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EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH BULLETIN

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OBITUARY **by Prof. P. Riley**

Bengt Larsson (1942-1998)

It is with deep regret that we report the death of Bengt Larsson. He died suddenly at home in Uppsala on 8th October 1998.

Bengt Larsson was born in Umea in 1942. He was proud of his Northern roots but had settled in Uppsala where he was Professor of Toxicology in the Biomedical Centre of Uppsala University. He entered the University of Uppsala in 1965 to read philosophy, literature and the humanities and went on to study mathematics, chemistry and geology. He had a deep interest in nature, especially in birds, and was also a gifted musician.

His career began when he joined the Department of Toxicology in 1973 to work with Nils Gunnar Lindquist and Sven Ullberg at which time he switched his attention to biology and medicine and was awarded his PhD in 1979. His knowledge of chemistry led him to pioneer the development of X-ray film that could be used for tritium autoradiography (now sold widely for this purpose as Tritiumfilm, Ultrofilm ^{3}H and Hyperfilm ^{3}H). Autoradiographic techniques were then being introduced for the detection of the biodistribution of materials and Bengt applied this to a wide variety of systems. His main research work work was related to the interaction between chemicals and melanin. He demonstrated the selective accumulation of drugs in melanogenic tissue and became a world authority in this field. He published many original papers pertaining to this topic and was frequently asked to review progress in this area, particularly in respect of the possible diagnostic or therapeutic potential in melanoma of agents selective for melanogenically active cells. His pre-eminence in his field also led to his involvement in many international research ventures and he was widely respected and admired.

Not only did Bengt Larsson's studies demonstrate melanin binding by a wide spectrum of compounds but the reasons for the affinity were explained in detail. His work emphasized the relative importance of electrostatic interactions and the formation of charge-transfer complexes in the binding of chemicals to melanin. He also showed the contribution of hydrophobic interactions to the melanin-affinity of compounds such as polycyclic hydrocarbons and aflatoxin B_1. The important cytotoxic consequences of melanin affinity to the ear and the extrapyramidal system (as in MPTP-induced Parkinsonism) was investigated with Lindquist and Annika Lyden-Sokolowski.

Bengt Larsson, together with Lennart Dencker, demonstrated the covalent uptake of thiols by melanogenic tissues and, in studies with Ulrik Ringborg, showed that radioiodine-labelled thiouracil has clinical potential as a diagnostic aid in melanoma. He was also involved in the possibility of using this vehicle for boron neutron capture therapy (BNCT) and, in collaboration with Amilcar Roberto and Ulla Mars, had developed a radiographic technique based on boron-thioureylenes. He was actively pursuing this area of radiopharmacology at the time of his death.

Bengt Larsson organised a most successful ESPCR Scientific Meeting in Uppsala in 1989. He was very proud of the important biological tradition centred on Uppsala, the home of Linnaeus, and enjoyed showing visitors round the museum at Hamarby. The Conference Reception was held on a warm summer's evening in the Botanical Gardens founded by Linnaeus. In 1991 he was elected to the Secretaryship of the ESPCR. At that time the Secretary of the Society was also the Treasurer and Bengt Larsson was very successful in building up the finances and was the first to obtain Industrial sponsorhip for the Society.

Bengt Larsson was elected President of the ESPCR in 1994 and carried out his official duties with distinction. He was unfailing in his support for the membership and his able and benign Chairmanship was greatly appreciated by the Council. He served on the Council of the IFPCS and was instrumental, as a member of the Publications Committee, in guiding the Federation through several difficult times.

He was, at the time of his death, Treasurer of the IFPCS. His patient and undemonstrative style was widely admired and he was painstaking and diligent in discharging his responsibilities.
Bengt was a deeply reflective man who felt most comfortable in the solitary grandeur of the natural world. He grew up in a liberal household and as a boy overheard many political conversations between his parents and visiting Party leaders and members of the parliament (Riksdag) which may have influenced his broadminded view of life. His childhood summers were spent on the small island of Holmon at peace in the contemplation of nature, and he returned there regularly with his family in later years. His love for the woods and the silent waters of his homeland seemed to be reflected in his quiet and generous nature. He was, in every sense, a gentleman. We have lost a fine scientist, a loyal servant of the ESPCR, and, most of all, a true and beloved friend.
He is survived by his wife, Pia, and daughter, Liselott, to whom we offer our deepest condolences.

OBITUARY **by Prof. G. Prota**

Bengt Larsson: A Tribute to a Friend

As Past President of the European Society for Pigment Cell Research and of the International Federation of Pigment Cell Societies, but first of all as an old friend of Bengt Larsson, I was sincerely urged to write these few words to commemorate through our Bulletin one of the dearest colleagues of the pigment cell community, whose sudden death left us astonished and with an unbelievable sense of loss. All too often, obituaries are laden with rhetoric and verbous sentences of condolence: no one less than Bengt, I am sure, would have liked this. His typical Anglosaxon style, with a peculiar sense of humour, his calm and relaxing appearance, totally devoid of exibitionism and exaggerations, gained him widespread appreciation among his colleagues. Adjectives like reserved, gentle, elegant, persuasive, serious could hardly be omitted in descriptions of his human profile and personal traits, in spite of his internationally recognized scientific competence and leading positions within the ESPCR and IFPCS. Bengt was one of the pillars of the international pigment cell family. I met him when he was still a student, and since then he has always been an aficionado of our workshops and meetings. In 1989 he took the responsibility of organizing the highly successful 2nd ESPCR meeting, after which he became increasingly implicated in the various affairs of the ESPCR, as member of the Council, as the Secretary, during my tenure as President, and then as the President. When he was nominated for this position, I was sure that the Society would have greatly benefited from his wisdom and harmonious personality, especially after years of turbulence. And, indeed, he contributed greatly to the success of the ESPCR and shared our pride in seeing its prolific growth in membership and quality of science. Bengt was the man who made everything easy: both in the running of the Society and in research. We had several opportunities to exchange views and ideas about delicate or troubling matters, and I don't remember I ever saw him disappointed or angry at anything. His phylosophy was marked by a basically optimistic attitude as, in his view, questions could be easily settled with a little of common sense.
A few words need to be spent about his scientific achievements. Bengt Larsson has tightly bound his name to the field of thiouracil and thioureylene melanoma seekers. He was internationally recognized for a number of outstanding contributions toward the mechanisms of action of melanin affinic drugs, through a very competent use of whole body autoradiographic techniques, and his interests had shifted very recently toward the drug binding properties of pheomelanins. Bengt is dearly missed by all of us who had the fortune to meet him personally. It will be hard for us to attend the next Pigment Cell Conferences and meetings and not to have him presenting his results or chairing scientific sessions, or telling anecdotes on the occasion of social events. Like his many scientific papers will provide a permanent record of his outstanding contributions to melanoma research, his pictures will leave vivid memories of a tall, slim gentleman.

MEETING REPORT

8th MEETING OF THE ESPCR, PRAGUE, 23-26 SEPTEMBER 1998

by Dr Sheila Mac Neil

This meeting was held at the time of the 650th Anniversary of Charles University, Prague and was organised by the 1st Faculty of Medicine, Charles University. The spirit of the city of Prague and of Charles University was evident in every aspect of the meeting. A strong sense of history and of continuity graced the proceedings, the kindness and gentle humour of our Czech hosts made this an extremely pleasant meeting.

Who was there?

The ESPCR meeting was attended by 142 participants from 17 different countries. In 2½ days there were 10 scientific sessions and 6 plenary lectures and 54 posters. A busy time but still with plenty of time for excellent music and food and wonderful beer and time to catch up with friends and colleagues.

Nature of report

Several colleagues have kindly contributed a summary of the highlights of sessions they chaired and have also identified particular talks or posters that they found raised their pulse rate. In this respect there was one particular plenary lecture which stood out above all others - **John Pawelek** and colleagues provided new experimental evidence that could change how we think about metastatic melanoma ... For details, see a fuller description later in this report (under "Our favourite things").

SESSION I Melanin-synthesis, properties and function

Report kindly provided by Professor Patrick Riley

Six papers were presented in this Session and 3 posters (P1, P3 and P52) were included in the discussion. The first talk was a brief and lucid exposition by **Professor Christopher Ramsden** of a series of chemical studies inspired by some new reactions found as a result of work on tyrosinase oxidation of analogue substrates. In this he outlined the production of the indoliumolate betanes and described work which led on to the study of the facile formation of quinomethanes from orthoquinones under conditions in which the alpha carbon has acidic character. This latter characteristic of these reactions enabled a reinterpretation of the famous Gates' synthesis of morphine. In the discussion of this paper **Dr. Edward Land** briefly mentioned the poster display P1 devoted to the generation of orthoquinones by pulse radiolysis, a technique that permits the measurement of the rate constants of subsequent reactions, such as cyclisation or isomerisation to form the corresponding quinomethanes.

Dr. Allesandra Napolitano then presented some new chemical evidence enabling a more detailed description to be given of the intermediates in the oxidation of cysteinyl dopa leading to the formation of benzothiazines. This talk was followed by a discourse by **Professor Bruno Nicolaus** concerning the fundamental structural features of melanins. In this he emphasised the importance of the chemical "backbone" of conjugated double bonds permitting the possibility of semiconductor properties of melanins. He pointed out that the melanisation of deep-sea vertebrates for example, where no light-absorbing function would be expected, have evolutionary value and leads to the expectation that there are other functions of melanins that are important. Whether melanin should be considered as jewel or garbage remained, however, an open question.

Dr. Jim Gallas then gave a spirited exposition of work on neutron diffraction analysis of experimental melanin solutions. He showed that there were specific aggregation patterns with a 3.4 Angström stacking characteristic, suggesting a layering phenomenon. These aggregates could be disrupted by hydrogen peroxide. **Professor Milan Elleder** then gave a brilliantly illustrated talk showing UV irradiation-induced fluorescence in pigmented tissue. This was also shown to be a feature of synthetic melanin and could be stimulated by prior treatment with hydrogen peroxide. The following talk by **Dr. Luciana Mosca** illustrated similar fluorescence in material generated by the oxidation of tyrosyl residues in opiate peptides. In discussion, the possibility that the fluorescence was dependent on degradation which involved Fenton chemistry, and thus bore similarities to the methodologies employed in posters P3 by **Donato** et al. and P52 by **Wakamatsu, Ito and Koch** was proposed. However, caution in the interpretation of the autofluorescence phenomena was urged by **Professor Tadeusz Sarna** who pointed out that, at least *in vivo*, there were a number of other compounds that could undergo autofluorescence and might be influenced by melanin in the micro-environment. **Professor Karin Schallreuter** strongly suggested that the fluorescence was related to other compounds that were known to be present in melanosomes such as the pterins, an interpretation that was not accepted by Professor Elleder who pointed that this could not be the case with synthetic melanins. The interesting differences between the case of induction of autofluorescence between eumelanins and phaeomelanins was also briefly mentioned, but lack of time prevented a full discussion of this interesting new data which may have diagnostic significance in view of the apparent increase in phaeomelanin synthesis in dysplastic naevi (a topic mentioned in a later session of the meeting).

SESSION II Melanogenesis

This contained 4 talks. Most controversial of these was that presented by Professor Karin Schallreuter. **Professor Tony Thody** comments on this session.

"One would have expected a little more on the MSH peptides in view of the current controversy concerning their significance as pigmentary hormones in humans (see Session IX for MSH and immunomodulation). The topic was at least touched on by **Karin Schallreuter** in her plenary lecture on pterins and pigmentation. It is now clear from her work that 6-tetrahydrobiopterin (6-GH_4) has an important role in melanogenesis by regulating the availability of L-tyrosine and tyrosinase activity. She now has new data which suggests that α-MSH figures in this control through its ability to bind 6-BH_4 and the implications are that α-MSH is able to regulate melanogenesis through activation of the MC-1 receptor and also through actions which are independent of the receptor. This is an extremely novel idea and hopefully we shall hear more on the subject at future ESPCR meetings".

