

February 2002



Newsletter Number 5

NEXT IMIG INTERNATIONAL MEETING

DECEMBER 1-4, 2002, PERTH, WESTERN AUSTRALIA

IMPORTANT CHANGES TO IMIG

1. From now on, IMIG will rely on its new website and e-mail for communication. This, we hope, will be the last newsletter in the current format! Newsletter information will be forwarded by e-mail or available on our website. Please refer to the developing website <http://www.imig.org/> for future information on the activities of IMIG. Changing to online and electronic mail will increase the speed and frequency of communication and eventually eliminate the cost of printing and mailing the newsletter. The website will have sections on Clinical Trials, Information on Mesothelioma for Patients, History of IMIG and more. The website will grow and evolve for communication among our members and with the public. Please contact Dr Courtney Broaddus at sfcourt@itsa.ucsf.edu with suggestions or with offers of contributions to the site.
2. SEND IN YOUR ONLINE APPLICATION FROM THE WEBSITE TO SUBMIT YOUR EMAIL ADDRESS FOR FUTURE MAILINGS EVEN IF YOU ARE CURRENTLY ON THE IMIG MAILING LIST. A new mailing list will be constructed from these forms. (Go to <http://www.imig.org/>, Select Membership from the Menu, Click on Online Membership Form, Fill out application and Submit). There is no fee for membership. Your e-mail address will be used for official IMIG business, not for any commercial purpose. For those without e-mail or access to the Internet, mailings will be maintained for the time being. Also, if Internet access is not available, a Membership Application Form has been included at the end of this newsletter.
3. The IMIG will now hold its international meetings every three years, instead of every two. To follow suit, the officers' terms will also be for three years. This increased interval should allow for more developed scientific and clinical presentations and more leadtime for the organisation of the meeting. The next meeting will be held in December 2002, in Perth Western Australia. Please see the Meeting Flyer included with the newsletter.

MESSAGE FROM THE PRESIDENT

I am greatly honoured to have been selected the President of the International Mesothelioma Interest Group for 1999-2002. I will try to keep the momentum begun by my predecessors, in particular Marjan Versnel, our outgoing President. My goals will be to continue to improve communication and interaction among our members and to bring more attention to the subject of mesothelial biology and mesothelioma research. One specific plan for my term is to make our IMIG website useful both for information and communication among our members <http://www.imig.org>. Any suggestions are encouraged. My email is sfcourt@itsa.ucsf.edu.

The most recent IMIG meeting, held at beautiful Stoke Rochford Hall in Grantham, England was excellent both for its science and its camaraderie. This Fifth International Meeting was combined with the Fifth International Meeting of PAX, the International Congress on Peritoneal Repair and Adhesions, allowing joint sessions and interchange among the like-minded scientists and clinicians. The summary of the IMIG meeting is included in this newsletter. Thanks to the chairpersons of the sessions for preparing the summaries.

The next IMIG meeting, December 1-4, 2002, is being planned for Perth, Western Australia. Professor Bruce Robinson has kindly offered to host the meeting. The four day meeting will include a three day IMIG meeting and a one day satellite meeting. Topics covered in the IMIG meeting will include: mesothelial cell repair, fibres and cell transformation, immunology and immunotherapy, pathology and disease staging, SV40 and infection, diagnostic advances, gene therapy, gene arrays, proteomics, clinical trials and recent advances in treatment, group meetings to discuss the development of international clinical trials, legal aspects of mesothelioma.

The satellite meeting, entitled "Recent advances in cancer technologies- from gene chips to gene therapy" will present state-of-the art reviews on 'hot' topics such as DNA microarrays ('gene chips'), proteomics, and SNP analysis and describe the clinical use of these technologies now and in the future. We hope to attract a wide range of scientists and clinicians to both the IMIG and satellite meeting.

Thanks must go in large measure to Steve Mutsaers, the Secretary of IMIG, and Marjan Versnel, the recent President, for the planning and organisation of the fine IMIG meeting in Grantham England and for their long-time contributions to IMIG. Thanks also to Per-Fredrik Ekhold who has served and will continue as the Treasurer. Several members of IMIG have agreed to join the Executive Committee, including Dr. Luciano Mutti, and Dr Paul Baas. Thank you in advance for your support and for your assistance.

V. Courtney Broaddus, MD

SUMMARY OF THE 5TH IMIG MEETING

The Fifth IMIG meeting was held from 5-8 October 1999 at Stoke Rochford Hall, Stoke Rochford, Grantham, UK. This meeting was combined with the International Congress on Peritoneal Repair and Adhesions (PAX), with the aim to bring together researchers in basic science and clinical practice who share common interests in areas of mesothelial and serosal biology, including tissue repair, adhesion formation, tumorigenesis, diagnosis and treatment. The meeting provided a successful forum for delegates of both groups to interact both scientifically and socially, forging new friendships and establishing future collaborations.

