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LETTER TO THE EDITOR
DISCUSSION, REVIEW,
SHORT COMMUNICATION, ...

Review

Oxidative Metabolism of Tyrosine in Insects

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1. Introduction

Insects utilise tyrosine, *inter alia*, for biosynthesis of biogenic amines, melanin pigments, and sclerotins. This review dicusses the enzymatic pathways, considering also differences in the corresponding pathways in vertebrates. Only a general outline can be given here and many details of the regulation of enzyme activities as well as differences in various insect species have to be obmitted. For in depth information, the reader is referred to the literature cited and references given therein.

2. Biosynthesis of biogenic amines

The distribution of neurotransmitters in the nervous system of insects has been studied in much detail (1,2). In contrast, little is known on the enzymes of their biosynthesis. Tyrosine hydroxylase (EC 1.14.16.1) occurs in vertebrates as a pterin and Fe^{2+} dependent rate limiting enzyme. It was long believed that the enzyme is absent from insects. However, more recent studies have demonstrated the occurrence of Dopa and tyrosine hydroxylase in *Drosophila melanogaster* (for review, see (3)). Low amounts of DOPA have been found also in the CNS of the tobacco hornworm, *Manduca sexta*, at a narrowly defined developmental stage (4).

Dopa is decarboxylated to dopamine by a rather specific DOPA decarboxylase as was shown first in locust brain (5). Besides, decarboxylation of tyrosine leads to tyramine which then is either β-hydroxylated to (*R*)-octopamine or ring hydroxylated to dopamine. Apparently, any monophenolic phenethylamine can be converted to a diphenol. Likewise, the side chain of either a mono- or a diphenol can be β-hydroxylated. However, due to the paucity of data on the enzymes and their specificity, it is sometimes difficult to judge whether a particular *in vitro* transformation is also physiologically significant. The amounts of noradrenaline in insect CNS are less than 10% of dopamine (6). The configuration of noradrenaline in insect nervous tissue has not been reported though stereochemical arguments are most critical with respect to the mechanism of β-hydroxylation (see section 4).

The phenolic phenethylamines are N-acylated and/or O-glucosylated (4,7). Eventually, these conjugates represent storage forms of neurotransmitters or intermediates of monoamine catabolism.

3. Biosynthesis of melanins

In contrast to the situation in vertebrates, insect melanins are always extracellular pigments. Melanin is formed in the blood of insects after wounding or invasion by pathogenic microorganisms. As the polymeric pigment has blood clotting properties and encapsulates pathogens, it is involved in wound healing and in immune response.

The pathway of eumelanin biosynthesis in insect haemolymph is similar to that in in vertebrates. L-Tyrosine is hydroxylated to DOPA by a Cu^{2+} dependent monophenol mono-oxygenase (tyrosin-ase, EC 1.14.18.1) which is localized in the hemocytes of the hemolymph. The same enzyme has also diphenoloxidase (o-diphenol: O_2 oxidoreductase, EC 1.10.3.1) activity. Thus, it should be expected that tyrosine hydroxylation by tyrosinase is followed immediately by oxidation of DOPA to dopachrome. However, insect haemolymph also contains a highly specific DOPA decarboxylase (EC 4.1.1.28) which is under control of the steroid hormone 20-hydroxyecdysone. Wounding activates both, DOPA decarboxylase and phenoloxidase, and it was concluded that the melanin involved in wound healing is derived from dopamine (8). Degradation of insect melanins yields dihydroxyindole and pyrrole carboxylic acids, but not dihydroxyindole carboxylic acid (review: (9)) and thus indicates that dopamine and dihydroxyindole, rather than DOPA and dihydroxyindole carboxylic acid are the precursors for insect melanins.

A second source of eumelanin in insects is the exocuticle, where the pigment is often found in the form of granules (9). Since cuticle is virtually devoid of cysteine, the pigment must be of the eumelanin type. Again, the precursor is dopamine and pigmentation is under endocrine control (8). The tyrosinase from pharate pupal cuticle of *Manduca sexta* differs in substrate specificity from vertebrate and mushroom tyrosinases. It converts tyrosine and tyramine to DOPA and dopamine and oxidizes diphenols to *o*-quinones with V_{max}/K_m values decreasing in the order N-β-alanyldopamine > N-acetyldopamine > dopamine > dihydroxyindole > DOPA (10). In addition, the cuticle contains a proteineous DOPA quinone conversion factor which accelerates the decarboxylation of dopachrome to dihydroxyindole.

4. Biosynthesis of sclerotins

Sclerotins are defined as chemically modified proteineous components of insoluble and stiff skeletal structures. In insects, they occur in the ootheca of cockroaches and in the exo-skeleton. Here, we will consider the latter only. Briefly, the process of "sclerotization" of insect cuticle is based on oxidative reactions of N-acyldopamines with proteins of mostly unknown structure and with chitin. Other diphenols may be involved. Some recent reviews on cuticle sclerotization are available (11,12).

Hydroxylation of tyrosine by tyrosinase is followed by decarboxylation of DOPA to dopamine. Insects have evolved regulatory mechanisms that divert dopamine from the melanin to the sclerotization pathway by N-acylation with acetyl and β-alanyl residues in hemocytes and epidermis. Storage forms of the diphenolic compounds are O-glucosides, O-phosphates and O-sulfates. Free dopamine and N-acyldopamines are translocated into the cuticle. The participating enzymes are under endocrine control.

It is generally believed that the diphenoloxidases required for oxidation of the catechols in the cuticle are the same enzymes as those found in the haemolymph. They

occur also in cuticle as proenzymes and are activated at the onset of sclerotization under control of 20-hydroxyecdysone. However, the picture is more complex, since, in addition to tyrosinase (EC 1.14.18.1) and *o*-diphenol oxidase (EC 1.10.3.1), also laccases (EC 1.10.3.2) and peroxidases (EC 1.11.1.7) may occur in cuticle.

Insect cuticles also contain N-acetylnoradrenaline. First indications for a fundamental difference in the mechanism of side chain hydroxylation in CNS and cuticle were suggested by stereochemical arguments. From *in vitro* oxidation mixtures of N-acetyldopamine and insect cuticle, *racemic* N-acetylnoradrenaline was obtained. This is consistent with a rearrangement of 4-alkyl-*o*-quinones to *p*-quinone methides and non-stereoselective addition of water to the latter, rather than with hydroxylation by a mono-oxygenase of the dopamine β-hydroxylase type (EC 1.14.17.1) (13,14). More recently, the *o*-quinone-*p*-quinone methide rearrangement was claimed to be accelerated by a tautomerase (EC not assigned) (15). This enzyme activity was also found in haemolymph of the fly *Sarcophaga bullata* (16). Furthermore, the rearrangement is observed upon oxidation of N-acyldopamines with tyrosinases and laccases from cuticles of various insects (17,18,19), and, to a low extent, with mushroom tyrosinase (13).

Eventually, the *p*-quinone methide generated from N-acetyldopamine-quinone, but not from N-β-alanyldopamine-quinone, may be further rearranged by yet another enzyme to the corresponding α,β-dehydro-N-acetyldopamine (20). Thus, the pattern of enzymatic diphenol oxidation in insect cuticle is more complex than that of melanogenesis, for which the minimum enzymatic requirement is tyrosinase, or of lignin biosynthesis in plants which requires principally peroxidase only (for review, see (21)).

Much progress has been made recently with respect to the mechanisms of oxidative polymerization of the catechols and structural protein modifications by reactive quinonoid intermediates (for review, see (21)). Linkage of imidazole-N^{τ} of histidine to the ring position of a dopamine metabolite is formed by 1,4-*Michael*-type reaction to the *o*-quinone, and to the β-carbon by 1,6-conjugate addition to the quinone methide, as is evident from CP-MAS NMR studies (22,23) and from *in vitro* reactions (24,25). Likewise, primary aliphatic amines, such as β-alanine and the ε-amino group of lysine may add to the ring and to the side chain of N-acetyldopamine (26). Polymerization of reactive intermediates *via* the side chain leads to benzodioxane oligomers (27) which may also be connected to protein residues (25). Also, biphenyltetrols (28,29), dibenzofuranes (29) and phenoxazines (30,31) were found recently. Crosscoupling of peptidic tyrosine residues with N-acylcatecholamines results in mixed type melanin-like materials (32).

Many variations exist in the colour of insect cuticles. Current theory holds that, as far as diphenolic precursors are involved, the colouration of cuticles is correlated with the nature of the precursors: black results from dopamine, brown from N-β-alanyldopamine, and light or colourless from N-acetyldopamine, where simultaneous participation of all types are possible. Genetic lack of N-acylation or transport of β-alanine through the epidermis results in black cuticles, as has been revealed with work on mutants of various insects (33).

5. Conclusions

Many questions are open for further research. Thus, the regulatory mechanisms leading to presence of low amounts of N-acylcatecholamines in the CNS as compared with rather large amounts occurring in haemolymph and cuticle are poorly understood. Another intriguing problem to be solved concerns the fact that the oxidation of tyrosine

by tyrosinase leads to DOPA but not to melanin. Much work has to be done on the various oxidative enzymes occurring in CNS, haemolymph, and cuticle. The isolation and identification of those enzymes from various organs of insects presents a formidable problem. There is always the danger of contamination of the tissues with haemolymph. Eventually, the application of tissue cultures will lead to solutions of some of the most crucial problems.

Despite many similarities in oxidative pathways of tyrosine metabolism in insects and vertebrates, some fundamental differences exist, particularly with respect to the hydroxylation of tyrosine to DOPA and the intermediacy of quinone methides in oxidation of N-acylcatecholamines. It is expected that the results of future research will add to our knowledge not only on melanin chemistry and biochemistry in general, but will also provide new aspects that are of mutual interest for the vertebrate and the invertebrate melanin scientist.

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CURRENT LITERATURE

We acknowledge the valuable assistance of
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1. Melanins and other pigments chemistry

- Akiu S.
Methods for quantifying melanin. Nippon Koshohin Kagakkaishi 15:172-176, 1991.
Abstract : A review with 13 references, on quantitation of melanins by methods, including spectrophotometry, fluorometry, HPLC, and ESR.

- Bridelli MG, Crippa PR, Ugozzoli F.
X-ray diffraction studies on melanins in lyophilized melanosomes. Pigm Cell Res 3:187-191, 1990.
Abstract : A series of experiments was performed on lyophilized melanosomes to analyze the melanin in the natural state as polymd. into these organelles and to verify in such biol. amorphous material the possibility of obtaining intensity scattering curves from which Bragg distances can be calculated. The results confirm the feasibility of the method and show that melanins in melanosomes maintain many structural features of the purified form and that the biochem. compound of the organelles can be responsible for the obsd. differences in the diffractograms. The presence in melanosomes of supramol. paracryst. aggregates was also clearly demonstrated.

- Crippa PR, Martini F, Viappiani C.
Direct evidence of electron-phonon interaction in melanins. J Photochem Photobiol B 11:371-375, 1991.
Abstract : A very efficient electron-phonon coupling is active in eumelanin, as evidenced by the effect of phonon amplification. This observation strongly supports the proposed model of action of cutaneous (and possibly extracutaneous) melanins.

- Duthel JM, Vallon JJ.
Indolic urinary melanogens: separation and identification by gas chromatography with selected-ion monitoring mass spectrometry of 5-hydroxy-6-methoxyindole-2-carboxylic and 5-methoxy-6-hydroxyindole-2-carboxylic acids. J Chromatogr 570:166-172, 1991.
Abstract : Two isomeric urinary melanogens, 5-hydroxy-6-methoxyindole-2-carboxylic acid and 5-methoxy-6-hydroxyindole-2-carboxylic acid, have been separated by gas chromatography with selected-ion monitoring mass spectrometry. After chemical synthesis of one of these two isomers, 5-methoxy-6-hydroxyindole-2-carboxylic acid, and the establishment of the mass spectrum of its trimethylsilylated derivative, a 30-ml sample of a melanotic 24-h urine was adjusted to pH 1 and extracted twice with 10 ml of ethyl acetate. The extract was evaporated to dryness and the residue derivatized with methyl-8, followed by Tri-Sil/TBT. Silylated derivatives were analysed by gas chromatography with selected-ion monitoring mass spectrometry. The mass spectrum of the 5-methoxy-6-hydroxyindole-2-carboxylic acid allowed the determination of the retention times of both isomers.

- Emary WB, Allegri G, Costa C, Frison G, Traldi P.
Structural characterization of two isomeric dimethoxyindoles of biological interest, using high- and low-energy collisional spectroscopy. Rapid Commun Mass Spectrom 3:413-416, 1989.

Abstract : It is not possible to distinguish isomers of biologically important dimethoxyindoles using electron-ionization mass spectra, but they may be distinguished by collisionally activated dissociation. In particular, energy-resolved mass spectrometry yields the best data for distinguishing between these isomers.

- Flood PR, Deibel D, Morris CC.
Filtration of colloidal melanin from sea water by planktonic tunicates. Nature (London) 355:630-632, 1992.
Abstract : Pelagic tunicates of the genus Oikopteura produce, live in and pump water through mucous structures termed houses. Because these houses contain filters with submicrometer pores, oikopleurids have been proposed as important consumers of particulate org. carbon (POC) in the sea. They also consume dissolved org. carbon (DOC) (such as melanin) in the colloidal size range down to about 0.2 .mu.m in diam. Such colloids are more abundant in the sea than previously believed, and have an important role in the global flux of carbon. Oikopleurid tunicates have the potential to filter a significant fraction of the water mass every day, and to repack much of the colloidal DOC into their houses, fecal pellets and bodies. Oikopleurids are also known prey for several fish species. Thus, the oikopleurid tunicates may mediate a substantial energy flow, from DOC through a two-step food-chain, to fish of com. interest, by-passing energy-consuming respiration by bacteria and small planktonic protozoa.

- Hall SJ, Youson JH.
Distribution of ferric iron in larval lampreys, Petromyzon marinus L. Histol Histopathol 3:7-20, 1988.
Abstract : The distribution and abundance of ferric iron in larval lampreys (Petromyzon marinus L.) were investigated using light microscopy and the Prussian blue stain. Animals from various watersheds contained different concentrations of iron, although the sites of deposition were the same for all animals. A major portion of iron is within adipose tissue, while the liver, and cartilage contain predominantly low to trace amounts of iron, respectively. Iron is associated with fibrous connective tissue in several places in the body, and this association may have particular significance in the inner ear. Iron is also located in cells of the meninges. The presence of iron in the epithelial cells of the posterior intestine may reflect elimination of the metal through the extrusion of iron-loaded cells into the intestinal lumen. Iron within mucous cells of the epidermis, suggest elimination of iron during mucous secretion. Iron-loaded cells of bipolar shape are also present in the epidermis, but are particularly prominent around the branchiopore. Low concentrations of iron are observed within in melanin-containing macrophages (melano-macrophages) in regions of iron absorption, erythrophagocytosis, and haemopoiesis. High levels of iron in the epithelia and lumina of pronephric tubules are concomitant with degeneration of this organ. These data are evidence of the wide spread distribution of iron in lamprey tissues and additional evidence for the potential value of lampreys for the study of iron metabolism in vertebrates.

- Hill HZ.
The function of melanin or six blind people examine an elephant. Bioessays 14:49-56, 1992.
Abstract : The pigment melanin is found in all living kingdoms and in many different structures and forms. When its various functions are examined separately, its behaviors seem disparate and conflicting. It has a clear role in camouflage and sexual display. Other major roles are examined critically. It can act as a sun screen but is not a very effective one. It can also scavenge active chemical species, but this, too, is not done very effectively. It produces active radicals that can damage DNA. It binds to drugs in ways that are either beneficial or deleterious. Aside from camouflage, its other roles can be brought together by a unifying hypothesis as first proposed by Proctor and McGinness nearly 20 years ago. Melanin is envisaged as an energy transducer with the properties of an amorphous semiconductor. It can absorb many different types of energy and dissipate them in the form of heat. However, if the energy input is too great, the output can be expressed in the form of activated chemical species that can damage cellular macromolecules resulting in cell death, mutations and cancer. The protective aspect of melanin in dark skin is seen as resulting from its high concentration and its confinement to ellipsoidal and densely packed organelles that can effectively shield the nucleus. In light skin, its radical nature is seen as potentially participating in

the carcinogenic process, particularly when overwhelmed by intense episodes of sunburn.

