President’s Message

Avrum I. Gotlieb

At this time of the year, I have two interesting academic tasks to do - review promotion dossiers for my faculty and then write the Chair’s supporting letter and interview medical students who are applying to our Department of Laboratory Medicine and Pathobiology for residency positions in one of our six laboratory medicine training programs. In both cases, I came away from the task very optimistic about the current state and the future prospects of academic pathology and laboratory medicine.

Besides reflecting the individual achievements of faculty members in teaching, research, and clinical care and the wonderful quality of our applicants, the two processes also highlight the full academic mission of our department within the medical school, the university and the national and international community.

What does this have to do with ASIP? I feel it has much to do with ASIP and other pathology organizations that support our academic enterprise. In order to have productive innovative faculty and motivated and enthusiastic trainees, we need an international community of colleagues to belong to and be part of. We, as individual scientists and clinicians, need to feel part of the global excitement of advances in understanding and communicating pathogenesis of disease, in diagnosis and prognosis, and in clinical care. We need to feel part of the explosion of new knowledge in molecular biology and informatics.

We need to be able to collectively address bioethical issues that affect our research, teaching and clinical care. We need to mobilize our efforts to maintain adequate support for our innovative and high quality teaching and research programs. We need to establish academic benchmarks that unite us in establishing high quality academic health sciences complexes.

Is the current mission of ASIP comprehensive enough to be able to meet today’s challenges and those of the future? We have indeed recognized emerging areas and have begun to address them.

Over the last few years, we have taken an active role in providing important consultations and viewpoints to legislative and scientific entities that are developing regulations and guidelines on the use of human biological materials in research, on biosafety in the laboratory, on ethical approaches to human research, and on new technologies and research areas including stem cell research.

We have introduced several initiatives to promote quality training for PhD, MD, (Continued on page 2)
and MD/PhD trainees. We have created an organized focus at the annual ASIP meeting at EB for graduate coordinators to meet and discuss topics important to graduate education in pathology and laboratory medicine. We have done this in collaboration with the Association of Pathology Chairs and have used their good offices to further our objectives in graduate education. We program several presentation sessions for trainees to present their research to faculty and peers, usually in a poster-discussion format. We also present the Chugai Symposium for Young Investigators. We encourage attendance at our annual meeting through competitive travel awards and we offer awards to outstanding trainees including the Experimental Pathologist-In-Training Award. We have not neglected the role of the research supervisor and thus have instituted an annual competitive mentorship award (Chugai Award for Excellence in Mentoring and Scholarship). Trainees are also welcomed at our annual mentoring luncheon hosted by our Committee for Career Development, Women and Minorities.

We have also developed a successful educational program at the annual meeting directed at non-pathologists. The Pathobiology for Basic Scientists Courses introduce attendees to basic pathobiology as it applies to various disease entities, e.g. neoplasia, inflammation. We have also run free-standing courses such as the Concepts in Molecular Biology Course.

In addition to new educational initiatives, ASIP has effectively helped new areas to come forward in pathology. NAVBO (North American Vascular Biology Organization) was fostered in its early days by ASIP. AMP (Association of Molecular Pathology) was supported by ASIP and ASIP has contributed to launching the New Journal of Molecular Diagnostics which is co-published by ASIP and AMP. There are several other societies which are located in the Bethesda ASIP offices, including APC (Association of Pathology Chairs), UAREP and the groups it has nurtured, API (Association for Pathology Informatics) and ISBER (International Society for Biological and Environmental Repositories).

Thus ASIP has been adapting to new issues as they appear on the pathology and laboratory radar screen. The ASIP Council has constituted a long range planning committee. These are exciting times in biomedical sciences, in education, and in clinical care. This committee will be reporting to Council in April in New Orleans to provide insights and recommendations for discussion. The focus is on how ASIP is adapting to the forever changing environment and what mechanisms are needed to facilitate the growth of our society while maintaining our current strengths and at the same time preparing for the present and the future.

From the Executive Officer's Desk

Mark E. Sobel

Here in Bethesda, we have had a relatively mild winter, the buds are visible on the trees, and we are looking forward to the peak of the cherry blossom season the first week of April. Spring brings with it our anticipation for the annual meeting, this year in New Orleans. ASIP received a record number of abstracts this year and we have planned a robust program of outstanding science and award lectures.