Nico Smit presented work on the flavonenzyme DT-diaphorase suggesting that this enzyme may enhance oxidative stress by generating redox cycling catecholes and depletion of NAD(P)H unless other detoxifying enzymes are present.

Benathan and colleagues looked at the effects of thiol-modulating agents on melanogenic activity of normal and malignant pigment cells. Their results suggested that the balance between cysteine and glutathione may play an important role in regulating melanogenic activity of pigment cells. **Ullrich Schraermeyer** et al. presented evidence that melanosomes in retinal pigment epithelial cells are active lysosomes involved in the degradation pathway of rod outer segments of the eye.

SESSION III Microphthalmia encoded Transcription Factor and melanogenesis
Report kindly provided by Professor Vincent Hearing.

Vincent Hearing and **Anthony Thody** co-chaired this brief but interesting session which centred around the role of MITF (Microphthalmia encoded Transcription Factor) and other transcription factors that regulate mammalian melanogenesis. It has been known for some time that MITF, a basic helix-loop-helix transcription factor, regulates tyrosinase gene expression (as well as TRP1/TyrpI and/or TRP2/Dct, although these have been disputed) through binding to the E-box upstream regulatory region present in all 3 encoded genes. In this session, we heard that at least one, and probably many other, factors also play important roles in this regulation. Initially, **M. Furumura** reported his studies looking at transcriptional modulation of TRP genes by murine ITF2, another bHLH transcription factor originally identified by him as being upregulated during pheomelanogenesis. ITF2 was able to trans-activate the TRP1 gene as strongly as MITF, stimulated tyrosinase gene expression somewhat, and TRP2 expression not at all. Interestingly, ITF2 was able to inhibit MITF stimulation of TRP gene expression, probably by generating inactive heterodimers between MITF and ITF2.

J. Vachtenheim next reported on the role of MITF in human melanoma cells; they showed that expression of MITF is repressed in some cultured melanoma cells, and that this was associated with downregulation of tyrosinase, TRP1 and TRP2 genes in those cells. They directly demonstrated MITF regulation of those genes in human melanocytes by transfecting MITF back into those cells and demonstrating consequent upregulation of one or more of those TRP genes in the transfected cells. Their data support the critical nature of MITF expression in the pigmented phenotype of human melanocytes, and further suggest that repressors may be present in unpigmented cells which may also play important roles in regulating expression and catalytic function of those enzymes. Finally, **S. Olaizola-Horn** reported on the regulation of MITF and tyrosinase genes. Tyrosinase expression can be regulated via the cAMP and PKC pathways, but intracellular signalling pathways regulating MITF expression are not yet known. This study showed that treatment of melanocytes with forskolin to stimulate cAMP levels induced MITF gene expression within 4 hours and tyrosinase gene expression within 48 hours. Depletion of PKC by prolonged TPA treatment resulted in a decrease in pigmentation but was accompanied by increased MITF mRNA levels. These results suggest that tyrosinase and MITF gene expression are both regulated via cAMP and PKC pathways, but independently. This study further shows that factors other than MITF regulate tyrosinase gene expression and thus human pigmentation. The general conclusion of this session is that MITF is an important regulatory factor in controlling TRP gene expression, but that one or more other transcription factors are also important at this level of regulation.

SESSION IV UV light, photoprotection, phototherapy
Report kindly provided by Professor Césarini.

This session was chaired by **Professor Tad Sarna** and **Professor Césarini.** The session was composed of 11 formal oral presentations to which 4 posters can be linked and were briefly discussed at the end (the programme of the session was organised in co-operation with the European Society for Photobiology).

Three major topics were exposed: photoprotection, progress in photodynamic therapy and some insights in melanoma cell biology.

J.P. Césarini and **H.C. Wulf** presented the natural photoprotection offered by melanins for different phototypes and the acquired photoprotection after serial exposures to UVA + B radiations. Topical sunscreens (Sun Protection Factor based on protection against erythema) are able to suppress the actinic erythema but other UV effects like immunosuppression or indirect evidence for genotoxicity, are still present in the absence of

erythema. The importance of skin-vehicle interaction was emphasised by **B. Gabard** and the skin penetration of UV filters seems a critical point for the quality of sunscreens. **R. Pedeux** had shown p53 expression in melanoma cells in culture. In work presented by **E. Wencz**, the association of UVA sensitivity and phaeomelanogenesis was found phototoxic, the melanin content being strongly correlated with UVA-induced single strand breaks in melanocytes.

The second part of the session was devoted to photodynamic phototherapy. **S.B. Brown**, after a review of the literature, explained how light source dosimetry and treatment protocols can be improved, and pointed also the need for more basic studies. **G. Jori** found that the tumour response (pigmented melanoma in mice) was affected by a variety of parameters and that hyperthermal conditions (43-44°C) contributed to the damage to the tumour, the photo bleached tumour being more susceptible to the PDT treatment. **M. Jiraskova** emphasised the red fluorescence observed after intralesional injection of PDT, the fluorescence being of great help for the evaluation of tumour extent. **G.M.J. Biejersbergen-van-Henegouwen** suggested that photobinding of chemical with DNA or proteins is a pre-requisite to obtain specific suppression of hypersensitivity in extra-corporeal phototherapy with UVA. The induced singlet oxygen produces immune suppression.

The third part was more specifically devoted to some biological aspects of melanoma. **H.Z. Hill** found that serum-free conditioned medium of cultured melanoma cells, following irradiation with ionising radiations, contains some antigenic proteins that increases the survival of melanoma cells. This may explain some drawback of radiotherapy and chemotherapy of melanoma. **E.M. Link** demonstrated that UV and ionising radiations may trigger the melanoma metastasis. Some "physiological" factors, like eicosanoids, may trigger the metastatic cascade. The production of eicosanoids was accompanied by the activation of ACTH and α-MSH mediated immune system (adrenal axis feedback loop).

SESSION V Pigment cell cultivation (My comments on this session).

Ullrich Schraermeyer reported on experience with both explant and enzymically dispersed culture of porcine and human iridial melanocytes. **Roger Bowers** reported on premature death of avian melanocytes in Barred White Leghorn feathers. He was able to induce premature death *in vitro* by the addition of L-dopa plus α-MSH or by not changing medium. Both led to an increase in oxygen radical accumulation and development of apoptosis in melanocytes. Using this model, he was then able to look at strategies to "rescue" melanocytes from oxygen radical accumulation. Addition of superoxide dismutase was particularly effective and he suggested that this avian *in vitro* system could be used to study premature ovarian melanocyte cell death analogous to that found in vitiligo.

Next was a presentation from **M. Regnier** from L'Oreal on the use of keratinocyte-melanocyte co-cultures and pigmented reconstructed human epidermis to study modulation of melanogenesis. Dr. Regnier demonstrated that co-seeding melanocytes and keratinocytes on acellular human dermis gave a model in which UV induction of pigmentation could be observed and the efficacy of topical applications of pro or de-pigmenting agents could be followed. In question time, I asked whether α-MSH induced pigmentation in these models and whether the model had ever been constructed with fibroblasts present. Dr. Regnier replied that MSH was not melanogenic in this model in their experience and the contribution or otherwise of the fibroblast had not been examined in this model.

This related to a presentation by **Paula Eves** et al. (from my own laboratory) where we found that the addition of fibroblasts to such a reconstructed 3D skin composite (based on sterilised human de-epidermised acellular dermis to which melanocytes and keratinocytes and fibroblasts were added) actually reduced the spontaneous pigmentation of the skin composites. In agreement with Dr. Regnier, however, we also find MSH to be without effect on pigmentation in this model irrespective of the presence or absence of fibroblasts.

Using this model we demonstrated that, in collaboration with **Professor Ghanem**, the human melanoma cell line (HBL), which is poorly invasive on its own, could be demonstrated to traverse the basement membrane when keratinocytes were also present. Keratinocytes on their own did not invade the basement membrane. This suggests some interaction between the melanoma cell line and keratinocytes which may be relevant to initial escape of melanoma cells from the primary tumour.

Sviderskaya et al. then reported on the establishment of 3 unpigmented lines of a new cell type from neonatal murine skin. These cells appear to be neural crest-like.

Aranberger et al. then gave a brief video (in the absence of any of the authors) of grafting of melanocytes and keratinocytes for patients with vitiligo.

SESSION VI Pigment cells and oxidative stress (My comments on this session).

For several years now pigment cell melanoma cell biologists have been asking whether melanocytes and melanoma cells differ in their handling of oxidative stress and indeed whether a failure to handle oxidative stress might contribute to melanocyte failure and their ultimate removal (as

in vitiligo) or even to melanocytic transformation.

Continued work on this theme from the group of **Professor Frank Meyskens** focused on differences in the basal levels of the superoxide anion and hydrogen peroxide in cutaneous metastatic melanoma cells and cultured melanocytes (I am indebted to **Dr. John Haycock** for this summary of this work). These authors found that metastatic melanoma cells have higher levels of both superoxide anion and hydrogen peroxide than normal human melanocytes as determined by FACS analysis etc.

Next, he reported that melanocytes did not respond to an oxidative stress with an increase in NF-kB DNA binding activity, whereas metastatic melanoma cells did. Also, the level of constitutive NF-kB activity in metastatic melanoma cells was higher than in melanocytes. This could be reduced by incubating the cells with two types of antioxidants: (i) pyrrolidine dithiocarbamate or (ii) 1, 10-ortho phenathroline (a metal ion chelator which acts as antioxidant by removing transition metal ions, thereby preventing metal catalysed oxidation proceeding by the Fenton reaction).

He speculated that an NF-kB response might be seen if a high enough oxidative stress were given. The absence of a response, he thought, was due to a high level of intracellular antioxidant protection.

The interest in NF-kB Rel family members was extended to include various heterodimer formations, identified in the two cell types by immunoprecipitation. These included various combinations of p50, p65, p75 and p52. Under basal (unstimulated) conditions some combinations of Rel dimers were either very low or undetectable in the metastatic melanoma cells in contrast to the melanocytes.

Mauro Picardo and colleagues gave a presentation continuing their work into investigating the anti-oxidative status of patients with melanoma. They presented evidence that whereas in normal subjects, there was a correlation between epidermal and peripheral blood mononuclear cell levels of superoxide dismutase, catalase and vitamin E, this correlation was not seen in melanoma patients suggesting that some patients with melanoma may have a constitutive metabolic alteration. This, in turn, may contribute to their susceptibility to external oxidative stress.

In a second presentation from this group, **Dr. V. Maresca** presented evidence that the potent inflammatory cytokine, TNF- α, can itself generate pro-oxidative stress in melanoma cells. The response of cells to TNF- α may differ depending on the levels of intracellular antioxidants and peroxidisable compounds in the cells.

The final talk from **Roger Bowers** and colleagues continued Roger's work in trying to (a) deliberately drive to the point of destruction his chicken melanocytes and then (b) rescue them from impending death by paying attention to their ability to cope with oxidative stress. In this study, he showed that the addition of iron to the failing melanocytes increased their mortality rate significantly and that, as expected, drugs which compromised the ability of the cell to cope with oxidative stress (via buthionine sulphoximine addition, a glutathione inhibitor) and a superoxide dismutase inhibitor (diethyldithiocarbamate) both increased mortality rate in the feather melanocytes of the Barred White Leghorn.

SESSION VII Neuromelanogenesis

This was chaired by **Professor M.G. Peter** and **Professor Bengt Larsson.** (Comments by myself)

The first presentation by **Vincent Hearing** concerned macrophage migration inhibitory factor (MIF). This was originally identified as a lymphocyte-derived protein that inhibited monocyte migration. More recently it has been found to catalyse the conversion of dopaminechrome and norapenaphrinechrome, toxic quinone products of the neurotransmitters dopamine and norapenaphrine to indole quinone derivatives that may serve as precursors in neuromelanin. He demonstrated that MIF rescue cells from dopaminechrome-induced death *in vitro* and speculated that as MIF was highly expressed in human brain, it may participate in a detoxification pathway for catacholamine products and could, therefore, have an important protective role for neural tissues.