- Hubbard-Smith K, Hill HZ, Hill GJ.
Melanin both causes and prevents oxidative base damage in DNA: quantification by anti-thymine glycol antibody. Radiat Res 130:160-165, 1992.
Abstract : The present study employs immunological methods to measure modified bases in DNA. A polyclonal antibody specific for thymine glycol was used to quantify the level of thymine glycol in calf thymus DNA gamma-irradiated in solutions containing varying concentrations of DOPA-eumelanin. Melanin decreased the number of thymine glycols produced by 200 Gy at low melanin concentrations. At high melanin concentrations, the number of thymine glycols increased. Thymine glycol was also produced in unirradiated DNA-eumelanin mixtures. DOPA-eumelanin was found to produce single-strand breaks in supercoiled phi X174 RF DNA. The breaks were measured by conversion of form I to form II as detected by agarose gel electrophoresis. The level of damage produced by melanin could be modulated by agents known either to stabilize or to scavenge active oxygen species. These studies demonstrate that melanin can both scavenge and generate active free radicals.

- Jacobsohn GM, Jacobsohn MK.
Incorporation and binding of estrogens into melanin: comparison of mushroom and mammalian tyrosinases. Biochim Biophys Acta 1116:173-182, 1992.
Abstract : The activities of mushroom and melanoma tyrosinases towards the estrogens were compared. While the fungal enzyme is capable of hydroxylating estradiol to the 2-hydroxy compound and to oxidize the latter to the quinone, the mammalian enzyme does not have this ability. With dopa as substrate and an estrogen present in the reaction mixture, both enzyme reactions yield melanin with the steroid firmly incorporated into the pigment, although with the mammalian enzyme the incorporation is small. The steroid appears to be incorporated by covalent linkage. It is suggested that the incorporation of estrogens into melanin produced by mammalian tyrosinase is via their oxidation by oxidized intermediates of the dopa to melanin transformation. Melanin itself may function as oxidant for the estrogens. Whole melanoma cells are capable of binding estrogens and incorporating small amounts into melanosomes. Similarly, fresh melanosomes in isolation can incorporate estrogens into their structure, presumably by covalent bonding to their melanin.

- Kosugi N, Katada T.
Production and physiological functions of S-lactoylglutathione (SLG). Fragrance J 20:30-34, 1992.
Abstract : A review with 16 references on production of SLG from methylglyoxal and glutathione via hemimercaptal using cell-free extracts of yeasts containing glyoxalase I and application of SLG. Antiinflammatory and melanin formation inhibitory activities of SLG are described.

- Oniki T, Takahama U.
Effects of redox reagents on ESR line shape of synthetic melanins. Bull Chem Soc Jpn 65:6-13, 1992.
Abstract : Melanins were synthesized from pyrogallol or beta-(3,4-dihydroxyphenyl)alanine(dopa), and their ESR spectra were measured. The pyrogallol melanin had four kinds of ESR signal; main and broad signals under anaerobic conditions, and inner and outer signals under aerobic conditions. The main, inner and outer signals disappeared after reduction of the melanin by NaBH4 or ascorbic acid, but the broad signal did not. After oxidation of the melanin by hexacyanoferrate(III), the intensity of the signals decreased, and the inner and outer signals were not observed under aerobic conditions. Hydrogen peroxide decreased these signals esp. under aerobic conditions at high pH. Superoxide treatment gave signals similar to those under aerobic conditions, but decreased the signals of the hexacyanoferrate(III)-oxidized melanin. ESR signals of dopa melanin showed similar behavior to that of pyrogallol melanin against redox reagents. The chemical structures around radicals in melanins were proposed from these results.

- Oniki T.
Reaction of synthetic melanins with redox reagents. II. ESR spectra using flow method. Bull Chem Soc Jpn 65:476-480, 1992.

Abstract : ESR spectra of synthetic pyrogallol melanin showed hyperfine structure at pH 13.0 under anaerobic conditions, but did not under aerobic conditions. The outer signal defined in a previous paper (Oniki T.; Takahama U., 1992) was observed in reactions with hexacyanoferrate(III) at pH 11.5 and with NaIO4 at pH 13.0. The reaction with NaIO4 indicated that the outer signal is split into two lines with a hyperfine coupling const. (hfcc) of 0.41 mT. Another signal, which is split into two lines with a hfcc of 0.65 mT, was observed in the reaction with NaBH4 at pH 13.0. Na2S2O4 solutions showed ESR signals under anaerobic conditions, but these signals disappeared in the presence of large amounts of melanins. The broad signal defined in a previous paper disappeared slowly in the presence of Na2S2O4 but not in the presence of NaBH4. Time courses of ESR signal in reactions of melanins with redox reagents were shown up to 30 min after mixing.

- Pierce JA, Rast DM.
Permanganate degradation of a fungal melanin and characterization of the decomposition products by infrared spectrometry. Physiol Chem Phys Med NMR 23:161-166, 1991.
Abstract : Diffuse reflectance Fourier-transform IR (DR FT-IR) spectrometry was used to characterize (microgram quantities of) the ether, Et acetate, CHCl3, and triethylamine extracts of melanin from Agaricus bisporus that was degraded by K permanganate. The identical pair of ether and Et acetate spectra are distinct from the indistinguishable pair of CHCl3 and triethylamine ext. spectra. A significant amount of amine groups is indicated in both sets of extracts, while longer chain lipids predominate in the CHCl3 and triethylamine extracts. The intense signals attributable to amine groups are suggested to arise from the presumptive precursor, gamma-glutaminyl-4-hydroxybenzene. DR FT-IR measurements of the degradation products of the melanin isolated from the common mushroom offer an attractive method to assess the constituents of this biopolymer.

- Porebska-Budny M, Sakina NL, Stepien KB, Dontsov AE, Wilczok T.
Antioxidative activity of synthetic melanins. Cardiolipin liposome model. Biochim Biophys Acta 1116:11-16, 1992.
Abstract : The inhibiting effect of melanin synthesized from dihydroxyphenylalanine (DOPA), dopamine, adrenaline and adrenolutin on the ultraviolet- or the Fe(2+)-ascorbic acid-induced peroxidation of cardiolipin liposomes has been studied. All these melanins are able to inhibit both the ultraviolet- and the Fe(2+)-ascorbic acid-induced lipid peroxidation. Antioxidative activity of melanins enhances in the order: dopamine-melanin less than melanin synthesized from dopamine in the presence of Cu(2+) less than DOPA--melanin less than melanin synthesized from adrenaline in the presence of Cu(2+) approximately equal to adrenolutin-melanin, and correlates with their ability to scavenge superoxide anion radical. The optical screening effect of the investigated melanins in the inhibition of lipid peroxidation was not higher than 15% for the most active melanins.

- Rodriguez-Lopez JN, Tudela J, Varon R, Garcia-Carmona F, Garcia-Canovas F.
Analysis of a kinetic model for melanin biosynthesis pathway. J Biol Chem 267:3801-3810, 1992.
Abstract : The kinetic behavior of the melanin biosynthesis pathway from L-tyrosine up to dopachrome has been studied from experimental and simulation assays. The reaction mechanism proposed is based on a single active site of tyrosinase. The diphenolase and monophenolase activities of tyrosinase involve one single (oxidase) and two overlapped (hydroxylase and oxidase) catalytic cycles, respectively. The stoichiometry of the pathway implies that one molecule of tyrosinase must accomplish two turnovers in the hydroxylase cycle for each one in the oxidase cycle. Furthermore, the steady-state rates of dopachrome production and O2 consumption from tyrosine and L-dopa, also fulfill the stoichiometry of the pathway: VO2T/VDCT = 1.5 and VO2T/VDCD = 1.0, where T represents L-tyrosine, DC represents dopachrome, and D represents L-dopa. It has been ascertained by high performance liquid chromatography that in the steady-state, a quantity of dopa is accumulated ([D]ss) which fulfills the constant ratio [D]ss = R[T]0. Taking this ratio into account, an analytical expression has been deduced for the monophenolase activity of tyrosinase. In this expression kcatT congruent to (2/3)k3(K1/K2)R, revealing that kcatT is not a true catalytic constant, since it also depends on equilibrium constants and on the experimental R = 0.057. This low value explains the lower catalytic efficiency of tyrosinase on tyrosine than on dopa, (VmaxT/KmT)/(VmaxD/KmD) congruent to (2/3)R, since a significant portion of tyrosinase is

scavenged from the catalytic turnover as dead-end complex EmetT in the steady-state of the monophenolase activity of tyrosinase.

- Rosei MA, Mosca L, De Marco C.
Melanins production from enkephalins by tyrosinase. Biochem Biophys Res Commun 184:1190-1196, 1992.
Abstract : Leu-enkephalin and Met-enkephalin are oxidized in vitro by mushroom and sepia tyrosinase giving rise to synthetic melanins whose production is dependent on incubation time and on enzyme concentration. The Enk-melanins formed are acid-insoluble brownish or reddish pigments showing a continuous absorbance in the visible region when dissolved in basic solution. The presence of the amino acid chain makes them fully soluble in pH 7.4 0.05 M phosphate buffer and methanol.

- Salopek TG, Yamada K, Ito S, Jimbow K.
Dysplastic melanocytic nevi contain high levels of pheomelanin: quantitative comparison of pheomelanin/eumelanin levels between normal skin, common nevi, and dysplastic nevi. Pigm Cell Res 4:172-179, 1991.
Abstract : The degree and type of melanogenesis, i.e., either eumelanin or pheomelanin, has been shown to be a reliable marker for the differentiation of the melanocyte. If exposed to UV light, these two melanins were reported to behave differently; eumelanin was photoprotective, whereas pheomelanin was phototoxic to cultured tumor cells. Previous study indicated that dysplastic melanocytic nevus (DMN) undergoes altered melanogenesis, forming pheomelanosome-like granules. The present study examined chem. the type and degree of melanin synthesized in 31 melanocytic nevi excised from 27 patients as compared with that occurring in the surrounding normal skin. The tissue content of eumelanin and pheomelanin was expressed by the amounts of pyrrole-2,3,5-tricarboxylic acid (PTCA) and aminohydroxyphenylalanine (AHP), resp. DMN lesions contain higher amounts of pheomelanin than either common melanocytic nevus (CMN) or normal skin. Differences in pheomelanin content between DMN and CMN could not be accounted for by inherently higher levels of pheomelanin within the skin in general from DMN patients. The present finding substantiates the authors' previous claim that epidermal melanocytes in DMN undergo deranged melanogenesis.

- Viviani F, Gaudry M, Marquet A.
Biosynthesis of melanin by Pyricularia oryzae: mechanism of reduction of polyhydroxynaphthalenes. NATO ASI Ser, Ser A 207:269-272, 1991.
Abstract : The reduction of 1,3,6,8-tetrahydroxynaphthalene by NADPH-naphthol reductase of P. oryzae is discussed with reference to kinetics, mechanism, and stereochem.

- Yamaguchi I, Kubo Y.
Target sites of melanin biosynthesis inhibitors. Target Sites Fungic Action (K. Wolfram, ed) CRC. Boca Raton, Florida, pp. 101-118, 1992.
Abstract : A review with 94 references of melanin biosynthesis inhibitors in Pyricularia oryzae and Colletotrichum species.

2. Biology of pigment cells and pigmentary disorders

- Abdel-Malek Z, Swope VB, Pallas J, Krug K, Nordlund JJ.
Mitogenic, melanogenic, and cAMP responses of cultured neonatal human melanocytes to commonly used mitogens. J Cell Physiol 150:416-425, 1992.
Abstract : The following studies have been undertaken to compare and correlate the effects of 12-O-tetradecanoylphorbol acetate (TPA), basic fibroblast growth factor (bFGF), cholera toxin (CT), and isobutyl methylxanthine (IBMX) on neonatal human melanocyte (NHM) proliferation, tyrosinase activity, and cyclic adenosine monophosphate (cAMP) concentration. NHM proliferated at a maximal rate in medium containing 8 nM TPA, 200 ng/ml CT, and 10(-4) M IBMX. TPA alone did not result in optimal melanocyte proliferation, and, as previously shown, its mitogenic effect was greatly

enhanced by the addition of CT and IBMX individually or concomitantly. Human recombinant (hr) bFGF could replace TPA in the NHM growth medium. Maximal proliferation was achieved using 3 ng/ml hrbFGF, 20 ng/ml CT, and 10(-4) M IBMX. The mitogenic effect of 1.2 ng/ml hrbFGF was potentiated in the concomitant but not individual presence of CT and IBMX. TPA alone in the absence of CT and IBMX caused a dose-dependent stimulation of tyrosinase activity. Maximal tyrosinase activity was obtained in the presence of 0.8 nM TPA, 20 ng/ml CT, and 10(-4) M IBMX. Unlike TPA, hrbFGF alone resulted in inhibition of tyrosinase activity. In the presence of hrbFGF, tyrosinase activity was potentiated by CT and IBMX, but not by CT alone. Neither TPA nor hrbFGF alone could increase intracellular cAMP levels. The effects of CT and IBMX on intracellular cAMP concentration were enhanced to a greater extent by TPA than by hrbFGF. Under our experimental conditions, in the presence of hrbFGF, CT but not IBMX resulted in a dose-dependent increase in cAMP concentration. Further studies on NHM will be aimed at determining the exact role of protein kinase C (PKC) in regulating proliferation and melanogenesis and the mechanism(s) activated by hrbFGF.

- Aliev GA, Rachkovskii ML, Ivanov AV, Ito S, Vakamatsu K.
Content of eumelanin and pheomelanin in wool of different breeds of lambs with various coloring genotypes. S-kh Biol 6:16-24, 1991.
Abstract : The eumelanin and pheomelanin content of wool of Tadjik, Karakul, and Gissar lambs with differing coloring phenotypes was detd. with HPLC and EPR spectroscopy.

- Anderson LL, Paller AS, Malpass D, Schmidt ML, Berger TG.
Chediak-Higashi syndrome in a black child. Pediatr Dermatol 9:31-36, 1992.
Abstract : Chediak-Higashi syndrome (CHS) is an uncommon genetic disorder with a constellation of clinical, pathologic, and immunologic manifestations. It is rarely reported in blacks. Pathognomonic intracellular inclusions in white blood cells are well recognized; however, characteristic abnormal melanin aggregation into giant melanosomes also occurs, as can be readily seen by histologic evaluation of hair. We present a case of CHS in a black child.

- Azanza MJ, Aisa J, Junquera C, Castiella T.
The autonomic innervation of the liver and gallbladder of Rana ridibunda. Histol Histopathol 4:405-410, 1989.
Abstract : 1--The innervation of the liver and gallbladder of Rana ridibunda has been studied by the following methods: (a) demonstration of cholinesterase activity; (b) FIF method for catecholamines; (c) immunohistochemistry for VIP and (d) electron microscopy. 2--The hepatocytes are arranged in regular rows of hepatic cords, very little connective tissue is distributed in the parenchyma, the innervation being restricted to the big branches of blood vessels. 3--Well defined cholinergic and adrenergic plexuses surround the hepatic arteries, portal veins and biliary ducts. The VIPergic innervation is scarce in the liver but a richly branched plexus spreads in the wall of the gallbladder. 4--Cholinesterase-positive cells are widely distributed accompanying the nerve trunks of the gallbladder. The innervation distribution is prominent in the portion of the gallbladder next to the hepatic hilus. 5--A population of melanin-storing cells besides free melanin granules are present in the liver parenchyma and are prominent in the gallbladder where the melanocytes are disposed in close contact with blood vessels and nerve structures. We have observed that the number of these visceral melanocytes considerably increases in winter, particularly in the liver.

- Benz G, Holzel D, Schmoeckel C.
Inflammatory cellular infiltrates in melanocytic nevi. Am J Dermatopathol 13:538-542, 1991.
Abstract : We examined 1,054 melanocytic nevi [137 (13%) simple lentigines, 158 (15%) junctional nevi, 337 (32%) compound nevi, and 422 (40%) dermal nevi] for the presence of lymphohistiocytic infiltrates. The following criteria were evaluated: age and sex of the patient, location, histological type, horizontal and vertical diameter, increase of melanocytes in the basal layer of the epidermis, increase of melanophages in the papillary dermis, melanin content of keratinocytes, and melanin content of nevus cells. Lymphohistiocytic infiltrates were measured semiquantitatively; their presence within the center, in the lateral margins, or both was also determined. The results were analyzed statistically by means of chi-square tests and univariate and multivariate analyses. We found that 824

lesions (78%) were associated with a lymphohistiocytic infiltrate; whereas 230 (22%) were not. This infiltrate was weak in 273 cases (33%), moderate in 411 cases (50%), pronounced in 130 cases (16%), and very strong in 10 cases (1%). Multivariate analyses revealed that the only criteria associated with the presence of lymphohistiocytic infiltrates were the increase of melanocytes in the basal layer and the vertical thickness in compound nevi. All other parameters were statistically insignificant. We conclude that melanocytic nevi with a junctional hyperplasia of melanocytes--i.e., mostly early stages such as simple lentigines, junctional nevi, and superficial compound nevi--are often associated with a moderate to pronounced cellular stromal reaction. Their presence may reflect the appearance of antigens on proliferating melanocytes. It may also represent a stromal reaction to necrotic tumor cells and keratinocytes within the dermoepidermal junction. These findings rule out any relationship to an increase of melanin pigment.

