Environmental Mutagen Society

The EMS Spring 2002 Newsletter (online version)

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KLONDIKE EXPRESS
WHITTIER, AK

EMS Goes North to Alaska!

by Larry Loeb, Program Chair

Alaska provided an exciting location for the 33rd Annual Meeting of the Environmental Mutagen Society, "Frontiers Beyond the Human Genome." We approached this site with trepidation: it is distant; the University is not a major source for cutting-edge research in environmental mutagenesis, and it could be cold. We were delighted at the warm hospitality of our Alaskan colleagues, and the people of Alaska. Kandace Williams and Josephine Simonetti guided us into this glistening white environment. Even though Anchorage is in the middle of a wilderness, it is a vibrant city, with restaurants, cafeterias, and unique side-trips that provided a social background for in-depth scientific discussions.

Foremost, I must thank the many people who helped to organize and bring the Anchorage Meeting to fruition: the Organizing Committee; the Symposia Chairs; and the Speakers worked many hours to develop a Program that was wide-ranging, and would appeal to the diverse interests of the Membership of EMS. The Administrative Organization, AIM, provided efficient and professional expertise that facilitated stepping over the many rough corners that one finds at such a meeting. I'm also thankful for the members of the EMS, who endured some of the unanticipated discomforts, such as insufficient space on the boat, not enough tables at the banquet, and computer glitches, that have characterized so many recent meetings throughout the world. It should be noted that the Organizing Committee suggested the topics; the Symposia Chairs picked the speakers, and a number of volunteers went through the abstracts to prioritize the Short Presentations. It is this generosity and camaraderie that characterizes the membership of the Environmental Mutagen Society.

Science: The meeting in Alaska spanned the gamut from toxicology to nanotechnology. The emphasis was on mechanistic studies at the forefront of environmental mutagenesis. I believe that the speakers were of an exceptionally high caliber, and they punctuated the meeting with exciting highlights. The first symposium focused on mitochondrial DNA damage, aging,

and carcinogenesis. It brought into focus the unique phenomenon of homeoplasty, and the sensitivity of mitochondrial DNA to damage and to mutation accumulation. The last symposium focused on nanotechnology, and the possibility of sequencing single DNA molecules.

We inaugurated, as an experiment, a series of Short Presentations to give younger members of our Society an opportunity to present their research to a diverse audience. I think the experiment was a success. These presentations could facilitate the efforts of young investigators to establish their careers. We noted that most of the Short Presentations were very well attended.

Keynote Lectures: There were four keynote lectures that were centerpieces for the meeting. Bruce Ames (the Ames assay) presented the importance of micronutrients as disease preventatives. Mary-Claire King (BRCA 1 and BRCA 2) revealed to us the importance of analyzing genomes during human history. We soon discovered that we are all an amalgamation of many genetic parents. Manfred Eigen, (Nobel Laureate who initiated the concept of a quasi-species) presented the diversity of genetic populations within viral species and the concept of an error threshold. Lee Hood (the inventor of sequencers for DNA and proteins) considered the importance of systems biology in defining cell's responses and disease states. These keynote lectures highlighted different aspects of environmental mutagenesis.

Attendance: Despite our trepidation, attendance was excellent - some 456 members attended the meeting, as well as affiliates, wives, and associates. This was despite the distance, the cost of coming to Alaska, and the miasma engendered by 9/11. The local University did not have a large number of students or facilities to help coordinate the meeting. We had to rely on the generosity of the EMS members to guide us through many of the problems that occur during a dynamic meeting.

Hollaender Symposium: This year's presentation of the Hollaender International Fellow Award was particularly rewarding. The award was given to Princess Chulabhorn of Thailand for her work in science, her leadership in organizing the Chulabhorn Institute of Environmental Medicine in Thailand and the promotion of yearly meetings on environmental mutagenesis. It was a delight to have her and her accompanying colleagues attend the meeting.

Conclusion: The Alaskan meeting exposed us to new frontiers in science. These areas are likely to have major impacts on our understanding of how environmental factors effect human health. The world is changing and the EMS will change with it. Our Society must grow, yet remain cohesive. As we meet the challenges of yet newer frontiers, we must evolve, question, and embrace new scientific concepts.

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Editor's Airs

Alaska weather was cold as expected but the people were warm and interesting. The long daylight hours took a little getting used to (sunset near midnight!) but it was great to still see the mountains after a long day indoors at the sessions.

The speakers captured our attention by day and the scenery by night. Choosing the photos for this issue was tough. Special thanks to Kathleen Hill for contributing some great pics from the glacier tour.

Alas, by the time the talks were over and we could finally find a restaurant for dinner, we were too pooped to dance this year. We'll make up for it in Miami.

Pam & Jenness

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The President's Corner

This year, the EMS has turned some sharp corners, both administrative and intellectual. The society has established a new administrative arm, AIM, who

offer expertise in coordinating the meeting and in facilitating all administrative aspects of the Society. Their ability to immediately take over a meeting that was planned many years ago, and implement many of the changes with facility, was very impressive. Tonia Masson and Clarissa Wilson deserve our deep thanks for their expertise, grace and good humor at times when everything appeared to be in chaos. I am happy to report that the administrative functions of our Society now are in excellent hands! We anticipate that our membership will increase as we continue our tradition of excellent meetings. Our current President-Elect, David Eastmond, and future Presidents-Elect will be able to concentrate on the scientific excellence of our Annual Meetings, without having to be unduly concerned about logistics or amenities.

The intellectual transition was one from a society whose main modality was in toxicology and DNA damage, to a society that supports and fosters advanced basic and applied sciences in a spectrum of areas that impinge on human health. As outlined in the strategic plan, these include DNA exposure, detection, and metabolism of DNA damage; mechanisms of mutagenesis; epidemiology; and new technologies that allow us to assess the human risk of environmental agents. Therefore, the society needs to bring into its membership leaders in each of these fields who will affect - and in the long range shape - new directions for understanding mechanisms of environmental mutagenesis. The attraction of a diverse membership, and enlarging the scope of the society is necessary for its scientific vitality and for its financial stability. We are all indebted to the Program Committee for the Alaska meeting, who made this a reality.

The meeting in Alaska was exciting - from the superb Plenary Speakers, to the excellent Symposia, and Short Presentations. The Short Presentations were implemented to give our junior members an opportunity to orally present their ideas to a large audience, and to further develop their presence within the scientific community. We are pleased that these functions were very well attended within the meeting, thus giving us reason to hope that our junior members were well-served by this innovation.

Two of the meeting's highlights were a trip to the glaciers, and the surprise recipient of the Hollaender International Fellow Award. The trip to the glaciers exposed us to the ruggedness and frontiers that make up the Alaskan wilderness. It was interesting to observe that there are communities of human beings who live for an entire winter in one large building, never venturing outside. The second highlight was the presentation of the Hollaender International Fellow Award to Princess Chulabhorn of Thailand. The Princess is a scientist who has devoted her scientific expertise, financial resources, and personal prestige to advancing the field of environmental mutagenesis. She has been responsible for organizing a yearly symposium and establishing an Institute devoted to environmental mutagenesis. It is unusual to have a Princess as a recipient of a scientific award and some of us were a little flummoxed by the large retinue who accompanied her to the meeting, as well as by the press and social coverage. We concluded that she is a true scientist, who happens to have the advantages and disadvantages of also being a princess.

The financial status of the Society continues to be good. The meeting in Alaska made a profit of about $12,000 - somewhat of a surprise, since there were many expenses we could not adequately predict.

The Executive Board spent considerable time during the meeting on implementing and evaluating the suggestions from our new administrative organization, AIM. They provided innovative and refreshing ideas for enlarging and strengthening the Society, increasing its cohesiveness, and maintaining its scientific excellence.

Lastly, I would like to conclude this President's Corner with thanks to David DeMarini. His guidance, boundless energy, enthusiasm, and good humor were inexpressibly important to me during this administrative transition. There have been times when I had to concern myself about the costs of coffee, laser printers, and many other such vital underpinnings - but we scientists are never trained to think about these nuts-and-bolts concerns. David's sense of humor, reasonable and practical suggestions, smoothed my time and disposition as "President-Elect and Program Chairman" and substantially contributed to the excellence and organization of the Alaska meeting. When you see David, please thank him!

Larry Loeb, President

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Anchorage Summary of Symposia & Platform Talks

Mitochondrial Damage in Aging

This well-attended lively symposium gave our members a glimpse of one of the growth areas of modern biogerontological research. The Co-Chairs, George M. Martin (Seattle) and Douglas C. Wallace (Atlanta, but soon to move to Irvine) gave broad overviews. Martin introduced the concepts of "gerontogens" and "gerontogenes." Gerontogens were defined as putative environmental agents that may modulate the times of onset and/or the rates of development of specific aspects of the senescent phenotype. Cigarette smoking serves as a cogent example; enhanced rates of mitochondrial mutations are among its many effects. Gerontogenes can be defined as genes affecting longevity, either reducing or increasing average or maximum lifespans. Examples include certain mutations in the daf2 pathway of *C. elegans* and in homologous pathways in *D. melanogaster* and possibly in certain dwarf mice.

Wallace summarized our knowledge of the structure and function of the mammalian mitochondrial genome, including the variety of constitutional mutations known to lead to specific disease entities. His lab has investigated a number of interesting mouse models of mitochondrial pathology. One such model, SOD2 knockout mice, has been used to demonstrate lifespan extension and a rescue of spongioform encephalopathy. A series of studies have also documented the accumulation of mitochondrial mutations in a variety of somatic cells. Using a sensitive PNA-directed PCR clamping technique, DNA mutations have been noted in skeletal muscle, but not in brain. This theme of the tissue-specificity of mitochondrial mutations was also elaborated upon by Giuseppi Attardi (Caltech). A mutation at position 414, within the promoter for the mtDNA replication primer, was found in fibroblasts from the majority of individuals above 65 years of age, while it was absent in skeletal muscle, brain, and leukocytes. By contrast, two different mutations, which were virtually absent in fibroblasts and other tissues, were found to accumulate with aging at position 189, very close to the main origin of mtDNA replication, and at position 408, in the promoter of the primer for DNA replication, in mtDNA of skeletal muscle from the majority of individuals above 50 years of age. The striking tissue specificity of aging-related mtDNA mutations occurring at control sites for mtDNA replication strongly points to their functional relevance.

William C. Copeland (Research Triangle Park) reviewed the status of our knowledge of mitochondrial DNA replication. Human mitochondrial DNA is replicated by the two-subunit DNA polymerase g (pol g). Copeland and his colleagues investigated the fidelity of DNA replication by pol g, with and without exonucleolytic proofreading and the p55 accessory subunit. Pol g has high base substitution fidelity due to efficient base selection and exonucleolytic proofreading, but low frameshift fidelity when copying homopolymeric sequences longer than four nucleotides. His group has also determined that the majority of errors produced *in vivo* are produced through DNA replication. Progressive external ophthalmoplegia (PEO) is a rare disease characterized by the accumulation of large deletions in mitochondrial DNA. Recently, the Y955C mutation in DNA polymerase g was shown to be associated with this disease. Copeland's group generated the Y955C mutation and analyzed the fidelity of DNA synthesis by purified mutant DNA polymerase. The Y955C enzyme retains a wild-type catalytic rate but suffers a 45-fold decrease in apparent binding affinity for the incoming dNTP. The Y955C derivative is also much less accurate than is wild-type pol g, with error rates for certain mismatches elevated by 10- to 100-fold. The error prone DNA synthesis observed for the Y955C pol g is consistent with the accumulation of mtDNA mutations in patients with PEO.