M. Miranda et al. then presented data of possible relevance to Parkinson's disease. In Parkinson's disease there is degeneration of the dopaminergic cells in the nigro-striatum system. A low level of tyrosine hydroxylase prevents transformation of L-tyrosine to L-dopa. A common therapy has been the administration of the dopamine precursor (L-dopa) but it does have severe side-effects. An alternative approach of stereotactic injection of liposome-entrapped tyrosinase was used to significantly increase the levels of dopamine in the rat brain.

SESSION VIII Gene expression in pigment cells
Chaired by Friedrich Beermann and myself! (Comments by myself).

This contained 5 talks.

In the first from **Richard King** and colleagues, transcripts of the Hermanski Pudlak Syndrome (HPS) chain were mapped. They identified several mutations and polymorphisms in this gene in individuals with HPS.

G. Kraehn and colleagues then presented work on differential expression of receptor tyrosine kinases in melanocytic skin lesions.

Staying with differentially expressed genes, the next presentation from **R. Hipfel** et al. searched for differentially expressed genes in malignant melanoma and congenital nevi biopsies. Using the technique of differential display more than 120 melanoma-specific and about 100 nevi-specific products were cloned and screened. Of these, 10 melanoma-specific transcripts were confirmed and sequenced. Three of these genes were singled out for particular interest as they concerned a cysteine protease, a protein proteinase inhibitor and a gene product that is mainly expressed in the brain and may function as a transcription factor.

The next presentation from **J. Utikal** et al. focused on c-myc oncogene expression and reported over-expression of c-myc with late stage melanoma which the authors speculated might be due to an increased number of c-myc - chromosome-8 copy number.

The last presentation from **U. Leiter** et al. concerned the apoptotic pathway in melanoma. These authors concluded that bcl2 gene expression increases in malignant melanoma which might reflect an increased malignant potential caused by an inhibition of apoptosis conferring a growth advantage in melanoma metastasis.

SESSION IX Melanoma - experimental aspects
This was chaired by Professor Doré and Professor Garbe. (Comments by myself).

It contained the most exciting presentation of the meeting (not just my opinion but resoundingly confirmed by **Tony Thody, Frank Meyskens, Jan Borovansky** and no doubt many others). For details of this presentation by **John Pawelek**, please see under "Our favourite things".
There were 6 other talks in this very lively session.

Friedrich Beermann and colleagues have used transgenic mice methodology to develop animals with tumours of the retinal pigment epithelium. This has been achieved using SV40 transforming sequences directed to the developing RPE using the promoter of tyrosinase-related protein-1 (TRP-1) in transgenic embryos. Work has advanced to the stage that primary tumour cell lines and metastasis derived from these have now been established and characterised.

Ruth Halaban and colleagues presented work in which they have examined to what extent the retinoblastoma tumour suppressor protein (RB) contributes to tumourigenicity in melanocytes. They were able to neutralise RB function and this led to releasing melanocytes from their normal cell cycle constraints but these melanocytes remained phorbol ester dependent and underwent accelerated cell death in the absence of phorbol ester. Thus, it appears that loss of this protein is insufficient for melanocytic transformation but clearly contributes to regulation of melanocytes by external growth inhibitory signals.

The next talk was from my own laboratory (**B. Richardson**) on the influence which sex steroids can exert on melanoma cell invasion (at least *in vitro*). Epidemiological studies show female survival benefit in advanced metastatic melanoma which is largely unexplained. Using a very simple model of a melanoma cell line (A375-SM cells) invading through a layer of human fibronectin over 20 hours, we were able to show that the female steroid 17β-oestradiol and, to an even greater extent, oestrone, significantly reduce invasion of cells. Other androgenic and adrenal steroids were ineffective. This *in vitro* data begins to offer an explanation to the apparent female survival advantage in metastatic melanoma.

The next talk was from **Dr. J. Haycock** from my laboratory working in collaboration with **Professor Ghanem**. Jointly, the two laboratories have previously shown that α-MSH is able to oppose the actions of the pro-inflammatory cytokine TNF-α in both melanocytes and melanoma cells. The current study progresses this work to show that α-MSH can be demonstrated to oppose the actions of TNF-α at the level of activation of the transcription factor NF-kB. Thus, TNF-α would normally activate NF-kB to a maximal degree within 1-2 hours in cutaneous and ocular melanocytes and

melanoma cells. We have demonstrated that α-MSH can reduce this activation by 50% on average, demonstrating for the first time in melanocytes and melanoma cells that the immunomodulatory action of α-MSH may rise by inhibiting the normal cytokine induced activation of NF-kB in both melanocytes and melanoma cells.

The next talk from **P. Parsons** et al. concerned the anti-tumour activity of agents which affect acetylation of histone. Cell killing was accompanied by hyperacetylation of histone H4.

The last talk in this session was from **Stan Pavel** and colleagues. They presented evidence that the composition of melanin in melanosomes of dysplastic naevi is very abnormal with increased concentrations of sulphur and, hence, phaeomelanin. According to Frank Meyskens - "they are building a compelling case that the naevi are under chronic oxidative conditions and, hence, internal genotoxic stress".

SESSION X Melanoma - clinical aspects
Report kindly provided by **Professor Frank Meyskens.**

Progress in the clinical area lags behind that of the tremendous advances occurring in our basic understanding of melanoma. There were, however, a couple of novel observations reported. **Blum** and his colleagues (Tuebingen) reported on a large comparative study of clinical examination to ultrasound evaluation of regional lymph nodes. Comparison to histopathological analysis indicated that ultrasound was more effective than palpation. Also, from the same group **(Blaheta)** was presented the results of another large study showing that sentinel node evaluation and biopsy combined with RT-PCR for tyrosinase in apparently negative cases increased the diagnostic accuracy. If the results of these two studies can be confirmed, their usage will be important in determining who might and might not benefit from adjuvant interferon, a difficult and expensive intervention. The Ulm group **(Kaskel)** also reported a large series in which S-100 was evaluated as a marker of disease. Its elevation in serum was found to correlate with high frequency with the appearance of metastatic disease; however, more extensive studies will need to be done to determine its usefulness as a prognostic or response (to therapy) marker. The remainder of the presentations of the papers in this session dealt with the epidemiology of melanoma in Germany and, although of interest to workers and the public in Germany, did not provide new or unexpected information about the disease.

OUR FAVOURITE THINGS

The presentation which attracted most attention and probably has caused many of us to go away and re-evaluate some of our ideas was that from **John Pawelek** in which he showed that experimentally mouse melanoma cells can fuse with macrophages to form hybrids, many of which are more aggressive metastatically *in vivo* than the parent cell line. *In vitro*, these cells were found to be more heavily pigmented and responsive to MSH than the parent cell line. The hybrids also responded to MSH with increased chemotaxis - a property not noted in the parent cell line.

John took great pains to point out that this is not a new idea - fusion of cancer cells with macrophages has been previously noted for other cancers including melanoma **(Munzarova** and colleagues, Lancet 1987 and Melanoma Research 1992) and it offers another explanation for how melanoma cells acquire metastatic success. Quoting from Munzarova et al. "We are of the opinion that the rapid assimilation of multiple properties from various populations of cells (and especially those of macrophages) obtained by fusion and processes after it are a better explanation of many of these qualities than the requirement of a single cell lineage to undergo sequentially so numerous mutagenic alterations" (Munzarova et al. Neoplasma 1992; 39: 70-86). This fusion behaviour which John and colleagues demonstrated can happen reproducibly *in vitro* **(Rachkovsky** et al. Clinical Experimental Metastasis, 1998, 16: 299-312) offers a new paradigm for the study of melanoma cells and their host interactions. It has implications for detection of metastatic melanoma, for drug resistance and, down the line, it may offer new avenues for therapeutic and preventive intervention.

Does this occur clinically? Is this what is going on with advanced metastatic melanoma? It was unfortunate that John's talk was delivered near the end of the meeting so that there was less opportunity for discussion of the import of this work which is potentially enormous.

Other plenary lectures

In addition to **John Pawelek** and **Karin Schallreuter** (already mentioned in this report), we had excellent contributions from **Professor Pat Riley, Professor Tadeusz Sarna, Dr. Nico Smit** and **Professor M. Elleder.**

Professor Riley gave a plenary lecture explaining that the unusual kinetic behaviour of tyrosinase is due to its activation by dihydric phenol substrates which are formed indirectly (including dopa which is not a direct product of the tyrosinase reaction) as previously proposed by Raper and his co-workers (my thanks to Jan Borovansky for this succinct summary of Pat Riley's talk).

Professor Sarna looked into the complex question of whether melanins act as antioxidants and how phototherapy of pigmented tissues must take into account the ability of melanin to bind photosensitisers. Also, oxidative degradation of melanin can significantly reduce its antioxidant efficiency. Professor Sarna's talk underlined once more that the exact role of melanin in photoprotection remains unclear.

Dr. Nico Smit, in a plenary lecture emphasising how much the culture conditions can influence the pigmentary biology of the melanocyte, made a plea for some standardisation of culture conditions in order to be able to compare results obtained in different laboratories.

Finally, **Professor Elleder** gave an excellent review of lipopigments. Frustratingly, the chemical nature of lipopigments is still unknown despite serious analytical effort in this area. He pointed out that lipopigments may contain a number of associated compounds, one of which may be melanin although this is the subject of some debate. The best understood lipopigment is that occurring in a fatal neurodegenerative disease where the origin of the pigment is an agregate of extremely hydrophobic proteins (enzyme subunits of a mitochondrial enzyme).

We were also delighted at this meeting to, as a Society, offer honorary life membership to **Professors Riley** and **Duchon** in recognition of their considerable achievements to research in pigment biology and their unflagging support of the European Society for Pigment Cell Research.

Prize-winning posters

First prize went to "Expression of the epidermal growth factor receptor (EGFR) gene and chromosome-7 aneuploidy in cutaneous neoplasias and metastasis" - Authors: M. Udart, J. Utikal, R.U. Peter and G. Krahn.

Second prize went to "Molecular characterisation of c-kit from the Mexican axolotl" - Authors: K.A. Mason, N.B. Parker, D.M. Parichy and S.R. Boss.

Third prize went to "Chemical characterisation of dopamine-melanin: application to identification of melanins in butterfly wing" - Authors: K. Wakamatsu, S. Ito and P.E. Koch.

2. Biology of pigment cells and pigmentary disorders

(Dr M. Picardo)

Schallreuter, Slominski, Pawelek, Jimbow K. and Gilbrest in a very interesting revue, published with feature of controversy, have explored how the melanogenesis is controlled. Schallreuter propose that a major regulatory step in melanogenesis is the availability of L-tyrosine, which is regulated by phenylalanine hydroxylase (PAH) and its co-factor 5,6,7,8 tetrahydrobiopterin ($6BH_4$). Further, $6BH_4$ regulates melanogenesis through specific binding sites on both tyrosinase and MSH. $6BH_4$ bioproducts are also regulatory. MSH activates tyrosinase directly by removing $6BH_4$ from a tyrosinase: $6BH_4$: inhibitor complex. UVB both increases the tyrosine supply trough activation of PAH, and causes removal of $6BH_4$ from the inhibitor complex. MSH can be converted into melanin through oxidation of its tyrosine residue by tyrosinase. In summary, the relative intracellular concentration of $6BH_4$ and α-MSH could hold the key to the fine control of constitutive and *de novo* pigmentation. Slominski postulates a cutaneous UV-sensitive proopiomelanocortin (POMC)/receptor system in the control of melanogenesis. This concept has its roots in work showing that cultured keratinocytes and melanocytes exhibited UVB-sensitive MSH receptors and that these cells also produced POMC, MSH, and ACTH following UVB. These two different viewpoints are commented by Paweleck, Jimbow and Gilbrest. Several studies have been conducted about the influence of UVB radiation on melanogenesis. Tada et al. have demonstrated the role of endothelin (ET-1) as paracrine regulator that modulates the response of human melanocytes to UV rays (UVRs). Et-1 has a dose-dependent mitogenic effect on human melanocytes and a biphasic effect on melanogenesis: a stimulatory effect at subnanomolar concentrations, and an inhibitory effect at concentrations equal to or higher than 1 nM. Human melanocytes express ET B receptors. Brief treatment of melanocytes with ET-1 caused up-regulation of alpha-MSH receptor mRNA but did not alter ET B receptor mRNA level. ET-1 modulates the response of human melanocytes to UVRs. Treatment of melanocytes with 10 nM ET-1 immediately after exposure enabled them to overcome the G_1 growth arrest. However, ET-1 did not inhibit p53 accumulation of p21 overexpression, nor did it reverse the hypophosphorylated state of pRb or the reduction in Bcl2 level in irradiated melanocytes. Dissanayake and Mason have studied, in a novel two-stage culture model, the possible involvement of paracrine factors, like transforming growth factor-beta1 (TGF-β1) or ACTH, in the generation of the adaptive response in skin to ultraviolet radiation. Human melanocytes or keratinocytes were first irradiated or sham-irradiated and then the conditioned media collected from these cells after
24 h were used to treat unirradiated skin cells. Immunofluorescent staining for TGF-beta1 and for ACTH also were increased in UV-irradiated keratinocytes compared with sham-irratiated cells. Increased TGF-beta1 was also detected in the culture media of irradiated keratinocytes. Treatment of unirradiated keratinocytes with conditioned media collected from UV-irradiated keratinocytes resulted in increased tyrosinase activity of unirradiated melanocytes and also in increased absolute numbers and percentages of cornified envelopes per well compared with treatment with conditioned media from sham-irradiated keratinocytes. Both these effects were mimicked by authentic ACTH or TGF-beta1, respectively. These results provide evidence to support the involvement of TGF-beta1 and ACTH in the cornification and pigmentary responses respectively of skin cells after UV exposure.