WEDNESDAY 6TH OCTOBER 1999

The first day of the meeting had combined IMIG/PAX sessions with concurrent sessions on the following two days. Wednesday morning commenced with Dr. Steven Mutsaers (conference organiser, IMIG), Dr. Marjan Versnel (IMIG President) and Mr. Jeremy Thomson (conference organiser, PAX) giving their welcoming addresses. The first scientific session entitled “**Inflammation and Fibrin Regulation**” was chaired by Mr. Jeremy Thompson (London, UK) and Professor Jack Gauldie (Hamilton, Canada). Professor Steven Idell (Tyler, USA) commenced the session by presenting some of his studies on post-translational regulation of the urokinase receptor by mesothelial and mesothelioma cells. Urokinase-type plasminogen activator (uPA) has been implicated in the pathogenesis of neoplastic growth and studies have shown that various factors implicated in pleural injury and neoplasia upregulate and stabilise the message for the uPA receptor (uPAR). Professor Idell described studies where he identified a 50 kDa uPAR binding protein that binds a fragment of uPAR mRNA that is involved in posttranslational regulation of uPAR mRNA. Overexpression of the uPAR mRNA binding protein binding region doubled uPAR expression at the cell surface that increased cell proliferation and invasiveness. These data demonstrate that posttranslational regulation of the fibrinolytic system can modify the role of mesothelial cells in mesothelial and mesothelioma cells in pleural remodelling after injury or in pleural neoplasia.

Professor Lena Holmdahl (Göteborg, Sweden) followed describing some of her studies characterising proteases that participate in the breakdown of extracellular matrix, particularly in the peritoneal cavity. Changes in local expression of plasmin may play a role in the establishment of post-operative adhesions either directly or through the regulation of other

proteases such as members of the matrix metalloproteinase family (MMPs) or through proteolytic activation of latent growth factors. It was proposed that variability in the expression of plasmin may explain differences in adhesion severity.

The late morning session was chaired by Professors Steven Idell and Lena Holmdahl and continued the theme of inflammation and fibrin regulation. Dr. Teake Kooistra (Rotterdam, Netherlands) presented a study designed to determine the temporal expression of fibrinolytic effector proteins during the development of peritoneal adhesions in a rat model. Analyses of fibrinolytic parameters in peritoneal lavage and biopsy samples were conducted to elucidate how differential expression of fibrinolysins, mainly tPA, and plasminogen activator inhibitors interact to influence adhesion formation. Dr. Kooistra's interpretation of the data was that the findings suggested that determinants of increased fibrin formation rather than decreased local fibrinolytic activity were chiefly responsible for increased extravascular fibrin deposition and adhesion formation in the model. Expression of fibrinolytic parameters was next studied in an *in vitro* model system using human mesothelial cells. It was proposed that interventions designed to up-regulate fibrinolytic activity of these cells could potentially be exploited to increase endogenous fibrinolytic capacity after operative peritoneal injury and thereby limit adhesion formation.

Dr. Geoff Bellingan (London, UK) then presented a descriptive analysis of macrophage-mesothelial cell adhesive interactions that occur in models of acute versus more chronic peritoneal injury. Inflammatory cells were harvested from acute or chronic injury, labelled with a fluorescent dye and analysed for their ability to adhere to monolayers of MeT5A mesothelial cells. While the peak of macrophage adhesion to the MeT5A cells differed between

cells harvested from the two models, the authors concluded that, in both cases, peak adhesion was found when resolution of the inflammatory response began. This study confirms that myeloid-mesothelial cell interactions may regulate inflammatory cell traffic during the course of peritoneal inflammation.

The next two presentations dealt with different aspects of the regulation of mediator expression in the context of peritoneal injury. Mr. Tom Wilkinson (Cardiff, UK) presented work designed to use transgenic animals to elucidate the role of interleukin-6 (IL-6) in the control of inflammatory cell traffic in a model of peritoneal injury. Mice with a homozygous deficiency of IL-6 were used. The preliminary data demonstrated that neutrophil influx into the peritoneal exudate was increased in mice deficient in IL-6, an effect that was associated with increased levels of MIP-2. The data suggest that IL-6, possibly derived from the mesothelium, is a key determinant of neutrophil traffic in inflammatory peritonitis induced by cell-free supernatants of cultures of *Staph. Epidermidis*.

Dr. Cathy Hoff (McGaw park, USA) concluded the session and presented work in which rat mesothelial cells were genetically engineered to overexpress rat interleukin-10 (IL-10) to inhibit mediator expression by macrophages. The genetically modified cells were able to inhibit cytokine expression by rat NR8383 macrophages, an effect that was attributable to rIL-10 based upon antibody neutralisation studies. The stable transfectants could be transplanted into the peritoneum of rats, providing a potential avenue to influence the course of macrophage-derived mediator expression in peritoneal injury.

