



PASPCR

Newsletter

Volume 3 Number 4

December, 1995

Introduction . . .

by the Publications Committee

The *PASPCR Newsletter* is published quarterly and is intended to serve as a means of communication for the members of our Society. As such, we invite our membership to actively contribute to the *Newsletter*; help us to update the Job Listings, Calendar of Events, Meeting Reports, Abstracts in press and other items of general membership interest. If you attend a scientific meeting at which you heard about work which you think will be of interest to the membership of the **PASPCR**, please write a few paragraphs summarizing what was presented and share it with us. If you should have a change of affiliation or address, we'd like to know that, too. This is **your Newsletter**, and we depend upon you to help us make sure it best serves the Society's needs. Contributions and comments can be sent to any of the members of the Publications Committee.

NEW! A WorldWideWeb Page for the PASPCR. The PASPCR now has its own **WWW** page. We plan this to be a major source of current information for the PASPCR membership. The address for the page is: <http://lenti.med.umn.edu/paspcr>. This site contains information on the goals of the society, future meetings, council information, past issues of the PASPCR newsletter as well as links to other sites including the InterPig data base and the International Federation of Pigment Cell Societies (IFPCS). We will be also finalizing the membership directory. You should soon receive a mailing that will allow you to state what information about yourself that you want included in this directory. This will be an important part of this web site, in that changes in the membership directory can be easily made, providing access to up to date membership information. The PASPCR WWW page is still under construction and we want to know if there is any other information you would like located on this site.

Please check out the PASPCR web site and send any comments and/or suggestions to either Bill Oetting at bill@lenti.med.umn.edu or Vince Hearing at hearingv@dc37a.nci.nih.gov.

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**PanAmerican Society for
Pigment Cell Research**

c/o **Dr. Richard A. King**
Department of Medicine
University of Minnesota
516 Delaware St, SE
Minneapolis, MN 55455
FAX: (612) 624-6645

Officers

Vincent J. Hearing
President
Sally Frost-Mason
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Council Members

Zalfa A. Abdel-Malek
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Gert M. Jacobsohn
William S. Oetting
Seth J. Orlow
Dewayne Townsend
Walter C. Quevedo, Jr.

IFPCS Representative

James Nordlund
Past-President

The **PASPCR Newsletter** is published quarterly; for further information and/or to submit articles, contact the:

Publications Committee:

Dr. William S. Oetting (chair)

University of Minnesota
16-262 Moos Tower
515 Delaware St., S.E.
Minneapolis, MN 55455-0311
FAX: (612) 626-4027
E-mail: BILL@LENTI.MED.UMN.EDU

Dr. Alan N. Houghton

Memorial Sloan-Kettering Cancer Center
Chief, Clinical Immunology Service
1275 York Avenue
New York, NY 10021
FAX: (212) 717-3036

Dr. Walter C. Quevedo, Jr.

Brown University
Division of Biology and Medicine
Box G
Providence, RI 02912
FAX: (401) 863-1971

Calendar of Events :

Dec 2 - 3, 1995 Meeting of the Japanese Society for Pigment Cell Research, to be held in Osaka, Japan (contact: Prof. Toshiteru Morita, Dept of Biology, Osaka University, 560 Osaka, Japan; FAX: +81 6/850-5613)

Dec 9 - 13, 1995 Annual Meeting of the American Society for Cell Biology, to be held in Washington DC (contact: ASCB National Office, 9650 Rockville Pike, Bethesda, MD 20814-3992; FAX: 301/530-7139)

May 1 - 4, 1996 Annual Meeting of the Society for Investigative Dermatology, to be held in Washington DC (contact: SID Office, Suite 500A, 11001 Cedar Ave, Cleveland, OH 44106; FAX: 216/844-6810)

Oct 29- Nov 3, 1996 XVIth International Pigment Cell Conference, to be held in Anaheim, California, (contact: MMC/UCI Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428, FAX: 310/933-2012)

Dec 7 - 11, 1996 Annual Meeting of the American Society for Cell Biology and 6th International Congress on Cell Biology, to be held in San Francisco, CA, (contact: ASCB Secretariat, 9650 Rockville Pike, Bethesda, MD 20814-3992; FAX: 301/530-7139)

Jun 15- 18, 1997 VIIth PASPCR Annual Meeting, to be held in Providence, RI (contact: Dr. Walter C Quevedo, Jr., Brown University, Division of Biology and Medicine, Providence, RI 02912; FAX: 401/863-1971)

Welcome to New Members

by Richard A King

We welcome the following new members to the PASPCR .

Susan M. Holder

Georgios Kroumpouzou

Stuart T. Leonard

Harish Mahalingam

If anyone is interested in joining our Society or wishes to sponsor a member, application forms can be obtained from Dr. Richard King at the PASPCR Secretary/Treasurer's office.

Corporate Sponsors

by Richard A King

The PASPCR would like to acknowledge and thank our Corporate Sponsors; the list below reflects contributions over the past 2 years. Financial gifts from these sponsors have allowed our Society to increase benefits to the membership far out of proportion to the actual dues collected from members. Monies contributed by these sponsors have been used over the years to support various PASPCR functions including our Young Investigator Award program, meeting travel stipends, annual meeting expenses and this Newsletter.

GOLD Corporate Patrons

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1995 PASPCR Elections

by Richard A King

The PASPCR is currently holding its annual elections. Ballots are due by the end of this calendar year and the results will be announced in the first Newsletter of 1996.

for President-Elect: Richard A. King

for Secretary/Treasurer: James J. Nordlund

for Council members: Kenneth Mason Frank Meyskens David A. Norris
Robert J. Smyth John D. Taylor

XVIth IPCC (International Pigment Cell Conference)

by Roger Bowers, Frank Meyskens

The XVIth International Pigment Cell Conference will be held from October 29th to November 3rd, 1996 at the Disneyland Hotel in Anaheim, California. Frank Meyskens is the Organizer of this meeting with Roger Bowers and Alistair Cochran serving as co-chairs of the Organizing Committee. Following is the initial draft of the Conference Program:

XVIth International Pigment Cell Conference - Tentative Conference Agenda

Tuesday, October 29, 1996

3:00 - 7:00 pm Pre-registration/View Exhibits

7:00 - 10:00 pm Welcome Reception: Fashion Show: "*Safe and Sexy in the Sun*"

Wednesday, October 30, 1996 Conference Attendees

7:00 - 8:00 am Registration/Continental Breakfast/View Exhibits

8:00 - 8:05 am Welcome: Chairman, Frank L. Meyskens, Jr.