Ota and co-worker have characterized the induction of melanogenesis and the expression of tyrosinase,tyrosinase-related protein (TRP) and lysosome-associated membrane protein (LAMP) gene families in the cultured melanocyte lines of non-agouti mice with four major genetic loci, i.e. melan-a2 (black, wild type), melan-b (brown, TRP-mutation), melan-s (black, piedaldism mutation) and melan-c (white, tyrosinase mutation) in response to repeated exposure to ultraviolet (UV) B (5 mJ/cm^2, 7 consecutive days). Their study indicated: 1) that melanogenesis induction and melanocyte death are two photobiological processes occurring simultaneously after repeated UVB exposure; 2) that in response to an up-regulation of tyrosinase mRNA and enzyme activity, there was a co-ordinated up-regulation of the LAMP_1 gene in wild type melan-a2, while no up-regulation was found in melan-s and melan-b mutants; 3) and that UV-induced melanocyte death is related to the up-regulation of the tyrosinase gene, induction of new melanogenesis and mutation of TRP-1 gene in immortal murine melanocytes. Chakraborty and co-worker have studied with biological techniques the inhibitory effect of arbutin, a naturally occurring beta-D-glucopyranoside derivative of hydroquinone, on melanogenesis by using human melanocytes cultured in the presence of different concentrations of arbutin. The melanin synthesis was significantly inhibited in the cells treated with concentrations approximately 20% after 5 days, compared with untreated cells. This phenotypic change was associated with the inhibition of tyrosinase and DHICA polymerase activities, and the degree of inhibition was dose dependent. Western blotting experiments revealed there were no changes in proteins content or in molecular size of tyrosinase, TRP-1 or TRP-2, indicating that inhibition of tyrosinase activity by arbutin might be due to effects at the post-translational level. Pedeux report that the thymidine dinucleotide pTpT induce melanogenesis both in human normal adult melanocytes and in human melanoma cells. Thymidine dinucleotide is non-toxic to melanoma cells and does not induce apoptosis in these cells, but induces S phase cell cycle arrest and a proliferation slow down. Because thymidine excess in culture medium leads to the synchronization of cells in S phase, the authors have investigated wheter this phenomenon was involved in the increase in melanin synthesis. They show that melanin synthesis is specifically triggered by the dimeric form of the thymidine and not by the monomeric pT. Thus, these data support that thymidine dinucleotides pTpT mimic at least part of the effects of ultraviolet irradiation, and may hence represent an invaluable model in the study of the

molecular events involved in melanogenesis induction triggered trough DNA damage. Ando and co-worker have evaluated the effects of unsaturated fatty acids on ultraviolet-induced hyperpigmentation of the skin. An efficient lightening effect was observed following topical application of linoleic acid or alpha-linolenic acid to UV-stimulated hyperpigmented dorsal skin of brownish guinea pigs. The number of melanocytes in the treated skin was similar to the number in the skin of the pigmented control, indicating that the pigment-lightening effect was not due to depletion of melanocytes. In vitro experiments using cultured murine melanoma cells, showed that melanin production was inhibited most effectively by alpha-linolenic acid, followed by linoleic acid and then by oleic acid. Furthermore, the turnover of the stratum corneum, which plays an important role in the removal of melanin pigment from the epidermis, was accelerated by linoleic acid and alpha-linolenic acid. Taken together, the results suggest that the pigment-lightening effects of these substances are, at least in part, due to suppression of melanin production by active melanocytes, and to enhanced desquamation of melanin pigment from the epidermis.

Smit et al. have examined the influence of different culture media on melanin pigment production. They have observed that there were notable passage-to-passage variations in the synthesis of melanin, in particular of phaeomelanin. Basic differences in the pigmentation pattern between melanocytes isolated from light-skinned and dark-skinned individuals remained preserved in the corresponding cultures as observed by electron microscopy. Also, the total melanin content was higher in a skin type VI melanocyte culture than in skin type I and II melanocyte cultures. In contrast to total melanin, the phaeomelanin concentration of skin type VI cells was similar to that of the skin type I melanocytes. With higher L-tyrosine concentrations in the medium, as well as increased eumelanin synthesis, phaeomelanogenesis was also stimulated in all cultures tested. This stimulation was particularly prominent in skin type I melanocytes. These preliminary experiments also showed that a melanocyte culture from atypical naevus cells exhibited a similar preference for pheomelanogenesis when pigmentation was stimulated. Donois was compared two methods of quantitating eumelanin and pheomelanin, in nevus cell and stimulated HBL melanoma cells. One is based on the HPLC quantitation of specific degradation products of each melanin type. The other requires image analysis, transmission electron microscopy, and stereology. The results showed a good correlation between both methods for total melanin, eumelanins and pheomelanins with an r equal to 0.99, 0.91 and 0.93, respectively, when all the points were used in the linear regression analyses. In the melanoma cell group the chemical and morphometric estimations were not parallel in the case of eumelanins and pheomelanins. In addition, the stereologic and HPLC pheomelanins to eumelanins ratio were still not correlated. These results demonstrate the relevancy of the stereologic method, but the low level of melanization, the possible lack of specificity of melanogenesis in melanoma cells, and a problem of sensitivity of the stereologic method in this context seem to be obstacles in obtaining better results. Wenczl and co-worker, in order to evaluate the role of melanin upon UVA irradiation, have measured DNA single-strand breaks (ssb) in human melanocytes differing only in the amount of pigment produced by culturing at two different concentration, basic (0.01 mM) or high (0.2 mM), of L-Tyrosine. In parallel, pheo- and total melanin contents of the cells were determined. Identical experiments were performed with two melanocyte cultures derived from a skin type I and skin type VI individual. For the first time the correlation between UVA-induced genotoxicity and pheo/total melanin content has been investigated. The skin type VI melanocytes contained 10 times more total melanin and about seven times more pheomelanin than the skin type I melanocytes. Elevation of tyrosine level in the culture medium resulted in an increase of both pheo- and total melanin levels in both melanocyte cultures, however, the melanin composition of skin type I melanocytes became more pheomelanogenic, whereas that of skin type VI melanocytes remained the same. The skin type VI melanocytes cultured in basic medium demonstrated a very high sensitivity toward UVA that is probably related to their high pheo- and total melanin content. Their UVA sensitivity, however, did not change after increasing their melanin content by culturing at high tyrosine concentration. In contrast, the skin type I melanocytes demonstrated a low sensitivity toward UVA when cultured in basic medium, but increasing their melanin content resulted in a 3-fold increase in their UVA sensitivity. These results demonstrate that UVA-irradiated cultured human melanocytes are photosensitized by their own synthesized chromophores, most likely pheomelanin and/or melanin intermediates.

Prota et al. have determined the presence of eumelanin and pheomelanin in irides from eyes of various colors. These pigments were quantified by a highly specific microanalytical procedure based on chemical degradation. Significant differences in the type of melanin were observed in the stroma and iris pigment epithelium (IPE). Melanin from the IPE is essentially eumelanin, while the pigment in IPE-scraped iris proved to be both eumelanic and pheomelanic. A pheomelanic-type pigmentation was associated with green irides, while green-blue mixed-color irides were mostly eumelanic, by contrast, green-brown mixed-color and brown irides could not be placed into either of the two categories and probably feature a mixed pigment content. Analysis in cultured iridial melanocytes in the growning stage IPE-scraped tissues, providing evidence that growth of iridial melanocyte induce a marked change of melanin metabolism. After senescence, cultured melanocytes exhibited a marked increase in pigment content, most of the variation was associated with the eumelanin content. These results represent the first direct evidence for the presence of eumelanin and pheomelanin in human irides, and suggest that differences in stromal pigmentation are due not only to the quantity, but also the nature of the melanin pigment. Medalie and co-workers have characterized a skin equivalent model that supports melanocyte growth and function in vitro and in vivo. They have transplanted in athymic mice the grafts of melanocytes from one or mixed skin donors and in both they have observed foci of pigmentation. Histologic examinations have revealed that the foci from one skin donor corresponded to clusters of melanocytes that proliferated and migrated, instead the grafts from mixed skin donors were entirely repopulated with melanocytes and contained distinct zones of melanocytes that were of exclusively dark or light skin origin. Mizushima et al. have investigated about the origin of dormant melanocytes in the dermis. Funasaka et al. have studied the modulation of MSH receptor binding activity and melanocortin-1 receptor gene expression on normal melanocytes as responses to the effects of UVB, IL-1, endothelin-1 and TNF-α. They postulate the existence of a regulatory system that would enable normal human melanocytes to respond to MSH more efficiently and induce an increase of melanization of the skin through the MSH/MSH-R system after UVB radiation. Haddad and co-workers have summarized the present knowledge on aging of melanocytes in vivo and in vitro, with a focus on the role of melanin as

a determinant for proliferation and terminal differentiation. They describe that excessive melanin deposition by cyclic AMP-inducing agents results in increased expression of the cyclin-dependent kinase inhibitors p27Kp-1 and p21SD1-1/Waf-1, increased binding of p16 to CDK4, and terminal differentiation. They propose that terminal differentiation is a tumor suppressor mechanism that becomes less efficient under imperfect eumelanization. Potterf and Hearing have examinated whether stimulation of melanogenesis affects melanosomal tyrosine transport. Tyrosine up-take increased almost 2-fold in melanosomes derived from melanocytes treated with MSH, which acts to increase intracellular cAMP levels, resulting in the up-regulation of many genes involved in melanogenesis. Their experiments demonstrate either that a pool of transporters greater tyrosine transporting pre-exists, or that a greater number of tyrosine transporters reside within the melanosomal membrane.

Terashi et al. have suggested that gastrin releasing peptide (GRP) acts as an autocrine growth factor for nevus cells and normal melanocytes. The melanocortin receptors MC1 and MC2 have structural similarities and bind melanocyte peptides but with different affinity profiles. Schioth and co-workers have constructed a series of chimeric MC1/MC3 receptors to identify the epitopes that determine their selectivities for natural melanocyte peptides and synthetic analogues. Kunisada et al., by targeting expression of steel factor (SLF) to epidermal keratinocytes in mice, have observed extended distribution of melanocytes in a number of sites including oral epithelium and footpads where neither melanocytes nor their precursor are normally detected. These results provide direct evidence that SLF stimulates migration of melanocytes in vivo. Jackson has observed that melanocytes but not keratinocytes express nitric oxide synthase III (eNOS) mRNA. Hu et al. have studied the effect of TGF-beta2 on growth of uveal melanocytes in vitro and have compared the dose-dependent inhibitory effect of TGF-beta2 with the known concentration of TGF-beta2 in acqueos umor. Their experiments indicate that TGF-beta2 is a potent growth inhibit factor of uveal melanocytes and may play an important role in maintaining the non proliferative, relatively quiescience status of uveal melanocytes in vivo. Luca and Bar-Eli have founded that both genes, the tyrosinase-kinase receptor c-KIT and the cell adhesion molecule MCAM are regulated by the transcription factor AP-2 and that metastatic melanoma cells do not express AP-2. They therefore propose that loss of AP-2 might be a crucial event in the progression of human melanoma.