I would like to take this opportunity to update you on a number of important events that have occurred since the last ASIP Bulletin and to let you know about some new opportunities for ASIP members.

ASIP has new phone numbers. In February, the executive office modernized its phone system. We have added new phone lines so that ASIP staff can be reached directly. You may now reach most ASIP staff directly and you can leave voice mail messages on their direct lines when they are unavailable to answer the phone. In addition, the ASIP main number has been changed to 301-634-7130, although the previous number will still receive calls for the next few months. ASIP's fax line, 301-571-1879 has not been changed. In addition, there are new phone and fax numbers for AJP and JMD. The new journal phone number is 301-634-7959, and the journal fax number is now 301-634-7961. Again, the old journal numbers will still receive calls for the next few months. Each journal staff member has a direct phone number. You may leave voice mail messages at the main journal number as well as directly with the specific journal staff member you are trying to reach. We

(Continued on page 9)
Joe Wheeler Grisham Wins Gold-Headed Cane

Dr. Joe Wheeler Grisham, Chair Emeritus of the Department of Pathology and Laboratory Medicine at the University of North Carolina at Chapel Hill, is the winner of the 2002 Gold-Headed Cane, ASIP's highest honor. In addition to more than 150 published papers and landmark research into liver pathology, Dr. Grisham is noted for his 26-year chairmanship of the UNC-Chapel Hill Pathology Department, for his mentoring of dozens of today's leaders in the field, and for his public advocacy on behalf of pathology.

Dr. Grisham is credited with transforming his department into a national leader in education in pathology and laboratory medicine. He insisted on originality from his professors, always keeping the curriculum fresh. He encouraged and participated in their research, often eschewing credit for himself. And he peppered the courses with lectures of his own. Once, when one of his professors, Dr. David H. Walker, was departing to become Pathology Chair at the University of Texas Medical Branch at Galveston, Dr. Walker asked for Dr. Grisham's top ten pointers for doing the job. He answered, "There's only one. Put the effort into developing your faculty members' careers above all else."

Still, Dr. Grisham made some significant contributions of his own, particularly in the areas of hepatic biology. He co-authored landmark studies in liver regeneration and the study of stem cells. He coined the universally used term "facultative stem cells." His analyses of commonly accepted markers of malignancy contributed to the important insight that malignant transformation does not necessarily follow a single path. Subsequently, he found that the transfer of a part of human chromosome 11 could suppress the malignant behavior of certain malignant clones. His laboratory has mapped the region of the suppressor gene to a small part of the transferred chromosomal fragment.

You have to look back nearly 40 years to find the beginning of Dr. Grisham's contributions to pathology. Early in his career, he authored two seminal studies. One defined the timing and progressive zonal localization of DNA synthesis during regeneration of the rat liver. Another identified the role of the hepatic oval cell as a stem cell for hepatocytes following hepatic injuries. Later, Dr. Grisham achieved the long-term culture of epithelial cells from liver tissue. Those cells were extensively cloned and studied, leading to breakthroughs that narrowed the search for a tumor suppressor gene on human chromosome 11. This work has also had an impact on the understanding of malignant transformation and its relationship to age.

In addition to his research, teaching and administrative accomplishments, Dr. Grisham found time to be a leader of, and public advocate for, pathology. He served as President of the American Association of Pathologists (currently the ASIP), as special reviewer of the Extramural Research and Training Division of NIH, and as President of FASEB. He spent four years each as chair of Pathology Study Section A and B at NIH, and has chaired numerous Advisory Panels and Research Committees. From 1987-1991 Dr. Grisham chaired the FASEB Public Affairs Committee, where he advocated public awareness of, and education in, pathology, and worked to increase appreciation in Congress for the importance of pathological research.

Nominating Dr. Grisham for the Gold-Headed Cane, Dr. David G. Kaufman, Professor of Pathology and Laboratory Medicine at UNC, says his work "represents an outstanding record of accomplishment that has had a profound influence on the study of hepatic cell biology and hepatic carcinogenesis." Dr. Kaufman calls Dr. Grisham "one of the outstanding scientific figures in the field."

A Tennessee native, Dr. Grisham received his BA (1953, Chemistry, Cum Laude) and his M.D. (1957) from Vanderbilt University.