While there is much insight into the DNA repair mechanisms in nuclear DNA, much less is known about the process as it occurs in mitochondrial DNA. It was thought for a while that mitochondria could not repair their DNA, but it is now evident that they can efficiently repair base modifications after oxidative DNA damage. This area of research was reviewed by Vilhelm Bohr (Baltimore). A number of base excision repair proteins have been detected in mitochondrial fractions. Bohr and his colleagues have observed that the important base lesion 8-hydroxyguanine (8-oxoG) is repaired very efficiently in mitochondria. In fact, mitochondrial repair of this lesion is even more efficient than its repair in an active, endogenous nuclear gene. This lesion does not appear to be repaired by transcription coupled repair. Using mouse knockout cells, Bohr's lab showed that the OGG1 glycosylase, known to be involved in the cellular DNA repair of 8-oxoG, is also responsible for the repair of this lesion in mitochondria. Mice without this gene accumulate more 8-oxoG lesions in their mitochondrial DNA than in their nuclear DNA, suggesting that OGG1 is an essential enzyme in the repair of this lesion in the mitocondrial DNA and that it plays a more important role in mitochondrial repair than in nuclear repair. It has been observed in many laboratories that 8-oxoG accumulates in the genome with increased age. This accumulation is most dramatic in mitochondrial DNA. Whereas Bohr and others have detected a decline with age in nuclear DNA repair of 8-oxoG, Bohr's group has observed an increase in repair of this lesion in the mitochondrial DNA of older rodents. Perhaps the OGG1 enzyme can be induced by accumulating lesions, but even the increased repair capacity is not enough to counter the age-associated increase.

We can conclude that the various age-associated declines in mitochondrial structure and function will be occupying more of our attention at future meetings of our society.

George Martin, Chair

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Exposure, Detection, and Toxicity

Toby Rossman, (NYU School of Medicine) presented further evidence using the *in vivo* Skh1 mouse UV irradiation model supporting the notion that arsenite may be a co-carcinogen rather than a direct carcinogen, acting perhaps through inhibition of DNA repair. **Barbara Parsons** (FDA/NCTR) reported on a potential new biomarker for human skin cancer risk based on the utilization of allele-specific competitive blocker PCR to detect tandem UV-induced CC to TT substitution in a single p53 codon. Presentations by **Paula Muehlbauer** (Pfizer) and **Maik Schuler** (Pfizer) reported the use of the mitosis-specific histone 3-P monoclonal antibody in flow cytometry of human lymphocytes to sensitively measure mitotic index. Additionally, it was proposed that this method may have future applicability in detecting ploidy changes and perhaps even aneugenicity in chemically-treated lymphocytes. Another use of flow cytometry for detecting clastogenicity in human lymphocytes was reported by **Stephen Dertinger** (Litron Labs).

Using antibodies directed against the CD71 transferrin receptor to identify reticulocytes, micronuclei in the most immature erythroid cell population were detected and quantified in blood from splenectomized and normal human donors. Such a system could have obvious value in assessment of human exposure to genotoxic agents. **Larry Claxton** (USEPA) provided an update on the clean-up of the Exxon Valdez oil spill in Prince William Sound. The data presented demonstrate that the bioremediation efforts of the EPA were successful in reducing (eliminating?) any detectable mutagenicity from collected organic samples. **Stefano Bonassi** (Ist Nazionale Ricerca Cancro, Genova, Italy) reported that human bronchoscopy and nasal mucosal samples were suitable materials for the detection of DNA adducts and that within the limits of their study, polymorphisms of metabolic genes had no effect on adduct formation or type. **Regina Montero-Montoya**, (Ciudad University of Mexico), presented evidence suggesting that parasitic infection in rats can elevate CYP450 activities and in so doing, can increase the genotoxicity of agents known to require specific CYPs for activation to genotoxic forms. **J.R. Stringer** (University of Cincinnati) reported on the detection of frameshift mutations in an *in situ* transgenic [placental alkaline phosphatase (PLAP) transgene] mouse tumor model in which recoverable mutations in the PLAP gene arise via loss of G from a run of 11 Gs. **Kathleen Hill** (City of Hope Medical Center) reported that spontaneous tandem mutations in the Big Blue mouse system are tissue specific and probably occur as single mutational events at hotspots in the lac I gene. Interestingly, spontaneous tandem mutations were not observed in the murine or human germline. **Ron Snyder** (Schering-Plough Research Institute) revisited the question of appropriate indices of cytotoxicity in standard cytogenetics assays providing evidence that loss of membrane integrity as quantified by ATP depletion immediately following treatment may be the most sensitive and relevant measure.

Ron Snyder, Chair

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Double-Stranded Breaks: The Ultimate End Game

Michael Resnick began the session by discussing the results of screening a complete library of yeast deletion mutants for genes affecting ionizing radiation (IR) sensitivity. A mutant in the frataxin gene, whose homolog in humans is involved in Friedreich's ataxia, results in loss of mitochondrial DNA, nuclear damage, increased chromosomal instability including recombination and mutation, and greater sensitivity to DNA-damaging agents. Maria Jasin has continued the use of elegant assays of homologous recombination (HR) in mammalian cells that use a site-specific enzymatically generated double-strand break (DSB) whose repair can be precisely characterized. HR is elevated in DNA-PK deficient cells and highly deficient in mutant cells that are defective in Rad51, Rad51 paralogs, or BRCA2. The common XRCC3 human variant Thr241Met has normal repair in this assay. Larry Thompson discussed the role of the Rad51 paralogs in HR, including chromosome stability and the characteristic resistance to killing by IR that is normally present in S

phase cells. An increasing number of paralog mutants are available in hamster and chicken cell lines for structure-function studies. David Schild described experiments showing that human cells possess two different complexes, *i.e.*, Rad51C/XRCC3 and Rad51B/Rad51C/Rad51D/XRCC2. IR treatment did not change the level of any of the paralog proteins in human cells, nor did IR alter the complexes. Evidence was presented that the human PIAS1 and PIAS3 proteins, which are E3 ligases for SUMO-1 (small ubiquitin-like modifier), interact with both the human Rad51 and Rad52 proteins.

Patrick Sung described a series of studies with purified human and yeast HR proteins to elucidate their biochemical functions. Human Rad52 helps promote the displacement of RPA from single-stranded DNA and allows Rad51 to bind. The competition by RPA for Rad51 substrate binding can be partially alleviated by Rad51B-Rad51C, thereby promoting Rad51's strand exchange activity. Roland Kanaar discussed the dynamics of HR in living cells using proteins tagged with green-fluorescent protein. Upon treatment with IR, these proteins accumulate at sites of DNA damage into discrete foci that are dynamic structures. Rad51 is a stably associated core component, whereas Rad52 and Rad54 rapidly and reversibly interact with the structure. Kanaar thinks that executing DNA transactions through dynamic multi-protein complexes, rather than stable holo-complexes, allows flexibility. James Cleaver discussed polymerases that bypass lesions, with emphasis on PolH, the enzyme defective in XP variant cells. UV-irradiated XP-V cells show high levels of nuclear foci for -H2AX, a phosphorylated histone that is a specific marker for DSBs. Breaks that arise during DNA replication in UV-irradiated XP-V cells are repaired by HR, as evidenced by the high levels of Mre11 foci, their co-localization with for -H2AX foci, and increased sister-chromatid exchange.

Larry Thompson and Michael Resnick, Chairs

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When Polymerases are Arrested, Who is at Fault, and What are the Options?

This symposium (chaired by Joann Sweasy and Phil Hanawalt) considered the properties of polymerases; how their fidelity is controlled and how they behave when they encounter obstructions. An intact DNA template is a prerequisite for the accurate replication of the genome or transcription of its genes to produce functional RNA copies. A problem may arise when a translocating polymerase encounters a DNA lesion. Mistakes may be introduced, and if the polymerase is arrested, it must be displaced to permit verification that a lesion caused the arrest, as well as to facilitate repair. Phil Hanawalt (Stanford) introduced the symposium by outlining possible options at an arrested replication fork or an arrested transcription complex, pointing out that an immobilized RNA polymerase at a lesion could pose an insurmountable obstacle for an advancing replication fork.

Joann Sweasy (Yale University School of Medicine) discussed the accuracy of DNA polymerase beta. She showed that some amino acid residues, important for fidelity, are far removed from the active site and have no contact with the DNA or nucleotide substrates. One residue, in a hinge region, mediates the closing of the polymerase such that its active site geometry is able to exclude mispairs. Alteration of the hinge residue results in a less accurate polymerase. Another residue, in the middle of two Helix-hairpin-Helix motifs, positions the template into the active site and stabilizes the primer to avoid slippage during polymerization. Thus, Pol beta appears to employ several mechanisms to ensure accurate DNA synthesis.

Janice Pata, (Yale University) presented her 2.3 Angstrom-resolution crystal structure of a catalytic fragment of the DinB homolog (DBH) polymerase from *Sulfolobus solfataricus*, and showed that it is non-processive and can bypass an abasic site. The structure of the catalytic subdomain is nearly identical to that of the classical polymerases, demonstrating an evolutionary relationship that was not apparent from sequence similarity. Homology modeling based upon related structures suggests minimal contact between the protein and DNA; that the nascent base pair binding pocket is quite accessible; and that the apo-enzyme is already in the closed conformation characteristic of ternary polymerase complexes. These observations, later supported by the ternary complex structure of a closely related polymerase, may well explain the low fidelity DNA synthesis displayed by the Y-family polymerases; that are responsible for translesion DNA synthesis, and include human Pol eta, iota, and kappa.

Fred Guengerich (Vanderbilt University) discussed why DNA-carcinogen adducts not only compromise polymerase fidelity but also cause stalling or "idling" which may then contribute to misincorporations. Kinetic experiments were conducted to address the mechanism of stalling of T7 DNA polymerase and HIV-1 reverse transcriptase during replication of primer/template DNA containing guanine, O6-methylguanine (m6G), or O6-benzylguanine. Both Pols preferentially incorporated dTTP opposite O6-alkylG. Pre-steady-state experiments in the presence of trap DNA revealed two rates of incorporation (differing by ~100-fold) at the adduct site. Kinetic modeling fit the data only if the mechanism included an inactive E –DNA- dNTP complex, that was hypothesized to explain polymerase kinetics at O6-alkylguanine adducts.

Kristin Eckert (Pennsylvania State University) presented evidence that the "fault" in T4 polymerase arrest lies in the competition between the polymerization and 3' - 5' exonuclease activities. Studies of the 3' - 5' exonuclease used MNU-treated DNA templates as well as m6G and abasic lesion-containing oligonucleotides. The exonuclease removed bases opposite these lesions with different efficiencies, resulting in different biological outcomes. The T4 exonuclease was inefficient as a "proofreading" activity for m6G, as both nonmutagenic and mutagenic m6G basepairs were removed at similar rates. Partitioning assays between the polymerase and exonuclease activities, in the presence of dNTPs, resulted in repeated incorporation and excision events opposite the m6G lesion and less than full-length product. A model was proposed wherein the exonuclease activity contributes directly to cellular cytotoxicity of m6G during long patch DNA repair synthesis. The exonuclease can "proofread" bases opposite an abasic lesion, as the rate of excision is highest for an X A substrate (where X is a template abasic lesion). Therefore, the abasic lesion "A-rule" applies to both the forward and reverse enzymatic activities, as the same lesion-containing DNA form (X-A) is the preferred substrate for both the polymerase and the exonuclease. In the presence of dNTP substrates, the wild-type T4 exonuclease activity dominates for all abasic substrates, resulting in little translesion synthesis. In the presence of dNTP substrates, the wild type polymerase remained associated with the lesion-containing substrates.

Fumio Hanaoka (Osaka University, Japan) reviewed his pioneering discovery that DNA polymerase eta is the product of the gene for the xeroderma pigmentosum variant in humans. It localizes in replication foci after UV, showing association with PCNA and preferential binding to primer-template DNA structures, whether they contain pyrimidine dimers (CPD) or not. Pol eta is intrinsically inaccurate (1 mistake per 25 nucleotides) in undamaged DNA, but it prefers CPDs over two undimerized thymines in the template, and incorporates two adenines with high fidelity, as likely to be its dedicated role. However, Pol eta can also bypass other classes of damage including AAF, cis Pt, abasic sites, and 6-4 photoproducts.