The afternoon session, co-chaired by Professor Geoffrey Laurent (London, UK) and Dr. Simon Whawell (London, UK), was focused on “**Serosal Repair**”. Professor Elizabeth Hay

(Boston, UK) opened the session by describing her studies on epithelial-mesenchymal transformations (EMT). She carefully described these events as part of normal embryogenesis and in the development of mesothelium from primitive streak mesenchyme. Of particular interest were studies describing the dramatic EMT of primary corneal fibroblasts following transfection with E-cadherin, where cells changed morphology to resemble stratified epithelium and expressed tight junctions and desmosomes. This has particular relevance to tumour biology as current studies indicate that tumour cells can convert to a less invasive phenotype by E-cadherin transfection. The involvement of c-src in EMT was also discussed.

Professor Jack Gauldie (Hamilton, Canada) described the effects of transient overexpression of TGF β ₁ on the peritoneal membrane. It is thought that fibrosis of the peritoneum may result as a complication of dialysis in patients with renal disease. In general, adenovirus mediated transfections into mesothelial lined spaces was thought to be a very effective system of gene delivery. TGF β ₁ transfection in lung, liver and rectum resulted in submesothelial fibrosis but only in the peritoneum did such events lead to adhesion formation.

The final lecture of the session was delivered by Dr. Wolfgang Sendt (Freiburg, Germany) and described co-culture experiments of mesothelial and endothelial cells as a model to study the physiology of the peritoneal membrane. Endothelial cells were grown on the bottom of a collagen coated 3 μ m pore size culture insert, with mesothelial cells on the top. Careful immunohistochemical studies were performed to confirm the identity of the cells and the model was used to study transmigration of stimulated polymorphonuclear neutrophils from the lower to the upper compartment.

Following afternoon tea, the theme of serosal repair continued, chaired by Professor Agnes Kane (Providence, USA) and Mr. David Scott-Coombes (London, UK), with the emphasis of identifying the origin of the regenerating mesothelial cell. Mesothelium, unlike other epithelial-like surfaces, does not heal solely by centripetal migration of cells from the edge of the wound towards the wound centre. This is evident as both small and large mesothelial lesions heal in exactly the same time. Mr. Andrew Raftery (Sheffield, UK) described some of his and others early studies on mesothelial healing and presented evidence to suggest that the regenerating mesothelium originates from subserosal fibroblast-like cells. Three papers followed showing evidence to suggest that the healing mesothelium may not originate in the subserosa but from cells in the surrounding mesothelium which divide, float in the serosal fluid and settle on the injured serosa to repopulate the wound. Dr. Steven Mutsaers (London, UK) presented kinetics data showing that in an experimental model, replenishment of the mesothelium was well under way even before submesothelial cells at the centre of the lesion had begun to divide. Mr. Talib Al Mishlab (London, UK) described an immunohistochemical study where he was unable to demonstrate differentiation of subserosal cells into cells with mesothelial characteristics at any stage of serosal healing. This study contradicted a previous study that suggested submesothelial differentiation on the basis of immunohistochemical studies. Mr. Adam Foley-Comer (London, UK) then presented data showing that application of fluorescently labelled cultured mesothelial cells to injured serosa resulted in attachment and incorporation of these cells into the healing mesothelium. He also presented preliminary data suggesting that free-floating cells may be derived from a precursor/stem cell population in the mesothelial monolayer.

THURSDAY 7TH OCTOBER 1999

Thursday morning began the concurrent sessions with presentations divided into IMIG and PAX. Only IMIG sessions will be described in the following summary. The session “**Disease Staging and Litigation**”, chaired by Professor Philippe Chahinian (New York, USA) and Dr. Paul Baas (Amsterdam, Netherlands) commenced with Dr. Valerie Rush (New York, USA), who summarised the different staging systems for pleural mesothelioma, starting with Butchart and ending with the IMIG system. The T factor has prognostic significance (T1-T2 better than T3-T4), as well as the N factor (lymph nodes negative or positive) and the epithelial cell type has the best survival rates. There was no major survival differences with the extent of surgery (extrapleural pneumonectomy versus pleurectomy-decortication).

Mr. James Early (New York, USA) then discussed legal issues associated with asbestos exposure and mesothelioma, and reviewed some early correspondence from different companies discussing the health effects of asbestos. It was clear that many asbestos related companies were fully aware of the detrimental effects of asbestos well before its use was stopped or adequate health and safety precautions implemented.

The late morning session, entitled “**Gene Therapy and Free Communications**” commenced with Dr. Steven Albelda (Philadelphia, USA) who presented his experience with gene therapy of pleural mesothelioma. This trial, using an adenovirus vector with the *H. simplex* thymidine kinase gene, is designed to transfer this enzyme to tumour cells and make them susceptible to systemic administration of gancyclovir. In the initial Phase I trial involving 26 patients, the MTD (maximum tolerated dose) was not reached. Dr. Albelda discussed also the future of this therapy using possibly other vectors (*H.*

simplex virus or liposomes) or heat shock protein to activate the immune response. Dr. Daniel Serman (Philadelphia, USA) described the results seen in the 26 patients treated in Philadelphia by the gene therapy approach discussed by Dr. Albelda. There was evidence of gene transfer, although it was superficial. There was one partial response, and 2 patients remained without evidence of disease at 3 years.

