction has been established between the coated pits/coated vesicles (involved in glycoprotein/GAG receptor-mediated endocytosis) and the highly organizational lysosomes (485, 486, 423, 136, 342, 577, 734, 631, 489, 82, 83, 727, 771, 402, 96, 30, 146, 397, 623, 755, 772). The glycocalical receptors (with or without being activated by nutrient-carrier proteins etc.) may be periodically removed from and recycled to the glycocalyx via the coated vesicles/receptosomes and the GERL-lysosomes. Thus, there appears to be a continuous cooperative organizational interaction between the coated pits/coated vesicles/receptosomes (which remove the glycoprotein/GAG receptors from the glycocalyx) and the lysosomes and related vesicles (which process them and/or replace them in the glycocalyx).

(See "Organization via Sustained Current"). In particular, this system appears to be adept at organizing the mesodermally-derived tissue components, such as those mesodermal components used by the blastema (the cellular mass of debris formed during tissue injury which then becomes the organizational site for tissue repair/regeneration in the adult) (183, 358, 548, 665, 38). Melanin, in the blastema, may effect this tissue regeneration and may be supplied to the blastema site by being: a) synthesized from local mast cells at the damaged area, b) synthesized and delivered to the area by eosinophils in the blood, c) delivered by lymphocytes and macrophages from other storage sites in the body, d) supplied by local Schwann (peripheral glial) cells, e) supplied by migrating melanocytes from the skin, peritoneum, etc. or f) simply derived from the endogenous melanin-containing lipofuscin already present in the injured tissue cells. Indeed, melanin may be the molecular "semiconductor" which Becker believes to produce the sustained/direct current of injury which apparently guides the regeneration of tissue, as has been found in salamanders, etc. (37, 38, 39, 499, 407, 67). Tissue repair/regeneration is a major part of the body's homeostatic system and is further discussed below.

5) A primary locus for many of melanin's organizational activities may turn out to be the mast cell. Okun has noted an apparent dual granulation in mast cells; that is, he has found them to synthesize both the usual metachromatic granules and melanin granules (457). He has electron microscopic evidence for what are apparently foci of melanization occurring within the mast cell metachromatic granules themselves. Mast cells and melanocytes have several similarities, including: a) the mast cell metachromatic granules (583) and the melanocyte melanin granules (705, 188) have both been designated to be forms of lysosomes (containing numerous "lysosomal" enzymes, including acid phosphatase); b) both of these organelles (and their respective major component molecules, the glycosaminoglycans and melanin) are outstanding cation exchange polymers (468, 280, 629); c) both bind particularly large numbers of zinc ions (468, 463, 539, 398); d) both contain the melanin-forming enzyme peroxidase (457, 458); e) both are capable of synthesizing melanin (457); f) both may be closely associated with mesectodermal mesenchyme (457), etc. Therefore, melanin present within mast cells, and especially within the metachromatic granules, leads one to reconsider the actual functions of the mast cell.

The functions of the mast cell are almost as enigmatic as the functions of melanin itself. Mast cells probably serve one or more major regulatory functions. Some that have been suggested include the ability of mast cells: a) to effect an immune response (see the following section); b) to initiate tissue repair and regeneration; c) to supply (zinc)-heparin locally to other cells as receptors for lipids and to regulate lipid metabolism (386); d) to percolate samples of extracellular material over its intracellular metachromatic granules (sometimes for extended periods) and to either homeostatically adjust its granule chemistry and/or modify the percolated material accordingly; e) to produce glycosaminoglycans for extracellular matrix functions; f) to be a vehicle for ion exchange; g) to function as a cellular "super-lysosome" in tissue organization; h) to perform numerous functions in the brain (particularly within the diencephalic circumventri-

cular organs) and in the meninges; etc.[1]

One exciting possibility suggested by Jaques, Riley, and Manadoo (286) is that the mast cell is a staging post within the sequence of events in the recycling of tissue glycosaminoglycans. For example, during response to tissue injury, the mast cells actively discharge granules into the extracellular matrix which the adjacent tissue cells, macrophages, and fibroblasts ingest and digest. This fuel primes the fibroblast, in turn, to secrete its own specific glycosaminoglycans into the extracellular matrix. As tissue repair approaches completion, the extracellular ground substance then shrinks and granulated mast cells reappear. In other words, these researchers propose that the glycosaminoglycans secreted by the mast cells into the ECM control the process of tissue repair/regeneration.

As mentioned above, the mast cells appear to have closely interacting metachromatic and melanin granules. Melanin may well be involved in organizing the mast cell metachromatic granule glycosaminoglycans which are then, in turn, secreted into the extracellular matrix in order to direct homeostatic mechanisms including the immune response and tissue repair/regeneration.

6) Melanin, as the postulated organizational molecule of living organisms, would be expected to regulate all major homeostatic functions, including tissue repair/regeneration and the immune and autonomic responses. Edelstein, for example, suggests that some of the intermediate compounds produced during the synthesis of melanin may be involved in one form of natural immunity, caused by the bacteriocidal effects of melanin's quinones and semiquinone free radicals, as well as by its NADH oxidation capacity which generates bacteriocidal hydrogen peroxide (157, 670). Both of these bacteriocidal effects may operate during the migration of melanocytes over the surface of fresh wounds, inducing the destruction of surface bacteria during or prior to re-epitheliazation of the wound (76, 613, 615).

"Skin window" studies by Wasserman show melanin to be transported to areas of tissue insult by the lymphocytes and macrophages (725, 615), both of which perform essential pivotal roles in initiating and carrying out the immune response (531, 550, 432, 686, 694, 103). Furthermore, melanin is synthesized in mast cells and leukocytes (such as eosinophils) that can also be made available to injured tissue. Leukocytes, with their phagocytic functions, are practically ubiquitous and are therefore immediately present at the site of tissue damage (103, 300, 410). In addition, macrophages, lymphocytes, and mast cells all quickly engage in expediting the immune response. Interferon, as a natural immuno-facilitator, may be activated by polyanions (581) such as melanin.

Tissue damage appears to generate a free radical signal (38, 516,

[1] The reader is referred to Padawer, Oomen, Persinger, and Rosenblum for a further discussion of some of the more intriguing possibilities for mast cell function (468, 463, 491, 548, 280).

424). As discussed above, melanin has both easy and immediate access to the blastema (the organizing region from which tissue repair/regeneration is initiated) and can produce a stable free radical signal as well as effectively seek and scavenge free radicals. Leukocytes generate oxygen free radicals, such as the superoxide radicals (103, 300, 410), which are known to function both in enhancing phagocytosis and in the initiation of the immune response (as well as facilitating the oxidative polymerization of melanin).

Melanin's association with the APUD/diffuse neuroendocrine system could account for production of the trophic peptides that attract other elements which accelerate and maintain the immune response (614). By controlling zinc ion release/uptake, vascularly transported melanin or local melanin from various sources (including the Schwann cells, skin melanocytes, as well as endogenous lipofuscin within the blastemal tissue itself) could control production of nerve growth factor and other trophic peptides known to be involved in nerve and tissue regeneration (208, 614).

Becker has repeatedly suggested that a "semiconductive substance" in the perineural (glial) cells is the source of the direct current which guides and regulates tissue repair and regeneration (37, 38, 39, 359). Jaffe suggests that this direct current associated with tissue regeneration originates within the skin (67, 282, 375). Regardless of the location of the direct current, melanin meets all the specified criteria, that is, it is a semiconductive molecule found in both the glial cells and the skin. Melanin's links with the mast cells and with the glycoproteins and glycosaminoglycans of the glycocalyx and extracellular matrix strongly suggest a direct or indirect connection with the glycocalical receptor's antigen recognition and antibody production response. Furthermore, melanin's connections with the purines, the polyamines, glutamic acid, and transglutaminase-mediated endocytosis would all be further means to ensure melanin's regulatory involvement with immune mechanisms. In particular, transglutaminase-mediated endocytosis has been shown to be involved with the HLA-A and HLA-B antigens (503) and subsequent cell membrane clustering. (These latter mechanisms will be covered shortly).

In addition to these cellular and molecular mechanisms, on a higher level the autonomic nervous system is also significantly involved in the immune response. (Since the vertebrate autonomic nervous system is itself a major homeostatic system, as is the immune system, a direct connection between these two stabilizing systems could reasonably have been anticipated.) The autonomic nervous system innervates the chief sites of antibody production, that is, the thymus gland (which produces the highly regulatory T-lymphocytes) and the spleen (which is involved in the humoral antibody response via the B-lymphocytes). The key aspect of this functional autonomic innervation of the thymus and spleen (741) is that these autonomic nerve fibers appear to terminate on mast cells within these organs. Because the inducer T-cells may regulate mast cell numbers and because mast cell products may affect T-cell functions, Nabel, et al (425) suggest that

zinc-related (197, 519) mast cell-T cell interactions[1] may constitute part of an immunoregulatory circuit. These observations all support our hypothesis that melanin, as the primary organizational molecule, is at the core of the organizational-homeostatic functioning of both the mast cells and the thymus cells, as well as the cells of the autonomic system. We can further note that much of the thymus as well as the entire peripheral autonomic nervous system is of neural crest origin (335, 336), neural crest being the embryological system for gross melanin dispersal. The melanin-laden neural crest-derivatives all appear to be homeostatic regulators.

Normal growth is under homeostatic regulation. That the neoplastic derivative of neural crest melanin, melanoma, is usually prefixed by the term "malignant" serves to indicate its remarkably rapid metastasis and lethal potential. Neuromelanin per se is not known to exhibit neoplastic transformation. Nevertheless, it has been shown that electrical stimulation (or more likely the electrical disruption) of the midbrain (the major "home" for neuromelanin, at the top of the brainstem) mediates neoplastic tumor growth and metastasis throughout the body (603). There are several possible explanations for this significant finding.

An increasing number of studies strongly suggest that hypothalamic functions (including eating, drinking, emotion, motivation, and autonomic responses) may be ultimately controlled by the brainstem melanin-monoamine system (melanin-dopamine/norepinephrine/serotonin connections). For example, hypothalamic lesion/stimulation studies (e.g. the lateral hypothalamic syndrome) which were previously offered as evidence for strict hypothalamic control over many motivational responses, have now been shown to be due to disruption/stimula-

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[1] Research is accumulating which indicates that arachidonic acid metabolites (leukotrienes and prostaglandins) are involved in local homeostasis, inflammation and immunity, and are connected with T-cell and mast cell functions (345, 199, 455, 431, 75, 582, 316). The prostaglandins, for example, are important pivotal molecules involved in the regulation of numerous metabolic reactions, and Horrobin has provided many hypotheses implicating prostaglandins in various strategic physiological regulations and pathological disorders (260, 261, 262, 263, 264, 265, 266, 267, 268). Melanin and prostaglandins share several intermediates and closely related molecules in their synthesis and metabolism, including free radicals, heme, peroxide, peroxidase, zinc ions, cyclic nucleotides, etc. (324, 494, 370). Other substances such as melatonin, peptide hormones, monoamine neurotransmitters, vitamin C, cholesterol, etc. are related to the functioning of both melanin and the prostaglandins. The diverse physiological/pathological associations and numerous common molecular relationships of both melanin and prostaglandins suggest a close functional relationship. The lysosomal phospholipases which initiate prostaglandin synthesis may perhaps be triggered in vivo by lysosomal melanin (137, 397, 772, 755). Furthermore, the free radical and peroxide activity of prostaglandin synthesis may directly correlate with melanin synthesis and functioning (772, 755, 623, 131, 584, 582, 324, 370, 494, 345).

tion of brainstem melanin-monoamine fibers permeating the hypothalamus (652, 211). Hypothalamic-immune interactions (121) may indeed be controlled by brainstem melanin-monoamine nerve fibers. For example, the paraventricular and supraoptic nuclei of the hypothalamus, which participate in autonomic and neuroendocrine modes of homeostatic control, are probably regulated by noradrenergic pathways originating in the brainstem melanin system (565, 64, 95, 17, 580).

Just as the peripheral neural crest melanin/APUD system produces peptide hormones and monoamine neurotransmitters (such as those that innervate the thymus, the spleen, the adrenal, etc.) the brainstem melanin/APUD system also produces monoamine neurotransmitters and peptide hormones, some released via connections with the hypothalamus, as pointed out above. These neurotransmitters, under active brainstem melanin control, may regulate the hypothalamic neuroendocrine and autonomic responses and consequently affect the higher regulatory aspects of the immune system. Such a brainstem melanin-hypothalamic-autonomic-immune circuit may function as a homeostatic network.

Consequently when the "brainstem" melanin system, extending from the peripheral autonomic ganglia to the top of the brainstem (35, 64, 580, 568), is in some way chronically "de-stabilized", then some instability of the dynamically responsive hypothalamic effector system and its associated autonomic and/or immune connections should follow (depending upon individual genetic or environmental variability). This instability might appear in various ways, including: a) mental/emotional instability (through aberrant melanin regulation and subsequent abnormal production and coordination of peptide hormone and monoamine neurotransmitter functioning (239, 240, 241, 45, 357, 15, 645, 261, 377, 185, 223, 527, 278, 608, 325, 726, 134, 193, 32)); b) abnormal autonomic nervous system functioning (276,569) giving rise to hypertension and cardiovascular abnormalities, gastrointestinal disorders, temperature fluctuations (544, 185, 290), abnormalities in endocrine and circadian rhythms (305, 78, 185), etc.; and c) abnormal immune functioning (559). Psychoneuroendocrinological regulation and dysfunction of the immune system has been reviewed by Solomon (616) and apparently applies to a) infectious, b) allergic, c) autoimmune, and d) neoplastic mechanisms. For example, one well-known manifestation of a chronic instability in this psychoneuroendocrinological system has been seen under situations involving prolonged or chronic stress (the "general adaptation syndrome" as elucidated by Selye). This chronic stress (297, 536, 745) results in the increased production of such hypothalamic-pituitary hormones as ACTH (thus leading to increased immunosuppressive adrenal corticosteroid release), growth hormone, prolactin, etc. (Chronic stress may also lead to abnormal autonomic system discharges, abnormal mast cell membrane phospholipid methylations, abnormal prostaglandin synthesis/functioning, etc.).

In addition to a more or less direct link-up between the brainstem melanin system, the hypothalamus, and the central autonomic nervous system, there is evidence for the presence of a tonically active forebrain GABA system, GABA being a major inhibitory neurotransmitter

which can significantly influence the central autonomic outflow (745). The brainstem melanin system, in turn (via the forebrain neuroglial network), probably influences this GABAergic system. This postulated (monoamine)-neuroglial control over the forebrain GABAergic regulation of the central autonomic nervous system (32) points to direct current as a more basic mechanism for homeostatic control. This current may also account for at least a major part of the other previously considered mechanisms involved in homeostatic regulation.

A direct current system (probably produced by the glial (perineural) network (618, 619, 620, 269, 38, 39, 388) and other strategic melanin loci) regulates the development and growth of embryological and adult tissues (602, 281, 282, 283, 284, 375, 446, 447), tissue repair and regeneration (67, 38, 39), and numerous other organizational mechanisms.[1] We propose here: 1) that the direct current of the peripheral glial system is controlled by neural crest melanin (primarily the melanin within the ganglionic small intensely fluorescent or SIF cells (164, 710, 472, 318, 717, 236)); and 2) that the direct current of the central neuroglial system is controlled by the brainstem melanin system, the origin of the brain's monoaminergic neuronal pathways. (See the companion article, "Melanin and the Mind-Brain Problem" (32)). Severe acute or chronic disruption of any part of this sustained current organizational system--either directly by compromise of the (neuro)melanin-(neuro)glia system or indirectly by compromise of the numerous other neurotransmitters (such as glutamate and GABA, which are, in turn, regulated by this system)--may variably affect all of the major homeostatic regulatory systems, including the autonomic, neuroendocrine, and immunological homeostatic systems.

7) Many researchers, using considerable circumstantial evidence, have proposed that melanin may either protect or damage cellular tissue (157, 418, 512, 513, 568). In their view, melanin serves a cytoprotective role in at least two ways. First, as a free radical trap, melanin may remove (and possibly constructively use) potentially harmful free radicals which are continuously generated during lipid and membrane peroxidation or cellular oxidation-reduction reactions,etc.

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[1] In addition to regulating tissue development, repair, and regeneration (407, 282, 283, 38), low-level direct currents have consistently been shown to be causally related to many other significant therapeutic effects (443, 38). For example, electrotherapy has been used clinically to effect tissue regeneration and healing, to induce sleep, to relieve pain, to change mood, to treat addiction effectively, to be involved with acupuncture mechanisms and results, to relate directly to mentation (260, 32) etc.

Patterson claims to have achieved significant results in treating human drug addiction by applying low intensity electrical current to the brain with apparent phasic "reset" effects on the central neuroendocrine system. Noting Patterson's apparent success with "neuroelectric therapy" (NET), a recent popular article states: "...Patterson's [NET] black box is helping to unlock the mysterious inner workings of that other black box: the human brain." (412). We agree and suggest that the complex black molecule neuromelanin (and its neuroglial

This "wear and tear" property supposedly results in the formation of lipomelanin polymers (lipofuscins)[1] which are apparently nontoxic to the cell, at least in moderate quantities. Second, melanin may protectively bind various metallic cations, such as the toxic heavy metals, as well as various aromatic, cyclic, and lipid-soluble compounds, including environmental herbicides (such as paraquat and "agent orange"), pesticides, aromatic industrial chemicals (including known carcinogens), pharmaceutical drugs, etc.

However, if melanin's intrinsic organizational capacities are compromised, and/or if its binding capacities are "overloaded" (either with excessive free radicals, heavy metals, or toxic aromatic and liposoluble compounds), then the possibility of cellular and tissue damage in regions of high melanin concentration increases (513). Melanin could "overload" in areas of high free radical activity (such as in areas where tissue is exposed to obvious damage from prolonged ultraviolet light exposure) or when exposed to excessive toxic cyclic and liposoluble compounds (such as the irreversibly bound herbicide paraquat, the antimalarial drug chloroquine, the consciousness-altering general anesthetics,[2] the local anesthetics, or the antipsychotic neuroleptics used in treating schizophrenia). Note that neuroleptics (such as the phenothiazines) can cause certain relatively common side effects (e.g. tardive dyskinesia) in melanin-related brain regions, and they can also affect other highly melanized areas including the eyes (especially the retina and retinal pigment epithelium), the ears (causing ototoxicity) and the skin (causing skin rashes and photosensitive dermatitis) (93, 176, 512).

Edelstein (157) has suggested that the catecholamines formed during neuromelanin synthesis may directly scavenge labile methyl groups, thus protecting other cell components from aberrant methylation during cellular metabolism (especially DNA and RNA functions and

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network) is the actual functional "black box" underlying the brain's electric (and neuroendocrine) control system.

[1] Lipofuscin (154, 16) does tend to accumulate in cells with time and has frequently been referred to as the "aging pigment" or "wear-and-tear pigment". However, these titles may be erroneous, as all organisms may actually be born with these pigments. For example, significant amounts of lipofuscin have been found in fetal and newborn human liver. Furthermore, evidence has accumulated which suggests an interconversion process between lipofuscin and neuromelanin in the brain via pseudoperoxidation (568). Lipofuscin, with its extensive distribution, may indeed be a suitable molecular vehicle for the storage and distribution of melanin/neuromelanin.

[2] Since general anesthetics have lipophilic properties and appear to affect the brainstem reticular formation (reticular activating system), melanin (as a lipophilic organizer of the reticular formation) would be an ideal candidate for the "organization" of consciousness and the site of action of the general anesthetics.

hemoglobin synthesis).[1]

Finally, as mentioned earlier, McGinness and Proctor have stressed a role for melanin in processing excited state energy via photon-(electron)-phonon coupling. Melanin apparently controls the dissipation of such high energy states by converting them into rotational and vibrational energy (i.e. heat). These researchers postulate that, in a manner similar and related to the melanin-free radical mechanisms, photon-(electron)-phonon properties may be either cytoprotective or cytotoxic, depending on chronic or acute overload circumstances.