The Gold-Headed Cane Award is given in recognition of long-term contributions to pathology. Dr. Grisham will receive a mahogany cane topped with a 14 karat gold head and engraved band.
Harold F. Dvorak Wins Rous-Whipple Award

Former ASIP President Dr. Harold F. Dvorak, Mallinckrodt Professor of Pathology at Harvard Medical School, Chief of the Department of Pathology at Beth Israel Deaconess Medical Center, and Associate Editor of Cancer Research, is the winner of the 2002 Rous-Whipple Award. The Rous-Whipple Award is given to a pathologist over the age of 50 who has had a distinguished career in research and continues to contribute to the field.

Nominating Dr. Dvorak for this award, Dr. Stephen J. Galli, Chair of the Department of Pathology at Stanford University School of Medicine, cites his “remarkably productive career” including “major contributions in two distinct but related areas: 1. Cellular immunity and inflammation, and 2. Tumor angiogenesis and tumor stroma generation.” Dr. Galli says Dr. Dvorak “has become a (some would say the) premier investigator of the mechanisms by which malignant tumors interact with the host to create their own stroma and to maintain their own blood supply.”

In his career, Dr. Dvorak demonstrated that adult mammals can express immunological tolerance, discovered cutaneous basophil hypersensitivity, identified enhanced vascular permeability and interstitial fibrin deposition as important components of delayed hypersensitivity responses, elucidated the biological importance of extravascular fibrin in vascular hyperpermeability, made fundamental contributions to the understanding of the pathogenesis of some of the cardinal features of inflammation, and discovered perhaps the most important tumor-associated angiogenesis factor – vascular permeability factor/vascular endothelial cell growth factor (VPF/VEGF).

It was in the mid-1970s that Dr. Dvorak surged into the area for which he is best known. He developed the concept of “tumors as wounds” and proceeded to the breakthrough discovery of VPF/VEGF. Dr. Galli calls this perhaps Dr. Dvorak’s “most important individual contribution” and “a wonderful example of keen biological intuition combined with dogged determination.” This led to a series of discoveries including the development of antibodies to VPF, an understanding of the consequences of VPF/VEGF and vascular hyperpermeability for the delivery of monoclonal antibodies and other forms of macromolecular therapy, and his current focus, elucidating the mechanisms of angiogenesis induced by various cytokines and devising approaches to limit this process.

Dr. Galli writes that Dr. Dvorak has had “a remarkable and still very active career,” and has opened new fields of investigation that could lead to therapies for disorders as diverse as tumor angiogenesis and stromal generation, atherosclerosis and other forms of vascular insufficiency, and pathological changes in retinal vascularization.

Another former president of ASIP, Dr. Peter A. Ward, Professor and Chairman of the Department of Pathology at the University of Michigan, and last year’s Gold Headed Cane winner, says Dr. Dvorak “is richly deserving” of the Rous-Whipple Award for his “remarkable scientific productivity...over many years and to the present.” Dr. Robert S. Kerbel, Head of Molecular and Cellular Biology Research at Sunnybrook & Women's College Health Sciences Center in Toronto calls Dr. Dvorak “one of the world’s truly great academic/research pathologists.” Dr. Kerbel calls Dr. Dvorak’s more than 40 years of research “a truly impressive body of work.”
Morris J. Karnovsky Wins the Chugai Award

Professor Emeritus Morris J. Karnovsky of Harvard Medical School has won the 2002 Chugai Award for Meritorious Mentoring and Scholarship. ASIP's newest award will have plenty of company in Dr. Karnovsky's trophy room, alongside the 1981 Rous-Whipple Award and the 1994 Gold-Headed Cane. Among Dr. Karnovsky's other awards are the 75th Jubilee Medical Award from the University of the Witwatersrand in his home country, South Africa, and the first Earl P. Benditt Research Career Award in 1999 from the North American Vascular Biology Organization.

Dr. Karnovsky's 45-year career at Harvard includes two two-year stints as acting-Chairman of the Department of Pathology and fourteen years as chair of the Program in Cell and Developmental Biology.