- Betterle C, Caretto A, Pedini B, Rigon F, Bertoli P, Peserico A.
Complement-fixing activity to melanin-producing cells preceding the onset of vitiligo in a patient with type 1 polyglandular failure [letter]. Arch Dermatol 128:123-124, 1992.

- Borisyuk LG, Kharat'yan EF, Zhdanova NN.
Localization and dynamics of melanin accumulation in cells of Cladosporium cladosporioides (Fresen) de Vries. Mikrobiol Zh (Kiev) 53:10-16, 1991.
Abstract : A comparative electron microscopic anal. of cells and protoplasts of C. cladosporioides and its nonpigmented alm mutant localized the melanin in the external layer of the cell wall rather than in the cytoplasm. Melanin synthesis was observed at the beginning of the exponential phase of growth and proceeded parallel to the growth for the whole life cycle. Ecol. interpretation of the results is given.

- Buffey JA, Hill SE, Bleehen SS, Thody AJ, Mac N.
Evidence for a calcium/calmodulin involvement in density-dependent melanogenesis in murine B16 melanoma cells. Pigment Cell Res 4:112-119, 1991.
Abstract : Previous work from our laboratory has shown that both cyclic AMP and calcium/calmodulin appear to be involved in the regulation of melanogenesis in murine B16 melanoma cells. In these cells as in murine Cloudman S91 cells, melanogenic responsiveness to melanocyte-stimulating hormone (MSH) varies with cell density in culture. Our objective in this study was to learn more about the intracellular systems involved in the control of melanogenesis, particularly the role played by calcium. The melanogenic response to alpha MSH was compared to the response to drugs affecting intracellular free calcium and calmodulin over a range of cell densities in B16F1 cells. alpha MSH-stimulated melanin production was extremely density-dependent but alpha MSH-stimulated cyclic AMP production was independent of cell density. The melanogenic response to agents that increased intracellular calcium (A23187) or inhibited intracellular calmodulin varied with cell density. A drug (TMB8) that lowered intracellular free calcium, however, increased melanogenesis independently of cell density. At high cell density it was found that an elevation in calcium decreased melanogenesis, whereas agents that reduced calcium or inhibited calmodulin activity increased melanogenesis. At low cell density, however, the inhibitory response to A23187 was lost and in some experiments even stimulated melanogenesis. These data suggest that the calcium/calmodulin signalling system has an inhibitory influence on melanogenesis, and its expression, which depends upon cell density, may also modulate the response to stimulatory agents such as alpha MSH.

- Claudy AL, Levigne V, Boucheron S.
Serpentine supravenous hyperpigmentation induced by the nitrosourea fotemustine. Dermatology 184:70-72, 1992.
Abstract : Two cases of serpentine supravenous hyperpigmentation developing in the area of fotemustine infusions are reported. Histological features showed an increased melanin synthesis and the presence of melanophages without focal degeneration of basal cells or dermal inflammatory infiltrate. Perls' strain was negative. Hypotheses concerning the mechanisms of increased melanin synthesis over the veins are discussed.

- Fligiel SE, Inman DR, Talwar HS, Fisher GJ, Voorhees JJ, Varani J.
Modulation of growth in normal and malignant melanocytic cells by all-trans retinoic acid. J Cutan Pathol 19:27-33, 1992.
Abstract : Human epidermal melanocytes were examined for proliferation under various conditions in the presence or absence of all-trans retinoic acid (RA). Under conditions which supported proliferation, RA at concentrations of 0.25-1.0 microgram/ml inhibited cell growth but was not cytotoxic. When melanocytes were cultured under conditions which by themselves did not support growth, RA did not overcome the growth limitation. Treatment of melanocytes with RA altered their morphological appearance. Alterations included retraction of dendritic processes, increased flattening, and a slight darkening of the cytoplasm in some of the cells. However, when examined biochemically, there was no significant change in the amount of malanin per cell or in tyrosinase activity. RA also inhibited proliferation of six different malignant melanoma lines. Inhibition was observed over the same RA concentrations and over the same time course in the melanoma cells as was seen in melanocytes. Inhibition of melanocyte and melanoma cell proliferation was slowly reversed following removal of RA from the culture medium. These results indicate that RA can inhibit proliferation of melanocytic cells.

- Fryer JM, Werth VP.
Pregnancy-associated hyperpigmentation: longitudinal melanonychia. J Am Acad Dermatol 26:493-494, 1992.

- Guillet G, Helenon R, Guillet MH, Gauthier Y, Menard N.
Progressive and confluent hypomelanosis of the melanodermic metis. Ann Dermatol Venereol 119:19-24, 1992.
Abstract : Melanodermic half-castes may develop a progressive and extensive hypomelanosis presenting as an original skin condition. The course of the disease is characteristic: it occurs mainly in females from 18 to 25 years of age with a progressive development of hypochromic and coalescent macules on the back and abdomen. This disease may regress spontaneously within 5 years and healing seems to be facilitated by UV exposure. Decreased epidermal melanin is the only histological feature. Ultrastructural examination has led to characterize this bizarre disease by a switch from stage IV single melanosomes negroid type to small type I-III aggregated melanosomes (caucasoid phenotype of melanogenesis). Although the pathogenesis of the disorder remains obscure, it may be stated that the variation in skin coloration in these patients is due to a variation in melanosome size and distribution. It is possible that this variation is due to a decrease in production of type IV melanosomes and that this apparent change of ultrastructural phenotype represent the consequence of a simple imbalance in melanosomes production favoring small I to III melanosomes. This disease is not restricted to a limited geographic group: it is present in melanodermic half-castes of different areas and therefore deserves to be known and recognized.

- Haase E, Ito S, Sell A, Wakamatsu K.
Melanin concentrations in feathers from wild and domestic pigeons. J Hered 83:64-67, 1992.
Abstract : Vanes from secondary remiges and greater converts (i.e., feathers that form the wing bars of the wild coloration type) were analyzed for their eumelanin and pheomelanin contents. The samples were taken from wild rock pigeons and from domestic breeds representing different coloration types of known genetic background. The bars in the wild rock pigeons and in similarly colored domestic birds are eumelanic but also contain some pheomelanin. In ash red (BA) pigeons, the bars are pheomelanic with drastically reduced eumelanin concns., and in brown (b) specimens they are of a pheomelanic to mixed type. Mutant S (spread) eliminates the differences in the melanin concns. between the bars and the adjacent areas, resulting in a uniform coloration. Its effects on eumelanin and pheomelanin contents vary in dependence from the alleles at the color locus and from other genes. Recessive red (e e) pigeons are pheomelanic. The effects of the diln. factor (d) cannot be described by a single diln. index but depend on combination with other genes. These suggest that the greater variation of coloration in domesticated animals than in their wild ancestors is caused by mutations that affect the distribution, amts., and proportions of pigments but not their chem.

- Henninger JM, Beresford WA.
Is it coincidence that iron and melanin coexist in hepatic and other melanomacrophages? Histol Histopathol 5:457-459, 1990.
Abstract : Use of a Prussian-blue histochemical method shows iron in some but not all hepatic melanomacrophages of turtle, alligator, caiman and anole. The hypothesis prompted is that melanomacrophages in general synthesize melanin to render less noxious free radicals arising from catalysis by the iron.

- Hirone T.
Human melanocyte. Saibo 23:519-523, 1991.
Abstract : A review with 17 references, on human melanocytes, discussing the localization, ontogeny, morphol. and structure of melanocytes, melanin and melanosome formation, nos. of melanocytes, and skin coloration, and disorders in skin pigmentation.

- Hudon J.
Unusual carotenoid use by the Western Tanager (Piranga ludoviciana) and its evolutionary implications. Can J Zool 69:2311-2320, 1991.
Abstract : The author used spectrophotometric, chromatographic, and chemical means to establish that rhodoxanthin, a 3-keto-retrodehydro carotenoid, was the only red pigment in the head feathers of the Western Tanager (P. ludoviciana). In contrast, the red head and body feathers of a close relative, the Scarlet Tanager (P. olivacea), exhibited several 4-keto-carotenoids. Other tanagers and emberizids also displayed 4-keto-carotenoids. The deposition of presumed canary xanthophylls and phaeomelanins differed quant. between the Western Tanager and other tanagers belonging to the genus Piranga. Uniquely among the Piranga species examined, the head feathers of the Western Tanager had flattened bards without barbules. Partly because the head colors of the Western and Scarlet tanagers were indistinguishable either in the hand or when examined by reflectance spectrophotometry. The authors excluded selection for a variant color as the basis for the observed chemical and morphological differences. Biochemical costs, including putative costs associated with the endogenous production of 4-keto-carotenoids, could have led to the conversion in the Western Tanager to an available dietary pigment. This tanager, unlike the other species studied, has access to an abundant source of rhodoxanthin in the coniferous forests of western North America. The pigment changes in the Western Tanager could have taken place with minimal effect on head color.

- Kao CH, Yu HS, Ko SS.
Dyschromatosis universalis hereditaria: report of a case. Taiwan I Hsueh Hui Tsa Chih 90:1205-1210, 1991.
Abstract : The case of a 43-old-year woman who had a generalized asymptomatic pigmentary disorder with onset at about age 20 is presented. Tracing back her family history, we found that her father and six of her siblings had also suffered a similar skin pigmentary defect with onset at the same approximate age. In depigmented lesions, three distinct histopathological features were observed: (1) decreased epidermal melanin content and lower density of melanocytes in the upper dermis; and (3) ultrastructural vacuolar degeneration in the focal melanocytes and in the keratinocytes immediately nearby. No deposit of amyloid was observed in the biopsied skin specimens. In hyperpigmented lesions, the histopathological features included: (1) increased melanin content and high density of melanocytes; (2) few melanophages in the papillary dermis of focal areas, but no vacuolar degeneration of the epidermal cells; and (3) an increased number of melanosomes in the basal and suprabasal keratinocytes. Direct immunofluorescence examination revealed no deposit of immunoglobulins in either the hyperpigmented or depigmented lesions. By indirect immunofluorescence examination, the serum of the patient was found to contain antinuclear antibodies (ANA, IgG, class, homogeneous pattern); however, the maximal positive dilution titer of sera against cultured human cells was much higher in melanocytes (1:500 dilution) than in keratinocytes (1:50 dilution) or fibroblasts (1:10 dilution). The pathogenesis of dyschormatosis universalis hereditaria remains unclear; however, hereditary genetic defects may play an important role in alternating regular melanogenesis, which results in a pigmentary anomaly.

- Key JM, Waner M.
Selective destruction of facial telangiectasia using a copper vapor laser. Arch Otolaryngol Head Neck Surg 118:509-513, 1992.
Abstract : Copper vapor lasers emit pulsed light at 511 and 578 nm. The 578-nm option corresponds with a peak in the absorption of oxyhemoglobin and a diminished absorption by melanin. The pulse width of this light (20 nanoseconds) is significantly shorter than the thermal relaxation time of typical facial telangiectatic vessels (20 to 100 milliseconds). This laser is therefore able to selectively destroy facial telangiectatic vessels with little damage to the overlying epidermis. Twenty patients with facial telangiectasia were treated with the 578-nm option of a copper vapor laser. Treatment was administered in an office-room setting, and no anesthesia was used. Eighteen of the 20 patients experienced satisfactory clearance of their telangiectasia. Three patients developed temporary postinflammatory hyperpigmentation, which cleared within 6 to 8 weeks, and one patient developed a small depressed scar, which was not noticeable at 3 months. Copper vapor lasers are thus safe and effective in treating facial telangiectasia.

- Kubota Y, Shimura Y, Shimada S, Tamaki K, Amamiya S.
Linear and whorled nevoid hypermelanosis in a child with chromosomal mosaicism. Int J Dermatol 31:345-347, 1992.

- Lacour JP, Gordon PR, Eller M, Bhawan J, Gilchrest BA.
Cytoskeletal events underlying dendrite formation by cultured pigment cells. J Cell Physiol 151:287-299, 1992.
Abstract : In contrast to neurite outgrowth, pigment cell dendrite formation is relatively unstudied. Keratinocyte-conditioned medium (KCM) induces a striking dendricity in human melanocytes and B16 melanoma cells that is detectable within 30 min, maximal in 24-48 hr, and quantifiable by computerized image analysis. Cytochalasin B (CB), known to disrupt actin microfilaments, completely blocks dendrite formation if added to cultures before or with KCM. This effect is rapidly reversible, and dendrites appear within 1 hr after refeeding with KCM alone. In contrast, CB treatment fails to disrupt existing dendrites previously induced by KCM. Agents known to cause microtubule disassembly (colchicine, nocodazole, or vinblastine) do not inhibit dendrite formation if added before or with KCM. In contrast, these agents disrupt established dendrites. Inhibition of protein synthesis with cycloheximide or actinomycin D completely blocks dendrite formation, but if cultures are provided fresh KCM lacking protein synthesis inhibitors, dendrites reappear within 24 hr. Actin microfilaments visualized with a monoclonal antibody or rhodamine-phalloidin are poorly organized in untreated cells, but form numerous fibers localized along dendrites in KCM-treated cells. Microtubules visualized with a monoclonal anti-tubulin antibody are localized in the center of dendrites. These cytoskeletal changes occur without altering beta actin or beta tubulin mRNA levels. Taken together, these data implicate actin microfilaments in dendrite outgrowth, but not in maintenance, and conversely microtubules in dendrite maintenance but not in formation. These keratinocyte-induced changes involving beta actin and beta tubulin polymerization appear to require both new protein synthesis and post-translational regulation. The observed similarities between melanocytes and other neural crest-derived cells suggest that cutaneous pigment cells might serve as an alternative model for studies of neurite outgrowth.

- McHam ML, Fulton A.
Albinism. Int Ophthalmol Clin 32:185-200, 1992.

- Nappi AJ, Carton Y, Vass E.
Reduced cellular immune competence of a temperature-sensitive dopa decarboxylase mutant strain of Drosophila melanogaster against the parasite Leptopilina boulardi. Comp Biochem Physiol [B] 101:453-460, 1992.
Abstract : 1. The melanotic encapsulation response made by larvae of a temperature-sensitive dopa decarboxylase (DDC) mutant strain of Drosophila against the parasitic wasp Leptopilina was severely compromised in hosts with reduced levels of DDC. 2. Dopa and 5,6-dihydroxyindole (DHI) were two hemolymph components identified in hosts exhibiting a melanotic encapsulation response. 3. This

is the first study to implicate DDC in insect cellular immune responses, and to provide chemical evidence that the pigment formed during such responses is eumelanin derived from tyrosine.

- Obuch ML, Baker G, Roth RI, Yen TS, Levin J, Berger TG.0
Selective cutaneous hyperpigmentation in mice following zidovudine administration. Arch Dermatol 128:508-513, 1992.
Abstract : C57BL/6N mice fed zidovudine in their drinking water develop selective hyperpigmentation of the tails and footpads. Zidovudine-fed and identical control mice were observed and sequential biopsy specimens were obtained. Routine light microscopy, electron microscopy, and image analysis of unstained biopsy specimens were used to evaluate the extent, nature, and amount of cutaneous hyperpigmentation. Beginning at day 14 selective hyperpigmentation of the tails and footpads of the mice was noted. Histologic evaluation revealed a gradual increase in melanin, beginning in the lower levels of the epidermis, with eventual pigmentation of the stratum corneum. Electron microscopy demonstrated a sixfold increase in melanosomes in the tail skin of the zidovudine-fed mice. Using image cytometry, melanin was quantitatively shown to increase, paralleling the clinically apparent hyperpigmentation. The hyperpigmentation was reversible on discontinuation of zidovudine. This animal model parallels the human in developing reversible and selective hyperpigmentation on administration of zidovudine. In this model the increased pigmentation is due to increased numbers of melanosomes within epidermal keratinocytes. Image cytometry may be useful in semiquantitatively studying the pathogenesis of various disorders of hyperpigmentation.