Introduction: Laurel Wilkening, Chancellor, Univ of California, Irvine

8:05 - 8:35 am **Special Lecture**, R. Sherwood Rowland, Nobel Laureate, 1995, Chemistry
"Ozone Depletion, Ultraviolet Light, and the Pigment Cell"

Symposium I: Economic and Societal Implications of Melanin and Melanogenesis
8:35 - 9:00 am Keynote Speaker
9:00 - 10:30 am Invited and Competitive Abstract Speakers
10:30 - 11:00 am Break
11:00 - 12:30 pm **Workshop A: "Extracutaneous Melanin"**
Posters and Discussion #1 TBN* (11:00 - 12:00 Viewing; 12:00 - 12:30 Discussion)
12:30 - 2:00 pm Lunch on your own

Symposium II: Molecular Biology of Pigment Cells
2:00 - 2:30 pm Keynote Speaker
2:30 - 4:00 pm Invited and Competitive Abstract Speakers
4:00 - 4:05 pm IFPCS/WWW: Vincent Hearing
4:05 - 4:15 pm Break
4:15 - 6:15 pm **Workshop B: "Regulating Mechanisms of Melanocyte Proliferation"**
4:15 - 6:00 pm Posters and Discussion #2 TBN* (4:15 - 5:30 Viewing; 5:30 - 6:00 Discussion)
5:30 - 7:00 pm **Workshop C: "Biophysics of Melanin"**
6:15 pm Adjourn Free evening

Accompanying Guests (8:00 - 11:00 am) Welcome/Introduction: Buffet Breakfast;
(12:00 - 5:00 pm) Group Activity

Thursday, October 31, 1996

7:00 - 8:00 am Continental Breakfast/View Exhibits
8:00 - 8:30 am **Seiji Lectureship:** Introduction: Giuseppe Prota, President, IFPCS

Symposium III: Melanoma Research: Basic and Applied
8:30 - 9:00 am Keynote Speaker
9:00 - 10:30 am Invited and Competitive Abstract Speakers
10:30 - 11:00 am Break
11:00 - 12:30 pm **Workshop D: "Control of Melanogenesis"**
11:00 - 12:30 pm Simultaneous Business Meetings of Regional Societies
12:30 - 2:00 pm Lunch on your own

Symposium IV: Photobiology of Melanocytes: Etiology and Prevention
2:00 - 2:30 pm Keynote Speaker
2:30 - 4:00 pm Invited and Competitive Abstract Speakers
4:00 - 7:00 pm **Workshop E: The "Blues" Symposium**
4:00 - 7:00 pm Poster Viewing
Adjourn - Free evening

Friday, November 1, 1996

7:00 - 8:00 am Continental Breakfast/View Exhibits
8:00 - 8:30 am Introduction: Vincent Hearing, President PASPCR
Gelb Lectureship: Seth Orlow

Symposium V: Melanogenesis and Pigmentary Disorders
8:30 - 9:00 am Keynote Speaker
9:00 - 10:30 am Invited and Competitive Abstract Speakers
10:30 - 11:00 am Break
11:00 - 12:30 pm **Workshop F: "Biology and Biochemistry of Melanosomes"**
11:00 - 12:30 pm Posters and Discussion #3 TBN* (11:00 - 12:00 Viewing; 12:00 - 12:30 Discussion)
12:30 - 1:15 pm **Controversy Session: "Semiquinone Radicals are not Important during Melanin Synthesis"**
Pro: Patrick Riley Con: Stan Pavel
1:15 pm Adjourn Scientific Session
1:15 - 6:30 pm Break
6:30 - 7:30 pm Reception
7:30 - midnight Banquet, Awards and Dancing

Saturday, November 2, 1996

7:00 - 8:00 am Continental Breakfast/View Exhibits
8:00 - 8:30 am **Presidential Address:** Giuseppe Prota, President IFPCS

Symposium VI: Comparative Developmental Biology of Pigment Cells
8:30 - 9:00 am Keynote Speaker
9:00 - 10:30 am Invited and Competitive Abstract Speakers

10:30 - 11:00 am Break
11:00 - 12:30 pm **Workshop G: "Genetic Aspects of Albinism"**
11:00 - 12:30 pm Posters and Discussion #4 TBN* (11:00 - 12:00 Viewing; 12:00 - 12:30 Discussion)
12:30 - 2:00 pm Lunch on your own
2:00 - 4:00 pm **Educational Forum: "Living with the Sun"**
4:00 - 6:00 pm Family Farewell Reception and Wine Tasting

Sunday, November 3, 1996

8:00 - 5:00 pm

1. *Satellite Meeting (all day): Classification of Cutaneous Melanoma:* Alistair Cochran
2. *Satellite Meeting (3 hours): Safety of Sunscreens and Tanning Parlors:* J.P. Césarini, et al.
3. *Satellite Meeting (3 hours): Ocular Melanin:* Giuseppe Prota

Workshops and poster and poster discussion sessions will be simultaneous. The poster sessions and discussions will feature areas that do not overlap with the workshop. The chairs of these sessions will be selected from submitted competitive abstracts and the Chairman in turn will organize this session with help from the Organizing Committee.

Farewell Letter from the President :

by Vincent J Hearing

I would like to take this occasion to thank each of you for your confidence in my ability to run our Society over the past 3 years (or at least in keeping quiet about your lack of confidence). I would especially like to thank the Council Members who have served during that time and who have taken on the bulk of the work; it is a tribute to all of them that they responded eagerly and capably to every task put to them. Obviously also, the lion's share of credit for our progress in the past 3 years also goes to my fellow Officers (Drs. Frost-Mason, King and Nordlund) who have counceled and stood by me through it all. I also need to especially acknowledge the efforts of the Organizers of the two PASPCR meetings that were held during my tenure; Drs. Jacobsohn and Frost-Mason put on exceptionally attractive and dynamic meetings that allowed us the opportunity to share our work, our ideas and our friendships. The value of such meetings to the success of the Society simply can not be overestimated.

