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

Discussion

Neuromelanin: Past, Present, Future

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The "International Colloquium on Neuromelanin and Parkinson's Disease", held in Sorrento (Naples, Italy) on the 6th - 8th May of this year, (Chaired by Prof. G. Prota) gave me the occasion to make the state of art about neuromelanin structure, function and involvement in neurodegenerative syndromes such as Parkinson's disease. As we will discuss later in this review we expect much from future work concerning neuromelanin function and structure, in fact past and present work reports have not yet provided conclusive results about those topics.

Some more progress has been achieved as concerns the involvement of neuromelanin in drug, for instance MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or metal caused parkinsonism in primates and man (1-6).

PAST:

Since the first description of a dark brown pigment occurrence within the brain stem of humans by d'Azur (7), much time has flown before an experimental approach to investigative the biochemical nature of the brain pigment was performed. Especially the pigment found in the substantia nigra and in the locus coeruleus catecholaminergic neurons rised much scientific interest, due to the loss of pigmented neurons in some neurodegenerative diseases (8-9). A recent review on the different aspects of neuromelanogenesis may be found in ref. 7.

The brain melanin chemical composition was investigated by several authors and was found to differ considerably from the other known melanins (10-15); moreover neuromelanin was reported to be the oxidation product of dopamine and norepinephrine, however also L-Dopa (L-3,4-dihydroxyphenylalanine), epinephrine and serotonin can be incorporated into neuromelanin (11-17), that when bleached, is similar to lipofuscin (18). No definitive conclusions have been obtained from spectrometric, biochemical and histochemical studies on neuromelanin, neither as concerns the chemical composition nor as regards the synthesis, enzymatic or by autooxidation from catecholic and indolic precursors (17).

The phylogenetic distribution of neuromelanin in Mammalia has been reviewed and investigated within 49 species from 11 orders (19), however due to the technique used it has been questioned that all of those species investigated have neuromelanin (20). In Primates this

pigment is well evident and they share with man similar neuromelanin related disorders (21).

The occurrence of pigmented neurons has been reported in Amphibians too, where they may have roles similar to those they have within man and Primates (22).

The amount of neuromelanin increases during ontogenesis, even if there is a wide range of reported appearances, from midterm gestation to 4 years of age in the substantia nigra, while in the locus coeruleus from 5 months of gestation to 3 years of age. At about 30-40 weeks of gestation neuromelanin becomes evident in the dorsal nucleus of vagus (20). During the life neuromelanin increases in the dopaminergic neurons up to 60-70 years and after, the cellular content decreases (23); the changes of cellular neuromelanin content varies linearly with age up to about 70 years (23). The accumulation of neuromelanin with ageing would be responsible for the pigmented neurons degeneration in older people and perhaps in some individuals (Parkinson's disease affected); the accumulation of this substance may result in the decrease of ribosomal RNA content and finally into nucleolar lesions (23). Other authors think that catecholamine metabolism per se, due to quinones, radicals ecc., i.e. cytotoxic species, may be detrimental to the dopaminergic cells (24).

Neuromelanin is compartmentalized in granules showing tripartite and globular structure consisting of vesicular bodies protruding from a granular or linear lattice (18). A lower amount of pigment, with respect to normal individual, has been found the substantia nigra of phenyl-pyruvic oligophrenics (25).

Many researches spent energies in looking for an enzyme able and responsible for neuromelanin synthesis, however the following findings supported a conflicting enzymatic origin of the pigment: a) albinos show pigmented substantia nigra (26): b) no clear neuromelanin production by substantia nigra or locus coeruleus homogenates was observed (17); c) some brain tissues, other than pigmented nuclei, promote incorporation of melanin precursors (17); d) histochemical evidence as been provided of the occurrence of tyrosinase-like activity in the substantia nigra (27); e) electrophoretic evidence has been reported of the occurrence of a tyrosinase - like activity, phenylthiourea sensitive, able to oxidize L-DOPA, dopamine and 5,6-dihydroxyindole, in human substantia nigra, that is lower in the youngest and Parkinson's disease affected individuals, if compared to the normal mid-age ones (28). The enzyme involved are monoamine oxidase, peroxidase and tyrosinase (17,26-27); however no conclusion was obtained until now.

Many putative roles have been assigned to neuromelanin, as ion metal scavenger (29), phonon-electron coupler (30), drug scavenger and releaser (6), free radical sinker (31), biocybernetic function (32), however other hypotheses have been provided, i.e. the activation of tyrosine-hydroxylase (EC 1.14.16.2) by melanin as a polyanion (33) similarly to the polyanion activation of phenylalanine hydroxylase (34). In this respect it is interesting that tyrosine hydroxylase activity is greatly decreased in the nigro-striatum of Parkinson's disease affected people (33,35-36).

PRESENT:

In the recent few years some new insights concerning neuromelanin chemical structure have come from some european and japanese laboratories (13-15), but as we will discuss later, even if novel components of neuromelanin have been found, such as cysteinyl-dopa, 5-S-cysteinyl-dopamine or an indole derivative of cysteinyl-dopamine or cysteinyl-dopa, bound to palmitic acid (14), the question is not yet settled. The japanese group failed to find incorporation of cysteinyl-dopamine into neuromelanin and its presence in human substantia nigra melanin (13), although the occurrence of cysteinyl catechols derivatives in neuromelanin may explain the pheomelanic component of this pigment. The lack of cysteinyl-dopamine incorporation in neuromelanin rises very intriguing questions.

The apparent present state of the art, as concerns neuromelanin chemical structure, is the same of the past one, uncertainty: does human substantia nigra neuromelanin contain sulfur aminoacid deriving moieties or not? The findings reported above were mainly obtained from degradative studies, followed by HPLC, pyrolysis-GC, and MS. None, at the present, has answered the points whether neuromelanin is auto-oxidatively produced or synthesized under enzymic control, as expected for substances with possible important functions (28).

The present neuromelanin age appears to be more fruitful of studies about the implication of radical species, such as active oxygen, electrophilic species scavengers such as GSH or cysteine and about the enzymes involved in these scavenging processes such as SOD (superoxide dismutase), catalase, peroxidases, glutathione-S-transferase, glutathione reductase ecc. due to the hypothesis that Parkinson's disease and related conditions may be the result of oxidative stress (38). This point have been largely discussed at the Sorrento meeting on "Neuromelanin and Parkinson's disease" by many speakers, so that, one of the main conclusion, that might be drawn from that conference, was the detrimental function of neuromelanin. This point will be the object of some consideration in the next section of this review.

Only a few reports exist on the null role of neuromelanin in Parkinson's disease and among them, the interesting involvement of bFGF-like proteins (basic fibroblast growth factor) in the substantia nigra neuron degeneration proposed by McGeer et al. (39).

Most of the present concern in neuromelanin, free radicals and related neurodegenerative diseases sprang from the MPTP induced parkinsonism (2), the cytotoxicity of catecholamine oxidation products (24), and the free radical content of melanins (40-42); however many agents such as drugs, metals, viruses, CO and trauma, may produce parkinsonian symptoms, thus we expect much from the future research findings to clear both the genesis, the chemical and spacial structures, the normal and pathological functions of neuromelanin.

THE FUTURE:

As we have previously discussed, virtually large room exists for neuromelanin investigations. No conclusive findings have been obtained as regards the neuromelanin molecular structure, the compartmentalization of neuromelanin synthesis, and as whether or not, the derangement of intracellular neuromelanin compartmentalization may be responsible for cytotoxic species efflux, from the neuromelanogenesis sites to the rest of the cell, resulting this in enzyme, genome or structural damages, that may cause a pigmented dopaminergic neuron loss; however this is only a face of the medal involving neuromelanin in Parkinson's disease. Recent reports suggest that neuronal loss in the substantia nigra may be related to the ageing process, affecting the dopamine transporter mRNA levels after the fifth decade, when a steep decrease of tyrosine hydroxylase mRNA, that declines linearly with age, is found (43). An important finding moreover comes from studies on the tyrosine hydroxylase, substance P and calbindin D28K distribution within cell tiers in the substantia nigra, where the most vulnerable cells in Parkinson's disease appear to be the less rich of neuromelanin (44), in spite of reports that suggest a higher vulnerability of the most pigmented neurons in the substantia nigra (45).

The findings reported above rise the questions whether or not neuromelanin has some role in the loss of dopaminergic neurons; in fact the idiopathic abnormal decrease of dopamine transporter and/or tyrosine hydroxilase in the substantia nigra pigmented cells does not seem to be correlated to the neuromelanin content of neurons, in fact the most vulnerable ones seem to be the less rich of pigment. As we can see no clear relation appears between neuromelanin and dopaminergic neuron death. If we give confidence to Nagatsu et al. (33), we should expect that neuromelanin is not detrimental but useful due to tyrosine hydroxylase activation. Mc Geer pointed out, at the Sorrento Colloquium, that great research efforts are displayed to demonstrate the negative function of neuromelanin while, very few people claims that neuromelanin should have a positive function in the pigmented neurons physiology. A major question is: why has not

neuromelanin been discarded by natural selection? Why does neuromelanin occur within the highest phylogenetic levels (even if pigmented neurons occur within Amphibia but not easily traceable back to substantia nigra neurons)? Which is the role of bFGF-like proteins in the physiopathology of the nigro-striatal pathways? Does exist any evidence that acatalasia (Takahara disease), progeria, peroxidase or SOD deficiencies are linked with a higher incidence of Parkinson's disease and parkinsonisms? Is neuromelanin synthesized under enzymatic control? We have recently found a melanogenic protein fraction from the rabbit and mouse brain and also shown that purified dopamine-ß-hydroxylase (EC. 1.14.17.1.) has some catecholamine oxidase activity (46).

To my opinion the future research in the neuromelanin field should first discover the physiological function of this substance(s), if any, and subsequently demonstrate that it is a detrimental phylogenetic result; cells are not detrimental to the organism but cancer indeed.

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Commentaries

Fluorescence and time resolved photoacoustics of the photoprotective pigment pheomelanin

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Summary

A spectroscopical study was performed on synthetic pheomelanin with the aim to improve at a molecular level the knowledge of the photophysiological properties of such a protective epidermal pigment.
Both absorption and fluorescence spectra show a rather complex behaviour dependent upon pH changes. The time-resolved photoacoustic calorimetry gives values of quantum yields for non radiative relaxation of the optically exited states, that agree with the fluorescence data. Such high values (about 0.97), suggest that pheomelanin, like the black eumelanin, relaxes mainly through thermal transition, leaving only a little part of the electronic energy available for photochemical reaction putatively involved in pathological changes as solar eritheme and skin cancer.

Dynamic and light scattering studies on melanin aggregation

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Summary

The biosynthesis of melanins is a very complex in which non enzymatic steps follow the initial stages of transformation of the elemental precursors by tyrosinase.

