PIGMENT CELL RESEARCH BULLETIN

PUBLISHED BY THE EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

N° 12 - April 1991

Editor: Professor F. Serri, Foundation for research in Dermatology, Catholic University, Largo A. Gemelli 8, 00168 Rome, Italy. Phone: 06-338.54.51 Fax: 06-305.13.43
Editorial Office: Dr G. Ghanem (Assit. Edt), C. Henrotte (Production Assist.), Lab. of Oncology and Exp. Surgery, Institut J. Bordet, Rue Heger-Bordet 1, 1000 Brussels, Belgium. Phone: 32-2-539.23.43 Fax: 32-2-537.47.34

CONTENTS

Review *Molecular biology of melanogenic proteins*
Hearing V.J. *188*

Commentary *Pigment Cell Research : Editor's Report*
Bagnara J.T. *196*

Review of the literature *198*

1. Melanins and other pigments chemistry *198*
2. Biology of pigment cells and pigmentary disorders *202*
3. MSH, MCH, other hormones, differentiation *205*
4. Photobiology and photochemistry *206*
5. Neuromelanins *207*
6. Genetics *208*
7. Tyrosinase and other enzymes *211*
8. Melanoma *211*
9. Eye *214*
10. Other *215*

Call for contributions *216*

Announcements and related activities *219*

Periodico quadrimestrale della European Society for Pigment Cell Research (Associazione Europea per la Ricerca sulla Cellula Pigmentaria), realizzatto con il contributo della Fondazione Pro Ricerca Dermatologica e della Pfizer Italiana.
Direttore Responsabile: Prof. Giuseppe Prota, Presidente ESPCR, Dip. di Chimica Organica e Biologica, Università di Napoli, Via Mezzocannone 16, 80134 Napoli.
Autorizzazione del Tribunale di Napoli n. 3684 dell'11/12/87.

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

Review

Molecular biology of melanogenic proteins

Vincent J. Hearing
Laboratory of Cell Biology, National Cancer Institute,
National Institutes of Health, Bethesda, MD 20892 USA

The 14th meeting of the IPCC held recently in Kobe, Japan (chaired by Dr Y Mishima) gave heavy emphasis to topics concerning the molecular biology of pigment cells; this was reinforced by a Molecular Biology Symposium held immediately thereafter in Sendai (chaired by Dr T Takeuchi). It is the purpose of this review to provide an overview of research in this field, and perhaps supply some insight as to where such studies might be heading. The field of molecular biology encompasses many different disciplines and approaches, but at this time primarily revolves in pigment cell research around two broad classes of genes, i.e. oncogenes and pigment-related genes. Studies on both have examined the expression, structure, and function of these genes, the effects of various mutations on the properties of their encoded proteins, and their effects on cells following transfection. In this review, I will confine my summaries and comments to the pigment-related genes.

As we all know, tyrosinase represents a critical regulatory point in the pathway of melanin formation, and is the key lesion in many types of albinism. Because of its prominent role in the modulation of visible pigmentation, and its potential application as a genetic marker, there has been tremendous interest in the cloning of its gene. The genes for tyrosinases from lower species [1-3] had been available for some time, and have served as useful tools for structural and functional studies; however, since primary sequence data for mammalian tyrosinase was not available, the direct approach of synthesizing probes by which the mammalian gene could be identified and isolated could not be used. Various laboratories used different alternative and indirect approaches for cloning the tyrosinase gene, and several candidate clones were obtained from murine and human systems [4-8]. Interestingly and unexpectedly, several putative but distinct clones were identified which shared significant sequence homology. More importantly, each of those clones encoded proteins that had many properties predicted for tyrosinase, including melanocyte specificity, the correct size (i.e. ~60-70 kD), a transmembrane region, two potential copper binding domains, multiple glycosylation sites, and so on

[reviewed in 9]. Much of the research currently being pursued revolves around identifying mutations which affect the functions of those gene products, and how those encoded proteins normally interact to regulate melanin production.

The Albino Locus Gene

Structure: The albino locus has historically been proposed as the structural locus for tyrosinase. This interpretation results from the dramatic lack of pigment produced by mutations at that locus, but is not consistent with studies demonstrating significant tyrosinase activity in several of those albino mutants [cf 9 for review]. cDNAs which mapped to the albino locus were originally cloned from murine [7] and human [6] melanocytes; the original sequence reported for the murine gene was a prematurely truncated version of the full length transcript - the full sequence has been subsequently published [10-12]. The albino gene in mice (and its human homologue) is composed of 5 exons and 4 introns, and is predominantly untranslated material. In mice the gene is ~70 kb [13] and in humans it is >35 kb [17], while the processed mRNAs are ~2.4 kb in length; thus the precursor mRNA synthesized must be processed to delete the introns. This process does not always occur accurately, and misspliced mRNAs (10 to 40% of the total) are generated which translate into altered proteins [13-15]. This may represent an important regulatory step since those altered proteins are apparently not competent catalytically as tyrosinase, although whether they fulfill some other role in the melanocyte has yet to be determined. Although the albino gene is present as a single copy (chromosome 7 in mice, chromosome 11 in humans), it has been shown by in situ hybridization [16] that there is a second site (on human chromosome 11) that is partially homologous. This second site has now been shown to be a pseudogene [17] composed of exons 4 and 5 of the authentic sequence. The fact that the protein encoded by the albino locus is expressed in melanocytes as a single chain with the amino and carboxy termini predicted by the nucleic acid sequence has been confirmed using antibodies generated against synthetic peptides which correspond to those sequences [18].

Function: The ability of the protein encoded by the albino gene to function as tyrosinase has now been shown by several approaches. Initially, transfection of the gene into tyrosinase deficient cells resulted in the expression of tyrosinase activity [10,19]; not only was it shown that the full length and correctly spliced mRNA encoded active tyrosinase, but that several aberrantly spliced mRNAs encoded proteins that were catalytically incompetent [10]. In subsequent studies, minigenes (which contain the tyrosinase coding sequence as well as a competent regulatory sequence) were used to produce transgenic mice [20-22]. Although the transgenic animals were not fully and normally pigmented, there were dramatic increases in pigmentation and it was shown that the pigmentation was restricted to melanocytes. Since the regulatory sequence used to construct the minigene was derived from the authentic 5' flanking region of the tyrosinase gene, that regulatory sequence is thought to be critical and sufficient for the tissue specific expression of tyrosinase. The ability of the albino-locus encoded protein to function catalytically as tyrosinase has also been shown by immunopurification protocols [18,23]. At this time, I believe that all laboratories would agree that the albino locus encoded protein is tyrosinase, and that its function is crucial to the production of pigment; whether it is the sole protein which can perform as a tyrosinase, and exactly how it interacts with

other melanogenic proteins is still under discussion. It is also interesting to note that while expression of albino locus encoded tyrosinase seems to be necessary for pigment production, it is not the only determininant, since many melanocyte lines with normal expression of the tyrosinase mRNA and/or protein are unpigmented [10,19,24]. Similarly, while melanogenic agents which stimulate pigmentation (such as αMSH) typically increase the transcription and translation of the albino gene 2 to 3-fold [11,25], such stimulations are not sufficient to explain the much greater increases in tyrosinase activities noted, suggesting that other control points in the pathway are also critical to the regulation of melanogenesis.

Mutations: The characterization of mutations, be they natural or mutagen induced, on the structure and function of proteins encoded by the mutated gene can provide important insights into the mechanisms of biologic processes. This is most obvious with mutations at the albino locus, which lead to dramatic changes in pigmentation; initial studies in this field depended on animal models, but recently, melanocyte cell lines derived from coat color mutants have become available for study [26,27]. Studies with these cells have demonstrated that heterokaryons of brown and albino mutant cell lines produce normal black pigment, showing that these genes are complementary in culture, thus opening the door for future studies on their interactions in vitro [27]. Other studies on mutations at the albino locus (including Himalayan and chinchilla) have shown that such mutations result in the production of tyrosinases with significantly altered properties. With the albino mutation, catalytic activity is virtually quantitatively lost, while with the Himalayan mutation, there is an alteration in glycosylation which results in a temperature sensitive phenotype; with the chinchilla mutation there is an increased sensitivity to proteolytic inactivation, and thus a decrease in enzyme function [26]. The mutations that elicit these changes are now being detailed in mice [20,28-30] and should be invaluable in the future for understanding the functional properties of the enzyme. Perhaps the most dramatic recent revelation has been the characterization of the exact amino acid change which is responsible for the albino phenotype; it is a point mutation which results in the change of a conserved cysteine to a serine in the first cysteine-rich domain of tyrosinase [31]. This single change in primary structure causes the virtually quantitative loss of catalytic function, although the exact reason (i.e. alteration in secondary structure, loss of metal binding activity, etc.) has not yet been determined. However, in light of the virtually identical nature of the point mutation causing the brown phenotype (cf below), there can be no doubt that future studies will be intensely directed at this domain of tyrosinase which appears to be so critical to its activity. All strains of albino mice examined had this same mutation suggesting that all were derived from the same initial mutation [31]. Naturally there has been tremendous interest in defining mutations which are critical to tyrosinase activity in humans. To date, many different mutations in oculocutaneous albinos have been described, all of which appear to result in loss of tyrosinase activity and thus in melanin production. Space considerations don't allow a thorough discussion of the mutations described to date, other than to say that they now number in the dozens, occur at various areas on the enzyme (i.e. they are not confined to a single region or domain), and result from a variety of mechanisms, including point mutations and insertions, which occur in the structural or the promoter region of the gene [32-36]. In both humans and mice, polymorphisms have been described (these are nondestructive point mutations which do not demonstrably alter enzyme function) as well as the mutations noted above.

It is obvious from the meetings held in Japan that many groups are currently working on defining: (1) the exon-intron structures of the genes, (2) mutations which lead to various forms of coat color mutations, (3) the structure of the regulatory regions (functional promoters and enhancer-like elements), and (4) mechanisms of splicing and aberrant splicing. Of particular interest, a minigene has been created [37] with only 1 kb of human tyrosinase 5' flanking sequence, which was fused with murine structural locus and used to create transgenic mice. This resulted in pigmentation of the mice only in melanocytes, suggesting that there is a common or highly similar mechanism between gene regulation in mice and humans; this sequence is located in the 5' flanking region. Several groups [38,39] have described more than 12 different genetic mutations in the tyrosinase gene; these cluster in a non-random fashion, but are not localized to any distinct area. Two new mutations were described [40] for type 1B OCA (yellow) which are novel; the defect is either within an intervening sequence of tyrosinase gene, or distant to it. A point mutation in the human gene was also described [41] which results in a temperature sensitive tyrosinase which is analogous to the Himalayan mutation in mice.

TRP1: The Brown Locus Gene

Structure: The first cloned pigment related gene proposed to be the structural locus for tyrosinase [4] was quickly mapped to the brown locus on chromosome 4 in mice [8,42]. The structure and organization of this gene is similar to the albino gene, and the predicted protein has all of the features noted above which would be predicted for tyrosinase [cf 9 for review]. There is only a single copy of this gene in the genome, and the analogous gene has now also been found in humans and cloned [43,44]. In general there is about 90% sequence identity between the brown protein expressed by murine and human melanocytes (this is similar to the conservation found between murine and human tyrosinase), and there is about 55% nucleic acid identity overall between the brown and albino genes (and about 43% primary sequence identity). The conservation of residues is much higher in several areas of the proteins which are thought to be important to their structure and/or function (such as the copper binding and cysteine rich domains) and is almost completely lost elsewhere, such as in the transmembrane region and cytoplasmic determinant at the carboxyl termini of the proteins. Interestingly, although the brown locus gene (~18 kb in mice) is broken up into 8 exons and 7 introns [45], no data has yet been reported which suggests that alternative processing occurs with this gene, as it does with the albino gene.

Function: The specific function of the brown locus encoded protein is not altogether clear as yet. Phenotypically, we can see that a mutation at this locus causes the production of brown rather than black melanin, but what this means chemically and/or enzymatically is as yet undefined. Nevertheless, it is obvious that whatever the role of the brown protein, it must somehow elicit the production of black (vs. brown) melanin in wild-type animals. The brown protein has been postulated by various groups to be: (a) DOPAchrome tautomerase (nee DOPAchrome conversion factor or oxidoreductase) [8], (b) Dihydroxyindole conversion factor [10]; (c) a melanosomal specific catalase [23]; or (d) another tyrosinase [18,46]. Although my laboratory favors the latter possibility (in fact we presented evidence at these meetings that this protein acts synergistically to

stimulate the albino locus encoded tyrosinase), the substrates and products of reactions catalyzed by the brown protein have not yet been identified conclusively, and the question remains open at this time. It has become evident that the brown protein is present in a higher quantity (typically ~10-fold) in melanocytes as compared to the albino protein; it is also expressed in similar quantities by human melanocytes [44,47]. As far as I know, a human mutation of the brown locus has not yet been identified, but surely will be before long, now that the human gene has been cloned and sequenced. It is also an indication of the important function of this protein that there is typically a better correlation of its expression with visible pigmentation than there is with the expression of the albino protein. As noted above, the brown and the albino loci complement each other [27].

Mutations: There are multiple mutations at the brown locus in mice, and several of them are currently under active study (including cordovan and light) [48,49]. As with the albino mutation, the critical molecular lesion resulting in the brown phenotype has been identified [49], and it results from a point mutation leading to the replacement of a conserved cysteine residue with a tyrosine. This critical replacement occurs in the first cysteine-rich domain of the protein, at a residue only 3 amino acids away from the critical cysteine mutation that occurs in albino mice. This could perhaps be coincidence, but in light of the recent proposal [23] that these cysteines may be involved in an iron binding site, the importance of this domain to the structure and function of these pigment-related proteins is sure to draw much interest in the coming years. It is an important feature to note that, as with the basic albino mutation, all brown mice from numerous different strains have the same mutation, suggesting that all brown mice derive from the same original mutation [8].