Extending the photon-(electron)-phonon and free radical concepts further into specific pathological diseases, Proctor (512, 513) proposes that many so-called "charge transfer" diseases (such as Parkinson's disease, Wilson's disease, hyperuricemia, chlorpromazine toxicity, etc.)--which produce one or more of the clinical triad of: a) mental disturbance, b) extrapyramidal disorders, and/or c) pigmentary disorder--are related to aberrant photon-(electron)-phonon mechanisms.

Although the scientific literature has emphasized the cytotoxic and "negative" aspects of melanin (such as are seen in malignant melanoma) more than its cytoprotective and "positive" aspects, we have chosen in this paper to emphasize the functionally positive (specifically the organizational) aspects of melanin. Melanin's hypothesized photon-(electron)-phonon properties gain added significance when viewed in relation to: a) the known cellular enzyme cascade systems which can tremendously amplify minute signal input by instantaneously effecting reversible covalent modifications (630, 98); and b) the known ability of certain neuronal systems, utilizing electrotonic processing, to be triggered by as little as one photon, or by auditory input near Brownian motion (574, 576), thereby potentially influencing major molecular/cellular/tissue functions (56, 504).

In addition, new research and theory points to the probable existence of an ancient biophotochemical system of cell communication, which is also apparently extant in more advanced living systems. Popp, et al, have reviewed these findings and have advanced some theoretical speculations about this fascinating subject in their book Electromagnetic Bio-Information (504). Since melanin has been present at least since the inception of life, it is a strong candidate for the role of the core organizational molecule in this ancient biophotochemical system, and its photon-(electron)-phonon and free radical-redox mechanisms undoubtedly play a major part in this system. Because the in vivo photon-(electron)-phonon mechanisms may be extremely difficult to study with our present technology, other basic organizational properties of melanin are more likely to be elucidated first.

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[1] Altschule and Hegedus have provided a review of some of the functions and diseases connected with normal and aberrant visceral melanin (and heme) metabolism (16).

8) One proposed property of in vivo melanin which is potentially accessible to sophisticated research involves melanin's ion exchange capability (584, 328, 508), which may be pivotally important in regulating general cellular metabolism.

We propose that melanin controls (both binds and releases) diverse metal ions (56) that are involved in activating numerous cellular enzymatic reactions and in regulating various peptides and proteins (271, 391, 605, 612, 509, 496, 125). The zinc ion provides a dramatic example. Melanin's particularly high quantity of zinc (also found in high quantity within mast cells, the thymus gland, etc.) may activate/deactivate many significant peptides and proteins (540, 101, 51, 310, 496, 125, 509).including: a) carbonic anhydrase, with its crucial role in regulating intracellular pH; b) nerve growth factor, responsible for peripheral and possibly central nerve growth (and/or regeneration); c) insulin, needed for the metabolism of glucose (552); d) carboxypeptidase, involved in modifying and/or terminating the actions of certain peptides and peptide hormones; e) cytoskeletal proteins, such as tubulin; f) DNA polymerase, DNA-dependent RNA polymerase, and thymidine kinase, all involved in the essential functions of the nucleic acids; g) and especially membrane-bound enzymes such as guanylate cyclase (producing cyclic GMP), adenylate cyclase (producing cyclic AMP,) Na^+, K^+, ATPase, Ca^{++}ATPase, and microsomal NAD(P)H oxidase; etc.

In addition to activating/deactivating the above selected enzymes and peptides, zinc appears to have many other functions (51, 101). Particularly, zinc: a) has been implicated in regulating prostaglandin biosynthesis, possibly at the level of phospholipase A_2, (137, 772, 755, 30, 397, 423, 623), prostaglandins having numerous known and postulated functions; b) alters the permeability of membranes to specific compounds (e.g. sodium in leukocytes, glucose in the intestine, etc.); c) affects the in vitro assembly of microtubules (310), the vital structural and functional cytoskeletal components which interact with biomembranes; d) convers increased thermal stability to membrane lipid bilayers (while transition metal ions conversely have a destabilizing effect); e) significantly enhances fibroblast proliferation and wound healing; f) has an effect on cystine metabolism and is possibly involved in transsulfuration; g) is involved in the function of growth and sex hormones; h) is essentialy for all tissues to develop properly; etc.

Chvapil and co-workers (51, 101) have proposed the following functions for zinc at the cell surface: a) interaction with enzymes controlling the integrity of the membrane; b) involvement with macromolecular components of the membrane by changing their conformation or enzyme-substrate specificity, and c) involvement with metal-catalyzed membranal lipid peroxidation.

In an excellent review of zinc and biomembrane interactions (51) Bettger and O'Dell emphasize zinc's key functions by noting that: a) a substantial amount of zinc is located in the plasma membrane of cells; b) elevated extracellular zinc concentration increases zinc in the membrane, and this has a stabilizing or protective membranal effect;

and c) depressed extracellular zinc concentration decreases plasma membrane-associated zinc, and this destabilizes and alters membrane properties. These researchers accordingly suggest that the zinc ion is a structural component of biomembranes and as such has specific functions which other ions cannot perform. These functions of zinc may be as critical to the normal physiology of cells as are its numerous roles in metallo-enzyme regulation. Bettger and O'Dell conclude that zinc plays a "critical" role in the structure and function of biomembranes in general.

An evolutionary means to control the binding and releasing of in vivo metal ions (particularly zinc, but also including the other ions such as copper, calcium, selenium, magnesium, manganese, iron, cobalt, etc.) would be a major means for organizationally controlling nearly all aspects of living organisms, from nucleic acids to key enzymes, neurotransmitters (152, 524) and trophic hormones, from the cytoskeleton to the biomembranes. We propose that the potentially self-organizing (autopoetic) biopolymer melanin may be responsible for at least a major part of this in vivo metal ion control.

9) In addition to its ion exchange properties and its postulated role in functionally controlling the body's minerals, melanin also, appears to closely associate with many of the body's essential vitamins and other cofactors. For example, it reversibly binds riboflavin (451) and hence may help regulate the numerous reactions involving the flavoproteins. Melanin may be involved with the ubiquitous redox reactions of $NAD(P)/NAD(P)H^+$ and therefore with niacin. Melanin reversibly binds the pteridines (25, 451) including the pteridine-constituted vitamin, folic acid (70) which will be discussed shortly. In addition, it has a link with vitamin B-12 via that vitamin's heme core, its central cobalt ion, and its pteridine-related synthesis/function. It will probably be found to be intimately involved with other water-soluble vitamins[1] in addition to riboflavin, niacin, folic acid and vitamin B-12.

Melanin has a close phylogenetic association with the isopentenoids (24, 25, 273), as well as a close functional neuroendocrine relationship (such as is seen in the intricate interactions of the melanin-laden adrenal medulla and the isopentenoid-laden adrenal cortex; the melanin-laden retinal pigment epithelium and the isopentenoid-laden retinal rods and cones; or the gonadal steroids and the brainstem melanin system (13, 243, 682). Therefore, melanin should closely interact with the isopentenoid-containing fat-soluble vitamins (140, 393), such as vitamin A (141, 195, 226), vitamin D (720, 445), vitamin E (656, 429, 739, 466), and vitamin K (659, 184). In addition to containing an isopentenoid segment, vitamin Q or ubiquinone also contains an obvious quinone core (534), which is the basic unit of melanin itself. Ubiquinone is a crucial electron carrier in terminal electron transport

[1] Vitamin C is a water-soluble reducing agent involved in melanin, pteridine, and glycosaminoglycan dynamics, and neuroendocrine functioning. See "Folic Acid and the CNS" section for connections between melanin and vitamin C.

reactions and in oxidative phosphorylations. It is the collecting point in the respiratory chain for reducing equivalents derived from other substrates that are linked directly to the respiratory chain through the flavoprotein dehydrogenases.

Since melanin has exceptional lipid-binding (membrane-associating) properties (664); since melanin appears to be associated with the flavoproteins, the cytochromes, and the connecting element, ubiquinone; and since melanin may be produced (in small amounts) in the mitochondria where oxidative phosphorylation occurs, it may actively "bias" the mechanisms of cellular energy production and utilization in vivo.

Summary of Properties

The composite picture of melanin that emerges from this review of its established and proposed properties clearly suggests the need for a functional re-interpretation beyond the conventional view that melanin is a "breakdown polymer" or a "metabolic waste product". Melanin, a heterogeneous polymer composed of stacks of planes of ringed molecules (incorporating various ringed precursors and conjugated molecules such as tyrosine and tryptophan derivatives, as well as ions and free radicals), is one of the most complex and stable macromolecular structures found in nature. Melanin's conjugated ringed structure makes it an ideal photon/electron receptor. It converts excited energy states into molecular rotation and vibration (i.e. heat) as well as the reverse process (i.e., the so-called photon-(electron)-phonon conversion processes). Melanin's polyanionic properties potentially allow it to selectively bind and release metal ions essential for enzyme activation and cellular membrane regulation. It is a powerful scavenger and producer of functional free radicals, apparently employing extraordinary oxidation-reduction mechanisms which are necessary for covalent modification processes and for cellular energy storage and release. Melanin seems capable of regulating a wide range of molecular interactions and metabolic processes through: photon-(electron)-phonon conversions, free radical-redox mechanisms, and ion exchange mechanisms.

Melanin's long evolutionary history, its hormone-like transport throughout the entire body via the vascular system, the strategic location of neural-crest derived melanin in areas such as the autonomic and sensory ganglia and diffuse neuroendocrine loci; and increasing concentrations of neuromelanin in the brains of higher animals all point to a highly significant functional role. (See Table 1).

As we gain further understanding of the properties of melanin (and this is obviously a high priority area for research) the exact nature of its functioning in living systems will also become more clear. Already established semiconductive properties of melanin may prove the key to understanding how melanin regulates the neuronal network. Proposed superconductive properties for both melanin and nucleic acids at room temperature may further critically connect melanin as the "organizational" molecule and DNA as the master or "dominion" molecule. Proposed cytoprotective and energy storage/release roles (through melanosomes/lysosomes) suggest further highly significant melanin functions in cellular processes.

The most important gains from melanin research, however, may occur in the healing process, more specifically in an understanding of the immune response and of the mechanisms of tissue repair and regeneration. Melanin's proposed roles in generating and organizing the direct current, in guiding embryological differentiation and tissue regeneration, in controlling mast cell functioning; and in homeostatically regulating the neuroendocrine, immunoregulatory, and autonomic nervous systems and other complex systems all bear directly upon this central concern.

In addition to research on the properties of melanin per se, a second direction for research is in the area of understanding the "melanocentric systems"--key molecular systems in which melanin appears to play a central if not controlling role. We now turn our attention to some of these associated functional systems.

THE MELANOCENTRIC SYSTEMS

In searching for a unifying role for melanin and/or an initial direction for further research, notable developmental associations between melanin and two other important molecular systems may offer us key clues for further understanding. These are: 1) the purine-pteridine system and 2) the APUD/neuroendocrine system.

Bagnara, et al (24, 25, 273) have demonstrated that within neural crest-derived chromatophores (and also within neural tube-derived melanized cells, such as the retinal pigment epithelium), melanin has a close phylogenetic and ontogenetic association with the purines and the pteridines (as well as with such isopentenoids[1] as the carotenoids and cholesterol). In fact, the purines and pteridines not only closely interact with melanin and accompany melanin throughout embryological development, but also are constituents of melanin. All of the common primordial intracellular pigment organelles (containing melanin, purines, and/or pteridines) appear to be derived from the nuclear membrane-endoplasmic reticulum. Close interactions and interconversions involving melanin, purine, and pteridine organelles occur in living organisms and in pigment cell tissue cultures. In tissue cultures, for example, reflecting platelets (composed of purines) and pterinosomes (composed of pteridines) convert totally into melanosomes (composed of melanin), but the reverse has not been established (273). Furthermore, purines and pteridines, which are almost identical structurally, interconvert. Purines, pteridines, and melanin have all been shown to be intimately associated within the same pigment cell (even within the same pigment organelle).

Purines and pteridines, like melanin, are also light-absorbing (and reflecting) molecules which contain conjugated molecular rings with

[1] Because of the diverse sources and types of data available for melanin-isopentenoid interactions as well as obvious gaps in our present knowledge, the postulated functional organizational connections between melanin and the isopentenoids will not be developed in this paper. Nevertheless, such a connection between these two organizational polymers should be kept in mind.

resonating electrons. The photo-active properties of these ringed molecules and their intimate interactions and interconversions with melanin strongly suggest that melanin can extend its proposed photon-(electron)-phonon properties to its purine- and pteridine-associate/constituent molecules. Such photon-(electron)-phonon interactions between melanin and the purines and pteridines occurring in vivo, along with the subsequent "heat" made available from these rotational and vibrational energy transitions, would probably allow melanin to have a subtle "trigger" control over these two photoactive molecules.

Furthermore, melanin's free radical-redox-ion exchange mechanisms allow for its potential organizational control over both the enzymes and the reversible enzyme cascade systems which control the purines and pteridines. Guanylate cyclase, for example, is the enzyme responsible for the functional availability of the second messenger molecule cyclic GMP, a universal purine molecule with multiple functions. Guanylate cyclase, in turn, appears to be regulated by oxygen free radicals (396, 405) whose supply may be directly regulated by melanin.

If melanin does indeed regulate the purines and pteridines via such mechanisms, then melanin could regulate the gamut of intracellular covalent modifications. The reason for this hypothesis is that both purines and pteridines are absolutely required for in vivo covalent modifications, including phosphorylation, methylation, adenylation, uridylation, acetylation, transsulfuration,etc. These and other intracellular covalent modifications of the various enzymes, peptide hormones, etc. all interest life scientists because of their vital and diverse cellular organizational capacities. These numerous functional modifications of the "stable" covalent bond allow for organizing and maintaining the functional integrity of a molecule, a cell, or an entire organism.

A second significant "melanocentric" system is the APUD/diffuse neuroendocrine system.[1] Although melanin granules are present in oocytes and continuously found throughout embryological development (ontogeny), these granules coalesce dramatically at a crucial stage in vertebrate embryological development to form the grossly visible neural crest system. This mysterious heavily melanized organizational system is seemingly "born" as its two pigmented folds bring together and close the embryo's neural tube (the structure which is to become the central nervous system). No doubt many other cells containing melanin pigment enter the forming neural tube or disperse elsewhere before the grossly visible neural crest cells form. However, the bulk of this grossly visible melanin pigment concentrates in these neural crest cells. Most of these neural crest cells (after the neural folds close, forming the neural tube) strategically disperse throughout the body to form all the autonomic and dorsal root (sensory) ganglia, the peripheral glial (perineural) cells and other important structures, especially including the APUD/diffuse neuroendocrine system. (The peripheral nervous system may be considered to be a part of the APUD system). APUD stands for

[1] "Neuro" represents the amine neurotransmitters and "endocrine" represents the peptide hormone neuromodulators.

amine precursor uptake and decarboxylation, named by its discoverer, the noted histochemist A.G.E. Pearse. This organizational system, though predominantly located in the brain and in the gastrointestinal tract, is also diffusely scattered over the body and may be the major site of formation of both the peptide hormones and the monoamine neurotransmitters (482, 483, 484, 299).

The APUD concept, though quite helpful in explaining many physiological and pathological conditions, has had a history of continuous theoretical modifications, and its explanatory efficacy has recently been challenged. A clarification of the APUD system that may meet these challenges is presented later in this paper.

We now need to examine in greater depth both of these two major melanocentric systems: 1) the ancient melanin-purine-pteridine (covalent modification) system and 2) the APUD (or diffuse neuroendocrine) system. (See Figure 5.) These two systems are related in numerous ways in addition to their obvious anatomical and developmental associations. For example, the pteridine cofactor is required for the functioning of the rate-limiting enzymes which synthesize the monoamine neurotransmitters (430, 105). Likewise, the purine-containing cyclic nucleotides are usually required (as second messengers) for the functional activities of both the peptide hormones and the monoamine neurotransmitters (210, 47, 525, 740). Since steadily increasing research has focused on the purines and the pteridines, a brief summary of this research will help in establishing their interactive connections with melanin and their strategic functional significance.

THE PURINERGIC CONNECTION

Purines have enjoyed a high status in the scientific literature because of the numerous ways in which they are essential to life. For example, the purine bases adenine and quanine are key constituents of the nucleic acids, but this is only one of their many crucial roles. Adenine is a key component of three molecules which are essential in almost all metabolic processes: 1) adenosine triphosphate [ATP], 2) acetyl coenzyme A [CoASH], and 3) the oxidized and reduced forms of nicotinamide adenine dinucleotide (phosphate) [$NAD(P)^+/NAD(P)H$]. ATP and CoASH function as "reagents" which are used by enzymes to activate designated molecular substrates for metabolic reactions. The redox couple $NAD(P)^+/NAD(P)H$ is the mediator of most enzymatic oxidations and reductions. Purines have been proposed to be the primordial neurotransmitters (671).

Adenosine and 2-deoxyadenosine significantly affect the following cellular metabolic functions: 1) production of cyclic AMP, 2) pyrimidine biosynthesis, 3) phosphoribosylpyrophosphate synthesis, 4) production of S-adenosylhomocysteine, 5) nucleic acid synthesis, 6) urea synthesis, 7) thiamine synthesis, 8) protein kinases, 9) maintenance of ATP levels, 10) various immune responses, 11) cellular morphology, 12) blood vessel dilatation, 13) secretion of various hormones, 14) lipolysis activity, 15) histamine release, 16) liver glycogen storage, etc. (177).

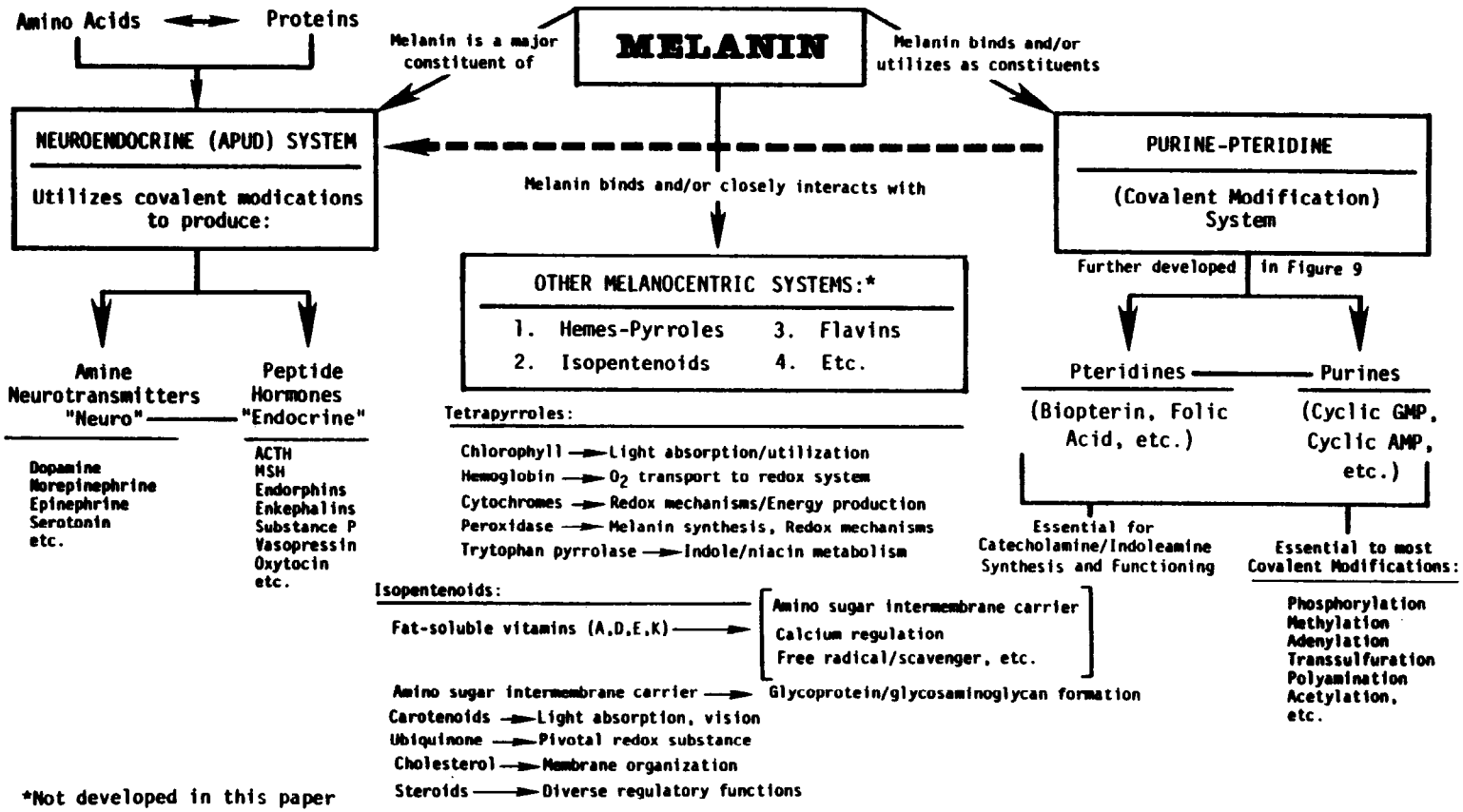

Fig. 5 Melanocentric Systems (Molecules That Are Intimately Connected With Melanin)

This list, which continues to grow, only concerns the purine adenine. The purine guanine is also being further recognized for its essential diverse roles.