Several aspects of this process can be mimicked by *in vitro* synthesis following standard procedures.

The *in vitro* synthesis kinetics, as studied by absorption and fluorescence spectroscopies and dynamic light scattering technique, put in evidence the superimposition of many effects, dependent mainly on the presence of the enzyme solution composition, and pH and suggests a possible anomalous effect in the enzymatic catalysis.

The evidence of the coexistence of different regimes of aggregation together with the presence of few dimensional critical values possibly related to internal structure and hydration of the final aggregates make it possible to formulate a tentative model that must be in any case confirmed by further measurements.

CURRENT LITERATURE

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1. Melanins and other pigments chemistry

(Comments by Prof. M. Peter)

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Interaction of Fe3+, Cu2+ and Zn2+ with melanin and melanoproteins from bovine eyes. Acta Biochim Pol 39:85-88, 1992.
Commentary: Melanoproteins bind lower amounts of metal ions than protein-free melanin.

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Novel approaches to the bleaching of stained and pigmented wool. Proc. Int. Wool Text. Res. Conf., 8th, 4:330-9, 1990.

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The effect of sodium iodate and melanin on the formation of glyoxylate. Pigment Cell Res 5:394-395, 1992.
Commentary: With respect to selective damage of retinal pigment epithelium, the paper suggests an involvement of melanin in oxidative deamination of glycine, mediated by iodate. Relevance for toxicology of xenobiotics in the retina.

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Bleaching of pigmented fibers using copper salt catalysts. Proc. Int. Wool Text. Res. Conf., 8th, 4:319-29, 1990.

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Synthesis of eumelanin pigment precursors. II. 6-hydroxy-5-methoxy- and 5-hydroxy-6- methoxyindole. Sb Lek 91:225-229, 1989.
Abstract: Following up of specific melanogenesis metabolite excretion in the cours of malignant melanoma disease is useful for the disease prognosis assessment. The authors elaborated a modified synthesis technique of 6-hydroxy-5-methoxy and 5-hydroxy-6-methoxyindole, eumelanin pigment precursors. The elaborated synthesis is economically and temporally reasonable and the synthesized compounds accord, as proved by means of elementary analysis, thin layer (TLC) and high performance liquid chromatography (HPLC) and last but not least by nuclear magnetic resonance (NMR), with demands for reference compounds needed for isomer hydroxymethoxyindole quantification in urine.

- Chedekel MR, Ahene AB, Zeise L.
Melanin standard method: empirical formula 2. Pigment Cell Res 5:240-246, 1992.
Commentary: Similar to Pigment Cell Res. 5:143-147, 1992.

- Chedekel MR, Murr BL, Zeise L.
Melanin standard method: empirical formula. Pigment Cell Res 5:143-147, 1992.
Commentary: Elemental composition calculated after correction for amino acid contents in natural and synthetic melanins. Surprise: amino acids were even detected in chemical tyrosine melanin. Artifacts by co-chromatography of degradation products with standard amino acids? Such an approach must be used very critically.

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Melanin biosynthesis from dopamine. II. A mass spectrometric and collisional spectroscopic investigation. Pigment Cell Res 5:122-131, 1992.
Commentary: On the basis of MS (EI and FAB, collisional activation), evidence is presented for the occurence of quinone intermediates in melanogenesis from DA. Though rather lengthy, this paper presents an interesting approach towards the study of reactive intermediates in melanogenesis. No quantitative data.

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Commentary: ^{13}C-NMR indicates that binding of melanin to cationic porphyrins (cf. Ito AS, et al., Biophys. Chem. 45:79-89, 1992) including indium (III) complexes, occurs via "strong interactions comparable to chemical bonds". Line broadening is observed both in resonances of quaternary N-alkyl carbons of lignards, as well as of methine carbons of the porphyrin macrocycle. Interesting methodology.

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Abstract: A review, with 46 refs., on chem. and chem. structure of melanin and dermatol. significance of melanin , discussing melanin in skin compn., metab. and function of melanin in the skin, and melanin in UV iradn.-induced pigment darkening and tanning and pigment disorders.

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Inactivation of ornithine decarboxylase by intermediates of tyrosinase-catalyzed reaction. Int J Biochem 25:353-358, 1993.
Commentary: Sound work on reactions of sulfhydryl groups of ornithine decarboxylase with quinone intermediates of melanogenis. Covalent binding to enzyme demonstrated by radiolabelling and subsequent degradation to peptides. Active site of enzyme is involved also. Reactivity decreases in the order dihydroxybenzylamine > DOPA > tyrosine.

- Ito AS, Azzellini GC, Silva SC, Serra O, Szabo AG.
Optical absorption and fluorescence spectroscopy studies of ground state melanin-cationic porphyrins complexes. Biophys Chem 45:79-89, 1992.
Commentary: Synthetic L-DOPA melanin binds non-covalently to prophyrins which are derivatized by cationic N-methyl or N-benzyl pyridine residues. Binding results in UV red shift and quenching of fluorescence. Important paper with respect to binding of xenobiotics to melanin. Significance: MPTP, Parkinson.

- Ito AS, Azzellini GC, Silva SC, Serra O, Szabo AG.
Optical absorption and fluorescence spectroscopy studies of ground state melanin-cationic porphyrin complexes. Biophys. Chem. 45 305, 1993.
Abstract: Optical absorption and fluorescence spectroscopies were employed in the study ofthe interaction between synthetic L-dopa(dihydroxy-phenylalanine) melanin and the cationic porphyrins tetrakis(4-N-methylpyridyl) porphyrin (TMPyP), tetrakis(4-N-benzylpyridyl) porphyrin (TBzPyP), zinc etrakis(4-N-methylpyridyl) porphyrin (ZnTMPyP) and zinc tetrakis (4-N-benzylpyridyl)porphyrin (ZnTBzPyP). Optical absorption and fluorescenceproperties of the porphyrins were dependent on the symmetry of the central ring. No evidence was found for dimerization of the porphyrins in phosphate buffer, pH 7, in the concentration range between 4 x 10(-8) to 5 x 10(-5) M. Addition of L-dopa melanin red shifted the optical absorption spectra of porphyrins, concomitant to broadening and reduction in intensity of the bands. L-Dopa melanin also strongly quenched the fluorescence of the porphyrins. Time resolution of the fluorescence decay of porphyrins showed at least two lifetimes that were only slightly modified in the presence of melanin. The interaction between melanin and porphyrin resulted in the formation of non-fluorescent ground state complexes. It was found that there are two different classes of binding sites in melanin for complexation with cationic porphyrins and the values of dissociation constants are of the order of 10(-8) M. These values and the number of binding sites are dependent on the nature of the porphyrins. It was shown that the binding has electrostatic origin, but it is also affected by metal coordination and hydrophobic interaction.

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High-performance liquid chromatography (HPLC) analysis of eu- and pheomelanin in melanogenesis control. J Invest Dermatol 100:166, 1993.

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Regulatory factors of pheo- and eumelanogenesis in melanogenic compartments. Pigment Cell Res. Suppl 2:36-42, 1992.
Commentary: Review on molecular and cellular biochemistry of melanogenesis.

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The stability of 5-S-cysteinyldopa and 6-hydroxy-5-methoxyindole-2-carboxylic acid in human urine. Pigment Cell Res. Suppl 2:304-7, 1992.
Commentary: Concentration of title compounds followed up for up to eight weeks in urine. Best stability after addition of acetic acid and storage at -20 < T < 8°C. Relevant for clinical chemistry; diagnostics of melanoma.

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Abstract: A review with 31 refs. on the title topic with discussion on the possible rational use of melanin in regulation of biochem. processes.

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Interaction of enomelanin with colloidal constituents associated with clouding in must and wine. Izv. Vyssh. Uchebn. Zaved., Pishch. Tekhnol.42-45, 1991.
Abstract: Interactions of enomelanin (EM) with colloidal constituents of mustand wine were studied at different pH values (from 2 to 6), in the presence of different electrolytes [NaNO3, Ca(NO3)2, and Al(NO3)3], at different molar ratios of EM to grape protein (from 0.1 to 4.0), at different temps. (5-60.degree.), and mechanisms of anticlouding effects of EM are suggested. In pilot-scale expts., treatment of grape wine with EM decreased total colloids by 60%, proteins by 85%, polysaccharides by 65%, lipids by 65%, phenols by 15%, and Ca by 60%. EM can be used not only for clarification and stabilization of wines but apple and grape juices also.

- Orlow SJ, Osber MP, Pawelek JM.
Synthesis and characterization of melanins from dihydroxyindole-2-carboxylic acid and dihydroxyindole. Pigment Cell Res 5:113-121, 1992.
Commentary: Chemically or enzymatically synthesized DHICA gives soluble (at pH > 5) brown pigment, while DOPA, DOPAchrome or DHI form black insoluble melanin. Mixtures of DHICA and DHI give copolymers. Properties of DHICA pigment: precipitates at ph < 5; DP: 100-1000; UV spectra. Conclusion: brown pigments in hair, melanoma, feathers are made from DHICA. Many chemical data. Important.

- Pilipenko TD, Mank VV, Kornilov MY, Zherebin YuL, Litvina TM.
NMR determination of water mobility in solutions of biological macromolecules at different temperatures. Izv. Vyssh. Uchebn. Zaved., Pishch. Tekhnol: 208-211, 1991.
Abstract: NMR spectra were detd. for model solns. of agar-agar, agar-sucrose, pectin-sucrose-citric acid, agar-sucrose-citric acid (or malonic acid), collagens, melanin pigments, and other biol. macromols. at different temps. (+20 to -40.degree.) to est. water mobility. The NMR method was efficient in detn. of free, weekly bound, strongly bound, and hydrated or esp. strongly bound water in response to temp. of solns. During freezing solns. of polysaccharides, polypeptides, and polyphenols at 0.degree., about 70% of total water gets frozen, including 3% weakly bound and 17% strongly bound water. At -38.degree., 13.4% of the water remains unfrozen, which represents hydrate-bound water.

- Prota G.
The role of peroxidase in melanogenesis revisited. Pigment Cell Res. Suppl 2:25-31, 1992.
Commentary: Useful review on in vitro peroxidase catalysed formation of oligomers od DHI and DHICA. Comparison with tyrosinase. Kinetics. Coupling of DHI via 2-4 and 2-7 positions, of DHICA via 4-7 positions of the indole nucleus. Peroxidase catalyzes conversion of DOPA to DOPAquinone and oligomerzation. Discussion of role of peroxidase in melanosomes.

- Ragnelli AM, Pacioni G, Aimola P, Lanza B, Miranda M.
Truffle melanogenesis: correlation with reproductive differentiation and ascocarp ripening. Pigment Cell Res 5:205-212, 1992.
Commentary: Histochemical analysis of DOPA oxidase and tyrosinase activities in Tuber aestivum and T. melanosporum. Many pictures, little text.