Dr. Jeremy Steele (London, UK) discussed the results of a Phase II trial of vinorelbine in 29 patients with mesothelioma. There were 7 partial responses (26%), which is remarkable in view of the lack of efficacy of previous vinka alkaloids in this disease. About half of the patients reported symptomatic improvement. Dr. Richard Lake (Perth, Australia) investigated the different antigens associated with mesothelioma. The majority of these were nuclear antigens, and serum reactivity was seen in 30% of patients, without an obvious prognostic implication. Miss Claire Vivo (Creteil, France) described the cellular effects of interferon gamma in human mesothelioma cell lines. There was a decrease in tritiated thymidine uptake and a G2/M block in sensitive cell lines. This was independent of p53, p21 and p27. No cell line expressed SV-40.

After lunch, Dr. Courtney Broaddus (San Francisco, USA) and Professor Bruce Robinson (Perth, Australia) chaired a “**Free Communication and Poster Discussion**” session. A variety of talks and posters were presented and discussed concerning mesothelioma characteristics, role of SV40, clinical information on mesothelioma, and application of new technologies for identification of surface epitopes or genetic differences.

Examining malignant mesothelioma characteristics, Dr. Katalin Dobra (Stockholm, Sweden) used subtractive hybridisation to show that mesothelioma cells with an epithelial phenotype tended to express more genes,

including syndecan-2 and -4, which suggested a more differentiated state than mesothelioma cells with a fibrous phenotype. Dr. John Edwards (Leicester, UK) found higher activity of MMP-2 and -9, the gelatinases, in mesothelioma tissue than in benign pleural tissue. Dr. Pascale Harvey (Norwich, UK) similarly found that human mesothelioma cell lines expressed the gelatinases, MMP-2 and -9. In addition, all lines expressed the tissue inhibitor of metalloproteinases, TIMP-1 and -2. Hepatocyte growth factor (HGF) increased expression of some metalloproteinases and also TIMP-1. Dr. Pier-Giacomo Betta (Alessandria, Italy) showed that N- and E-cadherins, cell-cell adhesion molecules reported to be mutually exclusive markers for mesothelioma and adenocarcinoma in tissue samples, respectively, were both expressed in mesothelioma cell lines. Dr. Yasushi Inoue (Hyogo, Japan) presented data suggesting that CD44, a hyaluronate receptor, may be a useful immunohistochemical marker for distinguishing mesothelioma from lung cancer. Dr. M. Valle (Italy) showed that mesothelioma cells can present recall antigens and can block interferon-gamma production, presumably by the production of TGFβ.

The role of SV40 in mesothelioma pathogenesis was also discussed. In several studies, PCR amplification of SV40 from mesothelioma tissue was presented. Dr. Luciano Mutti (Borgosesia, Italy) found a trend in the appearance of SV40 and decreased one-year survival from mesothelioma. Dr. Rudy Foddìs (Pisa, Italy) was able to amplify SV40-like sequences from paraffin-embedded mesothelioma tissue. Dr. Kazuhiko Takabe (Ibaraki, Japan), also found SV40 sequences in paraffin-embedded mesotheliomas. Interestingly, SV40 sequences could be amplified from peripheral blood cells in 3 (12%) patients: one with mesothelioma, one with malignant lymphoma and one with non-malignant disease. In contrast, in another study, no evidence of SV40 could be found. Dr.

Roland Hübner (Antwerpen, Belgium) varied the methods of genomic DNA extraction, used several primers specific for SV40 or inclusive of other polyomaviruses BK and JC, included positive controls, used different stringencies and sequenced every amplicon. No SV40 DNA was found, although JC viral DNA was identified in one human mesothelioma. The discussion of this talk and the posters addressed the importance of incorporating controls in these studies (e.g. non-mesothelioma tumours, non-malignant tissues), as well as sequencing all amplified DNA to distinguish SV40 from other polyoma viruses. Indeed, standardisation of techniques and sharing of tissues appears necessary to resolve different results.

With the application of new techniques to mesothelioma, Dr. Joost Hegmanns (Rotterdam, Netherlands) presented a phage-antibody-display approach to isolating antibodies specific to cell surface molecules. Phages bound to mesothelioma cells were eluted, propagated and repeatedly selected and purified. Currently, 7 mesothelioma-specific phage antibody clones have been identified. This approach may provide useful reagents for diagnosis, for immunotherapy and for investigating mesothelioma-specific membrane proteins.