The initial foresight used by the founding PASPCR Officers and Council Members left little challenge for me when I assumed office. Everything was running smoothly and efficiently and my major task was to avoid undoing all of that early work. My concept of what our Society needed 3 years ago, and still needs, was: (1) to expand our membership base to involve more researchers in our field in the PASPCR, and (2) to improve communications and collaborative interactions among our members. I think that we have made great strides in both those directions over the past several years. Our membership has grown by about 40 to 50% (which is excellent) but there are many active researchers in our field in North and South America that still need to be recruited to the Society. We have established our PASPCR Newsletter and that has fostered dramatic increases in collaborative interactions among our members that have significantly improved our collective productivity. We have established the PASPCR HomePage and the InterPig Database as sources of available materials and reagents and the usefulness of those will increase in the coming years as more members contribute entries and access the DataBase over the InterNet.

Much work remains to be done in those directions and in others. It is a pleasure to hand over the office of the Presidency to the very capable hands of Sally Frost-Mason; I have absolute confidence in her ability to lead all of us to new heights of achievement during her tenure. I would encourage each of you to become more active in the Society, both politically and scientifically - the rewards are great. I have established so many new friendships and collaborations that it is more than worth the time invested. I thank each of you again for your support and will look forward to seeing you in the coming years at our meetings and elsewhere. If Sally gets anywhere near the support that I have received, the future of the PASPCR looks very bright indeed. Best wishes to all.

PASPCR Secretary / Treasurer's Report : by Richard A King

Following is a synopsis of the PASPCR Council Meeting held by teleconference on June 25, 1995 . . .

Hearing opened the meeting and a quorum was declared present. The April 20, 1995, council meeting minutes were approved. The 1994 financial records were reviewed: The balance on 12/31/94 was \$27,353.72. A total of 14 travel awards for \$300 have been awarded from the Kansas City meeting. From 1989 to 1995, a total of \$21,689 have been given in travel awards by the society.

Membership Committee: Orlow gave the report on criteria for Honorary Membership. The Bylaws make no statement about whether or not the Honorary Membership should be a member of the society or still be active in research. Hearing reviewed the general concepts that honorary members would most likely be individuals from outside the society or those who were finishing an outstanding research career. Orlow stated that the committee felt that Honorary Memberships should be for individuals from outside the society. King proposed an amendment to Rule and Regulation #6 regarding honorary members, as follows: "Honorary members will be elected from individuals who are not current members of the society". The amendment was unanimously accepted. Awards Committee: Nordlund stated that the Young Investigator Awards for the PASPCR will be awarded during the PASPCR business meeting during the 1996 IPCC in Anaheim. There will be no Career Achievement Award or Honorary Membership awarded during the IPCC. A motion was made and accepted that the Career Achievement Award in general will not be given at the IPCC meetings and will only be given during the PASPCR meetings.

Quevedo reviewed the arrangements for the PASPCR meeting in Providence on June 15 - 18, 1997. The meeting will start on Sunday afternoon with a reception. Social activities will include a trip to Newport on Monday afternoon and a banquet at the Brown University on Tuesday night.

Old business: King reviewed the Young Investigator Award trial of nominations for the 1995 meetings. A total of 6 nominations have been made for Young Investigator Awards, and the Secretary-Treasurer, appointed an anonymous committee to pick the awardees from these nominations. The mechanism for nominations of Young Investigator Awards will be continued for the 1996 IPCC meetings and that announcements for the nominations will be sent to all PASPCR members before abstract submission.

New business: a Rule and Regulation for IFPCS officer rotation was proposed. Currently Rule and Regulation #5 does not address the rotation of membership for the PASPCR Members. The proposed amendment is as follows: "Any PASPCR representative that are serving as an officer in the IFPCS council will complete their term of office on the IFPCS council even if the PASPCR term expires prior to the end of the IFPCS term. The normal rotation for PASPCR representative on the IFPCS council will resume at the completion of this term of office." The amendment to Rule and Regulation #5 was unanimously accepted. Hearing reviewed the request for information for the InterPig database of the IFPCS and noted there had only been 4 contributors for the PASPCR. He encouraged all members of the council and members from their laboratory to participate.

New business: potential interactions between the PASPCR and American Society of Photobiology (ASP) were reviewed. Helene Hill was asked to serve as liason with the ASP.

The minutes have been prepared by R. King, Secretary-Treasurer

Members in the News

Harish Mahalingam received a Young Investigator Award at the PASPCR Annual Meeting in Kansas City (his name was inadvertently left off the last Newsletter).

Richard Spritz delivered a Keynote Address at the ESPCR Meeting in Lausanne entitled "Molecular Basis of Genetic Hypopigmentary Disorders".

Positions - Wanted and Available :

Predoctoral Position - Opportunity available to do graduate studies towards a doctoral degree at the University of Cincinnati College of Medicine. Graduate program is through the Department of Cell Biology, Neurobiology, & Anatomy. Dissertation project would focus on molecular biology of the melanocyte physiology and pigmentary diseases. For information contact: Raymond E. Boissy, Ph.D., Department of Dermatology, University of Cincinnati College of Medicine, 231 Bethesda Avenue ML-592, Cincinnati, Ohio 45267-0592; (513)558-6242 [TEL]; (513)558-0198 [FAX]; boissyre@ucbeh.san.uc.edu [eMAIL].