- Sato M, Hayakawa K, Nisino K, Itokawa Y.
Effect of drugs on the binding of thiamin to melanin Bitamin 67:57-65, 1993.

Commentary: Thiamin binding to melanin is inhibited by c > 1 mM chlorpromazine, kanamycin, chloroquin, streptomycin, paraquat, hidralazin, quinidine, nortriptyline, amitryptiline, and imipramine. Binding thermodynamics (Langmuir, cooperative) determined (article in Japanese; abstract in English).

- Shibata T, Prota G, Mishima Y.
Non-melanosomal regulatory factors in melanogenesis. J Invest Dermatol 100:274, 1993.

- Tomita Yasushi.
Melanin , active oxygen, and free radicals. Kassei Sanso, Furi Rajikaru 3:284-290, 1992.
Abstract: A review with 9 refs. on the prodn. of oxygen radicals during melanin synthesis and UV irradn. of melanin, and function of radical scavengers on melanin free radicals.

- Townsend E, Moni R, Quinn R, Parsons PG.
Reversible depigmentation of human melanoma cells by halistanol trisulphate, a novel marine sterol. Melanoma Res 1:349-357, 1992.
Commentary: Treatment of melanoma cells results in reversible decrease of melanosomes and tyrosinase activity. Action of HTS is on postranscriptional level (maturation of tyrosinase).

- Wiewior A, Buszman, E.
Amino acid composition of human hair melanoproteins. Acta Biochim Pol 39:81-84, 1992.
Commentary: Amino acid analysis of black, brown, red, dark and light blond, and grey hair. No significant differences found.

- Zeise L, Addison RB, Chedekel MR.
Bio-analytical studies of eumelanins. I. Characterization of melanin the particle. Pigment Cell Res. Suppl 2:48-53, 1992.
Commentary: Focus on Sepia melanin. Particle size and amino acud analysis. The paper is similar to: Zeise L, et al. Pigment Cell Res.5:132-142, 1992.

- Zeise L, Chedekel MR.
Melanin standard method: titrimetric analysis. Pigment Cell Res 5:230-239, 1992.
Commentary: "Bioavailable" carboxylic groups are determined (Sepia melanin: 185 μEg, tyrosinase tyrosine melanin: 68 μEg,chemical tyrosine melanin: 490 μEq/g).Interesting methodology and approach.

- Zeise L, Murr BL, Chedekel MR.
Melanin standard method: particle description. Pigment Cell Res 5:132-142, 1992.
Commentary: Standard procedure for isolation of melanins suggested (neutral pH, low temperature). Pigments obtained as polyanions with potassium as counterion (Melanin-K^+). Particle size determined: Sepia melanin occurs in granular form while synthetic melanins are not composed of discrete particles. Useful background information on melanins (natural Sepia, tyrosine-enzymatic, tyrosine-chemical).

- Zherebin YuL, Litvina TM.
Isolation of water-soluble phytomelanins. Khim. Prir. Soedin.733-735, 1991.
Abstract: Phytomelanins (PM) are anticancer, radioprotective, lysoprotective, growth-stimulating, and bacteriostatic copolymers with extended actions.A method was developed for manuf. of uniform,.ltoreq.20% water-sol. PM NH4+ salts from low-cost byproducts, such as cottonseed and sunflower hulls, and extd. sugar beet and grape pulp, by extn. of 1 part with 8-10 parts 5% NaOH or, for materials contg. >3-5% pectin, 10-15 parts 5% NaOH, followed by pptn. with 1% dild. HCl at pH 3.0-3.5, rinsing with water to pH 6.0-6.5, repeated extn. with NH4OH and pptn. with HCl, another extn. with NH4OH and fractionated pptn. with EtOH at pH 8.5-9, dissoln. in water, gel filtration on Sephadex G-25, and elution with 0.001% NH4OH at pH 9.8. Thus standardized prepns. had a uniform activity, stimulating Fe redn. in a NAD.H2-K3Fe(CN)6 system 2.5-3.0-fold, by phenolic .dblarw. quinoid PM transition with a 4.0-4.1 logK at 25.degree.. Physico-chem. characteristics of the std. product are given.

2. Biology of pigment cells and pigmentary disorders

(Comments by Dr M. Picardo)

- Broekhuyse RM, Kuhlmann ED.
Experimental autoimmune anterior uveitis. The preparation of uveitogenic ocular melanin. Invest Ophthalmol Vis

Sci 34:698-700, 1993.
Abstract: PURPOSE. The purpose of this study was to develop a rapid procedure for the preparation of melanin with a specific, highly uveitogenic activity. METHODS. A crude melanosome fraction was isolated from bovine choroids (containing remnants of adhering retinal pigment epithelium). The fraction was extracted with hot 2% sodium dodecyl sulfate, and Lewis rats were immunized with the purified melanin, using pertussis toxin as coadjuvant. RESULTS. The purified melanin was free from pathogenic photoreceptor antigens and other accompanying or adsorbed proteins. It was able to evoke severe, acute, anterior uveitis with the typical characteristics of experimental autoimmune anterior uveitis (EAAU; without retinitis or pinealitis), even at the level of 1 micrograms melanin protein. CONCLUSIONS. The rapidly prepared ocular melanin exhibits the same qualities as purified choroidal or retinal pigment melanins obtained by much more laborious procedures (which also deliver other subcellular fractions for investigation). It is suitable for the study of the immunopathogenesis of EAAU, which is a new model for human acute anterior uveitis.

- Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, Finkel LJ, Hamilton TA, Ellis CN, Voorhees JJ.
Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. N Engl J Med 328:1438-1443, 1993.

- Calleja E.
Prostatic melanosis. Actas Urol Esp 16: 701-703, 1992.
Abstract: Melanin presence in the prostate can be accurately localized in epithelial cells (nevus) or in the stroma (prostatic melanosis). This article describes a new case and compiles all recorded cases as well as the theories concerning their origin.

- Fitzpatrick RE, Goldman MP, Ruiz-Esparza J.
Laser treatment of benign pigmented epidermal lesions using a 300 nsecond pulse and 510 nm wavelength. J Dermatol Surg Oncol 19:341-347, 1993.

- Fukazawa K, Sakagami M, Umemoto M, Fujita H, Matsunaga T.
Electron microscopical observations of melanin in the endolymphatic sac. Acta Otolaryngol Suppl (Stockh) 501 :72-75, 1993.
Abstract: Endolymphatic sacs of pigmented guinea pigs were examined by light and electron microscopy. Melanocytes were located not only in the subepithelial connective tissue but also in the intercellular spaces between the epithelial cells. They projected their dendrites into the epithelium extensively. Melanosomes in several stages of maturation and well-developed Golgi apparatus were seen in the cytoplasm of the melanocytes. Melanosomes were also observed in the membrane-bound vacuoles of the epithelial cells. These findings suggest that melanocytes in the endolymphatic sac are highly capable of producing tyrosinase, synthesizing melanin and transferring melanosomes to the epithelial cells, while melanocytes in the other parts of the inner ear do not show signs of melanogenesis under normal conditions.

- Hearing VJ.
Unraveling the melanocyte. Am J Hum Genet 52:1-7, 1993.

- Ho KK, Dervan P, O'Loughlin S, Powell FC.
Labial melanotic macule: a clinical, histopathologic, and ultrastructural study. J Am Acad Dermatol 28:33-39, 1993.

- Imokawa G, Motegi I.
Skin organ culture model for examining epidermal melanization. J Invest. Dermatol. 100:47-54, 1993.
Commentary: The regulatory mechanisms of skin pigmentation are multiple and complex. Different models have been used to evaluate the tyrosinase activity and the melanin content in skin during normal conditions or following different stimuli. However it is difficult to evaluate all the complex steps involved in the production of pigment. The authors have defined a skin organ culture model for examining epidermal melanization. Using different in vitro systems they were able to reproduce the increase of melanogenesis following UV irradiation or following the treatment with arachidonic acid metabolites and cytokines. The tests have shown results similar to those obtained in normal human skin in vivo or in culture of melanocytes. The authors concluded that the defined system might provide an opportunity to examine the mechanism of action of epidermal melanization. Possibly a similar system may be useful to evaluate the effect of factors and drugs which are able to modify the normal process of melanization or reduce the melanocyte activities.

- King RA, Wiesner GL, Townsend D, White JG.

Hypopigmentation in Angelman syndrome. Am J Med Genet 46:40-44, 1993.

- Laaff H, Kuhnl-Petzoldt C.
HMB 45 positive balloon cells in combined nevi. Hautarzt 43:566-568, 1992.
Abstract: The combined naevus is made up of two components, one resembling a melanocytic naevus, the other a blue naevus. Clinically, these naevi do not give any obvious cause for concern. Histological examination shows that the combined naevus consists of a superficial melanocytic naevus and a deep-seated spindle cell blue naevus. There is a rare variant in which the pigmented spindle cells of the "blue" naevus are replaced by large balloon cells varying in melanin content. These combined naevi, because of the large cells with abundant cytoplasm, closely resemble malignant melanoma. As a further aid to diagnosis we used the monoclonal antibody HMB 45. In our study, the vesicular cells in all seven combined naevi examined reacted strongly with HMB 45. It is suggested that HMB 45 is not always helpful in differentiating between melanoma and naevi.

- Le P.
Presence or absence of melanocytes in vitiligo lesions: an immunohistochemical investigation. J Invest Dermatol, 100:816-822, 1993.
Commentary: Different efforts have been devoted to define if in the vitiligo lesion the melanocytes are still present or are completely absent. The problem rises from the possibility of repigmentation of the recent lesion to establish if the melanocytes derive from unidentified precursors or quiescent cells in the white spots or derive from the migration of follicular cells. These authors, using a panel of monoclonal antibodies against different antigens expressed by melanocytes, have clearly established that melanocytes are not detectable in the depigmented spots of vitiligo subjects neither by electron-microscopy or by immunohistochemically. The elegant paper has probably concluded any debate about the persistence of melanocytes in vitiligo spots.

- Matsuda H, Nakamura S, Shiomoto H, Tanaka T, Kubo M.
Pharmacological studies on leaf of Arctostaphylos uva-ursi (L.) Spreng. IV. Effect of 50% methanolic extract from Arctostaphylos uva-ursi (L.) Spreng. (bearberry leaf) on melanin synthesis. Yakugaku Zasshi 112:276-282, 1992.
Abstract: Effects of 50% methanolic extract (U-ext) from the leaf of Arctostaphylos uva-ursi (L.) Spreng. (bearberry leaf) on melanin synthesis were investigated in vitro. The U-ext and arbutin isolated from the bearberry leaf had an inhibitory effect on tyrosinase activity. Furthermore, the U-ext inhibited the production of melanin from dopa by tyrosinase and from dopachrome by autoxidation. These results suggest that the bearberry leaf was found to be an effective inhibitor of the production of melanin.