In regard to the nervous system per se, Burnstock, et al (87) have reviewed the impressive evidence supporting a "purinergic" (i.e. a non-adrenergic, non-cholinergic) autonomic neurotransmission system which has potentially profound significance. This discovery apparently abolishes the dogma of a strictly adrenergic-cholinergic autonomic nervous system (which is still being taught in most basic neurophysiology courses). Even the adrenergic-cholinergic system may use a purinergic "second messenger" to effect a response.

One of the most heavily studied areas of neuroendocrinology in recent years is the "second messenger system". Most neurotransmitters and peptide hormones produce their cellular effects by a purine cyclic nucleotide second messenger, either cyclic AMP or cyclic GMP. Greengard (210) notes that, in general, cyclic nucleotides play key roles in regulating cell growth, cell differentiation and cellular metabolism in many (if not all) tissues, and are involved in translating and transducing hormonal messages from outside to inside the cell. The organizational or regulatory effects of the cyclic nucleotides upon the phosphorylation (309) of a large number of specific proteins are too numerous to list here. Even a general review of the cyclic nucleotides' regulation of the nucleic acids leads to many potential organizational possibilities. For example, the peptide hormones may affect cellular protein biosynthesis via the cyclic nucleotides at one or several levels of control, including: 1) mRNA transcription of DNA, 2) posttranscriptional processing and transport of mRNA, 3) mRNA stability, and 4) mRNA translation into "raw" cytoplasmic protein (549).

Adenosine itself appears to be intimately involved in regulating the nervous system and has been thoroughly reviewed by Phillis and Wu (497) and Stone (651). Adenosine found in the brain appears to be derived primarily from its precursor nucleotide by the enzyme 5'-nucleotidase (497). Though this is controversial, Kreutzberg (311) and Cammer et al (91) believe this enzyme to be predominantly located on or within astrocytes and oligodendroglia, and both of these central nervous system perineural cells (neuroglia)[1] are capable of interconversion, at least in tissue culture (474).

Adenosine is a neuronal modulator that the neuron releases during nerve cell activity along with the principle neurotransmitter that the neuron produces (311, 497, 592). Such neuronal monoaminergic output is probably integrated with adenosine-induced cyclic AMP generation.

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[1] Supporting evidence is presented (in "Melanin and the Mind-Brain Problem") for the control of the neuroglial system (and, hence, for control of its postulated organizational direct current system) by the various monoaminergic neurotransmitters, whose release is, in turn, controlled by neuromelanin. The reader is advised to keep this close functional connection between melanin and the glial cells in mind, whenever regulatory functions of the glia cells are discussed.

Adenosine modulates synaptosomal dopamine activity (providing a direct link for melanin's postulated control of dopamine) (394). Adenosine may stimulate Na^+/K^+-activated membrane ATPase (534), and it may regulate the level of cyclic AMP in presynaptic nerve terminals by a receptor on the presynaptic membrane (302). Adenosine affects nerve cell activity (including Ca^{++} transmembranal fluxes and presynaptic transmitter release) and, by its vasodilatory action, it may even regulate local neuronal blood supply (497, 311).

Kreutzberg and Schubert (311) have succinctly summarized the functions of nervous system adenosine by stressing that adenosine may be a type of universal "signal" which neurons secrete and which a variety of target cells can receive, thereby eliciting a range of heterogeneous effects. Adenosine carries the "message" that neurons have been activated, and its purpose may be to evoke a coordinated reaction among the different elements of a functional nerve/end organ unit. Adenosine's probable regulation of local blood flow, which affects cellular metabolism, may further allow it to elicit long-lasting modulation of cellular functions in response to neuronal activity.

Lux and Schubert also suggest (and Schmitt, et al, emphatically reiterate) that adenosine may modulate electronic dendritic input to the neuron (311, 574). Since electrotonic dendritic processing is apparently a major control mechanism in neuronal homeostasis (574, 576, 83, 32), adenosine's proposed modulation of this processing is quite important. Adenosine's potential electrotonic dendritic modulation appears to be regulated by the neuroglial system, the primary source of 5'-nucleotidase. Since the glial system is the probably source of the sustained (direct) current detected in the brain (which presumably modulates the dendritic graded potential), and is, in fact, probably regulated by the brainstem melanin system via monoaminergic discharge, we now have suggested at least one major mechanism available for neuromelanin in regulating the electrotonic organization of the central nervous system (32, 618, 619, 620, 570, 546, 114, 550, 499, 239, 240, 241, 5, 6, 7, 8, 9, 269, 38, 597, 83, 574, 576).

A brief look at the guanine cyclic nucleotide (cyclic GMP) and the nucleotide GTP reveals further systems potentially available for melanin's control. For example, the guanine nucleotides serve as essential intermediates in all purinergic second messenger phenomena (3, 545, 625). Therefore, the purine guanine plays a pivotal role in neuroendocrine functioning.

An extensive list of other functions performed by the purine guanine is rapidly accumulating. Cyclic GMP is necessary for exciting the retinal rods and cones (625) and thus for vision itself (perhaps via photon-free radical mechanisms). Numerous studies have suggested that cyclic GMP may mediate peptide hormone and neurotransmitter actions (210, 405). Of particular interest is the proposal that cyclic GMP may act as second messenger mediating the response of acetylcholine (637, 650, 405).[1] This frequently suggested functional association

[1] It is frequently suggested in the neurophysiological literature

between acetylcholine and cyclic GMP, if conclusively established in vivo, would clearly elevate even further the universal importance of cyclic GMP (and melanin). Of inestimable importance to cellular functioning is the role of guanine nucleotides in controlling the cytoskeletal microtubular system (625, 146). Such a means for regulating the diffuse microtubular network within the cell controls the transfer of various molecules throughout the cell, the mobility of various intracellular organelles, the movement of the plasma membrane (including protein lateral mobility), cellular animation, etc. (146, 727, 442, 573, 330, 423, 69).

The following facts suggest some interesting possibilities about melanin's postulated control over guanine. Not only do melanin and

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that the monoamines utilize cyclic AMP, while acetylcholine utilizes cyclic GMP, respectively, as second messengers (650). Wenk, et al (733) and other researchers have strongly emphasized that both a cholinergic and a monoaminergic (e.g. adrenergic) system [essentially keyed to the brainstem melanin system] appear to closely interact in regulating cortical activity and major brain functions. The close connections between the cholinergic and adrenergic neurons of the peripheral nervous system have been functionally (and anatomically) compared to the cholinergic and adrenergic neurons of the central nervous system. (The peripheral autonomic ganglia, with pluripotential capabilities, may produce either acetylcholine or norepinephrine (256, 282, 349, 363, 250, 272, 323, 336, 477), and noradrenergic neurons of the superior cervical ganglion (of the peripheral autonomic system) may actually travel into the CNS (e.g. the hippocampus) to re-establish disrupted adrenergic-cholinergic connections (117). The ultimate functional origin of the peripheral neuronal system may be the small intensely fluorescent (SIF) cells of the ganglia, whereas the origin of the central neuronal system may be the melanized brainstem loci. (Both the individual SIF cells and the individual brainstem melanin loci are highly melanized and may produce the different types of monoamines--dopamine, norepinephrine, serotonin--which apparently closely interact in the modulatory control of the nervous system.)

In a manner similar to the peripheral autonomic nervous system, Vizi (714) has offered evidence that CNS norepinephrine--(released from the axonal varicosities of nerves originating in the locus coeruleus, the melanized brainstem origin of norepinephrine, comparable to the noradrenergic SIF cells peripherally)-modulates the cortical release of acetylcholine. Villegas (713) has produced intriguing research indicating a significant interrelationship and effect of acetylcholine on peripheral glia (e.g. hyperpolarization). Since cyclic GMP has apparently been localized to the neuroglia of the CNS by immunofluorescence (123, 124) and since acetylcholine has been proposed to function via cyclic GMP (637, 650), then perhaps Vizi's studies indicating an adrenergic control of (cortical) acetylcholine and Villegas' studies indicating a significant acetylcholine effect on (peripheral) glial current may allow us to further unravel the complex mechanisms of the adrenergic-cholinergic modulation of the glial direct current in vivo, both centrally and peripherally.

guanine maintain an apparent phylogenetic and ontogenetic association (as do melanin and adenine), but the neuroglia (which have a close functional relationship with neuromelanin and adenosine) also maintain a close relationship with neuromelanin and guanosine. For example, immunofluorescence research suggests that cyclic GMP is localized on the neuroglia in the rat central nervous system (123, 124).

One of the most promising clues to a functional melanin-guanine link concerns free radical activity. Both superoxide ion and hydrogen peroxide can lead to the formation of hydroxyl radicals. As regards a potential melanin-guanine (or GMP) link: 1) hydroxyl radicals are involved in the pseudo-peroxidative (i.e. copper ion) synthesis of melanin (467), and 2) hydroxyl radicals activate guanylate cyclase, the enzyme producing cyclic GMP (396, 405). These hydroxyl radicals and the concomitant redox mechanisms triggered by them can explain the frequent observation of altered guanylate cyclase activity and cyclic GMP accumulation in tissues exposed to oxidizing and reducing agents. Since melanin is intimately involved with scavenging, maintaining, and apparently regulating in vivo free radical activity (in addition to using free radicals such as the hydroxyl radical in its own synthesis), melanin may very well employ a free radical-redox activation mechanism in physiologically regulating guanylate cyclase activity and cyclic GMP formation (755, 192, 655, 623, 772, 303, 634, 301, 622, 172, 638, 216). Furthermore, via its ion exchange properties (56, 584), melanin may control the in vivo binding/release of the copper, zinc, and manganese ions necessary to activate the superoxide dismutase enzymes (410); in turn, this enzyme(s) plays a major role in regulating the availability of the oxygen free radicals.

If melanin does indeed regulate the purines in vivo, and especially if it regulates the purine-containing cyclic AMP and cyclic GMP second messengers, then melanin has instant access to the organizational "reins" of living systems. Various neurotransmitters (such as dopamine, norepinephrine, epinephrine, serotonin, histamine, acetylcholine, glutamate, and prostaglandin E_1) and all types of peptide hormones, all appear to use this purine-mediated second messenger system in order to effect diverse intracellular protein phosphorylations (210, 309). This major type of covalent modification elicits a seemingly unlimited number of biological organizational effects (309, 525, 740).

However, in addition to phosphorylation-dephosphorylation, purines have been directly or indirectly implicated in many other types of reversible covalent modifications (750, 698, 630, 98) such as: 1) methylation-demethylation, 2) adenylation-deadenylation, 3) uridylation-deuridylation, 4) acetylation-deacetylation, and 5) S-S/SH (thiol) interconversions. These and other reversible covalent modifications provide the key means for ongoing organizational control in living organisms. Vital organizational processes such as: 1) chemotaxis, 2) exocytotic secretory processes, 3) membrane transport of ions and metabolites, 4) cytoskeletal contractile processes, 5) other diverse neurochemical phenomena, neuron-glia functions, enzyme-peptide-antibody functions, etc.--in other words, "life" itself--all require these reversible covalent modifications.

The key enzymes involved in these vital functions are arranged (and very rapidly covalently modified) within finely tuned cascade systems, in order to accurately and effectively produce the above effects. Stadtman's group (630, 98) has found that these strategically arranged enzyme cascades, controlled by reversible covalent modifications, serve as very powerful amplifier systems for both signal response and catalytic potential. They propose that these enzyme cascade systems may be the core means for metabolic regulation, with stimulus-responses occurring within the millisecond time range. We propose that melanin, by methods previously discussed, "triggers" these covalently modified enzyme cascade systems and is therefore the major organizing molecule in living systems.

THE PTERIDINERGIC CONNECTION

Keeping in mind the previous mechanisms of melanin's interrelationships with the purines and the incredible diversity of purine functions, let us now examine the pteridine molecules (191). Pteridines, along with the purines, have an important effect on the process of methylation, one of the cell's major means of covalent modification. S-adenosyl-methionine is the universal methyl group donor and is composed of the purine adenosine and the sulfur-containing amino acid methionine (696, 763). Pteridines are essential for the synthesis and transfer of methyl groups from homocysteine to form methionine (696, 687, 70, 41, 191).

The codon AUG (with the purine adenine leading) is not only the initiator codon for all mRNA strands involved in protein synthesis, but AUG also is the codon for methionine. Therefore, methionine is the amino acid that initiates all protein synthesis (86, 351). In addition, eukaryotic cell RNA's have two other interesting characteristics involving purines: 1) the 5' end of eukaryotic mRNA is "capped" with a 7-methyl-guanosine group, and 2) the 3' end contains a string of from 50 to 200 adenine nucleotides (called the poly A "tail"). Though many mechanisms have been suggested to explain these two sequences, their exact role remains unclear (86). The obvious involvement of both the purines and pteridines in these covalent modifications of the end sequences of mRNA may indicate a signalling and/or directing role for these covalent modifications in the interface between transcription and translation (351, 533). Since guanosine is necessary for the synthesis of the pteridine moiety (i.e. biopterin) and since the purines and pteridines may interconvert, a brief review of the pteridines will be helpful.

The pterin (2-amino-4 hydroxypteridine) moiety has two major functions in mammalian metabolism (688). First, as a core component of the folic acid molecule, it is involved with all of the diverse actions of folates. Second, as biopterin (pteridine cofactor) it is involved in hydroxylating tyrosine and tryptophan, the rate-limiting event leading directly to the synthesis of the catecholamines and the indoleamines, i.e the monoaminergic neurotransmitters. As previously noted, this hydroxylation is possibly a direct means for melanin to control monoamine neurotransmitter synthesis (428, 430, 687, 688, 689).

The functions of folic acid in living systems, like the functions of the purines, are numerous and vitally important (70). The folate coenzymes derive from tetrahydrofolic acid (FH_4) which functions in the transfer of one-carbon groups in a wide variety of vital biochemical metabolic reactions. For example, folic acid is necessary for pyrimidine and purine metabolism and thus for nucleic acid synthesis. It also appears essential for nervous system maturation and for controlling synaptic dynamics (317, 465). The diverse functions of folic acid in the nervous system (70) are fundamentally involved with many neurological and psychological disorders (e.g. schizophrenia, myelination disorders, mental retardation, epilepsy, etc.)

Ordonez (465) points out that the following pathways are closely interdependent: 1) methionine metabolism, 2) transmethylation, 3) transsulfuration, and 4) polyamine biosynthesis. All these metabolic systems rely on the pteridine-containing folate cofactor to function properly. For example, after synthesizing de novo the methyl groups used in one carbon transfer, the pteridine moiety can transfer the one-carbon/methyl unit to homocysteine via the vitamin B-12-requiring enzyme, B-12 transmethylase, to form methionine. Methionine can then participate in: 1) protein synthesis, or by conversion to S-adenosylmethionine (SAM), can bring about 2) all transmethylation reactions, and 3) it is essential in the biosynthesis of the polyamines spermidine and spermine. In addition, homocysteine can allow 4) transsulfuration reactions by its conversion to cystathione, cysteine, and taurine.

Transmethylation and Cellular Organization

Transmethylation reactions (696) are involved in all aspects of cellular organization, including the functions of nuclear DNA, the cytoplasmic secretory vesicles, the cell membrane, etc. (628, 181, 251). The effect of transmethylation upon the functioning of membranes in particular is vitally important in cellular functioning. For example, the methylation of membrane phospholipids by the universal methyl group donor, S-adenosylmethionine (SAM), has been thoroughly studied by Hirata and Axelrod (251). SAM-mediated asymmetrical methyltransferase enzymes in the cell membrane can cause the methylation of the membrane phospholipids phosphatidylethanolamine and phosphatidylcholine (presumably due to triggering by the cell's glycocalical surface receptors). Methylation of these membrane phospholipids translocates them, reducing membrane viscosity[1] and giving rise to numerous significant effects.

[1] The isopentenoids appear to play a major role in membrane visocity, the control of which is a major means of membrane organization. The steroid isopentenoids, in particular, have a major effect on membrane phospholipids, and these effects have been reviewed by Nelson (433). The isopentenoid cholesterol, found in essentially all eukaryotic membranes and a major constituent of glial cell myelin sheaths, provides membrane organization and stability. Alteration of membrane cholesterol can lead to changes in the plasma membrane functioning, including changes in ionic permeability, membrane fragility and microviscosity, protein lateral diffusion, protein-lipid interactions, molecular rearrangements, etc. (270).

For example, such diverse agents as catecholamine neurotransmitters (522), chemotactic peptides, lectins, immunoglobins, etc. can elicit such membrane phospholipid methylations when they bind to the cell's surface (251). This methylation is coupled to Ca^{++} influx across the cell membrane and to the release of arachidonic acid and its metabolites (which may also provide free radical activity) including such functionally significant molecules as the prostaglandins. In addition, such methylations often lead to the generation of cyclic AMP, which can subsequently effect molecular phosphorylations. This linking of methylation with phosphorylation, and thus of pteridines with purines, further indicates their interconnections in cellular functioning.

Transmethylations have major effects on behavioral control and signal transduction involving proteins, phospholipids, nucleic acids, etc. (628, 181). In a review of DNA methylation, Razin and Riggs (529) suggest that the methylation of DNA is a key element in the hierarchy of control mechanisms governing vertebrate gene function, expression, and differentiation. The essential role of folic acid in DNA synthesis is also well established.

Folic Acid and the Central Nervous System

Returning to folic acid (a key carrier of pteridine) let us review some of its roles in the functioning of the nervous system. Laborit (317) has reviewed the role of folic acid in the central nervous system and stresses that the carbon atom of the formyl group of tetrahydrofolic acid participates in several important reactions:

1) The formyl group is the source of carbons 2 and 8 in the formation of the purine nucleus which is the precursor of adenine and guanine.

2) Folic acid acts in the synthesis of proteins involved in establishing long-term memory and hence in the functional activity of the nervous system.

3) Folic acid participates in converting the amino acid serine to glycine. Glycine is a potent inhibitory neurotransmitter, whereas serine can be further metabolized to ethanolamine and then to choline; the acetylation (by acetyl-coenzyme A) of choline produces the well-known neurotransmitter acetylcholine. In addition, folic acid leads to the formation of taurine,[1] an abundant putative neurotransmitter in the brain.