TRP2: The Slaty (?) Locus Gene

The clone originally identified by Jackson (termed 5A [8]) which was initially thought to be identical to the brown locus gene, has now been identified as a distinct gene, but one which shares significant sequence homology to tyrosinase [50]. This gene has been mapped to chromosome 14 and tentatively assigned to the slaty locus, and has common features with the genes discussed above, including a transmembrane region, highly conserved putative copper binding sites, two conserved cysteine-rich domains, potential glycosylation sites and a signal peptide. The size of the protein encoded by this gene (~75-80 kD) is somewhat larger than the products of the albino and brown loci (unpublished). The function of this gene is currently unknown.

Pmel 17-1: The Silver (?) Locus Gene

This clone was originally termed Pmel17-1 [6]; the expression of its mRNA was specific for melanocytes, could be induced with MSH (again ~2-fold) or IBMX, and its abundance correlated well with pigmentation [5]. It was known that the protein encoded by this gene was homologous to the albino locus, and it has been reported that the encoded protein has a predicted molecular weight similar to tyrosinase (~70 kD), and also had putative glycosylation sites and a transmembrane region [51]. There is

approximately 95% identity between the sequence of the human and the murine protein. This gene has been mapped to chromosome 12 in humans and to chromosome 10 in mice, and has been tentatively assigned to the silver locus of mice. The function of this protein is also unknown.

Final Comments

The molecular biology of pigmentation is becoming both more interesting and complex every minute. The plethora of genes belonging to a tyrosinase family was totally unexpected and has underscored the complexity of the regulation of mammalian melanogenesis -a process once thought to be a simple one enzyme:one product system. The next several years will see the characterization of even more pigment related genes, since clones have now been derived from the agouti, dilute and pink-eyed dilution loci, and more information should soon be forthcoming from those gene sequences. I would expect the following types of studies to provide interesting new approaches to elucidating the regulatory controls of mammalian melanogenesis in the immediate future:

A) What are the critical regulatory elements within the tyrosinase gene which control the tissue specific and timely expression of these pigment related genes? Recent studies have begun to describe the promoters and enhancer-like elements which may be critical to the regulation of the expression of these tyrosinase-related genes [52-54].

B) Does alternative splicing play a role in the regulation of tyrosinase activity? We now know that responses of melanocytes to environmental stimuli involve increased levels of transcription and translation of the albino and brown loci, but not enough to explain the dramatic increases in melanin production by those cells. This suggests either that post-tyrosinase factors are important to controlling melanin production and/or that the accuracy of processing of precursor mRNA might improve, leading to increases in functionally competent enzyme(s).

C) What are the catalytic functions of these cloned gene products and how do they interact to determine melanogenic function? Such studies are underway using many different approaches in a variety of laboratories.

D) What are the intracellular processing and delivery pathways involved in the delivery of these gene products to the melanosome? Are all of these melanogenic proteins transported to the melanosome en masse within the vesicles, or are they segregated in different vesicles and combined only following their arrival at the melanosome? The latter pathway would provide a potential mechanism whereby melanogenesis might be delayed until all melanogenic factors are in place in the melanin granule; preliminary evidence supporting this was presented at the meeting by Drs. Jimbow and Boissy.

E) What roles do melanogenic inhibitors and post-tyrosinase factors play? These points of regulation have gained added significance in light of what we now know about the regulation of gene expression as noted above, and the variety of post-tyrosinase

'factors' which play a role in the determination of melanin formation.

The next International meeting in London (chaired by Dr. Riley) in 1993, and indeed the intervening Regional meetings, should provide us with exciting new developments in these areas in the future.

References

1. Bernan V, Filpula D, Herber, W, Bibb M, Katz E: Gene, 37, 101-110, 1985
2. Huber M, Hinterman G, Lerch K: Biochem, 24, 6038-6044, 1985
3. Kupper U, Niedermann DM, Travaglini G, Lerch K: J Biol Chem, 264, 17250-17258, 1989
4. Shibahara S, Tomita Y, Sakakura T, Nager C, Chaudhuri B, Muller R: Nucl Acids Res, 14, 2413-2427, 1986
5. Kwon BS, Halaban R, Kim GS, Usack L, Pomerantz SH, Haq AK: Mol Biol Med, 4, 339-355, 1987
6. Kwon BS, Haq AK, Pomerantz SH, Halaban R: Proc Natl Acad Sci USA, 84, 7473-7477, 1987
7. Yamamoto H, Takeuchi S, Kudo T, Makino K, Nakata A, Shinoda T, Takeuchi T: Jpn J Gen, 62, 271-274, 1987
8. Jackson IJ: Proc Natl Acad Sci USA, 85, 4392-4396, 1988
9. Hearing VJ, Jiménez M: Pigment Cell Res, 2, 75-85, 1989
10. Kwon BS, Wakulchik M, Haq AK, Halaban R, Kestler D: Biochem Biophys Res Commun, 153, 1301-1309, 1988
11. Müller G, Ruppert S, Schmid E, Schütz G: EMBO J, 7, 2723-2730, 1988
12. Terao M, Tabe L, Garattini, Sartori D, Mintz B: Biochem Biophys Res Commun, 159, 848-853, 1989
13. Ruppert S, Muller G, Kwon BS, Schütz G: EMBO J, 7, 2715-2722, 1988
14. Shibahara S, Tomita Y, Tagami H, Muller RM, Cohen T: Tohoku J Exp Med, 156, 403-414, 1988
15. Porter S, Mintz B: Gene, (in press) Jan, 1991
16. Barton DE, Kwon BS, Francke U: Genomics, 3, 17-24, 1988
17. Takeda A, Matsunaga J, Tomita Y, Tagami H, Shibahara S: Tohoku J Exp Med, 159, 333-340, 1989
18. Jiménez M, Tsukamoto K, Hearing VJ: J Biol Chem, 266, 1147-1156, 1991
19. Bouchard B, Fuller BB, Vijayasaradhi S, Houghton AN: J Exp Med, 169, 2029-2042, 1989
20. Yamamoto H, Takeuchi S, Kudo T, Sato C, Takeuchi T: Jpn J Gen, 64, 121-135, 1989
21. Beermann F, Ruppert S, Hummler E, Bosch FX, Müller G, Ruther U, Schütz G: EMBO J, 9, 2819-2826, 1990
22. Tanaka S, Yamamoto H, Takeuchi S, Takeuchi T: Development, 108, 223-227, 1990
23. Halaban R, Moellmann G: Proc Natl Acad Sci USA, 87, 4809-4813, 1990
24. Tamate HB, Hirobe T, Wakamatsu K, Ito S, Shibahara S, Ishikawa K: J Exp Zool, 250, 304-311, 1989
25. Eller M, Naeyaert JM, Gordon PR, Gilchrest BA: J Invest Dermatol 94, 521, 1990
26. Halaban R, Moellman G, Tamura A, Kwon BS, Kuklinska E, Pomerantz SH, Lerner

AB: Proc Natl Acad Sci USA, 85, 7241-7245, 1988
27. Bennett DC, Cooper PJ, Dexter TJ, Devlin LM, Heasman J, Nester B: Development, 105, 379-385, 1989
28. Kwon BS, Halaban R, Chintamaneni: Biochem Biophys Res Commun, 161, 252-260, 1989
29. Shibahara S, Okinaga S, Tomita Y, Takeda A, Yamamoto H, Sato M, Takeuchi T: Eur J Biochem, 189, 455-461, 1990
30. Takeuchi S, Yamamoto H, Takeuchi T: Biochem Biophys Res Commun, 155, 470-475, 1988
31. Jackson IJ, Bennett DC: Proc Natl Acad Sci USA, 87, 7010-7014, 1990
32. Spritz RA, Strunk K, Oetting W, King R: Nucl Acids Res, 16, 9890, 1988
33. Tomita Y, Takeda A, Okinaga S, Tagami H, Shibahara S: Biochem Biophys Res Commun, 164, 990-996, 1989
34. Giebel LB, Strunk KM, King RA, Hanifin JM, Spritz RA: Proc Natl Acad Sci USA, 87, 3255-3258, 1990
35. Spritz RA, Strunk KM, Giebel LB, King RA: New Eng J Med, 322, 1724-1728, 1990
36. Takeda A, Tomita Y, Matsunaga J, Tagami H, Shibahara S: J Biol Chem, 265, 17792-17797, 1990
37. Tanaka M, Tanaka S, Miura H, Yamamoto H, Kikuchi H, Takeuchi T: Proc XIV IPCC, p113, 1990
38. King RA, Handoko HY, Mentink MM, Oetting WS: Proc XIV IPCC, p115, 1990
39. Spritz RA: Proc XIV IPCC, p66, 1990
40. Giebel LB, Tripathi RK, Strunk KM, Spritz RA: Proc XIV IPCC, p116, 1990
41. Spritz RA, Giebel LB, Tripathi RK, Strunk KM, King RA: Proc XIV IPCC, p116, 1990
42. Bennett DC, Huszar D, Laipis PJ, Jaenisch R, Jackson IJ: Development, 110, 471-476, 1990
43. Cohen T, Muller RM, Tomita Y, Shibahara S: Nucl Acids Res, 18, 2807-2808, 1990
44. Vijayasaradhi S, Bouchard B, Houghton AN: J Exp Med, 171, 1375-1380, 1990
45. Shibahara S: Prog Clin Biol Res, 256, 263-271, 1988
46. Jiménez M, Maloy WL, Hearing VJ: J Biol Chem, 264, 3397-3403, 1989
47. Vijayasaradhi S, Houghton AN: Int J Cancer, (in press), 1991
48. Jackson IJ, Chambers D, Rinchik EM, Bennett DC: Genetics, 126, 451-460, 1990
49. Zdarsky E, Favor J, Jackson IJ: Genetics, 126, 443-450, 1990
50. Jackson IJ: personal communication, 1990
51. Kwon BS, Chintameneni C: Proc XIV IPCC, p89, 1990
52. Takeuchi T: Proc XIV IPCC, p65, 1990
53. Takeuchi S, Yamamoto H, Takeuchi T: Proc XIV IPCC, p114, 1990
54. Ruppert S, Beermann F, Kluppel M, von Langsdorff M, Hummler E, Schmid E, Schütz G: Proc XIV IPCC, p119, 1990

Commentary

PIGMENT CELL RESEARCH
Editor's Report

Joseph T. Bagnara

With the completion of volume 3, it seems appropriate to summarize some of the major events that have transpired during the first three years that **Pigment Cell Research** has been in existence. This is the first report of this type that I have prepared after the completion of a volume and I am now establishing a precedent so that in the future, such a report will be prepared after the last issue of earch year.

As Editor, I consider a major role for **Pigment Cell Research** is to serve the community of scholars and researchers who deal with animal pigments and pigmentation. In particular, we wish to serve those members of the societies which have supported the Journal with their good names, European Society for Pigment Cell Research (ESPCR), Japanese Society for Pigment Cell Research (JSPCR) and PanAmerican Society for Pigment Cell Research (PASPCR). A measure of our service and thir support is attested by the fact that about 90 percent of the manuscripts so far published in regular issues of **Pigment Cell Research** have been authored or co-authored by members of one or more of the soponsoring societies. Of these, approximately 10% have come from Japan, 35% were from the western hemisphere, mostly North America, and of the remaining 55%, most were submitted from Europe. Acceptance of manuscripts has been based solely upon scientific merit and the relative subfield represented by any particular manuscript has had no effect upon its acceptability. This is in keeping with a fundamental aim of **Pigment Cell Research,** to represent the diversity of disciplines that comprise the total area of pigmentation research.

With the obvious relationship between the societies and **Pigment Cell Research,** the growth of the journal has been somewhat linked to the growth of the societies. When **Pigment Cell Research** was founded in 1987, only the ESPCR and the International Pigment Cell Society (IPCS) were in existence. With the evolutionary changes that have taken place with the latter as the JSPCR and the PASPCR came into existence, a formalized and legal agreement between the publisher of **Pigment Cell Research** (Alan R. Liss, Inc.) and the IPCS never materialized. This may have had an effect upon the growth of **Pigment Cell Research**; however, what really did set back the Journal was the puchase of Alan R. Liss, Inc. by John Wiley & Sons in 1988. This led to a period of indecision on the part of Wiley/Liss that had a profound impact upon **Pigment Cell Research.** The journal suffered and the publication of several issues of volume 3 were markedly delayed during the sale of **Pigment Cell Research** to our present publisher, Munksgaard International Publisher, Ltd. (Copenhagen). The sale occurred in February 1990 and the agreement involved a gradual transition of **Pigment Cell Research** production from Wiley/Liss to Munksgaard. The production events were in the hands of McLaurine & Co. and involved the use of the auspices of Wiley/Liss for the first three issues of volume 3. After this, the production of **Pigment Cell Research** has been entirely in the hands of Munksgaard although it continues through the auspices of McLaurine &

Co. which serves a similar function for several other scientific journals which were also purchased by Munksgaard from Wiley/Liss.

I want to emphasize with enthusiasm the fact that we are now in the hands of an excellent publisher which is especially understanding and cooperative. The transition has been smooth and easy and my office has interacted efficiently with that McLaurine & Co. I look forward to a period of growth and success under our new owners, Munksgaard International Publisher, Ltd.