- Medrano EE, Farooqui JZ, Boissy RE, Boissy YL, Akadiri B, Nordlund JJ.
Chronic growth stimulation of human adult melanocytes by inflammatory mediators in vitro: implications for nevus formation and initial steps in melanocyte oncogenesis. Proc Natl Acad Sci U S A 90:1790-1794, 1993.

- Morelli JG, Norris DA.
Influence of inflammatory mediators and cytokines on human melanocyte function. J Invest Dermatol 100:191, 1993.

- Nogaj P, GoLek A, Bogacz A, Piatek K, Buszman E, Mossae IB.
59Fe distribution and elimination after melanin administration in mice. Acta Biochim Pol 39:89-94, 1992.
Abstract: The aim of this work was to prove how far the administration of melanin into white mice (which do not contain melanin in their hair) and black mice (contg.the melanin pigment) effects 59Fe distirubution and elimination.

- Prezioso JA, Damodaran KM, Wang N, Bloomer WD.
Mechanism(s) regulating inhibition of thymidylate synthase and growth by gamma-L-glutaminyl-4-hydroxy-3-iodobenzene, a novel melanin precursor, in melanogenic melanoma cells. Biochem Pharmacol 45:473-481, 1993.
Abstract: A proposed mechanism for the melanoma specific activity of phenolic amines is based upon the ability of the enzyme tyrosinase to oxidize these prodrugs to toxic intermediates. In this study, we synthesized an iodinated analog of gamma-L-glutaminyl-4-hydroxybenzene (GHB) with increased antimelanoma activity in both human and murine melanoma cell lines. GHB and gamma-L-glutaminyl
-4-hydroxy-3-iodobenzene (I-GHB) were shown to be substrates for both mammalian and mushroom tyrosinase. Glutathione, a cellular antioxidant, inhibited tyrosinase mediated formation of gamma-L-glutaminyl-3,4-benzoquinone (GBQ) from GHB, inhibited melanin production, and blocked the inhibition

of the enzyme thymidylate synthase by oxidized GHB. Buthionine sulfoximine (BSO) depletion of cellular glutathione enhanced the growth inhibitory activity and the inhibition of in situ thymidylate synthase by phenolic amines in melanoma cells. GHB and I-GHB were shown to be approximately 5- and 10-fold more cytotoxic, respectively, in highly metastatic B16-BL6 cells than in weakly metastatic B16-F1 cells with approximately equal tyrosinase activity. B16-BL6 cells had approximately 20-fold higher gamma-glutamyltranspeptidase (gamma-GTPase) activity than B16-F1 cells which suggested the possible involvement of this enzyme in the activation of the cytotoxicity of the phenolic amines. 4-Aminophenol, a product of gamma-GTPase reaction with GHB, was a substrate for tyrosinase and a potent inhibitor of in situ thymidylate synthase activity in melanogenic cells. In pigmented melanoma cells containing the enzyme tyrosinase, the quinone mediated mechanism of phenolic amine cytotoxicity may be uniquely important and the cellular antioxidant glutathione essential in the detoxification of these quinone-generated intermediates.

- Rowett MA, Fleet MR.
Albinism in a Suffolk sheep. J Hered 84:67-69, 1993.
Abstract: This report introduces the second form of true albinism to be documented in sheep, which appears mild enough not to cause serious undesirable side effects yet apparently effective enough to have the potential for general usage in the sheep industry. Based on the matings conducted to date, the albinism is inherited like an autosomal recessive. Histochemical tests reveal a defective melanin synthesis involving a block to the conversion of tyrosine to dopa but not the subsequent reactions that lead to melanin. The enzyme tyrosinase is a product of the C locus and catalyzes the conversion of tyrosine to dopa and the following reaction (dopa to dopaquinone). Therefore, it is proposed that the albinism arises from a gene in the C locus that encodes a defective tyrosinase. The gene is provisionally named albino marrabel, the gene symbol is cmar, and the locus allele symbol is Ccmar.

- Schallreuter KU, Wood JM, Lemke R, LePoole C, Das P, Westerhof W, Pittelkow MR, Thody AJ.
Production of catecholamines in the human epidermis. Biochem Biophys Res Commun 189:72-78, 1992.
Commentary: A new aspect of the research on the catecholamine metabolism in the skin has been introduced by these authors. Starting from the demonstration that human keratinocytes express high density of beta-2-adrenoreceptors, the authors have evaluated the possibility that epinephrine may be produced in human epidermis. In cell free extracts of human keratinocytes the authors were able to show the presence of biopterin-dependent tyrosine hydroxylase and phenylethanolamine-N-methyl transferase activities. These enzymes are involved in the synthesis of epinephrine, and therefore it is plausible that the skin is capable of synthesising epinephrine. This characteristic seems to be exclusively due to keratinocytes, since the same enzymes cannot be detected in melanocytes and fibroblasts.
The authors proposed an interesting correlation between the production of epinephrine and the epidermal cell activities. The synthesis of epinephrine in the keratinocytes is regulated by the intracellular calcium concentration through a feed-back mechanism. Melanocytes also express beta-2-adrenoreceptors and it seems that epinephrine biosynthesis in human keratinocytes regulate the calcium homeostasis in the epidermis and the melanin biosynthesis in melanocytes.
These results together with the reported susceptibility of melanocytes to oxidatives stress, are the base for a new hypothesis of vitiligo which has been presented by the same authors at the International Pigment Cell Conference in London, and certainly offer new insights into the pathophysiology of different skin diseases.

- Yohn JJ, Morelli JG, Walchak SJ, Rundell KB, Norris DA, Zamora MR.
Cultured human keratinocytes synthesize and secrete endothelin. J Invest dermatol 100: 23-26, 1993.

Commentary on the litterature listed below by Dr N. Smit:

In the light of melanocytes taking part in the skin immune system the paper of Morelli and Norris give an nice overview of the effects of inflammatory mediators on melanocytes and how this may be regulated in the skin. The work of Medrano et al gives a more detailed view of how such mediators can be involved in changes in the melanocyte phenotype. Porchet-Hennere and Vernet give a completely different model of how melanin can be important in cellular immunity in the annelid.
Induction of a new type of ocular disease is reported by Broekhuyse et al after immunization of Lewis rats with a pigment epithelial polypeptide of 65 kDa (PEP-65).
The work of Kammeyer et al about the production of monoclonal antibodies against (methylated) indolic intermediates could result in a sensitive method for detection of these compounds as markers of melanoma in serum of patients and in the follow up during treatment.

- Broekhuyse RM, Kuhlmann ED, Winkens HJ.

Experimental autoimmune posterior uveitis accompanied by epitheloid cell accumulations (EAPU). A new type of experimental ocular disease induced by immunization with PEP-65, a pigment epithelial polypeptide preparation. Exp Eye Res 55:819-829,1992.

- Porchet-Hennere E, Vernet G.
  Cellular immunity in an annelid (Nereis diversicolor, Polychaeta): production of melanin by a subpopulation of granulocytes. Cell Tissue Res 269:167-174,1992.

3. MSH, MCH, other hormones, differentiation

- Bagutti C, Eberle AN.
  Synthesis and biological properties of a biotinylated derivative of ACTH1-17 for MSH receptor studies. J Recept Res 13:229-244, 1993.
  Abstract: A biotinylated derivative of [beta-Ala1,Lys17]
  -ACTH1-17-NH-(CH2)4-NH2 (ACTH1-17) was synthesized and biologically characterized. The heptadecapeptide with free N-terminus and blocked side-chains was prepared by the solid-phase method using TentaGel resin and a 4-aminobutylamide linker. Biotinyl-beta-Ala-OH was then coupled to the terminal amino group and the resulting[Nalpha-(biotinyl-beta-alanyl)-beta-Ala1,Lys17]-ACTH1-17-NH-(CH2)4-NH2(Bio-ACTH1-17)cleavedfrom the resin, purified and analyzed. Competition binding assays with mouse B16-F1 and human D10 and HBL melanoma cells using [125I]-alpha-MSH as radioligand gave dissociation constants for Bio-ACTH1-17 of 1.67 +/- 0.07 nM (B16-F1), 0.02 +/- 0.005 nM (D10) and 0.21 +/- 0.02 nM (HBL). The EC50 for Bio-ACTH1-17 in the B16 melanin assay was 4.15 +/- 1.0 nM. Analysis of the binding characteristics of [125I]-Bio-ACTH1-17 demonstrated that in human melanoma cells this radioligand was displaced by ACTH1-17 as well as alpha-MSH whereas in B16-F1 cells the tracer was only displaced from the binding site by ACTH1-17. Studies of Bio-ACTH1-17 with streptavidin showed that the peptide is to a large extent trapped specifically through reaction with biotin. These results demonstrate that (1) the biological characteristics of Bio-ACTH1-17 are almost identical to those of ACTH1-17, (2) Bio-ACTH1-17 is bound by avidin, and (3) Bio-ACTH1-17 may become a useful tool for MSH receptor targeting.

- Burchill SA, Ito S, Thody AJ.
  Effects of melanocyte-stimulating hormone on tyrosinase expression and melanin synthesis in hair follicular melanocytes of the mouse. J. Endocrinol. 137:189-195,1993.

- Halaban R, Rubin JS, White W.
  Met and HGF-SF in normal melanocytes and melanoma cells. EXS 65:329-339, 1993.
  Abstract: HGF-SF stimulates the proliferation of normal human melanocytes in the presence of synergistic factors, one of which is bFGF, and promotes motility and expression of high levels fo tyrosinase activity and melanin content. Melanocytes from a recurrent blue nevus were also stimulated by HGF-SF, whereas cells from advanced primary and metastatic lesions either did not respond, were only slightly stimulated or, in one case, were inhibited. Signal transduction was mediated by tyrosyl-phosphorylation of met and several other proteins, including MAP kinase/ERK2. Met expression and phosphorylation in response to HGF-SF was normal in human melanoma cells, and HGF-SF-transduced mouse melanocytes wer not tumorigenic. Taken together, the results show that met is not constitutively active in human melanomas and that its activation by an autocrine loop is not sufficient to confer the tumorigenic phenotype. They raise the possibility that exogenous HGF-SF may play a role at early stages of malignant conversion by acting synergistically with bFGF and by promoting the dispersion of factor-dependent cells to ectopic sites.