Faculty Position - Massachusetts General Hospital, Harvard Medical School, Cutaneous Biology Research Center. The Cutaneous Biology Research Center (CBRC) seeks a molecular, cellular or developmental biologist to establish a program in fundamental research relevant to skin pigmentation. Areas of research can include but are not limited to pigment synthesis and transfer in melanocytes, genetics of mouse coat color and development/migration of neural crest cells. Applicants must have a Ph.D. and/or M.D. degree and relevant postdoctoral experience. Only applicants with a strong research record and the potential to develop extramurally supported research programs will be considered. Individuals with a demonstrated ability to develop imaginative approaches to important biological questions are particularly encouraged to apply. Rank/salary/start-up funds and space are negotiable depending on experience and qualifications. The CBRC occupies 45,000 square feet of fully equipped laboratory space in a new multidisciplinary research facility. Interested individuals should send curriculum vitae, reprints, a statement of research and future directions, along with the names, addresses and telephone numbers of three references to: Dr. Paul F. Goetinck, Chair, Faculty Search Committee, Cutaneous Biology Research Center, Massachusetts General Hospital - East, Building 149, 13th Street, Charlestown, MA 02129

Director, Section of Basic Science Research - the Department of Dermatology and the Research Institute of the Cleveland Clinic Foundation are seeking applications for a full-time research scientist. Candidates should possess an M.D. and/or Ph.D. degree and have research experience in one of the following areas: wound healing, keratin/collagen biochemistry, or cancer immunology/molecular biology. The successful candidate will have the ability to work as an independent investigator and be the focus for dermatological research in a dynamic, multi-disciplinary and supportive environment. Preference will be given to individuals who have demonstrated prior success in obtaining extramural support. Salary and title will be commensurate with training and experience. A University affiliation is available. Send C.V. to: Charles Camisa, M.D., Vice-Chair, Department of Dermatology, A61, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195-5032.

INTERPIG DataBase

by Vincent Hearing

The INTERPIG database is on the InterNet! You can now access the InterPig DataBase at the following address: <http://lenti.med.umn.edu/paspcr/interpig.html>. Please note that as of this time, I estimate that less than 5% of the various IFPCS members have contributed entries. Think of how useful and complete this list would be if everyone took the time to supply their own information. Please take a moment to fill out the database data entry form and send it back to Dr. Hearing (a copy of the entry form is inserted into this Newsletter, and it can be photocopied).

IFPCS Council

by Vincent Hearing

The annual meeting of the IFPCS Council was held in Japan early this December in conjunction with the JSPCR Annual Meeting held in Osaka (chaired by Prof. Morita) and the Symposium on Melanogenesis and Melanoma (chaired by Prof. Hori). This annual meeting of the IFPCS Council is hosted by the three Regional Societies on a rotating basis and the two previous meetings had been held

at the Philadelphia PASPCR meeting (chaired by Prof Jacobsohn) and at the London IPCC (chaired by Prof Riley).

The IFPCS Council, under the direction of the President (Prof Protá), has been involved in a number of areas in these past three years, briefly including:

1. Nomination and selection of IFPCS Officers and Committee members, and establishing a mechanism for fair and adequate representation of all Regional Societies; current Officers are Prof Protá (President), Prof King (Vice-President) and Prof Ito (Secretary/Treasurer).
2. Appointment of a Publications Committee (Hearing, Larson and Matsumoto) to select the Editor of the IFPCS-sponsored journal *Pigment Cell Research* to succeed Dr. Bagnara at the end of his term (Prof Takeuchi has taken over that position for the next 5 years and all will agree he has done an outstanding job, as had Dr. Bagnara his predecessor). This Committee will also consider all other pertinent issues of publication, including facilitating interactions between organizers of the IPCC and Munksgaard for publication and distribution of abstracts and Proceedings, and in increasing the quality and circulation of the journal.
3. Initiation of novel approaches to improving interactions and research by all members of the Regional Societies; among those are a Vitiligo Interest subgroup (chaired by Nordlund), an Albinism Interest subgroup (chaired by King), a Comparative Biology Interest subgroup (chaired by Frost-Mason) and the InterPig DataBase (coorganized by Hearing, Riley and Takeuchi). These groups are actively seeking to foster collaborations among our members, and even outside of our membership base, and to set acceptable standards (e.g. nomenclature) to be used by all.
4. Selection of sites for future IPCC and assistance to IPCC Organizers to ensure that the Program is as internationally-based and of the highest scientific merit possible (Dr. Meyskens presented his report on the upcoming IPCC to be held in Anaheim next year and his plans were enthusiastically endorsed - that meeting promises to be an outstanding one).
5. Determination of procedures for nomination and selection of the awardees of the Seiji Memorial Lecture and the Myron Gordon Award.
6. Sponsorship of other scientific meetings that are consistent with the goals of the IFPCS; to date we have agreed to sponsor the 4th World Conference on Melanoma to be held in Sydney, Australia in 1997.

In sum, the IFPCS Council has been active in facilitating interactions between the Regional Societies and their members. The next meeting will be during the IPCC in Anaheim next year; if you have concerns or suggestions that you think merit consideration at the IFPCS level, please contact one of the three IFPCS Council members from the Society.

Bibliography :

The Bibliography published in this issue covers the period February, 1995 through April, 1995. If you notice a paper that was not detected by this search that should be included, please send it to us and we will include it in the next issue. We have attempted to highlight any publications which include a member of the PASPCR with a star.

MELANINS, MELANOGENS & MELANOGENESIS

- Ⓟ Barker D, Dixon K, Medrano EE, Smalara D, Im S, Mitchell D, Babcock G, Abdel-Malek ZA: Comparison of the responses of human melanocytes with different melanin contents to ultraviolet B irradiation. *Cancer Res* 55:4041-4046 (1995).

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***** News and Views from the ESPCR *****

Beginning with this issue, the ESPCR and PASPCR are exchanging items and columns of mutual interest for publication in our respective Newsletters. Dr. Ghanem Ghanem (editor of the ESPCR Bulletin) and Dr. Vincent Hearing (of the PASPCR Newsletter) are initiating this to further promote interactions between our members. Please contact us if you have suggestions or comments about this, or wish to contribute articles for future publication. The following articles are reprinted with permission from the ESPCR Bulletin.

Meeting Report :

by Sheila MacNeil

6th Annual Meeting - European Society for Pigment Cell Research October 19-21, Lausanne

As a new Council Member I have been asked to write a report of this Meeting which I am very pleased to do. What follows is a highly personal view of this meeting and I would like to apologise in advance to all those whose work I may misrepresent, offend or in any way overlook. As always with the ESPCR Meetings, there was an atmosphere of much enthusiasm, goodwill and considerable alcohol which promoted the multi-disciplinary approach to understanding the melanocyte. It is no coincidence that year after year people find time for this multi-disciplinary friendly event in their busy conference schedule. This year there were some very nice developments and some coming together of previously separate areas and hints of new and broader vistas of what the melanocyte may be up to.