- Phelan AM, Lange DG, Kues HA, Lutty GA.
Modification of membrane fluidity in melanin-containing cells by low-level microwave radiation. Bioelectromagnetics 13:131-146, 1992.
Abstract : The treatment of a B16 melanoma cell line with 2.45-GHz pulsed microwaves (10 mW/cm2, 10-microseconds pulses at 100 pps, 1-h exposure; SAR, 0.2 W/kg) resulted in changes of membrane ordering as measured by EPR (electron paramagnetic resonance) reporter techniques. The changes reflected a shift from a more fluid-like phase to a more solid (ordered) state of the cell membrane. Exposure of artificially prepared liposomes that were reconstituted with melanin produced similar results. In contrast, neither B16 melanoma cells treated with 5-Bromo-2-Deoxyuridine (3 micrograms/day x 7 days) to render them amelanotic, nor liposomes prepared without melanin, exhibited the microwave-facilitated increase of ordering. Inhibition of the ordering was achieved by the use of superoxide dismutase (SOD), which strongly implicates oxygen radicals as a cause of the membrane changes. The data indicate that a significant, specific alteration of cell-membrane ordering followed microwave exposure. This alteration was unique to melanotic membranes and was due, at least in part, to the generation of oxygen radicals.

- Prota G, Misuraca G, Napolitano A, Palumbo A.
Regulatory mechanisms in melanin pigmentation: a biomimetic approach. Top Mol Organ Eng 8:55-72, 1991.
Abstract : A review with 55 references, of the biosynthetic mechanism for melanin formation and it's regulation in vivo.

- Roewert HJ, Ackerman AB.
Large-cell acanthoma is a solar lentigo. Am J Dermatopathol 14:122-132, 1992.
Abstract : On the basis of a study of 54 specimens each of large-cell acanthoma, solar lentigo, reticulated seborrheic keratosis, and lichen planus-like keratosis, it is concluded that clinically, histopathologically, and biologically, large-cell acanthoma is a variant of solar lentigo, and solar lentigo (including the large-cell variant) is a stage in the evolution of reticulated seborrheic keratosis and of lichen planus-like keratosis.

- Sanchez Y.
Large-cell acanthoma is a distinctive condition. Am J Dermatopathol 14:140-147, 1992.
Abstract : We have studied the clinical and histopathologic features of 44 biopsy specimens of large-cell acanthoma (LCA) from 35 patients. There were 19 women and 16 men, 34-88 years of age (mean

75). The lesions were mainly located on the head and extremities, usually solitary, less than or equal to 10 mm in diameter, and of greater than or equal to 1 year's duration. However, there were also cases of multiple and larger lesions, and those of shorter duration. The most frequently offered clinical diagnoses were seborrheic keratosis, Bowen's disease, and LCA; two cases had the clinical features of stucco keratosis. Histologically, 41 of the specimens could be classified into three patterns: 16 lesions showed a basic pattern (mild to moderate acanthosis, hyperkeratosis, large cytoplasms and nuclei, hyperpigmentation, and bulbous rete ridges); 12 specimens showed a verrucous pattern (papillomatosis and hyperkeratosis resembling church spires); and 13 lesions exhibited a flat-hyperkeratotic pattern (compact hyperkeratosis arranged in horizontal layers of corneocytes lying on a band-like acanthotic stratum malpighii that lacks both rete ridges and papillae). Some cases exhibiting this latter pattern showed focal bowenoid changes. Some mixed and intermediate lesions demonstrated the existence of a spectrum. We have concluded that LCA is a distinctive condition with various stages of development and is probably related to stucco keratosis. It can clearly be separated histologically from solar lentigo and from solar keratosis. As other epidermal tumors, LCA can sometimes exhibit features of Bowen's disease.

- Takada K.
Application of tissue culture for evaluation of melanogenesis. Nippon Koshohin Kagakkaishi 15:177-181, 1991.
Abstract : A review with 16 references, on the use of cell-organ culture systems, such as melanoma, melanocyte, and skin culture system, in the evaluation of melanin synthesis and metabolic regulation.

- Veraldi S, Cavicchini S, Benelli C, Gasparini G.
Laugier-Hunziker syndrome: a clinical, histopathologic, and ultrastructural study of four cases and review of the literature. J Am Acad Dermatol 25:632-636, 1991.
Abstract : Four cases of Laugier-Hunziker syndrome are described. In all patients (two men and two women between 39 and 57 years of age) pigmentation of the lower lip and hard palate was found. in addition, two patients had involvement of the buccal mucosa; another patient also had pigmentation of the upper lip, the gums, the soft palate, and the fingers of both hands. Histopathologic examination demonstrated an accumulation of melanin in the basal layer keratinocytes and an increase in the number of melanophages in the papillary dermis. Ultrastructural study showed the presence of numerous mature melanosomes in the cytoplasm of the keratinocytes of the basal layer and of the melanophages in the papillary dermis. Alterations of the melanocytes were not observed.

3. MSH, MCH, other hormones, differentiation

- Compagnone N, Fellmann D, Bugnon C.
Expression of peptides derived from the melanin-concentrating hormone precursor in serum-free culture of rat fetal hypothalamic neurons: role of attachment factors. Dev Neurosci 13:417-423, 1991.
Abstract : A serum-free medium culture was developed in order to study the secretory behavior of neurons producing the melanin-concentrating hormone (MCH) precursor. The present results show that our culture conditions (supplemented RPMI 1640, poly-D-lysine substrate) are efficient in promoting attachment and growth of MCH neurons dissociated from rat fetal hypothalamus. These neurons acquire a differentiation stage in which neuropeptides of interest to us are expressed in a pattern similar to that observed on tissue sections: (1) coexpression of salmon MCH, growth-hormone-releasing factor (GRF37), alpha-melanocyte-stimulating hormone and acetylcholinesterase immunoreactivities, and (2) different intracellular distribution of salmon MCH and 1-37 sequence of GRF37 staining. Neurite growth was rapid and interneuronal connections were observed early. These observations suggest that our model of defined medium culture is suitable for functional investigations on MCH neurons.

- Jezova D, Bartanusz V, Westergren I, Johansson BB, Rivier J, Vale W, Rivier C.
Rat melanin-concentrating hormone stimulates adrenocorticotropin secretion: evidence for a site of action in brain regions protected by the blood-brain barrier. Endocrinology 130:1024-1029, 1992.
Abstract : Melanin-concentrating hormone (MCH) is a peptide reported to inhibit ACTH and cortisol secretion in teleost fish. Its ability to modify the activity of rat corticotrophs, however, remains controversial. We report here that while the peripheral injection of rat (r) MCH failed to alter plasma ACTH levels of conscious rats with an intact blood-brain barrier (BBB), it significantly activated the hypothalamic-pituitary-adrenocortical axis of rats with increased BBB permeability induced by protamine sulfate administration into the internal carotid artery. Similarly, the intracerebroventricular injection of this peptide into rats with intact BBB measurably released ACTH. The ACTH response to rMCH was markedly, but not totally, inhibited by passive immunoneutralization of CRF. These results indicate that rMCH acts within the central nervous system to stimulate the hypothalamic-pituitary-adrenocortical axis of rats, and that the site of action of the peptide is located in brain structures protected by the BBB. Activation of CRF-secreting neurons represents an important final pathway, although other regulatory factors also seem to be involved.

- Nanninga PB, Ghanem GE, Lejeune FJ, Bos JD, Westerhof W.
Evidence for alpha-MSH binding sites on human scalp hair follicles: preliminary results. Pigm Cell Res 4:193-198, 1991.
Abstract : alpha-MSH, considered an important pigmentation hormone, binds to melanocytes and is thought to stimulate melanogenesis through a cAMP-dependent mechanism. The binding of alpha-MSH to follicular melanocytes has been investigated in human hair of different colors, ranging from black to blond and senile white. Hairs were plucked, the follicles were cut off, and an alpha-MSH binding assay, using a radiolabeled alpha-MSH analog, was performed on these bulbs. As controls of each assay, fragments of hairs of the same person were used. The results show a dose-response relationship and the assay seems to be specific for alpha-MSH, because other peptides, such as ACTH, beta-LPH and beta-endorphins do not compete for binding sites as alpha-MSH does. These binding sites seem to be present only on melanin-synthesizing melanocytes, since the controls and follicles of senile white hair, which do not contain active melanocytes, show negative results. All the assays were performed on raw material, i.e., whole plucked hair follicles. This is the first time that binding sites for alpha-MSH have been demonstrated on human scalp hair follicles. In addition, their presence was found to be associated with active melanin production; their absence was demonstrated on senile hair white hair follicles.

- Nahon JL, Presse F, Schoepfer R, Vale W.
Identification of a single melanin-concentrating hormone messenger ribonucleic acid in coho salmon: structural relatedness with 7SL ribonucleic acid. J Neuroendocrinol 3:173-183, 1991.
Abstract : Melanin-concentrating hormone (MCH) is a cyclic neuropeptide possessing antagonistic function to alpha-MSH and ACTH-releasing factor in the control of melanosome dispersion within melanophores and ACTH release in fish. MCH cDNAs from coho salmon (Oncorhyncus kisutch) were isolated and characterized. The precursor protein predicted by the longest cDNA consists of 132 amino-acids with a characteristic signal peptide at the N-terminus and the biol. active salmon MCH (sMCH) peptide at the C-terminus. The coho sMCH mRNA and protein sequences are very similar but not identical to the previously reported chum or chinook salmon counterparts, suggesting the existence of species polymorphism. Sequence similarities were revealed between alpha-MSH and part of the C-terminal domain of sMCH precursor. Two sMCH genes were found in coho salmon. By contrast to other salmon species, only one major sMCH mRNA was detected in coho species, suggesting that differential MCH gene expression might occur in salmon. In addition, under low stringency, oligoprobes complementary to the sMCH RNA recognize a 0.3-kb RNA which was identified as the 7SL RNA. The regions conserved between those RNAs fold in a similar secondary structure. These similarities might reflect common ancestry which may have functional significance.

- Presse F, Nahon JL.
Structural and functional resemblance between atrial natriuretic peptide, brain natriuretic peptide and melanin-concentrating hormone. Serono Symp Publ Raven Press 76:241-250, 1991.

Abstract : Structural similarities among atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, and melanin-concentrating hormone are discussed, together with the functions of these peptides in control of fluid and electrolyte homeostasis during normal development.

- Quinn J, Eckenstein FP, Baughman RW.
Novel antigenic determinant expressed in neurons of the dorsolateral hypothalamus in rat and human. J Neurosci Res 31:715-723, 1992.
Abstract : Previous studies have identified a group of cells in the dorsolateral hypothalamus that project to many different areas in the CNS, such as thalamus, diagonal band of Broca, basal ganglia, cerebral cortex, hippocampus, and olfactory bulb. Their role is presently unknown, but the cells have been reported to stain for an intriguing array of putative neurotransmitter-related substances, including alpha-melanocyte-stimulating hormone (alpha MSH), melanin-concentrating hormone (MCH), human growth-hormone-releasing factor 1-37 (hGRF 1-37), corticotropin-releasing factor (CRF), metorphamide, and acetylcholine esterase. A monoclonal antibody produced in the present study, alpha C11, stains both the cell bodies of this system in hypothalamus, with a punctate pattern, and varicose fibers in the various target areas. In double-label immunocytochemical experiments in rat DLH, alpha C11 and MCH staining exactly overlaps. Concentrations of alpha MSH and MCH high enough to completely block staining with the corresponding antisera had no effect on staining with alpha C11. Similarly, CRF, hGRF 1-37, and metorphamide were unable to block alpha C11 staining. The results suggest that the antigenic epitope for alpha C11 is not contained in alpha MSH, MCH, CRF, hGRF, or metorphamide, and thus, that alpha C11 is detecting another antigen uniquely expressed in these neurons. The punctate appearance of staining in the hypothalamus and the concentration of staining in fiber varicosities suggests that the alpha C11 epitope may be involved in synaptic function.

- Risold PY, Fellmann D, Rivier J, Vale W, Bugnon C.
Immunoreactivities for antisera to three putative neuropeptides of the rat melanin-concentrating hormone precursor are coexpressed in neurons of the rat lateral dorsal hypothalamus. Neurosci Lett 136:145-149, 1992.
Abstract : Antisera (AS) raised against rat melanin-concentrating hormone (rMCH) and against 2 addnl. peptide sequences derived from the rMCH precursor (neuropeptide glutamic acid-isoleucineamide (NEI), and neuropeptide glycine-glutamic acid (NGE)) exclusively stained the hypothalamic neurons previously described using AS to salmon MCH (sMCH), human somatocrinin 1-37 (GRF37) and alpha-MSH Liq. phase and dot-blot controls for specificity indicated that rMCH-, NEI-, and NGE-AS bound epitopes recognized by sMCH-, alpha-MSH-, and GRF37-AS, respectively. The distinct intracellular patterns of immunoreactivity obtained in control animals with rMCH-, NGE-, and NEI-AS, as well as the changes observed after intracerebroventricular injection of colchicine, matched previous findings using sMCH-, GRF37, and alpha-MSH-AS.

- Siligardi G, Campbell MM, Gibbons WA, Drake AF.
Conformational analysis of the melanin-concentrating hormone core by circular dichroic spectroscopy. Disulphide bridge and tyrosine contributions. Eur J Biochem 206:23-29, 1992.
Abstract : A detailed circular dichroic (CD) study of the conformational flexibility of the melanin-concentrating hormone core [MCH(5-14)] is reported. Variable pH (2-10) and temperature (-80 degrees to +80 degrees C) in aqueous media reveal that CD contributions from tyrosine, disulphide bridge and the amide backbone can be discriminated. Only below -10 degrees C does a preferred -S-S-conformation (P chirality, dihedral angle phi = 90 +/- 10 degrees) dominate. The amide backbone CD contribution varies over all temperatures (-80 degrees to +80 degrees C) providing evidence for a type-II beta-turn at low temperatures, with the emergence of a type-I beta-turn at higher temperatures. Tyrosine exhibits a special behaviour at pH 7. These conclusions are in broad agreement with published NMR studies. Nevertheless, the MCH(5-14) core is seen to be conformationally flexible in aqueous solution at ambient temperatures. Conformation differences are observed in a non-aqueous environment.

- Sukhanov VA, Voronkova IM, Shvets SV, Dyakov VL, Morozova LF.
Melanocyte-stimulating hormone (alpha-MSH) inhibits the growth of human malignant melanoma cells with the induction of phosphatidyl inositol and myo-inositol phosphate levels. Biochem Int 24:625-632, 1991.
Abstract : It has been shown that alpha-MSH inhibits the growth of amelanotic cells of human malignant melanoma (BRO) without their melanization or the expression of tyrosinase activity. alpha-MSH changed the activity of cytosol and microsomal forms of phosphatidyl inositol kinase and phosphatidyl inositol-4-phosphate kinase determining the concentration of phosphatidyl inositol-4-phosphate and phosphatidyl inositol-4,5-bisphosphate. It also induced an "outburst" in the levels of myo-inositol phosphates (mono-, bis- and 1,4,5-trisphosphates). Changes in the levels of myo-inositol phosphates occurred within seconds, and are suggested to play a certain part in the hormonal regulation of melanoma cell growth.

4. Photobiology and photochemistry

- Cohn BA.
The significance of dark skin in photoprotection [letter]. J Am Acad Dermatol 26:281-282, 1992.

- Dalziel KL.
Aspects of cutaneous ageing. Clin Exp Dermatol 16:315-323, 1991.
Abstract : Ageing is a multistep, multifaceted, time-dependent phenomenon characterized by the decreased ability of a system to respond to exogenous and endogenous stress from either physical, chemical or biologic agents. Cutaneous ageing provides a visible model of the interaction between endogenous (intrinsic) factors and exogenous (extrinsic) factors. In skin, the principal extrinsic-factor is ultraviolet light (UV) which is responsible for the constellation of changes termed photoageing. In recent years, much interest has been directed towards defining the ageing processes in skin and excellent comprehensive reviews have been compiled. This review aims to highlight several areas of developing knowledge, and focuses on the potential importance of environmental changes as they influence skin ageing and carcinogenesis. Repeated reference to the effects of UV on the skin are inevitable in any review of skin ageing and this is scarcely surprising as the skin contains many cells as well as subcellular and extracellular chromophores which are capable of absorbing energy within the UV spectrum. Cellular chromophores include among others keratinocytes, melanocytes, Langerhans cells, dermal fibroblasts and mast cells. Subcellular chromophores include keratin, melanin, collagen, elastin and a number of proteins, lipids and steroids (such as vitamin D). Urocanic acid, a photoisomerization product of the amino-acid histidine, may provide some limited photoprotection and some believe it to be important in UV induced immunosuppression. Understanding events at the molecular and biochemical level has unfortunately not been paralleled by clinical advances and the common, troublesome skin-problems of old age such as cancer, xerosis and pruritus remain a major cause of morbidity and yet are poorly explained.