4) Folic acid is key to such crucial methylation conversions as:

[1] Taurine appears to constitute a real enigma for researchers. Mandel (364) considers two main possibilities for the function of taurine in the brain: 1) as a putative neurotransmitter and 2) as a regulator of calcium and potassium fluxes. This latter hypothesis would be significant in neurotransmission and in secretory mechanisms in general and is highlighted by the fact that taurine is rapidly taken up by glial cells. Taurine also stimulates pineal N-acetyl-transferase activity and thus melatonin production (737). Other potential mechanisms for taurine have been postulated (26).

homocysteine to methionine (leading to many metabolic pathways); uracil to thymine (yielding essential nucleotide interrelations); and serine to choline. Choline, the precursor of the neurotransmitter acetylcholine (287), is achieving renewed interest because of its association with such mental functions as memory. Laborit notes that choline turnover (which reflects the equilibrium among its synthesis, utilization, and degradation) is regulated by the amount of available tetrahydrofolate. He also notes that ascorbic acid[1] (which appears to be concentrated in regions of melanin accumulation, such as the adrenal-chromaffin system and the brainstem melanin system), participates in reducing the pteridine nucleus and thus in producing and protecting the reduced form of tetrahydrofolate.

5) Folate participates in synthesizing phospholipids such as lecithins (phosphatidylcholine) and sphingomyelins by the intermediary action of choline. Folate effects cephalin (phosphatidylethanolamine) synthesis by forming ethanolamine from serine, and it effects phosphatidylserine synthesis via serine derived from glycine. Laborit concludes that folic acid is important in the synthesis of neuronal membranes and of myelin. This pteridine-mediated synthesis of neuronal membranes and myelin is a crucial factor in nervous system organization. Eppig and Hearing (162) present data supporting a role for phospholipids in optimizing tyrosinase activity, thereby enhancing melanin synthesis. This pteridine-membrane link may provide a major means for melanin (and perhaps the isopentenoids) to establish, maintain, and progressively modify the intricate membranal components and arrangements which are necessary for cellular organizational processes (644, 304, 426, 502).

6) Finally, a major function of folic acid in the C.N.S. (and one which requires a discussion of some closely related but functionally divergent molecules) is its participation in forming glutamic acid (glutamate) (167) by histidine degradation. The functional potential of glutamate in the C.N.S. is tremendous (387, 167, 515, 590). It is an important pivotal amino acid which may be converted into several other amino acids, into gamma aminobutyric acid (GABA), into glutamine, and into glutathione, all of which can provide further opportunities for organizational connections between melanin and the neuronal machinery. Interestingly, not only is the pteridine component of folic acid involved in glutamate formation, but folic acid per se contains from 2 to 7 (or more) glutamic acid residues which may participate in either glutamate or folic acid-related pathways (100). Such an intimate connection, within the same molecule, clearly supports a close functional link between pteridine and glutamate.

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[1] Ascorbic acid (Vitamin C) is abundant in brain tissue, yet relatively low concentrations have been shown to influence the sodium pump, receptor binding, second messenger functions, catecholamine biosynthesis, and the release of neurotransmitters (518, 296, 654, 67j). Depolarizing stimuli which normally release neurotransmitters concomitantly induce a marked increase in the concentration of vitamin C in the extracellular matrix (395) where its involvement with glycosaminoglycans is well established.

Current research is steadily uncovering evidence for glutamate-related mechanisms in major C.N.S. control systems. For example, a combined involvement of the purine adenosine with glutamate has been demonstrated in the depolarization-elicited neuronal accumulation of cyclic AMP (598). In addition, glutamate apparently participates in the important oxyglutarate reductive carboxylation pathway (127) which generates production of the C_2 (acetyl) units used for such acetyl CoA-requiring processes as fatty acid and cholesterol biosynthesis (both of which are essential for neuronal membrane and myelin sheath synthesis and maintenance).

Glutamate is probably the major excitatory neurotransmitter in the brain, yet its decarboxylation forms GABA, probably the major inhibitory neurotransmitter in the brain (167, 590, 591, 521). A wide variety of neurochemical experiments indicates that within the vertebrate C.N.S. there is a net flux of both the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA from the neurons into the astroglia, where a metabolic conversion of these amino acid neurotransmitters into glutamine occurs. Shank and Aprison (591) have reviewed those mechanisms which constitute this "glutamine cycle." They note that this process probably reflects the involvement of the astrocytic glia in maintaining very low extracellular levels of glutamate and GABA, by their uptake. Their subsequent conversion into glutamine allows glutamine to serve as a metabolic storage precursor for replenishment as needed, of neuronal transmitter pools of glutamate and GABA. In summary, following their respective roles in producing excitatory and inhibitory neurotransmission, both glutamate and GABA appear to be actively taken up by glial cells and are then converted into glutamine. Glutamine formation requires the enzyme glutamine synthetase, which is used as a glial marker since it appears almost exclusively within glial cells (708). If neuromelanin, by its control of the monoaminergic input to the neuroglia (32, 239, 240, 241, 701, 344, 730) can regulate the in vivo biochemical biasing of the neuroglia (e.g. by influencing the glutamine cycle) then neuromelanin may indirectly regulate the major means of excitatory and inhibitory neurotransmission within the brain (235, 249, 578, 646).

According to Seiler (586, 587, 588) another potential pathway for GABA formation in the brain is from the pteridine-related polyamine, putrescine. The mysterious enzyme ornithine decarboxylase, which produces putrescine, may be stimulated by either cyclic AMP or by glutathione (743), the latter molecule being a combination of the three amino acids glutamate, glycine, and cysteine.

Melanin is closely related to glutathione, cysteine, and the thiols[1] in general. For example, glutathione has been implicated in the control of melanogenesis (514, 106). Furthermore, the enzyme gluta-

[1] The phaeomelanins (and perhaps the lipofuscins to some degree) owe their variety of different colors (differential light absorption/reflection) to the sulfur present in cysteine, glutathione, etc.

thione peroxidase is involved in coupling dopamine (or serotonin) oxidation (i.e. through monoamine oxidase activity) to glutathione oxidation by generating hydrogen peroxide (362). (Perhaps melanin, by ion exchange mechanisms, controls in vivo glutathione peroxidase by regulating the availability of the selenium ion, which is essential for this enzyme's functioning).

Another important glutamate-related molecule is the controversial enzyme, γ -glutamyl transpeptidase (γ -GTP), known to be associated with the brain's vascular endothelial cells and with the neuroglial cells (138, 599). Several investigators suggest that γ -GTP functions in the degradation of glutathione, while others contend that γ -GTP translocates both peptides and amino acids across both the blood-brain barrier and cell membranes (387, 515). This enzyme may play a major role in peptide hormone regulation by mechanisms such as de-activating these peptides through cellular uptake or by adding a γ -glutamyl group. Prusiner (515) suggests that γ -GTP may indeed regulate the availability of biologically active peptides. Whether functioning as neuroendocrine hormones or trophic agents, etc., peptides have numerous essential roles (including nerve growth and maturation, emotion, motivation, memory, and other dynamic processes). Therefore, it is of special interest that neuroglial cells appear to both concentrate γ-GTP and to provide the inductive force for increasing vascular endothelial γ-GTP activity. In other words, by controlling γ -GTP, the neuroglia appear potentially able to control the availability of the biologically active peptide hormones (515, 138, 599) just as they apparently regulate the availability of glutamate, GABA, and other neurotransmitters (591, 167, 249, 241, 708, 242, 244, 344, 32).

The above sections have shown that pteridine is essential for carbon atom transfer into other molecules. Pteridine is functionally closely related to glutamate and glutamine. Glutamine is involved in nitrogen atom transfer into other molecules and is, therefore, also involved in numerous important syntheses (387). For example, glutamine provides nitrogen needed for synthesizing the purine rings, GMP, NAD, asparagine, CTP (cytosine triphosphate), and especially the amino sugar glucosamine-6-phosphate. This latter activated molecule (and its related conversions) is important for synthesizing glycoproteins and glycosaminoglycans and warrants further discussion.

The Glycoproteins/Glycosaminoglycans of the Glycocalyx

Several frequently discussed biological polymers contain relatively simple monomeric constituent units. For example, the nucleic acids are composed of the nucleotide monomers; the proteins are composed of the amino acid monomers; the simple (homogeneous) polysaccharides (such as glycogen) are composed of simple monosaccharide monomers. However, three ubiquitous cellular biopolymers are composed of a much more complex arrangement of monomeric constituents: 1) melanin, 2) the isopentenoids, and 3) the "complex carbohydrates". The primary representatives for this latter group of polymers are the glycosaminoglycans (sometimes called mucopolysaccharides or proteoglycans), which are complexly branching polymers composed primarily of "amino sugars".

Glycosaminoglycans (GAG's) are composed of the amino sugar glucosamine (along with its interconversions to other amino sugars such as galactosamine, etc.) and contain regular monosaccharide units as well. Integral glycoproteins (392, 339, 44) extending from the plasma membrane into the extracellular cell surface (the glycocalyx) also contain "amino sugar" building blocks and fulfill functions similar to the GAG's[1] in the glycocalyx.

The GAG's can function as cation exchange polymers (as does melanin) and are the mysterious antennae-like polymers which extend from the plasma membrane out into the extracellular matrix (44, 113, 274, 440, 363, 367, 339, 82, 728, 442, 392, 609, 570, 546, 274). Considerable research has shown that these GAG's are involved in cellular "recognition-activation" phenomena, and that they form the specific functionally active receptor sites for peptide hormones, neurotransmitters, antibodies, etc. (5,6,7,8,9,84, 442).

Adey and others (7, 8, 570, 546, 32) propose that the GAG's forming the glycocalyx are "cooperative" or "non-equilibrium" recognition-activation polymers which enable the brain's cerebral cortex to respond to very weak electromagnetic fields. Adey (5, 6, 7, 8, 9) points out that extremely weak non-ionizing electromagnetic (EM) fields (which raise tissue temperature several orders of magnitude less than 0.1°C) can still effect major physiological changes which the raised temperature alone cannot cause. Furthermore, these weak EM fields produce their chemical, physiological, and behavioral effects only within certain "windows" of particular frequency and intensity (7).

For brain tissue, the maximum frequency sensitivity occurs between 6 and 20 Hz. Between these frequencies, two different intensity windows have been detected. One is at the level associated with the control of human biological rhythms ($\sim 10^{-7}$ V/cm), while the other is at the level of the electroencephalogram (EEG) generated by the brain ($\sim 10^{-1}$ V/cm). These gradients are several orders of magnitude less than those classically considered necessary to generate neuronal action potentials. Adey emphasizes that the measured electrical gradients in the extracellular fluid surrounding brain cells (which have the magnitude of the EEG, $\sim 10^{-1}$ V/cm) have previously been considered to have no effect in exciting brain neurons. Some researchers have even dismissed these EEG gradients as merely the "noise of the brain's motor" (7). However, the latest neurophysiological, neurochemical, and behavioral evidence strongly indicates that these small electrotonic gradients[2]

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[1] For brevity, the term glycosaminoglycans, abbreviated GAG's, is used to refer to all the glycoconjugates (glycoproteins, glycolipids, and glycosaminoglycans) of the glycocalyx/extracellular matrix.

[2] Glycoconjugates play an essential role in nerve fiber (neurite) growth (488). Furthermore, applied electric fields (electrotonic gradients) of 0.1 to 10 V/cm have striking effects on the orientation and growth of neuronal neurites (475). This remarkable organizational control of the spatial (and hence, functional) disposition of neuronal fibers by direct/analog current is postulated to occur by the analog current's effects on the cell surface (glycocalyx) glycoconjugates (475).

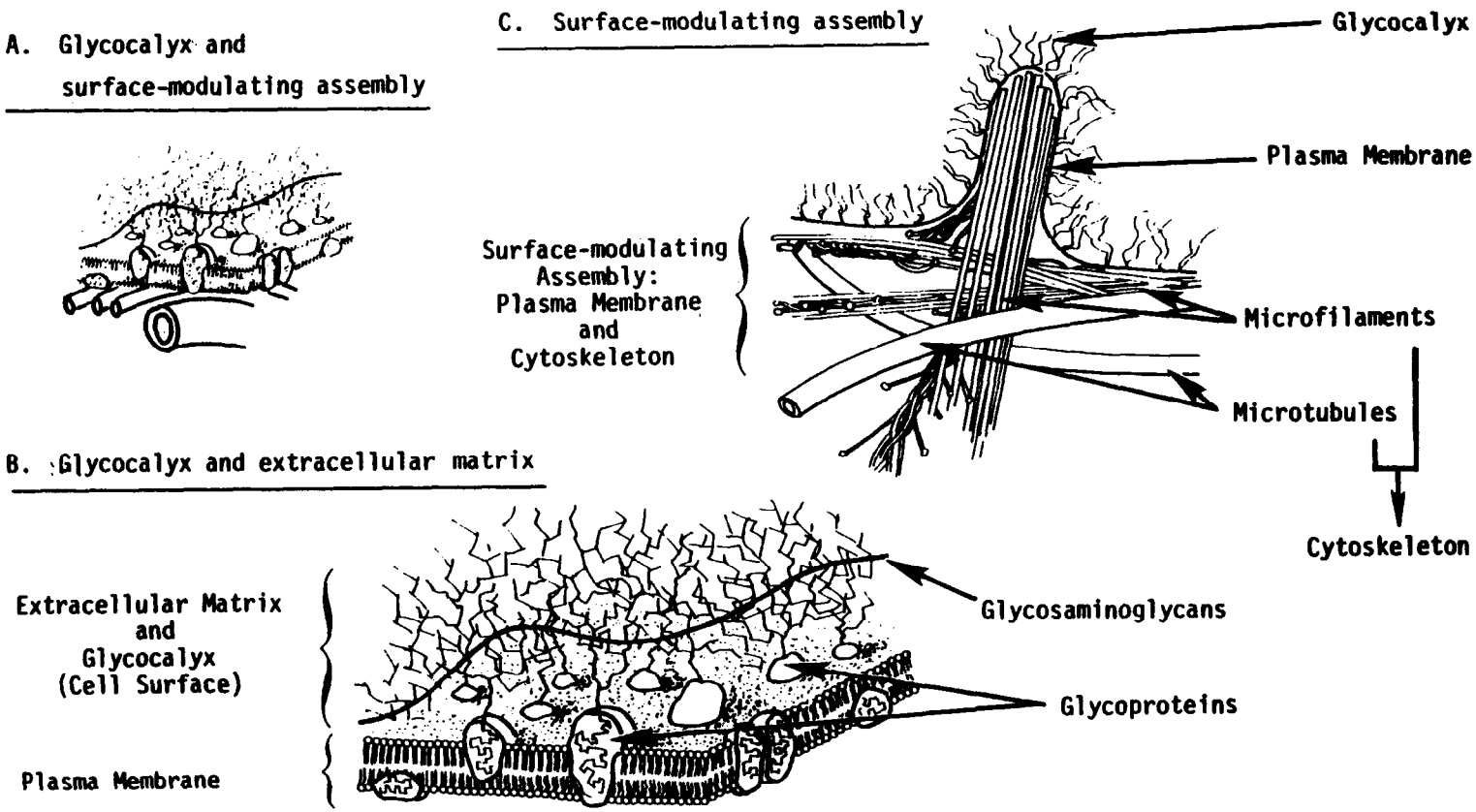


Fig. 6 The Glycocalyx and Surface Modulating Assembly

play an important modulatory role in the functioning of the brain (1, 7, 8, 574, 576, 83, 32).

The "cooperative" GAG's of the glycocalyx (of cerebral cortical neuronal dendrites (570, 546, 114, 5, 6, 7, 8), for example) appear to "recognize" specific molecular and electromagnetic input to the cell and accordingly "activate" the inner cellular machinery into a functionally meaningful response. The "recognition-activation" mechanism provided by these complex polymers at the cell surface would therefore appear to be an essential means for regulating each cell and would seem, therefore, to be of the highest priority for future research. (See Figure 6 and reference 442). What are some of the mechanisms available for the organizational control of these cell surface GAG receptor-activators?

First, consider these facts: 1) glucosamine and its interconversions constitute the essential amino sugar constituents of the GAG's; 2) glutamine is a functional precursor for glucosamine (though not necessarily the only precursor); 3) glutamine formation in the brain is apparently restricted to the glial cells. Though insufficient evidence is available to provide a definitive answer to the organization of the GAG's, these relationships indicate that the glia might regulate (e.g. via control of glutamine synthetase) the glutamine available for both the glia and the neurons. This glutamine could in turn, convert to glucosamine and then into the GAG's of the glycocalyx. (502, 426, 32). However, there may be other mechanisms for supplying glucosamine (and related amino sugar monomers) to the brain for GAG formation.

Second, the pteridine moiety (as folic acid) is intimately involved in the maturation and functional dynamics of both the neuronal plasma (e.g. synaptic) membrane and the myelin sheath of the oligodendroglia (317). Perhaps the involvement of pteridine in both glutamine synthesis and in brain cell membrane synthesis is a key factor in establishing and maintaining the GAG's of the cell surface.

Third, the melanin-related isopentenoids appear to play a major role in forming glycocalical GAG's. The isopentenoid cholesterol is essential for the organizational functions of in vivo membrane and is accordingly present in significant amounts within neuronal membranes. It is found in particularly high amounts in the myelin sheaths of the oligodendroglia which surround neuronal axons. However, the most dramatic isopentenoid mechanism known to participate in establishing the glycocalical GAG's involves the isopentenoid (polyprenol) carriers.[1] These lipid-soluble isopentenoid carriers (719, 141, 751, 403) carry at least some of the activated constituents of the GAG's across the plasma membrane and into the extracellular matrix, resulting in the

[1] The most common isopentenoid involved in proteoglycan and glycoprotein synthesis is dolichol, an isopentenoid of 80-100 carbons. The isopentenoids vitamin A and vitamin K may also function as activated sugar carriers (719). Phosphorylated dolichols have been shown to be involved in glycoprotein synthesis and simultaneously involved in cholesterol biosynthesis (403).

functional formation of the glycocalical-extracellular GAG's and, hence, the cell surface receptors.

Finally, the coated pits/coated vesicles (or coated pits/receptosomes) of the cell, in combination with the lysosomes, appear to periodically remove, process, and replace the glycocalical/cell surface receptors (485, 486, 136, 527, 631). (See Figure 8.) The lysosomes (and melanolysosomes) are the cellular organelles which both synthesize and store most of the cell's melanin and which also compartmentalize and sequentially utilize an enormous storehouse of enzymes (96, 734, 631, 244). If the melanin within these lysosomes can selectively activate and control these various lysosomal enzymes (by the mechanisms previously discussed), then melanin could be the organizational entity responsible for the periodic processing of the cell surface GAG's, modifying them as needed.

Some or all of the above mechanisms (in addition to other conceivable mechanisms that have been suggested for glycocalical GAG receptor regulation) may also make use of another well-established factor involved in synthesizing the "complex carbohydrates". That is, the amino sugars and the other activated sugars that compose the glycocalical GAG's usually first combine with nucleotides to form "sugar nucleotides" before crossing the plasma membrane into the glycocalyx (113, 44, 82, 367). These sugar nucleotides could be the possible missing link between the nuclear (genetic) potential of the cell and its extra-cellular (environmental) influences (609).