Dr. Kettunen's poster, presented by Dr Sakari Knuutila (Helsinki, Finland) showed findings of cDNA microarray technology analysis of 4 mesothelioma lines. Approximately 20 genes that were down regulated compared to benign mesothelial cells (< 0.5 expression) included VEGF R-2, PDGF-alpha receptor, retinoic acid receptor, tenascin-C and MMP-19. Approximately 30 genes that were most upregulated (> 3 times expression) included cytokeratin 4, FGF-3, JNK1, PDGF-beta receptor, NGF-2, cdc25b and cyclin D1 and D3.

Under the heading of "Epidemiology, clinical presentation and treatment of mesothelioma", Dr. Valeria Ascoli (Rome, Italy) reported an

interesting cluster of 5 cases of mesothelioma in a family that has a strong history of respiratory tract cancer, suggesting a genetic predisposition as well as an environmental influence. Dr. John Edwards (Leicester, UK) presented retrospective data on 140 patients with mesothelioma in Leicester. Median survival was 4.9 months and one year survival was 25.7%. When these patients were stratified into published prognostic groups, they had equivalent survival statistics to those of other western countries. Dr. Edwards also reported that a measure of angiogenesis, Chalkley microvessel counts, correlated inversely with prognosis in mesothelioma. Dr. Gunnar Hillerdal (Stockholm, Sweden) found that a group of immigrants from Turkey with a high risk of mesothelioma due to erionite exposure did not have benign pleural changes on chest radiograph, suggesting that mesothelioma can develop without prior benign pleural disease.

Dr. Aija Knuutila (Helsinki, Finland) reported that, although irinotecan (CPT-11, an active metabolite of ethylcamptothecin) appeared to be highly active against mesothelioma cells *in vitro*, it was disappointing in clinical trials. Irinotecan combined with docetaxel was toxic and not active in 15 patients with mesothelioma. The discussion included comments by those who find value in irinotecan and proposed that different dosing schedules should avoid limitations of toxicity.

The late afternoon session focussed on "**Pathogenesis and Carcinogenesis of Mesothelioma**". Papers presented in this session were related to markers in mesothelioma, potential new ways to challenge tumour proliferation, and effects of asbestos fibres on mesothelial cells *in vitro* and *in vivo*.

The poor effects of chemotherapy in mesothelioma may, in part, be explained by less efficient apoptotic mechanisms. Dr. Courtney Broaddus (San Francisco, USA) presented her

studies on the effects of the TNF-related Apoptosis-inducing Ligand (TRAIL). This factor was given to tumour cell cultures alone and in combination with bleomycin or doxorubicin or when simultaneously hindering apoptosis with a proteasome inhibitor (MG132). TRAIL caused a substantial decrease in cell viability in two out of three cell lines, while no such effect could be obtained with TNF. The effect was due to apoptosis, and it was further enhanced when combined with chemotherapy and MG132.

Dr. Stephen Faux (Leicester, UK) exposed rat pleural mesothelial cells to carcinogenic crocidolite and erionite and non-carcinogenic milled crocidolite and chrysotile *in vitro* and examined EGR-R and PCNA expressions by confocal microscopy. In low serum conditions, carcinogenic samples produced enhancement of EGF-R and PCNA staining compared with the non-carcinogenic preparations. The data suggest an activation of the cell proliferation cascade by the carcinogenic fibres.

The effects of crocidolite and chrysotile asbestos fibres and non-fibrogenic particles on MCP-1 secretion was examined in rat pleural mesothelial cells (RPMCs) *in vitro* by Professor Elliot Kagan (Burlington, USA). Asbestos exposure upregulated both expression and secretion of MCP-1, a stimulation that appeared faster in the presence of TNF α . RPMCs challenged with asbestos fibres also showed increased attachment of leucocytes, which was correlated to a simultaneous upregulation of VCAM-1. The findings suggest that MCP-1 secretion and leucocyte adhesion have a role in asbestos-related lesions.

Early studies on the expression of cyclo-oxygenase-2 (cox-2) in MM, a factor that downregulates immunity and upregulates angiogenesis, were presented by Dr. John Edwards. Cox-2 staining was demonstrated by immunohistochemistry in all 10 samples of surgically resected mesothelioma investigated in

this study. These results support a role for cox-2 in the pathogenesis of mesothelioma and it was proposed that cox-2 antagonists may be novel candidates as therapeutic agents.

Mr. Vincent Williams (Perth, Australia) presented a careful assessment of the association between retained total lung fibre burden and the risk of mesothelioma. The study was based on 138 cases of mesothelioma and 248 controls. The odds ratio was 1.23 for log(asbestos bodies/g; 95% CI = 1.04 - 1.44) and 1.65 for log(crocidolite fibres/g; 95% CI = 1.33 - 2.04). There was no evident threshold value.

Dr. Benjamin Nissam (Jerusalem, Israel) investigated a series of serum tumour markers in 228 patients with different respiratory diseases. Tissue polypeptide specific antigen (TPS) showed the highest sensitivity (63%) in mesothelioma followed by CYFRA21-1 (53%) and CA125 (26%). Interestingly, thrombocytosis and levels of TPS, CA125 and CYFRA21-1 increased with the progression of the disease. Thus measurement of TPS and CA125 allowed the authors to monitor the effect of chemotherapy and the sensitivity in such monitoring could be increased by the combination of 2 markers: TPS and CA125 (84%). The analysis of CEA in combination with TPS or CYFRA21-1 was suggested as a tool to discriminate mesothelioma from lung carcinoma.