- Hessen DO, Soerensen K.
Photoprotective pigmentation in alpine zooplankton populations. Aqua Fenn 20:165-170, 1990.
Abstract : The presence of photoprotective pigments was investigated in sympatric populations of the crustacean zooplankters Daphnia longispina and Heterocope saliens from 5 neighboring alpine ponds. Cuticular melanin pigmentation was recorded in the 2 Daphnia populations inhabiting the most UV-transparent localities. All Daphnia populations had far lower concentrations of carotenoids compared to the calanoid Heterocope, on the av. 0.86 (.+-.0.45) vs 7.96 .+-. 1.51) .mu.g/mg dry wt. This suggests either higher light tolerance in Daphnia, or different light protective mechanisms in the 2 species or that selection against pigmentation is stronger in Daphnia than Heterocope. The lowest content of carotenoids was recorded in the most heavily melanin-pigmented Daphnia population (0.33 .mu.g/mg), but in general no clearcut correlation was found between UV-transparency of the localities and level of carotenoid pigmentation in any species. The strongly melanin-pigmented Daphnia population differed from the others with regard to absorbance patterns

of carotenoids. Absorption peaks of extracted carotenoids were 473.6 (.+-.0.9) and 478.1 (.+-.0.4) nm for Daphnia and Heterocope, resp. These different max., as well as different absorption properties in the UV-region suggest that these 2 species possess different compound of carotenoids.

- Im S, Lee S, Hann SK, Park YK.
The ultraviolet B protection effects of topically applied melanosomes onto human skin. Yonsei Med J 32:330-334, 1991.
Abstract : Melanosome is a cellular organelle that is composed of a melanosomal matrix and a brown biochrome, melanin which is formed by tyrosine-tyrosinase reactions. The melanosome is formed within the melanocyte and transferred to the surrounding keratinocytes through dendritic processes. Human skin color is related to the number, size, type and distribution of melanosomes, and the major role of melanosomes is to prevent skin from injurious nonionizing ultraviolet radiation. Controlled NaOH hydrolysis and centrifugation of human hair make it possible to isolate large amounts of melanosomes which are synthesized within the follicular melanocytes and transferred to hair matrix cells. In this study, the sun protection factors of topically applied melanosomes isolated from human hair were evaluated using ultraviolet B phototesting. Topically applied melanosomes increased the minimal erythemal doses. And the sun protection factors of each 50% and 25% melanosomal preparation were 12.3 +/- 5.5 and 3.1 +/- 1.3 respectively, and these ultraviolet B protection effects showed statistically significant differences from 10%, 5% and 1% melanosomal preparations and vehicle. Form these results, the dose-related photoprotective role of melanosomes was confirmed.

- Olsen EA, Katz HI, Levine N, Shupack J, Billys MM, Prawer S, Gold J, Stiller M, Lufrano L, Thorne EG.
Tretinoin emollient cream: a new therapy for photodamaged skin. J Am Acad Dermatol 26:215-224, 1992.
Abstract : Tretinoin administered topically in 0.1% concentration has been shown to improve the wrinkling and irregular pigmentation of photoaged skin. The purpose of this study was to assess the safety and efficacy of various concentrations of tretinoin in a new emollient cream base in the treatment of photoaged skin. Three concentrations of tretinoin (0.05%, 0.01%, and 0.001%) in a new emollient cream formulation were compared with vehicle in a 24-week, double-blind, randomized, multicenter study of 296 subjects with photodamaged facial skin. Tretinoin emollient cream 0.05% gave a significantly better global response to therapy than vehicle ($p < 0.001$), with 68% of subjects exhibiting improvement at the end of therapy, compared with 43% of subjects in the vehicle group. An excellent or good response was found in 26% of subjects treated with tretinoin emollient cream 0.05% versus 11% of vehicle-treated subjects. Fine wrinkling, mottled hyperpigmentation, and roughness were more improved in subjects who received tretinoin emollient cream 0.05% than in vehicletreated subjects (p less than 0.05). No significant difference was found between vehicle and tretinoin emollient cream 0.01% or 0.001%. Histologic examination showed increases in epidermal and granular layer thickness, decreased melanin content and compaction of the stratum corneum after therapy with tretinoin emollient cream 0.05% or 0.01%. Mild to moderate skin reactions, such as erythema, peeling, and burning, were the most common side effects and, although most prevalent in the group using the 0.05% concentration, generally did not limit tretinoin use. Tretinoin emollient cream 0.05% appears to be safe and effective in the treatment of photodamaged skin.

- Poelman MC, Duval C, Coutable J.
ESR study of free-radical scavengers on photoirradiated pheomelanin. Cosmet Toiletries 106:39-44, 1991.
Abstract : The aim of this work is to develop a simple and rapid in vitro method, which closely resembles the in vivo situation, permitting the screening of substances capable of inhibiting free-radical reactions of photoirradiated pheomelanin.

- Rapp LM, Smith SC.
Evidence against melanin as the mediator of retinal phototoxicity by short-wavelength light. Exp Eye Res 54:55-62, 1992.
Abstract : Albino and pigmented (black-hooded) rats of the Sprague-Dawley and Long Evans strains,

respectively, were compared in terms of their susceptibility to retinal damage by ultraviolet-A light. Anesthetized animals were exposed to ultraviolet-A light (lambda max = 360 nm) for 4 hr and retinal damage was assessed 1 week later by electroretinographic analysis and measurement of outer nuclear layer thickness. Albino and pigmented animals showed approximately the same severity of ultraviolet-A retinal damage as a function of exposure irradiance. Furthermore, both pigmentation strains showed swelling and vesiculation of rod inner segment mitochondria as an early manifestation of damage. An abbreviated study on a congenic rat strain (F344-c/+) of albino and pigmented littermates again demonstrated an equal susceptibility to ultraviolet-A phototoxicity for both pigmentation phenotypes. These findings provide evidence that melanin is not the mediator of short-wavelength phototoxicity to the retina, since damage readily occurred in albino animals completely lacking this chromophore.

- Slawinska D, Slawinski J.
The role of aminochromes in ultraweak luminescence accompanying oxidative metabolism of catecholamines in model systems in vitro. Physiol Chem Phys Med NMR 23:247-260, 1991.
Abstract : Ultraweak luminescence (UWL) accompanying oxidative transformations of catecholamines (CA) into melanins, particularly adrenaline and noradrenaline in the model system CA + Fe(CN)6(3-) + OH(-) + H2O2 in vitro was investigated by spectroscopic methods. Separate steps of the oxidative transformations from CA to melanins were analyzed with respect to their energetic/spectroscopic properties in order to evaluate the possibility of chemiexcitation and light emission. Results of experiments with pure adrenochrome + H2O2 + OH- provided evidence pointing to the key role of the interaction between aminochromes and active oxygen species.

- Stierner U.
Melanocytes, moles and melanoma--a study on UV effects. Acta Derm Venereol Suppl (Stockh) 168:1-31, 1991.
Abstract : To investigate the UV effect on epidermal melanocytes, 21 volunteers and 11 patients with dysplastic nevus syndrome (DNS) received UVB irradiation three times weekly during 17 days. Skin biopsies were take before and three weeks after the last irradiation (on day 37) from exposed and covered buttock skin. The epidermal melanocyte population density was estimated in dopa-stained split skin preparations. The biopsies taken on day 37 revealed that repeated UVB irradiation induces an increase in the number of melanocytes not only in exposed but also in covered skin. This increased mitotic activity might be a link between sun exposure and melanoma development in covered skin. The size of the proliferative response was inversely correlated to the basal melanocyte number. The larger population increase in skin with few melanocytes might amplify the propagation of DNA damage and increase the likelihood of tumor development. The pigment metabolite 5-S-cysteinyldopa (5-S-CD) was measured in urine before the irradiation and twice weekly until day 38. No correlation was found between the basal 5-S-CD excretion and the size or activity of the melanocyte organ, suggesting that the basal 5-S-CD excretion is mainly of non-melanocytic origin. Despite numerous nevi, DNS-patients did not differ from controls in their 5-S-CD excretion. The normal upper range for the tumor maker 5-S-CD is therefore valid in these melanoma-prone subjects. During the irradiation, subjects with a low tanning ability developed a more pronounced erythema and excreted more 5-S-CD than those with a good tanning ability. This suggests that the UVB-induced 5-S-CD excretion is rather due to melanocyte damage than to an increased melanin synthesis. To investigate the influence of sun exposure on the development of nevi and melanoma (CMM), the distribution over the body surface of CMM, common nevi (CN) greater than or equal to 2 mm and dysplastic nevi (DN) was registered in 121 melanoma patients and 310 controls. Four times as many nevi were found in a sun-exposed area than in a comparable sun-protected area, demonstrating that sun exposure plays an important role in nevus development. Subjects with DNA had a larger difference in nevus counts between the two areas than subjects without DN, indicating a different UV-dose and/or a higher sensitivity to the "nevogenic" effect of UV-light than subjects without DN.

5. Neuromelanins

- Barrenas ML, Axelsson A.
The development of melanin in the stria vascularis of the gerbil. Acta Otolaryngol (Stockh) 112:50-58, 1992.
Abstract : One factor that influences noise susceptibility is pigmentation. The aim of this study was to investigate the development of melanocytes, other melanin-containing cells and the amount of melanin in stria vascularis from birth to adult age in the gerbil which has a uniform pigmentation of the fur and eyes, is born without hearing but establishes hearing function at 14-18 days after birth. Changes in the melanin morphology, concentration and distribution have been correlated to the development of the inner ear and to the time period during which hearing function is established, which indicates that the melanocytes in stria vascularis are of importance for the hearing function.

- Jurecka W.
Pigmented neurofibrosarcoma mimicking a large haemangioma [letter]. Clin Exp Dermatol 16:481, 1991.

- Nakashima S, Sando I, Takahashi H, Hashida Y.
Temporal bone histopathologic findings of Waardenburg's syndrome: a case report. Laryngoscope 102:563-567, 1992.
Abstract : A histopathological study of the temporal bones of a 3-year-old black girl who had bilateral deafness associated with Waardenburg's syndrome type II showed a similar pattern of pathology in both ears. The most striking findings were an absence of pigmentation in the inner ear and cochleosaccular abnormality. This is, to our knowledge, only the third report on human temporal bone histopathology in Waardenburg's syndrome and the first report of such a case with absence of pigment (melanin) in the inner ear. A possible association of hearing loss with absence of inner ear pigment in this case is discussed.

- Patt S, Gertz HJ, Gerhard L, Cervos-Navarro J.
Pathological changes in dendrites of substantia nigra neurons in Parkinson's disease: a Golgi study. Histol Histopathol 6:373-380, 1991.
Abstract : Neurons of the substantia nigra show severe morphological changes in Parkinson's disease. Pathological alterations of cell bodies have been described, whereas those of neuronal processes have hardly been investigated. Golgi impregnation has been the chosen method for demonstrating neuronal processes and dendritic and somatic spines. We therefore used the Golgi-Braitenberg method to qualitatively and semi-quantitatively study the substantia nigra of eight patients with Parkinson's disease compared with eight control cases. Golgi impregnation of substantia nigra neurons was good in all control cases. In full agreement with the analysis of Braak and Braak (1986) three neuronal types within the substantia nigra were found. In cases of Parkinson's disease, severe pathological changes such as decrease of dendritic length, loss of dendritic spines and several types of dendritic varicosities were found only in the melanin-containing pars compacta neurons. Pars reticulata nerve cells were intact. These findings support the predominant role played by the dopaminergic efferent pathway in the degenerative process. The afferent pathway was not affected. This suggests that the substantia nigra lesion is primary in Parkinson's disease. Loss of neurons found in H & E sections corresponded to a lesser amount of impregnated pars compacta neurons in cases with Parkinson's disease when compared to controls. Evidences exist that the duration of the disease may be related to the extent of pathologically altered Golgi-impregnated pars compacta cells. The amount of Lewy bodies in H & E sections corresponded to the quantity of round varicosities in impregnated pars compacta neurons. These round dendritic varicosities were considered to be Lewy body inclusions.

- Richards JG, Saura J, Ulrich J, Da P.
Molecular neuroanatomy of monoamine oxidases in human brainstem. Psychopharmacology (Berl) 106:S21-S23, 1992.
Abstract : Specific, high-resolution techniques (quantitative enzyme radioautography and in situ

hybridisation histochemistry) have revealed distribution, abundance and cellular localization of the isoenzymes MAO-A and MAO-B and their mRNAs in human post-mortem brainstem. Whereas MAO-A protein and mRNA are expressed by noradrenergic neurons of the locus coeruleus, MAO-B protein and mRNA are expressed by serotoninergic neurons of the raphe nuclei. In the substantia nigra, MAO-B was more abundant than MAO-A; the former was localized in the reticular zone and the latter in the compact zone (where melanin-containing dopaminergic neurons are found). To date, it has not been possible to detect mRNA for either MAO-A or MAO-B in the substantia nigra or in glial cells of the brain regions investigated, suggesting either that the technique has limited sensitivity, or the possible existence of MAO-A and MAO-B subtypes.

- Rogers SL, Gegick PJ, Alexander SM, McGuire PG.
Transforming growth factor-.beta. alters differentiation in cultures of avian neural crest-derived cells: effects on cell morphology, proliferation, fibronectin expression, and melanogenesis. Dev Biol 151:192-203, 1992.
Abstract : Neural crest cell differentiation is responsive to a variety of extrinsic signals that include extracellular matrix (ECM) mols. and growth factors. Transforming growth factor-.beta. (TGF-.beta.) has diverse, cell type-specific effects, many of which involve regulation of synthesis of ECM mols. and their cell surface receptors. Both sep. and potentially interrelated influences of ECM and growth factors on crest differentiation have been studied, and that TGR-.beta. alters several aspects of crest cell behavior in vitro is reported here. Clusters of quail neural crest cells were cultured in the presence and absence of 400 pM TGF-.beta.1 and examd. at 1, 3, and 5 day. When examined at 5 days, there was a dramatic decrease in the no. of melanocytes in treated cultures, regardless of the onset or duration of TGR-.beta. treatment. With continuous TGF-.beta. treatment, or with treatment only during crest cluster formation on explanted neural tubes, many cells increased in area, becoming extremely flat. These changes were evident beginning on Day 3. While quant. analyses of video images documented the size increase, several aspects of motility were relatively unchanged. Synthesis of fibronectin (FN) by approx. 11% of cells on Day 3 and 31% of cells on Day 5 was demonstrated by immunocytochemistry and was associated with a 6-fold increase in FN mRNA by Day 5. Experiments which correlated FN immunoreactivity with incorporation of bromodeoxyuridine suggested that the population of large, flat, FN-positive cells did not proliferate selectively and that there was a slower rate of proliferation in TGF-.beta. treated cultures than in untreated cultures. The large FN-immunoreactive cells resemble cells derived from cephalic neural crest and raise interesting questions concerning potential roles for TGF-.beta. in regulating crest differentiation in vivo.

- Thibaudeau G, Frost-Mason SK.
Inhibition of neural crest cell differentiation by embryo ectodermal extract. J Exp Zool 261:431-440, 1992.
Abstract : The white mutation in Mexican axolotls has long been thought to be a defect associated with the embryonic extracellular environment, but not with embryonic neural crest cells. Thus it was believed that pigment cells in white axolotls disappear from the skin during early development, not because they are intrinsically defective but because they have no choice but to move into an unfavorable environment. We present evidence to suggest that: (1) white neural crest cells are in fact intrinsically different from dark (wild-type) cells, and (2) an inhibitor is produced in white embryonic ectoderm that actively suppresses the migration, differentiation, and survival of pigment cells in this animal. How these observations fit into the existing body of literature on the white mutant and a model for how the white phenotype might develop are discussed.