Some statistics on the first three volumes of ***Pigment Cell Research***

Refereed Articles	
Total received	186
Total accepted with revision	141
Total accepted with revision and revised	133
Number of outright rejections	24
Number of outright rejections resubmitted and accepted	4
Total number of articles published	151
Average number of articles per issue	7.1
Average number of pages budgeted per issue	
volumes 1 & 2	72
volume 3	48-64
Total duration of review process per manuscript	25.8 days
Unrefereed Articles	
Number of reviews published	5
Number of reviews rejected	1
Number of symposium articles (two symposia)	34
Programs and abstracts	4
Supplements (to volume 1)	1

****

CURRENT LITERATURE

We acknowledge the valuable assistance of
Ms Linda Albrecht and the financial support
of Lawrence M. Gelb Research Foundation.

1. Melanins and other pigments chemistry

- Ando H, Mishima Y.
Inhibition of melanogenesis by linoleic acid. Fragrance J 18:86-93, 1990.
Abstract : The effect of 10-30.mu.M linoleic acid (LA) was studied in mouse melanoma B16 cells for 3 days. LA decreased tyrosinase activity and suppressed melanin polymer formation within melanosomes. LA activated protein kinase C at 25 .mu.M and inhibited melanogenesis. In in vivo, UVB(1J/cm2, 4 times) induced pigmentation of guinea pig skin. After the radiation, 1%LA in EtOH sol. 0.05mL/day was applied to pigmented skin for 20 days. The pigmentation clearly decreased. Inhibition of melanogenesis, the activation of protein kinase C, and the inhibition of hypermelanosis are discussed.

- Andrzejczyk J, Buszman E, Wilczok T.
Metal ion binding to DOPA-melanin-HSA complexes. Stud Biophys 136:27-36, 1990.
Abstract : By the use of radiochem. and ESR anal., the metal ions binding to synthetic DOPA-melanin and to DOPA-melanin-HSA (human serum albumin) complexes was detd. Isotopes 65Zn, 54Mn, 64Cu, and 59Fe in the chloride form were applied to both types of polymer, and it was shown that HSA significantly modifies the amt. of bound metals. Only Zn was found in higher amt. in the melanin-HSA-Zn complexes compared with protein-free complexes. A decrease in Mn, Cu, and Fe binding to melanin polymers was obsd. in the presence of HSA.

- Aroca P, Garcia-Borron JC, Solano F, Lozano JA.
Regulation of mammalian melanogenesis. I: Partial purification and characterization of a dopachrome converting factor: dopachrome tautomerase. Biochim Biophys Acta 1035:266-275, 1990.
Abstract : A protein that catalyzes the decoloration of dopachrome has been partially purified from B16 mouse melanoma tumors. The enzyme is preferentially associated to the melanosomes, but it is also found in the microsomal and cytosolic fractions of cellular homogenates. The protein is clearly different from tyrosinase, and should be related to the dopachrome oxidoreductase (Barber et al. (1984) J Invest Dermatol 83, 145-149) and the dopachrome conversion factor (Korner and Pawelek (1980) J Invest Dermatol 75, 192-195) since the reaction product of dopachrome conversion is 5,6-dihydroxyindole-2-carboxylic acid. The protein appears to have an oligomeric structure, with a molecular mass slightly higher than 300 kDa estimated by gel filtration, whereas the molecular mass of the monomer might be approx. 46 kDa estimated by SDS-PAGE electrophoresis. Its Km for dopachrome is around 100 microM. The enzyme is competitively inhibited by indoles and is unaffected by metal chelators. It also has the ability to increase the amount of melanin formed from L-tyrosine by melanoma tyrosinase, and therefore, cannot be considered an 'indole blocking factor' as was suggested for the related dopachrome oxidoreductase. Since the reaction catalyzed by the enzyme is a tautomeric shift on dopachrome, we would propose dopachrome tautomerase (EC 5.3.2.3) as the most precise and informative name.

- Bathory G, Szoko E, Magyar K, Deutsch T.

Properties of the melanin binding of p-bromomethylamphetamine (V-111). Pol J Pharmacol Pharm 42:19-27, 1990.
Abstract : The aim of the present study was to obtain detailed information on the binding properties of p-bromomethylamphetamine (V-111) to melanins under in vitro and in vivo conditions. The results obtained by the methods of both equil. and dynamic dialysis revealed that the binding of V-111 to bovine eye melanin was reversible, at least for the part of the binding sites, whereas the dissocn. of V-111-melanin adduct was slow. The binding capacity of 2 different classes of binding sites of bovine eye melanin and dissocn. consts. of the drug-melanin complexes have been detd. The in vivo melanin binding of V-111-1-14C was studied by the method of whole body autoradiog. Extensive accumulation and retention was obsd. in the eyes of the pigmented mice while in the albino animal uptake was low in the corresponding tissues. In conclusion, V-111 may most probably be accumulated and retained for long periods in the pigmented cells of intact animals. The data also imply that melanin in the pigmented cells serves as a depot, which gradually releases V-111 resulting in a prolonged local effect of this compd.

- Clark MB. Jr.
Studies of polymer interfacial structure: (A). Electron and secondary ion mass spectrometry of natural and synthetic eumelanin biopolymers. (B). Electron and vibrational spectroscopy of homopolymer blends. 255 pp., 1989. Avail. Univ. Microfilms Int., Order No. DA9013043 From: Diss., Abstr. Int B 50:5576-5577, 1990.

- D'Ischia M, Napolitano A, Tsiakas K, Prota G.
New intermediates in the oxidative polymerization of 5,6-dihydroxyindole to melanin promoted by the peroxidase/H2O2 system. Tetrahedron 46:5789-5796, 1990.
Abstract : The oxidative oligomerization of 5,6-dihydroxyindole with peroxidase-H2O2 at physiol. pH to give, after acetylation, tetraacetoxybiindolyls I and II and the related trimers III and IV is reported. The peroxidase-H2O2 system is more efficient for the oxidative polymn. then tyrosinase. Aspects of the most probable reaction mechanism are discussed.

- Galvao DS, Caldas MJ.
Theoretical investigation of model polymers for eumelanins. II. Isolated defects. J Chem Phys 93:2848-2853, 1990.
Abstract : Defects in initially ordered polymers of 5,6-indolequinone in different redox forms were studied. The defects included aggregation of the carboxyl radical into one skeleton monomer, the aggregation of a host monomer in a lateral misplaced position, and faults in the polymn. sequencing. Huckel .pi.-electron theory results are compared to the perfect structures studied previously. The results indicate that the end-type defect suggested as an electron capture center is not deactivated by these structural defects, and that new capture centers might be introduced that could also be responsible for the acceptor behavior of melanins.

- Jara JR, Solano F, Garcia-Borron JC, Aroca P, Lozano JA.
Regulation of mammalian melanogenesis. II: The role of metal cations. Biochim Biophys Acta 1035:276-285, 1990.
Abstract : Melanogenesis can be divided into two phases. The first one involves two tyrosinase-catalyzed oxidations from tyrosine to dopaquinone and a very fast chemical step leading to dopachrome. The second phase, from dopachrome to melanin, can proceed spontaneously through several incompletely known reactions. However, some metal transition ions and protein factors different from tyrosinase might regulate the reaction rate and determine the structure and relative concentrations of the intermediates. The study of the effects of some divalent metal ions (Zn, Cu, Ni and Co) on some steps of the melanogenesis pathway has been approached using different radiolabeled substrates. Zn(II) inhibited tyrosine hydroxylation whereas Ni(II) and Co(II) were activators. Ni(II), Cu(II) and Co(II) accelerated chemical reactions from dopachrome but inhibited its decarboxylation. Dopachrome tautomerase also decreased decarboxylation. When metal ions and this enzyme act together, the inhibition of decarboxylation was greater than that produced by each agent separately, but amount of carboxylated units incorporated to the melanin was not higher than the amount incorporated in the presence of only cations. The amount of total melanin formed from tyrosine was increased by the presence of both agents. The action of Zn(II) was different from other ions also in the second phase of melanogenesis, and its effect on decarboxylation was less pronounced. Since tyrosine hydroxylation is the rate-limiting step in melanogenesis, Zn(II) inhibited the pathway. This ion seems to be

the most abundant cation in mammalian melanocytes. Therefore, under physiological conditions, the regulatory role of metal ions and dopachrome tautomerase does not seem to be mutually exclusive, but rather complementary.

- Jastrzebska MM, Stepien K, Wilczok J, Porebska-Budny M, Wilczok T.
Semiconductor properties of melanins prepared from catecholamines. Gen Physiol Biophys 9:373-383, 1990.
Abstract : D.C. dark- and photocond. measurements were performed with synthetic melanins prepd. by oxidative polymn. of dopamine, adrenaline, adrenochrome, and adrenolutin. The melanins examd. show significant differences in cond., thermal activation energy and photocurrent intensity values. The differences in semiconductor properties obsd. between the malanins reflect the structure differences of catecholamine-melanin polymers.

- Kiuchi Y.
Changes in ocular hypotensive effect of griseolic acid with isoproterenol, timolol and melanin. Nippon Ganka Gakkai Zasshi 94:663-672, 1990.
Abstract : Griseolic acid-ester (GA-ester), one of the strongest cAMP phosphodiesterase inhibitors, was combined with isoproterenol and timolol in this study to evaluate the effect on intraocular pressure (IOP). Furthermore, the ocular hypotensive effect of GA-ester in pigmented and albino rabbits was compared, and the binding ability of GA-ester to synthetic melanin was examined. GA-ester markedly enhanced the hypotensive effect of isoproterenol, and the combination of GA-ester with timolol resulted in an additional fall in IOP. No differences in the hypotensive effect of GA-ester between pigmented and albino rabbits were observed. GA-ester did not bind to synthetic melanin. GA-ester has unique characteristics as an ocular hypotensive agent.

- Kocherginskii NM, Demochkin VV, Maslov SA, Dontsov AE, Rubailo VL, Ostrovskii MA.
Cation transport through melanin-containing biomimetic membranes. Zh Fiz Khim 64:2479-2484, 1990.
Abstract : The immobilization of melanin on the surface of pores of nitrocellulose microfilters impregnated with liq. analogs of lipids leads to the significant and selective increase of permeability of the membranes for Cu2+ ions. An occurrence of an active transport of Cu2+ in exchange for H+ was demonstrated. The kinetics of the process was studied and a mech. of the active transport was discussed. It was assumed that the processes of ion exchange on carboxyl groups of melanin play a significant role in the active transport mech.

- Lambert C, Land EJ, Riley PA, Truscott TG.
A pulse radiolysis investigation of the oxidation of methoxylated metabolites of indolic melanin precursors. Biochim Biophys Acta 1035:319-324, 1990.
Abstract : The rate constants associated with the series of successive transient absorptions initiated by one-electron oxidation of 6-hydroxy-5-methoxyindole (6H5MI) and its isomer 5-hydroxy-6-methoxyindole (5H6MI) have been studied by pulse radiolysis. These close analogues of 5,6-dihydroxyindole (DHI) are metabolites of the oxidative melanogenic pathway. The species initially produced from N3. oxidation of both methoxyindoles at pH 7.2-7.4 are assigned as the corresponding semiquinones. That from 6H5MI shows peak at 500, 370 and 330 nm, very close to those of the semiquinone of DHI, whereas the semiquinone of 5H6MI shows no absorption at 500 nm but bands at 420 and 340 nm. These spectral differences are attributed to marked changes in the degrees of electron delocalisation for the two types of radical, both rings of the indole being involved for the 6H5MI radical but only the benzenoid moiety for the 5H6MI radical. In both cases, the radicals decayed, probably by disproportionation, into products which absorbed in the 400-420 nm region. For 6H5MI, the subsequent decay in this region was best fitted by two consecutive first-order processes which were both strongly base-catalysed. The first of these processes is assigned to partial decay via deprotonation of the corresponding quinonoid cation to form an equilibrium mixture of this cation and the corresponding quinone methide. The second process is assigned to reaction of the quinone methide with water yielding hydroxylated product(s) which may subsequently react with remaining quinonoid cation or quinone methide to give dimeric product(s) with broad absorption centreing in the 550 nm region detected 0.5 s after the pulse. For 5H6MI, the decay at 430 nm fitted a single first-order process, which was weakly base-catalysed. This process is attributed to deprotonation of the corresponding quinonoid cation to the corresponding quinone imine absorbing below 350 nm, which was stable for at least tens of seconds. The

current experiments suggest that our previous analogues observations (Lambert et al. (1989) Biochim Biophys Acta 993, 12-20) on the oxidation of the melanogenic precursors DHI and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) may be interpreted, as with 6H5MI, in terms of the corresponding indolequinones decaying into equilibrium mixtures of quinone, quinone imine and quinone methide. These decay via reaction of the methide with water generating hydroxylated species which proceed to give the coloured product(s) absorbing in the 550 nm region.

- Meybeck A, Bonte F, Dumas M.
Pharmaceutical composition containing kaempferol and its derivatives. PCT Int Appl, 24 pp., 1990.
Abstract : A pharmaceutical compn. comprises kaempferol (I; R1, R2, R3, R4 = H, C1-4alkyl, C1-12 aliph. arom. acyl, a sugar residue), or a plant ext. contg. such compds. is useful for stimulating skin pigmentation. Kaempferol was added to murine melanocytes culture and melanin formation was measured after 5 days. The amt. of melanin/106 cells were 143 as compared to 90.5 .mu.g for control. A pharmaceutical cream contained kaempferol 0.5, soya lecithin 1.5, and perhydrosqualene 83 g.