Silvia Tornaletti (Stanford University) described the behavior of RNA polymerase at DNA lesions. Utilizing an *in vitro* transcription system she found that a CPD, a 1,3-d(GTG) cisplatin adduct, or a 1,2-d(GG) cisplatin adduct in the transcribed strand posed a strong block to T7 RNAP and RNAP II, and that RNAP II complexes arrested at these lesions undergo transcript cleavage mediated by elongation factor SII to produce a population of transcripts up to 35 nucleotides shorter that those arrested at a CPD. Transcript cleavage resulted in polymerase back up, thereby providing access of photolyase to the arresting CPD. These results are consistent with a model for transcription-coupled DNA repair that proposes that an RNA polymerase arrested at a lesion translocates from the lesion site to allow access of repair proteins. Thymine glycol and 8-oxoguanine, oxidative lesions normally repaired by the base excision repair pathway but also subject to TCR, only partially blocked transcription by T7 RNAP and did not affect RNAP II elongation, suggesting that additional factors may be required to ensure RNAP II arrest and initiation of transcription-coupled repair *in vivo*.

Phil Hanawalt, Chair

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New Perspectives from Functional Genomics and Proteomics

Probing the Action of Non-mutagenic Carcinogens and BRCA1 Action Using Genomic Approaches

The field of toxicogenomics encompasses two types of studies, comparative and functional. Comparative studies involve development of predictive patterns that define signatures of compound actions or of toxicities from technologies such as microarray analyses. Functional studies use genomics approaches to glean specific information about test systems or compounds. We are conducting studies to determine the risk factors associated with breast cancer by monitoring gene expression changes following exposure to estrogenic compounds in both *in vitro* and *in vivo* models. Mutations in the BRCA1 tumor suppressor gene confer high risk to breast and ovarian cancer. We have been studying the function of this gene with the purpose of elucidating other molecular targets of susceptibility or carcinogen action for breast cancer. Previous studies suggest that BRCA1 may function as a transcription factor. We used a molecular technique, called CASTing (cyclic amplification of sequence targets) to screen for a BRCA1 binding sequence. We found that BRCA1 complexes with other cellular proteins to form a complex that specifically binds a DNA consensus sequence motif. The complex contains USF-2 and is formed dependent on the presence of estrogen, serum. We have extended these studies to show that the regulation of DNA binding and transactivation *via* this binding site is altered by mutations in the BRCA1 protein. Computational screening of promoter sequence motifs indicates that BRCA1 binding may mediate the transcription of a number of repair genes, growth factors in addition to estrogen regulated genes. We hypothesize that BRCA1's most critical function may be to mediate transcription of genes involved in surveillance of DNA damage incurred by estrogen exposure.

Cynthia A. Afshari, Chair

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Mechanisms of Mutagenesis

On Thursday May 2nd, a session consisting of selected platform talks was held, entitled "Mechanisms of Mutagenesis," co-chaired by Tom Kunkel and Roel Schaaper, NIEHS. The session provided an exciting overview of several pertinent issues in the field of mutagenesis.

Roel Schaaper started off the session by briefly introducing some basic concepts of mutagenesis research. He then presented results from his collaborative work with Dr.

Iwona Fijalkowska (Polish Academy of Sciences) on leading- *vs.* lagging-strand fidelity differences during *E. coli* chromosomal replication. Their data show that the two strands are not replicated with equal fidelity, and that most likely the leading strand is the most error prone. Higher error rates for leading-strand replication may result from additional fidelity mechanisms available only to the lagging strand, such as polymerase dissociation from terminal mismatches. Interestingly, under conditions where error prone polymerases such as pol V are overexpressed, most mutations appear to arise from the lagging strand, presumably due to increased access of pol V to mismatches in this strand. No strand differences were observed for UV mutagenesis, perhaps consistent with UV mutagenesis in *E. coli* occurring temporally and spatially away from replication forks, such that pol V access to the lesion is no longer a primary rate-limiting factor.

Stuart Linn (University of California, Berkeley) showed interesting data on the subcellular localization of human pol epsilon. Using immunofluorescence and confocal microscopy, pol epsilon was shown to colocalize with PCNA at sites of DNA synthesis in late S phase. In contrast, in early S-phase pol epsilon localized at sites adjacent to, but spatially separable from the PCNA/replication sites. These data suggested that pol epsilon and PCNA have separable, but spatially associated functions early in S phase, and that pol epsilon may primarily participate in replicating DNA, presumably present as heterochromatin, in late S phase.

M. Hartenstine (University of Southern California) presented evidence *in vitro* indicating that human DNA polymerase beta expands trinucleotide repeats at simple DNA strand breaks (nicks or one-base gaps) *via* strand slippage and gap-filling. Pol beta expands repeats by gap-filling at physiological dNTP concentrations, while at higher dNTP concentrations strand displacement inhibits further expansion by extending 3' primer ends into surrounding non-repeating template. The results suggest that a single strand break within a repeat tract may be sufficient to cause significant triplet repeat expansion in the presence of DNA polymerase beta alone.

Ertan Glick (University of Washington) presented data on high-throughput *in vitro* production and screening of mutant DNA polymerases. Their system is based on random mutagenesis methods yielding large libraries of mutant genes, and the production of the corresponding mutant enzymes by coupled *in vitro* transcription-translation. The mutant enzymes are then screened in 96-well format for a variety of properties, which can be done using automated robotic procedures. These methods are likely to be helpful in generating medically and technologically important enzyme variants.

M. Kanuri (Sealy Center for Molecular Science) presented data investigating the mutagenicity of the gamma-hydroxypropano-deoxyguanosine adduct in COS-7 cells using a single-stranded site-specifically-modified pMS2 vector. The adduct had a pronounced mutagenic potential causing mutations at an overall frequency of 7.4×10^{-2}/translesion synthesis. *In vitro*, gamma-HOPdG strongly blocks DNA synthesis by two major eukaryotic polymerases, pol delta and pol epsilon, although in the presence of PCNA mutagenic bypass of the adduct could be observed. It was hypothesized that in order to bypass the adduct *in vivo*, specialized translesion synthesis polymerases may be recruited.

Veronica Maher (Michigan State University) showed interesting experiments addressing the role of the mutagenic bypass polymerase hRev3 and its accessory factor hRev1 in mammalian cell mutagenesis. By transfecting human cells with antisense RNA against the Rev3 and Rev1 transcripts it was shown that expression of the antisense RNAs significantly decreased the frequency of carcinogen-induced mutations. At the same time, no significant increase in the cells' sensitivity to the cytotoxic effect of the DNA damage was observed, suggesting that cells lacking the target polymerase had made increased use of alternative damage-tolerance mechanisms.

Takehiko Nohmi (National Institute of Health Sciences, Tokyo, Japan) presented new data on *E. coli* DNA polymerase IV. Pol IV has been known to play a role in untargeted or spontaneous mutagenesis. Here, he showed that pol IV has an additional ability to promote chemically-induced frameshift mutagenesis. When a plasmid containing the *E. coli dinB* gene (encoding pol IV) was introduced into an Ames *Salmonella* frameshift tester strain, the resulting strain exhibited extremely high sensitivity to the mutagenicity of polycyclic aromatic hydrocarbons (PAHs). This strain may be useful for efficiently detecting mutagenic PAHs in the environment.

Carrie Valentine (National Center of Toxicological Research) discussed the identification of *in vivo* mutants using the X174 gene A transgenic mouse system (Malling mouse). She demonstrated that careful analysis of the burst size of gene A mutant phage upon recovery in *E. coli* – which distinguished between true *in vivo* mutants (high burst size) and mutants generated in the bacterium (low burst size) - leads to a dramatic decrease in control but not induced mutant frequencies. Using this method, a mouse transgenic embryonic cell line showed a ten-fold lower spontaneous mutant frequency, while the frequency of mutants induced by 9 mJ/cm^2 UVAB light was essentially unchanged, resulting in a 46-fold increased mutant frequency. Similar large effects (>44-fold) were demonstrated in lymphocytes of ENU-treated mouse.

Adonis Skandalis (Brock University) presented evidence of the significant potential of mRNA splicing to corrupt genetic information by generating apparently aberrant mRNA transcripts even in the absence of DNA mutations. He reported investigating the presence of aberrant HPRT and BETA POLYMERASE transcripts in primary human fibroblasts from individuals of various ages. Several truncated HPRT transcripts were detected that were missing entire or partial exons, and the frequency of aberrant transcripts increased 5-fold between the ages of 40 and 60 years. Disabling the Nonsense Mediated Decay

pathway with emetine allowed detection of several more aberrant transcripts including a partial intron inclusion. These aberrant length transcripts may have a yet unidentified function. However, aberrant transcripts likely reflect either RNA polymerase II errors that destroy splice sites or spliceosome errors. The mutator potential of aberrant transcripts was demonstrated by one of the detected BETA POLYMERASE transcripts, missing exon 11. This transcript was previously shown to be associated with cancer and to code for a polymerase with a dominant negative function.

Tom Kunkel (NIEHS) concluded the highly successful session by briefly reviewing progress on eukaryotic DNA polymerases. Relatively recent discoveries of several DNA polymerases with novel properties, including the ability to efficiently bypass lesions in DNA, has generated a great deal of interest, and uncertainty, about the nature and number of specialized DNA transactions that occur *in vivo* to avoid or generate mutations.

Roel Schaaper, Chair

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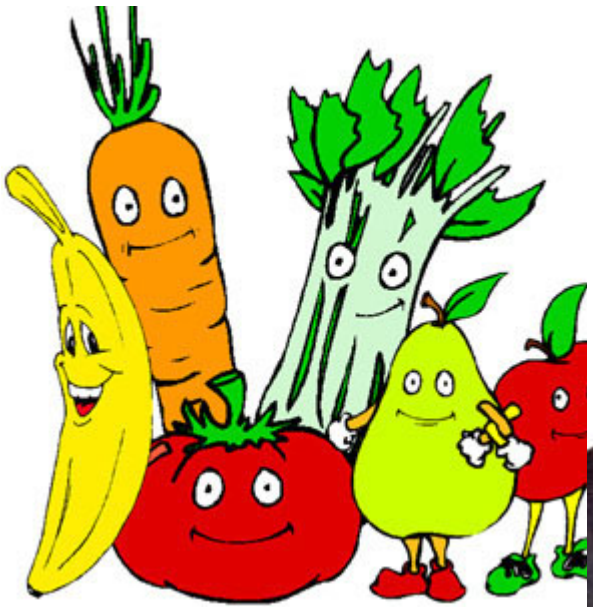
Keynote Lectures

Mutations & Micronutrients - "We Are What We Eat"

Dr. Bruce Ames gave an informative and entertaining examination of the important role of diet in aging and cancer. He summarized the work of many labs, including his own, on this topic and he showed that it matters what we eat. One of the clearest admonitions was to eat plenty of fruits and vegetables, which epidemiological studies have demonstrated can reduce the risk for various types of cancers. Dr. Ames urged the consumption of a daily multi-vitamin pill–just for insurance. He highlighted the important work of our previous EMS President, James MacGregor, who demonstrated the need for sufficient levels of folate to maintain chromosomal (genomic) stability. Despite the onslaught of mutagens to which we are exposed



daily, the body clearly has enormous defense capabilities–primarily in the form of DNA repair mechanisms. Thus, life is a two-edged dinner plate, with diet contributing 1/3rd to our cancer risk, but also being the primary source of anti-mutagens and anti-carcinogens. Buon Appetite!