- Uchihara T, Kondo H, Kosaka K, Tsukagoshi H.
Selective loss of nigral neurons in Alzheimer's disease: a morphometric study. Acta Neuropathol (Berl) 83:271-276, 1992.
Abstract : Loss of neurons from the substantia nigra (SN), which is sometimes observed in Alzheimer's disease (AD), was quantitatively analyzed in 10 cases of presenile AD and 19 age-matched controls. On sections from the upper and lower portions of the SN, the pigmented zone (zona compacta) and the non-pigmented zone (zona reticulata) were delineated, and these zones were partitioned into quarters: medial, mid-medial, mid-lateral and lateral. This approach clarified

topographical preference of neuronal depletion in the SN of AD; namely (1) pigmented neurons were more severely affected than non-pigmented neurons, (2) neuronal depletion was more marked in the lower SN (-38%, P less than 0.001), where the pigmented neurons in the medial quarter were most severely affected (-51%, P less than 0.001), (3) in the upper SN (neuronal loss: -21%, P less than 0.01), the pigmented neurons in the mid-medial quarter were most severely affected (-43%, P less than 0.01). These findings suggest that some groups of nigral neurons are primarily involved in presenile AD. Gallyas staining after bleaching of melanin pigments uncovered a large number of neurofibrillary tangles (NFTs) mainly in the pigmented zone, especially in the medial quarter. A large number of NFTs, scarse senile plaques, and substantial depletion of neurons form an unique combination of Alzheimer pathology in the SN not well recognized so far.

- Zecca L, Mecacci C, Seraglia R, Parati E.
The chemical characterization of melanin contained in substantia nigra of human brain. Biochim Biophys Acta 1138:6-10, 1992.
Abstract : The pigment of substantia nigra human brain has been extracted by a mild procedure consisting of washes with phosphate buffer, methanol and incubation with SDS-proteinase. Pyrolysis gas chromatography mass spectrometry, infrared spectrometry, termogravimetric analysis and elemental analysis were the techniques used for the chemical characterization. An indole moiety bound to a sulfur containing amino acid and to palmitic acid were the main aspects found in the structure. The presence of a 7% inorganic component was observed. This probably contains Fe, Cu, Zn and Cr which are also relevant, for the formation and the role of melanin in substantia nigra neurons. The fatty acid moiety is chemically bound to the indole structure as it was not eliminated by repeated methanol washing. The same situation occurs for the sulfur containing group. Considering these data and the most abundant molecules present in substantia nigra the precursor of neuromelanin seems to be a cysteinyl-catechol, to which is then bound a palmityl group.

6. Genetics, molecular biology

- Iwamoto T, Takahashi M, Ohbayashi M, Nakashima I.
The ret oncogene can induce melanogenesis and melanocyte development in Wv/Wv mice. Exp Cell Res 200:410-415, 1992.
Abstract : We recently reported the establishment of transgenic mouse lines carrying the mouse metallothionein/ret fusion gene in which severe melanosis and melanocytic tumors developed. In the present study, we demonstrate that a significant number of pigmented hairs developed in Wv/Wv mice crossed to one of the transgenic mouse lines. The pigmented hair of Wv/Wv mice carrying the ret oncogene did not lose color during aging and reappeared after shaving, indicating that the melanocytes in the hair follicle function. The melanocytic tumors also developed in these mice, although the incidence was lower than that in the wild transgenic mice. Furthermore, the neutral tube culture of mouse embryos indicated that neural crest cells of the transgenic mice gave rise to a cell population that autonomously produced melanin even in the absence of melanocyte stimulating hormone. These results strongly suggested that the introduced ret oncogene could compensate for the defect of c-kit in Wv mice during both embryogenesis and postnatal life and induce a high level of melanin synthesis in the process of melanocyte development.

- Jackson IJ.
Mouse coat colour mutations: a molecular genetic resource which spans the centuries. Bioessays 13:439-446, 1991.

- Murty VV, Bouchard B, Mathew S, Vijayasaradhi S, Houghton AN.
Assignment of the human TYRP (brown) locus to chromosome region 9p23 by nonradioactive in situ hybridization. Genomics 13:227-229, 1992.
Abstract : The TYRP (brown) locus determines pigmentation and coat color in the mouse. The human homolog of the TYRP locus has been recently identified and shown to encode a 75-kDa

transmembrane melanosomal glycoprotein called gp75. The gp75 glycoprotein is homologous to tyrosinase, an enzyme involved in the synthesis of melanin, forming a family of tyrosinase-related proteins. A genomic clone of human gp75 was used to map the human TYRP locus to chromosome 9, region 9p23, by nonradioactive fluorescent in situ hybridization. Specificity of hybridization was tested with a genomic fragment of human tyrosinase that mapped to a distinct site on 11q21. The 9p region has been reported to be nonrandomly altered in human melanoma, suggesting a role for the region near the TYRP locus in melanocyte transformation.

- Nahon JL, Joly C, Levan G, Szpirer J, Szpirer C.
Pro-melanin-concentrating hormone gene (PMCH) is localized on human chromosome 12q and rat chromosome 7. Genomics 12:846-848, 1992.
Abstract : Melanin-concentrating hormone (MCH) is a cyclic neuropeptide that may be involved in regulation of the stress response and food intake behavior in mammals. MCH and two other putative neuropeptides, NEI and NGE, are encoded by the same precursor, designated pro-melanin-concentrating hormone (PMCH). A panel of somatic cell hybrids segregating either human or rat chromosomes was used to determine the chromosomal localization of the PMCH locus. It was assigned to human chromosome 12q and to rat chromosome 7. This is the first neuropeptide-encoding gene found in this new synteny group conserved in rat and human.

- Tibbetts MW, Hafner EW, Morgenstern MR, Skinner DD, Denoya CD.
Cloning of a DNA fragment involved in pigment production in Streptomyces avermitilis. FEMS Microbiol Lett 70:9-13, 1992.
Abstract : Streptomyces avermitilis has the ability to synthesize a diffusible, brown, melanin-like pigment, a common property among many Streptomyces species. A region of the S. avermitilis chromosome involved in the production of this pigment was cloned in Escherichia coli. Production of the brown pigment was attained in E. coli, and is optimal when medium is supplemented with copper ions, tyrosine and IPTG. The cloned S. avermitilis pigment-producing DNA fragment is under the control of the lac promoter carried in the E. coli vector. The gene involved in pigment production could be used as a tool to analyse gene expression in S. avermitilis, and as an alternative cloning marker in Streptomyces-Escherichia coli vectors.

7. Tyrosinase, TRP1, TRP2 and other enzymes

- Aso Y.
Melanin biosynthesis-related enzymes of insects. Kagaku to Seibutsu 29:760-761, 1991.
Abstract : A review with 7 references, on phenoloxidase and dopa quinone imine conversion factor which are involved in the tyrosinase-mediated rapid melanization in insect larvae, Bombyx mori and Manduca sexta.

- Bennett DC, Huszar D, Laipis PJ, Jaenisch R, Jackson IJ.
Phenotypic rescue of mutant brown melanocytes by a retrovirus carrying a wild-type tyrosinase-related protein gene. Development 110:471-475, 1990.
Abstract : A mouse cDNA for the developmentally controlled, melanocyte-specific protein, tyrosinase-related protein 1 (TRP-1), was previously cloned and reported to show genetic linkage with the coat-colour locus brown (b) on mouse chromosome 4. The cDNA has been inserted into a retroviral vector derived from Moloney murine leukaemia virus, under the control of the human histone H4 promoter. This vector was used to infect melanocytes of the immortal line melan-b, which are homozygous for the b mutation and which display light brown pigmentation in culture. Infected cultures containing between 0.2 and 2 copies of provirus per cell displayed an altered phenotype: 20-50% of cells now had the black to dark brown colour characteristic of cultured wild-type (Black, B/B) mouse melanocytes. Thus the TRP-1 gene complements the brown mutation. We conclude that TRP-1 is the product of the wild-type b-locus.

- Burchill SA.
Regulation of tyrosinase in hair follicular melanocytes of the mouse during the synthesis of eumelanin and phaeomelanin. Ann N Y Acad Sci 642:396-405, 1991.
Abstract :Tyrosinase activity, synthesis, mRNA, and its posttranslational processing were compared in hair follicular melanocytes of the C3HHeAvy mouse during eumelanogenesis and phaeomelanogenesis. Tyrosinase activity was increased during eumelanogenesis; this increase was accompanied by an increase in tyrosinase synthesis. Tyrosinase activity was also increased during phaeomelanogenesis, but only to a peak level that was 50% of that during eumelanogenesis. However, tyrosinase synthesis and mRNA levels were the same in follicles during eumelanin and phaeomelanin synthesis. The lower level of tyrosinase activity is, therefore, presumably due to posttranslational regulation. Less tyrosinase was associated with the particulate fraction during phaeomelanogenesis than during eumelanogenesis. Glycosylation of tyrosinase during phaeomelanogenesis was also reduced and may be the mechanism of control. Bromo-adenosine 3,5-cyclic monophosphate sodium salt increased glycosylation in both eumelanin and phaeomelanin, producing follicles; but this did not result in an increased uptake of tyrosinase onto the melanosome membrane. Therefore, although cAMP increased glycosylation of tyrosinase, the uptake of tyrosinase by the melanosome membrane appeared to be regulated by other systems that are limiting during phaeomelanogenesis, resulting in a lower level of tyrosinase activity.

- Granholm NH, Opbroek AJ, Harvison GA, Kappenman KE.
Tyrosinase activity (TH, DO, PAGE-defined isozymes) and melanin production in regenerating hairbulb melanocytes of lethal yellow (Ay/a), black (a/a), agouti (AwJ/AwJ) and albino (a/a/c2J/c2J) mice (C57BL/6J). Pigm Cell Res 3:233-242, 1990.
Abstract : Tyrosinase activity (TH, DO, and native PAGE-defined isoenzymes) and melanin production were compared in particulate and sol. fractions of hairbulb melanocytes of lethal yellow (Ay/a C/C), nonagouti black (a/a C/C), and albino (a/c c2J/c2J) of 3-, 6-, 9-, and 12-day regenerating hairbulbs. With respect to tyrosine hydroxylase (TH) and dopa oxidase (DO) activities, Ay/a melanocytes possessed only 25-35% of the activity of a/a; there were no genotype differences in either the subcellular distribution of activity in sol. and particulate fractions or in the relative increases of activity over the 12-day developmental period. TH data on wild-type agouti (AwJ/AwJ) mice over the 3-11 day regeneration interval showed an activity intermediate between that of a/a and Ay/a; the rate of TH increase reflected black and yellow phases of the agouti hair cycle. Analyses of the no. and densities of dopa-sensitive bands following native PAGE of 3-, 6-, 9-, and 12-day hairbulb fractions of a/a and Ay/a mice suggested stage-dependent patterns. A comparison of rates and amounts of melanin prodn. in 3-, 6-, 9-, and 12-day fractions showed consistent melanin production in Ay/a to be 10-20% that of a/a; however, fold increases in melanin production over the 4 stages were similar between genotypes. Overall, tyrosinase activity data support the notion that agouti locus modification of tyrosinase activity is a graded or quant. rather than an qual. phenomenon.

- Johnston JD, Winder AF, Breimer LH.
An MboI polymorphism at codon 192 of the human tyrosinase gene is present in Asians and Afrocaribbeans. Nucleic Acids Res 20:1433, 1992.
Abstract : Albinism is an inherited, generalized hypomelanotic condition, caused by impaired melanin synthesis. Tyrosinase catalyzes the conversion of tyrosine into melanin. Mutations in its gene (tyr) have been described in a few albinos. A polymorphism for MboI at codon 192 of the human tyrosinase gene has been described in Caucasians but was absent from Indian Asians and Orientals. Hence, the region of tyrosinase encoded at the polymorphic site might det. the enzyme active as ethnic pigmentation differences are due to the amount of melanin per cell and not the no. of melanocytes. PCR amplification used 2 primers 5'-GCTCCTGGCTGTTTTGTACT-3' and 5'-CTGCCAGAGGAAGAATG-3' for exon 1. MboI digestion yields fragments of sizes 483, 247, and 87 bp (MI) when the segment contains 2 MboI sites (at codons 163 and 192). The absence of the MboI 192 site yields bands of sizes 483 and 334 bp (M2). The distribution of alleles in the Caucasians is similar to that reported by L.B. Giebel and R.A. Spritz (1990) but the MboI 192 polymorphism is present in Indian Asians contrary to that report. It is also present in Afrocaribbeans. This has not previously been reported. No polymorphism was in Orientals as in previous reports. Its absence may

be related to their sep. development.

- Terao M, Tomita K, Oki T, Tabe L, Gianni M, Garattini E.
Inhibition of melanogenesis by BMY-28565, a novel compound depressing tyrosinase activity in B16 melanoma cells. Biochem Pharmacol 43:183-189, 1992.
Abstract : The mechanism of a novel melanin synthesis inhibitor, BMY-28565, was studied using mouse B16 melanoma cells. This compound was active in depressing the intracellular accumulation of melanin with an IC50 of 5 microM. At dose levels causing no cytotoxicity, the melanolytic effect of this compound was correlated strongly with depression of the enzymatic activity of tyrosinase (monophenol oxygenase, EC 1.14.18.1), the key enzyme in the melanin synthesis pathway. Transcription of the tyrosinase gene was not inhibited by BMY-28565, as determined by RNA blotting analysis. BMY-28565 and three other active derivatives of this compound caused increased glycosylation of proteins in B16 melanoma cells, as assessed by radioactive mannose incorporation. It is, thus, suggested that the mechanism of inhibition of tyrosinase might be related to modifications of the sugar moiety of this enzyme or of a protein(s) that is essential for the expression of its enzymatic activity.

- Tsukamoto K, Jackson IJ, Urabe K, Montague PM, Hearing VJ.
A second tyrosinase-related protein, TRP-2, is a melanogenic enzyme termed DOPAchrome tautomerase. EMBO J 11:519-526, 1992.
Abstract : The production of melanin pigment in mammals requires tyrosinase, an enzyme which hydroxylates the amino acid tyrosine to DOPA (3,4-dihydroxyphenylalanine), thus allowing the cascade of reactions necessary to synthesize that biopolymer. However, there are other regulatory steps that follow the action of tyrosinase and modulate the quantity and quality of the melanin produced. DOPAchrome tautomerase is one such melanogenic enzyme that isomerizes the pigmented intermediate DOPAchrome to DHICA (5,6-dihydroxyindole-2-carboxylic acid) rather than to DHI (5,6-dihydroxyindole), which would be generated spontaneously. This enzyme thus regulates a switch that controls the proportion of carboxylated subunits in the melanin biopolymer. Efforts to clone the gene for tyrosinase have resulted in the isolation of a family of tyrosinase related genes which have significant homology and encode proteins with similar predicted structural characteristics. Using specific antibodies generated against synthetic peptides encoded by unique areas of several of those proteins, we have immuno-affinity purified them and studied their melanogenic catalytic functions. We now report that TRP-2 (tyrosinase related protein-2), which maps to and is mutated at the slaty locus in mice, encodes a protein with DOPAchrome tautomerase activity.

- Zawistowski J, Biliaderis CG, Eskin NAM.
Polyphenol oxidase. Oxid Enzymes Foods, 217-273 (Robinson, Stuart, Eskin, eds), Elsevier, London, UK., 1991.
Abstract : A review with >300 references on polyphenol oxidase (I) and its role in enzymic browning of edible plant products and crustaceans, occurrence and localization of I, methods of I detn., reaction mechanism, heterogeneity and mol. structure, substrate specificity, applications of I in tea manuf., medicinal uses, and biotechnol. and melanin formation.

8. Melanoma and other pigmented tumours

- Abreo F, Sanusi ID.
Basal cell carcinoma in North American blacks. Clinical and histopathologic study of 26 patients. J Am Acad Dermatol 25:1005-1011, 1991.
Abstract : Basal cell carcinoma is rare in blacks. A clinical and histopathologic review of 43 basal cell carcinomas in 26 black patients is reported. Basal cell carcinoma was found to be more common in women than in men. Our data indicated a lower prevalence on the nose and trunk compared with other reports. Multiple tumors were more common in our series. Our study included the youngest black patient with a pure basal cell carcinoma, the first reported superficial basal cell carcinoma, the

second reported perianal basal cell carcinoma, and one albino patient with 12 tumors. Histologically there was a positive correlation between the maximum depth of tumor invasion and the maximum diameter of the lesion. Of three basal cell carcinomas arising in scars, metastasis developed in one. Our report includes a review of basal cell carcinomas in North American blacks.