- Mishima Y, Shibata T.
Mechanism and regulation of melanogenesis. Fragrance J 18:8-19, 1990.
Abstract : A review, with 28 refs., on the mechanism of melanin polymer formation and its controlling factors such as tyrosinase, glutathione reductase and SH-compds., metal ions, catalase, peroxidase and kojic acid.

- Saito N, Morishima T.
Eumelanin and pheomelanin contents in hairs of healthy Japanese and patients with oculocutaneous albinism, and 5-S-cysteinyldopa and 5-hydroxy-6-methoxyindole-2-carboxylic acid levels in urine of oculocutaneous albinism. Nippon Hifuka Gakkai Zasshi 100:853-861, 1990.
Abstract : The contents of eumelanin and pheomelanin in the scalp hairs of 4 Japanese patients with total albinism (3 tyrosinase-positive and one negative) and 100 healthy Japanese were measured by the melanin microquantitation method of Ito and Fujita. The urinary 5-S-Cysteinyldopa (5-S-CD) and 5-Hydroxy-6-Methoxyindole-2-Carboxylic acid (5H6MI2C) contents in the 4 albino subjects were also determined. Our findings included that (1) Regardless of ge, black hairs of all the healthy subjects contained phemelanin at a level of about 5% of the total melanin contents. The hair color of the 3 tyrosinase-positive subjects was pale-yellow, and their hairs contained only pheomelanin. The hair color of the one tyrosinase-negative subject was white, and neither eumalanin nor pheomelanin could be detected. (2) Urinary 5H6M12C, an indicator of eumelanin production in the body, could not be detected in either the tyrosinase-positive or tyrosinase-negative subjects, while the urinary 5-S-CD content of the tyrosinase-negative subject was much lower than that of the tyrosinase-positive subjects. These results suggested that the yellow hair color of patients with tyrosinase-positive albinism is attributable to the production of only pheomelanin and that the urinary 5-S-CD content does not necessarily reflect the ability to produce melanin.

- Singh S, Dryhurst G.
Further insights into the oxidation chemistry and biochemistry of the serotonergic neurotoxin 5,6-dihydroxytryptamine. J Med Chem 33:3035-3044, 1990.
Abstract : The neurodegenerative properties of the serotonergic neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) are widely believed to result from its autoxidation in the central nervous system. The autoxidation chemistry of 5,6-DHT has been studied in aqueous solution at pH 7.2. The reaction is initiated by direct oxidation of the indolamine by molecular oxygen with resultant formation of the corresponding o-quinone 1 and H2O2. A rapid nucleophilic attack by 5,6-DHT on 1 leads to 2,7'-bis(5,6-dihydroxytryptamine) (6) which is more rapidly autoxidized than 5,6-DHT to give the corresponding diquinone 7 along with 2 mol of H2O2. The accumulation of 6 in the reaction solution during the autoxidation of 5,6-DHT despite its more rapid autoxidation indicates that diquinone 7 chemically oxidizes 5,6-DHT (2 mol) to quinone 1 so that an autocatalytic cycle is established. The H2O2 formed as a byproduct of these autoxidation reactions can undergo Fenton chemistry catalyzed by trace transition metal ion contaminants with resultant formation of the hydroxyl radical, HO., which directly oxidizes 5,6-DHT to a radical intermediate (9a/9b). This radical is directly attacked by O2 to yield quinone 1 and superoxide radical anion, O2.-, which further facilitates Fenton chemistry by reducing, inter alia, Fe3+ to Fe2+. A minor side reaction of 1 with water leads to formation of at least two trihydroxytryptamines. Diquinone 7 ultimately reacts with 6, 5,6-DHT, and perhaps

trihydroxytryptamines, leading via a sequence of coupling and oxidation reactions to a black indolic melanin polymer. Enzymes such as tyrosinase, ceruloplasmin, and peroxidase and rat brain mitochondria catalyze the oxidation of 5,6-DHT to form dimer 7 and, ultimately, indolic melanin. The role of the autoxidation and the enzyme-mediated and mitochondria-promoted oxidations of 5,6-DHT in expressing the neurodegenerative properties of the indolamine are discussed.

- Smit NP, Pavel S, Kammeyer A, Westerhof W.
Determination of catechol O-methyltransferase activity in relation to melanin metabolism using high-performance liquid chromatography with fluorimetric detection. Anal Biochem 190:286-291, 1990.
Abstract : A new sensitive method for the detn. of catechol O-methyltransferase activity has been developed. The method is based on the O-methylation of the indolic intermediates to melanin metab. The substrate, 5,6-dihydroxyindole-2-carboxylic acid, is converted by the enzyme to 2 O-methylated products, which can be sepd. by HPLC and measured with fluorometric detection. The physiol. presence of both substrate and products could be detected in crude melanoma cell exts. The limit of sensitivity for detection of the O-methylated products was <0.5 pmol per injection. The method was compared with an earlier described HPLC method which makes uses of UV detection of O-methylated products of 3,4-dihydroxybenzoic acid. The described method will be used to study the importance of catechol O-methytransferase as a protective enzyme in (malignant) melanocytes.

- Viviani F, Gaudry M, Marquet A.
Melanin biosynthesis: a study of polyphenol deoxygenation. J Chem Soc Perkin Trans 1:1255-1259, 1990.
Abstract : The 1,3,6,8-tetrahydroxynaphthalene (T4HN) reductase of Verticillium dahliae was studied in a cell-free system. The use of specifically labeled 4(R)- and [4(S)-2H]NADPH in the redn. of T4HN to scytalone reveals that the label is specifically transferred in the case of [4(S)-2H]NADPH whereas no deuterium transfer occurs with the 4R-isomer. Thus, the T4HN reductase of V, dahliae is a NADPH-dependent dehydrogenase and belongs to class B.

2. Biology of pigment cells and pigmentary disorders

- Ando S, Suemoto Y, Yamamoto S, Ohyama Y, Mishima Y.
Separation of melanogenic inhibitors in pigment cells and melanogenesis control activities. Fragrance J 18:78-85, 1990.
Abstract : Melanogenic inhibitors derived from hamster amelanotic melanoma (D178 cell) and human amelanotic melanoma (G-361 cell) were studied by in vivo cell multiplication. Melanogenic inhibitors were classified into 3 types according to their mol. wt. (alpha < 6000, 6000 .ltoreq. beta < 30,000, gamma .gtoreq. 30,000). Sepn. and properties of alpha-type inhibitors from D178 cells were studied. Alpha-type inhibitors were further divided into alpha1 inhibitors and alpha2 inhibitors. Alpha1 inhibitor inhibited tyrosinase activity, whereas alpha2 inhibitor inhibited tyrosinase isoenzyme synthesis. Alpha-type inhibitors showed a whitening effect against mouse B-16 cells; the effect of alpha2 inhibitor was dose dependent and was greater than that of the alpha1 inhibitor. Alpha3 inhibitor from G-361 cells inhibited tyrosinase activity, but its effect was different from that of alpha1 inhibitor derived from D178 cell.

- Hamada M, Itakura C.
Ultrastructural morphology of hypomelanosis in equine cutaneous papilloma. J Comp Pathol 103:199-213, 1990.
Abstract : The morphology of hypomelanosis occurring in experimentally induced equine papillomas was investigated. Histologically, dopa-positive functioning melanocytes were decreased in number from the basal layer in the epidermis. Electron-microscopically, melanogenic organelles in the melanocytes were degenerate and melanosomes were decreased in number and size. In addition, the melanocytes had some abnormal melanosomes including melanosome complexes and giant melanosomes. Some abnormal melanosomes were also present in the keratinocytes. The hypomelanosis seemed to be related to a disturbance in melanin synthesis and melanocytic-keratinocytic interaction in the epidermal melanin unit.

- Hara K.
Melanin-formation preventing skin preparations containing kojic acids and UV absorbers. Jpn Kokai Tokkyo Koho, 6 pp., 1990.
Abstract : Melanin formation-preventing skin prepns. contain kojic acid (I) or its derivs. and .gtoreq.1 UV absorber chosen from p-aminobenzoic acids, salicylic acids, methoxycinnamic acids, and benzophenones. The UV absorbers prevent discoloration of the prepns. A skin prepn. was prepd. from poly(oxyethylene) hydrogenated castor oil 1.00, EtOH 15.00, Et p-hydroxybenzoate 0.10, citric acid 0.10, Na citrate 0.30, 1,3-butylene glycol 4.00, di-Na edetate 0.01, I 0.50, tetrahydroxybenzophenone 0.50, and H2O to 100 g.

- Hazuka MB, Edwards-Prasad J, Newman F, Kinzie JJ, Prasad KN.
Beta-carotene induces morphological differentiation and decreases adenylate cyclase activity in melanoma cells in culture. J Am Coll Nutr 9:143-149, 1990.
Abstract : Several studies suggest that beta-carotene reduces the risk of some cancers. Except for its function as an antioxidant, the effect of this vitamin on mammalian cells remains poorly defined. This study was performed to show whether beta-carotene treatment of murine B-16 melanoma cells in culture induces differentiation and alters the adenylate cyclase (AC) system. The AC system mediates the action of agents which regulate cell differentiation and transformation. Results showed that beta-carotene treatment for a period of 24 h or more caused morphol. differentiation without changing the level of melanin, and reduced basal and melanocyte-stimulated hormone (MSH)-, sodium fluoride (NaF)-, and forskolin-stimulated AC activity in vitro. Retinol, a metabolite of beta-carotene, inhibited growth without morphol. differentiation and reduced basal and MSH- and NaF-stimulated AC activity. Butylated hydroxyanisole, a lipid-sol. antioxidant, also reduced growth without morphol. differentiation, but it failed to alter basal or MSH-stimulated AC activity. The present and previous studies show that the AC system represents a common site where some antitumor-promoting vitamins (beta-carotene, retinol, retinoic acid, and alpha-tocopheryl succinate) act.

- Kita T, Hayashiba Y, Minoda M, Furuya Y.
Image analytic studies of melanin granules of human hairs with transmission electron micrographs. Sangyo Ika Daigaku Zasshi 12:335-341, 1990.
Abstract : Using electron micrographs of human hairs, we measured the minor axis and density of melanin granules by an image analyser. The melanin density of the outer hair cortex was higher than that of the inner hair cortex, and significant differences were evident especially in the minor axis and density of melanin granules among individuals. These quantitative analyses as to the minor axis and density of hair melanin granules are a reliable tool for the measurement of hair color.

- Matsui K, Ando Y, Tsuboi M, Kojima H, Shinkawa Y.
Logwood extracts containing melanin formation inhibitors for skin cosmetics. Jpn Kokai Tokkyo Koho, 6 pp., 1990.
Abstract : A skin-lightening cosmetic contains haematein (I) or haematoxylin extd. from logwood (Haematoxylon campechianum) to control melanin formation in the skin. A skin cream was prepd. which contained 0.04% by wt. of logwood ext.

- Micale V, Perdichizzi F.
A quantitative and histochemical study on melano-macrophage centers in the spleen of the teleost fish Diplodus annularis L. J Fish Biol 37:191-197, 1990.
Abstract : The incidence and histochem. features of melano-macrophage centers in the spleen of the teleost fish D. annularis were studied with respect to starved and fed fish. Tissue catabolism following complete starvation appears to induce formation of new centers contg. melanin and lipofuscin pigments. However, a change in the amt. of melano-macrophages was also recorded in fed fish, suggesting that some other factor(s), internal to fish, may affect the presence of such structures within the spleen of D. annularis.

- Mishima Y, Oyama Y, Kurimoto M.
Process for preparing melanogenic inhibitor, and pigmentation-lightening agent containing the same. Eur Pat Appl, 9 pp., 1990.
Abstract : A melanogenic inhibitor comprising unsatd. fatty acids or glycerides or phospholipids contg. these fatty acids are prepd. by extn. of animal cell line lysates. Namalwa cells were cultured then homogenized in

acetone. A compn. contg. C15:1, C18:1, C18:2, C18:3, and C20:4 fatty acids was prepd. by HPLC of the acetone ext. Various dosage forms were prepd. with this compn., e.g. injections, tablets, and ointments. The compn. inhibited pigmentation formation by mouse, hamster, and human melanoma cell lines.

- Nimmo JE, Gawkrodger DJ, O'Docherty CSJ, Going SM, Percy-Robb IW, Hunter JAA.
Plasma 5-S-cysteinyldopa as an index of melanogenesis. Br J Dermatol 118:487-495, 1988.
Abstract : Plasma 5-S-cysteinyldopa (5-S-CD) concns. measured in healthy volunteers in Edinburgh, Scotland (latitude 56 .degree.N) showed only minor changes during the day. However, when measurements were performed over a 12-mo period, a significant rise in 5-S-CD concn. was found. Skin pigmentation and hair color were not related to plasma 5-S-CD levels. Patients with psoriasis treated with UV-B or photochemotherapy (PUVA) developed an almost 2-fold increase in their plasma 5-S-CD level within the 1st 5 treatments, before pigmentation developed, subsequent increments of up to 4-fold the pretreatment level being found in the PUVA group. Dithranol treatment caused an increase in plasma 5-S-CD in some psoriatic patients, suggesting a possible assocn. between skin erythema and elevated 5-S-CD levels. The value of plasma 5-S-CD in the follow-up of patients with malignant melanoma does not seem to be invalidated by unavoidable exposure of the subjects to sunlight in a temperate climate such as that of South East Scotland.