Nominating Dr. Karnovsky for the Chugai Award, Patricia A. D'Amore, Ph.D., Senior Scientist and Professor of Ophthalmology (Pathology) at The Schepens Eye Research Institute in Boston, calls Dr. Karnovsky "knowledgeable, innovative and talented" and "a giant in the field of experimental pathology, and a pioneer in the field of cell biology." Dr. D'Amore lists among Dr. Karnovsky's most significant research accomplishments the introduction of the HRP (horseradish peroxidase) technique of tracing endocytic uptake from the glomerular infiltrate into cells of the proximal tubules, and development of one of the first animal models for studying graft vasculopathy. In addition, Dr. Karnovsky conducted a variety of studies of in vitro and in vivo systems to determine how heparin and endogenous heparan sulphate exert antiproliferative activity. One of Dr. Karnovsky's most important findings is the formaldehyde-glutaraldehyde fixative known as "Karnovsky's fixative" which revolutionized immunohistopathology.

In addition, and particularly relevant for the Chugai Award, Dr. Karnovsky has mentored more than 50 scientists who are today prominent in many fields across the country and around the world. One of them, who began with Dr. Karnovsky in 1978, is Dr. John Castellani, Professor of Anatomy and Cell Biology at Tufts University School of Medicine. He writes, "I can think of no other experimental pathologist who has enriched the field with so many seminal scientific contributions and accomplished trainees... To this day I am still influenced strongly by his creative, rigorous and analytical approach to analyzing complex phenomena."

Another Karnovsky trainee, Dr. Elazer R. Edelman, Professor and Director of the Harvard-MIT Biomedical Engineering Center writes, "Outside of my relationship with my parents, no experience I have had has been as influential and nurturing, and at times as intense, as the relationship I have with Morris. To this day he serves as my teacher in the truest sense of the word... There is no greater mentor than he." Dr. Edelman adds, "Those who have left Morris' laboratory have not left his spell. We all still seek Morris out like students did with Plato and Socrates, for he teaches with the purest joy, an intellectual curiosity that is infectious and a love that only comes from a father-teacher." Dr. Edelman recalls lunchtime walks with Dr. Karnovsky and still prizes the personal art work his mentor gave him, as he did to all his post-doctoral trainees.

Begun in 2000, the Chugai Award was created by the Chugai Pharmaceutical Company to honor a member of ASIP for a distinguished career in experimental and investigative pathology, demonstrated through excellence in mentoring, and sustained productivity in research. Dr. Karnovsky will receive a cash award and a plaque, will chair the Chugai Symposium for Young Investigators at the 2002 ASIP meeting, and will present the keynote lecture of that session.

Profiles in Pathology
will resume with our next issue

Want to recommend a subject?

Contact Newsletter Editor: Richard Lynch - richard-lynch@uiowa.edu
Dr. Martin M. Matzuk, Professor of Pathology at the Baylor College of Medicine, is the winner of the 2002 Pfizer Outstanding Investigator Award. This award was formerly known as the Warner-Lambert/Parke-Davis Award. It is presented annually to a young (under age 43) member of the American Society for Investigative Pathology.

Nominating Dr. Matzuk, Dr. Michael W. Lieberman, Chair of the Department of Pathology at Baylor, called him “an absolutely outstanding investigator who has developed an international reputation in reproductive biology.” Dr. Lieberman went on, “He is one of the brightest, most creative, dedicated and hard-working investigators that I have ever known. He has an absolutely unmatched level of contribution to the molecular biology of reproduction and is now recognized as one of the pre-eminent authorities in the world. He is scholarly and one of the few leaders in his field who commands universal respect.”

Dr. Matzuk received his M.D. and Ph.D. degrees from Washington University in 1989, and is already co-author of more than 130 published papers. Among them are three manuscripts published in the March 24, 1995 issue of *Nature*. For the year 2001, Dr. Matzuk has 15 manuscripts published, in press, or submitted.

His major field of study is reproduction. Dr. Matzuk’s Ph.D. thesis, “Structure-function studies of the glycoprotein hormones using mutagenesis, chimeric genes, and gene-transfer,” included the unprecedented recombinant production of all four human glycoprotein hormones. The recombinant human FSH genes used in those studies are now used in the clinical preparations of Puregon by Organon. The work led to a Dr. Philip Needleman Prize for Excellence in Pharmacology Research.