FRIDAY 8TH OCTOBER 1999

The Friday morning session began with several presentations on “**Mesothelioma Epidemiology**”. Professor Julian Peto (Belmont, UK) presented data demonstrating that the rate of new cases of mesothelioma at age 40 was higher in 1990 than it had been in 1940. Asbestos exposure had increased progressively up to those having started work in approximately 1965. Lifetime risk of dying from

mesothelioma was increasing with birth year up to 1% for 1945. Currently there are 1300 UK deaths per year, and the number is still rising. Professor Peto believes that this was due to peak unregulated use of asbestos materials in building trades during the 1960's. The situation in Europe appears similar, although based not on true mesothelioma incidence but on the broader "pleural cancer". Projections of increasing incidence and mortality may be slightly exaggerated due to increasing awareness of the disease and hence increasing diagnosis.

Dr. James Leigh (Sydney, Australia) presented the most recent data from the Australian Mesothelioma Register, the most complete mesothelioma registry extant. In Australia, crocidolite was removed from new use in 1967; peak use was in 1965. By 1975, asbestos use peaked at 700,000 tons per year; mainly chrysotile. Chrysotile use continued until at least 1985. Mesothelioma incidence, lagged 40 years, almost perfectly matches asbestos consumption with mean latency 37 years, and as in Europe and the United Kingdom incidence is still increasing. By 2020, 10,000 new cases are expected. Dr. Leigh corrected some misimpressions of the Australian situation concerning Wittenoom. For the years 1980-1999, 38% of all cases came from New South Wales, and only 16% from Western Australia (where the mine was located). Even within Western Australia, only about half of all cases had been exposed in or around Wittenoom. Thus, more than 90% of cases of mesothelioma in the last two decades have come from other areas and exposures.

Dr. Bruce Case (Montreal, Canada) reported pathology validation for 19 female pleural and peritoneal malignancies within and 104 outside asbestos mining regions in Quebec, 1970-1990. Less than 25% of female mesotheliomas were associated with asbestos exposure. Cases were circulated, double-blind, to Drs. Andrew Churg and Victor Roggli. Agreement between expert pathologists was 'substantial' (86.84% vs.

53.22% predicted; Kappa 0.72, $p < .0001$) for next-adjacent category on a four-point scale. Churg and Roggli found over-diagnosis of mesothelioma at the local hospital level by approximately 28%. Pleural and peritoneal tumours classified as other tumours by local hospital pathologists were conversely under-diagnosed. Measurable improvement in diagnosis with the introduction of immunohistochemical assays after 1985 was offset by a falling autopsy rate. Diagnostic accuracy at the local level for definite asbestos-exposed cases was very high. Dr. Case concluded that pleural and peritoneal tumours diagnosed prior to 1985 should be regarded with extreme caution in epidemiological study: expert pathology review is mandatory. Conversely, knowledge of putative 'environmental' asbestos exposure leads, at least in this population, to over-diagnosis of mesothelioma.

The late morning session entitled "**Gene Regulation**" was chaired by Dr. Steven Albelda (Philadelphia, USA) and Dr. Marjan Versnel (Rotterdam, Netherlands). Inactivation of the tumour suppressor gene p16 has been reported to be one of the most common molecular abnormalities found in mesothelioma tissues and cell lines. Two abstracts addressed this issue. Dr. Kazuhiko Takabe (Ibaraki, Japan) used immunohistochemistry and PCR to ask the question whether the loss of p16 was due to genomic loss or hypermethylation of the promoter. The analysis confirmed loss of p16 in 75% of mesothelioma tumours. Hypermethylation was actually rare; most cases showed genomic loss of p16. Dr. Agnes Kane (Providence, USA) used a murine model of mesothelioma to study p16 along with the associated proteins p15 and p19. Mesotheliomas were induced by weekly intraperitoneal injections of asbestos. Sixteen cell lines obtained from these animals were established and studied. Approximately one half of these cell lines showed deletions in p16 with no

expression of mRNA. Many of these lines had associated loss of p15 and p19. These studies confirm that loss of the p16 gene locus is common in malignant mesothelioma and may have an important role in pathogenesis of tumour progression.