Li Y. et al. have characterized the expression of the alpha2-macroglobulin associated protein in both normal human epidermal melanocytes and six different human melanoma cell lines, by the use of the flow cytometry and Western blotting analysis. They showed that all the melanoma cell lines and the normal melanocytes express the receptor-associated protein at similar level, with most located intracellularly. Grammatico and co-workers in order to evaluate if the alteration of the antioxidants could be the basis of an increased sensitivity to exposure to peroxidative agents, have determined in cultured melanocytes from normal subjects and from melanoma patients the superoxide dismutase and the catalase activities, and the levels of vitamin E and of polyunsaturated fatty acid of cell membranes. Also the effect of a peroxidazing agent, as cumene hydroperoxide, on these cultured cells was evaluated. Their results suggest that a constitutional alteration of the scavenger system could be present in normal melanocytes from melanoma patients and that this could be the basis for an increased sensitivity to pro-oxidant agents.

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Melanocyte cultures
(Dr N. Smit)

In two papers the role of micrphtalmia is investigated for its role in melanogenesis. Next to B16 melanoma cells Aberdam et al use melb-a cells, an immortalized murine melanoblast line , which can be induced to differentiate to melanocytes by forskolin or "-MSH. Thus the involvement of microphtalmia in both, (CAMP stimulated) melanoblast differentiation and melanogenesis, and the inhibition of these processes by agouti signal protein, could be studied in these cells. Next to B16 cells Bertolotto et al also use normal human melanoytes to study the role of microphtalmia as a signal transducer in the cAMP-mediated responses in these cells. The effects of stem cell factor (SCF) on melanocytes was studied by Grichnik et al by injecting SCFin skin xenografts. The results indicate that the SCF/KIT pathway is not only important for melanocyte development but influences several functions of the adult melanocyte as well. Schallreuter et al describe disturbed Pterin metabolism in melanocytes from Hermanski-Pudlak Syndrome patients as compared to control melanocytes. Total levels of 6- and 7-biopterin and enzyme activities of phenylalanine hydroxylase and 4a-hydroxy-6BH4-dehydratase were decreased in the HPS-homozygotes. Uptake of phenylalanine and its turnover to tyrosine in normal melanocytes was investigated and the role of calcium discussed. In two culture systems of the frog melanotrope cells (Gallas et al) and rat mammotrope cells (Nunez and Frawley) the regulation of calcium levels and the effects of thyrotropin-releasing hormone (TRH) and "-MSH on calcium responses have been investigated. Four different melanocyte lines of non-agouti mice were used to study melanogenesis after UVB irradiations; melan-a2 (black, wild type), melan-b (brown, TRP-1 mutation), melan-s (black, piebaldism mutation) and melan-c (white, tyrosinase mutation). UV-induced melanocyte cell death was related to upregulation of the tyrosinase gene and induction of new melanogenesis with the highest level of viable cells in the melan-c melanocytes after 7 consecutive daily doses of 5 mJ/cm2.
Funusaka et al describe that the melanocortin (MC)1-receptor mRNA expression can be induced by UVB or IL-1, endothelin-1 and also TPA. The results may be useful for other studies aimed at measuring MSH responses in cultured human melanocytes. In our study (Smit et al) we have measured total and phaeomelanin levels in human melanocyte cultures of different origin during many subsequent passages. Rather strong variations especially in phaeomelanin concentrations in the cells were found although culture conditions were maintained equal during all passages. This indicates that the regulation of melanogenesis in the cultures is dependent on a delicate balans of the different mediators used in the cultures which may also be illustrated in several of the other papers mentioned above. Nevertheless the melanin measurements in the melanocyte cultures show the differences in production of total and phaeomelanin in cells originating from different skin types and how this can be influenced by varying culture medium compositions and growth factors. The papers by Donois et al describe an additional new method to study melanogenesis next to the measurements of eumelanin and phaeomelanin by HPLC described previously (Ito and Fujita, Anal Biochem 144: 527, 1985). In cultured melanocytes, nevus cells and melanoma cells melanin production was studied at the ultrastructural level by image analysis, transmission electron microscopy and stereology. The results show that the stereologic image analysis method may be useful for the quantitation of melanins especially in cells with sufficiently high levels of melanization.

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3. MSH, MCH, other hormones, differentiation

(Dr B. Loir)

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5. Neuromelanins

(Prof. M. d'Ischia)

The close association between neuromelanin, dopamine oxidative metabolism and Parkinson's disease features prominently in two articles (Li et al., 1998; Ikemoto et al., 1998) that appeared during the last few months. As a continuation of previous studies on the generation and oxidation chemistry of benzothiazine derivatives produced by oxidation of dopamine in the presence of cysteine, Dryhurst and his associates demonstrate that one of these putative dopamine metabolites, referred to as DHBT-1, can be oxidatively converted to species that inhibit mitochondrial complex I activity and can covalently bind to reduced glutathione via the SH group.
The authors go on to postulate a role for these compounds in decreased mitochondrial complex I activity and glutathione loss, two biochemical hallmarks of Parkinson's disease. The longstanding, still pending issue of whether tyrosinase is involved in neuromelanin formation is the subject of the paper by Ikemoto et al.. In this, antibodies against human tyrosinase and tyrosine hydroxylase have been used in human substantia nigra neurons and, for comparison, in melanoma, to show that while intense tyrosinase-like, but not tyrosine hydroxylase-like, immunoreactivity is present in melanoma, the opposite applies to pigmented substantia nigra neurons. On the basis of this evidence, it is concluded that tyrosinase is not involved in dopamine oxidative metabolism and nuromelanin formation. This finding argues apparently against recent reports on the identification of tyrosinase promoter activity in the substantia nigra in adult brain (see Tief et al., Brain Res. Mol. Brain. Res.53, 308-311, 1998), and indicates that further work is needed before the issue is definitively settled. Of some relevance to the differential susceptibility of dopaminergic neurons in Parkinson's disease is the observation by Nishio et al. that high percentages of neurons in the medial part of the substantia nigra pars compacta express NGF-like immunoreactivity, whereas a lower number of immunopositive neurons are detectable in the lateral part

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6. Genetics, molecular biology

(Dr. F. Beermann)

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7. Tyrosinase, TRP1, TRP2 and other enzymes

(Prof. J.C. Garcia-Borron)

Several papers referenced in this issue refer to the regulatory role of protein kinase C (PKC) in mammalian melanogenesis. This is an important and puzzling issue, since the data in the literature are clearly different depending on the source of melanocytes employed in each study. Generally speaking, most researchers working on mouse melanocytes will agree that PKC activation leads to decreased tyrosinase activity and melanin formation (see Shoji et al, Biosci-Biotechnol-Biochem. 61(12): 1963-7, and , Bertolotto et al., Oncogene 16(13): 1665-70) while the opposite seems to be true when human melanocytes are considered (see Watters et al., Biochem-Pharmacol. 1998 55(10): 1691-9, and Gilchrest et al, 1988, The photobiology of the tanning response, in The Pigmentary System, Physiology and Pathophysiology, Chapter 26, Oxford University Press, for a recent review). The pertinent question is therefore whether or not mouse and human melanocytes are so different, at least as related to the regulatory role of PKC. At first glance, one might think that most of the discrepancies can be due to the experimental design of the experiments carried out in different laboratories. Many of these experiments rely on the use of phorbol esters as specific activators of PKC, but we are all aware of the problems in the use of these compounds that elicit a rapid activation of PKC followed by a strong down-regulation of the enzyme. The time window of the experiments is therefore a very critical parameter and may vary from cell line to cell line. However, the french group lead by Robert Ballotti has convincingly shown that PKC activity does indeed lead to decreased tyrosinase in B16 mouse melanocytes, using a constitutively active form of the enzyme (Bertolotto et al., Oncogene 16(13): 1665-70). Moreover, the effect of PKC seems to be exerted mainly at the level of gene expression, since the kinase apparently interferes with the binding of microphtalmia to its target sequence in the tyrosinase promoter. Therefore, this report leaves little doubts as to the inhibitory action of PKC in the case of mouse melanocytes. On the other hand, the effect of PKC in human melanocytes is thought to be mediated by direct phosphorylation of tyrosinase (rewieved in Gilchrest et al, 1988, The photobiology of the tanning response, in The Pigmentary System, Physiology and Pathophysiology, Chapter 26, Oxford University Press). This phosphorylation would occur in serine residues located in the cytoplasmic tail of the enzyme, and would increase the catalytic activity of the enzyme. Interestingly, these Ser residues are not located in canonical PKC target seequences, and mouse tyrosinase also contains serine resides in similar environments in its cytoplasmic tails. As far as I know, there are no reports on PKC phosphorylation of mouse tyrosinase. Clearly, the role of PKC in the regulation of melanogenesis remains enigmatic, and we should be looking forward for further work trying to reconcile the mouse and human data. Naish-Byfield and Riley have used a very elegant approach (Pigment-Cell-Res. 1998 Apr; 11(2): 94-7) to show that the diphenolic cofactor of tyrosinase is not generated by the enzyme catalyzed hydroxylation of the monophenolic substrate, but rather in subsequent chemical rearrangements of intermediates. The recent (and abundant) work of Patrick Riley is changing our view of L-dopa within the melanogenic pathway.

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TRAVEL AWARDS FOR ESPCR / IFPCS CONFERENCES
by Prof. Martin G. Peter, Potsdam, Oct. 25, 1998

The European Society for Pigments Cell Research will provide a limited number of travel awards for attendance at ESPCR or IFPCS meetings. Depending on the number of applicants selected and the funds available, awards may cover travel (economy return air, rail fare or car fuel costs), conference registration, and in some cases accomodation (economy class). For deatils and further information, see http://www.ulb.ac.be/medecine/loce/espcr.htm

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Have no other source of funds for this purpose, including supervisor's or University funding. If funds from elsewhere are subsequently obtained, ESPCR should be informed immediately and the application for ESPCR funding withdrawn, or the ESPCR award declined/returned if already made, so that another applicant can be funded.

Application Procedure:

The deadline for applications is eight weeks before the deadline for early conference registration.

Please send an informal letter of application to:

Prof. Dr. Martin G. Peter
Chair, ESPCR Travel Awards Committee
Institut für Organische Chemie und Strukturanalytik - University of Potsdam
Am Neuen Palais 10
D - 14469 Potsdam, Germany

Enclosing: Proof of status (usually a short statement from the supervisor or Head of Department), including the date or expected date of completion of PhD or medical qualification.

Evidence of non-availability of other funds (usually part of the statement from the supervisor or Head of Department). Please state if other applications for funding are being made.

Submitted abstract of the oral or poster contribution. Estimates of the costs of travel, accommodation and conference registration. Applicant's full address, phone and fax numbers, and e-mail address where available.

Awards

Unless all applicants can be funded, awards will be made by the Travel Awards Committee on a competitive basis. Applicants will be notified of the outcome by the Chair of the Committee, by letter, fax, or e-mail, no later than two weeks before the early registration deadline. The award will be paid by cheque after submission of all relevant receipts including the original air or train tickets and the receipt for the registration fee. In exceptional cases, the award may alternatively be paid directly to a travel agent (or railway company, airline etc), and to the conference organizers, on submission of the original invoices.

ANNOUNCEMENTS & RELATED ACTIVITIES

GENERAL ASSEMBLY
8th MEETING OF THE ESPCR, PRAGUE, 23-26 SEPTEMBER 1998

Agendas were distributed to all who attended the General Assembly.