- Bedrick AE, Ramasamy G, Tchertkoff V.
Histochemical determinations of copper, zinc, and iron in pigmented nevi and melanoma. Am J Dermatopathol 13:575-578, 1991.
Abstract : Histochemical determinations of copper, zinc, and iron in intradermal pigmented nevi and melanomas revealed the presence of copper and iron in melanoma but not in nevi. Zinc was not detected in either melanomas or nevi. However, melanin was removed from the tissues prior to staining; therefore, it is possible that zinc was also removed by the procedure. Although the function of copper and iron in the melanoma cell is not known, they may be components of abnormal enzymes.

- Cheung LK, Piette EM, Tideman H.
Melanotic neuroectodermal tumour of infancy: a case report emphasizing the importance of computed tomography. Dentomaxillofac Radiol 20:172-174, 1991.
Abstract : A case is reported of the rare melanotic neuroectodermal tumour of infancy involving the maxilla of a 4-month-old girl. The role of CT is discussed with particular reference to the diagnosis.

- Cohen ME, Hudson DL, Banda PW, Blois MS.
Neural network approach to detection of metastatic melanoma from chromatographic analysis of urine. Proc Annu Symp Comput Appl Med Care, p 295-299, 1991.
Abstract : Chromatographic analysis of sera or urine is important in medicine for the evaluation of patients whose clinical status is associated with the presence of specific biochemical markers. Malignant melanoma has been a model for such studies due to the elaboration of melanin precursors and pigment as the tumor metastasizes. Computer-assisted methods for categorizing chromatographic data and clinical status are imperative due to the large number of detectable compounds and possible correlations. In addition, computer-based analysis of the data can readily extract patterns that are not obvious by visual inspection. In this paper, we present a neural network analysis of melanoma chromatographic and clinical data that categorizes subjects into normals, NED patients (No Evidence of Disease), and metastatic patients. The set of marker compounds for metastatic disease represents a significant advance over the correlations derived by visual inspection.

- Fujita S, Takahashi H, Tsuda N, Okabe H.
Immunohistochemical localization of S-100 protein and its subunits in melanotic lesions in the oral mucosa and skin. J Oral Pathol Med 20:429-432, 1991.
Abstract : Immunohistochemical localization of S-100 protein, S-100 alpha and beta subunits was examined in 23 pigmented nevi, 20 malignant melanomas and 8 metastatic melanomas originating from the oral mucosa and skin. Primary oral mucosal melanomas demonstrated no beta subunit immunoreactivity while one metastatic lesion from oral melanoma that showed only a small number of melanoma cells reacted with the beta subunit. In contrast, most cutaneous melanomas and their metastatic lesions showed immunoreaction with the S-100 beta subunit. As for pigmented nevi, immunoreactions with the three antibodies were frequently detected regardless of the site. The differences in the expression of S-100 protein beta subunit between cutaneous and mucosal melanomas may be related to differences in inductive interactions between the melanoma cells and the connective tissues and skin and mucosa.

- Furukawa M.
Behavior of murine melanoma cells cultured in or on the type I collagen gel. Osaka-shi Igakkai Zasshi 40:241-62, 1991.
Abstract : B16 murine melanoma cells were cultured in or on type I collagen gel to develop an in vitro model of melanoma cells infiltrating the dermis. Under these conditions, the melanoma cells became elongated or dendritic, as compared with findings in those cultured on plastic. In or on the

type I collagen gel, the cell growth was suppressed as compared with the conventional monolayer culture on plastic. This suppression was found in a microcinematog. study to be due to an extension of the cell cycle time. There were differences in the growth between the cells cultured on type I or IV collagen film and those cultured on plastic. Though no significant difference in the effect of retionic acid (10-5 M and 10-6 M) was observed with the two approaches, the effect of DTIC (100 and 500 ng/mL) on melanoma cells was weakened in the case of culture in collagen gel. The tyrosinase activity and melanin production, important differentiating functions of melanoma cells, were enhanced on and in the collagen gel cultured 2 to 3 times, as compared with findings when plastic was used. B16 melanoma cells inoculated on the gel surface actively infiltrated into the collagen gel and the rate was suppressed by the addition of retinoic acid (10-6 M). The gel contracted slowly during culture of melanoma cells and this contractility differed with various melanoma cell lines. The present observations raise the possibility of interaction between melanoma cells and type I collagen. Culture systems using type I collagen gel as a substrate may be useful for the in vitro study of tumor metastasis and invasion.

- Hisaoka M, Ohta H, Haratake J, Horie A.
Melanocytic schwannoma in the spinal canal. Acta Pathol Jpn 41:685-688, 1991.
Abstract : A case of melanocytic schwannoma, a rare form of schwannian neoplasm, in the thoracolumbar spinal canal of a 52-year-old man is presented. Histopathologically, the tumor was composed of irregularly interlacing spindle-shaped cells showing cystic degeneration, with occasional pigmented tumor cells. The tumor cells showed a low degree of nuclear pleomorphism without any mitotic figures. These histological features were considered to be consistent with a benign schwannian tumor showing pigmentation. Most of the pigments were considered to be melanin histochemically and immunohistochemically. According to the pathological features of the present tumor and those described previously in the literature, the neoplastic Schwann cells were assumed to have melanogenetic capacity, and the concept of the common neural crest origin of Schwann cells and melanocytes appeared to be demonstrated in the present tumor.

- Jori G.
Far-red-absorbing photosensitizers: their use in the photodynamic therapy of tumors. J Photochem Photobiol A, 62:371-378, 1992.
Abstract : A review with 30 references. Light in the 600-1000 nm spectral region is scattered to a relatively small extent by most mammalian tissues and is poorly absorbed by endogenous chromophores such as melanin, cytochromes, and Hb. As a consequence, red light possesses a high penetration power into human tissues and can be selectively absorbed by photosensitizing agents (e.g., porphyrins, chlorins, phthalocyanines, naphthalocyanines) localized in predetermined sites of the organism. Recently developed procedures allow for the specific loading of tumor tissues by several red-light-absorbing photosensitizers; this property is the basis of a novel phototherapeutic modality for the treatment of a variety of solid tumors. The efficacy of the light plus photosensitizer combination in inducing tumor regression (the technique is often defined as photodynamic therapy) is dependent on the photophys. properties of the photosensitizer and its affinity for malignant tissues.

- Kamino H, Tam ST.
Immunoperoxidase technique modified by counterstain with azure B as a diagnostic aid in evaluating heavily pigmented melanocytic neoplasms. J Cutan Pathol 18:436-439, 1991.
Abstract : Heavily-pigmented melanocytic neoplasms are difficult to evaluate on routine hematoxylin and eosin stained slides because pigmented melanocytes are difficult to distinguish from the numerous melanophages that are usually seen in the background of these lesions. Immunoperoxidase staining for S100 protein or HMB-45 antibody using diaminobenzidine (DAB) as chromogen, which forms a brown product, does not adequately distinguish melanocytes from melanophages. We modified this technique by replacing hematoxylin as the counterstain with azure B, which stains melanin green-blue. Thus, positive melanocytes appear brown while melanin granules in their cytoplasm are green-blue. However, negative melanophages only stain green-blue. This technique is useful in evaluating heavily pigmented melanocytic lesions such as malignant melanomas, melanosis of regressing malignant melanoma, residual malignant melanoma in areas of granulation tissue with

melanophages, blue nevi, pigmented spindle cell variant of Spitz's nevi and combined nevi.

- Kapila K, Kharbanda K, Verma K.
Cytomorphology of metastatic melanoma--use of S-100 protein in the diagnosis of amelanotic melanoma. Cytopathology 2:229-237, 1991.
Abstract : The cytomorphological features of cells from 52 cases of metastatic melanoma obtained by fine needle aspiration cytodiagnosis were studied. Morphologically, 11, 19 and 22 cases were classified as spindle, epithelial, and mixed cell types of metastatic melanoma respectively. There were 34 melanotic and 18 amelanotic melanomas. Besides melanin, the presence of intranuclear cytoplasmic inclusions, eosinophilic macronucleoli and giant cells were helpful in the diagnosis of a melanoma. Where attempted, staining for S-100 protein was positive in all the 19 cases (eight amelanotic and 11 sparsely pigmented melanomas). In addition eight cases of metastatic tumour where a differential diagnosis of poorly differentiated carcinoma or large cell lymphoma was entertained, were also studied for localization of S-100 protein and all were found to be negative. Electron microscopy was performed in five cases and showed the presence of melanosomes and/or premelanosomes.

- Merello M, Esteguy M, Perazzo F, Leiguarda R.
Impaired levodopa response in Parkinson's disease during melanoma therapy. Clin Neuropharmacol 15:69-74, 1992.
Abstract : A patient with melanoma and sporadic positive melanuria developed Parkinson's disease. Treatment with levodopa failed to modify tumoral progress. However, during chemotherapy with dacarbazine, the patient experienced a significant impairment to levodopa response.

- Packer S, Coderre J, Saraf S, Fairchild R, Hansrote J, Perry H.
Boron neutron capture therapy of anterior chamber melanoma with p-boronophenylalanine. Invest Ophthalmol Vis Sci 33:395-403, 1992.
Abstract : Boron neutron capture therapy (BNCT) is a form of radiation therapy that requires selective uptake of boron by the tumor and irradiation with thermal neutrons. Phenylalanine is an amino acid precursor of melanin and when boronated (p-boronophenylalanine [BPA]) was found to be selectively taken up by Greene melanoma cells in the anterior chamber of rabbits. This tumor model was irradiated 24 hr after oral administration of BPA and was used for biodistribution studies that compared BPA and sodium pentaborate. Three groups were irradiated: group 1 (11 rabbits) received BPA followed by thermal neutron irradiation, group 2 (9 rabbits) received thermal neutron irradiation only, and group 3 (9 rabbits) served as unirradiated, undrugged control animals. Eight of the 11 tumors in group 1 were treated successfully; all tumors in groups 2 and 3 grew. Histopathologic examination did not reveal vascular or retina damage in group 1. These preliminary experiments confirm that newer boronated compounds, such as BPA, used in BNCT and improved neutron beams can provide selective irradiation of ocular melanomas.

- Schaumburg-Lever G, Metzler G, Kaiserling E.
Ultrastructural localization of HMB-45 binding sites. J Cutan Pathol 18:432-435, 1991.
Abstract : Three malignant melanomas, two melanoma metastases, two junctional dysplastic nevi, and normal skin were embedded in Lowicryl. Ultrathin sections were incubated with HMB-45 and a gold-labeled anti-mouse antibody. Gold particles indicating the presence of HMB-45 were found in melanosomes Stage 1 and 2 and in the non-melanized portion of melanosomes Stage 3. Melanosomes Stage 4 and melanosome complexes in keratinocytes, as well as in melanophages, were consistently negative. No specific labelling with HMB-45 was seen in eccrine glands of normal skin.

- Slootweg PJ.
Heterologous tissue elements in melanotic neuroectodermal tumor of infancy. J Oral Pathol Med 21:90-92, 1992.
Abstract : Two cases of melanotic neuroectodermal tumor of infancy (MNTI) contained highly cellular stromal areas consisting of spindle cells exhibiting mitotic activity. In one case, single spindle cells exhibited the same immunohistochemical profile as tumor cells forming part of the epithelial

component. In the other case woven bone was formed in a dense fibroblastic stroma. These tumor parts were judged to be heterologous tissue elements that also may be observed in other kinds of neuroectodermal tumors and that reflect the potential of the neural crest to differentiate into various mesenchymal tissue types.

- Soffer D, Lach B, Constantini S.
Melanotic cerebral ganglioglioma: evidence for melanogenesis in neoplastic astrocytes. Acta Neuropathol (Berl) 83:315-323, 1992.
Abstract : A composite melanotic glial-ganglionic tumor was resected from a 17-year-old girl who presented with a 5-year history of epilepsy. Grossly, the tumor was partly cystic, partly solid, located superficially in the temporal lobe. Histologically, its glial component was composed of spindle and pleomorphic cells, including tumor giant cells, which were associated with Rosenthal fibers, eosinophilic granular bodies and marked desmoplasia. The cells had immunohistochemical and ultrastructural features of astrocytes, and some were invested by incomplete basal lamina. Thus, the tumor had many features in common with pleomorphic xanthoastrocytoma. However, its most striking feature was the presence of melanin pigment in numerous neoplastic cells. Immunoelectron microscopy revealed glial fibrillary acidic protein-positive intermediate filaments in tumor cells bearing melanosomes and premelanosome, proving their astrocytic nature. This case demonstrates, for the first time, melanosomal melanogenesis in human cells with astrocytic phenotype, and provides additional evidence for the ability of central neuroepithelial cell derivatives to produce melanin.

- Witheiler DD, Cockerell CJ.
Histologic features and sensitivity of diagnosis of clinically unsuspected cutaneous melanoma. Am J Dermatopathol 13:551-556, 1991.
Abstract : The purpose of this study was to assess the sensitivity of clinical diagnosis of cutaneous malignant melanoma and to evaluate histologic characteristics of lesions not clinically diagnosed as such. Of 1,784 cases of histologically proven cutaneous malignant melanoma submitted routinely to a university dermatopathology laboratory between 1985 and 1990, 583 (33%) were not clinically suspected. The overall sensitivity in clinical diagnosis was 67%. Histologic features evaluated included presence of melanin, pagetoid spread of melanocytes, degree of inflammation, regression, presence and degree of sun damage as evidenced by solar elastosis, presence of melanin in the cornified layer, and coexisting nevus cells. Melanomas clinically thought to be nevi had less solar elastosis and most frequently had associated nevus cells. Those thought to be basal cell carcinomas had less melanin in lesions and less melanin in the cornified layer, and most often had foci of regression. Lesions thought to be keratoses showed melanin in the cornified layer 70% of the time, more often than any other type of lesion. Melanoma may be unsuspected clinically in a significant number of cases and can be mistaken for less serious cutaneous neoplasms. Histologic features of these lesions correlated well with original clinical diagnoses.

- Wong KC.
Premalignant skin lesions associated with occupational exposure during the manufacture of herbicide paraquat. Hifu 33:101-104, 1991.
Abstract : Fifteen male workers from paraquat factories were studied because of appearance of skin lesions. The working duration varied from one to twelve years. Their ages ranged from 29 to 50 yr, the skin manifestations were brownish hyperpigmented macules and papules of various size over their face, neck, forearms, and dorsal hands. Among them, six patients had erythematous hyperkeratotic, crusted papules, and plaques, which developed on the irregular pigmented macules on their neck, forearms, and dorsal hands. Histopathol. studies revealed hyperkeratosis, epidermal hyperplasia, epidermal dysplasia, and increase melanin in the basal cell layer. Three patients had Bowen's disease, in which the histopathol. studies showed vacuolization of the atypical keratinocytes in the epidermis of bowenoid lesions. The paraquat manufg. process in Taiwan was the high temp. sodium plant. In this process, only 35% of the pyridine consumed was converted to 4,4'-bipyridyl and substantial quantities of bipyridyl isomers, polypyridyls and tars byproducts were produced. Workers were exposed to the above stated materials during centrifugation and dehydration. They also handled the residual wastewater and intermediate chems. The distinct clinical sign, the distribution and clustering

of similar cases in one factory should enable us to believe that the disease was related to this occupation.

- Yamada K, Walsh N, Hara H, Jimbow K, Chen H, Ito S.
Measurement of eumelanin precursor metabolites in the urine as a new marker for melanoma metastases. Arch Dermatol 128:491-494, 1992.
Abstract : This article introduces a rapid high-performance liquid chromatographic assay to measure urinary pheomelanin and eumelanin metabolites, 5-S-cysteinyldopa and indoles, 5(6)-hydroxy-6(5)-methoxyindole-2-carboxylic acid. Our high-performance liquid chromatographic study clearly showed (1) urine of melanoma patients with positive metastasis revealed significant amounts of 5-S-cysteinyldopa and indoles (5,6-dihydroxyindole-2-carboxylic acid plus 6-hydroxy-5-methoxyindole-2-carboxylic acid) above 1 mumol/d and 2 mumol/d, respectively; and (2) in patients with metastasis-free melanoma these melanin metabolites might be excreted into the urine but always less than the two values cited above. As there is a discrepancy regarding the specificity of 5-S-cysteinyldopa as a marker for estimation of melanoma metastasis, high-performance liquid chromatographic measurement of urinary indoles will provide an additional assay in the detection of melanoma metastasis from an early stage. Both melanoma markers were increased in the urine of patients with metastatic melanoma.