In reviewing cell surface DNA, Reid and Charlson (530) have proposed that if the enzymes pyrophosphatase and glycosyltransferase (498) exist at the cell surface (as appears to be the case), then a mechanism is available within the glycocalyx for the simultaneous formation of both DNA and GAG's/glycoproteins. That is, as the nucleotide is enzymatically separated from its (amino) sugar constituent, each separate constituent may simultaneously be synthesized into its respective DNA or GAG/glycoprotein polymer. (Furthermore, evidence has been presented for the synthesis of distinct nucleic acids extracellularly (653, 404) and for the presence of distinct GAG's within the nucleus (649)). Such a potential environmental/genetic link (609) could explain both normal (343) environmentally influenced development (ontogenetic and phylogenetic) as well as known pathological environmental influences upon development. For example, Skolnick, et al (606) have presented research strongly suggesting an "environmental" influence upon the genetic transmission of stress-induced ulcers in rat progeny. Reid and Charlson's proposal (or a modification of it) for a direct cell surface GAG-DNA connection is a potentially important integrative hypothesis deserving further sophisticated scrutiny. (See Fig. 7 and reference 530).

Polyamines and Transglutaminases

Another important group of molecules derived through pteridine metabolism is the polyamines (743, 383, 588, 596), ubiquitous small molecules which, as polycations, can bind to such polyanions as melanin,

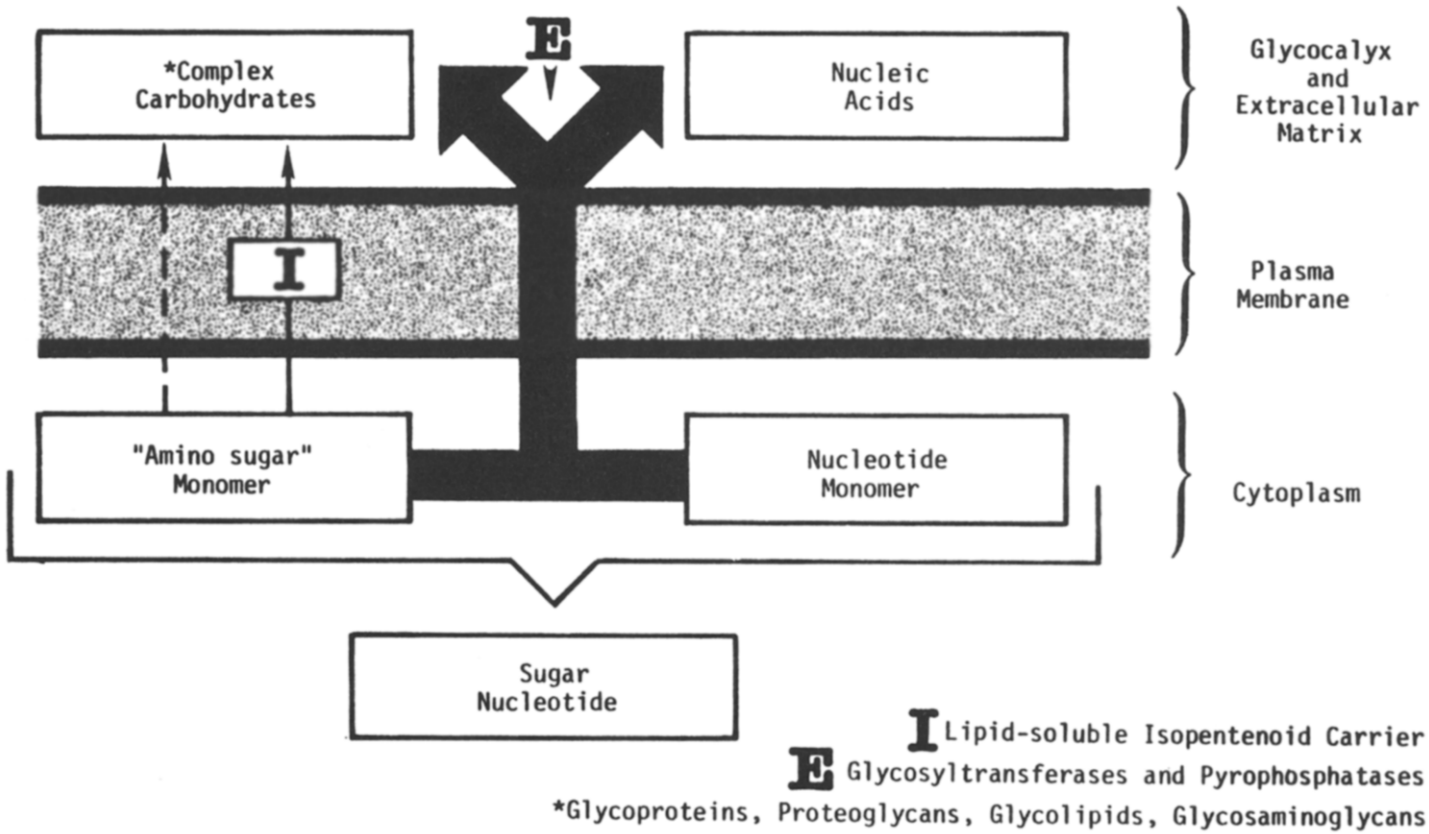


Fig. 7 The Reid-Charlson Hypothesis

nucleic acids, GAG's, phospholipids and myelin. In fact, many of the known polyamine reactions closely resemble those of divalent cations such as Ca^{++} and Mg^{++}. Polyamines are particularly well known for their binding to nucleic acids, and during any kind of cellular (and nuclear) proliferation, the polyamines rapidly increase in quantity and are therefore thought by some to be involved in stimulating DNA synthesis (743, 658, 2). Polyamines are derived from methionine (through pteridine metabolism) and may be involved in numerous diverse cellular functions. For example, polyamines might regulate the immune response (674, 156). In addition, they have been proposed to modulate calcium-dependent secretory processes as well as other calcium-dependent cellular activities by several mechanisms, including methylation and phosphorylation reactions.

Williams-Ashman and Canellakis (743) have shown that the polyamines can selectively influence the copying (transcription) by RNA polymerases of one strand of the DNA templates. They also note that the polyamines can influence the translation of specific mRNA's in isolated ribosomal systems. Furthermore, the polyamines spermidine and spermine can variously affect in vitro cell-free systems that synthesize, degrade, and modify nucleic acids, or utilize nucleic acids for protein synthesis. These effects may be either positive or negative, depending upon the concentrations of spermidine and spermine as well as many other factors, including the system's ionic strength, pH, temperature, and Mg^{+++} levels. These latter factors are all accessible to control by melanin.

Purine- and pteridine- mediated SAM is essential for the synthesis of the polyamines and 5'-methylthioadenosine, the latter a terminal product formed during polyamine synthesis. 5'-methylthioadenosine is important because it seems to be a natural re-cycler of the raw purine adenine, allowing adenine to be re-used in many other metabolic reactions (743).

The rate-limiting enzyme for polyamine synthesis is ornithine decarboxylase (ODC). This fascinating enzyme, having the shortest half-life of any enzyme yet examined, occurs in a multiplicity of forms which apparently result from various post-translational covalent modifications (743). Both the thiol compounds and cyclic AMP have been proposed to activate this enzyme covalently. In the brain ODC activity has been shown to be affected by thyroxine, cortisol, growth hormone, prolactin, insulin, and nerve growth factor (743, 383, 588).

Polyamination is another mechanism through which melanin may affect cellular functions. Rennert, et al, (532) in a review of protein polyamination have proposed that polyamines may: 1) effect specificity in cell growth; 2) be transported by proteins to various areas of need; 3) signal for specific protein degradation; 4) bind to the cell surface (glycocalyx) and cause numerous secondary effects, and 5) be involved in endocytosis and other cellular uptake processes. These latter two functions in particular appear to be stimulating interest in polyamines. These cell surface functions seem to center

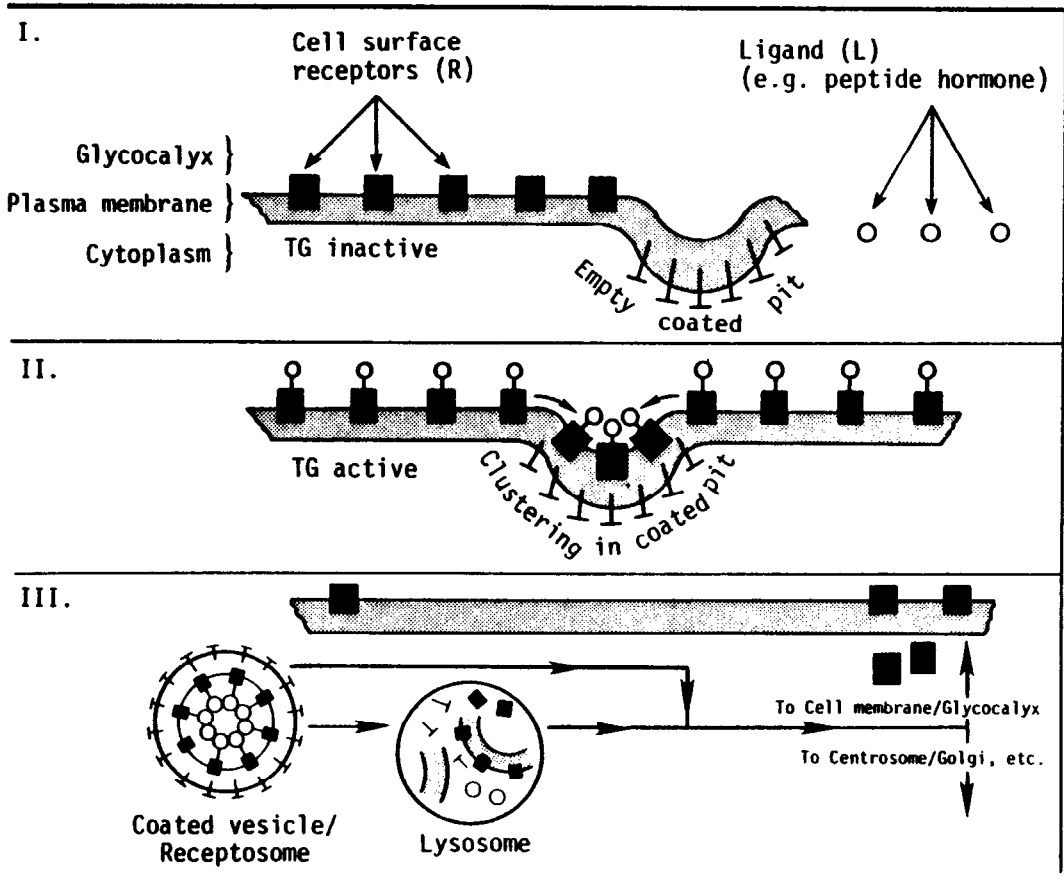
upon enzymes called transglutaminases which use both polyamines and glutamine.

Transglutaminases are enzymes which act as catalysts in coupling polyamines to the γ -carboxyl aspect of the glutamine residues of proteins (744, 174, 743). Of major importance is that this cross-linking form of covalent modification has been implicated in the cycling of coated pits and coated vesicles/receptosomes (486, 489). In particular, this transglutaminase-mediated cross-linking, occurring at the glycocalyx-plasma membrane, may control receptor-mediated endocytosis, and consequently the cellular uptake of cholesterol, α 2-macroglobulin, various peptide hormones, etc. (136, 342, 80, 81). (See Figure 8.) Furthermore, such transglutaminase-mediated protein-protein or polyamine-protein linking may be one mechanism through which the immune response and other membrane recognition-activation responses may occur (156). These linkages are undoubtedly involved in membrane clustering events and appear to bind the glutamine residues in the HLA-A and HLA-B antigens (503).

In addition to their involvement in the process of receptor-mediated endocytosis (via transglutaminase-activated mechanisms), polyamines stabilize membranes and could modulate plasma membrane protein lateral mobility by modifying the proteins of the cytoskeletal surface-modulating assembly (571). In fact, polyamines may be required for the maintenance and functioning of both the microtubules and the microfilaments (487). Further important roles for these ubiquitous polyamines can be anticipated.

As regards the cytoskeleton, the purines and pteridines may effectively regulate the cytoskeletal surface-modulating assembly (see Figure 6) by several mechanisms, including: 1) regulation of the synthesis and distribution of the polyamines, 2) involvement in transglutaminase-activated receptor-mediated endocytosis (involving both the polyamines and glutamine), 3) regulation of the assembly and functioning of the cytoskeletal microtubules (under guanine nucleotide control), 4) regulation of calcium ion-related membrane and microtubule functioning by regulation of calmodulin,[1] etc.

[1] Calmodulin (97, 385, 647) is a protein found to regulate Ca^{++} functioning in the cell. A most distinctive feature of this calcium ion-regulatory protein is that the amino acid lysine (located at position 115) is post-transcriptionally trimethylated (385). This multiple methylation preserves the positive charge and may have a significant control function for calmodulin per se. Hirata et al (182) have presented evidence that the enzymatic post-translational methylation of calmodulin inhibits its stimulatory effect upon cyclic nucleotide phosphodiesterase. Furthermore, this group has presented additional evidence that carboxyl methylation of calmodulin occurs in intact cells. Therefore, melanin, via post-translational covalent methylation, may regulate calmodulin and hence a multitude of cellular responses keyed to calcium ion control. In addition to control of calmodulin by covalent modification, one generalized theory of zinc-calcium antagonism is centered on the zinc-related control of calmodulin (29, 51). Melanin's proposed regulation



I. Diffuse mobile receptors of glycocalyx

II. 1) Ligand-receptor (L-R) binding

2) Clustering of L-R complexes in coated pit

3) Activation of transglutaminase (TG) with covalent cross-linking and progressive accumulation of L-R complexes

III. 1) Endocytosis of coated vesicle/ receptosome

2) Fusion of coated vesicle/receptosome with lysosome

3) Lysosomal processing and receptor recycling

Fig. 8 Transglutaminase and Receptor-Mediated Endocytosis

In summary, pteridine- and purine-mediated covalent methylations regulate innumerable mechanisms which are collectively responsible for cellular behavioral control and signal transduction and which are major means for effecting and maintaining organization within living organisms. In addition, the pteridine-purine connection is potentially involved in the synthesis and control of the neurotransmitters glutamate, GABA, glycine, acetylcholine, taurine, etc., and, via δ-GTP, in the regulation of peptides (both hormones and trophic factors). Furthermore, this pteridine-purine connection extends to the polyamines, with their numerous postulated organizational involvements, especially the process of membranal transglutaminase/receptor-mediated endocytosis (which may turn out to be one of the chief mechanisms for controlling the immune response, cholesterol cycling, peptide hormone response, and other reactions involving the coated pits/coated vesicles/receptosomes). Finally, the synthesis and functioning of the nucleic acids and the glycosaminoglycans, as well as the membrane phospholipids and myelin are all dependent upon purine- and pteridine- related mechanisms. Since melanin has numerous means of controlling the purines and pteridines, we can again see the potential for melanin to be the major organizational molecule of the cell (See Figure 9).

AN OUTLINE OF CELLULAR PROCESS

Before proceeding to the discussion of the APUD system, which takes us from molecular systems (such as enzyme covalent modification cascades) to advanced embryological tissue/organ systems (such as the vertebrate neuroendocrine system), we should briefly review the organizational unit which is totally responsible for the origin and maintenance of the negentropic process called "life" (organic organization)--the cell. Molecular systems outside the cell (such as DNA-containing viruses) are without "life", whereas primitive and advanced tissue/organ systems are entirely dependent upon the negentropic processes of the underlying cell for their origin and maintenance.

A review of the cell's functionally discrete subcellular components should further illuminate melanin's organizational capacity. The following is a brief systematic analysis of the functional organellar components of the cell. It is not comprehensive but is offered as a general outline of organellar functioning in relation to cellular process as a whole (See Figure 10).

1) The eukaryotic nucleus (derived from the original membrane-bound nucleic acids of the prokaryocyte) is responsible for the potential genetic development of all parts of the cell.

2) The nuclear membrane-endoplasmic reticulum (and sarcoplasmic reticulum in muscle cells) is a continuous dynamic fluidic complex

(binding/release) of the zinc ion, which, in turn, may control calmodulin, would be a plausible means for melanin to regulate *in vivo* the calcium ion (in addition to melanin's own direct binding and release of these ions).

Melanin's interactions (via the purines and pteridines) in the formation of 1) membrane systems, 2) the glycocalyx, 3) neurotransmitters, and in the functioning of 4) major covalent modification systems.

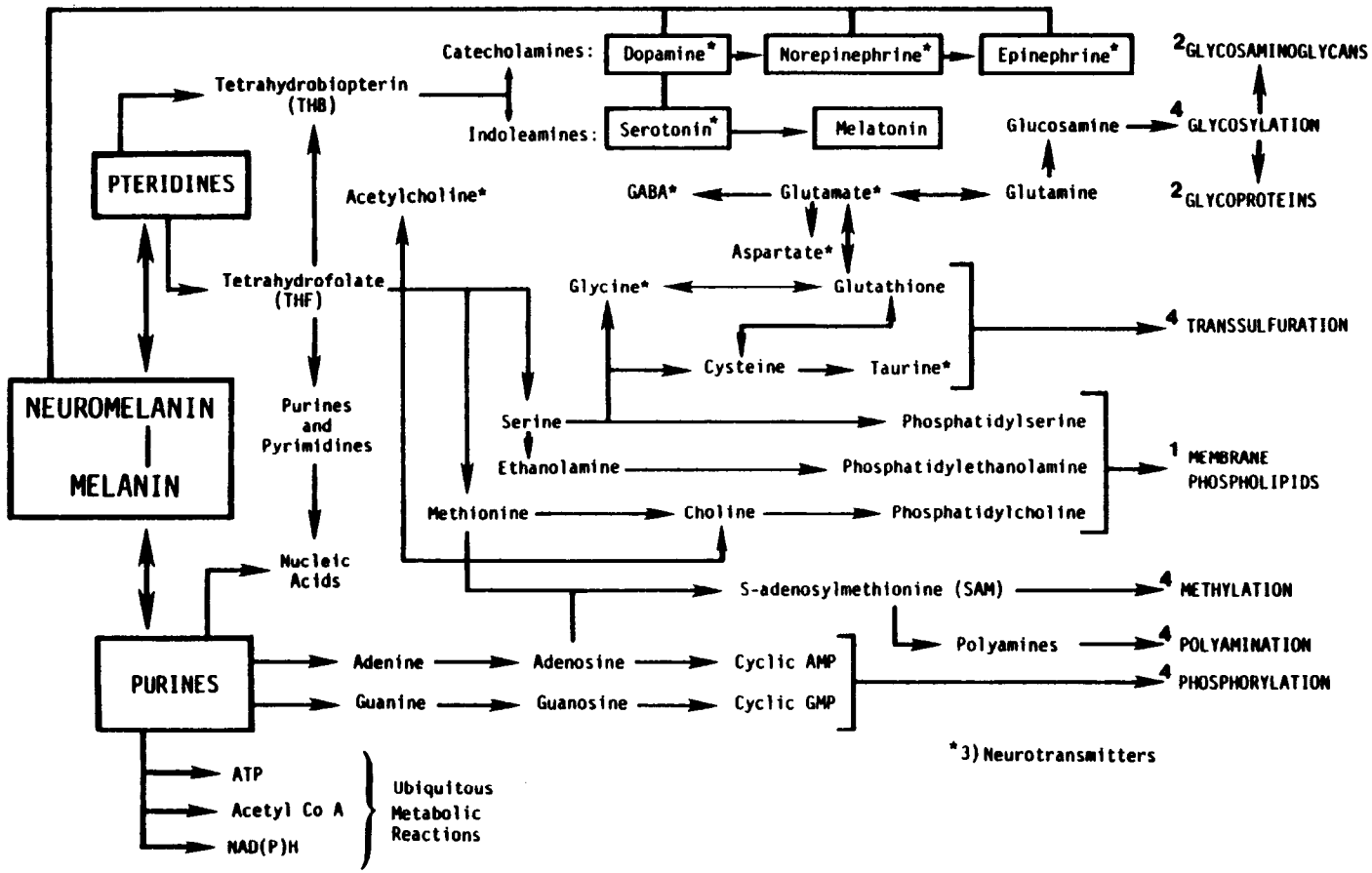


Fig. 9 The Melanin-Purine-Pteridine Molecular Organizational System (Abbreviated)