- Morozova LF, D'iakov VL, Sukhanov VA.
  The effect of alpha-melanocyte-stimulating hormone and its analog on the growth of human melanoma cell lines with different phenotypes. Tsitologiia 35:101-104, 1993.
  Abstract: Investigation of physiological effects of alpha-MSH and its analog (NLe4, D-Phe7)-alpha-MSH on human melanoma cells with different phenotypes has shown that these peptides have a growth-modulating activity. The effect of inhibition or activation of the growth of melanoma cells depended on their phenotypes. (NLe4, D-Phe7)-alpha-MSH activated 1.5-2.5-fold the growth of amelanotic BRO cells at concentrations of 10(-6)-10(-12) M, but inhibited the growth of melanin-producing MS cells under the same conditions not affecting the growth of human lung fibroblasts.

- Sawchenko PE, Imaki T, Potter E, Kovacs K, Imaki J, Vale W.

The functional neuroanatomy of corticotropin-releasing factor. Ciba Found Symp 172:5-21, 1993.

- Solca FF, Chluba-de T.
  B16-G4F mouse melanoma cells: an MSH receptor-deficient cell clone. FEBS Lett 322:177-180, 1993.

- Sukhanov VA, Voronkova IM, Shvets SV, Morozova LF.
  Melanocyte-stimulating hormone induces growth of human malignant melanoma amelanotic cells with a change in cAMP, phosphatidylinositols, and inositol phosphate concentration. Biokhimiia 58:211-223, 1993.
  Abstract: The melanocyte-stimulating hormone (alpha-MSH) used at 10(-6)-5 x 10(-8) M concentrations inhibited the growth of amelanotic cells of human malignant melanoma BRO and influenced cell morphology without any effect on melanization or tyrosinase activity. Inhibition of tumour cell growth was accompanied by marked elevation of intracellular cAMP levels but not that of cGMP. Dibutyryl-cAMP and the cAMP-dependent protein kinase A inhibitor also inhibited the cell growth. alpha-MSH increased mono-, di- and 1.4.5-myoinositol triphosphate concentrations and influenced the activities of phosphatidylinositol kinase and phosphatidylinositol-4-phosphate kinase determining phosphatidylinositol-4-phosphate kinase and phosphatidylinositol-4.5-diphosphate levels. Myoinositol phosphate concentrations changed on a second scale and levelled off by the 3rd-5th min, whereas that of cAMP increased drastically by the 30th min.

- Touzani K, Tramu G, Nahon JL, Velley L.
  Hypothalamic melanin-concentrating hormone and alpha-neoendorphin-immunoreactive neurons project to the medial part of the rat parabrachial area. Neuroscience 53:865-876, 1993.

4. Photobiology and photochemistry

- Ahmed FE, Setlow RB.
  Ultraviolet radiation-induced DNA damage and its photorepair in the skin of the platyfish Xiphophorus. Cancer Res 53:2249-2255, 1993.

- Gia O, Mobilio S, Palumbo M, Pathak MA.
  Benzo- and tetrahydrobenzo-psoralen congeners: DNA binding and photobiological properties. Photochem Photobiol 57:497-503, 1993.

- Narurkar V, Smoller BR, Hu CH, Bauer EA.
  Desipramine-induced blue-gray photosensitive pigmentation. Arch Dermatol 129:474-476, 1993.

- Pawelek JM, Chakraborty AK, Osber MP, Orlow SJ, Min KK, Rosenzweig KE, Bolognia JL.
  Molecular cascades in UV-induced melanogenesis: a central role for melanotropins? Pigment Cell Res 5:348-356, 1992.

- Pawelek JM, Chakraborty AK, Osber MP, Bolognia JL.
  Ultraviolet light and pigmentation of the skin. Cosmet. Toiletries 107:61-68, 1992.

- Ramirez-Bosca A, Bernd A, Werner R, Dold K, Holzmann H.
  Effect of the dose of ultraviolet radiation on the pigment formation by human melanocytes in vitro. Arch Dermatol Res 284:358-362, 1992.

- Stepien K, Porebska-Budny M, Hollek AM, Wilczok T.
  The inhibiting effect of catecholamine- melanins on UV-induced lecithin peroxidation. J. Photochem. Photobiol., B, 15(3):223-31, 1992.

- Yohn JJ, Lyons MB, Norris DA.
  Cultured human melanocytes from black and white donors have different sunlight and ultraviolet A radiation sensitivities. J Invest Dermatol 99:454-459, 1992.

5. Neuromelanins

- Ben-Shachar D, Youdim MB.
Iron, melanin and dopamine interaction: relevance to Parkinson'sdisease. Prog Neuropsychopharmacol Biol Psychiatry 17:139-150, 1993.
Abstract: 1. Interaction between iron and melanin may provide a reasonable explanation for the vulnerability of the melanin containing dopaminergic neurons in the substantia nigra (SN) to neurodegeneration in Parkinson's disease (PD). 2. Scatchard analysis of the binding of iron to synthetic dopamine melanin revealed a high-affinity (KD = 13 nM) and a lower affinity (KD = 200 nM) binding sites. 3. The binding of iron to melanin is dependent on the concentration of melanin and on pH. 4. Iron chelators, U74500A, desferrioxamine and to a lesser extent 1,10-phenanthroline and chlorpromazine could displace iron from melanin. In contrast, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its metabolite 1-methyl-4-phenyl-pyridinium (MPP+), which cause Parkinsonism, were unable to displace iron. 5. Melanin alone reduced lipid peroxidation in rat cortical membrane preparations. However, iron induced lipid peroxidation,which could be inhibited by desferrioxamine, was potentiated by melanin. 6. Iron bound to neuromelanin in melanized dopamine neurons was detected only in parkinsonian brains and not in controls. The interaction of iron with neuromelanin as identified by x-ray defraction technique was identical to iron interaction with synthetic dopamine melanin. 7. In the absence of an identified exogenous or endogenous neurotoxin in idiopathic Parkinson's disease, iron-melanin interaction in the SN may serve as a candidate for the oxygen-radical induced neurodegeneration of the melanin containing dopaminergic neurons.

- Gai WP, Geffen LB, Denoroy L, Blessing WW.
Loss of C1 and C3 epinephrine-synthesizing neurons in the medulla oblongata in Parkinson's disease. Ann Neurol 33:357-367, 1993.
Abstract: We used immunohistochemical analysis to determine whether medulla oblongata neurons containing phenylethanolamine N-methyltransferase (PNMT) are affected in patients who died with idiopathic Parkinson's disease (n = 7) compared with age-matched control subjects who died with nonneurological diseases (n = 8). Transverse sections (50 microns) of medulla were prepared either for conventional neuropathological examination or for the immunohistochemical demonstration of PNMT. Immunopositive neurons at approximately 30 rostrocaudal levels, evenly spaced throughout the whole medulla, were mapped and cells in each section were counted with a camera lucida system linked to a computer. In the ventrolateral medulla, from the level of the obex to 11 mm rostral to the obex where the C1 group of neurons is located, there were 7,631 +/- 844 PNMT-positive neurons in control brains and 3,604 +/- 1,051 in brains affected by Parkinson's disease (47% of control). Many PNMT-positive neurons contained Lewy bodies. We observed a previously undescribed midline (C3) group of PNMT-positive neurons in normal brains, and this group was also severely affected (12% of control) in parkinsonian brains. Neither the C2 group nor the small PNMT-positive neurons in the nucleus tractus solitarii were significantly reduced in numbers but there was a reduction in the numbers of melanin-pigmented cells in both the ventrolateral (50% of control) and the dorsomedial (79% of control) region. Our results demonstrate a selective loss of C1 and C3 PNMT-positive neurons, providing the first quantitative evidence for damage to these presumed brainstem sympathetic premotor neurons in Parkinson's disease. These changes may underlie some of the autonomic symptoms occurring in this condition.

- Jellinger K, Kienzl E, Rumpelmair G, Riederer P, Stachelberger H, Ben-Shachar D, Youdim MB.
Neuromelanin and nigrostriatal dopamine neuron degeneration. J Neurochem 60:1976-1977, 1993.

- Jellinger KA, Kienzl E, Rumpelmaier G, Paulus W, Riederer P, Stachelberger H, Youdim MB, Ben-Shachar D.
Iron and ferritin in substantia nigra in Parkinson's diseas. Adv neurol 60:267-272,1993.

- Tooyama I, Kawamata T, Walker D, Yamada T, Hanai K, Kimura H, Iwane M, Igarashi K, McGeer EG, McGeer PL.
Loss of basic fibroblast growth factor in substantia nigra neurons in Parkinson's disease. Neurology 43:372-376, 1993.
Abstract: Basic fibroblast growth factor (bFGF) has a neurotrophic effect on mesencephalic dopaminergic neurons in vitro and in vivo. To explore whether an abnormality in bFGF expression occurs in Parkinson's disease (PD), we examined the substantia nigra (SN) of six PD and eight control cases immunohistochemically using a monoclonal antibody to bFGF. The mean number of melanin-positive neurons in sections of PD SN was 30.3% of the control mean, but the number of bFGF-immunopositive neurons was only 4.7% of the control mean. bFGF-immunoreactivity was present in only 8.2% of PD, but in 93.7% of control melanin-positive neurons. These results suggest a profound depletion of bFGF in surviving dopaminergic neurons of the SN in PD, and this depletion may be related to the disease process.

6. Genetics, molecular biology

- Ando S, Ando O, Suemoto Y, Mishima Y.
Tyrosinase gene transcription and its control by melanogenic inhibitors. J Invest Dermatol 100:150, 1993.
Abstract: The levels of tyrosinase mRNA and tyrosinase activity were analyzed in two amelanotic melanoma cell lines, D1(178) (hamster) and G-361 (human). Neither tyrosinase mRNA nor tyrosinase activity were detected in D1(178) cells. On the other hand, both tyrosinase mRNA and weak tyrosinase activity were detected in G-361 cells. Assuming that the different types of melanogenic inhibitors affected melanogenesis in these two amelanotic melanoma cells in different manners, we performed a screening of melanogenic inhibitors in these two cell lines. As an isolated tyrosinase suppressive melanogenic inhibitor, ascorbic acid and glutathione were identified from D1(178) cells and G-361 cells, respectively. Furthermore, lactic acid was identified from D1(178) cells as an isolated tyrosinase non-suppressive melanogenic inhibitor. B-16 mouse melanotic melanoma cells were depigmented by treatment with lactic acid. The melanogenesis suppression by lactic acid in B-16 cells was found to be due to inhibition of tyrosinase gene expression.

- Jackson IJ.
Molecular genetics. Colour-coded switches [news]. Nature 362:587-588, 1993.