- Nozue AT, Ono S.
Exposure of newborn mice to adenosine causes neural crest dysplasia and tumor formation. Neurofibromatosis 2:261-273, 1989.
Abstract : In the first part of this paper, we show that intraperitoneal injection of adenosine into newborn mice causes multiple neural crest tumors, neural crest hyperplasia, and heterotopic melanin pigmentation. In the second part, we review published data to propose (1) that microtubule proteins, phosphorylated through the action of calmodulin-dependent kinase and cyclic adenosine monophosphate and the adenosine A2 receptor of neural crest cells, may participate in neurotransmission and (2) that at least some neural crest tumors may be associated with disorders of neurotransmission in embryonic neural crest cells.

- Ogawa T, Shinomiya T.
Skin-tanning cosmetics containing melanin releasing factor. Jpn Kokai Tokkyo Koho, 3 pp., 1990.
Abstract : The title prepn. contains melanin-releasing factor isolated from mammalian serum. Thus, a skin-tanning prepn. contained beeswax 3.0, stearic acid 8.0, cetanol 3.0, squalene 4.0 mono-K glycyrrhetinate 6.0, methylparaben 0.1, perfume 0.5, melanin-releasing factor (bovine) 10.0, propylene glycol 3.0, glycerin 3.0, Na borate 0.4%, and balance distd. water. The prepns. are safe to use and beneficial to the skin.

- Pietsch P, Schneider CW.
Two-eyed versus one-eyed salamanders: does binocularity enhance the optically evoked skin blanching reactions of Ambystoma larvae ? Physiol Behav 48:357-359, 1990.
Abstract : A wide variety of visual functions show increases attributable to binocularity, and the question pursued here was whether a second eye enhances the visually stimulated skin blanching reaction of the larval salamander. Dermal melanin spots (produced by the aggregations of melanosomes within dermal melanophores and which contract or expand to lighten or darken the skin) were measured in eyeless (controls), one-eyed and two-eyed Ambystoma punctatum larvae after chronic adaptation of the subjects to a white background (i.e., stimulus conditions for maximum blanching). The eyeless subjects showed no blanching (thus remained dark) in white cups, and they exhibited melanin spots 7 or 8 times the size of those of the other two groups. All one-eyed or two-eyed subjects exhibited blanching reactions; planometric comparison revealed a significantly larger melanin spot area for one-eyed than for two-eyed animals; i.e., the binocular condition permitted greater contraction of the pigment spots than did the monocular condition. Analytical data compared favorably with independently ascertained pigmentation indices. The results indicate that a second eye quantitatively elevates the blanching maximum of a larval salamander.

- Saito N, Morishima T.
Eumelanin and pheomelanin contents in hairs of healthy Japanese and Japanese patients with oculocutaneous albinism, and 5-S-cysteinyldopa and 5-hydroxy-6-methoxyindole-2-carboxylic acid levels in urine of oculocutaneous albinism. Nippon Hifuka Gakkai Zasshi 100:853-861, 1990.
Abstract : The contents of eumelanin (I) and pheomelanin (II) in the scalp hairs of 4 Japanese patients with

total albinism, 3 tyrosinase (Tase)-pos. and 1 Tase-neg., and 100 healthy Japanese were measured by the melanin microquantitation method of Ito and Fujita. The urinary 5-s-cysteinyldopa (5-SCD) and 5-hydroxy-6-methoxyindole-2-carboxylic acid (HMICA) contents in the 4 albino subjects were also detd. Regardless of generations, black hairs of all the healthy subjects contained I at a level of about 5% of the total melanin contents. The hair color of the 3 Tase-pos. subjects was pale yellow, and their hairs contained only II. The hair color of the one Tase-neg. subject was white, and neither I nor II could be detected. Urinary HMICA, an indicator of I prodn. in the body, could not be detected in either the Tase-pos. or -neg. subjects, whereas the urinary 5-SCD content of the Tase-neg. subject was much lower than that of the Tase-pos. subjects. These results suggested that the yellow hair color of patients with Tase-pos. albinism is attributable to the prodn. of only II and that the urinary 5-SCD content does not necessarily reflect the ability to produce melanin.

- Tomita K, Fukuda M, Kawasaki K.
Mechanism of arbutin inhibitory effect on melanogenesis and effect on the human skin with cosmetic use. Fragrance J 18:72-77, 1990.
Abstract : The inhibitory effect of arbutin (p-hydroxyphenyl-beta-D-glucopyranoside or hydroquinone-beta-D-glucopyranoside) on the tyrosinase activity the mushroom and on the melanogenesis in cultured B16 melanoma cells was biochem. studied. Arbutin inhibition of mushroom tyrosinase was a competitive inhibition process as detd. by a Lineweaver Burk plot. The max. arbutin concn. without cell growth inhibition was 5 .times. 10-5 M. Melanin content per cell significantly decreased compared with untreated cells at more than 10-5 M of arbutin. The effect of 3% arbutin cream was studied in human skin with the double blind test. Arbutin inhibited the UV induced pigmentation with the efficacy rate of about 90%. The efficacy of the cream was obsd. in the skin of 82.3% humans.

- Torihara M, Tamai Y, Shiono M, Tasaka K.
Alkylresorcinol skin depigmental agents. Eur Pat Appl 10 pp., 1989.
Abstract : Skin depigmentation compns. contain alkylresorcinols (I, R = C2-12 alkyl). I depigmentation effects were measured by their ability to inhibit tyrosinase activity which takes part in the formation of melanin. Tyrosine hydroxylation and dopa oxidn. activities were also measured. A lotion was prepd. contg. 8 wt. % 4-isoamylresorcinol.

- Umnova EF, Ryzhkova VM, Terent'ev PB.
Pigments of a Curvularia lunata strain with steroid hydroxylase activity. Khim.-Farm Zh 24:60-62, 1990.
Abstract : Black and pink pigments were isolated from a com. strain of Curvularia lunata with steroid hydroxylase activity. The black pigment was identified as melanin from UV and IR spectra and other data. Based on mass, UV, and IR spectral observations, the pink pigment was identified as a polycondensed arom. ring system.

- Watanabe Y, Takada K, Yamagata Y, Sugiyama K, Kyomiya A.
Hair preparations containing adenosine phosphates and nonionic surfactants for preventing gray hairs. Jpn Kokai Tokkyo Koho, 8 pp., 1990.
Abstract : Compns., which promote melanin formation and prevent or control gray hair, contain .gtoreq.1 compds. chosen from adenosine 3',5'-cyclic phosphates I and II (R1, R2 = H, C1-6 acyl; M = H, cation; X = H, O- or S-contg. group, C1-6 alkylamino, halo) and .gtoreq.1 nonionic surfactants with HLB 3-19. A hair tonic consisted of I (R1 = R2 = COPr, M = Na, X = H) 0.05, poly(oxyethylene) lauryl ether (HLB 6) 1.0, poly(oxyethylene) hydrogenated castor oil 4.0 (HLB 13), propylene glycol 2.0, EtOH 50, biotin 0.01, and fragrances, H2O to 100.0%.

3. MSH, MCH, other hormones, differentiation

- Brown DW, Campbell MM, Kinsman RG, White PD, Moss CA, Osguthorpe DJ, Paul PKC, Baker BI.
Melanin-concentrating hormone: a structural and conformational study based on synthesis, biological activity, high-field NMR, and molecular modeling techniques. Biopolymers 29:609-622, 1990.
Abstract : A series of melanin-concg. hormone (MCH) fragments were synthesized and their biol. activities

compared with the parent peptide. The substructural units, 5-14 linear and 5-14 cyclic, were used as models for MCH in 1H NMR conformational studies. Conformational features predicted by mol. dynamics analyses found support in the NMR expts.

- Chakraborty AK, Orlow SJ, Pawelek JM.
Stimulation of the receptor for melanocyte-stimulating hormone by retinoic acid. FEBS Lett 276:205-208, 1990.
Abstract : Treatment of Cloudman S91 melanoma cells with retinoic acid (RA) has been reported to inhibit MSH-induced tyrosinase activity and melanin formation. However, in spite of inhibiting MSH-induced pigmentation, RA treatment caused a marked increase in MSH binding capacity for both cell surface and internal MSH binding sites. The stimulation was dose and time dependent and reversible, with half-maximal effects at 2 .mu.M RA. Stimulation of MSH binding was seen as early as 3 h after exposure of cells to RA. Cell surface and internal binding activity increased in concert. Scatchard analyses indicated that increased MSH binding resulted from a 3-4 fold increase in the no. of sites with no difference in their affinity for MSH. In suppressing MSH-induced melanogenesis, RA apparently elicited a compensatory up-regulation of the MSH receptor system.

- Navarra P, Tsagarakis S, Coy DH, Rees LH, Besser GM, Grossman AB.
Rat melanin-concentrating hormone does not modify the release of CRH-41 from rat hypothalamus or ACTH from the anterior pituitary in vitro. J Endocrinol 127:R1-R4, 1990.
Abstract : It has been suggested that melanin-concg. hormone (MCH) possesses potent ACTH inhibitory activity, on the basis of the inhibitory effects displayed by salmon MCH on ACTH release from either trout or rat isolated pituitary fragments. Thus, the putative inhibitory activity of synthetic rat MCH was examd. on basal and stimulated ACTH secretion from freshly-dispersed rat pituitary cells or incubated rat pituitary fragments, as well as on KCl- or noradrenaline-evoked release of ACTH-releasing hormone-41 (CRH-41) from rat hypothalamic explants in vitro. There were no effects of rat MCH on either CRH-41 or ACTH release in vitro.

- Presse F, Nahon JL, Fischer WH, Vale W.
Structure of the human melanin concentrating hormone mRNA. Mol Endocrinol 4:632-637, 1990.
Abstract : The melanin-concg. hormone (MCH) is a cyclic neuropeptide which induces skin paling and may be involved in the control of the pituitary adrenal axis in teleost fishes. The salmon and rat MCH mRNAs were recently cloned and characterized. Cloning and sequencing of the human MCH mRNA is reported. The deduced human MCH (hMCH) precursor is 165 amino acids long and as for rat and salmon, encodes the MCH peptide at the C-terminus. The human and rat MCH precursors are very similar to one another but differ extensively from the salmon counterpart. Strong sequence conservation was found in the regions of mammalian prohormones encoding the novel putative neuropeptides named NGE and NEI which were originally identified in the rat MCH precursor. Furthermore, sequence identities, with perhaps functional implications, were found among the MCH, human ANF, and Aplysia peptide A hormone precursors.

4. Photobiology and photochemistry

- Claudy AL, Perrot JL.
Hyperpigmentation induced by UVB at the application site of estradiol. Dermatologica 181:154-155, 1990.
Abstract : We report a case of a 48-year old woman who presented with chronic essential pruritus and was successfully treated with the transdermal estradiol system because of menopausal discomfort. Suberythemogenic UVB phototherapy was proposed to the patient in order to control her pruritus. She developed hyperpigmentation at the application site of estradiol. To the best of our knowledge, this is the first report suggesting a direct relationship between estrogen and melanin synthesis in humans.

- Diwu Z, Zhang M, Jiang L.
Hypocrellin A-sensitized photooxidation of indoles. (II). Isolation and identification of products of hypocrellin A-sensitized photooxidation of tryptophan. Chin Sci Bull 34:401-406, 1989.

Abstract : The hypocrellin A-sensitized photooxidn. of tryptophan gave several products, e.g. NH3, CO2, melanine, I, and II. The above photooxidn. is a complicated process in which both singlet oxygen and electron transfer are involved, but the singlet oxygen is predominant.

- Ellis CN, Weiss JS, Hamilton TA, Headington JT, Zelickson AS, Voorhees JJ.
Sustained improvement with prolonged topical tretinoin (retinoic acid for photoaged skin. J Am Acad Dermatol 23:629-637, 1990.
Abstract : We performed a 22-month trial of topical tretinoin (retinoic acid) in the treatment of photoaging. Thirty patients participated in a 4-month, randomized, blinded, vehicle-controlled study that has been reported previously; 21 patients continued tretinoin therapy on an open-label basis, participating in the study for a total of 10 months, and 16 patients continued for 22 months. During the open-label study, the statistically significant improvement that had occurred in fine and coarse wrinkling and skin texture during our original study was sustained, despite reductions in dose or frequency of application of tretinoin. The number of discrete lentigines decreased by 71% compared with the number before therapy. Histologic findings included a statistically significant thickening of the epidermis. Side effects were limited to a cutaneous retinoid reaction that diminished as therapy proceeded.

- Hajizadeh-Saffar M, Feather JW, Dawson JB.
An investigation of factors affecting the accuracy of in vivo measurements of skin pigments by reflectance spectrophotometry. Phys Med Biol 35:1301-1315, 1990.
Abstract : Factors affecting the accuracy of the in vivo measurement of cutaneous pigments and blood oxygenation by reflectance spectrophotometry have been examined. It was found that stray light, the amounts of haemoglobin and melanin, and the level of blood oxygenation all contributed to the measured reflectance and had to be taken into account when calculating quantitative indices of skin pigments. Measurements on isolated sheets of epidermis demonstrated that over 50% of normally incident radiation is transmitted in a forward direction within 17 degrees of the incident direction and approximately 20% is backscattered between 90 degrees and 180 degrees out of the sample, approximately 6.0% of it by specular reflection at the surface. The effective optical pathlength in suspensions of whole red cells was found to be 7% greater than in simple solutions containing the same concentration of haemoglobin.