Currently, Dr. Matzuk’s research team carries three R01 NIH grants from the National Cancer Institute and National Institutes of Child Health and Human Development. The work focuses on using transgenic mice to generate models for studying oncogenesis, development, and reproduction. His team has been a leader in defining the roles of inhibins, activins, FSH, growth differential factor-9 (GDF-9) and other proteins in ovarian function. His recent studies suggest that GDF-9 may be a key target for contraceptive and *in vitro* fertilization research. In addition, Dr. Matzuk is involved in research on birth defects, male fertility, glutathione, fatty acid metabolism, and early embryonic development.

Dr. Matzuk is a highly sought-after speaker around the world and the recipient of numerous awards. Between 1998 and 2000 he was invited to speak at no fewer than 35 symposia around the world. During that period, he was the inaugural Ernst Knobil Lecturer at the University of Pittsburgh, the Bruce Stewart Memorial Award Lecturer for the American Society for Reproductive Medicine, and the winner of the HypoCCS Award from Eli Lilly. He is on the editorial boards of *Molecular Endocrinology* and *Journal of Endocrinology*, and has been asked to review manuscripts for 26 journals including *Nature, Nature Genetics*, and *Science*. The Board of Trustees of Baylor College of Medicine appointed Dr. Matzuk the first Stuart A. Wallace Professor in the Department of Pathology in 1999, and he won the Department’s O’Neal/Spjut Award in 2001.

As the Pfizer Award winner, Dr. Matzuk will receive a monetary prize and a bronze medallion. He will speak at the ASIP annual meeting on Sunday, April 21 and his paper will be published in *The American Journal of Pathology*.

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*Congratulations to the 2002 Meritorious Awards Recipients!*
Congratulations to our Student Award Winners!

The Experimental Pathologist-in-Training Award will be presented to James Wohlenschlegel of Brigham & Women's Hospital for his abstract: "Biochemical Studies of the DNA Replication Factors MCM10 and Geminin" (co-authored with Johannes Walter and Anindya Dutta). His work will be presented at the Chugai Symposium for Young Investigators, Monday, April 23, 8:30-11:30 a.m. His work will also be presented in poster format in the Cell Cycle Dysregulation in Cancer, Wednesday, April 24, 7:30 a.m.-5:00 p.m.

Alan Rowe Schenkkel, Ph.D. of Weill Medical College of Cornell University has earned the ASIP Merit Award for a Postdoctoral Fellow for his abstract, "Molecules Involved in Transendothelial Migration of Monocytes" (co-authored with William A. Muller). He will also present his work at the Chugai Symposium for Young Investigators. In addition, his work will be presented in two sessions entitled, Leukocyte-Endothelial Cell Interactions: the poster session on April 22 and the poster discussion on April 24, 8:00 - 11:00 a.m.

Sharon L. Ricketts, University of North Carolina, has won the ASIP Merit Award for a Predoctoral Student for her abstract, "Evaluation of Candidate Liver Tumor Suppressor Transcripts From Human Chromosome 11p11.2-p12 in Human Hepatocellular Carcinoma Cell Lines" (co-authored with J.C. Carter, S.S. Thongrassam, J.W. Grisham, W.B. Coleman). She will present her work in the Minisymposium: Genomic and Proteomic Approaches to Cancer Detection and Molecular Therapies on April 23, 2:00 - 5:00 p.m. in addition to the Chugai Symposium for Young Investigators.

Trainee Travel Awards:

Dita Gratzinger, Yale University School of Medicine
Abstract: "Role of Platelet-Endothelial Cell Adhesion Molecule (PECAM-1) and the Protein Tyrosine Phosphatase (PTPase) SHP2 in Endothelial Cell Motility and Morphology." Co-authors: Adeline Tucker and Joseph A Madri.
Presentations: Highlights: Graduate student posters in pathology (Saturday, April 20 5:00-7:30 p.m.); Vascular Cell and Molecular Biology (Poster, Sunday, April 21); Vascular cell and molecular biology I Poster Discussion (Tuesday, April 23, 2:00-5:00 p.m.); Career pathways in pathology for physician scientists (Saturday, April 20, 9:00 a.m.-12:00 p.m.)