- Kwon BS.
Pigmentation genes: the tyrosinase gene family and the pmel 17 gene family. J Invest Dermatol 100:134, 1993.
Abstract: We propose that at least two families of genes regulate the melanin biosynthesis. The first is the tyrosinase gene family, which is comprised of tyrosinase (c locus), gp75 (b locus) and DOPAchrome tautomerase (slt locus). The second is the pmel 17 gene family, which is composed of pmel 17 (putative si locus) and chicken melanosomal matrix protein (MMP) 115. It appears that the tyrosinase gene family regulates melanin synthesis in the proximal steps of the melanin biosynthetic pathway and the pmel 17 gene family might be important at distal steps of the pathway.

- Larue L, Dougherty N, Bradl M, Mintz B.
Melanocyte culture lines from Tyr-SV40E transgenic mice: models for the molecular genetic evolution of malignant melanoma. Oncogene 8:523-531, 1993.
Abstract: Transgenic Tyr-SV40E mice previously produced on the C57BL/6 inbred-strain background, with SV40 oncogenic sequences specifically expressed in pigment cells, are predisposed to melanoma [Bradl, M., Klein-Szanto, A., Porter, S. & Mintz, B. (1991). Proc. Natl. Acad. Sci. USA, 88, 164-168]. Separate lines of these animals differ genetically only in the number of copies and chromosomal site of integration of the transgene. Skin melanocytes from young mice with no apparent skin lesions were established in continuous culture from hemizygous donors with low, medium and high numbers of transgene copies, and from a homozygous offspring of the low-copy mouse line. The standard culture conditions enable C57BL/6 wild-type melanocytes to become stably immortalized without transformation. The transgenic cell lines all changed over time in an orderly progression. However, with greater numbers of transgene copies, the cells more rapidly displayed shorter doubling times, increased anchorage independence, reduced serum and growth factor requirements, decreased tyrosinase expression and melanin content, increased oncogene expression, and capacity to form malignant melanomas when tested by grafting. Melanocytes with the lowest number of transgene copies were of special interest. They grew more rapidly than the wild-type cells from the outset, but did not become tumorigenic until an apparently small number of still-unknown genetic changes had spontaneously occurred, or until the number of transgene copies was increased slightly by homozygosity. In contrast to the hemizygous low-copy cells, the homozygous counterparts underwent striking and rapid transformational changes and early conversion to malignancy. Thus such low-copy transgenic melanocyte lines afford an exceptional opportunity for molecular analysis of somatic genetic evolution toward malignant melanoma.

- Oetting WS, King RA.
Molecular basis of type I (tyrosinase-related) oculocutaneous albinism: mutations and polymorphisms of the human tyrosinase gene. Hum Mutat 2:1-6, 1993.
Abstract: Type I (tyrosinase related) oculocutaneous albinism (OCA) results from mutations of the tyrosinase gene on chromosome 11q that lead to reduced or absent melanin pigment synthesis. The phenotype of Type I OCA is broad, ranging from a total lack to only a moderate reduction of melanin, and the phenotypic variation is associated with different mutant alleles at the tyrosinase locus. A total of 36 mutations have been identified in Type I OCA including 24 missense, 4 nonsense, and 8 frameshift mutations. The majority of affected individuals have been compound heterozygotes with different maternal and paternal alleles. Six polymorphic sites for haplotype analysis have been identified in the tyrosinase gene including 2 in the promoter region, 2 in the coding region

associated with alternative amino acids in the protein, and 2 RFLPs in the first intron.

- Takeuchi T, Tanaka S, Tanaka M.
Expression of tyrosinase gene in transgenic mice: programmed versus non-programmed expression. J Invest Dermatol 100:141, 1993.
Abstract: The transgenic experiment is a useful tool for the study of cell type-specific expression of genes during embryogenesis. We constructed a minigene, mg-Tyrs-J, by fusing a tyrosinase cDNA, Tyrs-J, with the 5' upstream region of genomic deoxyribonucleic acid (DNA) clone, G3L, and microinjected this minigene into fertilized eggs from albino BALB/c mice. It was expected that a melanin pigment would be produced and deposited in the melanosomes of melanocytes of BALB/c mice if the mg-Tyrs-J was expressed in a cell type-specific manner. In the transgenic mice, melanin pigments were observed only in melanocytes and in hair shafts of hair follicles, and in the choroid and pigmented epithelium of the eyes. However, Southern blot analysis of the genomic DNA of the transgenic mice showed that the transgene was present in all tissues examined. These results apparently indicate that the introduced transgene is integrated into a chromosome(s) and distributed among somatic cells, whereas the gene is expressed exclusively in melanocytes, i.e., the transgene is expressed in a cell type-specific manner. Some founder mice were crossed with BALB/c albino mice to establish transgenic lines. Each line and subline shows inherited characteristic phenotypes; in particular, offsprings from two founders exhibited a patched phenotype. The possible mechanism of this interesting expression of these transgenes is discussed in comparison with the results of other investigators who observed both programmed and non-programmed expression of the tyrosinase gene in transgenic mice.

- Yoshii T, Tamura K, Ishiyama I.
Presence of a PCR-inhibitor in hairs. Nippon Hoigaku Zasshi 46:313-316, 1992.
Abstract: A polymerase chain reaction (PCR) system was used to amplify the noncoding 333-bp region of mitochondrial DNA (mt333DNA) contained in DNA extracts from single human hairs, and the following results were obtained: 1) Using natural black hairs, mt333 DNA was always amplified from a 5-cm length of hair shaft sampled within a region 11 cm from the hair root, but it was not always amplified from a 5-cm region adjacent to this 11-cm region, and was not amplified in almost all cases when a 5-cm length of hair shaft was sampled from a region more than 16 cm distant from the hair root. DNA preparations not responding to PCR were colored dark brown. 2) Using natural white hairs, mt333DNA was amplified from almost all specimens even up to a length of 31 cm. 3) When natural black hairs were stained with an oxidation-type hair-staining agent (Bigen-5Ge), mt333DNA was never amplified even from the hair root portion, whereas the same staining treatment of white hairs did not influence the amplification of mt333DNA. In the cases showingno response on PCR, DNA preparations were also colored dark brown. 4) These dark brown DNA preparations inhibited completely the amplification of mt333DNA even after addition of purified DNAs. These results suggest that the dark brown substance in the DNA preparations inhibits the amplification of mt333DNA by the PCR method. We therefore investigated the mechanism responsible for the development of this inhibitor. It was found that hydrogen peroxide (a component of hair-staining agent) induced formation of water-soluble melanins from insoluble melanins.

7. Tyrosinase, TRP1, TRP2 and other enzymes

Comments by Prof. J.C. Garcia- Borron:

The litterature listed below emphasizes the growing interest of two areas of research in pigment cell enzymology. On one hand, the cloning of tyrosinase and the availability of powerful mutagenesis and expression techniques is allowing for a dissection of the structure-activity relationships of tyrosinase. These studies will undoubtly lead to a clear understanding of the molecular basis of some forms of albinism. They will also provide useful information on the complexity of the catalytic cycle of tyrosinase. On the other hand, the litterature reflects the fact that the regulation of melanin synthesis is largely unknown and a matter of active research. With the characterization of dopachrome tautomerase and of the catalytic potentials of TRP1 (still under debate), the pigment cell community has realized that the potential sites of control of melanogenesis are multiple and far more complex than originally thought. The available data are still scarce but seem to indicate that the overall rate of pigment formation, as.well as the quality of the pigment formed, can be controled by changes in the activity of any of these factors. These changes could be brought about by alterations in gene expression but also by post-translational events. Moreover, it is becoming increasingly evident that not only the proteins mentioned above can be regulated with concomitant changes in the rate of melanogenesis. The regulation of the process might also involve the control of the levels of specific tyrosinase inhibitors (see, for example, Talwar et al, JID, 100, 800-805, 1993, Iozumi et al, JID 100, 806-811, 1993, and Kameyama et al, JID, 100, 126-131, 1993). It can be predicted that the characterization of these

inhibitors will be an active field of research in the near future.

- Giebel LB, Spritz RA.
The molecular basis of type I (tyrosinase-deficient) human oculocutaneous albinism. Pigment Cell Res. Suppl 2:101-6, 1992.

- Iozumi K, Hoganson GE, Pennella R, Everett MA, Fuller BB.
Role of tyrosinase as the determinant of pigmentation in cultured human melanocytes. J Invest Dermatol 100:806-811, 1993.
Abstract: Variations in human pigmentation among different racial groups are due to differences in the production and deposition of melanin in the skin. Although melanin synthesis is known to be controlled by the rate-limiting enzyme tyrosinase, the role of this enzyme as the principal determinant of skin pigmentation is unclear. Results from studies with human melanocyte cultures derived from different racial skin types reveal an excellent correlation between the melanin content of melanocyte cultures and the in situ activity of tyrosinase. Melanocytes derived from black skin have up to 10 times more tyrosinase activity and produce up to 10 times more melanin than melanocytes derived from white skin. However, the higher level of tyrosinase activity in melanocytes derived from black skin is not due to a greater abundance of tyrosinase. Results from immunotitration experiments and Western immunoblots reveal that the number of tyrosinase molecules present in white-skin melanocytes may equal the number found in highly pigmented black skin types. Moreover, approximately equivalent levels of tyrosinase mRNA are present in white and black skin cell strains. In contrast, melanocytes derived from red-haired neonates with low tyrosinase activity contain low numbers of tyrosinase molecules and low levels of tyrosinase mRNA. These results show that tyrosinase activity and melanin production in most light-skinned people is controlled primarily by a post-translational regulation of pre-existing enzyme and not by regulating tyrosinase gene activity. In contrast, melanocytes from red-haired (type I) people have low levels of tyrosinase protein and mRNA, suggesting that transcriptional activity of the tyrosinase gene is suppressed.

- Kameyama K, Takemura T, Hamada Y, Sakai C, Kondoh S, Nishiyama S, Urabe K, Hearing VJ.
Pigment production in murine melanoma cells is regulated by tyrosinase, tyrosinase-related protein 1 (TRP1), DOPAchrome tautomerase (TRP2), and a melanogenic inhibitor. J Invest Dermatol 100:126-131, 1993.

- Kappenman KE, Dvoracek MA, Harvison GA, Fuller BB, Granholm NH.
Tyrosinase abundance and activity in murine hairbulb melanocytes ofagouti mutans (C57BL/6J-a/a, Ay/a, and AwJ/AwJ). Pigment Cell Res. Suppl 2:79-83, 1992.

- Martinez-Liarte JH, Solano F, Garcia-Borron JC, Jara J R, Lozano JA.
Alpha-MSH and other melanogenic activators mediate opposite effects on tyrosinase and dopachrome tautomerase in B16/F10 mouse melanoma cells. J Invest Dermatol 99:435-439,1992.

- Orlow SJ, Boissy RE, Moran DJ, Pifko-Hirst S.
Subcellular distribution of tyrosinase and tyrosinase-related protein-1: implications for melanosomal biogenesis. J Invest Dermatol 100:55-64, 1993.