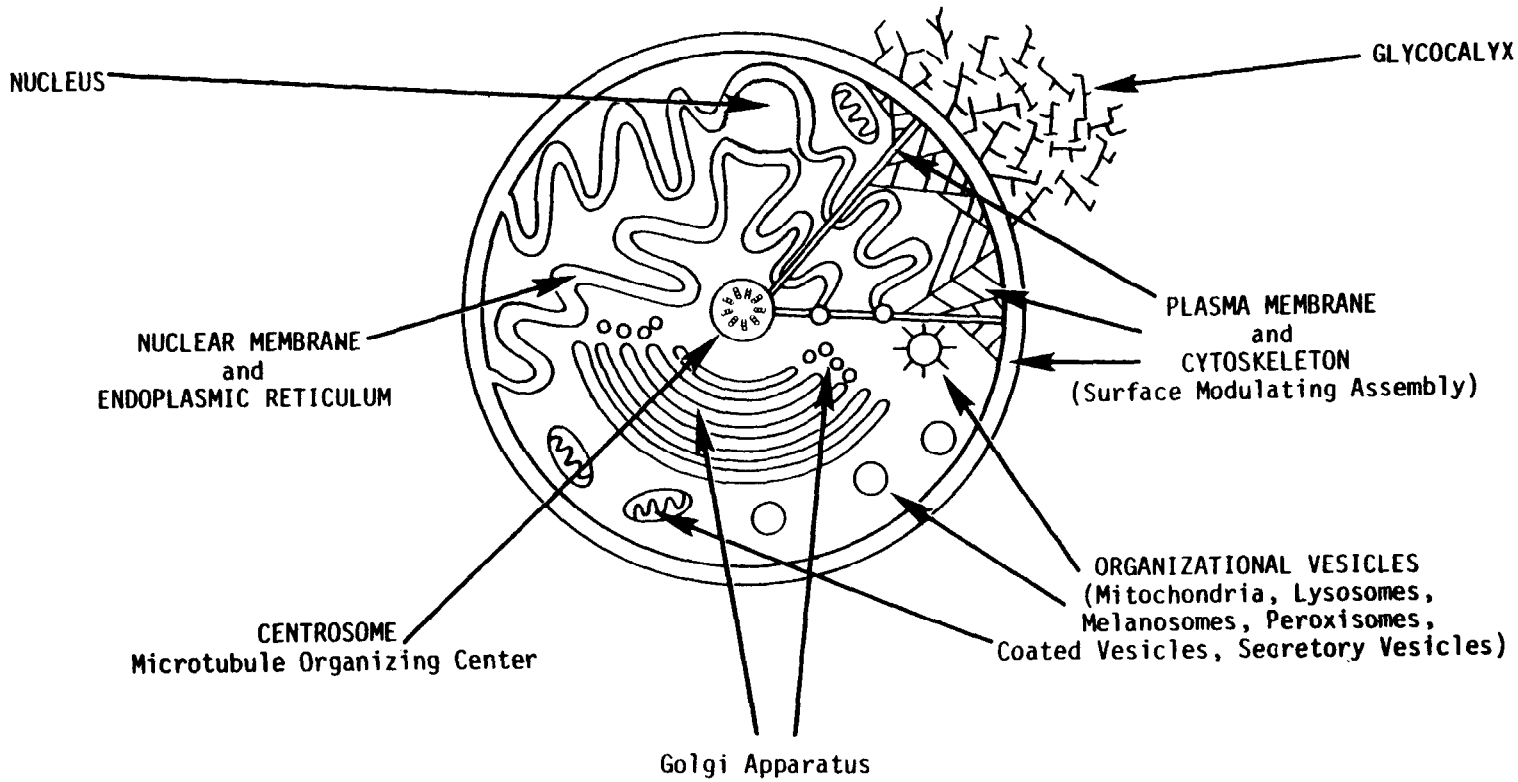


Fig. 10 Subcellular Organelles

of membranes which show remarkable binding properties. This organellar system binds the ribosomes from the nucleus and acts as a repository and transport system for the newly translated "raw" proteins. Furthermore, the endoplasmic reticulum (and sarcoplasmic reticulum) is the binding site for numerous ions (particularly calcium ions (237)) which provide the charge necessary for accomplishing many dynamic activities (including enzyme catalysis, secretory processes, etc.). In addition, this system is the site of extensive free radical formation and electron transfer (redox) dynamics (104). Finally, this primordial reticular substance is an energized membranal precursor for the organizational vesicles. (See below).

3) The centrosphere or centrosome (with its centriolar complex or microtubule-organizing center) appears to stabilize the cell by establishing the cell's fixed center from which the dynamic cytoskeleton is controlled (69). In addition the centriolar apparatus may regulate the form[1] or shape of the cell by its cytoskeletal control. For example, the centrosphere appears to regulate the spatial organization of cell organelles such as the endoplasmic reticulum and the Golgi apparatus (69).

4) The Golgi apparatus functions as a sort of factory or packaging plant for the contents of the "organizational vesicles" and appears to have an ordered sequence, with a beginning and end to its processing (736, 667, 554). The membranes of the mature (or terminal) aspects of the Golgi have significant increases in cholesterol (464), a membranal organizational isopentenoid. The Golgi apparatus appears to function as a combinational system in that: a) it contains both tubular-like cisternae (similar to the endoplasmic reticulum) and vesicles; b) its membranes' width and constituents seem to be a mixture between the endoplasmic reticulum and the plasma membrane; c) it links the fluidic endoplasmic reticulum (with its incomplete products) to the very complex plasma membrane (with its completed, highly functional components), and d) it has been proposed (with considerable support) to be a combination of two organelles, operating in tandem (554, 667, 736). The terminal or mature aspect of the Golgi (the membrane plus its contents) produces

[1] In an attempt to study the ontogenesis of subcellular organelles, Guraya (214) has integrated a tremendous amount of data concerning organellar maturation in animal oocytes. In particular, Guraya notes that Balbiani's vitelline body (also called the yolk nucleus) is the centrosomal equivalent of the early oocyte, which is destined to become the centriolar complex in the mature oocyte. This centrosomal organelle (located in the center of the cell) very early accumulates nucleoprotein (ribosomal material) and gradually forms, centers, and spatially distributes the ribosomal-endoplasmic reticulum (as well as the other organelles). In addition, this primitive centrosphere appears to be the source of relatively large amounts of phospholipids, apparently used in the formation of membranes of the cellular organelles. Guraya's review thus provides additional evidence for the centrosome's core function of establishing the spatial arrangement of the subcellular organelles and hence providing the spatial information or form of the cell.

secretory vesicles for delivery to the plasma membrane, etc.

5) Numerous vesicular organelles, such as the lysosomes, the peroxisomes, the melanosomes, the coated vesicles/receptosomes, secretory vesicles, and the synaptic vesicles, (as well as the mitochondria--a special case) are closely interrelated and appear to function chiefly as compact organizational vesicles (242, 769, 380, 723, 135, 89, 485, 489, 24, 55). These membranal systems compartmentalize, integrate, organize, and selectively release various enzymes, neurotransmitters, peptide hormones, plasma membrane/glycocalyx components, etc., which influence or accomplish numerous organizational metabolic processes.[1]

The organizational vesicles frequently appear to use the fluidic endoplasmic reticulum (with its flexible and energized membranes) as a precursor substance. For example, such organizational vesicles as the lysosomes and the peroxisomes may derive directly from the smooth endoplasmic reticulum (55, 380). Furthermore, all pigment organelles (24, 690) appear to derive primarily from nuclear membrane-endoplasmic reticulum (with content contributions from the Golgi). Electron microscopic studies of neurons have shown that the mitochondrion appears to fuse its outer membrane with the membrane of the endoplasmic reticulum in order to transport itself through the cell (346). In fact, the outer membrane of the mitochondrion may be entirely derived from the membrane of the endoplasmic reticulum.

6) The cytoskeleton (consisting of the microtubules, the microfilaments, and the intermediate filaments) and the plasma membrane are collectively referred to as the surface-modulating assembly (158, 409). All (or parts) of this assembly are the principal means for molecular, organellar and cellular animation. The involvement of the cytoskeletal network in modulating the plasma membrane (including protein lateral mobility) and in transporting organizational vesicles to and from the plasma membrane (allowing for such functions as endocytosis and exocytosis) is of paramount importance (442, 330, 423, 573, 727).

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[1] Lysosomes, which have an extraordinary variety of forms, contain melanin in varying amounts and are thought to be a primary site of synthesis of neuromelanin (705, 452). Peroxisomes contain peroxidase (and catalase), which is involved in melanin synthesis. Mitochondria, whose outer membrane may be of endoplasmic reticulum origin, have been shown to contain (and possibly synthesize) melanin. Other organizational vesicles, such as the coated vesicles/receptosomes, and the synaptic vesicles, should be investigated for the presence of melanin. In fact, Maul and Brumbaugh (539) suggest that the multi-vesicular bodies (vesicular aspects of melanosome formation) are actually derived from coated vesicles, which lose their "coat" when they are incorporated into melanosomes. "Coated vesicles" (derived from "coated pits" of the plasma membrane during receptor-mediated endocytosis but minus the bristles) have been called "receptosomes" (489). Receptosomes appear to migrate from the cell surface to the centrosome and to process their contents through the Golgi, the lysosomes, etc. This glycocalyx-centrosome shuttle system should be kept in mind when we consider the interactions of melanin with the centriole.

7) The glycocalyx, extending from the cytoskeletally animated plasma membrane outside the cell and projecting into the extracellular matrix, consists of antennae-like integral glycoproteins, glycolipids, and glycosaminoglycans (all containing complex carbohydrate polymers of amino-sugar monomers). These glycocalical molecules are the sites of cellular recognition-activation phenomena (including such recognition-activation properties as are seen in antigen-antibody reactions, peptide hormone responses, neurotransmitter responses, and electromagnetic windowing, etc.) Through exercising such recognition-activation capabilities the glycocalyx would appear to have dominion over the cell and over its interactions with other cells and with the extracellular environment.

Furthermore, if Reid and Charlson are correct, both glycoproteins/glycosaminoglycans (GAG's) and DNA are simultaneously formed extracellularly in the glycocalyx. (In addition, the nucleus itself contains both nucleic acids and glycosaminoglycans.) In short, this postulated interconnection between the extracellular glycocalyx and the intracellular nucleus offers a potential solution to the long-sought problem of genetic vs. environmental control of the cell (which is most dramatically illustrated during embryological differentiation). This postulated cooperative interaction between the glycocalical molecules and the nuclear molecules seems to complete the circuit of cellular process and to bridge the gap between nuclear (genetic) potential and glycocalical (environmental) dominion.

SELECTED MOLECULAR AND ORGANELLAR MECHANISMS FOR POTENTIAL MELANIN-DIRECTED CELLULAR ORGANIZATION

The centrosome (or microtubule-organizing center) with its cytoskeletal extensions throughout the cell is a promising site for further investigation of possible mechanisms for cellular organization. This cellular complex is analogous to a bicycle wheel with all the spokes (microtubules) centering on the hub (the centrosome). A close functional interaction occurs between the components of the cytoskeleton (the microtubules, intermediate filaments, and microfilaments) and the plasma membrane (and, by extension from the latter, the glycocalyx) (442). Edelman (158, 409) calls this dynamic functional system the surface-modulating assembly (SMA). (See Figure 6.)

The control center of this SMA is also the cell's center (the centrosome, centriolar complex, or microtubule organizing center). M. Bornens (69) has presented a brilliant integrative theory that the centriole, by controlling the cytoskeleton, acts as a gyroscopic oscillator with the ability to coordinate all cellular activity, including growth, division, metabolism, circadian rhythms, etc. (See Figure 11 and references 69 and 506.) A current review of the centrosome and its cytoskeletal "freeway system" in the neuron (330) has emphasized the importance of this system and makes Bornen's theory even more likely. The review concludes that the centrosome-SMA combination is intimately involved in the growth (plasticity) and functional maintenance of the neuron and in the complex communication between the widely separated regions of this highly asymmetrical cell.

The centriole contains measurable amounts of steroids (435), nucleic acids (530), and silicon (69). The exact function of the centriolar nucleic acids remains to be elucidated. Steroids, being isopentenoids[1], bind to the regulatory acidic proteins of the nucleus (92) which effect mRNA transcription and subsequent protein synthesis. These nuclear acidic proteins (e.g. tubulin, actin, myosin, etc.), affected by steroid binding, appear to be the major means for activating the various genes within the nuclear DNA molecule (632, 92). They are also the same type of proteins which compose the cytoskeleton. In another article, Bornens shows a direct connection between the centriole and the nucleus (371). Other researchers suggest that the cytoskeletal proteins not only connect with the plasma membrane but also penetrate the nucleus, providing an intracellular "membrane-gene linkage" (576, 624, 404). These acidic nuclear proteins may attach directly to the DNA strands and may control the "on-off" effects of the various genes. Finally, Bornens (69) proposes that the silicon (noted for its semiconductor properties in computer microcircuits), which is found in relatively large amounts in the centriole, may function as a piezoelectric crystal. He suggests that this silicon-mediated signal emanates from the centriole and may be transmitted to the cell surface and throughout the cell via the hollow microtubules extending from the center to the periphery of the cell. A similar function for the microtubules has been proposed by Popp et al. (504).

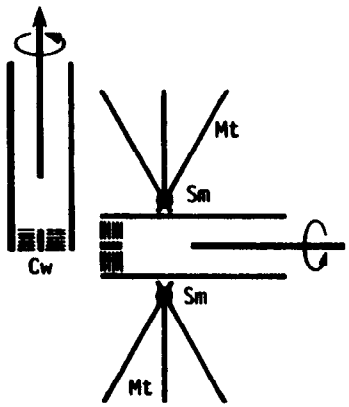
Bornens (69) discusses other possibilities for the centriole as an organizational center for cellular metabolism. He notes, for example, that all light-absorbing cells (such as the rods of the eye and the functional light receptors of the pineal "third eye"), as well as the cellular motility components of the cilia and flagellae, derive from a centriolar prototype. This light-sensitive centriolar complex could indeed be a major organelle involved in establishing circadian rhythms and receiving electromagnetic signals since the centriole appears to connect with the cell surface via the cytoskeleton and could therefore receive information from the glycocalical surface network by means of the latter's "windowing" of very weak electromagnetic radiation (7).

In summary, the centrosome (and its dynamic surface-modulating assembly) may represent a cellular center for the organizational mechanisms which allow for the subtle modulation and coordination of cellular activities. Any serious contender for the role of "cellular organizational molecule" might therefore be expected to have the capacity to accumulate at the centriolar complex. (For example, steroids accumulate in the centrosome and may be considered to be "organizational molecules"). This raises the question of whether melanin has functional access to the centrosome.

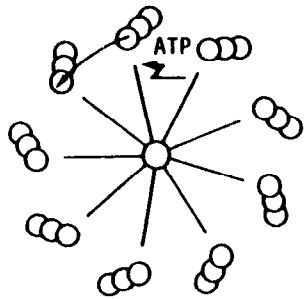
Within fish, amphibian or reptile chromatophores, grossly observable melanin granules have been shown to be capable of almost instantaneous movement to and from the cell center (436, 573, 506, 767, 677, 320),

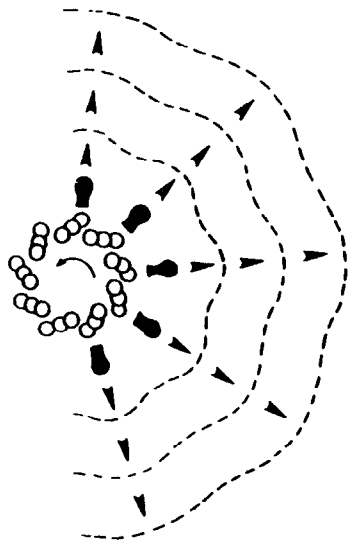
[1] Siperstein's group has shown that mevalonate, the immediate precursor of the various isopentenoids, has an essential role in DNA replication (520).

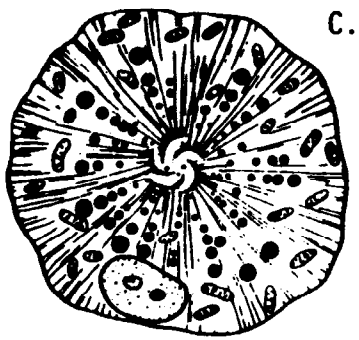
A. Schematic illustration of the two orthogonal rotating centrioles (within the centrosphere). Note the microtubules (Mt) and their association with the centriolar satellite masses (Sm) and the centriolar cartwheel structure (Cw).



B. A head-on view of the cartwheel structure of the proximal centriolar cylinder indicating ATP-activated stepwise rotation of centriolar triplets with respect to cartwheel spokes.







C. An illustration of the melanosomes utilization of the cytoskeleton (in chromatophores) for rapid movement to and from the centrosome.

D. Schematic representation of the origin centriolar cylinder's proposed role of oscillator for the propogation of phased signals in the cell. Microtubules are not shown here

Fig. II The Centrosome (Centriolar Complex/Microtubule-Organizing Center)

resulting in a gross change of color (such color change being used for emotional-motivational-protective purposes, etc.). The molecules which (directly or indirectly) bring about this dramatic coordinated subcellular movement of melanin to and from the centrosome are both peptides (such as MSH, ACTH and MIF)[1] and monoamines (such as melatonin, dopamine, and epinephrine). However, these "melanin-mobilizing" molecules (which maintain close phylogenetic and ontogenetic connections with melanin) move these pigment organelles in a grossly obvious manner only in lower animals with distinct chromatophores (676, 677, 436).

In higher animals, such as mammals, these "melanin mobilizing/immobilizing" molecules located in the brain and pituitary (e.g. pro-opiomelanocortin peptide derivatives such as MSH and ACTH; oxytocin peptide fragments such as PLG/MIF-1; melatonin, etc.) have evolved numerous roles far beyond their control of the gross color change seen within chromatophores (676, 677, 702, 85, 378, 384, 147, 148, 149, 150, 703, 704, 192, 655, 634, 172, 633). These roles include memory, emotion, motivation, attention, value, sexual behavior and development, etc. (which will be examined in the companion paper (32)). Such advanced behavioral functions effected by the "melanin-mobilizing" molecules of higher animals may indeed be directly related to these molecules' phylogenetic capacity to move melanin instantaneously to and from the centrosome (but in a much less dramatic, though undoubtedly more informationally sophisticated, manner than that observed in lower vertebrate chromatophores).

All cells (and especially the neuroendocrine cells) may use this ancient evolutionary mechanism for the nearly instantaneous accumulation and dispersion of melanin pigment around the centrosome and strategically to organizational loci throughout the cell. That is, relatively minute amounts of melanin found dispersed throughout the cell may, for organizational purposes, be inconspicuously transported to and from the centrosome and elsewhere in the cell when activated by the peptide hormones (and the numerous active cleaved fragments of these peptides) and/or amine neurotransmitters that bind to the glycocalical cell surface receptors. Release of these various "melanin-mobilizing" (or immobilizing) neuroendocrine (APUD) molecules and their continuously-processed in vivo fragments may, in turn, be ultimately regulated by the (neuro)melanin within master neuroendocrine cells elsewhere. Such hierarchically advanced neuroendocrine cells may be found within the brainstem melanin system and the diffuse neuroendocrine system (including the hypothalamus, pituitary, pineal, and adrenal glands).

Porter (506) suggests that the cytoplasmic ground substance transports pigment granules to the cell center. McGuire and Moellman (420) demonstrate that microfilaments mediate the movement of such

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[1] MSH is melanocyte-stimulating hormone; ACTH is adrenocorticotrophic hormone; and MIF-1 is melanocyte-stimulating hormone inhibiting factor.

pigment granules. Spoerri (626) has studied advanced primate and human brains, and based on his electron microscopic studies, has proposed a role for microtubules in the transport of pigment granules. (Furthermore, Spoerri has noted that the glial cells of the brain appear to use microtubular transport mechanisms to accumulate large amounts of pigment).