1. The minutes of the Council meeting were read by Dr. S. Mac Neil, approved by the members present and signed by the President.
2. Dr. Mac Neil asked everyone for communication details (eg. fax number, telephone number, e-mail addresses) for ease of communication.
3. Dr. Mac Neil read out the composition of the newly established Awards Committee. This Committee will consider nominations for awards for the Myron, Seiji, Raper and Takauchi medals. Professor Hans Rorsmann will chair this Committee and Professor Rona Mackie, Professor Giuseppe Prota and Professor Fritz Anders and Dr. Stan Pavel will serve on this Committee.
4. Dr. Martin Peter read through the Financial Report for 1997. No questions were asked. The financial situation is healthy and the report was approved. Dr. R. Peter gave his review for this year's accounts. It was decided that Honorary members do not have to pay as requested.
   The above will appear in the bulletin for members.
5. Professor Ghanem gave details on the ESPCR bulletin. There would be 2 pages dedicated to 1999's meeting. There was plenty of fresh information. It was reported that the third page is for members only and that a password was needed for this page. If passwords were lost then Professor Ghanem can be contacted for the retrieval of these. Professor Ghanem ran through his statistics of 1082 hits/year (an average of 3/day).
   Professor Karin Schallreuter said that the website was good but expressed concern that the Society was not taken seriously enough. There needs to be an attraction for younger people to join the Society. She also pointed out that perhaps the website was not suitable in some aspects as not everyone who would be interested may have access to a computer (India was given as an example).
   Professor Ghanem pointed out that this wasn't just for the Society but for people all over the world and patients too.
   Dr. Pavel pointed out that this was good public relations and any suggestions to trying to attract new, younger members would be greatly appreciated.
   A member of the audience asked whether you could access the members page without a password. Ralf Peter replied that money is paid for this page (100 US dollars/year) so this should be restricted to paying members only.
6. With regards to election of Council officers, according to the Constitution officers must be replaced by elections. A postal ballot was arranged by Stan Pavel, 10 ESPCR members were nominated and 8 were elected for a period of 4 years.
7. The forthcoming meetings were summarised:

1999	International Meeting:	Japan
2000	ESPCR Meeting:	Poland
2001	TO BE DECIDED	
2002	(At this point there were 3 offers of venue: Germany, The Netherlands and Italy)	

   There were no questions asked. It was decided that a market survey of opinions for the venue of the next International Meeting to be held in Europe would be held at the Gala Dinner. There was a little dissatisfaction expressed at this but it was pointed out that attendance at the General Assembly was usually low (as on this occasion), therefore, the best time to catch nearly everyone would be at the Gala Dinner. Also there were no rules on how or where to select the next meeting place. It was decided that this would be a more democratic way to do this ie. to canvas opinion on the 3 choices of venue for 2002. This was agreed.
   Professors Prota and Riley pointed out that this decision should be taken by the Council and then proposed to the IFPCS. Dr. Pavel said that he had discussed this with the President of the International Federation who had no objection to the ESPCR selecting its venue by such an informal vote or opinion poll. Dr. Martin Peter suggested that, on principle, this should be an "opinion" and not a "vote". This was agreed.
8. With regards to travel awards it was agreed that there was a strong need to attract young members. Dr. Martin Peter volunteered to chair a 3 member ad hoc Committee to put together some guidelines for applications for awards and for judging awards on a competitive basis. Dr. Friedrich Beermann and Dr.

Dorothy Bennett are to assist Dr. Martin Peter in this respect. It was decided that when the roles are drafted by the members of the Committee then they should be publicised as early as possible.
Martin Peter informed everyone at the General Assembly that the guidelines, once established, would be put on the bulletin and website. Those eligible for applying for travel awards would be junior members and Ph.D. students who must be ESPCR members. The amounts available for awards could be around 20% of the value of the account of the ESPCR. Applications for awards would be judged on scientific merit.
Dr. Pavel asked if there were any questions. Tony Thody pointed out that currently there were a limited number of applicants for awards as there weren't many students who are members of the Society. It was agreed that the Committee would consider the question of eligibility as part of its brief.

10. Any Other Business Ralf Peter mentioned the question of raising funds and suggested corporate membership for pharmaceutical firms. There was some discussion of corporate membership and its implications based on experiences in other Societies. The general idea would be that pharmaceutical firms would pay a fee such as 1000 DM for membership which would give them access to developments but would not allow them to influence the direction of the Society. Patrick Riley agreed that this idea of corporate sponsorship was a good one. The issue of the level of the fee should be left to the Treasurer's discretion to investigate - this was approved.
Dr. Pavel then read article 7.2 of the by-laws. The Society will be dissolved in January 2001. This provides time to consider any changes to the by-laws and he stated that while the original by-laws were very good, there were still small areas worth reconsidering. It was decided that any changes or suggestions made to the Council will need to be discussed in the next 2 years.
11. Dr. Pavel closed the meeting.

MINUTES OF THE ESPCR COUNCIL MEETING
PRAGUE, 23-26 SEPTEMBER 1998

Present: Dr. S. Mac Neil, Dr. B. Larsson, Dr. A. Thody, Dr. M. Parsons, Dr. S. Pavel, Dr. J. Borovansky, Dr. M. Peter, Dr. G. Ghanem, Dr. P. Riley, Dr. J-G. Garcia-Borron
Miss S. McGinley (secretary to Dr. S. Mac Neil and present by invitation)

1. Opening of Meeting Dr. Stan Pavel opened the meeting by welcoming everyone to Prague and wished everyone a successful meeting and a wonderful stay.
2. Apologies Apologies for absence reported by Dr. S. Mac Neil were offered from Professor M. d'Ischia and Professor H. Pehamberger.
3. Minutes of the ESPCR Council Meeting in Bordeaux 1997 Copies of the minutes of the above had been circulated to members in 1997 and were also circulated at this meeting. Dr. Mac Neil asked if any changes were to be made. The only point related to the fact that the Council contained two Drs. Peter - Ralf Peter and Martin Peter. Martin Peter is the former Treasurer of the ESPCR and Ralf Peter is the current Treasurer. Martin Peter suggested that in referring to them, the initial should always be used and he pointed out that the ESPCR letterhead needs to be amended.
Dr. Pavel signed the minutes.
4. Secretary's Report Dr. Mac Neil gave the Secretary's report. She said that e-mail communication was working well for most Council members and that we needed to complete e-mail addresses for new Council members. She reported that she wrote to the membership in November 1997 reminding members to fix the dates of the Prague meeting in their diaries and that she wrote to Council members requesting their help with supporting the Prague meeting with respect to sponsorship, strengthening the ESPCR membership, recruiting new Council members and nominating candidates for awards. She reported that there was a good number of nominations from members to serve as Council members and a good response from the Council members to a request for help in putting together an Awards Committee (see item 11).
However, she reported that the Society had not been very active in putting forward names to be nominated for awards. Also, she reported that her own attempts to attract commercial sponsorship for the Prague meeting had been unsuccessful.
Dr. Pavel asked for comments to which there were none. Dr. Pavel said that the Society was less active with regards to the nominations for awards than the American and Japanese Societies. The report was approved.
5. Treasurer's Report The financial report for 1997 was approved. Dr. Martin Peter discussed the report (see attached) and asked for any questions. Dr. T. Sarna said that with regards to the ESPCR Bordeaux meeting in 1997 that the total was just 5,000DM and asked if this was correct. Dr. Peter reported that 2 donations were received and included in this amount.

The report was approved and Dr. M. Peter signed this and handed this over to Dr. Mac Neil.
It was also noted that Dr. R.U. Peter had sent subscription renewals out to all members.

6. ESPCR Bulletin Report Professor Ghanem reported that the bulletin was to schedule and that there were no problems. He said that the Editorial Board had done a good job with it. He then read through the names and titles which were included in the bulletin. It was noted that nothing had yet been received from Dr. R.U. Peter. Dr. Pavel noted that Dr. R.U. Peter was now Head of the Department and, accordingly, his commitments would have increased. Dr. Borovansky suggested that there should also be a section on melanosome cytology and morphology.
   Dr. Mac Neil commented on the excellent quality of the review sections of the bulletin and Dr. Pavel passed on the thanks of the ESPCR Council to Professor Ghanem for his continued excellent work as Editor of the bulletin.
7. Management of ESPCR Website Professor Ghanem reported that there had been major enhancements made to the website. The first page had been changed to show a members page which required a keyword for members which had been circulated previously which has been fine up to now. Access to other pages was made easier. He said that now you don't have to download the bulletin as you did previously which is an advantage. Professor Ghanem said that there were now photos on the website (which apparently no-one has seen). He reported statistics of the website - in October 1997 there were less than 40 hits but now there are 100 hits per month! Dr. Sarna said not to be discouraged - it will be visited more often in the future. Professor Ghanem explained that as different versions of software were used, this meant that page quality would be different with each version. Dr. Pavel thanked Professor Ghanem for his efforts in organising the website and again expressed the appreciation of the council.
   With respect to the financial status of the bulletin and the website, he reported that both were stable and the maintenance cost for the website was only 100 dollars per year.
   Dr. Martin Peter suggested that the current Treasurer (Dr. Ralf Peter) could contribute to the running of the website. Professor Parsons suggested advertising for website contributions. While this was generally agreed by all Council members, Professor Ghanem reported that the hit numbers were too low to attract any contributions. Advertisers would not be interested until we had more hits. It was noted that students use the website most frequently.
8. Report of the Organisers of the 1998 ESPCR Meeting in Prague Dr. Borovansky welcomed all to Prague and announced that the weather report was good for the week. He gave details of the venue for the meeting on the following day and practical matters. He also asked for nominations from the Council members to help assess posters. After some discussion, it was decided that Professor Hill, Professor Anders and Professor Duchon (as an academic member of Charles University involved in pigmentation research) should read and assess the posters and award prizes. The results for the prizes were to be declared on the night of the Gala Dinner.
   Dr. Borovansky also gave details of the non-scientific aspects of the conference.
   Dr. Borovansky asked if there were any questions - there were none. Dr. Borovansky thanked Dr. Sarna for his contribution in the Joint Photobiology section and for financial help.
   There was then some discussion of ideal dates for the next ESPCR meeting. Dr. Mac Neil reported that August was not good as many people were on holiday. Dr. Borovansky reported that September was also a holiday period. After some discussion, it was generally agreed that the end of September was preferable to other times. Dr. Riley suggested that the membership should be consulted about the ideal time of year for the ESPCR meetings - Dr. Mac Neil agreed to do this.
9. Report from the Publication Committee Dr. Pavel reported that in response to the poor sales of Pigment Cell Research journal, Dr. Vincent Hearing had been instrumental in obtaining funding (from a number of companies including Shiseido and Unilever, a USA company and a French company) to provide for the purchase of a further 100 copies of the journal to initially boost sales of the journal and, more importantly, to try to persuade scientists to continue their subscription to this journal. It was decided that young members of the Society should receive free copies of Pigment Cell Research together with the members from post-communistic countries and reviewers and Editorial Board members of ESPCR bulletin Recipients of the journal will be approached to continue receiving the journal after their initial free introductory offer. There was general agreement that this was an excellent idea to provide a short to medium-term solution to the continuity of the journal.
   With respect to the renewal of the post of Editor-in-Chief, Dr. Pavel said that at present there were no rules concerning the rotation of the Editorial Office between the Japanese, American and European Societies. The current Editor-in-Chief is Professor Matsumoto and a new Editor is required from January 2000. Vincent Hearing has agreed to be Editor-in-Chief from January 2000 and has already made some plans to reduce the number of Editorial Board members (47 at present) to a much smaller number. Although there are no rules for rotation of the Editor-in-Chief, it has been decided by the Federation that the next Editor should be from Europe (in 2005).
   Dr. Sarna asked if Vincent Hearing will present his views for dealing with the journal. Dr. Pavel responded that Vincent Hearing is requesting each Society to put forward a small number of active members who would

be willing to act as Associate Editors in different areas. It is expected that he will choose his Associate Editors from the willing volunteers. It is also expected that the next European Editor-in-Chief will probably be one of these Associate Editors from Europe.