- Peinado P, Martinez-Liarte JH, Solano F, Lozano JA.
Effect of amphotericin B on dopachrome tautomerase activity and other melanogenic parameters in cultured B16/F10 melanoma cells. Pigment Cell Res 5:400-403, 1992.

- Shibata T, Pavel S, Smit NP, Mishima Y.
Differences in subcellular distribution of catechol-O-methyltransferase and tyrosinase in malignant melanoma. J Invest Dermatol 100:222, 1993.
Abstract: The activities of catechol-O-methyltransferase (COMT) and tyrosinase were measured in subcellular fractions obtained from transplantable melanotic and amelanotic hamster melanoma. The results showed that there was a substantial difference between the localization of these enzymes. Whereas tyrosinase was localized mainly in the large granule fraction, the highest COMT activity was found to be in fractions abundant in microsomal structures. As expected, subcellular fractions obtained from amelanotic melanoma contained low or undetectable tyrosinase activity. On the other hand, the same fractions exhibited higher COMT activity than those from the pigmented tumor. Relatively low specific activity of COMT in fractions containing coated vesicles does not support the idea that this enzyme could be responsible for the inhibition of melanin polymerization in these structures. Because melanogenic intermediates, such as 5,6-dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid, are compartmentalized within membraneous structures, the preferential localization of COMT in cytosol and cytosolic

membrane network might be advantageous for a detoxification role in (melanotic) melanocytes that produce dihydroxyindoles.

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Differential regulation of tyrosinase activity in skin of white and black individuals in vivo by topical retinoic acid. J Invest Dermatol 100:800-805, 1993.

- Thody AJ, Burchill SA.
Tyrosinase and the regulation of coat color changes in C3H-Heavy mice. Pigment Cell Res 5:335-339, 1992.

- Tripathi RK, Hearing JV, Urabe K, Aroca P, Spritz RA.
Mutational mapping of the catalytic activities of human tyrosinase. J Biol Chem 267:23707-23712, 1992.

- Tsukamoto K, Jimenez M, Hearing VJ.
The nature of tyrosinase isozymes. Pigment Cell Res Suppl 2:84-9, 1992.

8. Melanoma and other pigmented tumours

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Differences in the post-translational modification of proteins by polyamines between weakly and highly metastatic B16 melanoma cells. Int J Cancer 53:792-797, 1993.

- Chetty R, Clark SP, Taylor DA.
Pigmented pheochromocytomas of the adrenal medulla. Hum Pathol 24:420-423, 1993.
Abstract: Three primary pigmented pheochromocytomas of the adrenal gland are presented. The pigment in all cases proved to be melanin. Two of the pheochromocytomas were sporadic and histologically typical, except for a focal spindle cell configuration in one. It is believed that the morphologic appearance of these tumors represents divergent differentiation from neural crest, expressing typical pheochromocytoma (polygonal cells) and melanocytic features (melanin pigment).

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Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) in the duodenum: the first visceral case. Histopathology 22: 255-259, 1993.

- El Gamoussi R, Threadgill MD, Prade M, Stratford IJ, Guichard M.
Relationship between the melanin content of a human melanoma cell line and its readiosensitivity and uptake of pimonidazole. Cancer Chemother. Pharmacol. 31:277-282, 1993.

- el Gamoussi R, Stratford IJ, Guichard M.
Relationship between intracellular concentration and radiosensitizing effect of pimonidazole and etanidazole on two human melanoma cell lines. Int J Radiat Biol 63:27-36, 1993.

- el Gamoussi R, Threadgill M D, Prade M, Stratford IJ, Guichard M.
Relationship between the melanin content of a human melanoma cell line and its radiosensitivity and uptake of pimonidazole. Cancer Chemother Pharmacol
31:277-282, 1993.
Abstract: The intra-cellular uptake ofthe weakly basic radiosensitiser pimonidazole (PIMO) was determined as a function of the pigmentation of Na11+ human melanotic melanoma cells in vitro. Two experimental conditions were considered: exponentially growing cells (Exp.) and plateau-phase cells (Pl.). The melanin content of Na11+ cells ranged from 500 micrograms/g cell weight in exponentially growing cells to 6000 micrograms/g in heavily pigmented plateau-phase cells. Cells were exposed to PIMO (medium dose, 0.2 mmol/dm3; 58.2 micrograms/ml). The intra-cellular concentration ranged from 163 micrograms/g in Exp. to 900 micrograms/g in pigmented Pl.; the latter being equivalent to an intra-to extracellular concentration ratio (Ci/Ce) of 17. However, this increase in the cellular uptake of PIMO was not accompanied by an increase in radiosensitising efficiency. In comparison, the Ci/Ce for etanidazole (ETA), a radiosensitiser that is uncharged at physiological pH, remained approximately constant at 1 for all values of melanin contents. Treatment of Na11+ tumours in vivo with [3H]-PIMO resulted in a tumour:blood ratio of about 3 at 30-60 min after administration.However, at 24 h a grain count of label

derived from [3H]-PIMO showed picnotic areas of tumours contained levels that were some 40 times greater than the background value. This high level oflabel was coincident with areas of highest apparent melanin content. In conclusion, PIMO accumulates in very heavily pigmented melanoma cells present in necrotic zones with picnosis. As these cells are probably non-clonogenic, PIMO is not suitable for use in melanoma-

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Effects of interferons and cytokines on melanoma cells. J Invest Dermatol 100:239, 1993.

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Milky spots as the implantation site for malignant cells in peritoneal dissemination in mice. Cancer Res 53: 687-692, 1993.

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Exploitation of pigment biosynthesis pathway as a selective chemotherapeutic approach for malignant melanoma. J Invest Dermatol 100:231, 1993.

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Cytologic diagnosis of metastatic malignant melanoma of the lung in sputum and bronchial washings. A case report. Acta Cytol 37:403-408, 1993.

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Cellular accumulation of 18F-labelled boronophenylalanine depending on DNA synthesis and melanin incorporation: a double-tracer microautoradiographic study of B16 melanomas in vivo. Br J Cancer 67:701-705, 1993.

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Occurrence of melanin in pheochromocytoma. Mod Pathol 6: 175-178, 1993.

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Is the argon laser contraindicated in the summer? Hautarzt 44:248, 1993.

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Agminate blue nevus combined with lentigo. A variant of speckled lentiginous nevus? Am J Dermatopathol 15:162-165, 1993.

- Matsuno A, Hashizume K, Suzuki K, Tsuzuki N, Shibayama E, Ishikawa H.
A case of primary intracranial malignant melanoma showing leptomeningeal dissemination. No To Shinkei 44:935-939, 1992.
Abstract: A 28-year-old woman was hospitalized in drowsy state with signs of increased intracranial pressure. CT scans revealed diffuse increased density with marked enhancement in the subarachnoid space, as well as ventricular dilatation. V-P shunt operation was performed to control intracranial pressure. Repeated cytological examinations of CSF couldn't determine the tumor origin. CT scan of thoracic spine showed a cystic tumor in its dorsal aspect. T2-weighted MRI revealed multiple spotty low intensity, specific to melanin granules, throughout the whole spine. Her thoracic spine was explored, and the intradural tumor was partially removed. Histopathological examination revealed the tumor cell which had dark nucleus with conspicuous nucleolus and cytoplasmic granules. These findings were compatible with malignant melanoma. Her general condition were deteriorated progressively and she died about 5 months after her admission. Postmortum examination showed diffuse leptomeningeal invasion of dark tumor throughout the entire central nervous system, and metastasis to peritoneum and omentum via V-P shunt system. Histopathological examination proved the tumor to be malignant melanoma. Electrone microscopic examination also revealed melanosome in the cytoplasm. Primary intracranial malignant melanoma is divided in two groups, nodular type and leptomeningeal type. In the latter type, early diagnosis is very difficult, just as in our case, because only a little tissue specimen can be obtained. In a case of leptomenigeal carcinomatosis, possibility of primary malignant melanoma, though rare, should always be kept in mind, and specific staining such as Fontana-Masson's staining should be tried.

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Molecular strategies of melanoma progression. Acta Med. Rom. 30:232-234, 1992.
Abstract: On the basis of studies on the interaction between DNA and intermediates of melanin synthesis and on

the leakage of active oxygen or cytotoxic intermediates within liposome models of melanosomes, a model to explain melanoma clonogenicity is presented. Exptl. evidence obtained with toad embryo melanosomes shows that at pH 5.6 active oxygen is accumulated.

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Blue nevus of the prostate. Actas Urol Esp 17:130-131,1993.

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Enhancement of pulmonary metastasis formation and gamma-glutamyltranspeptidase activity in B16 melanoma induced by differentiation in vitro. Clin Exp Metastasis 11:263-274, 1993.

- Takeyama H, Hoon DS, Saxton RE, Morton DL, Irie RF.
Growth inhibition and modulation of cell markers of melanoma by S-allyl cysteine. Oncology 50:63-69 1993.
Abstract: A sulfur-containing amino acid compound, S-allyl cysteine (SAC), derived from garlic extract inhibited proliferation of nine human and murine melanoma cell line in a dose-dependent manner (1.2-10 mM) assessed by a 3Hthymidine incorporation assay. Three control human lymphoblastoid cell lines were not inhibited by SAC concentrations < 5 mM. Four human melanoma cell lines in a soft-agar assay also showed dose-dependent inhibition of colony formation by SAC. Melanin content was increased up to 95% compared to the same untreated cell lines in these four human melanoma and two B16 murine melanoma sublines. Expression of cell surface gangliosides, cellular-differentiation and transformation markers, decreased after SAC treatment. Significant morphological changes including 'flattening and/or dendritic-like elongations' were also observed. Thus SAC inhibited cellular growth and proliferation and modulated major cell differentiation markers of melanoma. radiotherapy.

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Psammomatous melanotic schwannoma. A new cutaneous marker for Carney's complex. Arch Dermatol 129:202-204, 1993.

9. Eye

- Fukuda M, Sasaki K.
Intraocular penetration of norfloxacin into the pigmented rabbit eye. Atarashii Ganka 10:431-434, 1993.
Abstract: The method of melanin-bound norfloxacin (NFLX) extn. from the iris-ciliary body was studied in pigmented rabbit eyes, and the intraocular dynamics of NFLX were examd. in albino and pigmented rabbit eyes. Strong alkali (6N KOH) was useful as an extn. solvent in measuring the NFLX concn. in the iris-ciliary body of the pigmented rabbit eye. Using both local and systemic administration, the concn. of NFLX in the iris-ciliary body of the pigmented rabbit eye was 10 times higher than that in the albino rabbit eye. Therefore, it is important to choose the most appropriate exptl. animals for basic studies.