One common unifying theme which has been growing steadily relates to the role of the melanocyte in stress management in the broader sense. Everyone has their own personal portrait of the melanocyte - however, these are not always recognisable to our colleagues - to the chemist the melanocyte may be palate of complex indole-quinones which challenge the very limits of quantitative analysis techniques - to the biochemist the regulation of tyrosinase may be a complex kinetic problem involving some uncalled for and complex hormones - the developmental and cell biologists will admire the apparent range of behaviour and roles of this energetic little cell - the immunologist will ask personal questions of the melanocyte concerning its relationship with T lymphocytes and macrophages - the oncologist, meanwhile, may view the transformed melanocyte with considerable respect and horror.

In the format of this meeting (for which the organisers should be warmly congratulated) we are positively discouraged from taking home, our own family snapshots of the melanocyte - what was particularly exciting about this meeting was some of the links being made between these previously disparate views of this cell.

There are still an embarrassingly large number of questions you can ask about the melanocyte most of which for me personally can be summed up under the two big questions - "why do we have melanin at all?" and "is α MSH important in man?" (I think all the other questions hang from these).

In a meeting of 51 oral presentations and 48 posters, it is possible to weave together some of the well established data with some of the newer findings to present a story of the melanocyte occupying a stress/defence role in the skin (not a new idea) but also to begin to see, at this meeting, how it relates to an overall stress management strategy for mammals. With a total disregard for the programme I am going to begin with an excellent presentation by Vaudry detailing how the expression of the proopiomelanocortin (POMC) gene in the pituitary is under complex neuro-endocrine control. Working on frog pars intermedia he reported that the processing of POMC and the release of α MSH is under multifunctional control by neuronal and peptidergic factors. In particular, he described a 36 amino acid peptide, melanostatin which belongs to a highly conserved family of peptides of which NPY (found in high abundance in vitiligo) is the most well known. Melanostatin can completely block the release of α MSH. The intracellular mechanisms of its action were discussed and this talk was a very timely reminder that neuroendocrine factors affect the expression of the POMC gene, processing of POMC proteins and the release of α MSH in a coordinate manner.

Is α MSH important in man? An exciting shaft of light has broken through on this question. Previous studies in mice have shown that mutations in the MSH receptor (MC1R) gene affects the synthesis of eumelanin or pheomelanin resulting in coat colour changes in mice. Valverde *et al.*, reported at this meeting that variations in the MC1R gene were found in 21 out of 30 red haired individuals who tanned poorly but in none out of 30 dark haired individuals who tanned well. Individuals with red hair have a predominance of pheomelanin in hair and skin and are well known

for their failure to tan well and for their susceptibility to melanoma. (This oral presentation received the award of the Golden Melanocyte). The significance of this work is that it restores the status of the MSH receptor (and of MSH) to an important control point in the regulation of skin pigmentation in man as well as in mice.

Are melanocytes entirely dependent on delivery of MSH from the pituitary? For a number of years there has been considerable debate on whether malignant melanocytes can produce their own MSH- a presentation by Loir *et al.*, confirmed the presence of the full-length POMC transcripts in 8 human and mouse melanoma cell lines. α MSH cell content was detectable in 5 out of these 8 lines while the α MSH receptor was present in 6. The authors suggest that taken together this data strongly supports an auto- paracrine MSH/MSH-receptor loop active within the malignant melanocyte.

Are there other factors which control the response to MSH? - A protein encoded by the agouti locus in mice has been found to antagonise the ability of MSH to stimulate melanogenesis in cultured cells. However, the mechanism of the agouti protein action is not clear. Several presentations addressed this point (Sakai *et al.*, Hunt & Thody and Siegrist & Eberle). The protein appears to be able to inhibit melanogenesis both independent of any actions on the MSH receptor but also has the ability to induce down regulation of the MSH receptor. Thus, although its mechanism of action does not appear to be dependent on the presence of the MSH receptor, it would clearly influence and down-regulate the ability of MSH to induce pigmentation. A further factor-melanocyte concentrating hormone (Drozdz and Eberle) has also been found to have receptors on melanoma cells. As with the agouti factor, the expression of these receptors is not dependent on the simultaneous presence of MSH receptors. This factor causes skin paling in bony fishes and authors pointed out that it has been proposed to function as a stress related neuropeptide.

What is the role of α MSH in man? It appears to regulate eumelanin but not phaeomelanin synthesis. Put simply, in response to a pituitary release of α MSH one would expect the ratio of eumelanin to phaeomelanin to increase. Three structurally related enzymes - tyrosinase, TRP1 and TRP-2 - are responsible for eumelanin production via DHI and DHICA metabolites in mammalian skin and hair and these enzyme activities can be regulated by hormones derived from the POMC peptide. However, there is strong evidence emerging from studies on extracutaneous melanogenesis that eumelanin can be formed by tyrosinase independent routes and there are many different precursors to melanin and many different routes (enzyme dependent and independent) to this synthesis of coloured melanin. Why are there so many different precursors and do they all have biological significance and where does phaeomelanin fit in? In the chemistry/biochemistry of melanins Marco d'Ischia made a very strong case for the biological importance of the colourless melanins (such as 5-S-cysteinyl-dopa, 5-S-CD) and 5,6- (DHI) rather than for the coloured pigments we see. The latter may be equivalent to the discarded kitchen garbage which indicates that a good meal was prepared and eaten sometime earlier. d'Ischia further proposed a very attractive theory that melanocytes may act as an outpost of the skin's immune defence system by activating macrophages. He reported that DHI is capable of inhibiting the oxidation of arachidonic acid (and thus blocking leukotriene synthesis). Further DHICA was found to be capable of stimulating nitric oxide production by macrophages. Both actions would be consistent with the role of the melanocyte responding to local skin injury (e.g. inflammation). Nitric oxide was found to stimulate melanogenesis in a human melanoma cell line (d'Acquisto and d'Ischia) thus completing the loop in that the macrophage-induced nitric oxide production would stimulate a melanocyte to produce the colourless melanin precursor DHICA which can stimulate nitric oxide production in murine macrophages. The idea proposed was that DHICA serves a protective function in acute and chronic skin inflammation.