Dr. Pavel also said that he had written a personal letter to members who did not subscribe asking them to do so. According to Munksgaard's data, there has been more than a 10% increase following the Society's last appeal to try and increase the number of people subscribing. There was some discussion over how the European Society might have an input into the choice of Associate Editors. On this point, Dr. Garcia-Borron said that Professor Matsumoto, the current Editor-in-Chief, should be approached for his advice on his recommendations for active Associate Editors based on his experience. Dr. Mac Neil agreed to do this.

In discussing how changes were to be made in the journal, Dr. Martin Peter wondered whether it would be worthwhile to dissolve the present Editors completely and start anew to which Dr. Pavel replied that this was the intention.

Dr. Garcia-Borron asked how long the Editor would stay and Dr. Pavel replied that a period of 5 years is sufficient for the new Editor for Pigment Cell Research and he/she could then nominate a new Advisory Board.

Professor Thody requested clarification on the role of the Associate Editor. Dr. Pavel answered that the Associate Editor will allocate referees and edit themselves or send to other colleagues.

Patrick Riley asked if the Society was to suggest names or Vincent Hearing. Dr. Pavel said that the Society is to suggest names and Dr. Larsson said that he was waiting for suggestions from Dr. Pavel. Three or more people will probably end up acting as Assistant Editors from the European Society, one of whom would be expected to act as potential Editor-in-Chief for the journal in 2005.

10. Report from the IFPCS Council Meeting - Snowmass, Colorado, USA In the absence of the Secretary, Dr. Mac Neil, Dr. Dorothy Bennett attended the IFPCS Council Meeting together with Dr. Larsson and Dr. Pavel. Dr. Larsson gave the report on the IFPCS Council Meeting. He reported that the financial side of the meeting so far looked good. There would be money for travel stipends, possibly three per Society. There is a need to allocate possibly two more from the ESPCR? He said that the composition of the preliminary programme was discussed. There were discussions concerning publications policy, keynote speakers/invited speakers and the performance of expert groups from each Society. He said there were no issues from the Council meeting that required discussion at this point. Dr. Pavel asked if there were any questions. Dr. Sarna asked whether there was sufficient financial support for the meeting reported by Professor Ito. Dr. Larsson replied that there had been 15,000 dollars contribution from the IFPCS to running the IFPCC. Dr. Riley then said that Bill Oeting had worked on the website search engine so that it was now feasible to search databases for keywords. Dr. Larsson reported that Bill was doing a very good job and suggested that it would be a good idea to invite him to Japan. This had the broad approval of the Council.
11. Awards Committee Composition Dr. Pavel said that at the meeting next year there will be the opportunity to confer the Myron, Seiji, Raper and Takeuchi medals on recipients. The ESPCR is responsible for the Raper medal but we badly need more nominations for candidates to receive the medal.

    Dr. Mac Neil reported that there had been a generous response from the Council to requests to set up an Awards Committee but that on reflection and advice from Dr. Riley, we had decided to make the composition of this Committee volunteers from outside of the Council so that it would be clear that this Committee was independent of the Council. Accordingly, Professor Rorsman will chair this Committeee and Professor Prota, Professor Mackie and Professor Anders will be on this Committee. The Council discussed the desirability of having 5 members on the Committee and it was generally agreed that the fifth member of the Council should be the Chairman of the ESPCR (Dr. Pavel). Dr. Pavel confirmed his willingness to act in this capacity when it was suggested by the Council members.

    Dr. Mac Neil said that she would now confirm the composition of the Awards Committee to the Council members and to the ESPCR membership.

    Dr. Mac Neil said that one problem that had arisen so far was that the ESPCR was not very pro-active in putting forward names for nominations for awards. Dr. Riley enquired for the deadline date for nominations to which Dr. Pavel replied that there was no deadline for the Raper medal. Nominations for this medal had already been put forward by the American and Japanese Societies.

    Dr. Mac Neil further stated that the only names nominated appropriately had so far been given by Dr. Riley. After some discussion, it was agreed that a deadline of 1 January should be set for nominations for the Raper medal (the Raper medals are currently in the safe keeping of Dr. Mac Neil). The date of 1 January was agreed and Dr. Mac Neil agreed to send out a letter to the membership. Dr. Pavel also suggested that this should be put onto the website and the bulletin.

    Dr. Riley asked whether the nominations would be publicised or would they be anonymous. Dr. Pavel said that there were no rules but that he was happy to inform the Council of the nominees. The names of the awardees are to be published in the bulletin. Dr. Mac Neil further agreed to list the names of previous awardees when requesting further names for the Raper medal.
12. ESPCR Council Member Election Every 4 years there is a re-election for Council members. In 1998, 10 candidates were put forward for a postal ballot of whom 8 candidates were elected (Professors Ghanem,

Westerhof, Martin Peter and Thody and Drs. Bennett, Beermann, Garcia-Borron, Picardo and Westerhof). There were no questions.

13. Travel Awards for Meetings Dr. Mac Neil pointed that there did not appear to be a very visible policy for travel awards. She suggested that 3 members of the Council could form a small ad hoc Committee to look at applications for awards and to devise some simple clear rules for competitive applications for travel awards which could be publicised clearly in advance of each meeting. Dr. Martin Peter reported that there had been travel awards in the past but, again, there were no guidelines. The Council gave its approval to the idea of a Travel Awards Committee. Dr. Martin Peter volunteered to chair the Committee and come up with some first thoughts on the running of the travel awards. It was decided that travel awards should be limited and should go to junior members who do not have a high income but are members of the Society and contributing work to the meeting in question. It was agreed that the financial limit should now extend to a fixed amount. Dr. Martin Peter said that the limit and eligibility should be examined by the Committee. Dr. Mac Neil reported that in another Society to which she belonged (the British Society of Investigative Dermatology) awards were competitive and based on merit and generally added to the level of interest in the meeting. Dr. Pavel suggested that the issue of travel awards should perhaps be discussed with the new Council members and this was approved.
    Dr. Mac Neil announced that there was to be a brief meeting for the new Council members after the General Assembly and this could be discussed at this meeting. Dr. Pavel asked if there were any questions. There were none. He reported that so far he had received two applications for travel awards to the Prague meeting and one for an application to Nagoya. As there had been so few applications for the Prague meeting, these were approved without any discussion.
    Dr. Sarna put foward the point of funds for an applicant visiting one or two laboratories. Dr. Pavel said that this information would be put into the bulletin and that there was a need for improved collaborations between laboratories. It was agreed that this also should be made clearer and applications based on merit could also be examined by the Travel Awards Committee. It was agreed that applications could come from Europe or elsewhere for such an award to facilitate interaction between laboratories.

14. Plans for Future Meetings (1999 - 2002) Dr. Pavel gave an update on plans for future meetings. The next meeting is to be in Nagoya in 1999, the International Pigment Cell Conference. In 2002 the ESPCR meeting will be in Krakow (organiser Tad Sarna). At this point in the meeting, no venue had been decided for 2001 which was to be in Europe (an offer from Mauro Picardo to hold this meeting in Rome was made the following evening and received the broad but unofficial approval of those present at the dinner which were the majority of the participants at the Prague meeting).
    The next International Pigment Cell Conference is to be in Europe and at the time of this meeting there were 3 venues offered - Germany, The Netherlands and Italy. In order to get an informed view from the membership, it was decided that an informal opinion would be achieved at the Gala Dinner by asking those present for their preferred choice for the 2002 meeting.
    Dr. Pavel asked if there were any questions. Dr. Riley pointed out that the business of choosing the venue for the next International Pigment Cell Conference should legitimately reside with the Council members. Dr. Pavel agreed to this but said that it would be very useful to have the views of the membership on this issue (as this might reflect their support for the meeting). There was broad agreement from the Council that this was a reasonable and pragmatic way to decide on the venue as we were fortunate enough to have 3 excellent offers of venue from 3 Council members (Dr. Ralf Peter, Germany; Dr. Stan Pavel, The Netherlands and Dr. Mauro Picardo, Italy).

16. Any Other Business Dr. Sarna mentioned that this year there was a combined symposium with the Society for Photobiology. Depending on the success or otherwise of this, it will be decided whether such collaborations should continue.
    Dr. Borovansky read out a list of 7 new members to the Society following his successful appeal to increase the membership. A number of further application forms had been received from young members interested in joining the Society.
    Dr. Pavel emphasised the need to attract new members particularly younger members. Dr. Mac Neil emphasised that making competitive travel awards available to attend the Society meetings would help in this.

17. Adjournment Dr. Pavel expressed appreciation for all the work achieved by the organisers of the Prague meeting and adjourned the Council meeting.

ESPCR Financial Record 1997

all figures in DEM (Deutsche Mark)

Giro-Account Deutsche Bank, Bonn	Credits	Debits	Balance
Previous Balance 31.Dec.1996	12,590.53		
Members fees	13,114.66		
Donations	7,525.00		
Transfer from Savings Account	10,430.77		
Bank charges		-924,87	
IFPCS Contribution 1996/97		-5,272.69	
ESPCR'97 Bordeaux		-5,549.76	
Office expenses		-919.07	
Bulletin		-3,169.32	
other expenses (P. Riley; medal)		-967.97	
Balance Giro 31.Dec.1997	**43,660.96**	**-16,803.68**	**26,857.28**

Savings Account Deutsche Bank, Bonn			
Balance per 31.Dec.1996	10,149.72		
Interest	281.05		
Transfer to Giro		-10,430.77	
Balance Savings 31.Dec.1997	**10,430.77**	**-10,430.77**	**0**

Potsdam, Sept. 15, 1998

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Martin G. Peter

Calendar of events:

Also available in more details from address: http://www.ulb.ac.be/medecine/loce/espcr.htm

1999 **VITILIGO: WHERE DO WE STAND? Rome, January 28**
Contact: Mrs Rosella Ferri
Triumph P.R. S.r.l., Organizing Secretariat
Via Proba Petronia 3
I - 00136 Roma
Phone: 39 06 39727707
Fax: 39 06 39735195
E-mail: triumph@tin.it

1999 **3rd Int. Conference: The adjuvant Therapy of Malignant Melanoma, London, March 19-20**
Contact: CCI Ltd
Palmerston Court 2
Palmerston Way
London SW8 4AJ
Phone: 44(0) 171 720 0600
Fax: 44(0) 171 720 7177
E-mail: cci@confcomm.demon.co.uk
Conference Website: http://www.confcomm.demon.uk/INTRODUCTION.html

1999 **XVIIth International Pigment Cell Conference: Nagoya Congress Center, Japan, October 30 - November 3**
Contact: Kazumasa WAKAMATSU, Ph.D.
Secretary-General, IPCC - Nagoya
Fujita Health University School of Health Sciences
J - Toyoake, Aichi 470-1192
Phone: 81-562-93-2518
Fax: 81-562-93-4595
E-mail: kwaka@fujita-hu.ac.jp

2000 **9th ESPCR Meeting: Krakow**
Contact: Prof. T. SARNA
Jagellonian University
Al. Mickiewicza 3
Poland 31-120 Krakow
Phone: 48-12-342008(direct) or 48-12-341305(switchboard)
Fax: 48-12-336907
E-mail: tsarna@mol.uj.edu.pl

New Members:

The ESPCR is delighted to welcome the following colleagues to membership and hope that they will play a full and active part in the Society.

Dr. Gabriela NEGROILL
Institute of Biochemistry
Dept. Molecular Glycobiology
Splaiul Independentei, 296
ROMANIA - 77700 BUCHAREST

Dr. Stefana-Maria PETRESCU
Romanian Academy
Institute of Biochemistry
Splaiul Independentei, 296, Sector 6
17 - 37, Bucharest 17
ROMANIA - 77700 BUCHAREST

Miss Paula EVES
Clinical Sciences Centre
Northern General Hospital
Dept. of Medicine
Herries Road
UK - SHEFFIELD S57AU

In Memoriam - T. T. Tchen (1924 - 1998) by John D Taylor

Tche Tsing (*aka* T. T.) passed away on August 26, 1998 at Saint Francis Memorial Hospital in San Francisco. A week earlier he was stricken while playing squash, lost consciousness, and never emerged from a coma. His squash opponent revealed that T. T. had just beaten him and was expressing a smug smile of victory at the time he was stricken.