To reiterate, the centrosome is an ideal center for coordinating the numerous activities of the cell, and melanin may utilize the cytoskeletal system for rapid transport to and from the centrosome. Melanin's semiconductive and ion exchange properties (including regulation of silicon) fit nicely with Bornens' proposal for a centriolar silicon-mediated piezoelectric signal. Furthermore, melanin's photon-regulating and lipid- (e.g. steroid)--binding properties are in accord with these proposed centriolar-coordinated mechanisms. In addition, melanin may regulate the guanine nucleotides (and polyamines) necessary for microtubular functioning. Melanin may also regulate microtubule assembly by the binding and release of zinc ions and by the pteridine/purine-mediated covalent modification (and zinc-related regulation) of calmodulin--both of which are involved in cytoskeletal modulation.

Finally, melanin's control of the microtubules and microfilaments (771, 469) and the associated acidic nuclear proteins may be one means for melanin to activate and deactivate various nuclear genes (via the "membrane-gene link"). Centrosomal melanin has a perinuclear location and may use numerous other means for significantly affecting the nucleic acids in the nucleus (including direct superconductive communication; microtubule-conducted electromagnetic communication; control of steroids and other isopentenoids and their effect on the nuclear regulatory proteins; control of purines, pteridines, polyamines, etc. with their multiple effects on nucleic acid synthesis and functioning; control of the various ions (212, 605), especially zinc, which activate the enzymes involved in the functioning of nucleic acids, etc.). Numerous other mechanisms for a DNA-melanin link could be postulated, with melanin (as an information-processing "phase-timing device") monitoring the cellular milieu and signaling its requests to the nuclear nucleic acids for the delivery of various protein effectors in order to maintain cellular organization.

In addition to melanin's postulated connection to the centrosome, the cytoskeleton, the glycocalyx, and the nucleus, its presence in the organizational vesicles is equally important. Within the mitochondria, melanin may modulate the various other pigment molecules (e.g. flavoproteins, ubiquinone, cytochromes) which are involved in producing energy for the cell. Within the lysosomes (in which melanin accumulates), melanin may selectively activate the numerous enzymes (by ion exchange, covalent modification, etc.) which are required to organize and maintain the numerous subcellular functions (402, 96, 244). Such melanin-triggered lysosomal functions as peptide cleavage (inactivating one peptide hormone while simultaneously activating its functional fragments) may account for a continuum of

behavioral responses.[1] Furthermore, the synaptic (and coated) vesicles which store and release peptide hormones and monoamine neurotransmitters may perform this crucial function via such mechanisms as melanin's triggering of covalently modified enzyme cascades, its control of second messenger systems, etc. Finally, receptosomes provide a convenient continuous means for connecting the centrosome with the plasma membrane and glycocalyx and, hence, another means for cellular organizational by melanin.

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[1] The cleavage (and other modifications) of peptide hormones into functionally significant fragments, their relation to (neuro)melanin, and their various "linear" (32, 756, 759) effects are discussed in greater detail in the companion paper (32). Such melanin-regulated peptide covalent modifications result in higher physico-mental functions of the greatest importance. Some key references pertaining to melanin-related peptide modifications and functions are the following: 32, 147, 148, 149, 150, 96, 85, 145, 204, 218, 294, 165, 346, 369, 523, 676, 677, 99, 49, 153, 221, 709, 702, 715, 704, 703, 691, 454, 556, 557, 575, 193, 384, 378, 40, 216, 622, 303, 301, 634, 655, 638, 192, 172.

The companion paper correlates the neuroendocrine system with the functional brain systems, such as the neuromelanin-(monoamine)-neuroglia system. This latter electrotonic network functions as the coordination/organization system of the brain and uses numerous mechanisms to carry out this role. For exmaple, the brainstem neuromelanin-neuroglia system is strategically involved in the processing of the telencephalic septo-hippocampus (32, 379, 198). This region of the brain functions in the activation of "comparison"--i.e. the simultaneous comparison of a) current sensorimotor reality with b) anticipatory memories, plans, intentions. In particular, the subiculum appears to be the key site within the hippocampal formation where a phasic theta wave-related ratiocination/comparison occurs (198). The hippocampus accumulates serotonin-related pigment (neuromelanin/lipofuscin) very early in its development (73, 74) and the subiculum in particular contains an abundance of melanin in its plane of electrotonically-coupled dendrites. This makes the subiculum (198) an ideal locus for ratiocination/comparison (32) and, perhaps, for holographic processing (510). In addition to the electrotonic regulation of the hippocampal neuroglia and subicular dendrites (primarily through monoaminergic/cholinergic pathways), the neuromelanin system has access to numerous other mechanisms for hippocampal processing, some of which are suggested in the following references: 198, 379, 641, 675, 399, 592, 329, 216, 655, 192, 633, 172, 622, 303, 301, 634, 378, 384, 149, 150, 703, 704, 243, 682, 277, 338, 428, 365, 755, 772, 32. Furthermore, strategically located "planes" of neuromelanin/lipofuscin are found throughout the brain, from the retinal pigment epithelium to the very complex patterns of pigment noted in the cerebral cortex (73, 74). Such diffuse neuromelanin loci are suggested to be critically involved in neuroendocrine (covalent modification) processing.

THE DIFFUSE NEUROENDOCRINE (APUD) SYSTEM

In addition to its potential regulatory control over the purines and pteridines and its potential control over covalent modifications in general, melanin probably controls the synthesis and release of two functionally very important types of molecules: 1) the peptide hormones and 2) the amine neurotransmitters. Though discovered in advanced organisms such as vertebrates where most functional studies have occurred, the neuroendocrine system has now been found even in the most primitive of organisms and has been postulated to occur throughout the phylogenetic (and ontogenetic) spectrum (10, 153, 319, 434, 555, 671). Unravelling the organizational function(s) of this apparently ubiquitous cellular system is therefore of major importance. This paper will concentrate on the major functions of the peptides and amines in advanced vertebrates. (See Figure 12.) The peptide hormones appear to be the neuromodulators (151, 27, 32) which mediate one's subjective experience, including one's value (pain-pleasure), emotion, motivation, memory, etc. (32, 384, 378, 40, 454, 147, 148, 149, 703, 704, 709). On the other hand, the monoamine/amino acid neurotransmitters seem to mediate one's objective experience, including one's sensory input, "raw" (unevaluated) digital data transmission, and motor output (421, 105, 277, 400, 401, 32).[1]

[1] Actually it is the amino acid neurotransmitters (such as glutamate, GABA, glycine, aspartate, etc.) which primarily transmit digitally, while the monoamines (such as dopamine, norepinephrine, and serotonin) are "bootstrap" molecules with a higher organizational function. This distinction is important and is clarified in the companion paper (32). Though the companion article will also clarify "objective" and "subjective" experience, a brief discussion may help here. Pearse has proposed a central and a peripheral "diffuse" neuroendocrine (APUD) system (484), which we roughly equate with the brainstem melanin-diencephalic system and the neural crest system, respectively. The peripheral diffuse neuroendocrine system contains the neural crest-derived sensory, autonomic, and glial systems, which produce both amine neurotransmitters and peptide hormones (32, 254, 255, 46). (In addition to producing peptide hormones and monoamine neurotransmitters, these melanized pluripotential systems (e.g. the autonomic ganglia) have the ability to produce acetylcholine, and the potential to switch between norepinephrine and acetylcholine).

A reasonable interpretation of current neurophysiological data suggests that the neurotransmitters per se transmit the classical digital ("on-off") action potentials (mediating "raw" or unmodulated sensory input, interneuronal data transmission to and from the C.N.S., and motor output). These digital "all-or-nothing" neurotransmitter signals (objective data) are, in turn, subtly and continuously modulated (32, 27, 151) and given "value" (subjective experience) by the various peptide hormones. The peripheral ganglia-neurons mediate one's crude reflexive "subjective" experience (pleasure-neutral-pain) via such peptide neuromodulators as the enkephalins and substance P, while the higher CNS neuroendocrine system mediates one's more sophisticated "subjective" experience (memory-associated emotivational experience) via such peptide neuromodulators as ACTH, MSH, β-endorphin, vasopressin, oxytocin, etc. (Neuro)melanin is proposed to

Several years ago, Pearse and coworkers developed the concept of the APUD system (482, 483, 484, 299, 319, 555, 434, 10) which is becoming more frequently referred to as the "diffuse neuroendocrine system". Pearse astutely noted that certain collections of diffusely scattered cells have the following common characteristics:

1) the ability to synthesize, store, and release both peptide hormones and amine neurotransmitters.

2) several histochemical and ultrastructural similarities.

3) a common metabolic pathway which could explain how certain tumors of diverse organ systems can produce clinically functional peptide hormones and amine neurotransmitters (APUDomas).

4) an apparent common embryological origin from the neural crest, a highly melanized embryological system.

Table 2 shows some of the known derivatives of the neural crest system. Since the theory's original formulation, the number of peptides and amines in this diffuse neuroendocrine system has constantly expanded. Table 3 shows a partial listing provided by Pearse (484) of some of these peptides and amines along with their neuroendocrine locations. Unfortunately, this listing is now significantly outdated, as numerous other peptide hormones (synthesized primarily in the diencephalon) are transformed via covalent modifications and transported throughout the brain. In addition, new research has demonstrated several peptides and amines in the same cell, especially the autonomic and sensory ganglia-neurons.

Pearse has provided and since expanded a pathological model which unifies many diverse disease states and which is of unquestionable value. His formulation is supported by a comprehensive review of the "neurocristopathies" (the multiple unique diseases involving cells derived from the neural crest) by Kissel, Andre, Jacquier (299).

In spite of the explanatory efficacy of Pearse's model, some of his proposals have been seriously challenged.[2] For example, it appears that neuroendocrine cells of the gut, such as the enterochromaffin cells, are derived from endoderm and not from neural crest (which is considered to be specialized neuroectoderm). Pearse has modified his theory to account for these anomalies but nevertheless inconsistencies remain.

In order to resolve the controversies pertaining to Pearse's APUD (diffuse neuroendocrine) system, it will be necessary to review briefly the core mechanisms of embryological organization which lead to the

integrate and regulate both objective and subjective experience, both the neurotransmitters and the peptide hormones (i.e. the entire neuroendocrine system). For a more precise philosophical distinction between subjective (or projective) experience and objective reality (scientifically controlled behavior), see Young's "A Formalism for Philosophy", reference 759.

[1] Succinct criticisms of Pearse's APUD model have been formulated by Skrabanek (607) and Andrew (21).

1. All the spinal dorsal root (sensory) ganglia - neurons
2. All the peripheral autonomic ganglia - neurons
3. Ganglia - neurons of the 5th, 7th, 9th, 10th cranial nerves
4. Schwann and sheath (peripheral glial) cells
5. Glia and satellite cells of dorsal root and autonomic ganglia
6. Melanocytes of dermis, mesenteries, internal organs, epidermis, meninges, etc.
7. Melanophores of the iris
8. Adrenomedullary cells and other adrenergic paraganglia
9. Thyroid calcitonin - producing cells
10. Carotid body type I and II cells
11. Connective tissue of the thymus, thyroid, and parathyroid glands
12. Bones, cartilage, connective tissue, dermis, etc. of the face and neck
13. Stroma of the cornea and the ciliary muscles
14. Striated muscles in the facial and visceral regions
15. Musculoconnective tissue of the large blood vessels

Table II Some Examples of Well-Established Neural Crest Derivatives

The Central Division of the DNES		
Cell Type	**Peptide Products**	**Amine Products**
Pineal	Arginine vasotocine, Lutropin releasing hormone	Melatonin Serotonin
Hypothalamic (magnocellular)	Arginine vasopressin, Arginine vasotocine	Dopamine Norepinephrine Serotonin
Hypothalamic (parvocellular)	Releasing factors Release inhibiting factors	
Pituitary (pars distalis)	FSH, LH, TSH STH, PRL, ACTH MSH, B-LPH B-Endorphin Gastrin, Calcitonin	Dopamine Norepinephrine Serotonin Histamine
Pituitary (pars intermedia)	ACTH, MSH B-LPH B-Endorphin, Calcitonin,	

The Peripheral Division of the DNES			
Cell Type		**Peptide Products**	**Amine Products**
Pancreas	B, A D, D_2 (F)	Insulin, glucagon Somatostatin, PP	Serotonin Dopamine
Stomach	G, AL, EC_1 ECL D	Gastrin, Enkeph., ACTH Glucagon Substance P —— Somatostatin	—— —— Serotonin Histamine ——
Intestine	EC_1 EC_2 (M) L,S, I, D_1 (P) D,K, N, H	Substance P Motilin Glicentin, Secretin CCK, (Bombesin) Somatostatin, GIP Neurotensin VIP	Serotonin Melatonin —— —— —— —— —— ——
Lung	K (Feyrter)	Bombesin	——
Parathyroid	Chief	Parathyrin	——
Adrenomedullary	E, NE	——	Epinephrine, Norepinephrine
Sympathetic	Ganglion SIF	VIP ——	Norepinepnrine Dopamine, Serotonin Norepinephrine
Carotid body	Type 1	——	Dopamine, Norepinephrine
Thyroid/ ultimobranchial	C	Calcitonin, Somatostatin	(Serotonin)
Urogenital tract	EC U	—— ——	—— ——

Table III The Diffuse Neuroendocrine (APUD) System

development of the neural crest system and to its subsequent dispersal to strategic sites throughout the body.

EMBRYOLOGICAL ORGANIZATION VIA SUSTAINED CURRENT

An impressive amount of data strongly suggests that sustained electrical current guides embryological patterns of development (407, 38, 281, 282, 283, 284, 67, 542, 543, 446, 447). This sustained current is variously called steady current, direct current, or analog current. This graded potential electrical current differs from the "on-off" digital current system seen in the "all-or-nothing" action potential of classical neuronal systems.

Such ancient direct currents are found throughout living systems, plant and animal. The relatively large oocytes of various plants and animals have become a central focus for studying the mechanisms producing these organizational direct currents (542, 446, 447). Robinson (542), for example, notes that a ubiquitous feature of nonmammalian egg cells is the conspicuous presence of an animal-vegetal axis. The poles of this axis can be easily distinguished (in amphibian eggs (308), for example) by melanin pigment accumulation at the animal pole (making it dark) and by the yolk mass accumulation at the vegetal pole. Superimposed on this grossly visible polarity is a developmental polarity--the highly pigmented animal pole gives rise to the ectoderm of the embryo and the vegetal pole to the endoderm. Furthermore, this pigment-defined axis also defines the path of the sustained current, with an inward direct current flow occurring at the pigmented animal pole.

Studies on Pelvetia eggs show that light controls the axial orientation (542, 375). Shining a light from any direction orients the animal (melanin) pole toward the light and predicts the germination site on the oocyte. Germination in the Pelvetia egg begins with changes in the cytoplasm and includes the movement of vesicles containing materials needed for germination to the site of germination (375, 407). "Cortical vesicles" (213) contain glycosaminoglycans which are then secreted into the glycocalical region at the germination site, and this secretion apparently modifies the glycocalyx and the extracellular matrix, providing the means for further development. Jaffe and Nuccitelli, through their meticulous studies using a tiny vibrating electrode probe, have shown that the inward sustained current is always located at the potential germination site on the melanized animal pole (283, 542, 375, 282). This inward current can be detected in the animal pole of Pelvetia eggs at least 6 hours before budding begins. If done early enough, the location of this inward current can be changed simply by changing the orientation of the incident light.

The full subcellular mechanisms involved in producing this direct current remain unknown. Only some basic ionic mechanisms involved with the sustained current have received attention. In searching for the origin of the organizing direct current system within the oocyte (542, 225, 308), one must also seriously consider certain other

cellular components and their interrelationships.[1]

During the earliest divisions of this original oocyte, low resistance gap junctions develop between the plasma membranes separating these daughter cells, providing continuous intercellular communication and metabolic coupling (256, 247, 352, 42, 490). Research suggests that the control of these gap junctions provides a major means for control of embryological organization and development (43, 54, 352, 247, 143). Gap junctions permit ion flow between the cells, allowing electrotonic processing (via modulations of the sustained current), and thus coordination between the cells and developing tissues. In addition to controlling the ion flow (and thus the sustained current flowing between the cells and through the developing glycocalyx-extracellular matrix system), these gap junctions also control the intercellular exchange of various molecular monomers plus the purines and pteridines.

Kaneseki (289) has provided electron microscopic evidence for a close link between the organizational vesicles (and in particular, the neuronal synaptic vesicles), the gap junctions, and membranal calcium deposits. A related finding of particular interest is the ability of calcium ion fluxes to open and close gap junctions thereby diverting the ion flow and subtly modulating the sustained current (42, 247). The electron micrographs (289) demonstrate that these organizational vesicles may be involved in actually transporting the small hexagonal particles found in the membranes of gap junctions.

Another mechanism for regulating the opening and closing of the gap junctions is through control of intracellular pH (627, 448, 685, 376, 547, 32). Though the exact means of intracellular pH control remains unknown, several mechanisms may be considered. For example, since melanin pigment granules are located at the site initiating the inward current flow in the oocyte, and since many of melanin's known functions appear to intimately depend upon exact pH control, melanin may therefore be a key factor in controlling intracellular pH (at least localized intracellular pH), and thus could also control gap junctions.

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[1] The following subcellular systems should be recalled: 1) the glycocalical cell surface possesses recognition-activation mechanisms and has the ability to "window" electromagnetic energy into the cell. It also appears to possess, according to Adey and others, "cooperative" ion control mechanisms. 2) The centriole, which resembles a prototype light receptor, is located in the center of the cell and controls the entire cytoskeletal transport system (connecting to the cell membrane and controlling the membrane protein lateral mobility, which can effect ion flow). 3) The light-absorbing melanin pigment vesicles (which possess photon-phonon, free radical-redox, and ion control mechanisms, etc.) have a strong association with both the centriole and the glycocalyx and consistently define both the site for the inward flow of the organizing sustained current as well as the developmental axis (which defines the future orientation and pattern of the developing embryo).

Calcium ion uptake and release by the different "organizational vesicles" (and these vesicles' in vivo control of the calcium-binding endoplasmic reticulum) may play a major role in gap junction opening and closing. Furthermore, pH-controlling enzymes such as carbonic anhydrase may also be involved. Carbonic anhydrase is activated by zinc ions (which are abundantly bound by melanin). Therefore melanin need only selectively release and bind zinc ions in order to activate carbonic anhydrase, changing the pH and thereby opening and closing gap junctions and subtly modulating the intracellular sustained current. (Zinc ions are also involved in ion-related membrane enzymes such as Na^+, K^+, ATPase, Ca^{++}ATPase, adenylate cyclase, and guanylate cyclase.)

Regardless of the exact control mechanisms involved, gap junctions between cells offer at least one means for regulating the organizing flow of sustained current which apparently guides embryological development. Following their widespread presence, and their organizational efficacy in embryological development, gap junctions may be continuously removed and selectively "placed" in functionally strategic regions in mature and advanced organisms (593, 388, 289, 610, 215, 414, 669, 18, 32).

In addition to gap junction control, other melanin-related mechanisms may exist for maintaining a sustained current through ion control (1). This cell-linking sustained current returns to the cell through the extracellular matrix (ECM) surrounding the cell and contributing to the cell's glycocalical network (618, 619, 620). The glycocalyx-ECM undergoes subtle and continuous changes in both its composition and in its recognition-activation properties during embryological development, as does the sustained current (363, 77, 475, 488, 388, 502, 426, 144). The ECM is involved in influencing and directing the movements and differentiation of the numerous cells of the developing embryo. For example, the ECM is essential in directing the formation of the various tissues that differentiate during the stages of gastrulation and neurulation (600, 206). This has been especially well documented during neural crest dispersal and differentiation (77, 500, 144, 617). Neural crest cells appear to produce certain GAG's which apparently change the ECM, and the ECM then affects further neural crest cell migration. Gastrulation involves the formation of the primitive streak and the notochord and results in the development of the mesodermal somites, including the sclerotomes (bones), the myotomes (muscles), and the dermatomes (dermis and somatosensory receptors). Neurulation is the subsequent embryonic stage of development during which the neural tube (the future central nervous system) is formed.