Zahra Mamdouh, Ph.D., Weill Medical College of Cornell University
Presentations: Chugai Symposium for Young Investigators (Monday, April 23, 8:30-11:30 a.m.); Leukocyte-Endothelial Cell Interactions (Poster—Monday, April 22); Integrin activation and signaling during leukocyte-endothelial interactions (Tuesday, April 23, 10:10-12:10 a.m.)

Stephanie Lahousse, Brown University
Abstract: "Role of Aspartyl (asparaginyl) & β-Hydroxylase (AAH) in Neuroblastoma Cell Migration." Co-authors: Paul S. Sepe, Jack R. Wands, Suzanne M. de la Monte.
Presentations: Tumor angiogenesis, invasion and metastasis (Sunday, April 21 2:00-5:00 p.m.); Chugai Symposium for Young Investigators (Monday, April 23, 8:30-11:30 a.m.)

Fazilat Mohammed, Ontario Cancer Institute
Abstract: "Genetic Modulations of Pericellular Polysis Alters Liver Regeneration" Co-authors: Caroline Lundy, Dylan R. Edwards and Rama Khokha
Presentations: Highlights: graduate student posters in pathology (Saturday, April 20 5:00-7:30 p.m.); Hepatic progenitor cells, gene expression and regeneration (Sunday, April 21 2:00-5:00 p.m.)

(Continued on page 8)
Committee for Career Development, Women & Minorities

Nancy Thompson

Attention, MD/PhD Students!

Career Pathways in Pathology for Physician Scientists
9:00 AM, Convention Center, Room 238
Chair: D.G. Kaufman.

The discipline of Pathology is situated at the interface between clinical medicine and basic science. As such, it offers a variety of interesting careers quite suited for MD/PhD students and other medical professionals who are interested in combining their interests in medicine with cutting-edge research. A distinguished faculty will present a range of options for graduates of pathology residency programs to pursue including careers in academic medicine, private practice, and biotech/industry. In addition to this career-oriented discussion, the primary research of several present MD/PhD students will be presented.

9:00 a.m. - "Role of platelet-endothelial cell adhesion molecules (PECAM-1) and the protein tyrosine phosphatase (PTPase) SHP2 in endothelial cell motility and morphology." D. Gratzinger, A. Tucker and J.A. Madri, Yale Univ. Sch. of Med.

9:30 a.m. - "Comparative proliferation of genetically altered hepatocyte clones in transgenic mice." M.L. Figuereido and E.P. Sandgren, Univ. of Wisconsin - Madison.

10:00 a.m. - The clinician scientist training program: a proposal for a new NIH program for training medical students in clinical research. A. Mark, Univ. of Iowa Sch. of Med.

10:30 a.m. - "Discussion of careers for MD/PhD program graduates."
This prestigious honor is granted to a select number of outstanding scientists each year who have made significant contributions to science. I am sure that you join me in congratulating her.

Association for the Accreditation of Human Research Protections Programs (AAHRPP). AAHRPP is a new organization that has been formed to accredit human research protections programs. AAHRPP site visitors will examine the entire institutional approach to protecting human subjects in research studies (including use of human tissues). Reviews will include, but will not be restricted to, Institutional Review Boards. FASEB is one of the seven guarantors of AAHRPP. I am honored to have been named one of the 21 Directors of the AAHRPP Board. If you would like your institution to be accredited by AAHRPP, please e-mail me at mesobel@pathol.faseb.org and I will facilitate the arrangements.

American Board of Pathology eliminates credentialing year. After several years of controversy and discussion, the American Board of Pathology announced recently that, effective with the "entering" class of residents in July 2002, the credentialing year requirement for primary certification in pathology has been eliminated. This decision was strongly supported by the ASIP Council. ASIP is a cooperating society of the ABP.