T. T. was born in Beijing, China in 1924, and most of his early life was spent in Shanghai. He was educated in French schools; and it is for this reason that his last name is spelled Tchen rather than Chen. His father was a mathematics professor so T. T. was exposed to academic rigor early. He received a B.S. in chemistry from Auroa University in Shanghai in 1948. He matriculated to the biochemistry doctoral program at the University of Chicago and graduated in 1954.

In 1954, Konrad Block left the University of Chicago for an appointment as the Higgins Professor of Biochemistry in the Department of Chemistry at Harvard University. As a post-doc, T. T. accompanied Block to Harvard to work with him on the mechanism and regulation of the cholesterol and fatty acid metabolism for which Block and Feodor Lynen were awarded the Nobel Prize in Medicine or Physiology in 1964.

T. T. left Block's laboratory and arrived at Wayne State University in 1958 as an Associate Professor. His early years to the early '60s were spent with research dealing with various aspects of cholesterol biosynthesis. He next ventured into prokaryotic systems up to the early '70s, in which he studied developmental cellular biological principles that would remain with him during the rest of his research career. Seeking a eukaryotic model, he found one with Walter Chavin's ACTH-induced melanogenesis in the goldfish. Walter, at the time, was a professor of biology, and some of T. T.'s early pigment cell work was conducted in collaboration with him. Later, some significant findings dealing with goldfish melanophore emerged in collaboration with Funan Hu, who at the time was with the Michigan Cancer Foundation. The most prominent being that the hormone-induced melanogenesis resulted in an obligatory mitosis of the melanoblast yielding two daughter cells – another stem cell and a differentiating melanocyte (*Ann N.Y. Acad. Sci.*, 100:708, 1963).

It was also during the early '70s that T. T. discovered the electron microscope. Suddenly, a biochemist was given the gift of sight! With his new gift, he spent thousands of hours looking at specimens on our scopes. He knew enough about the operation of the scope in order to examine specimens, and then he would tell the student to take pictures of this or that. He took great delight in telling his chemistry colleagues about the wonders of ultrastructure – many seemed impressed.

In my view, it was the electron microscope and the pluripotency of the chromatoblast that shaped T. T.'s research interest for the next decade. It all started with indications that pterinosomes from goldfish xanthophores were tyrosinase positive. This was followed by ultrastructural studies of chromatophores from some amphibians and reptiles, which revealed pigmentary organelles common to more than one chromatophore. At the time, Joseph T. Bagnara (University of Arizona) took the lead with the pluripotency story which later climaxed with a paper appearing in *Science* (203:410, 1979). T. T. was one of several co-authors as he had made major contributions to the story. The discovery of mosaic chromatophores was focal to the pluripotency concept, but the role of the multivesicular body in goldfish melanosome formation as discovered by one of my doctoral students, William A. Turner Jr. (deceased), set the stage for the concept of a common precursor organelle. T. T. made major contributions to our understanding as to how tyrosinase, found in Golgi-derived vesicles, could insert and invert themselves into larger endoplasmic reticulum-derived vesicles, and then finally engage in melanin synthesis (*J. Ultrastruct. Res.*, 51:16, 1975). Hours spent on the electron microscope were beginning to pay off.

T. T. and I were fortunate that first Masataka (*aka* Matt) Obika and then Jiro Matsumoto, both from Keio University in Yokohama, decided to spend their sabbaticals with us. Matt brought us up-to-speed with the latest developments in pigmentary organelle translocations research; so as a result, we followed Matt's lead. Several important papers (*Cell Tiss. Res.*, 105:417 & *J. Exp. Zool.*, 205:95) represented the culmination of this important work.

Several interesting papers involving melanosome translocations came out of that collaboration; but it was the translocations of the carotenoid droplets found in xanthophores that would focus our attention in years to come. One of my doctoral students, John Lo (National Yang-Ming University, Taipei) started his studies by purifying goldfish xanthophores. Purified xanthophores were cultured, hormone-induced, and dissected ultrastructurally and biochemically by John and then later by a number of students who followed. Toward the

end of these studies, Tom J. Lynch and Robert J. Palazzo (University of Kansas) had focused our interests on the pathways affecting intracellular signaling responsible for carotenoid droplet translocations (*J. Biol. Chem.*, 261:4204,1986 & 261:4212, 1986; *Cell Motil. Cytoskel.*, 13:9, 1989 & 13:21, 1989). The goldfish xanthophore research ended with Victoria A. Kimler (University of Detroit Mercy). She, using our newly designed whole mount transmission electron microscope technique, demonstrated that carotenoid droplets were not isolated; but instead, were protrusions that were continuous with the smooth endoplasmic reticulum -- overall appearance similar to a cluster of grapes. Also of interest was that the membrane limiting the carotenoid was a lipid monolayer rather than a lipid bilayer. Tracing the continuum of the lipid monolayer back to the SER, it became a lipid bilayer at the carotenoid droplet-SER junction (*J. Exp. Zool.*, 267:510, 1993.

Jiro Matsumoto's sabbatical focused us on a number of interesting cell lines that he brought with him from Keio University. With Jiro's guidance, we explored the goldfish erythrophromoma cell line in terms of cellular differentiation against their normal counterparts. A *Science* paper (217:1149, 1982) represented the culmination of several important papers that resulted from this research

T. T. was generous with his time. He particularly enjoyed spending time with students. He was always challenging their thinking processes with a goal to make them creative thinkers. He graduated 15 masters students and 30 doctoral students. He received the Distinguished Graduate Faculty Award in 1990.

T. T. retired in 1993 and moved to a home in Oakland, California overlooking San Francisco and its bay. What surprised me was that he gave up science completely – stopped reading journals. Gave up the pipe and reduced coffee intake drastically. He focused his attention on gardening, Chinese cooking and squash. He felt that his knees would not allow him to be competitive in tennis and he would rather not play than not be competitive. He would return to Detroit at least once a year to visit one of his sons. Ken and I would get caught up on his activities over a dinner at one of T. T.'s favorite restaurants. T. T. and his wife, Ina, were well-known gourmet cooks and were close friends with the top chefs in the Metro-Detroit area.

T. T. is survived by his wife, Ina, and his two sons, Terence and Vincent. T. T Tchen, 1924 to 1998. Scientist, educator, tennis and squash player, gourmet cook and friend. We are diminished.

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A Letter from the President -

This past year has been a remarkable one, and I hope that you have been swept along by the exciting wave of progress in our field. Scientists (members and nonmembers alike) have made incredible advances in many disciplines of pigment cell biology, and these are now routinely published in the top journals internationally, as well as in the more specialized journals, including ***Pigment Cell Research***. Our horizons have been significantly widened in recent years based on such dramatic progress, and with current advances in technology, almost any experiment you can imagine, you can do (financial concerns notwithstanding).

Along with such successes, we must bear some bad news as well, with respect to the untimely deaths this year of several prominent scientists amongst us, namely Prof Bengt Larsson and Prof T. T. Tchen. Bengt's loss was a particularly difficult one to bear, not only because he was young, vigorous and in the middle of an ascending career, but because many of us had seen him and his wife Pia at the recent ESPCR and PASPCR meetings just prior to his death. Bengt was an extremely gentle but firm force in guiding the ESPCR and the IFPCS in many roles, most recently as Secretary/Treasurer of the IFPCS. He will be sorely missed by all who knew him, and we are all saddened by his loss.

The **IFPCS Travel Stipend** program has been sputtering along; who could have guessed there would be such reluctance to accept free and easy money to travel abroad? Although the ESPCR, JSPCR and PASPCR each have 3 such IFPCS Travel Stipends to award (up to $3,000 each), to date only 2 of those 9 Stipends have been awarded and used. Because of the nature of those donations and the upcoming rotation of IFPCS Officers in Nagoya this fall, any unused funds will be turned over to Prof. Ito as of August 1[st] to help support travel to the IPCC. I would urge each of you to watch your Society's solicitation of applications for those IFPCS Travel Stipends early this coming year, and apply for one if you have a valid need.

The 17[th] **International Pigment Cell Conference** will be held this next year in Nagoya from Oct 30[th] to Nov 3[rd] in 1999, under the chairmanship of Prof Ito. It is exciting to watch the IPCC Scientific Program develop. I hope that each of you will watch the maturation of the IPCC Program on its Web Site, and I hope that all have the opportunity to attend this Conference. Prof Ito has solicited nominations for Keynote Speakers and Symposium Topics from his IPCC International Program Committee, from his JSPCR Program Committee, from the various IFPCS Special Expert Groups, and other sources. The speakers chosen (almost all of whom have readily accepted) have provided

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the framework of an outstanding program that will span all the disciplines our members are interested in. There will be a number of Satellite Meetings held immediately before or after the IPCC and watch for information about those as well. Prof Ito is also arranging for a very generous travel support program to help with travel to Japan (especially for young scientists) and both the ESPCR and PASPCR have their own Travel Awards programs to help ease the financial burden. Be sure to watch for the announcements, application, registration, and abstract forms that should be coming to you in the near future. Anyone who has been fortunate enough to attend an IPCC or JSPCR meeting in Japan knows how gracious and thoughtful our Japanese hosts are; the 17th IPCC promises to be a special one and you won't want to miss it.

Among the various matters considered by the IFPCS Council at its annual meeting in Snowmass last August was the selection of the next **Editor** of ***Pigment Cell Research*** to follow Prof Matsumoto when his term ends in December, 1999. I am either happy or sorry to say that I was selected for this position, with the stipulation by the IFPCS Council that the next Editor to follow me should come from the ESPCR. I fully agree with this direction (despite the fact I have been an ESPCR member since its inception, probably not many think of me as that) and I have asked ESPCR President Stan Pavel to provide me with some candidates for potential future Editors from the ESPCR that could serve as Associate Editors when I take over in 2000. Once those ESPCR Associate Editors are selected, I plan to fill in the needed expertises in other disciplines with Associate Editors from the JSPCR and PASPCR. All Editors will be meeting in the next year (at least electronically) to discuss plans for streamlining and infusing ***Pigment Cell Research*** with new energy. I am hoping to make dramatic changes in the journal's operation and publication that will enhance its value to all of us, and also enhance its distribution. With all the recent exciting advances in our field, and its topical nature to science in general, there is no reason why ***Pigment Cell Research*** can't be in the forefront of the field. I hope you will all join me in this effort, and you don't have to wait until Jan 1, 2000 to get on board – start subscribing and submitting manuscripts now.

The IPCC in Nagoya next year will provide the opportunity to make a number of prestigious **IFPCS sponsored Awards** at the Conference Banquet. Many of the recipients have just recently been designated and I'd like to take this opportunity to inform you of the winners. I should begin by summarizing how these selections were made. By IFPCS Rules & Regulations, nominations for all of the IFPCS Awards noted below are made by the Regional Societies, which can foster such nominations as they wish (typically this is done by an Awards Committee and/or by the Society Council). Winners of the ***Raper Medal*** and the ***Takeuchi Medal***, awards which were initiated some years ago by the ESPCR and JSPCR respectively, are then selected from those nominations by the respective Society (again with a mechanism they determine). Winners of the ***Myron Gordon Award*** and the ***Makoto Seiji Lectureship***, awards initiated by the IPCC / IFPCS, are selected from those nominations by the IFPCS Awards Committee, which consists of all former recipients of the Myron Gordon Award who have remained active in the field. The winners of those honors are as follows:

Seiji Lectureship -	Dorothy Bennett
Gordon Award -	Shosuke Ito and Vincent Hearing
Raper Medal -	as yet undecided
Takeuchi Medal -	Gregory Barsh

Let me take this opportunity to wish each of you, your families and your colleagues, all possible success in 1999, and I'll look forward to seeing you in Nagoya.

Vince Hearing
IFPCS President