David DeMarini

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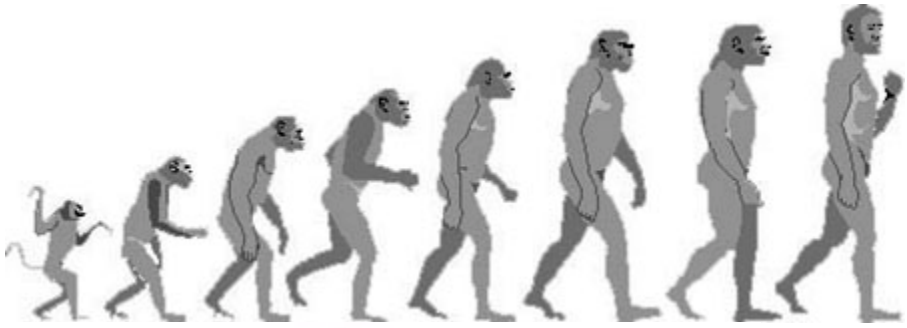

Genomic Views of Human History

Dr. Mary-Clair King took us on a fascinating tour of our ancestry through DNA sequence analysis. This journey illustrated the difference between genetic and cultural ancestry and, in the end, demonstrated that we are all one species with a single ancestry. She tackled the complicated issue of morphological differences *vs.* race, and noted that we should acknowledge the obvious morphological differences among us but not confuse them with racial stereotypes or the concept of race, which is a concept that has little, if any, biological meaning for modern humans as a species. Dr. King highlighted recent work showing that gene expression in the brains of developing

humans exceeds greatly that found in developing chimpanzees. This work helps to understand the considerable differences between the two species despite great similarities in DNA sequence homology. The complexity of human ancestry is difficult to reconstruct genetically and is complicated even further by real and perceived cultural ancestry. As Dr. King noted, genomics is providing a new tool for us to dissect our ancestry for us to know better than ever who we are and from where we came. Now, if we could only figure out where we are going.

David DeMarini

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Viral Quasispecies and Error Threshold

Professor Manfred Eigen received the Nobel Prize in Chemistry in 1967 for studies on fast chemical reactions. He developed technologies that enabled one to measure reaction rates at speeds previously never contemplated. Since then, one of his many efforts has been to understand the evolution of viruses.

He developed the concept of a "quasi-species," a population of viruses that evolve, not as a single clone, but as a collection of interlocking mutated genomes. Selection is at the level of the population, and not of the individual genome. The high error rate of copying viral genomes, and, in particular, genomes of RNA viruses such as HIV, was documented. The frequency of errors is so great that during each replication, new mutations are introduced into each progeny.

Dr. Eigen argued that the frequency of viral mutagenesis is near the error threshold for viability. Enhanced mutagenesis beyond this error threshold would be accompanied by the destruction of genetic information. This is analogous to a liquid-gas phase transition, the critical point at which information is entirely lost. His presentation was that of a physicist, trying to formulate a uniform theory of genetic evolution. We need to comprehend the infinite number of nucleotide arrangements within a genome, and then the rules that govern this. He introduced the concept of higher orders of dimensions, to explain the interplay between mutations during evolution. His lecture provided a glimpse of the infinite number of genetic variations that are possible, and the pathways that evolution has selected to obtain genetic stability.

Larry Loeb

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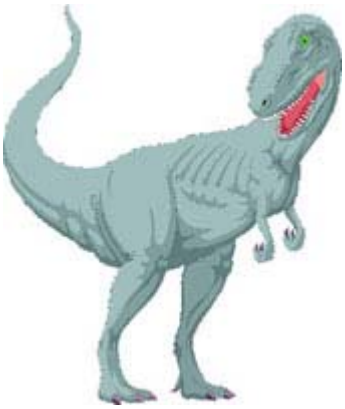
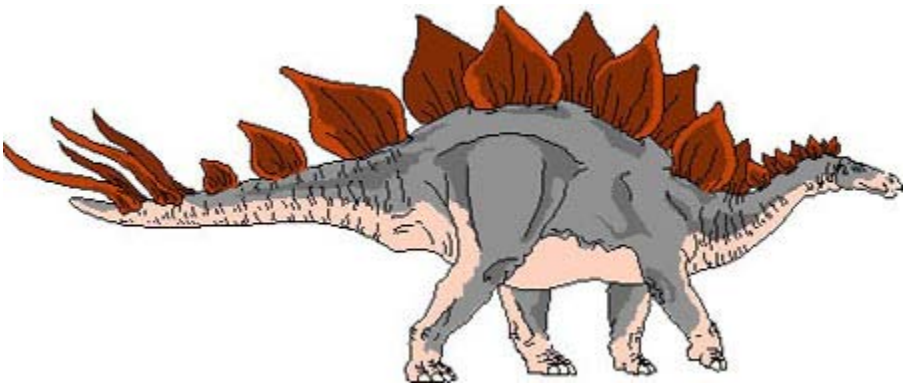
Genomics, Proteomics, and Systems Biology



The end of the meeting was highlighted by a glimpse into the future. Professor Leroy Hood, considered the complexity of biological systems. He recently established an Institute for Systems Biology that probes molecular mechanisms, using the most powerful techniques that underpin genomics and proteomics. He argued that the genome provides information that is digital, and that is unique in that it is ultimately knowable. Presented were changes in the arrays of messenger RNA during development; the hierocracy of proteins that sequentially bind to regulatory sequences controlling gene expression, and finally the interlocking redundancies that guard against environmental diversity.

Remaining problems were also highlighted: Why are there deserts of information in our genome and big genes that present challenges to our understanding of transcription? How can a gene of megabases in length be copied during each cell cycle? How can we obtain methodologies to understand the hierocracy of genetic regulation and its redundancies?



Professor Hood has pioneered the development of protein and DNA

sequences, ink jet arrays, oligonucleotide synthesizers, homolog searches, and techniques in bioinformatics. It is these technologies that have made possible the rapid success of the human genome project and its application to molecular medicine. His accomplishments can be documented by the assemblage of "Hood machines" in printing the information to produce dinosaurs in Jurassic Park. It should be noted that these "Hood machines" have so far not been used for nefarious purposes.

We in the Environmental Mutagen Society need to apply these emerging technologies to understand individual differences in the response of humans to environmental agents. A number of other symposia at the meeting addressed these problems.

Larry Loeb

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Alaska Events

Carl Hild: The Alaskan Wilderness

It was a real treat for EMS to have Carl Hild as our dinner speaker at the Awards Banquet this year. Carl is the Deputy Director of the Institute for Circumpolar Health at the University of Alaska, Anchorage and a long-time advocate for native Alaskans. He entertained us with slides and stories of native Alaskan life and customs and his own experiences with them.

He also told of the many difficulties, both technical and environmental, that occurred in the building of the Alaska pipeline. For example, he said that the columns that hold the pipline have to be refrigerated (even in the Arctic!) so that the heat from the oil passing through it won't thaw the permafrost beneath them and cause the structure to collapse!

Some of the other highlights of his talk showed photos of the 1964 earthquake and

tsunami which devastated Anchorage and surrounding areas.

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Glacier Tour

EMS members bundled up for a trip to the Alaskan glaciers started with a bus trip to Whittier. The scenery was spectacular along the way and the wildlife abundant: eagles, mountain sheep and goats, and even a moose! The grandeur and awesome size of the landscape was breathtaking. We even had to travel through a long one-lane tunnel under a mountain to reach Whittier.

The Klondike Express was our catamaran to the wilderness. We were served a delicious lunch as we glided through the sound to the many glaciers that reach the water. Surprisingly, this modern craft was piloted by joystick! EMS members were invited into the cabin to watch the captain maneuver her ship through floating chunks of glacial ice.


Phillips
CRUISES & TOURS
KLONDIKE EXPRESS


VIKING

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Alexander Hollaender Award

Dr. Sid Aaron

The Alexander Hollaender Award is conferred in recognition of outstanding contributions in the application of the principles and techniques of environmental mutagenesis to the protection of human health and for dedicated service to the Environmental Mutagen Society. This year it has been awarded to Dr. Sid Aaron. He has been active in genetic toxicology for over 30 years. Sid has published more than 65 papers in diverse aspects of the field and has worked in all arenas of science - including academia, major corporations, and the federal government. His unique background and his vision for this science and for this society have enabled him to promote and encourage scientific developments in mutagenesis to an exceptionally high degree within both the public and private sector.

Sid has promoted education in our field by organizing and teaching numerous continuing education courses in genetic toxicology for various organizations, including the Society of Toxicology, the American Chemical Society, the Society of Risk Assessment, as well as EMS.

He has served on the Scientific Advisory board for the National Institute for the Advancement of *In Vitro* Sciences, and he currently serves on the College of Basic Sciences Development Council for Louisiana State University.

For the EMS, Sid has served on Council, served as Treasurer, and has been our President. He has chaired numerous committees of the EMS and also served as a councilor to the International Association of Environmental Mutagen Societies. In addition, he has organized and chaired numerous conferences on genetic toxicology, including a Gordon Conference and the 2001 ICEM Satellite Meeting on Functional Genomics. Sid has served on the editorial board of *Mutation Research* and *Environmental Mutagenesis*, and he is currently a Distinguished Scientist at Pharmacia.

Of his many contributions to our Society, perhaps the single most significant accomplishment is the initiation and development of the Society's Strategic Plan. While President of EMS, Sid convinced the Executive Board of the urgent need to think hard about the long-range future of our science of the EMS itself. The Board subsequently embarked on a deeply introspective process out of which emerged the Strategic Plan. It is this Plan that focuses the development of our annual meetings and our outreach to other societies and other areas of science.

Implementation of the Strategic Plan has directed the Society to move beyond a mostly volunteer-driven organization to one that is managed professionally - thus, our new management company - AIM. The Strategic Plan also directed the Society to become more visible in the scientific community, which prompted us to join FASEB this past year. The Strategic Plan also streamlined our operations, resulting in a reduction of the number of committees from a staggering 26 to just 11. Finally, the Strategic Plan also implemented a series of financial controls that has resulted in cost savings and improved financial stability.

Dr. Sid Aaron has worked tirelessly and given selflessly of his time and creative efforts for many years to EMS, and perhaps no member in recent times has done more to assure the future success of EMS than he does.

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Words of Thanks from Sid Aaron

I thank Bill Lee and Frits Sobels whose mentorships converted me from a chemist to a geneticist/biologist. I also owe a great debt of gratitude Alex Hollaender.

Since 1972 when I began work with Bill, a great deal has changed in biology. The scientific method has not changed, however, and much of my understanding of it is due to Bill's mentorship and for that I am grateful. The EMS has always offered me a nurturing community in which to grow professionally and to evaluate central questions of

mutagenesis. People like Frits Sobels, Bill Russell, Jim Neel, Bruce Ames, Josh Lederberg, James Crow, Heinrich Malling, Phil Hanawalt, Dick Albertini, Fred DeSerres and others actively led the science and the Society. It has also been important to me have had clear thinking industrial scientists like Verne Ray (who passed away this past year), Sheila Galloway, Greg Probst, Ron Newton, Larry Kier, Dave Brusick, Dave Kirkland and Marilyn Aardema as role models. For those aspiring to an industrial career, you couldn't have a finer assembly of scientific mentors than exist in EMS; get to know them.

Part of the legacy of Alex Hollaender was expanding EMS Societies internationally. In addition, there are initiatives that have grown out of the USEMS Hollaender Committee under the leadership of Dr. William Au of UTMB. I have donated my award money to support the upcoming international initiative, the meeting being organized by William in Brazil in 2003.

Several years ago I began a "Strategic Planning Initiative" (in collaboration with Ray Tennant and Rosalie Elespuru). The Officers and Councilors of the Society held marathon meetings in Anaheim, Washington, and New Orleans to hammer out the plan. The underlying intention of the deliberations was to reinvent the Society with a focus on modern developments in molecular biology and informatics. Much has been done but much remains to be done.