9. Eye

- Bulow N.
The resonator theory of colour vision. Med Hypotheses 37:92-96, 1992.
Abstract : The resonator theory claims that light scattering by the melanin granules of the retinal pigment epithelium causes light to be reflected back through the outer segment of the cones, in a direction opposite that of the incident light. These two opposite directed wave motions may produce standing waves inside the cone outer segment, which then acts as a resonating cavity for light waves. The wavelength specificity of the single cone is determined by the length and the diameter of the cone outer segment. The variation of the length and the diameter of the cone outer segments throughout the retina is then the basis of colour discrimination.

- Chirila TV, Cooper RL, Constable IJ, Horne R.
Radiation-absorbing hydrogel-melanin blends for ocular devices. J Appl Polym Sci 44:593-604, 1992.
Abstract : Hydrophilic polymers and copolymers of 2-hydroxyethyl methacrylate, with low or high crosslinking d., are synthesized and then treated in aq. medium with epinephrine (adrenaline) at neutral or acid pH, at room temperature, and in the presence of O and light. During this treatment, a melanin is formed and uniformly dispersed in polymers. The resulting slightly colored hydrogels display radiation-absorbing properties in the UV and visible regions of the natural spectrum. This enhances significantly their value as materials for ocular devices (contact lenses, intraocular lenses) that should protect the retina of the patients without their natural lens from potential damage induced by UV and visible (violet and blue) radiation. The incorporation of common UV absorbers leads to transmittances similar to that of the natural human lens, i.e., 30% or less at 450 nm, 40% or less at 500 nm, and no more than 50% at 700 nm. The 2-phase morphol. of the melanized hydrogels, as investigated by TEM, revealed a very fine structure comprising melanin domains of 1 to 2 nm in size. Although no proof for a network interpenetration could be provided, it is believed that the novel blends are true sequential interpenetrating polymer networks.

- Coleman AL, Jampel HD, Javitt JC, Brown AE, Quigley HA.
Transscleral cyclophotocoagulation of human autopsy and monkey eyes. Ophthalmic Surg 22:638-643, 1991.
Abstract : We studied the effect of uveal pigmentation on contact Nd:YAG transscleral cyclophotocoagulation in 36 human autopsy and eight cynomolgus monkey eyes. Ten autopsy eyes from black individuals required less energy to create a lesion than 23 eyes from whites. The mean

lesion diameter at the posterior pars plicata was similar in all these eyes; however, the mean energy required was 4.4 J in the black and 6.4 J in the white eyes. Transscleral cyclophotocoagulation lowered intraocular pressure (IOP) in four monkey eyes with elevated IOP, but did not in four other eyes without elevated IOP. Treatment over conjunctival pigmentation burned the conjunctiva, even at the lowest energy tested (3.5 J). Contrary to other investigators' findings, transmission electron microscopy showed at least short-term loss of scleral architecture in both the human autopsy and monkey eyes.

- Glickman RD, Lam KW.
Oxidation of ascorbic acid as an indicator of photooxidative stress in the eye. Photochem Photobiol 55:191-196, 1992.
Abstract : When whole retinal pigmented epithelium (RPE) cells isolated from bovine eyes are incubated with 14C-labeled ascorbic acid and exposed to a visible laser, the ascorbic acid is oxidized to dehydro-L-ascorbic acid (DHA). The amount of ascorbic acid which is oxidized is proportional to the radiant exposure of the sample (i.e. the total amount of radiation per unit area delivered over the exposure time). Blue light is more effective than red light in driving the reaction. The amount of label appearing in the DHA fraction is increased if unlabeled DHA is present in the reaction mixture, indicating that some redox cycling of ascorbate is occurring in the RPE cells. The ascorbic acid oxidizing activity does not depend on intact cells, is not inactivated by heating the cells to 80 degrees C, and appears to reside mainly in the subcellular fraction which contains melanin pigment granules. The ascorbic acid oxidation may be caused by free radicals formed when melanin is illuminated with light. This reaction appears to be a useful method for quantifying the production of free radicals during photooxidative stress.

- Kaya M, Edward DP, Tessler H, Hendricks RL.
Augmentation of intraocular inflammation by melanin. Invest Ophthalmol Vis Sci 33:522-531, 1992.
Abstract : The inflammatory response in endogenous uveitis or after anterior segment surgery was noted to be substantially greater in heavily pigmented eyes. Because varying amounts of melanin are released into the anterior chamber after intraocular inflammation, it was hypothesized that a proinflammatory effect of melanin might account for the enhanced inflammatory response in these eyes. To test this hypothesis, albino (BALB/c) or pigmented (C57BL/6) mice were challenged in the anterior chamber 2 weeks after a subcutaneous foot pad injection of horse serum or conalbumin dissolved in Freund's complete adjuvant. The degree of inflammation in the challenged eyes was determined by histologic examination 72 hr after the challenge. In all cases, the inflammatory infiltrate consisted mainly of polymorphonuclear leukocytes suggestive of an Arthus reaction. An anterior chamber challenge of horse serum-sensitized BALB/c or C57BL/6 mice with horse serum alone resulted in mild inflammation, which was augmented markedly by challenge with a combination of horse serum and melanin. The presence of melanin in the anterior chamber similarly increased the inflammatory response of conalbumin-sensitized mice to anterior chamber challenge with conalbumin. Melanin in the anterior chamber also significantly (P less than 0.05) augmented the inflammatory response of conalbumin-sensitized mice to a horse serum challenge, but it did not significantly augment the inflammatory response of horse serum-sensitized mice to a conalbumin challenge. The heterologous antigens induced minimal inflammation in the absence of melanin. Injection of melanin alone did not evoke an inflammatory response. Ocular challenge with melanin alone or in combination with antigen induced minimal inflammation in nonsensitized mice. However, preincubation of melanin with sera from horse serum-sensitized mice significantly increased its proinflammatory capacity when injected with horse serum into the anterior chamber of nonsensitized mice. In vitro binding studies using fluorescein isothiocyanate-conjugated mouse immunoglobulin G showed a high binding capacity of melanin for immunoglobulin G. It was concluded that the presence of free melanin in the anterior chamber can increase intraocular inflammation. Although the mechanism(s) by which melanin augments inflammation has not been defined, these data suggest that the binding of serum components (such as antibodies) to melanin may contribute to its proinflammatory effect.

- Koh SW, Kane GJ.
VIP stimulates proliferation and differentiation of the cultured retinal pigment epithelium with disparate potencies. Cell Biol Int Rep 16:175-183, 1992.
Abstract : Previous studies showed that VIP modulates mediators of two signal transduction pathways, namely the adenylate cyclase and the nonreceptor tyrosine protein kinase pp60c-src in cultured chick retinal pigment epithelium (RPE). Here we show that VIP modulates simultaneously two disparate cellular events, namely the cell proliferation and differentiation of the RPE, however, with different potencies. The maximal effects on proliferation and differentiation are observed at 5 x 10(-9)M and 5 x 10(-7)M, respectively. Treatment with the maximally effective concentrations of VIP for 10 days increases the cell numbers and the melanin contents to 150% and 200% of the controls, respectively. The lowest concentrations of VIP showing significant stimulatory effect on cell proliferation and melanin synthesis are 5 x 10(-11) M and 5 x 10(-9)M, respectively.

- Putting BJ, Zweypfenning RC, Vrensen GF, Oosterhuis JA, Van Best JA.
Dysfunction and repair of the blood-retina barrier following white light exposure: a fluorophotometric and histologic study. Exp Eye Res 54:133-141, 1992.
Abstract : The purpose of this study was to pinpoint the site of blood-retina barrier disruption after white light exposure and determine the course of barrier repair. The retinas of 25 anaesthetized pigmented rabbits were exposed for 1 hr to the light of a xenon arc lamp filtered to eliminate ultraviolet and infrared light. The light intensities selected were near the threshold intensity causing visible retinal lesions in order to evaluate the function of the blood-retina barrier (BRB) in this range. Functional assessment of the BRB was made with vitreous fluorophotometry (VF), and electron microscopy (EM) after intra-arterial administration of horseradish peroxidase (HRP) as tracer. In 11 of the 14 rabbits exposed to threshold intensity (90-110 mW cm-2; retinal field of illumination, 0.64 cm2), a breakdown of the BRB was demonstrated by a 2-40-fold increase in the permeability of the BRB for fluorescein and by transcellular passage of HRP through the retina pigment epithelium (RPE). All 11 rabbits developed oedematous fundus lesions. Within a week, pigmentary alterations of the fundus were seen on ophthalmoscopy, while the BRB permeability for fluorescein and HRP had returned to normal. EM of the retina showed slight swelling of RPE during the period of increased permeability but no alterations of the neuroretina. After functional barrier repair, the RPE cells demonstrated irregularity of the melanin pigment alignment and some loss of the monocellular arrangement. In six rabbits exposed to subthreshold light intensity (65-89 mW cm-2) no fundus lesion developed and EM evaluation of the BRB was normal.2+ remains altered.

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Properties and function of the ocular melanin - a photobiophysical view. J Photochem Photobiol B 12:215-258, 1992.
Abstract : A review with 198 references on the biosynthesis and physicochemical properties of the ocular melanin. Age-related changes of melanin granules and the corresponding formation of lipofuscin pigments in the retinal pigment epithelium (RPE) are also described. Adverse photoreactions of the eye and, in particular, light-induced damage to the RPE-retina are reviewed in relation to the ocular pigmentation. A hypothesis on the photoprotective role of the RPE melanin is presented that is based on the ability of the cellular melanin to bind redox-active metal ions. Since bound-to-melanin metal ions are expected to be less damaging to the pigment cells, it is proposed that sequestration of heavy metal ions by the RPE melanin is an efficient detoxyifying mechanism. It is postulated that oxidative degradation of RPE melanin may lower its metal-binding capability and decrease its anti-oxidant efficiency. Cellular and environmental factors that may contribute to possible oxidative damage of the RPE melanin are discussed in connection with the etiology of age-related macular degeneration.

- Small KW, Scheinman J, Klintworth GK.
A clinicopathological study of ocular involvement in primary hyperoxaluria type I. Br J Ophthalmol 76:54-57, 1992.
Abstract : We performed a clinicopathological study on the eyes of a 3-year-old girl with primary hyperoxaluria type I. An examination one year before death disclosed a slightly diminished visual

acuity in both eyes with black, geographic central macular, subretinal patches. Calcium oxalate was deposited predominantly in the retinal pigment epithelium of the posterior pole, where these cells were markedly hyperplastic and hypertrophied round foci of oxalate crystals. Oxalate crystals were exceedingly sparse in other ocular structures and when present were not associated with an apparent tissue reaction in these other locations. A collagenous layer was evident between parts of the retinal pigment epithelium and the neurosensory retina, which contained occasional perivascular clumps of melanin laden cells. The predominant deposition of oxalate in the retinal pigment epithelium, with the exuberant response of these cells around the crystals, gives a clue to the pathogenic mechanisms of primary hyperoxaluria.

10. Other

- Okitsu M, Hiranuma Y, Shimazaki T, Nagamine K, Inada M, Yamamoto Y, Ohno J, Utsumi N. **Epidermoid cyst of the oral floor with massive deposition of melanin in the cystic epithelium.** Meikai Daigaku Shigaku Zasshi 19:418-423, 1990.
  Abstract : Dermoid cyst or epidermoid cyst of the oral cavity usually occurs in the floor of the mouth. We encountered a 21-year-old woman who had developed epidermoid cyst in the oral floor. Since infancy she had been aware of a swelling in the oral floor. Recently, the swelling began to grow larger gradually. The lesion was excised under general anesthesia by intraoral approach. The swelling was spherical in shape, measured 50 x 45 x 40 mm in size, and weighed 40 g. Histopathological examination revealed keratinized, stratified squamous epithelium on the cyst wall and marked deposition of melanin at the base of the epithelium.

- Tsambaos D, Sampalis F, Berger H. **Generalized cutaneous hyperpigmentation in hairless mice induced by topical dimethylbenzanthracene.** Exp Cell Biol 57:292-299, 1989.
  Abstract : The skin of hairless (Ng/Bln) mice topically treated with dimethylbenzanthracene (DMBA) was investigated by light microscopy, histochemistry, electron microscopy and autoradiography in order to gain some insight into the mechanisms by which the DMBA-induced cutaneous hyperpigmentation is mediated. The results of the present study indicate that this phenomenon is due to the DMBA-induced stimulation of both the tyrosinase system and the mitotic activity of dopa-inactive dormant melanocytes.

- Uematsu T, Miyazawa N, Okazaki O, Nakashima M. **Possible effect of pigment on the pharmacokinetics of ofloxacin and its excretion in hair.** J Pharm Sci 81:45-48, 1992.
  Abstract : The mechanism of excretion of the antimicrobial drug ofloxacin in human scalp hair was investigated. When black and white hairs were taken from a patient with grizzled hair, who had been treated with ofloxacin, a much larger quantity of the drug was detected in the black hair. To elucidate the cause, the ofloxacin (6, 20, and 60 mg/kg/day) was administered twice a day i.p. for 5 wk to albino and pigmented rats, whose backs had been depilated beforehand. In the last week of administration, the time-plasma concentration profile of ofloxacin was determined. One week after the last dosing, the newly grown hair on the depilated area was collected, and the drug concentration in the hair was measured. The concentration in the hair of the pigmented rats correlated with the daily dose, area under the plasma concentration curve (AUC), and max. plasma concentration (Cmax) at steady state, whereas that in the albino rats correlated with the dose and Cmax only, because AUC did not increase linerly with the dose in the albino rats. The drug concentration in the hair of the pigmented rats was always much larger than that in the hair of the albino ones, although AUC and Cmax did not differ greatly between both groups. Ofloxacin may be excreted in the hair in relation to the dose administered. The mechanism of the excretion may be closely linked with the presence of melanin.

- Zelikovitch N, Eyal Z, Kashman Y.
Isolation, purification, and biological activity of an inhibitor from Septoria tritici. Phytopathology 82:275-278, 1992.
Abstract : Methyl-3-indole carboxylate (3-indole carboxylic acid Me ester [ICA-Me]) was identified in liq. cultures of Septoria tritici. For physiol. studies, ICA-Me was synthesized from com. 3-indole carboxylic acid (ICA) by methylation with diazomethane. Inhibition of growth of the melanin-producing isolate ISR398 by ICA-Me on thin-layer chromatog. (TLC) plates was recorded at a concentration of 0.02 mg/mL. Inhibition by 3-indole acetic acid (IAA) was recorded at a concentration of 25-fold, whereas no inhibition was recorded for ICA at a concentration range of 0.02-0.5 mg/mL. Growth of S. tritici on liq. media was differentially affected by different concentrations of ICA-Me. Complete inhibition of S. tritici isolates ISR398 and ISR8036 was recorded at 0.08 mg/mL of ICA-Me, with only partial inhibition of ISR7901 at that concentration. The regulatory effects of those indole compounds were tested on wheat coleoptile and cucumber hypocotyl segments. IAA markedly increased growth of both coleoptiles and hypocotyls at 0.5-0.7 .mu.g/mL. Application of ICA and ICA-Me caused a slight decrease in hypocotyl growth and a slight increase in coleoptile growth at concentrations ranging from 0.4 to 20.0 .mu.g/mL. It is possible that ICA-Me may be involved in regulating the pathogen's population on the phylloplane and within wheat tissue.

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ANNOUNCEMENTS & RELATED ACTIVITIES

XV International Pigment Cell Conference
Kensington Town Hall
London, September 26-30, 1993

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Melanoma '93
Brighton Conference Centre
May 6-7, 1993

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To establish closer cooperation links and to strengthen the partnership between industrial environment and basic and clinically oriented investigators in the field of pigmentation, the ESPCR invites those prospective companies who are concerned to become Patrons of the Society. Sponsorship of this kind will be a momentous contribution to cover the costs contingent for the expansion of the activities and initiatives of the ESPCR while maintaining the membership fee at a modest level. We have every confidence that both supporting industries and the Society will greatly benefit from this privileged cooperation, which will give new impetus to research on pigmentation.

We recognize with appreciation the following companies who have supported the efforts and continued success of the ESPCR :

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They are experts on everything. They can be arrogant, and usually have strong opinions. Yet when they are wrong, they pass the blame or become defensive.

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You can identify them with their expressionless faces, weak handshakes and blank stares. Avoiding conflict and controversy at all costs, these people never offer ideas or opinions, and never let you know where you stand.

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