What other factors are relevant to the production of the various colourless and coloured melanins? Well, basically oxidative stress as perceived and responded to by the melanocyte. There is now a great volume of work which shows that melanocytes (as with other cells) have a range of strategies for coping with oxidative stress. To over simplify vastly, anything that affects oxidative stress management in the melanocyte will probably affect pigmentation and vice versa. The process of pigmentation will at some stages generate free radicals, at others "mop up" free radicals. An example of this was given in a presentation by Benathan. 5-S-CD levels were correlated with tyrosinase activity in normal and malignant melanocytes and thiocysteine was found to be a major player in the biosynthesis of 5-S-CD. But before talking further of the role of the melanocyte in coping with oxidative stress in the skin, one of the vexed questions regularly posed by Giuseppe Prota is what controls the production of phaeomelanins and why do we have them? For sometime now production of melanins via non-tyrosinase routes has been acknowledged and Rosei *et al.*, reported on a lipoygenase peroxidation of catecholamines and 5-S- catecholamines to give rise to eumelanin and phaeomelanin pigments. Also when H_2O_2 is high then another oxidative enzyme, xanthine oxidase can also behave as a peroxidase. Several talks confirm that the oxidative status of the cell has a profound influence on tyrosinase versus nono-tyrosinase. Tyrosinase activity has been reported to be inhibited by tetrahydrobiopterins (Wood *et al.*) when these are in a reduced configuration. In an oxidised form

these pterins will not bind or inhibits tyrosinase. thus, put far too simply, there are several enzymes in pigment cells which can process melanin precursors (L-tyrosine or L-dopa or catecholamines); which enzymes are active will depend to a large extent on the oxidative status of the cell which ultimately will determine the range of colourless and pigmented melanin precursors and melanins.

This undoubtedly complex area, nevertheless, seems to be the *raison d'etre* for the melanocyte and defects in the vitiligo melanocyte and melanoma cell ability to respond to oxidative stress have been studied intensively for a number of years. Major contributions by the groups of Piccardo and Schallreuter and Wood have been made over the years and in this meeting we heard of two approaches to treating vitiligo which have arisen from these lines of investigation. Piccardo *et al.*, reported that systemic administration of antioxidants in 112 patients with active vitiligo gave extremely encouraging results in arresting the progression of depigmentation in the majority of patients with some improvement in repigmentation in some patients. An alternative approach of twice daily topical application of a pseudocatalase and extracellular calcium combined with UVB short-term exposure twice a week has been used by Shallreuter and Wood who similiary reported very encouraging results in the treatment of vitiligo.

What of relationships between the melanocyte and the immune system? We heard in this meeting how the melanocyte and the macrophage might have an effective partnership in coping with inflammation in normal skin, however, it is apparent that in vitiligo and in melanoma, where melanocytes are arguably abnormal, the melanocytes provoke a deservedly hostile response from the immune system. A study from Van den Wijngaard *et al.*, proposed that immune infiltrates can induce melanocyte apoptosis and that this may occur in hypopigmentation (winner of the Silver Melanocyte for a poster presentation). Excitingly, nitric oxide, which is produced in large amounts during infection and inflammation, has been proposed to contribute to the detachment of melanocytes during the metastases of melanoma cells and possibly to the loss of melanocytes and hypo-pigmentary disorders (Ivanova *et al.*). Melanocytes containing pigment were less affected by the addition of nitric oxide releasing compounds than unpigmented cells.

Thus it is possible to see a role for the melanocyte emerging as a cell which is activated by α MSH as part of either a central or a local stress response. There may be several functions for the α MSH produced melanins - to respond to the increased production of free radicals by "mopping up" free radicals - to engage the services of the macrophages in helping mop up unwelcomed materials in the skin? - to terminate the local inflammatory response by blocking the synthesis of further leukotrienes. When the melanocyte, possibly through an intrinsic defect in its ability to respond to such oxidative stress, fails in its function, then it in turn appears to become a target for the immune system.

With respect to melanoma a review of new immunotherapeutic approaches to melanoma was given by Knudh. Treatment of melanoma remains very difficult and he made the point that several different approaches should be pursued such as, for example, antibodies to cell surface gangliosides and immunomodulatory therapy. Staying with melanoma tumours, TGF β expression in human tumours was found to be associated with tumour progression (Maretti) and a very careful study by Vetterlein *et al.*, showed that human melanoma cells can escape from negative growth control by TGF β . Normally TGF β inhibits proliferation of premature cells only, cells becoming insensitive to growth inhibition by TGF β , at which point TGF β stimulates melanogenesis. The relationship between proliferation, tyrosinase activity and melanin content of a range of human melanoma cells of different melanogenic potential was examined, from which the authors were able to conclude that there are at least two routes by which melanoma cells can escape from negative growth regulation by TGF1.

There was also a small volume of work examining how melanocytes, (normal, naevus and melanoma) interact with their extracellular matrix. Tyrosinase activity in normal adult melanocytes was found to be stimulated by a range of ECM proteins (Hedley *et al.*), but this was only detectable in the absence of strong mitogenic drives in the culture media, and naevus cells were found to adhere and migrate more strongly than normal melanocytes to ECM proteins (Mengeaud). In a comparison of ocular choroidal melanocytes and choroidal melanoma attachment to ECM proteins normal and neoplastic cells were found to differ in their substrate preference but both to show a similar dependency on intracellular calcium and calmodulin for attachment to ECM proteins (Wagner *et al.*, Winner of the Bronze Melanocyte for poster presentation). There was also a study of cell/cell adhesion in which melanoma cell binding to keratinocytes was found to be less than that of melanocyte/keratinocyte binding. E-Cadherin was found to play a major role in melanocyte/keratinocyte binding as antibodies to E-Cadherin reduced melanocyte binding. However, although melanoma cells expressed E-Cadherin, they bound weakly to keratinocytes suggesting some disturbance of the normal E-Cadherin relationship to the keratinocyte in these transformed cells (Nakazawa).

In conclusion, a very stimulating meeting in which one recurrent theme of the melanocyte playing a major role in coping with oxidative stress and, indeed, possibly being a part of the larger stress response (POMC, ACTH, Corticosteroid etc.) seemed to be emerging.