Dr. Martin Dyer (Sutton, UK) presented work on a newly identified tumour suppressor gene bcl-10, which *in vitro*, was pro-apoptotic, an inducer of NF- κ B and transforming upon truncation. In malignant mesothelioma, loss of heterozygosity of the 1p22 region, where bcl-10 has been mapped, has been described. cDNA of malignant mesothelioma cell lines exhibited the following sequence abnormalities: three alternative splice sites, alterations within the homopolymeric runs and point mutations. This phenomenon has been interpreted to be molecular misreading as in genomic DNA a much lower mutational frequency was found. In 50% of the primary malignant mesotheliomas bcl-10 has been found to be deleted. Knock out mice for bcl-10 will reveal more on the role of bcl-10 in malignancy. Professor Anton Berns (Amsterdam, The Netherlands) introduced a method for the production of conditional tumour suppressor gene knock out mice. Using this method genes can be switched off in a time-controlled and tissue specific manner. Candidate genes for the production of a mesothelioma mouse model are NF2, pRb, p16 and p53. Intraperitoneal and intrathoracic injection of NF2 and Rb or NF2 only resulted in multiple foci of tumour growth in the mesothelium. Although further characterisation of the tumour cells must be performed, these results indicate that NF2 contributed to the development of these mesotheliomas.

The afternoon session concentrated on “**Clinical Studies**” and was chaired by Dr. Daniel Sterman (Philadelphia, USA) and Dr. Per-Fredrik Eckhold (Fredrikstad, Norway). Professor Bruce Robinson (Perth, Australia) in his overview of new therapeutic approaches to mesothelioma,

proposed that the problem was not that the body does not recognise the tumour, but that its response to the tumour is inadequate and needs to be modulated/stimulated to cause rejection. For *in vivo* evaluation of the anti-tumour immune response, he and his colleagues transfected murine mesothelioma cells with the influenza hemagglutinin (HA) gene so that the cellular and humoral response to HA could be followed in transgenic mice with T cell receptors specific for HA. They also used a technique called CFSE to monitor *in vivo* analysis of antigen presentation and proliferation of antigen specific T cells. In Professor Robinson’s model of transgenic mice challenged with HA-positive tumour cells, significant T cell proliferation could be detected, sometimes even in the absence of gross tumour at the injection site. He was also able to show that T cell proliferation would not be maintained unless CD4 helper T cells were also present to potentiate the response.

Professor Robinson also discussed his group’s experience with chemotherapy and cytokine therapy. He reported a partial response (42%) with gemcitabine and cisplatin treatment and his studies with either direct infusion or viral-mediated transfer of cytokine genes; GM-CSF and interleukin-2 (IL-2) did not show any evidence of tumour regression.

The next speaker was Dr. Phillippe Chahinian (New York, USA) who presented his data regarding the use of the nude mouse model of human mesothelioma for testing of new chemotherapy agents and combinations. He described the use of xenotransplantation of human mesothelioma tumours into the flanks of T-cell deficient (‘nude’) mice to test the efficacy of single and combined agent chemotherapy to look for synergy. Significantly, testing of the combination of mitomycin and cisplatin together with alpha interferon and also paclitoxel (Taxol) revealed a significantly greater anti-tumour activity than either agent

used alone. This model, therefore, appears to be a useful testing ground for new chemotherapeutic agents and combinations in malignant mesothelioma.

Dr. Takashi Nakano (Hyogo, Japan) presented his groups experience with the use of the topoisomerase I inhibitor CPT-11 as part of combination chemotherapeutic regimens for patients with mesothelioma. In a recently completed pilot study of CPT-11 combined with the topo II inhibitor, adriamycin (ADR), a partial response has been seen with 2 from 9 mesothelioma patients.

Dr. Gunnar Hillerdal (Stockholm, Sweden) presented a Scandinavian Phase II study with high dose methotrexate and alfa and gamma-interferons. Objective response rate was 28% and stable disease 56% of a total of 39 patients. The duration of the response was more than 100 days on average but survival has not yet been finally analysed. Dr. Castagneto (Casale Monferrato, Italy) evaluated the toxicity of a fixed dosage of an escalation dose of mitomycin using a thoracic stop-flow technique in five patients. One patient had neurological grade 4 toxicity, but other side effects were mild. The dose finding study will continue. Dr. John Edwards (Leicester, UK) evaluated palliative debulking surgery in 35 patients with stage III and IV MM. Decortication was done in 26 and pleurectomy in 9. The operations gave symptom relief in both dyspnoea and pain of more than 50% evaluated at six weeks and three months. The results were thought to be due to expansion of the lung for reducing dyspnoea and decompression of nerves for the reduction of pain. A randomised study comparing debulking surgery with best supportive care was proposed.

In the closing remarks it was stated that we need bigger multicenter Phase II studies before we move on to Phase III randomised studies to establish standards for MM treatment. IMIG

should play an active role to promote co-operation between different centres.

Dr. Marjan Versnel closed the meeting by thanking everyone for attending and invited them to attend the 6th IMIG meeting to be held in Perth, Western Australia in December 2002. Updates will be announced on the IMIG webpage <http://www.imig.org/>

NEW INVESTIGATOR AND POSTER PRIZE

Congratulations go to Ms Claire Vivo (Créteil, France) for winning the IMIG New Investigator Prize of £300 for her presentation “Cell cycle analysis in interferon gamma (IFN γ) treated human mesothelioma cell lines (HMCLs)”.