Recently, I spoke with Sam Wilson, Deputy Director of the NIEHS. In 1997, his advice was that the Society should become engaged in the political process to ensure accurate information exchange. According to Sam, the distance between scientists and the public and the regulatory agencies is more critical at this juncture than in 1997. For example, he is deeply involved in ensuring public understanding of implications of genomics. He used as examples, the ethical, legal, and medical consequences of populations exposed to environmental toxicants; the scientific community as well as the populace and government need to move together in order to achieve harmony. Also important is the similar concern with respect to individualized medicine enabled with association studies using SNP analysis. The EMS can provide some insight and we should take an active part in ensuring that the best science is applied. With today's population, and particularly our lawmakers, confused and frustrated with the meaning of many of the words we use to express concepts in genetics, I urge the Society members to focus outreach efforts on how to define and relate to issues such as pharmacogenomics, cloning, gene therapy, and the like.

In summary, I thank the Society and the Awards Committee for the honor you have given me. I have had an excellent time in serving the Society. Thank you.

Sid Aaron

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Other Presentations

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EMS Award

Dr. Richard Setlow

by Phil Hanawalt

It is a great privilege for me as one of Dick Setlow's early graduate students, to accept this award on his behalf. It is remarkable that the reason that Dick was unable to come to this meeting to receive his award in person was because of a research grant site visit at his laboratory. Dick is 81 years young!

>Richard Setlow first showed that the genetic material is subject to turnover, a concept that up until that time (1964) would have been considered heretical. He originally discovered that pyrimidine dimers, induced by ultraviolet light are selectively released from the DNA in wild-type, but not in UV-sensitive mutants of *E. coli* and he postulated an error correction mechanism that we now know as excision-repair. Specifically, he proposed that damaged single-strand regions of genomic DNA are cut out and replaced with undamaged nucleotides, using the intact complementary strand as the template. It is remarkable that although we now understand the steps of excision-repair in complete enzymatic detail, the original model proposed by Setlow 38 years ago is still essentially correct. Dick Setlow may rightfully be considered the "Father of DNA Repair." The subsequent discoveries of the pathways of base excision-repair and of mismatch repair really built upon the original "cut and patch" concept that Setlow introduced. Setlow's 1978 article in *Nature* on "Repair deficient human disorders and cancer" was also a "classic" that greatly stimulated research in the field of DNA repair. His more recent work on UV induction of melanoma in a fish model system has helped to provide the crucial link between unrepaired DNA damage and carcinogenesis. It is now well established that the multiple pathways of DNA repair are as essential to the maintenance of genetic continuity as are the DNA transactions of replication and transcription. An increasing number of human hereditary diseases are characterized by deficiencies in DNA repair and predisposition to cancer.

Setlow has received many awards in recognition of his achievements, including membership in the National Academy of Sciences. In 1988, he won the highest scientific award offered by the U.S. Department of Energy, the Fermi Award, for which the citation reads: "For his pioneering and far-reaching contributions to the fields of radiation biophysics and molecular biology, beginning with the discovery and conceptualization of the processes of DNA repair that have had an impact on research in genetics, recombination, mutation and carcinogenesis." I could go on to list his extensive service on National Academy Committees, as President of the Biophysical Society; as co-author of the first textbook in Molecular Biophysics, and as author of over 250 publications.

Let me just conclude by reflecting that Dick Setlow has led the fields of UV photobiology and DNA Repair for many decades and that a very large number of us are

grateful for his contributions to our own scientific careers. The presentation of the EMS Award to Dick Setlow surely enhances the prestige of the award itself.

Dick Setlow's Response: "Obviously, I am very pleased and honored to be a recipient of the EMS Award. I am gratified that the discoveries that I've made have had wide application in many fields and that they have advanced scientific understanding of how genetics, the envrionment, and human health are interconnected. I regret that I shall not meet the many friends and colleagues at this EMS meeting. I hope to see you all next year. Best wishes, Dick"

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Princess of Thailand Received EMS-Hollaender International Fellow Award

P>*By William W. Au, Ph.D., Chairman, Alexander Hollaender Committee*

The EMS-Hollaender International Fellow award is given annually by the Environmental Mutagen Society (EMS) in honor of the late Dr. Alexander Hollaender, a pioneer in the study of environmental mutagens as a means to improve public health. The objective of the distinguished award is to recognize outstanding scientists from countries with developing environmental mutagenesis programs. In addition, these scientists have made significant contributions in promoting this field of science in their countries and internationally. This year, the honor went to Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol of Thailand. The Princess received the award in Anchorage, Alaska on April 30, 2002 as part of the proceedings of the Annual Meeting of the Environmental Mutagen Society.

Princess Chulabhorn was born in Bangkok, Thailand and she is the youngest child of His Majesty King Bhumibol Adulyadej and Queen Sirikit of Thailand. She received her Ph.D. degree in Organic Chemistry from Mahidol University, Thailand and she is also a candidate for the doctoral degree in medicine in the field of toxicology at the University of Tokyo Medical School. The Princess holds the title of Professor, Faculty of Medicine at the Siriraj Hospital, Thailand. She conducts scientific research in chemical carcinogenesis and natural products chemistry. She

has published more than 20 papers in scientific journals.

In 1987, the Princess founded the Chulabhorn Research Institute and she serves as the president of the institute. The institute promotes excellence in scientific investigations, and the application of science and technology to improve the quality of life. In 1990, the Princess founded the International Center for Environmental and Industrial Toxicology, which has since been designated "A Center of Excellence" by the United Nation Environmental Programme.

The Princess is active in promoting science, education, and public health initiatives in Thailand and elsewhere in the world. She provides valuable opportunities for scientists to conduct research in the Chulabhorn Research Institute, and she organizes the Princess Chulabhorn Science Congress for people to share the latest scientific developments. For example, a congress entitled "Evolving Genetics and Its Impacts on the World" is being planned for the year 2004 in Thailand. The Princess also organizes scientific workshops to provide hands-on training opportunities for many scientists. She has a variety of international appointments, as Special Advisor to the United Nations Environment Programme and as Ambassador of Goodwill in the World Health Organization.

Upon presenting the award to the Princess, the President of the EMS, Dr. David DeMarini, stated "the award recognizes the dedicated and exemplary efforts of Her Royal Highness in reaching out to students, teachers and scientists in Thailand and internationally to educate and to enhance collaboration in the field of environmental mutagenesis for the improvement of public health."

The Princess presented an eloquent acceptance speech in English to the members of the Society. She stated "The prestigious award that you have conferred on me is of very special significance to me since it demonstrates the close affinity between the work and goals of the EMS and those of the Chulabhorn Research Institute of which I have the honor to be the founding president." She emphasized that "environmental toxicological problems are global in nature." She indicated that she would like this occasion to begin the "close interaction that may lead to mutually rewarding collaboration between EMS

and Chulabhorn Research Institute." In conclusion, the Princess felt confident that "such collaboration will have an important impact on our endeavors to create a safer and healthier environment for all future generations."

Acknowledgement: The author appreciates the support provided by the EMS society, the Hollaender Committee and especially by Drs. Lawrence A. Loeb, David DeMarini, Philip C. Hanawalt, John M. Essigmann and Mathuros Ruchirawat.

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Student Achievement Awards

Name	**Sponsor**	School
Hannah Cheung	R.C. von Borstel	University of Alberta
Gord T. Cooney	J.G. de Boer	University of Victoria
Chiara Corso	J.M. Parry	University of Wales, Swansea
Lidia Cosentino	A. Wyrobek	Lawrence Livermore National Laboratory
Marlies De Boeck	M. Kirsch-Volders	Vrije Universiteit Brussel
Paurene Duramad	M.T. Smith / N.T. Holland	University of California, Berkeley
Alisson Gontijo	D.M.F. Salvadori	Universidade Estadual Paulista (UNESP)

Kyong Rim Lee	B.M. Lee	SungKyunKwan University, South Korea
Kristin L. Lockett	J.J. Hu	Wake Forest University School of Medicine
Matt Marengo	M. Plewa	University of Illinois
Andreas Rothfuss	P. Speit	Oregon Health Sciences University
Mark S. Rundell	M. Plewa	University of Illinois
Cindy C. Ruttan	B. Glickman	University of Victoria
Laura Schild	M.C. Poirier	National Cancer Institute, NIH
Eddie Sloter	A. Wyrobek	Lawrence Livermore National Laboratory
Thomas Tan	G. Chu	Stanford University
Ron Tapp	V. Wilson	Louisiana State University
Lisa Tomascik-Cheesman	A. Wyrobek	Lawrence Livermore National Laboratory
Maria Torres Carvajal	H. Groot	Universidad de los Andes
Hilde van Gijssel	M.C. Poirier	National Cancer Institute, NIH
GTA Travel Award Winners		
Weimin Gao	P. Keohavong	University of Pittsburgh
Laura Schild	M.C. Poirier	National Cancer Institute, NIH
Ana Claudia Velazquez-Wong	F. Salamanca	University of Mexico
FASEB / MARC Program Awardees		
Amal Abu-Shakra		North Carolina Central University
Gladys Bonilla		Universidad Metropolitana, Puerto Rico
Paurene Duramad	M.T. Smith / N.T. Holland	University of California, Berkeley
Lucy Hamilton	G. Bonilla	Universidad Metropolitana, Puerto Rico
Kristin L. Lockett	J.J. Hu	Wake Forest University School of Medicine
Crystal Mason	A. Abu-Shakra	North Carolina Central University
Maurice Martineau	G. Bonilla	Universidad Metropolitana, Puerto Rico

Shanta Mackinnon	A. Abu-Shakra	North Carolina Central University
Tomeca McLain	A. Abu-Shakra	North Carolina Central University
Annette Olieras	G. Bonilla	Universidad Metropolitana, Puerto Rico

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EMS 2002 Student & New Investigator Program

Students and new investigators had a great meeting in Anchorage this year. The numbers were down some because of the distance, but about 60 students and recent graduates had an exciting time both scientifically and socially. We had to make an important change in the usual student events because there was not enough room to exhibit the posters at the opening student and new investigator reception. Instead, we marked the posters with special placards during the regular poster sessions so they could be judged at that time. The result was that student and new investigator posters actually received much more attention than in the past. An evening poster session that was intended to be for judging the posters turned into an evening social hour for the whole society. (The cash bar probably helped). Many students told me that they had received lots of attention and felt very positive about the meeting. In the end the competition for awards for both poster and platform sessions was intense. The judges struggled to select a few winners from among many worthy presentations. We all owe a great debt of thanks to Kathleen Hill. She recruited the judges and kept the judges organized throughout the meeting. Her dedication and organization made this a very interactive meeting for our students and new investigators. I am sure Kathleen would ask me to thank all the judges. There were lots of them. They worked hard while many others were out having a good time or attending a fascinating symposium. We thank all of them for the sacrifices they made to make this a very student friendly EMS meeting.

The Student Education Award Committee, led by Lisa Tomascik-Cheeseman and Lidia Cosentino, selected none other than David DeMarini as the recipient of this year's award. His generous and effective mentoring of students is well known and the award well deserved.

Another exciting first this year was that we applied for, and received, a conference support (R-13) grant from the National Institutes of Health, which helped to provide travel awards for students. We will see if we can succeed two years in a row.

There seemed to be a lot of enthusiasm among students and new investigators at the meeting. Jennifer Sasaki asked students to volunteer to work on the Publicity and Program Committees. Several students stepped forward.

We hope that you are already planning for next year's meeting in Miami. How is the research coming along? The competition will be fierce, but fun, so plan your poster or platform presentation and get the data. We will look forward to seeing you in Florida.