The meeting organisers offered awards to the three best contributions by young researchers: 1. The Golden Melanocyte: awarded to Valverde P. *et al.* (Dept of Dermatology, University of Newcastle Upon Tyne); 2. The Silver Melanocyte: awarded to van den Wijngaard RMJGJ *et al.* (Depts of Dermatology and Pathology, Academic Medical Center, University of Amsterdam); and 3. The Bronze Melanocyte: awarded to Wagner M. *et al.* (University Dept of Medicine, Clinical Science Centre, Northern General Hospital, Sheffield).

Discussion : Has melanin a photoprotective role ?

by Paolo U. Giacomoni

It is currently believed that melanogenesis is a natural, protective response to solar irradiation in the course of which melanin is synthesized in the melanocytes and transferred to the keratinocytes. If no one questions the fact that the process is a natural one, the question can be asked about the protective qualities against sunlight (if any) of melanin inside the keratinocytes.

What makes us think that melanin is protective?

Nordlund and co-workers (1) reports that the idea that melanin is protective has an history, the origin of which has been pinpointed down to Benjamin Franklin. As a matter of fact, Franklin observed that "dark coloured cloths laid upon fresh snow on a bright sunny day melted the underlying ice crystals more rapidly than light colored cloth" in agreement with the observation that, all the rest being equal, black objects exposed to sunlight reach higher temperatures than white ones. "It was known that black-skinned individuals normally inhabited tropical regions and that white individuals came from the north. It seemed perverse to Franklin that nature would endow individuals living in the tropics with a type of skin which was inappropriate for the environment. Everard Home resolved this enigma ... He exposed both his hands to the sun. One was covered with a black cloth, and the other was left bare. He measured the temperature of his skin. He found that the black cloth did indeed elevate the temperature of his skin a few degrees. However, the exposed hand became sunburned. He concluded that pigment did indeed cause a slight warming of the skin but protected it from the nonthermal, i.e., scorching, effects of the sunlight. Thus was born the idea that melanin was a sunscreen which prevented sunburn, a concept which persists to modern age and is only now undergoing reconsideration".

An obvious comment to Home's experiment is that it would have been better to cover both hands with cloths of identical manufacture, the only difference being the colour. An obvious comment to Home's conclusion is that the experiment proves protective properties for topically applied dark coloured molecules, and that nothing can be said about the role of endogenous pigmented granules.

Apparently this is the historical reason for believing that melanin is a natural against sunlight, possibly conformed by the observation that melanin production is a painless consequence of exposure to sunlight.

Upon learning more about the physiology of black skin, it was realized that black-skinned individuals exposed to sunlight experience sunburn as well. Someone also realized that prehistorical men used not to live in the sun-exposed savannah but in the sun-protected rainforest and scientists started wondering about the selective advantage of being black in such an environment. It was pointed out that in a forest environment, some sort of camouflage would be essential and black skin, reflecting only 16% of visible light, could be very effective for this purpose, much more effective than white skin which reflects 45% of visible light. Another selective advantage comes from the fact that radiant energy from sunlight can be absorbed by melanin and converted to heat. As a matter of fact, pigmentation can thus contribute to the maintenance of body temperature and to the conservation of metabolic heat, and be very important for prehumans, who slept without the benefit of fire or clothing and were not always successful in hunting (2).

Of course these discussions did not answer the question about photoprotective properties of melanin inside the keratinocytes and a number of experiments were designed in order to contribute to the advancement of knowledge.

Once it is made clear that the biological properties of melanin depend on its chemical structure (there is not one melanin, there are many different melanins, grouped in the categories of eumelanins and pheomelanins), one of the first questions which can be asked, when the role of melanin is questioned, concerns cell survival after UV irradiation.

Brian Johnson and coworkers observed that sunburn cells contained granules which appeared to be similar to those, known to be melanin, in basal layer cells. They also observed that in biopsies from normal human volunteers, the fraction of sunburn cells in lightly pigmented skin increased linearly with the dose up to nearly 90 per thousand malpighian cells for 8 Minimal Erythral Doses (MED), while in vitiligo skin, in which no melanocytes are present, the fraction of sunburn cells remained nearly constant (~5 per thousand) with doses up to 16 MED. (It has to be noted that Brian Johnson used to work in Dundee, so that if the volunteers were autochthonous there are chances for their epidermis to contain phaeomelanin). Taking advantage of the fact that macrophages can phagocytose melanin from the environment, Brian Johnson and coworkers exposed to UV from FS 20 fluorescent tubes, macrophages from mouse peritoneum which had been incubated with squid ink melanin. They observed that macrophages incubated for 24 hours with melanin were slightly more sensitive to UV than macrophages which did not take up melanin (3).

Another question which can be asked concerns the formation of UV-induced DNA damage in cells containing or not containing melanin. Schothorst and coworkers (4) undertook to expose cultured human keratinocytes and melanocytes to monochromatic radiation in the UV range and measured the amount of Endonuclease Sensitive Sites (ESS) versus the dose at different wavelengths. Melanocytes were grown in a medium containing isobuthyl-methyl-xanthine, so it is reasonable to believe that they were pigmented, even though the authors did not present the reader with figures relative to the amount of melanin per cell. The outcome of this experiment is particularly interesting: no difference can be pointed out in the dose- and wavelength- dependence of ESS formation in keratinocytes or in melanocytes in the UV-C and UV-B regions, except for a small difference when 297 nm radiation is utilized, in this case melanocyte DNA is slightly more damaged than is keratinocyte DNA. An analogous experiment was performed by De Leeuw and coworkers, who measured the residual clone-forming ability of cultured human melanocytes and keratinocytes after monochromatic UV irradiation. They found that melanocytes are slightly less sensitive than keratinocytes to UVB and more resistant to UVA than keratinocytes (5).