- Ortonne JP.
The effects of ultraviolet exposure on skin melanin pigmentation. J Int Med Res 18 (Suppl 3):8C-17C, 1990.
Abstract : The main clinical, histological, ultrastructural and biochemical changes to the pigmentary system following photo-exposure are reviewed. Acute exposure to ultraviolet (UV) radiation induces an immediate pigment-darkening reaction, due to photo-oxidation of preformed melanin, followed by delayed tanning, the mechanism of which is unknown. Chronic exposure to UV induces photo-ageing with uneven pigment distribution. The most common pigmented lesions on chronically sun-exposed skin include ephelides, solar lentigines and pigmented solar keratoses. Idiopathic guttate hypomelanosis is also common in sun-exposed skin and may be considered as a manifestation of photo-ageing. Chronic UV also appears to induce cutaneous melanomas. Psolaren UVA lentigines and sunbed lentigines provide good arguments for the fact that UV exposure can induce melanocyte dysplasia. In addition, various tumours involving the keratinocyte population are associated with increased pigmentation, suggesting a concomitant alteration in melanocyte function, as in the case of pigmented epitheliomas and pigmented actinic keratoses. The exact nature of the interactions between photo-exposure and melanocytes has yet to be fully established.

5. Neuromelanins

- Blunt SB.
Fetal neural graft survival. Lancet 336:1131-1132, 1990.

- Chossegros C, Blanc JL, Cheynet F, Scheiner C, Gentet JC, Coze C, Gere E, Lachard J.
Melanotic neuroectodermal tumor of childhood or melanotic progonoma. Apropos of a case which recurred as an osteogenic tumor. Rev Stomatol Chir Maxillofac 91:368-373, 1990.

Abstract : We are yielding a case of recurring melanotic neuroectodermal tumor of infancy situated in the premaxilla, with a very quick evolution, haemorrhage, and which has precociously recurred after surgical removal. This tumor is studied on the paraclinical (CT scan, M.I.R.) and on the histological hand (immunohistochemical and ultra-microscopy). This observation is then compared with those of literature in which we find about 200 cases. The neurocristopathic histogenesis is actually doing the unanimity. The prognosis must now be quite reserved because of the recurrences (one case for six) and the possibility of malignant forms, some with metastasis.

- Gibb WR, Fearnley JM, Lees AJ.
The anatomy and pigmentation of the human substantia nigra in relation to selective neuronal vulnerability. Adv Neurol 53:31-34, 1990.

- Liessi G, Barbazza R, Sartori F, Sabbadin P, Scapinello A.
CT and MR imaging of melanocytic schwannomas; report of three cases. Eur J Radiol 11:138-142, 1990.
Abstract : Melanocytic Schwannomas are rare tumours which can arise in soft tissues, spinal nerve roots and in the central nervous system. The literature suggests that they have a malignant behaviour with local recurrence after surgery. We present three patients with this lesion, two in the thoracic spine and one in the head of the pancreas. The clinical outcome in these cases has been disappointing, since two patients died from complications due to local spreading of the tumour in spite of surgery and radiotherapy. CT could not distinguish these tumours from other neurogenic neoplasms. When these tumours occur near the vertebral body, CT could only detect early bone erosion. MR findings show promising features, with a high signal on T1-weighted images, due to melanin. However, more experience is necessary to establish the possible specific features of melanocytic Schwannomas in MRI.

- Rao CR, Visweshwaraiah LD, Veerapaiah KS, Satpute SD, Hazarika D, Bhargava MK.
Melanotic neuroectodermal tumor of infancy initially diagnosed by fine needle aspiration cytology. Acta Cytol 34:681-684, 1990.
Abstract : A five-month old male child presented with a tumor of the maxilla, which was clinically diagnosed as an eruption cyst or a rhabdomyosarcoma. Fine needle aspiration smears showed two types of cells: neuroblastlike cells and cells containing melanin pigment. A cytologic diagnosis of melanotic neuroectodermal tumor of infancy was made. This diagnosis was confirmed by histopathologic examination of the subsequently excised mass.

- Yamada T, McGeer PL, Baimbridge KG, McGeer EG.
Relative sparing in Parkinson's disease of substantia nigra dopamine neurons containing calbindin-D28K. Brain Res 526:303-307, 1990.
Abstract : The distribution of calbindin-D28K (CaBP)-pos. neurons was investigated by immunohistochem. in 4 controls, 5 cases of Parkinson's disease and a single case of strionigral degeneration. CaBP-pos. neurons were preferentially localized to the mediodorsal portion of the substantia nigra pars compacta (SNC) in the beta layer, while CaBP-neg., melanin-pos. neurons were concd. in the ventrolateral SNC in the alpha layer. In Parkinson's disease and the case of strionigral degeneration, there was a relative sparing of the CaBP-pos. neurons compared with CaBP-neg., pigmented neurons. These data imply that CaBP may confer some protection to SNC dopaminergic neurons against the pathol. process which is responsible for Parkinson's disease and strionigral degeneration.

6. Genetics

- Carefoot WC.
Test for linkage between the eumelanin dilution blue (B1), the extended black (E) allele at the E-locus and the linked pea comb (P) and eumelanin extension (M1) genes in the domestic fowl. Br Poult Sci 31:465-472, 1990.
Abstract : 1. A mating was made between a Blue Andalusian bantam male and a pea comb striped necked bantam female to produce a quadruple heterozygote of the linked pea comb (P) and eumelanin extension

(Ml) genes and of the eunmelanin dilution blue (Bl) gene and the extended black (E) allele at the E-locus. 2. Two pea comb blue females so produced were mated to a single comb striped necked bantam male, thus providing a backcross to the quadruple recessive. 3. Bl segregated independently with each of the other three genes whilst 25 crossovers occurred amongst the 55 progeny assessed for linkage between P and Ml, confirming loose linkage between P and Ml which had previously been shown to be approximately 46 units. Linkage of 0.3% had been previously reported (Crawford, 1986) between P and a "melanotic" gene isolated from a segregating gene pool. Evidence is presented to demonstrate that two different "melanotic" genes were being considered, thus explaining the apparently contradictory reports. Charcoal (cha) is suggested for the recessive gene linked with P by 0.3%. 4. Thirty-four crossovers occurred among the 97 progeny between P and E suggesting linkage of approximately 35 units. A further mating was made from among segregants in the backcross which confirmed P-E linkage with 17 crossovers in 55 gametes. Combining the tests produced a linkage value of approximately 34 units.

- Della-Cioppa G, Garger SJ, Sverlow GG, Turpen TH, Grill LK.
Melanin production in Escherichia coli from a cloned tyrosinase gene. Bio/Technology 8:634-638, 1990.
Abstract : A tyrosinase gene from Streptomyces antibioticus was cloned and functionally expressed in E. coli under the control of an inducible bacteriophage T7 promoter. Recombinant E. coli cells contg. the induced tyrosinase gene produced melanin pigments on agar plates and in liq. culture when supplemented with copper and tyrosine. The expression of an addnl. open reading frame from the mel gene locus of S. antibioticus was required for high-level melanin prodn. in E. coli. These results also show that it is possible to screen other classes of precursor compds. for incorporation into melanin pigments with unique colors and other biochem. features. In addn., it may be possible to screen for enhanced melanin prodn. in the absence of added precursors to identify overproducing mutants in the amino acid biosynthetic pathways of E. coli. The ability to screen for a melanin phenotype in recombinant E. coli provides new opportunities for prodn. of novel melanins and for protein engineering of tyrosinases with altered catalytic properties.

- Kupper U, Linden M, Cao KZ, Lerch K.
Expression of tyrosinase in vegetative cultures of Neurospora crassa transformed with a metallothionein promoter/protyrosinase fusion gene. Curr Genet 18:331-335, 1990.
Abstract : Wild-type Neurospora crassa, strain Singapore, was transformed with a N. crassa metallothionein promoter/protyrosinase fusion gene. Transformants produced tyrosinase during vegetative growth, as determined by Western analyses and activity assays. This is in sharp contrast to wild-type strains, where this enzyme is only expressed in situations of starvation or sexual differentiation. Complete integration of a 400 bp metallothionein promoter-fragment leads to constitutive expression of protyrosinase, whereas a 3.6 kb promoter-fragment conferred copper inducibility on the reporter gene in four transformants. A transformant with high constitutive tyrosinase levels was able to produce melanin on complete medium agar plates supplemented with 1 mg/ml L-tyrosine.

- Larue L, Mintz B.
Pigmented cell lines of mouse albino melanocytes containing a tyrosinase cDNA with an inducible promoter. Somatic Cell Mol Genet 16:361-368, 1990.
Abstract : Melanocyte cell lines, with characteristic dendritic morphol. and melanosomes, were established from young mice of wild-type (C57BL/6) and of 2 albino (C57BL/6-c2J/c2J and BALB/c) inbred strains. The albino cells were cotransfected with two plasmids: pMTtyr1, contg. the full-length tyr1 cDNA for tyrosinase encoded by the c locus, under the control of the inducible mouse metallothionein-I (MT-I) promoter; and pSV neo.beta., allowing selection of transformants by G418 resistance. The intrinsic albino defect was cor. by the tyr1 cDNA in transfected cells, thereby validating the coding capability of tyr1 for tyrosinase. Black melanin was formed in the genetically black (B/B) C57BL/6-c2J/c2J cells and brown melanin in the genetically brown (b/b) BALB/c cells. Pigment was produced even without adding heavy metal (for induction of the MT-I promoter), thus obviating the need for adding it, but was formed more rapidly upon addn. of ZnSO4 up to 100 .mu.M. Stable transfected albino melanocyte lines with active tyrosinase and melanization were obtained. Addn. of ZnSO4 at 200 .mu.M was lethal to the cells. However, this toxicity - attributable at least in part to melanin precursors - was prevented if the cells sojourned at 100 .mu.M ZnSO4 for 2 wk before being exposed to the 200 .mu.M level. Adaptation was lost when the cells were removed from 200 .mu.M ZnSO4 for 1 wk and then returned to it. Avoidance of toxicity under these conditions is thus the result of physiol.

detoxification mechanisms rather than selection for a genetic change.

- Nahon JL, Presse F, Bittencourt JC, Sawchenko PE, Vale W.
The rat melanin-concentrating hormone messenger ribonucleic acid encodes multiple putative neuropeptides coexpressed in the dorsolateral hypothalamus. Endocrinology (Baltimore) 125:2056-2065, 1989.
Abstract : Rat melanin-concg. hormone (rMCH) is purified and characterized. Here the cloning and sequencing of specific MCH cDNA isolated from a rat hypothalamic library is presented. The sequence of rMCH found by DNA sequencing confirms the sequence deduced from the purified peptide. The rMCH is located at the C-terminus of a protein precursor of 165 amino acid residues. Comparison of the amino acid sequence of prepro-MCH and that of the Aplysia peptide-A prohormone suggests that these proteins as well as other precursors may be evolutionarily related. Besides rMCH, 2 putative neuropeptides, termed NGE and NEI, might be generated from the same precursor. The rMCH precursor shared sequence identities with human growth hormone-releasing factor (hGRF) and mammalian CRF in the regions encoding NGE and NEI. Immunohistochem. studies established that the amidated C-terminus of NEI is recognized by some alpha-MSH and rat CRF antisera and that the C-terminal portion of NGE is responsible for the cross-reactivity revealed with one hGRF-(1-37) antiserum. These results explain the staining of a discrete population of dorso-lateral hypothalamic neurons by heretofore seemingly unrelated antisera and provide evidence for the prodn. of multiple novel neuropeptides from a common precursor.

- Sugiyama M, Nomura H, Nimi O.
Use of the tyrosinase gene from Streptomyces to probe promoter sequences for Escherichia coli. Plasmid 23:237-241, 1990.
Abstract : A promoter-probe vector was constructed utilizing the expression of a promoter-less tyrosinase derived from Streptomyces plasmid pIJ702. The vector, pMX100, has single sites for EcoRI, KpnI, BamHI, XbaI, SalI, and SphI for cloning promoter sequences. When the tac promoter was inserted into pMX100, E. coli harboring the chimeric plasmid produced the melanin pigment.

- Takeda A, Tomita Y, Matsunaga J, Tagami H, Shibahara S.
Molecular basis of tyrosinase-negative oculocutaneous albinism. A single base mutation in the tyrosinase gene causing arginine to glutamine substitution at position 59. J Biol Chem 265:17792-17797, 1990.
Abstract : Tyrosinase-neg. oculocutaneous albinism (OCA) is one of the classical inborn errors of metab., characterized by a complete lack of melanin pigments in the eyes and skin. The authors isolated and characterized the tyrosinase gene of one child (F. S.) affected with tyrosinase-neg. OCA. Sequence anal. reveals a single-base mutation in exon 1 (a G to A transition at nucleotide residue 312), causing the Arg (CGG) to Gln (CAG) substitution at position 59. This base change eliminates one MspI site and creates a new BstNI site in the patient's exon 1, which is invaluable for screening other OCA patients and heterozygote carriers for this mutation. The patient F.S. was homozygous for this OCA allele. The family members of the patient F.S. are phentotypically normal, but are shown to be heterozygote carriers. Transfection of the mutant gene fails to give rise to detectable tyrosinase activity in transient expression assays, suggesting that the mutation affects the stability or the catalytic activity of the enzyme. It is proposed that the albino phenotype of the patient F.S. is a consequence of the Arg to Gln substitution at position 59 caused by a point mutation in the tyrosinase gene.

- Tomita Y, Takeda A, Okinaga S, Tagami H, Shibahara S.
Human oculocutaneous albinism caused by single base insertion in the tyrosinase gene. Biochem Biophys Res Commun 164:990-996, 1989.
Abstract : Tyrosinase-neg. oculocutaneous albinism (OCA) is an inborn error of metab., characterized by a complete lack of melanin pigments in the eyes and skin. The tyrosinase gene was isolated from one affected child (S.S.) with tyrosinase-neg. OCA. Sequence anal. reveals a single-base insertion in the second exon that shifts the reading frame and introduces a premature termination signal (TGA codon) after the amino acid residue 298. Functional anal. of the mutated gene indicates that such a truncated tyrosinase lacking one potential copper-binding region is catalytically inactive. Thus, the albino phenotype of the patient S.S. is a consequence of the inactive tyrosinase caused by the nonsense mutation in the tyrosinase gene.