Jonathan B. Ward Jr., Chair

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Student Comment

I am Mr. Alisson Gontijo from Sao Paulo State University (UNESP), Brazil. Among others, I was awarded a Student Achievement Award in order to leverage my trip to attend the 32nd Annual Meeting of EMS-US, at Anchorage, Alaska. I would like to acknowledge the Organizing committee for the excellent Program and the Award committee, for I had the opportunity to talk to other awardees (students and new investigators) and see they all had posters of high scientific quality. The students and new investigators were exposed to top-notch lectures and poster presentations, together with breakfast discussions with notorious scientists. Job opportunities were posted, thus helping shy students to seek for post-doc positions. Moreover, others and me were able to present platform talks, which I felt brought more than responsibility for us, but also opportunity for open discussion and post-presentation side-talks with experts from around the world. I am therefore profoundly grateful for the Society for the acknowledgment of our achievements, including those from other dedicated overseas members. Finally, I had a wonderful time at the catamaran cruise through Prince William Sound, apart from making lots of friends at the meeting and local pubs!

Alisson Gontijo, B.Sc.
Departamento de Patologia
Faculdade de Medicina, UNESP
Botucatu, SP, Brazil

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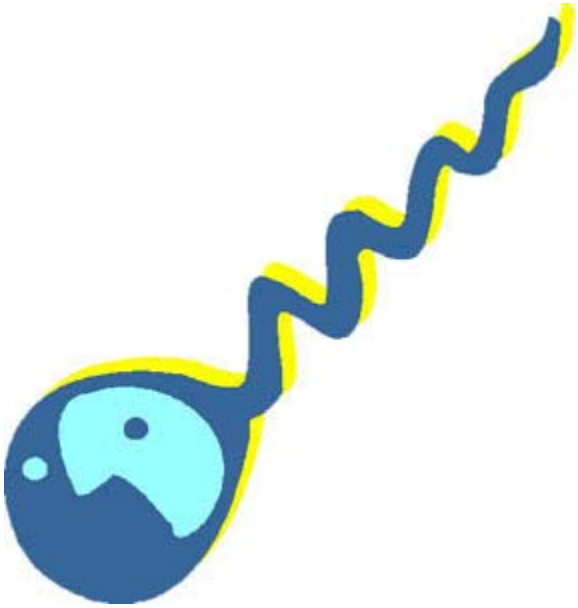
Germ Cell Mutagenicity Special Interest Group Breakfast

A surprisingly large group of awake and enthusiastic scientists met at 7:30 am at the Anchorage Hilton to discuss current issues in germ cell mutagenesis and human genetic disease. Dr. Jack Bishop opened the meeting with an overview of a planned workshop "Assessing and Applying New Genomic Technologies in the Detection of Human Germ Cell Mutagenesis and Associated Health Implications" which is scheduled for early 2003 in Alta, Utah, a location blessed by an abundance of the Greatest Snow on Earth. This conference is a follow-up to the 1984 Alta conference on germ cell mutagenesis. Jack informed the group that a list of potential topics has been prepared and some speakers have been approached about presenting at the conference. Approximately half the required funding has been pledged; additional funds are being sought. There have been two preliminary planning meetings thus far. Drs. David DeMarini and John Mulvihill

have been spearheading the organizational efforts. There was a strong affirmation among attendees of the need to study germ cell mutagens in human populations despite the continued lack of proof of the occurrence of these types of mutations. Drs. Sid Aaron and Stefano Bonassi stressed the need to add statistical expertise to the panel of experts at the Alta meeting, in order to explore associations among data sets and study results, and clinical/medical endpoints.



The use of animal models to explore questions of germ cell mutagenesis sparked some discussion, with Dr. Diana Anderson requesting that the group be given some clarification of the animal model designs, so that the appropriateness for human application might be explored. Dominant lethal studies, mainstays of mutagenesis research decades ago, are, for the most part, no longer conducted. In their place, animal studies using molecular approaches, such as the sperm FISH studies pioneered at LLNL, are being developed and used. Dr. Wendie Robbins reminded the group that the National Children's Study is in progress; it is a 20-year study designed to follow prospectively thousands of pregnancies. Data from this massive effort will go a long way, it is hoped, to provide useful data in the efforts to assess human germ cell mutagenicity issues. In addition, there are some study outgrowths of assisted reproduction technologies that may also provide data that potentially will elucidate some of the questions surrounding human germ cell mutagenesis.

Following the more general discussion on germ cell mutagenesis, Dr. Steve Sommers presented a talk on his research into germline mutations in the factor IX gene and the evidence for the predominance of endogenous mechanisms of mutation induction. There was lively interest and discussion of Steve's research among attendees. Following this, Dr. Sara Frias presented her results from studies of aneuploidy induction in sperm of Hodgkin's disease patients treated pre-and post-puberty. Observations from Sara's studies point out the importance of studying specific endpoints during treatments of children, and monitoring these endpoints into adulthood. Sara found no persistent effects in the patients treated as children, but persistent chromosomal damage was detected in several of the patients in Sara's study who were treated as adults.

As the meeting was adjourned, discussions continued and spilled out into the hallway. Clearly, the topics were of fervent interest to the attendees, and with each new point of discussion, additional avenues of research and additional scientific questions opened up. Hopefully these fruitful exchanges will continue *via* the germ cell interest group Website.

Kristine Witt

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Molecular Epidemiology Special Interest Group Breakfast

The meeting was held on April 30, 2002 and was attended by approximately 28 participants. William Au opened the meeting. This was followed by the presentation of the highlights of the colon cancer meeting that is being organized by Marti Veigl. The scientific program was found to be outstanding. A suggestion was made to develop a round table discussion involving scientists from the Food and Drug Administration. Stefano Bonassi, Martyn Smith and Fred Kadlubar presented the state-of-the-art techniques for molecular investigations. Discussions were center on the application of these new techniques and the validation of the results. Then, Fred Kadlubar presented the plan to organize a molecular biology workshop in the next EMS meeting in Miami. The workshop will be based on the following outline:

1. High throughput technologies and their applications to molecular epidemiology: study design, SNPs and gene expression arrays, proteomics
2. Statistical considerations: statistical approaches for evaluation of data, bioinformatics, data mining algorithms, neural networks.
3. Informed consent, ethical issues and handling of the collected information

William Au presented the scientific program for the 4th International Conference on Environmental Mutagens in Human Populations, Brazil, May 4-8, 2002.

Please address your comments to William Au (william.au@utmb.edu); comments and assistance to the molecular biology workshop can be sent to Fred Kadlubar (fkadlubar@nctr.fda.gov).

William Au

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Transgenic & *In Vivo* Mutagenesis Special Interest Group Breakfast

The Transgenic and *In Vivo* Mutagenesis Interest Group re-elected its past officers for another year, Carrie Valentine from the National Center for Toxicological Research (USA) and Barry Ford from the Radiation Protection Bureau (Canada). Barry is working on a Website for the interest group that should makes its debut on the EMS home page

this summer. We will include links to our e-mail interest group newsletter and a new feature including short reviews of papers of interest to our members.

Several speakers presented recent research results at the interest group meeting in Anchorage, AK. The first was Dr. Takehiko Nohmi, Section Chief, Laboratory of Molecular Mutagenesis, National Institutes of Health Sciences Division of Genetics and Mutagenesis, Kamiyoga, Japan. His presentation was titled "Mutation Frequency Decline in the Sampling Time of Transgenic assays." Dr. Nohmi presented data showing that in bone marrow, mitomycin C induced maximal mutations after one week followed by a decline to background at four weeks. Mutations were detected using thioguanine (point mutations) and Spi$^-$ (mostly 2-10 kb deletions) selection in his *gpt* delta mouse. He concluded that the presently recommended time of 28 days between *in vivo* exposure and tissue collection may be too long for a rapidly dividing tissue. Dr. Nohmi also reported that he has developed a *gpt* delta rat with several copies of the EG10 vector on chromosome 4.

The second speaker was Heinrich V. Malling, Senior Research Geneticist of the National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA, presenting "Three Origins of *am3* Revertants in Transgenic Cell Culture." Dr. Malling presented research to determine the size of a single burst that distinguishes an *in vivo* from an *in vitro* mutation, conducted with the reversion assay of the X174 transgenic mouse (also known as the "Malling Mouse"). Previously, he had based the cut-off on the smallest burst size of a non-revertant phage, which was 30. In this study he used mutagenic treatment to determine the smallest burst size that responded to treatment. He did the single-burst analysis of solvent-treated and ENU-treated animals (150 mg/kg) collected 100 days after treatment in order to avoid any residual damage to DNA from the treatment. This study showed that the induced mutant frequency was relatively constant between bursts 15–80 plaques in size. Only type 1 bursts (>60 PFUs/plates) responded to treatment by mutagen. Commercial X174 DNA produces many *in vitro* bursts. In solvent-treated cells (a mouse embryonic cell line), only 7% of mutant plaques recovered were *in vivo* bursts - or, 93% of spontaneous mutant plaques were fixed *in vitro*. When analyzed by mixed bursts, the mutant frequency was 0.82×10^{-6}, but when analyzed by single bursts, dropped to 0.006×10^{-6}. The mutant frequency for the 200 ug/ml-treated cells was 4.8 by mixed bursts and 4.1 by single bursts. This resulted in a 5.9-fold increase by mixed bursts, but a 68-fold increase by single bursts. A significant

finding was that the A:T>T:A mutation, characteristic of ENU, was found only among type I revertants, *i.e.* the *in vivo* mutations.

The third speaker was Mr. Jeffrey Wickliffe, graduate student at Texas Tech University, Lubbock, TX, USA, with Dr. Robert Baker, presenting, "Big Blue Mice in the Chornobyl (Ukranian sp.) Environment."

Mr. Wickliffe reviewed some facts surrounding the radioactive explosion at the Chernobyl power plant in Russia (Ukraine) in 1986. In 1992, an increased incidence of thyroid cancer was recognized followed by the observation of increased mutation rates in mtDNA and repetitive DNA elements in 1996-97. There have also been subsequent negative studies on increased mutation rates. He described a 90-day exposure of Big Blue mice to the Chornobyl environment in wire mesh cages in which the exposed animals received 3.3 mGy/day. This total dose as an acute dose causes a 5-fold increase in mutant frequency. Five animals were exposed, and 3 were placed in a control environment, unexposed to radiation. Animals were sacrificed on the site and tissues frozen for analysis in the USA. No significant difference in mutant frequency or mutations spectrum was observed. These results indicate that a chronic, low dose, is less mutagenic than the same dose delivered acutely.

Finally, Ms. Lya Herna dez, a graduate student at York University, Toronto, ON, Canada, with Dr. John Heddle, described some difficulties that were occurring in Dr. Heddle's laboratory with plating efficiency of plaques in the *cII* assay. They had found that only one batch of peptone would support adequate plating efficiency. During discussion, Dr. Tao Chen at NCTR, Jefferson, AR, USA, said that his *cII* assay was working with peptone from Sigma (St. Louis, MO, USA). Dr. Heddle reported that some batches of Strategene's packaging reaction were not effective, but had been told by Stratagene that no one else was having any problem. He encouraged others using their products to insist on replacements if they have a similar problem.

Carrie Valentine

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Other Articles and Features

EMS 2003: Sun, Sand & (Most Importantly) Science

Greetings! The 2003 EMS annual meeting will be held at the Fontainebleau Hilton Resort in Miami Beach, Florida on May 11-14. We are actively working on the Program and hope to make this one of the best EMS meetings to date. The overall theme for the meeting will be "Environmental Mutagenesis: From Mechanisms to Risk Assessment" and the Program will cover a wide range of topics that should be of interest to all members of the Society. We are planning to have 12 symposia, 3 platform sessions, 3 poster sessions, 2 short courses, and a number of plenary and keynote lectures. Currently, we are organizing symposia in the following areas:

- Embryonic and Fetal Exposure and Children's Health
- Children's Susceptibility to Environmental Agents
- DNA Damage Checkpoint Signaling
- Assembly and Regulation of DNA Repair Machines
- Excision Repair
- Genomic Instability
- Advances in Somatic Mutation Models

- Toxico- and Medical Genomics
- Potential Modifiers of Carcinogenesis at Low Doses
- Mode of Action in Genetic Risk Assessment
- Computational/Predictive Toxicology
- Environmental Mutagens and Carcinogens: An Update

In addition to these sessions, two short courses are planned for Saturday May 10 (the day preceding the meeting), one entitled, "New Developments in Molecular Epidemiology" being organized by Fred Kadlubar, and the other an "Overview of Genetic Toxicology" being organized by Paul White. There will also be several platform sessions with speakers chosen from among those submitting abstracts. Finally to crown the meeting, we will have a number of Plenary and Keynote lectures.