Of course, cultured melanocytes are not melanocytes in the epidermis, moreover their melanin is distributed in melanosomes within the dendrites and only occasionally is interposed between the cell's nucleus and the source of UV light. Therefore it seemed necessary to measure the protection against radiation of cells having ingested different amounts of melanin, making sure that these cells could not be suspected of digesting melanin as it could have been the case in the experiment with macrophages. Cell biology offers tools and methods for tackling this kind of problems. Ideally one should grow two samples of keratinocytes in the presence of homologous melanocytes, stimulate the first sample with UV light in order to include melanin synthesis and transfer of the pigment from the melanocytes to the keratinocytes, and treat the second sample according to a mock-irradiation protocol. After the transfer, which could be monitored by observation under the microscope, keratinocytes and melanocytes should be separated, the keratinocytes seeded, exposed to UV and checked for some physiological parameters (growth, DNA damage, loss of cytoplasmic enzymes, cell morphology and so forth). If melanin is photoprotective one expects sample one to be in a better shape after UV exposure than sample two. Of course such an experiment is extremely difficult to be carried out and some simplified protocols have been designed.

Hill and Hill induced B16 CL 4 mouse melanoma cells in culture to phagocytose melanin particles dispersed in the growth medium and subjected them to ionizing radiation. The result of the non-irradiated control was that after the incubation in the presence of melanin, the alkaline elution of labelled DNA reveals conspicuous nicking, the amount of which is dependent on the concentration of melanin to which cells were exposed. When cells preincubated with melanin are exposed to ionizing radiation, the results indicate that the nicking of DNA provoked by the two agents are additive (6). In another experiment, Hill and coworkers undertook to measure the survival of three Cloudman S91 mouse melanoma cell lines after exposure to ¹³⁷Cs radiation (7). The three cell lines contain different amount of melanin (respectively 1.2, 1.8 and 3.6 pg/cell) and, all the rest being equal, can be assumed to give responses to insults, which are dependent on the content of melanin. For low irradiation doses (below 5 Grays) there is a direct correlation between survival and melanin content. At 5 Grays, for instance, the surviving fractions for the three cell lines are 0.02, 0.09 and 0.3, respectively.

Of course this result gives information about the physico-chemical properties of irradiated melanin, but the phagocytosis of melanin particles is not equatable to the melanosomal transfer from cell to cell and it is not sure that, within a melanoma cell, melanin forms a cap around the nucleus as it forms in keratinocytes.

Because of the difficulty to learn in cultured cells about the role of melanin in human epidermis, Young and co-workers designed a clever experiment with human volunteers. In order to have cells containing more or less melanin, all the rest being equal, they exposed the volunteers to a series of suberythral UV irradiations from a solar simulator, either in the presence of a conventional

sunscreen, in order to maintain an "amelanotic" status, or in the presence of the same sunscreen added with trace amounts of 5-methoxypsoralen, in order to obtain an artificially generated "highly pigmented" status, or without xenobiotics in order to obtain a naturally "melanin enriched" status. One week after the end of the series of the suberythematous irradiations, the volunteers were exposed to an erythematous dose of UV and checked for several parameters, such as melanin content and stratum corneum thickness (taken as two possible natural sunscreens) and the extent of Unscheduled DNA Synthesis (UDS or DNA repair), taken as an indicator of the extent of DNA damage, which is a major target of sunlight (8). The results seem to indicate that acquired pigmentation affords better protection against DNA damage, at least in phototypes III, IV and V. Yet the authors conclude that "Photoprotection is often explained by induction of melanization and/or stratum corneum thickening. As such induction was independent of skin type and similar for the three types of treatment, there is no overall correlation between either or both these parameters with UDS levels, which indicates that photoprotection is more complex than previously thought".

A Symposium on "Melanin: Its Role in Human Photoprotection" was held in March 1994 in Washington, D.C. and the discussions pointed out that the consensus about the role of melanin is far from being reached. The major clinical observation, pointed out by Helene Hill as well as by Albert Kligman, John Pawelek and James Nordlund, that skin cancer rates correlate inversely with skin pigmentation, is the only major evidence in favour of a protective effect of melanin. Yet this protective effect does not necessarily imply that it is exerted via the sunscreen properties of melanin itself. One could for instance imagine that the vigorous activity of the melanocyte as a modulator of inflammation, manifested as dark or tanned skin, protects the individuals against skin cancers (Nordlund). One can also surmise that melanin can play several roles in oxido-reduction reactions triggered by UV radiation within exposed cells, and that the end result will depend on the initial oxidation status of the cell, that is to say, to every experiment a different result (Menter & Willis).

As a matter of fact the photochemical, photophysical and physico-chemical properties of melanins have been discussed by Miles Chedekel who stated that "melanin can contribute to photoprotection by directly scavenging free radicals, especially active oxygen species". On the other hand Menter and Willis wrote: "depending on the reductant, melanin either retards or accelerates ferricyanide reduction. Melanin also acts as an electron conduit in markedly accelerating the tyrosinase catalyzed oxygenation of p-hydroxyanisole...The net result of such melanin mediated processes, if they occur *in vivo*, could be either beneficial or deleterious to the organism". The outcome of the meeting was brilliantly expressed by the title of Kligman's abstract: Is melanin photoprotective? Answer: sometimes yes, sometimes no".

Some authors are considering the possibility that the properties of melanin might depend on its chemical and stereochemical properties. Melvin Eisner suggested that "the protective capabilities of melanin may be influenced strongly by the morphology of the melanin granule. The layered structures found *in vivo* do not seem to make full use of the optical absorptivity of the interior melanin, suggesting perhaps a separate quenching or sequestering role".

On the basis of all these considerations, an observation made in our laboratory might help in designing new experiments. We have indeed observed that in the presence of metal chelators such as ~1 millimolar EDTA or ~10 millimolar citrate or ~100 millimolar histidine, some melanins become water soluble at neutral pH and can be re-precipitated by the addition of millimolar amounts of divalent cations such as calcium, magnesium, iron, copper and so forth (10,11). The interesting aspects of the phenomenon is that: i) divalent cations can also precipitate eumelanin dissolved in sodium hydroxide ii) the precipitate forms particles the diameter of which can be submicrometric iii) conditions can be found in which the diameter increases slowly with time. These findings make it possible to prepare melanins with different physico-chemical properties in order to check Eisner's hypothesis. They also bring circumstantial evidence in favour of the model which suggests that some of the protective properties of melanin are linked to its capability to bind iron and other transition elements which might play a role in photofenton phenomena or in metal catalyzed oxidations.

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ESPCR next meetings:

1997 ESPCR Meeting: Krakow - Dr T. Sarna

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