A single poster prize was split between two worthy posters; Dr. Roland Hübner (Antwerp, Belgium), for his poster injecting caution into the field of SV40 amplification from mesothelioma and Dr. Kettunen (Helsinki, Finland) for her work on microarray analysis of mesothelioma. Our congratulations go to these two worthy recipients together with £50 each and a text book on serosal injury generously donated by Professor Gere diZerega (Los Angeles, USA).

RESULTS OF THE IMIG LOGO COMPETITION

It was decided that no first prize would be awarded in this competition as no design exactly matched the requirements for the IMIG logo. A logo has since been developed by a professional organisation. However, a second prize of £25 was awarded and congratulations go to Ms Ariane Galateau (Paris, France).

OBITUARY

J. Christopher WAGNER



Our scientific community is considerably saddened to learn that Christopher WAGNER died in May, 2000. For those involved in research on health effects of asbestos fibres, Chris was one of the most outstanding authorities on asbestos-related diseases, both from a pathological point of view and regarding his expertise on the experimental approach to asbestos toxicology.

Chris Wagner was born in Pretoria, South Africa, on April 11th 1923. His father was an eminent economic geologist, the Director of the South African Geological Survey. The family had emigrated from London in 1810. Chris was 6 years old when his father died.

Chris was educated in Johannesburg and Natal and went to the University of Natal in 1941. During World War II, Chris served in the South African army, taking part in the North African and Italian campaigns. After the war, he returned to Johannesburg, Witwatersburg School of Medicine graduating in 1951. Thereafter, he trained in Pathology at the South African Institute for Medical Research and in 1954 was appointed Asbestos Research Fellow at the Pneumoconiosis Research Unit, in

Johannesburgh. During this time, Chris published a famous paper on "Diffuse pleural mesothelioma and asbestos exposure in the North-Western Cape province", in the *Br. J. Indust. Med.* (Wagner, J.C., Sleggs, C.A., Marchand, P. 1960, 17: 260-271). In this paper, Chris established, for the first time, a relationship between pleural mesothelioma and asbestos exposure. It was also in this paper that mesothelioma was finally accepted as a separate pathological entity.

In 1962, Dr J. Gilson, Director of the MRC Pneumoconiosis Research Unit at Llandough Hospital in Wales, persuaded Chris to join his team. He worked there until retirement in 1988. Here, he was the first to establish a colony of rats with lungs free from organisms causing lung disease for use in following disease patterns after exposure to dusts. He established both intra-pleural and inhalation methods for the study of lung fibrosis, lung cancer, and pleural mesotheliomas. He and his team found that asbestos dimensions were an important parameter in the induction of pathogenesis.

He was engaged in collaborative research, in many parts of the United Kingdom and in other parts of the world such as Cyprus, Turkey, Greece and Canada, and gave freely of his help and advice.

For young researchers, the observations made by Chris Wagner gave an enthusiastic boost to investigations into the mechanisms of the pathogenicity of asbestos.

Chris Wagner married Margaret, a haematologist, in South Africa; they had one son and two daughters, and two granddaughters. Chris and Margaret retired to Dorset in 1988, where Chris continued to be consulted, until shortly before his death on 25 May 2000. His work was sound and he provided milestones in research work on

asbestos toxicity. His results were of paramount importance in the regulation of asbestos use, providing a better consideration of occupational asbestos-related diseases. In addition to his work on asbestos, Chris and his co-workers studied another type of fibre called erionite, in collaboration with Professor I. Baris, a Turkish clinician, who had discovered a high mortality rate due to mesotheliomas in some areas in Turkey. The findings of fibrogenicity and carcinogenicity of erionite in rats provided an important demonstration of the ability of other sorts of fibres to produce lung and pleural damage.

In 1985, Chris Wagner received the prestigious Charles S. Mott Prize from the General Motors Cancer Research Foundation for the most outstanding recent contribution related to the causes and ultimate prevention of cancer.

Chris was a quiet, philosophical person appreciated by his research co-workers. For those who encountered him during scientific meetings, he was a nice, warm friendly person with a good touch of humour. He will be sadly missed.

Marie-Claude Jaurand

MEETINGS

American Thoracic Society (ATS)
98th International Conference
Atlanta, Georgia, USA
May 17-22, 2002
<http://www.thoracic.org/>

Gordon Conference
Chemotherapy of Experimental and Clinical
Cancer
New London, New Hampshire, USA
July 14-19, 2002
<http://www.grc.uri.edu/>

Gordon Conference
Cancer
Newport, Rhode Island, USA
August 4-9, 2002
<http://www.grc.uri.edu/>

12th European Respiratory Society
Annual Congress
Stockholm, Sweden
14-18 September 2002
<http://www.ersnet.org/>

European Society for Medical Oncology
27th ESMO Congress
Nice, France
October 18-22, 2002
<http://www.esmo.org/>

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