The aggregation of heavily melanized cells, forming the grossly visible black pigmentation which moves into the folds of the neural groove and which appears to bring the folds of the neural tube together, defines the formation of the neural crest system. The neural crest brings together and fuses the two neural folds, forming the neural tube, thus initiating the complex process which gives rise to the central nervous system, i.e. the brain and spinal cord.

Melanin's direct control of the microtubular network could be responsible for effectuating the neurulation process (200, 563, 684). Simultaneously with the creation of these highly melanized cells at the top of the fused neural tube is their strategic migration to multiple sites throughout the embryo collectively forming many of the components of the APUD or diffuse neuroendocrine system, as well as other vital organizational structures.

Evidence has been presented which indicates that melanoblast (primordial pigment cell) differentiation actually occurs during the middle of gastrulation and prior to the onset of neurulation. Matsuda and Kajishima (381) conclude from their studies that the pigmented melanocytes, whose major characteristic appears to be the production of large quantities of melanin and whose origin was previously thought to be the grossly defined neural crest system per se, may be formed much earlier, during mid-gastrulation (preceding the grossly visible formation of the neural crest). Furthermore, when grossly identified neural crest cells are obtained and cultured before any contact with the mesodermal somitic mesenchyme (which appears to induce the differentiation of neural crest cells into various neuroendocrine organs), only melanocytes are formed (439).

To reiterate, these studies suggest that: 1) the key undifferentiated function of the neural crest system is the production of significant quantities of melanin, and 2) organizationally active melanized cells (pigment cells, in fact) are available for dispersion prior to gross neural crest formation. The early dispersal of melanized cells in mid-gastrulation and the even earlier presence of melanin-containing cells in the endoderm (and throughout embryological development) could easily account for those seemingly anomalous APUD or neuroendocrine cells (found in the gut, brain, etc.) whose origin from strictly defined neural crest cells appears doubtful.

In summary, we propose that the embryological melanin system, both before and during the formation of the grossly defined neural crest system, organizes the entire APUD or neuroendocrine system. This system includes APUD cells known to be derived from strictly defined neural crest cells as well as APUD cells apparently established before the formation of gross neural crest.

THE NEUROENDOCRINE SYSTEM AND HOMEOSTASIS

If melanin, through electrical and molecular mechanisms, does indeed regulate the dispersal and function of the diverse neuroendocrine cells throughout the body, then it may justifiably be considered to be a homeostatic molecule. Its stability and resistance to chemical change may parallel its stability as a homeostatic neuroendocrine regulator. As can be seen in Table 3, the neuroendocrine cells are dispersed strategically throughout the body and produce functional peptides and amines in these regions. For example, the carotid body cells are highly melanized cells derived from the neural crest which are located in the carotid body (i.e. the carotid artery) in order to homeostatically regulated one's cardio-vascular response (pulse rate, blood pressure, etc.). Likewise the diencephalon

(hypothalamus, pituitary, pineal)[1] produces numerous peptide hormones and amine neurotransmitters which are a) utilized locally, b) transported via long axons to other regions of the brain, c) selectively secreted into and taken up from the cerebrospinal fluid, and d) transported through the bloodstream to other neuroendocrine loci throughout the body (e.g. the adrenal, the thyroid, the intestine, the pancreas, the gonads, etc.). These diencephalic peptide hormones (and amine neurotransmitters) regulate the peripherally located neuroendocrine loci and receive feedback from them, thus serving a vital homeostatic role.

A significant imbalance in the release of these various neuroendocrine molecules could have severe or fatal consequences, and an instability in the neuromelanin system postulated to homeostatically regulate these neuroendocrine molecules could lead to various types of neuroendocrine instabilities (including general endocrine disorders, mental abnormalities, autonomic and immunoregulatory imbalances, etc.). An example of a probable instability in neuromelanin is the well-known disorder, Parkinson's disease, manifested by dysfunctional motor output and primarily involving an instability of the nigrostriatal neuromelanin system (180, 181, 84).

Another postulated instability of neuromelanin (with consequent neuroendocrine anomalies) is the relatively common disorder, manic-depression. The emotional and motivational disturbances prevalent in this abnormality will most likely be shown to be due to aberrant neuroendocrine functioning (193, 608, 227, 313, 357, 377, 695) which, in turn, we again propose to be secondary to an instability of neuromelanin (but in this case, predominantly involving the mesolimbic neuromelanin system (645, 639, 640, 422, 565)).

A particularly mysterious neuroendocrine instability is the spectrum of physico-mental aberrances collectively called "schizophrenia". The apparently subtle abnormal production of an unstable neuromelanin, perhaps a type of "rheomelanin" (which may be related to a certain chronically maintained functional instability of the monoamine neurotransmitters (15, 230, 231, 699, 700, 527, 683, 645, 45, 122, 278, 325, 538, 611, 695, 239, 240, 241), leading to the subsequent synthesis of a "dissipative" melanin (15, 205)) could very well account for the schizophrenic's sensori-motor and emotional-motivational aberrances. Abnormal neuroendocrine phase-timing (791, 792, 223, 427, 458, 379, 365, 374) could be the evasive etiological culprit of schizophrenia. For example, a subtle but significant increase in the production of aberrant neuromelanin/rheomelanin--(with consequent "dissipative" pathways and receptors, e.g. the diffuse neuroglia regulatory system)--could produce aberrant sensory input (e.g. sensory hallucinations), aberrant motor output (e.g. catatonia), aberrant emotion (e.g. fear, bliss), aberrant motivation (e.g. para-

[1] The diencephalon, formed at the top of the C.S.F.-containing neural tube, appears to be the chief source of peptide hormones. Its functions will be further delineated in "Melanin and the Mind-Body Problem."

noia), etc.[1] (373, 278, 538, 347, 118, 241). A disturbance in the nigrostriatal pathway, for example, leads to sensori-motor dysfunctions, while a mesolimbic pathway disturbance leads to emotional-motivational disturbances. Both these interacting dopaminergic pathways originate in contiguous and very highly melanized regions of the midbrain, at the top of the brain-stem.

Furthermore, other molecular abnormalities associated with schizophrenia (such as abnormal functioning of methionine, prostaglandins, various enzymes, peptides, etc.) could be associated with aberrant functioning of neuromelanin (193, 147, 611, 612, 134, 257, 259, 261, 745, 45, 695, 34, 88, 560, 657, 66). The neuroleptics (anti-schizophrenia drugs) may indeed stabilize, to some extent, these "schizophrenic" neuroendocrine aberrancies because of the neuroleptics' well-known ability to strongly bind (and presumably somehow stabilize) the "dissipative" neuromelanin (15, 206, 93, 564, 348, 349, 350, 678) which is postulated to be responsible for these aberrancies.[2]

A FUNCTIONAL TYPOLOGY OF THE NEUROENDOCRINE SYSTEM

Obviously the activation and regulation of neuroendocrine homeostasis is a vital function of living organisms. In considering the types of molecules involved in this organizational process and their specific functional roles, the following generalizations may be helpful. The nucleic acids may be considered to be the most advanced molecules (or "dominion molecules") because of their total sovereignty over the production of proteins; the proteins in turn, may be considered to be servile "animational (mobile effector) molecules" because of their dynamic multifaceted roles (including the transportation of various molecules, enzyme catalysis, immune antibody responses, trophic responses, emotion and motivation effects, gross muscular as well as cytoskeletal movement, etc.). In this paper, we have developed the thesis that the melanins (in addition to the isopentenoids) are the natural "organizational molecules." This designation is primarily due to melanin's postulated control over the covalent modification of "raw" (functionally inactive) protein and, hence, the generation of an organized (functionally active) protein response.

In short, nucleic acids exert the ultimate molecular ruling capacity (i.e. programming control) over the numerous dynamically responsive proteins, while melanin is proposed to functionally organize these "raw" proteins by directly and indirectly controlling the various means of covalent modification (as well as by its postulated

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[1] The cognitive and attentional anomalies related to schizophrenia are further considered in the companion paper, "Melanin and the Mind-Brain Problem" (32).

[2] Neuroleptics such as the phenothiazines act as an electron donar, while melanin acts as an electron acceptor. Furthermore, such drugs reduce the paramagnetic signal of melanin. Consequently, Forrest proposes that these neuroleptics (which anatomically and functionally bind melanin) be called "melanostatic" (176).

in vivo organizational control over ion activation of enzymes, etc.). For example, Wold (750) emphasizes that probably all protein products isolated from living cells have been covalently modified by proteolysis from the larger precursor sequence encoded in the mRNA.

The neuroendocrine system, which appears to be present in the most primitive of cells and throughout the phylogenetic spectrum (555, 10, 153, 319, 434, 671, 32), dynamically functions not only because of the "animational" peptide hormones, which are responsible for emotion-motivation-animation (i.e. the "subjective experience" of memory-value which ultimately brings about cytoskeletal or gross muscular movements), but also because of the amine neurotransmitters, which are responsible for objectively measurable sensory input-muscular output (i.e. the scientifically observable behavior constituting "objective experience"). However, both the peptide hormones (and all proteins) and the amine neurotransmitters are composed of amino acid precursors. Amino acids may also be converted into monosaccharides and nucleotides, which are the monomeric combinational units composing the various polymers (nucleic acids, melanin, carbohydrates, and proteins). Amino acids, the other monomers, and their non-polymeric derivatives (which include the amine neurotransmitters) may be considered functional "combinational molecules".[1]

The four groups of functional molecules involved in activating and maintaining neuroendocrine homeostasis may be displayed on two sets of perpendicular axes. (See Figure 12.) The vertical (nucleic acid-melanin) axis may be considered to be activational in nature but functionally static in response to stimulation. In contrast, the horizontal (peptide hormone-amine neurotransmitter) axis may be considered to be passively activated (by the vertical axis) but dynamically responsive. It is the dynamic response of the two latter types of molecules (the neuroendocrine molecules) which mediate "physical" experience (both "subjective" and "objective"). The molecules on the vertical axis, on the other hand, appear to actively regulate this passive-dynamic axis which mediates physical experience. These activational molecules may therefore be considered to be the molecules which correlate with "mental" activation.[2]

[1] The four functional categories used in this paper: combination, organization, animation, and dominion are actually the four terminal functional stages of any self-organizational system or process. Young (756, 759) has shown that any true process (whether molecular, cellular, embryological, etc.) may be topologically represented by a torus (nature's most complex natural feedback system, a self-referential (reflexive), self-organizational "time-structure" that requires seven stages to occur). Until a full statement of process theory is presented, the reader should refer to the four categories (757, 759,760) formed by the active-static and passive-dynamic axes ("mind-body" axes).

[2] The specific subjective (or projective) role of the GAG's and the objective role of melanin in mentation are further clarified in "Melanin and the Mind-Brain Problem", where they are correlated with specific brain systems, and they therefore will not be developed in this regard in this paper.

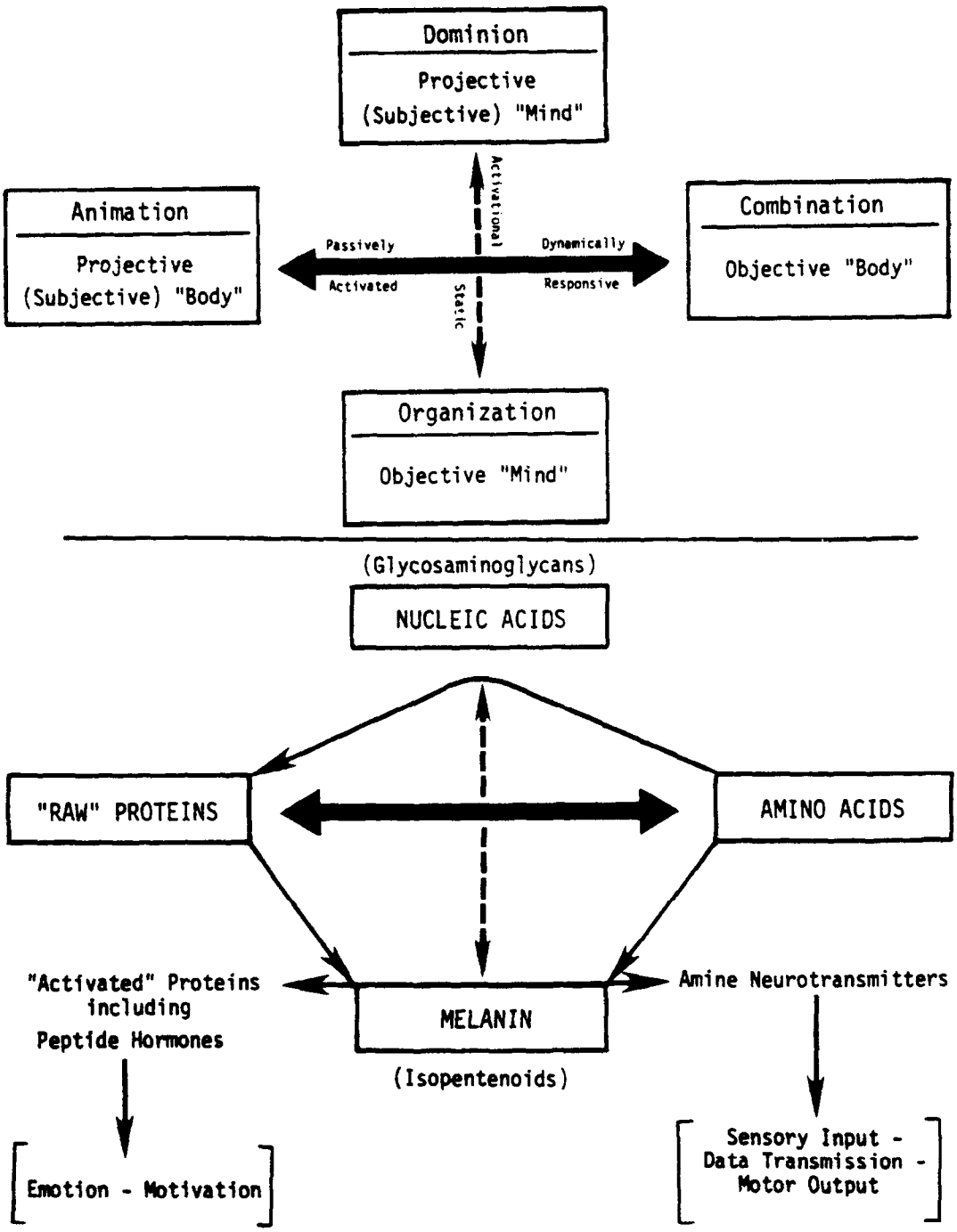

Fig. 12 A Functional Typology of the Neuroendocrine Process

A brief digression may help to clarify these theoretical functional classifications. For instance, the nucleic acids DNA and RNA exert an activational programming control, a sovereignty or dominion over the numerous passively activated, functionally dyanamic proteins. After being actively programmed, these proteins (e.g. enzymes) may actually be able to evoke their dynamic programmed responses in vitro (with proper substrate, proper pH, proper temperature, specific metal ion activators added, etc.) However, the nucleic acids per se require a living cellular milieu for their functioning. When placed in in vitro situations with various other molecules added (no matter which molecules or what conditions), the nucleic acids remain more or less static as far as their activational function is concerned. (Actively programmed enzymes such as DNA polymerase, DNA ligase, DNA repair enzymes, etc. may dynamically modify DNA which nevertheless remains static in vitro). Within the proper in vivo setting however, the nucleic acids may again spontaneously replicate and/or actively program proteins, etc.

The same "activational-static" classification given to DNA may be applied to melanin. In in vitro situations, outside the intricate cellular-organismic process which it is proposed to organizationally activate, melanin, like DNA, may appear to be static or inert. This is not to say that various in vitro manipulations of either the DNA or melanin molecules cannot evoke a response of some sort, but that the essential in vivo functional "activational" role of these molecules (molecular "dominion" for DNA and molecular "organization" for melanin) cannot be passively triggered in vitro. Both DNA and melanin would appear to require a living cellular process and a plethora of dynamically responding molecules in order to manifest their true activational roles. Such APUD molecules as peptide hormones and amine neurotransmitters serve as major examples of the dynamically responsive molecules which may be activated by melanin.

Just as DNA's incredible functional "dominion" role could never have been elucidated strictly in vitro, likewise melanin's postulated functional "organization" role will undoubtedly also require very sophisticated in vivo studies. Therefore, melanin researchers should be cautioned about extrapolations and conclusions regarding melanin's functions based solely on in vitro studies.

We postulate that melanin has evolved in its "activational-static" organizational capacity from the regulation of molecular-cellular-tissue systems in lower organisms (primarily by regulating covalent modifications) to an advanced central nervous system neuromelanin-neuroendocrine network in higher organisms and a subsequent self-conscious mental capacity in humans. Melanin's potential ability to integrate and organize the neuroendocrine (APUD) system and hence "inner" and "outer" physical experience, and its potential ability to do so by subtle "trigger" mechanisms (photon-electron-phonon conversions, free radical-redox control, ion exchange, enzyme cascade amplifications, semiconductive processes, electrotonic processing, etc.) would seem to necessitate the consideration of neuromelanin as a serious candidate for linking "mind" and brain (regardless of

monistic-dualistic considerations.)

CONCLUSION

This lengthy but condensed review of melanin has set forth background information on melanin and its potential in molecular, cellular, and embryological systems that we consider essential for future research and advances in scientific understanding. This article has attempted a preliminary organization of an extensive range of contemporary research based on the hypothesis that melanin, in conjunction with other pigment molecules, functions as the principal organizational molecule in living systems.

While much of the analysis has traced connections between melanin and other strategic molecules such as the purines (notably the purine cyclic nucleotide second messengers) and pteridines, elaborating possible hierarchies of control, melanin itself has remained the center of interest. (See Figures 5 and 9 for a summary overview.) The established properties of melanin, alone, indicate a far greater functional significance than has generally been recognized. Melanin's unusual and extremely stable structure of complicated stacks of resonating ringed planes; its properties of photon absorption and energy conversion; its ability to bind and release important liposoluble substances and strategic metal ions such as zinc; its scavenging and production of free radicals; its oxidation-reduction capabilities; its semiconductive properties; all suggest the need for an expanded interpretation of melanin functioning. The hypothesis that melanin's primary role is organizational, and possibly even self-organizational (autopoetic), leads us to anticipate the discovery of further remarkable properties including superconductivity; control of embryological differentiation through the genesis and control of direct current; and homeostatic regulation of the immune response, tissue repair and regeneration, and autonomic functioning. (See Table 1 for a summary listing of established and proposed properties of melanin.)

The hypothesized nucleic acid-melanin control axis in living systems, has been illustrated in a functional interpretation of the diffuse neuroendocrine system. DNA and melanin are held to activate and maintain neuroendocrine homeostasis of peptide hormones and amine neurotransmitters. Melanin accomplishes its organizational function primarily through effective control of the several types of covalent modification as well as metal ion-enzyme activator control. The utility of this preliminary functional analysis should be demonstrated in the further analysis of neuromelanin and basic brain systems that follows (32).

The scientific community will appropriately respond with caution to the first statement of such a sweeping hypothesis. We welcome a frank and open discussion on both the broader theoretical issues and the questions they raise and the specific referenced research on which this analysis has been based. As further research data becomes available, we anticipate significant additional theoretical modifications and extensions regarding the organizational capabilities and

mechanisms of this long-neglected and mysterious molecular "black box."

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