The meeting this coming year is somewhat unusual in that there will be a separate EMS-sponsored meeting on colon cancer entitled "Impact of the Environment on Colon Cancer," that will slightly overlap and immediately follow the shortened EMS meeting. The Colon Cancer meeting is scheduled for May 14-16, 2003 and is being organized by Marty Veigl and Curt Harris. We would encourage all members to take advantage of this unique opportunity and attend both meetings.

For up-to-date information about the Programs for both the EMS and the Colon Cancer meetings, watch the EMS Website or refer to the Program brochures which are scheduled to be mailed in late September. The deadline for abstract submission will be in early December with the first cut-off for advance registration scheduled for later that month.

As for the venue, the Fontainebleau Hilton Resort is one of Miami's most famous landmark hotels and has been the Miami hotel of choice for every President since Eisenhower as well as numerous other celebrities. It is situated along the beach among 20 acres of tropical vegetation. It boasts a half-acre lagoon-style rock grotto pool with cascading waterfalls surrounded by lush greenery. It has seven lighted tennis courts, as well as programs and activities for guests of all ages. EMS members may want to consider extending their stay and bring their families to take advantage of the hotel and its facilities. The adjacent two-mile seaside boardwalk leads to the famous Art Deco District of South Beach where there are enough dance clubs to keep even the most avid EMS dancers happy and tired. I look forward to seeing each of you in Miami.

David Eastmond,
Program Chair

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Letter from the Treasurer

Dear Colleagues,

This letter is from my report delivered at the Business meeting at the 2002 EMS meeting.

Introduction

Last year I presented a 10-year projection which demonstrated that, at the then current rates of income and expenses, EMS would become insolvent. We were consuming our investment income and principal to pay for operating expenses. The bleak financial situation was aggravated by the 2000-2001 recession and our balance sheet looked anemic due to our unrealized capital losses. During this year the EMS Officers and Executive Board worked hard to reverse this trend. We developed a long-term financial plan and we have made good progress to establish the financial stability of the Environmental Mutagen Society. This plan is a result of many discussions and thoughtful contributions by my fellow EMS Officers, members of Council, EMS members, our management team, the auditors at Huey and Associates, and financial consultants and staff associated with Federation of American Societies for Experimental Biology (FASEB). The membership took a decisive step in approving a dues increase at the 2001 Business Meeting in San Diego. Since that time, we engaged a new management firm, conducted a full audit and we have focused on limiting costs at all levels of the Society. The results of this report reflect fiduciary commitment of the EMS Officers and Council.

I am pleased to report that the plan to establish the financial stability of the Environmental Mutagen Society is progressing well. We conducted an intensive evaluation of the management needs for the Society and selected a new firm. Our new management firm, Association Innovation and Management, Inc. (AIM) and our Executive Director, Ms. Tonia Masson, established an efficient and cost-effective management of our Society. A three-month period in the summer of 2001allowed for a transition of past and present management firms. The integration of action and cooperation between AIM and the EMS officers is essential to forge a sound financial platform for our Society in order for us to meet our scientific goals and the expectations of the membership.

The Audit by Huey and Associates

During the transition period, while both management firms were under contract to EMS, we had a formal audit of the Society performed by Huey and Associates, P.C. The Society had not conducted a formal audit in at least a decade. The audit provided us with a platform from which to build our long-term financial plan. The primary sources of income include; (1) the membership dues, (2) revenues from EMS-sponsored meetings, (3) contributions and corporate sponsorships, (4) revenues from our journal, and (5) the investment income from our reserves. As of June 30, 2001 the total net assets of EMS was $600,163. This confirmed my estimate that EMS net assets declined by nearly a quarter of a million dollars during the past few years. The audit report highlighted a number of areas that should be addressed. Accordingly the following changes have been executed.

- The auditors indicated that it was not a good practice to hold money for another society in bank accounts under the EMS name. The accounts that EMS maintained for the International Association of Environmental Mutagens (IAEMS) have been transferred. EMS will no longer provide free financial or management services for IAEMS.
- The auditors questioned the restricted assets. After a discussion with past EMS Presidents and Treasurers it was decided that the money provided by the estate of Dr. and Mrs. Alexander Hollaender was consumed according to the restrictions of

the trust. The current money in the Hollaender Funds was provided by EMS resources and will be used in part to serve as seed money for the international outreach by our Society. However, they are no longer restricted and can be used by the Society to meet its needs.

- The auditors noticed that the Management Company and EMS officers did not share the same understanding regarding their respective roles, duties and deliverables. They also questioned the authorization for expenses incurred by the Management Company. We corrected this deficiency by changing management companies.
- The check writing process was found to be disorganized and that several accounts were open during the year which various people could write checks from. We have established a series of rules covering our check writing procedures with AIM. All checks and deposits are classified and accounted for as they are processed.
- The auditors indicated that the EMS investment accounts be updated and reconciled on a monthly basis. I shall reorganize the EMS investment program and begin our dollar-cost-average program during this fiscal year. This plan will be submitted to the Executive Board after the Anchorage Meeting.
- The total expenses generated by the Society for the FY ending on June 30, 2001 was $509,626. This value will be used in my recommendation regarding establishing a reasonable reserve for EMS.

EMS Sponsored Meetings

Due to the diligence, attention to detail, and the development of rational budgets by David DeMarini and Sid Aaron, the EMS-sponsored Breast Cancer meeting and the IAEMS satellite meeting on Functional Genomics were profitable as well as excellent scientific programs. I reduced the travel grants provided to invited EMS member speakers to the IAEMS meetings in Japan. The costs for these speakers supported our international outreach and will be charged to our Hollaender Funds.

Management of Society Expenses

The current administration has a commitment to reduce EMS expenses.

- We incurred very little expense for the mid-year Executive Board Meeting by meeting in Japan at the ICEM rather than have a separate meeting at the conference site in Alaska.
- The Executive Board and I established spending limits and budgets for several of our Society committees.
- We applied to NIH for a grant for student travel support. We received a good priority score and I have a good expectation for funding.
- We have established a sound negotiating team for dealing with vendors for the Alaska meeting.

EMS Journal Expenses

David DeMarini and I have paid special attention to our journal.

- The Editor-in-Chief and the Editorial Board will have sole authority over the scientific content and quality of the journal. However, the President and the Treasurer have fiduciary responsibility for the journal.
- The finances of the journal are complex indeed. It is essential that the journal be a financial as well as a scholarly asset for the Society. The problem is that revenues from the journal are consumed by the expenses of the Editor's office plus the excess page charges. In fact during the past 1.5 years, I paid over $40,000 in excess page charges incurred from past years. To solve this problem the Editorial Office no longer has the authority to print excess pages; this is a fiduciary responsibility of the Executive Board and Treasurer. In concert with AIM, the Society Officers, the Publisher, and the Editor, I hope that we will have our journal-related financial questions answered and have the journal profitable by the next fiscal year.
- In past years we paid about $14,000 per year to publish our annual meeting abstracts. After negotiating with the Publisher, David DeMarini has reduced this cost to $5,000 for the Anchorage meeting.
- Due to the efforts of Jenness Majeska and Liz Von Halle in establishing a corrected membership list, we have now stopped sending the journal to several hundred nonmembers at considerable expense (~$8,000 per year).

FASEB

This past December, I served as an alternate member (standing in for Peter Stambrook) on the Board of Directors of the Federation of American Societies for Experimental Biology (FASEB).

- During this meeting I had the opportunity to discuss the status of the EMS reserves with Mr. Andrew Lang who is the financial consultant for FASEB. His

advice was that EMS should build financial reserves that equal at least one year of total expenses. I agree with this sound advice, and it will be a goal to establish a process to bring our reserves to this level during my tenure as EMS Treasurer.

- I also participated as the EMS representative at the FASEB Annual Funding Conference. FASEB prepares a document that is used to lobby Congress in support of rational funding levels for basic and applied biological research by the Federal Government. As a member of FASEB, EMS now has a voice in the big league of American science. We should commend the efforts of the past two EMS Executive Boards in establishing the membership of EMS in FASEB. Being a member of FASEB is a significant step in the evolution of our Society.

Reserves and Investments

The income from the investment of our reserves has been very low because of the economic recession, the depressed equity market for a second year in a row, and the fact that the Federal Reserve Board reduced interest rates 12 times during the past 20 months.

- I have consulted a Certified Financial Planer at A.G. Edwards Co. to assist me with a complete review of our investment program for our reserves. With the audit completed I will begin again the dollar-cost-average investment strategy that was initially begun over 10 years ago.
- I will then immediately prepare a long-term investment program for our reserves to bring us to double our total annual expenses of $510,000. Thus, my goal is to prepare a long-term plan to raise our reserves to the million dollar range. It is the reserves that were established during the decade of past administrations that have kept EMS from insolvency.

Not including the income and expenses for the 2002 EMS annual meeting, the net assets of the Environmental Mutagen Society was $709,056.70. It has been an honor for me to serve the EMS as Treasurer. Thank you for your support and trust.

Sincerely,
Michael Plewa

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EMS Past Presidents

The annual group photo during what is jokingly referred by its members as the "Dead Presidents Reception" got a little lively in Anchorage. Seems the spirit of fun and adventure of the northern frontier state was contagious! Just goes to show that scientists have a great sense of humor.

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In Remembrance

Stephen J. Gould

Stephen J. Gould passed away last May. He was a speaker at the EMS Meeting in San Diego in 2001. Dr. Gould had renewed battle with cancer earlier in the Spring. Tom Gagnon, Dr. Gould's manager, said that "ne of my last conversations with him was about the EMS meeting he attended in San Diego - mentioning how much he really enjoyed speaking with the students."

Reflections on Stephen J. Gould

Last year, at the 32nd annual meeting of the EMS, we had he opportunity to listen to a distinguished evolutionary biologist. It was indeed a great occasion to meet Stephen Jay Gould, who lectured on his lifelong field of work: evolution.

Gould was one of the best known paleontologists of our time and one of the major and controversial contributors to evolutionary theory since Darwin. In 1971 he developed, together with Niles Eldredge, the theory of "punctuated equilibrium." It states that species remain "unchanged" for large periods of time and then, burst in a rapid change, associated with transcendental biological disasters. This hypothesis contrasts with the traditional view of a gradualistic mode of evolution, held until then, and not discarded even now.

Gould was a prolific essayist. Besides his numerous books, he wrote a monthly column for Natural History, a practice held for more than two decades and that wasn' interrupted as he himself liked to assert "for cancer, hell, floods, or the World Series." His contributions to the magazine were collected in a series of books, the last one I have landed, having been published early this year.

Gould was diagnosed 20 years ago with an abdominal mesothelioma, which is associated with asbestos exposure and one of the cancers with worse prognosis. The way he faced his diagnosis is beautifully recounted in his short essay "The median isn’t the message." Gould thought he had a better than not chance of surviving and tells about asking his scientific guru, as he called him, Sir Peter Medawar (himself having survived serious illness), for a prescription to succeed against cancer. Medawar replied without hesitation: "a sanguine personality." Gould surpassed for twenty years an expected median survival time of 8 months and apparently died of a second and unrelated cancer on May 20, 2002. Sanguine, indeed, must have been his personality.