7. Tyrosinase and other enzymes

- Kameyama K, Hearing VJ.
Regulatory factors of melanin production. Inhibitory factors of tyrosinase. Fragrance J 18:24-31, 1990.
Abstract : A review, with 32 refs., on the stimulating action of interferons on the activities of MSH receptors in murine melanocytes, a pos. correlation between melanogenesis and the expression of MSH receptors on the surface of melanocytes, and mode of action of a melanogenesis inhibitor produced by nonpigmented JB/MS-W cells.

- Rodriguez P, Rodriguez Lopez JN, Tudela J, Varon R, Garcia Canovas F.
Effect of pH on the oxidation pathway of alpha-methyldopa catalyze by tyrosinase. Biochem J 272:459-463, 1990.
Abstract : Quant. description of the effect of pH on the oxidn. pathway of alpha-methyldopa was studied. Tyrosinase catalyzes the oxidn. by mol. oxygen of alpha-methyldopa to o-alpha-methyldopaquinone, which evolves nonenzymically through a branched pathway with cyclization or hydroxylation reactions. The intermediates of the hydroxylation branch have been identified, and the corresponding rate consts. have been detd. These compds., which have been detected in melanosomes and in tumor cells, have great cytotoxic power and could have physiol. significance in acidic media.

- Yokoyama T, Silversides DW, Waymire KG, Kwon BS, Takeuchi T, Overbeek PA.
Conserved cysteine to serine mutation in tyrosinase is responsible for the classical albino mutation in laboratory mice. Nucleic Acids Res 18:7293-7298, 1990.
Abstract : Albinism, due to a lack of melanin pigment, is one of the oldest known mutations in mice. Tyrosinase (monophenol oxygenase, EC 1.14.18.1) in the first enzyme in the pathway for melanin synthesis, and the gene encoding this enzyme has been mapped to the mouse albino (c) locus. Mouse tyrosinase cDNA clones and genomic sequencing were used to study the albino mutation in lab. mice. Within the tyrosinase gene coding sequences, a G to C transversion at nucleotide 308, causing a cysteine to serine mutation at amino acid 103, is sufficient to abrogate pigment prodn. in transgenic mice. This same base pair change is fully conserved in classical albino strains of lab. mice. These results indicate that a conserved mutation in the tyrosinase coding sequences is responsible for the classical albino mutation in lab. mice, and also that most albino lab. mouse strains have been derived from a common ancestor.

8. Melanoma

- Kamino H, Tam ST, Alvarez L.
Malignant melanoma with pseudocarcinomatous hyperplasia; an entity that can simulate squamous cell carcinoma. A light-microscopic and immunohistochemical study of four cases. Am J Dermatopathol 12:446-451, 1990.
Abstract : We report four unusual cases of malignant melanoma in which squamous cell carcinoma was strongly considered in the differential diagnosis on routine hematoxylin and eosin-stained sections due to the near absence of melanin and the presence of pseudocarcinomatous hyperplasia. Ultimately, immunohistochemical staining for S-100 protein and keratin established the correct diagnosis of malignant melanoma in all cases.

- Kuwata Y, Miki Y, Sano A, Nishizawa S, Murakami M, Qtake S, Kawakami K, Mimura F, Masada T, Koyama M.
MR imaging of mucocutaneous malignant melanoma in the head and neck. Nippon Igaku Hoshasen Gakkai Zasshi 50:946-953, 1990.
Abstract : MR imaging was performed in three patients with mucocutaneous malignant melanoma of the head and neck, and surgical specimens were investigated in MR-pathological correlation. Two of 3 cases were revealed to be melanotic melanoma; one arose in the maxillary sinus, and another in the bulbar conjunctiva. The remaining case was amelanotic melanoma originating in the nasal cavity. Two cases of melanotic

melanoma showed different intensity on T1WI according to the melanin concentration; the more the melanin-producing process existed, the higher intensity in the tumor was shown. On T2WI there were also some differences in signal intensity; the case having more concentration of melanin changed lower partially in the areas where very high intensity was noted on T1WI, while another case remained unchanged. These findings are based on the inherent paramagnetic effect mostly compatible with the previous reports. On the other hand, the amelanotic melanoma was demonstrated as an intermediate intensity both on T1- and T2WI. Because of the higher incidence of hemorrhage in/around the tumor, it is an important diagnostic clue to this tumor, as in our case of amelanotic type. On reviewing the three cases, we consider that MR imaging offers a useful adjunct in the diagnosis of malignant melanoma.

- Lodding P, Kindblom LG, Angervall L.
Metastases of malignant melanoma simulating soft tissue sarcoma. A clinico-pathological, light- and electron microscopic and immunohistochemical study of 21 cases. Virchows Arch [A] 417:377-388, 1990.
Abstract : Metastases of cutaneous malignant melanoma (MM) of ordinary type can resemble various types of soft tissue sarcoma light microscopically to a degree which has not been previously recognized. Twenty-one cases are described, in which the tumours were originally diagnosed as a soft tissue sarcoma. Seven tumours were predominantly of blue and spindle-cell, fascicular type, resembling malignant peripheral nerve sheath tumour and at times monophasic synovial sarcoma. Ten tumours which were of fascicular and predominantly storiform type, and included uni- and multi-nuleated pleomorphic cells resembled malignant fibrous histiocytoma. Due to the presence of multivacuolated lipoblast-like tumour cells, 2 of these 10 tumours resembled pleomorphic liposarcoma. One had a predominantly myxoid and hypocellular appearance and 5 additional tumours included such areas. The diagnoses were revised after ultrastructural examination with the demonstration of melanosomes in 13 of 16 studied cases and the immunohistochemical demonstration of positivity using anti-S-100 protein antibodies and the anti-melanoma antibody NKI/C3 in all cases. The anti-melanoma antibody HMB 45 gave a positivity in 9 of 21 cases. Light microscopically, sparse amounts of melanin were noted in 7 tumours using the Whartin-Starry technique. Eleven tumours occurred at sites close to major lymph node groups and in 9 of these cases, lymphoid tissue was associated with the tumours, suggesting that they represented lymph node metastases. Following a review of the patients' clinical histories and renewed clinical examination, primary cutaneous MM was demonstrated in 10 of 21 patients and in 1 case an MM in regression was detected. The origin of the 10 tumours without a detected primary is discussed, including the possibility of an overlooked primary, spontaneous regression of a primary and a de novo origin from lymph nodes and soft tissues.

- Miura T, Jimbow K, Ito S.
The in vivo antimelanoma effect of 4-S-cysteaminylphenol and it n-acetyl derivative. Int J Cancer 46:931-934, 1990.
Abstract : Phenolic melanin precursors can be utilized for the development of anti-melanoma agents. The sulphur homologue of tyrosine, 4-S-cysteinylphenol (CP) and its decarboxylation product, 4-S-cysteaminylphenol (CAP) were shown to be substrates of melanoma tyrosinase, forming melanin-like pigment. Both, but in particular the 4-S-CAP, exhibited a significant in vivo depigmenting effect. Here, we report on the in vivo anti-melanoma effect of 4-S-CP, and 4-S-CAP and its N-acetyl derivative. In a previous in vitro study, it was shown that 4-S-CP and 4-S-CAP required a catalytic amount of dopa for optimal mammalian tyrosinase activity. To enhance the potential anti-melanoma effect of these two compounds. L-dopa and a decarboxylase inhibitor (carbidopa) were given concomitantly. We found that 4-S-CAP showed a significant growth inhibition of B16 melanoma inoculated s.c. into C57BL/6J mice. The anti-melanoma effect was increased significantly by combination of L-dopa and carbidopa. In addition, we tested the in vivo anti-melanoma effect of an N-acetyl derivative of 4-S-CAP (N-Ac-4-S-CAP). We found that N-Ac-4-S-CAP was the tyrosinase substrate and potent inhibitor of melanoma growth. N-acetyl 4-S-CAP showed a marked increase in water solubility. We suggest that N-Ac-4-S-CAP may prove to be a valuable model for the development of anti-melanoma agent using a metabolic pathway of melanin synthesis.

- Nordenberg J, Novogrodsky A, Beery E, Patia M, Wasserman L, Warshawsky A.
Anti-proliferative effects and phenotypic alterations induced by 8-hydroxyquinoline in melanoma cell lines. Eur J Cancer 26:905-907, 1990.
Abstract : The effect of the transition metal chelator, 8-hydroxyquinoline (8-HQ), was examined on the

growth and phenotype expression of B16 mouse melanoma cells. Micromolar concentrations of 8-HQ inhibited the growth of B16 cells as well as human melanoma cell lines. Removal of 8-HQ from the culture medium restored normal cell growth. Growth inhibition by 8-HQ was accompanied by phenotypic alterations that included changes in cell morphology, increased production of melanin and enhanced activities of the enzymes gamma-glutamyl transpeptidase and NADPH cytochrome c reductase. These changes might be associated with a better differentiated phenotype.

- Saijo S, Kato T, Tagami H.
Pigmented nail streak associated with Bowen's disease of the nail matrix. Dermatologica 181:156-158, 1990.
Abstract : We described a 59-year old male physician with Bowen's disease occurring on the nail matrix of his right 5th finger. The rapid growth of the pigmented nail streak accompanied by nail deformity led us to consider the possibility of subungual melanoma clinically. Histologic features, however, were compatible with those of Bowen's disease accompanied by melanocytes with melanin-rich long dendrites in the nail matrix. We speculate that his occupational exposure to X-rays for 25 years played an important role in the pathomechanism of the present case.

- Sharma SS, Venkateswaran S, Chacko A, Mathan M.
Melanosis of the esophagus. An endoscopic, histochemical, and ultrastructural study. Gastroenterology 100:13-16, 1991.
Abstract : Endoscopic, histological, and ultrastructural features of 21 cases of esophageal melanosis are described. These cases were detected during 1000 consecutive routine upper gastrointestinal endoscopies. Staining characteristics and ultrastructure of the pigment contained in the endoscopically visible lesions were found to be similar to those of true melanin.

- Taniyama K, Suzuki H, Sakuramachi S, Toyoda T, Matsuda M, Tahara E.
Amelanotic malignant melanoma of the esophagus: case report and review of the literature. Jpn J Clin Oncol 20:286-295, 1990.
Abstract : A case of amelanotic malignant melanoma of the esophagus in a 76-year old woman is reported. A whitish polypoid tumor, measuring 3 x 2 x 2.7 cm, surrounded by black pigmented mucosa, was detected in the middle intrathoracic esophagus. The tumor showed a lobulated surface lined by squamous cell layer, and had epithelioid and polyhedral cells forming alveolar clusters. Melanin pigments or stainability for the dihydroxyphenylalanine (DOPA) reaction were only observed in a few tumor cells. Junctional changes and mucosal melanosis, however, were found freely in the mucosa around the tumor. Many tumor cells showed a strongly positive immunohistochemical reaction for neuron specific enolase (NSE) and S100 protein. The patient died of widespread metastases six months after surgery. Further, a review of 106 reported cases of primary esophageal malignant melanoma, including 29 autopsies, was made; the melanomas were found to include 10 of amelanotic type, eight of which had been misdiagnosed at biopsy. Junctional changes could be found in the mucosa over or around the tumor, in four cases, and mucosal melanosis in one. Lymph node metastasis was the most frequently observed development at autopsy regardless of whether the tumor was amelanotic or melanotic. For correct diagnosis of melanomas of the amelanotic type, peripheral mucosal findings, such as junctional changes or melanosis, should be helpful; and, in order to obtain a good prognosis, a careful resection of the regional lymph nodes could prove valuable.

- Wang Y.
The clinicopathological analysis of melanoma of the oral mucous membrane. Chung Hua Kou Chiang Hsueh Tsa Chih 25:142-145, 1990.
Abstract : Forty-one cases with melanoma of the oral mucous membrane were studied by clinicopathology and immunohistochemistry. The incidence of the tumor is higher in old males. The mean age of patients is 46.15 years. The ratio of male to female is 2.15: 1. The tumor occurs most commonly in palate (46.34%), followed by gingiva, then lip, buccal and tongue membrane. The oral melanosis had been found in 41.46% of the cases months to years before tumour appeared and 51.22% of cases had concurrent or later-developing melanosis. The epithelium around tumour in 14 cases with pre-existing melanosis was observed. We found that the number of clear cells and s-100 protein positive cells in epithelium increased, and a lot of cells filled with melanin in the lamina propria were found. The result shows that the patients with this preexisting melanosis have higher risk of suffering from malignant melanoma.