National Board of Medical Examiners solicits new members of test committees. The National Board of Medical examiners and the Federation of State Medical Boards have established a three-step examination pathway to medical licensure in the United States. Examination materials of the United States Medical Licensing Examination (USMLE) are prepared by test material development committees composed of senior faculty members, teachers, investigators, and clinicians. ASIP has been solicited by the National Board of Medical Examiners to identify qualified individuals who might be interested in serving on the test committees. Please submit your name and a curriculum vitae to me (mesobel@pathol.faseb.org) if you would like to participate. It is vitally important that investigative pathologists play a role in this important endeavor.
Milestones . . .

in Investigative Pathology

Multipotentiality of Single Embryonal Carcinoma Cells
L.J. Kleinsmith and G. B. Pierce
Cancer Research 24:1544-1551, 1964

Differentiation of Malignant to Benign Cells
G. Barry Pierce and Carol Wallace
Cancer Research 31:127-134, 1971

In ground-breaking research published in 1964, Barry Pierce, then a faculty member in the Department of Pathology at the University of Michigan, and L.J. Kleinsmith, a student fellow in his laboratory, demonstrated that single undifferentiated cells isolated from a murine teratocarcinoma, when transferred into normal mice, gave rise to malignant teratocarcinomas that contained differentiated tissues representative of all three major germ cell layers (1). When examined by light microscopy, the teratocarcinomas consisted of foci of undifferentiated malignant cells interspersed with disorganized arrays of adult somatic tissues representative of endoderm, mesoderm and ectoderm in various stages of differentiation. The differentiated tissues included neural, gastrointestinal, skin, muscle, bone, cartilage, marrow, notochord and yolk sac. By morphological criteria, the differentiated somatic tissues in the teratocarcinomas were considered to be non-malignant. Pierce concluded that these murine teratocarcinomas were malignant tumors that consisted of a pool of replicating, multipotential tumor stem cells that gave rise to non-replicating differentiated cells whose organization mimicked normal tissue development. Based on these findings and on histological features routinely observed in many human and experimental cancers, Pierce hypothesized that most cancers contained a pool of malignant stem cells, some of whose progeny differentiated into non-malignant, non-mitotic tumor cells. In effect, Pierce was proposing that a malignant cell could become benign. This concept challenged the dogma "once a cancer cell, always a cancer cell", and Pierce found little enthusiasm for his concept among his cancer researchers. At the time the studies were published it was generally believed by oncologists that teratocarcinomas were not representative of other cancers and, as interesting as these tumors might be, they were oddities and not relevant to cancer in general. There were several unique characteristics of murine teratocarcinomas that fostered this skepticism.

Spontaneous testicular teratocarcinomas occurred only in the 129 strain of mice, these tumors developed in the gonad during fetal life, and it was possible to experimentally induce teratocarcinomas by injecting normal primordial stem cells from blastocysts of 129 strain mice into the testis of adult mice. Perhaps also operating in the background was the longstanding speculation by some scholars that teratocarcinomas actually reflected aberrant pathogenetic embryogenesis, a concept that is likely related to their designation by some as embryomas.

Pierce's concept linking differentiation and cancer was supported by the startling finding of Leroy Stevens (2) that the normal pleuripotent embryonic stem cells in a murine blastocyst, cells which if left in the blastocyst would develop into a mouse, developed into a teratoma or teratocarcinoma if they were injected into an adult testis. This finding appeared to complete a transformation circuit that linked tumorigenesis, embryogenesis and differentiation because, as already mentioned, Pierce had shown that cancer cells could give rise to normal differentiated adult cells. As a diagnostic pathologist, Pierce was aware of rare clinical instances in which highly malignant cancer cells in a patient appeared to spontaneously differentiate and the tumor regressed. When such cases were reported in the literature they were considered medical curiosities for which there was no explanation. An example is the report in The American Journal of Pathology in 1927 by Harvey Cushing and S.B. Wolbach that described a patient with a neuroblastoma in which the malignant neuroblasts spontaneously differentiated into mature ganglion cells to form a benign ganglionneuroma. Convinced of the merit of his concept, and having moved to the Department of Pathology at the University of Colorado, Pierce expanded the scope of his research to include investigations of other cancers besides the murine teratocarcinomas. In a milestone paper published in Cancer Research in 1971 (3), Pierce and Wallace used a rat squamous cell carcinoma to test the hypothesis that the cancer contained a pool of proliferating stem cells and a pool of non-proliferating, post-mitotic differentiated cells. Microscopically this cancer consisted of foci of heavily keratinized flattened epithelial cells designated as "keratin pearls" that were reminiscent of the cells in the upper layer of normal skin. These foci were separated from each other by areas of undifferentiated cancer
cells, many of which contained mitotic figures. When rats bearing this cancer were injected with tritiated thymidine and the tumors examined at various time intervals afterwards using light and electron microscopic autoradiography, it was observed that two hours after injection the thymidine label was present almost exclusively in the undifferentiated cells of the tumor. During the 96-hour period of observation there was a progressive increase in the number of labeled cells that were present in the highly differentiated areas of the tumor. The investigators concluded that the cells in the keratin pearls were not synthesizing DNA and that the growth of the pearls depended on incorporation of undifferentiated cancer cells into the pearls with subsequent differentiation. The electron microscopic analyses expanded and confirmed these findings. The initial thymidine incorporation occurred in ultrastructurally undifferentiated cancer cells and later the label appeared in tumor cells that had desmosomes and other features of the cells of the normal stratum spinosum of skin. At even later times the label appeared in tumor cells that had features of granular layer cells of normal skin. In addition to these morphological findings, Pierce and Wallace microdissected undifferentiated areas and differentiated areas from the cancer and transplanted these into normal rats. Squamous cell carcinomas developed in about a third of the rats injected with undifferentiated cells, but in none of the rats injected with differentiated cells. In later studies, Pierce and colleagues investigated chondrosarcomas, and adenocarcinomas of the breast and colon and made comparable findings and conclusions.