He lived just long enough for seeing his master work published: *The Structure of Evolutionary Theory*, a 1,400-page book encompassing the history of evolutionary thought and his own point of view on the subject.

I’m glad to have started my own scientific career having Gould's living reference at hand. Listening to him at the EMS 2001 meeting furthered my own interest in scientific research as he himself conducted it: with great passion.

Andrés Bendesky
Instituto de Investigaciones Biomedicas y Facultad de Medicina
UNAM, Mexico

David B. Busch, M.D., Ph.D.
July 25, 1953 - April 11, 2002

It is with great sadness that we announce the passing of our friend and colleague, Dr. David B. Busch who succumbed to leukemia on April 11 at the age of 48 years. He received an undergraduate degree in biochemistry with distinction in 1974, a masters in biophysics in 1976 and Ph.D. in biophysics in 1980 all at the University of California, Berkeley. His Ph.D. work was performed under the guidance of Nobel prize winner, Dr. Donald Glaser. He then earned an M.D. degree in 1982 at the University of Miami. This was followed by residencies in anatomic and clinical pathology at the University of Wisconsin in Madison which culminated in his becoming a Diplomate of the American Board of Pathology in 1986. The same year he joined the Armed Forces Institute of Pathology in Washington, DC where he spent his professional career as a Radiation Pathologist.

Professor Ed Nelson
November 3, 1950 - July 11, 2002

Ed was born on November 3, 1950, raised almost in the US, emigrated to Germany in 1982 and became a citizen there. He received his medical degree (Med.B.) in 1974, specializing in hygiene, and an interdisciplinary doctorate degree (Sc.D.) in experimental toxicology in 1987. He joined the medical faculty of Essen University, Germany, in 1982. Although working at the department of hygiene and occupational medicine, he focused on his activity in the field of toxicology and worked on a thesis to pursue professorial inauguration in Occupational Toxicology. He received a *venia legendi* for that field in 1989 and officially became an accredited professor of toxicology. He was an active member of several international scientific societies including EUROTOX, Society of Toxicology of the US, American College of Toxicology, American Association for Cancer Research, American Academy of Clinical Toxicology, US EMS, and the German Society of Pharmacology and Toxicology.

Dr. Nelson severely suffered from a sudden cardiac infarction in late 1992 but survived receiving a heart transplant in January 1993. Regardless of his immune suppression

caused by post-transplantation medications, he continued and in some regards even increased his scientific activities. He died on July 11, 2002 at the age of 51 because of heart failure. He is survived by his wife and two loving children, Shirley and Scott.

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Other Announcements

Special EMM Issue

Dear EMS Member,

It is my pleasure to announce the publication of a special issue of *Environmental and Molecular Mutagenesis*. The issue contains papers that are based on presentations made at the recent Environmental Mutagen Society-sponsored conference, "Breast Cancer and Environmental Mutagens: Bridging Molecular Research to Medicine and Public Health." Breast cancer is the most commonly occurring malignancy among women from the U.S. and many other countries. The role of environmental mutagens in this disease is poorly understood, and the conference covered the latest advances in our understanding of this area. I congratulate the Guest Editors, P. David Josephy and Pamela M. Klein, for assembling such an impressive collection and bringing it to us in a timely manner. I think that you will be impressed with the quality and scope of the contributions to this volume. I also want to acknowledge the assistance provided by the National Institutes of Environmental Health Sciences, the National Cancer Institute, Genentech, the U.S. Environmental Protection Agency, and the Genotoxicity and Environmental Mutagen Society. This special issue is available online through the following link www.interscience.wiley.com/em.

Robert H. Heflich, Ph.D., Editor-in-Chief, EMM

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PTID Meeting in Germany

Dear Scientist:

The annual scientific meeting of the International Society for the Prevention of Tobacco Induced Diseases (PTID Society) will be held from October 28 - 30, 2002, in Essen, Germany.

The topics for presentation include laboratory findings on genetic and genetic toxicology of tobacco smoke exposure. The deadline for submission of abstracts is April 30th. You are kindly encouraged to submit as many scientific abstracts for presentation from your working group as possible. A complete set of information including all application forms for registration, abstract submission, and hotel reservation are available on the Web (www.ptid2002.info). To benefit from a low registration fee by early registration, please check the deadlines on the Web.

Best Regards,

The Local Conference Organizers, PTID Society
Fax: +49.201.723-5956
E-Mail: TOXICOL98@AOL.COM
Mailing address: PTID-Society, Postfach 185431, D-45204 Essen, Germany.

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9th ICEM and Satellite Meetings!

Dear Colleagues:

The 9th International Conference on Environmental Mutagens will be held concurrently with our annual EMS meeting in beautiful San Francisco, September 3-8, 2005. We will convene in the Hyatt Regency Hotel at the Embarcadero Center to focus on the theme, "Global Issues in Genetic Toxicology and Mutagenesis." Mark your long-term calendars now and plan on participating in this exciting and timely international event.

We are now soliciting proposals for satellite meetings to be held before and after the ICEM. It is not too soon to begin planning for those special conferences and, in fact, we

need to have your initial proposals by the end of August *this year* so that the EMS Executive Board and the ICEM Organizing Committee can review them at their meeting on September 9th. The information we need from you this summer includes:

a. Title and theme for your satellite meeting
b. Suggested location and dates (Possible venues to consider include: Hawaii, Seattle, Vancouver, Asilomar, and Santa Barbara.)
c. Brief description of the meeting format, with a list of proposed session topics and speakers. (How many participants are anticipated?)
d. Realistic budget and likely sources of support. (This item is particularly important, so that fund-raising efforts can be coordinated among the various satellite meetings and the ICEM.

I am looking forward to working with you to ensure that the San Francisco ICEM will be a professionally rewarding and unforgettable experience. In the meantime I hope you have a great summer!

Best wishes,
Phil Hanawalt
Chair of the Organizing Committee, 9th ICEM

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4th ICEM on Environmental Mutagens in Human Populations

Dear Scientists,

On behalf of the organizing committee and my co-chairman, Dr. William Au, I am pleased to inform you that the Fourth International Conference on Environmental Mutagens in Human Population will be held in Florianopolis, Brazil, May 4-8, 2003. We have an outstanding scientific program that addresses genetic susceptibility, genome based technology for toxicology and health, unique concerns for environmental health, *etc.* The meeting will be held on a resort island outside of San Paolo. I encourage you to access our Website, www.4thicemhp.tmp.br, to obtain further information and to register for our conference.

I am also pleased to inform you that the Environmental Mutagen Society will hold the 2003 meeting in Miami, May 10-15. For many of you, you may consider attending the Miami meeting on your way home from our conference. Please visit the Website: www.ems-us.org for more information.

Some of you may need to have a letter of invitation in order to request your own support for attending the Brazil conference. Please let me know about this. I shall be glad to write an invitation letter to you and list the title of your presentation. I would like to make it clear that the invitation letter does not mean that we will provide financial support to you at this stage.

I look forward to seeing you in Florianopolis, Brazil next year.

Sincerely yours,

Lucia Regina Ribeiro- Co-chairperson of the Conference
Rua Emiliano Perneta, 288 / 2901
80010-050, Curitiba - PR, Brasil
Phone: 55 41 222 8770 / 55 41 9996 2524
Fax: 55 41 233 5189
E-mail: lribeiro@mais.sul.com.br

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Journal Discounts Available

Members of the Environmental Mutagen Society can now order the following Wiley Journals at a special reduced rate.

BioEssays	$99
Genes, Chromosomes, & Cancer	$270
Genesis	$60
Human Mutation	$215
Molecular Carcinogenesis	$270
Teratology	$99

(All the rates above are for North America, local shipping charges may be applicable for the rest of the world.)

To take advantage of this special offer, EMS members should contact Wiley Customer Service at:

Phone Number:	800-825-7550 (US only)
	212-850-6645

	(International)
Fax:	212-859-6021
Email:	subinfo@wiley.com

When calling, members must indicate which journal(s) they would like to order, that they are entitled to the Special EMS Rate, and provide proof that they are active members of the Society, to the Customer Service Representative.

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Remembering Bob Haynes with a Scholarship Fund

Of interest to the many friends and colleagues of the late Bob Haynes, we have recently learned of an R.H. Haynes Scholarship Fund at York University that has been set up in his memory. Contributions will be gratefully accepted by:

Dr. Brent Heath
Biology Department
York University
4700 Keele Street
Toronto, Ontario, M3J 1P3
Canada

Phil Hanawalt

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2002 - 2003 EMS Council

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Eighth International Conference on Mechanisms of Antimutagenesis and Anticarcinogenesis

Pisa, Italy, 4–8 October 2003

ICMAA–VIII will be the 8th in a series of successful conferences on mechanisms of antimutagenesis and anticarcinogenesis, held every 2–3 years since 1985.

Scope of the Conference

There is increasing evidence that cancer and other mutation-related diseases can be prevented not only by avoiding exposures to recognized risk factors but also by favoring the intake of protective factors and by modulating the defense mechanisms of the host organism. This preventative strategy, referred to as chemoprevention, can be pursued either by means of pharmacological agents and/or by dietary factors, based on risk-benefit and cost-benefit analyses. The efficacy and safety of chemopreventive agents can be evaluated according to a variety of methodological approaches, ranging from *in vitro* test systems to animal models and studies in humans. An essential step is to understand the mode of action of inhibitors of mutagenesis and carcinogenesis, which provides a rational basis for their application. In a period of exciting advancement of science in the general area of mutagenesis and carcinogenesis, ICMAA–VIII will update the state of the art of the mechanisms of inhibitors.

Scientific Contents

In the framework of the general objectives of this type of conference, the maximum emphasis of ICMAA–VIII will be given to mechanistic aspects rather than to effects and methodologies, although quite often it is difficult to distinguish between primary mechanisms and secondary effects. Since the choice of methods is crucial for exploring mechanisms, new methodological approaches of particular relevance, aimed at exploring mechanisms, will find a niche in the program. In addition, ICMAA–VIII will concentrate on protective mechanisms rather than on other issues related to mutagenesis and carcinogenesis. Data relevant to humans will be particularly welcome.

The conference site is located in Pisa, a beautiful town which used to be a prosperous Etruscan harbour and a glorious Marine Republic. "Campo dei Miracoli" (see the photograph) represents Pisan wealth and power expressed through superlative art, harmonizing Roman classicism with Byzantine refinement and Arab decorative drawing. The grand Basilica, the imposing Baptistery, the astonishing Churchyard and the worldwide famous Leaning Tower are marble masterpieces. They are surrounded by Romanesque and Gothic churches, squares and palaces traced out along the Arno River

and the ancient streets of this University town of great prestige, which was the birthplace of Galileo Galilei.

Pisa is in the region of Tuscany, which is placed at the heart of Italy. This region is a land of extraordinary beauty and harmonious nature, and is permeated everywhere by science, art and culture in towns like Florence, Siena, Lucca, San Gimignano, Volterra, and many others, and in the surrounding countryside.

For more information contace the Chairman of the Organizing Committee (G. Bronzetti) and the Chairpersons of the Scientific Program Committee (S. De Flora and L.R. Ferguson):

Giorgio Bronzetti g.bronzetti@imd.pi.cnr.it
Silvio De Flora sdf@unige.it
Lynnette R. Ferguson l.ferguson@auckland.ac.nz

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Joint Conference of PAEMS & SFRR-Africa

A joint conference of Pan African Environmental Mutagens Society (PAEMS) and the Society for Free Radical Research Africa (SFRR-Africa) will be held in Cairo, Egypt, on 2-7 March 2003. The topic will be "Child Health and Environmental Mutagens: An African Agenda for Prevention Research."

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Contact the EMS Webmaster with submissions, comments, and corrections.