9. Eye

- Schorderet M, Nowak JZ.
Retinal dopamine D1 and D2 receptors: characterization by binding or pharmacological studies and physiological functions. Cell Mol Neurobiol 10:303-325, 1990.
Abstract : 1. In the retinal inner nuclear layer of the majority of species, a dopaminergic neuronal network has been visualized in either amacrine cells or the so-called interplexiform cells. 2. Binding studies of retinal dopamine receptors have revealed the existence of both D1- as well D2-subtypes. The D1-subtype was characterized by labeled SCH 23390 (Kd ranging from 0.175 to 1.6 nM and Bmax from 16 to 482 fmol/mg protein) and the D2-subtype by labelled spiroperidol (Kd ranging from 0.087 to 1.35 nM and Bmax from 12 to 1500 fmol/mg protein) and more selectively by iodosulpiride (Kd 0.6 nM and Bmax 82 fmol/mg protein) or methylspiperone (Kd 0.14 nM and Bmax 223 fmol/mg protein). 3. Retinal dopamine receptors have been also shown to be positively coupled with adenylate cyclase activity in most species, arguing for the existence of D1-subtype, whereas in some others (lower vertebrates and rats), a negative coupling (D2-subtype) has been also detected in peculiar pharmacological conditions implying various combinations of dopamine or a D2-agonist with a D1-antagonist or a D2-antagonist in the absence or presence of forskolin. 4. A subpopulation of autoreceptors of D2-subtype (probably not coupled to adenylate cyclase) also seems to be involved in the modulation of retinal dopamine synthesis and/or release. 5. Light/darkness conditions can affect the sensitivity of retinal dopamine D1 and/or D2-receptors, as studied in binding or pharmacological experiments (cAMP levels, dopamine synthesis, metabolism and release). 6. Visual function(s) of retinal dopamine receptors were connected with the regulation of electrical activity and communication (through gap junctions) between horizontal cells mediated by D1 and D2 receptor stimulation. Movements of photoreceptor cells and migration of melanin granules in retinal pigment epithelial cells as well as synthesis of melatonin in photoreceptors were on the other hand mediated by the stimulation of D2-receptors. 7. Other physiological functions of dopamine D1-receptors respectively in rabbit and in embryonic avian retina would imply the modulation of acetylcholine release and the inhibition of neuronal growth cones.

- Traboulsi EI, Murphy SF.
A clinicopathologic study of the eyes in familial adenomatous polyposis with extracolonic manifestations (Gardner's syndrome). Am J Ophthalmol 110:550-561, 1990.
Abstract : The eyes of a 51-year-old woman with familial adenomatous polyposis and extracolonic manifestations (Gardner's syndrome) were obtained postmortem and studied by light microscopy and by transmission and scanning electron microscopy. We found a generalized abnormality in melanogenesis of the retinal pigment epithelium and at least three types of pigmented lesions. The histologic findings in one type of lesion were consistent with congenital hypertrophy of the retinal pigment epithelium or benign pigmented nevus of the retinal pigment epithelium. The other two types of lesion were most consistent with hamartomatous malformations of the retinal pigment epithelium featuring cellular hypertrophy, hyperplasia, and rarely retinal invasion and formation of a minute mushroom-shaped tumor. These histopathologic findings indicate a generalized effect of the familial adenomatous polyposis gene on the retinal pigment epithelium. This oncogene, which is responsible for tumor formation in the gastrointestinal tract, soft tissues, bone, and other locations in patients with familial adenomatous polyposis, also leads to a generalized defect in melanogenesis and focal lesions of the retinal pigment epithelium.

- White MP, Negi A, Hock PA.
Effects of hemicholinium-3 on the pigmented rabbit retina and pigment epithelium. Curr Eye Res 9:669-676, 1990.
Abstract : Hemicholinium-3 effects on the albino rabbit neural retina have been described, but effects on the retinal pigment epithelium (RPE) have not been closely examined. We have studied retinal morphology and function in Dutch belted (pigmented) rabbits after single intravitreal injections of Hemicholinium-3 or saline. DC electroretinogram recordings show a decrease in a, b, and c-wave amplitudes, with the c-wave affected first. Experiments with sodium iodate show that the early decrease in the c-wave results from a loss of the RPE component of the c-wave, rather than the retinal Slow PIII component. After two days, ophthalmoscopic abnormalities of the fundus are severe in a large area with pigmentary changes. A sharp boundary appears between normally pigmented and depigmented fundus, indicative of a critical threshold for damage. The RPE contains clumped melanin. Pigmented cells are seen away from the basement membrane, an early histological

observation temporally correlated with a loss of barrier function seen in fluorescein angiograms. After 10 days, apparent proliferation of non-pigmented RPE cells coincides with re-establishment of the barrier. Rod photoreceptor outer segments are lost 4-7 days after injection in the depigmented regions of the fundus, but outer segments are spared in normally pigmented fundus areas. This regional pattern is distinct from that seen in albino rabbit retina where outer segment loss is fairly uniform. We conclude that Hemicholinium-3 affects the RPE in pigmented rabbits in addition to known effects on retinal cholinergic neurons and photoreceptor disc synthesis.

- Zane PA, Brindle SD, Gause DO, O'Buck AJ, Raghavan PR, Tripp SL.
Physicochemical factors associated with binding and retention of compounds in ocular melanin of rats: correlations using data from whole-body autoradiography and molecular modeling for multiple linear regression analyses. Pharm Res 7:935-941, 1990.
Abstract : The relationship between the physicochemical characteristics of 27 new drug candidates and their distribution into the melanin-containing structure of the rat eye, the uveal tract, was examined. Tissue distribution data were obtained from whole-body autoradiograms of pigmented Long-Evans rats sacrificed at 5 min and 96 hr after dosing. The physicochemical parameters considered include molecular weight, pKa, degree of ionization, octanol/water partition coefficient (log Po/w), drug-melanin binding energy, and acid/base status of the functional groups within the molecule. Multiple linear regression analysis was used to describe the best model correlating physicochemical and/or biological characteristics of these compounds to their initial distribution at 5 min and to the retention of residual radioactivity in ocular melanin at 96 hr post-injection. The early distribution was a function primarily of acid/base status, pKa, binding energy, and log P(o/w), whereas uveal tract retention in rats was a function of volume of distribution (V1), log P(o/w), pKa, and binding energy. Further, there was a relationship between the initial distribution of a compound into the uveal tract and its retention 96 hr later. More specifically, the structures most likely to be distributed and ultimately retained at high concentrations were those containing strongly basic functionalities, such as piperidine or piperazine moieties and other amines. Further, the more lipophilic and, hence, widely distributed the basic compound, the greater the likelihood that it interacts with ocular melanin. In summary, the use of multiple linear regression analysis was useful in distinguishing which physicochemical characteristics of a compound or group of compounds contributed to melanin binding in pigmented rats in vivo.

10. Other

- Baran R.
Nail biting and picking as a possible cause of longitudinal melanonychia. A study of 6 cases. Dermatologica 181:126-128, 1990.
Abstract : Examination of individuals affected by onychotillomania led us to describe a new cause of longitudinal melanonychia (LM) of the finger-nails. Damage of the finger-nails was caused both manually and by chewing. The nail cuticles were usually pushed back, and biting caused pressure damage of the base of the nail. It is likely that finger-nails respond similarly to toe-nails and the matrix melanocytes can be stimulated by trauma. Such stimulation can apparently persist long after cessation of the trauma. Histological examination of the nail plates demonstrated that the pigment was melanin. In the matrix an increase in melanin content of melanocytes was found without melanocytic proliferation. LM due to onychotillomania should not be overlooked.

- Itoh H.
Functions and whitening effect of placenta. Fragrance J 18:67-71, 1990.
Abstract : The whitening effect on melanin (M) in placenta is discussed. The M formation can be accelerated by tyrosinase activity. Placental liq. (PL) inhibits 80.apprx.90% of dopa-chrome (precursor of M) formation. The inhibitory effect on tyrosinase of PL controls tyrosine .fwdarw. Dopa reaction at the 1st step more intensely than Dopa .fwdarw. M reaction. The keratolytic effect, the respiration accentuating effect, the peripheral blood circulation accelerating effect of PL accelerate the metab. in the skin, and the excretion of the pigmentary granules and the other substances yields a whitening effect.

Received in Brussels : Date :

PIGMENT CELL RESEARCH BULLETIN

NAME : .....

ADDRESS : .....

.....

PHONE : .....

CONTRIBUTIONS

I shall send my contribution in the form of :

COMMENTARY ☐•

DISCUSSION ☐•

REVIEW ☐•

LETTER TO THE EDITOR ☐•

TOPIC COVERED : .....

NUMBER OF PAGES : ..... (not exceeding 6 pages in double spacing, including references)

NB : when available, please send the information on a diskette running under DOS in any wordprocessing format along with a copy of your text.

ANNOUNCEMENTS

I wish to announce the following :

MEETING ☐•

COURSE ☐•

RESEARCH OPPORTUNITY ☐•

OTHER ☐•

• : please mark

Please send back to :

G. GHANEM
Assistant Editor
Laboratory of Oncology and Experimental Surgery
Institut Jules Bordet
Rue Héger-Bordet 1
B - 1000 Brussels

RECALL

Dear Reader,

We are preparing a special issue of the Bulletin entirely dedicated to informations about the pigment cell research in Europe.

You will find on next page a standard form which will be published as such about your group filled by yourself. Also, feel free to photocopy this form as many times as there are different teams or/and programs. Should you know other teams working in pigment cell research, please send them a copy of the form or provide us with their name and address.

May we emphasize that not filling and sending back the form would mean that you will not be included in this special issue.

Thank you in advance for your cooperation.

G. PROTA
President

SURVEY OF CURRENT PIGMENT CELL RESEARCH IN EUROPE
1990 - 1991

1. **FIELD OF STUDY** :

2. **TITLE / DESCRIPTION** :

3. **INVESTIGATOR(S)** :

4. **INSTITUTION** :

5. **ADDRESS** :

6. **TELEPHONE** :

7. **FAX** :

8. **COMMENTS** :

9. **TOPIC** :

Send back to : Dr G. Ghanem, Assistant Editor
L.O.C.E. - Institut Bordet
Rue Héger-Bordet 1
B - 1000 Brussels

ANNOUNCEMENTS & RELATED ACTIVITIES

Melanoma '91
The Brighton International Melanoma Conference
May 8th-11th 1991

ESPCR Symposium : "Progress in Experimental Treatments for Melanoma"
Chairmen : Giuseppe Prota and Patrick Riley

14.00 : Introduction by Prof. P. Riley (London)

14.15 : Toxicity of melanogens in human melanoma cell lines by Dr. Stan Pavel (Amsterdam)

14.45 : Melanoma targeting using α-MSH-melphalan by Dr. G. Ghanem (Brussels)

15.15 : ^{211}At-methylene blue : targeted radiotherapy for disseminated melanoma by Dr. Ewa Link (London)

15.45 : Boron neutron capture as a potential therapeutic strategy in melanoma by Prof. Bengt Larsson (Uppsala)

16.15 : Concluding remarks by Prof. G. Prota (Naples)

The 3rd Meeting of the European Society for Pigment Cell Research

will be held from September 8-11, 1991 in Amsterdam, The Netherlands.

Venue : Academisch Medisch Centrum
Medical Faculty
University of Amsterdam
Meibergdreef 9
NL - 1105 AZ Amsterdam

The program includes 3 guest lectures, symposia, plenary sessions, workshops and poster sessions.
Contact with the industries can be made at the commercial exhibition.

The topics to be addressed include:

Melanin : neuromelanins, biophysics, biochemistry

Melanocytes : culture methods, morphology, immunology, biology, biochemistry

Pigment disturbances : vitiligo, naevi, melasma, etc

Melanotropins : function, MSH-receptors

Melanoma : markers, growth factors, oncogenes, immunology, therapy

Sunscreens : natural, artificial

UV-light and pigmentation : skin types, tanning, colour measurement

Information : Dr. Wiete WESTERHOF
Chairman 3rd meeting ESPCR
Dept of Dermatology
Academisch Medisch Centrum
Meibergdreef 9
NL - 1105 AZ Amsterdam
Tel. 020.5662757
Fax. 020.5664440

A N N O U N C E M E N T

The Division of Dermatology and Cutaneous Sciences at the University of Alberta is pleased to announce that it will host the Third Meeting of the Panamerican Society for Pigment Cell Research on

July 11 - 13, 1991

at

Bernard Snell Hall
University of Alberta
Edmonton, Alberta, Canada

July 11 - Registration and Keynote Speakers

July 12 - Plenary Session, Workshop, Posters

July 13 - Symposium on Malignant Melanoma

The program includes four keynote speakers, workshops, symposium, plenary, and poster sessions, and exhibits.

Topics to be addressed included, among other subjects, Growth Factors and Regulators for Melanocytes and Melanoma, Molecular Biology of UV Phototoxicity, Melanoma Precursors, as well as contributed papers to be chosen at a later date.

The *call for abstracts* will be mailed in November, 1990, and travel stipends will be available for graduate students fellows and junior faculty members.

Send inquiries to:

Yolande Matsusaki
General Secretary of the Third Meeting
Conference Centre
#4 Lister Hall
University of Alberta
Edmonton, Alberta
T6G 2H6

Tel. 403-492-7200
Fax. 403-492-7032

Kowichi Jimbow, Ph.D., M.D.
Chairman of the Third Meeting
Division of Dermatology and
Cutaneous Sciences
Faculty of Medicine
260G Clinical Research Wing
Heritage Medical Research Centre
University of Alberta
Edmonton, Alberta T6G 2S2

Tel. 403-492-2425

FYM* ADMINISTRATIUM - PART II.

Administratium has a normal half-life of approximately three (3) years, at which time it does not actually decay, but, instead, undergoes a reorganization in which assistant neutrons, vice-neutrons, and assistant vice-neutrons exchange places. Early studies indicate that the atomic weight and viscosity actually increase after each reorganization.

Research at other laboratories indicates that Administratium occurs naturally in the atmosphere. It tends to concentrate at certain points such as government agencies, large corporations, universities and hospitals. Administratium can actually be found in the newest, best maintained buildings.

Scientists point out that Administratium is known to be toxic at any concentration and can easily destroy any productive reactions where it is allowed to accumulate. Attempst are being made to determine how Administratium can be controlled to prevent irreversible damage, but results to date are not promising.

* : For Your Misinformation

From Am. Society for Photobiology Newsletter, n° 128