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A histological and electronmicroscopic study of intracorneal melanin in benign and malignant melanocytic lesions. Histopathology 22:169-172, 1993.
Abstract: Intracorneal melanin is a feature quite frequently encountered in a range of melanocytic lesions, yet has rarely been described in the literature. We examined a variety of melanocytic lesions with increasing degrees of melanocytic atypia for this feature. The distribution and amount of intracorneal melanin is described and it was shown to be entirely within keratinocytes. In general, the amount of intracorneal melanin was related to increasing melanocytic atypia and was typically distributed in a disorderly fashion in malignant lesions.

- Oguz V, Korman U, Pazarli H, Demiroglu U, Kaner G, Altug A.
Malignant melanoma of the choroid in vivo. Comparative biometry using RX scanner and MRI. J Fr Ophtalmol 16: 75-79, 1993.
Abstract: Uveal melanomas are unique among the malignant tumors of the eye investigated by MRI in that both T1 and T2 are relatively shortened due to the paramagnetic effect of melanin. Bearing in mind this property, we conducted a comparative study between MRI and CT in 11 patients with histologically proven choroidal malignant melanoma. The results of this study confirm that MRI is far superior to CT in both differential diagnosis and in determining the extent of the tumor which is crucial if conservative treatment is to be undertaken.

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X-ray microanalysis of ocular melanin in pigs maintained on normal and low zinc diets. Exp Eye Res 56:63-70, 1993.

10. Other

- Inoue S, Matsumura K, Nishihara M, Misaki M
Pharmacokinetics of lomefloxacin in human aqueous humor, with special reference to its melanin binding. Atarashii Ganka 10:87-90, 1993.
Abstract: Lomefloxacin was administered orally at a dose of 200 mg, twice a day for 3 days, and its concns. in the aq. humor and serum were measured for 1-184 h after the end of administration. By 6 h, the concns. in both media had reached their peaks, at 1.37 .mu.g/mL in the aq. humor and 2.38 .mu.g/mL in the serum (aq. humor/serum ratio 57%). At 12 h, the ratio increased to 73%, and after 24 h, it went beyond 100%; i.e., at 24 h 119%, 48 h 217% and 72 h 387%. At 96 h, lomefloxacin was not detectable in the serum, whereas 0.15 .mu.g/mL remained in the aq. humor. It disappeared from the aq. humor only after 120 h. The apparently contradictory pharmacokinetics of lomefloxacin in human aq. humor may be explained by its melanin binding in the iris and ciliary body which act as a reseroir. In discussing the pharmacokinetics of fluoroquinolones in the eye, special regard should be given the fact that these agents have a strong affinity for melanin pigment, with a great amt. being absorbed by the uveal pigment.

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Liposomes can specifically target entrapped melanin to hair follicles in histocultured skin . In Vitro Cell Dev Biol 29A:192-194, 1993.

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Prospective problems of developing new lightening cosmetics and sun care products in 1990's. Fragrance J. 21:57-67, 1993.
Abstract: A review with 41 refs. on the effect of UV-light on human skin and the development of sunscreens and skin-lightening cosmetics. UV-ray absorbers (e.g. p-aminobenzoic acid, octyl p-methoxycinnamate), tyrosinase inhibitors (e.g. kojic acid), and melanin formation inhibitors (e.g. ascorbic acid phosphate Mg salt) are discussed.

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Effect of melanin, oxyhemoglobin and bilirubin on transcutaneous bilirubinometry. Acta Paediatr 82:19-21, 1993.
Abstract: To determine the effect of skin pigments on transcutaneous bilirubinometer readings, we measured the effect of bilirubin, melanin, and oxyhemoglobin solutions on transcutaneous bilirubinometer readings in vitro. Our results showed that the variability of the readings in vitro was related to the instrument's non-linear response to bilirubin and melanin concentration and an inaccurate oxyhemoglobin correction factor. These factors should be considered in developing a more accurate non-invasive method of monitoring serum bilirubin concentration.

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Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents. Laryngoscope 103:1-52, 1993.

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Protolytic properties of phytomelanin pigments of Helianthus annuus. Khim. Prir. Soedin.:856-858, 1991.
Abstract: Standardization of pharmaceutical prepns. of phytomelanins requires structural differentiation of H+-generating O-contg. polymol. functional groups, having a copolymeric structure. Detn. of protolytic equil. of H+-, NH4+- and Na+-forms of phytomelanins from sunflower hulls in pH 3-12 aq. solns. permitted discrimination using ionization consts., pK, and mass proportion. The pigment was a copolymer of the products of oxidative destruction of flavan-3,4-diols. The method may be used for the control of manuf. and quality checking.

ANNOUNCEMENTS & RELATED ACTIVITIES

Melanins and Melanogenesis

Giuseppe Prota

Universita Degli Studi di Napoli Federico II
Dipartimento di Chimica Organica e Biological, Italy

October 1992, 277 pp., isbn 0-12-565970-9
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This book focuses on all aspects of melanin pigmentation, providing a concise, comprehensive picture of new knowledge gained at the frontiers of research. It draws heavily on the authors's 30-year activity in the field and his continuing work with specialists of widely diverse disciplines. The core of the book deals with the structure, physicochemical properties, and biosynthesis of the major classes of melanin pigments, including neuromelanins. Other discussions include the biology of the various types of pigment producing cells, the structure and mode of action of tyrosinase, and the chemistry of urinary melanogens and their biomedical applications as metabolic markers of melanocyte activity, especially for the follow-up of malignant melanoma. Finally, the book considers progress in the photobiology and photochemistry of melanins, with special emphasis on the controversial role of these pigments in skin photoprotection. This book is ideally suited as a basic guide for newcomers, and a handy source of specific information for practioners in academic, medical and industrial settings.

CONTENTS : An Introduction to Melanin Research. Melanin Producing Cells. Tyrosinase. Natural and Synthetic Melanins. Eumelanins. Neuromelanins. Pheomelanins and Trichochromes. Pigment Cell Metabolism. Enzymatic and Chemical Control. Genetic and Hormonal Regulation of Melanogenesis. Photobiology and Photochemistry of Melanogenesis. Chapter References. Subject Index. List of Abbreviations.

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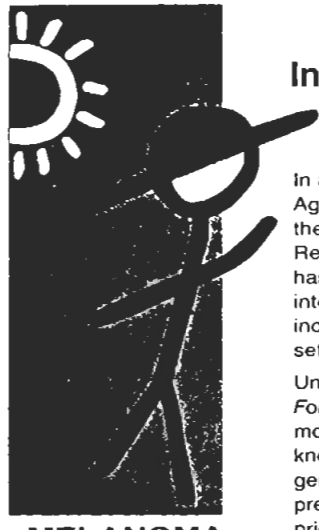
International Melanoma Conference

Brisbane, April 1994

The primary aim of this meeting is to identify appropriate directions of melanoma research, in plenary session on major topics and in subsequent discussion groups. This will involve the distinguished researchers listed, several more who have accepted since the brochure was printed, and some Australian speakers. However, we also intend to hold symposia, and proffered paper and poster sessions, hopefully but not necessarily linked to the plenary topics. The themes of these sessions will depend to a large extent on the interests of the people who attend. We hope to attract a wide range of interests, including postgraduate students, basic researchers, pathologists, clinicians and epidemiologists, and have them interact as much as possible. April is an ideal time to visit the subtropics and this area has much to offer in scenic trips close to Brisbane (beaches, rainforests, tropical agriculture) and, further north, the Great Barrier Reef. Some might be interested in seeing the melanomas on our homegrown animal model, goats (if available at the time).

The conference and "official" accommodation will be in the Sheraton Hotel, Brisbane; details will be available in the next circular, so request it from the conference secretariat.



MELANOMA
THE WAY
FORWARD

International Melanoma Conference

In association with the International Agency for Research on Cancer and the European Society for Pigment Cell Research, the Queensland Cancer Fund has invited prominent national and international experts to review the rising incidence of malignant melanoma and set the challenges for the future.

Under the theme *Melanoma – The Way Forward*, the conference will review the most important areas of advancing knowledge in melanoma biology, genetics, aetiology, clinical care and prevention. Recommendations for high priority activities over the next 5-10 years in respect of research, development, and implementation at both clinical and population levels will be formulated.

Confirmed Speakers

- Dr Anthony Albino, Ph.D., Laboratory of Mammalian Cell Transformation, Memorial Sloan- Kettering Cancer Centre, New York, USA
- Dr Bruce Armstrong, International Agency for Research on Cancer, Lyon, France
- Dr Natale Cascinelli, National Institute for the Study and Treatment of Tumours, Milan, Italy.
- Dr Nicholas Dracopoli, Ph.D., Centre for Genome Research, Massachusetts Institute of Technology, USA
- Professor Meenhard Herlyn, Program of Experimental Therapeutics, The Wistar Institute, Philadelphia, USA
- Professor Hubert Pehamberger, University of Vienna, Austria
- Professor Giuseppe Prota, University of Napoli Federico II, Naples, Italy
- Dr Richard Setlow, Brookhaven National Laboratory Associated Universities Inc, New York, USA

European Society for Pigment Cell Research

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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5th MEETING PANAMERICAN SOCIETY FOR PIGMENT CELL RESEARCH

Sunday, June 26 to Wednesday, June 29, 1994 - Philadelphia, PA.

LIST OF TOPICS

- Differentiation
- Disorders
- Enzymology
- Gene Action
- Hormones
- Melanocytes
- Melanogenesis
- Melanoma
- Molecular Biology
- Neuromelanin
- Regulation
- Water Interactions
- Your Suggestion

LIST OF FEATURED SPEAKERS

V. Adrian Parsegian
National Institutes of Health
Bethesda

Barbara Gilchrist
Boston University
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Beatrice Mintz
Fox Chase Cancer Center
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5th MEETING of the EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

Vienna, October 19-22, 1994.

SCIENTIFIC PROGRAM

*** Guest Lectures, Scientific Sessions, Satellite Symposia, Poster Sessions**
*** Guest Lectures include the following topics**
Melanocyte Biology and Regulation of Melanogenesis
Growth Factors and Signal Transduction of Melanocytes
Oncogenes and Tumor Suppressor Genes in Melanoma
Immune Surveillance and Immunological Treatment Strategie for Melanoma
Melanoma Progression and Metastasis
*** Scientific Sessions will deal with**
Biophysics of Melanins
Regulation of Melanogenesis
Growth Control of Melanocytes
Photobiology of Melanocytes
Disorders of Pigmentation
Moles: Typical and Atypical
Diagnosis and Diagnostic Markers of Melanoma
Melanoma Immunology
Systemic Therapy of Melanoma
Photoprotection
*** Satellite Symposia**
Interferons in Melanoma
Cytokines in Melanoma
Photoprotection
*** Poster presentations will form an important and integral part of the overall** program-opportunities to present results in open forum

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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 are 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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