In addition to the fundamental knowledge that these studies contributed to understanding the role of differentiation in cancer, they established the foundation of a novel strategy for treating cancers based on inducing the differentiation of malignant cells to a post-mitotic state.

The investigations of Barry Pierce and Leroy Stevens in the murine teratocarcinoma model facilitated the discoveries by Brinster (4) and by Illmensee and Mintz (5) that the malignant stem cells of the 129 strain teratocarcinomas, when injected into normal blastocysts from other strains of mice, produced normal offspring that were genetic mosaics. Thus, the same tumor stem cells that produced teratocarcinomas when injected into adult testes, differentiated into the full range of normal adult tissues in the mosaic mice that were produced when injected into normal blastocysts. These findings eventually led to the development of 129 strain teratocarcinoma stem cells as tools for constructing transgenic (6) and gene knockout mice. While considered by many in the beginning as non-relevant oddities, teratocarcinomas have yielded an abundance of fundamental knowledge about developmental biology and the pathobiology of cancer, and have contributed to the development of some of the most powerful genetic tools currently in use.


Congratulations to Frances A. Pitlick, Ph.D.

Named a Fellow of the American Association for the Advancement of Science 2002
News and Notes

Welcome to the following NEW Members:

Jean Benard, PhD
Institute Gustave Roussy

Juan F. Garcia, MD
Centro Nacional de Investigaciones Oncologicas

Shuji Ogino, MD, PhD
Univ of Pennsylvania Med Ctr

Robert Bowser, PhD
University of Pittsburgh School of Medicine

David A. Gerber, MD
Univ of North Carolina School of Medicine

Tim D. Oury, MD, PhD
University of Pittsburgh

John Castellot, PhD
Tufts University School of Medicine

Tara Haas, PhD
York University

Joseph L. Sailors, MD
University of Texas Southwestern Medical Center

John C. Cheville, MD
Mayo Clinic

Andrea Herrera-Gayol, MD, PhD, Msc
Bioniche Therapeutics

Carel J.M. van Noesel, MD, PhD
Academic Medical Center of Amsterdam

Charleen T. Chu, MD, PhD
University of Pittsburgh

Eric Hsi, MD
Cleveland Clinic Foundation

James Versalovic, MD, PhD
Texas Children’s Hospital

Brenda Lynn Coomber, PhD
University of Guelph

James M. Holland, PhD DVM
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Calendar of Events

National Hispanic Medical Association
Sixth Annual Conference - "Healthy Hispanic Communities"
March 22-24, 2002; Hyatt Regency Capital Hill Hotel, Washington, DC
Contact: NHMA Conference Committee, 1411 K St., NW Ste 200, Washington, DC 20005
Phone: (202) 628-5895, Fax: (202) 628-5898
Email: nhma@nhmad.org

NAVBO Annual Meeting/Third Conference on Atherosclerosis, Thrombosis and Vascular Biology
April 5-8, 2002; Grand America Hotel, Salt Lake City
Contact: Bernadette Engiert
(301) 634-7938
Fax: (301) 571-1879
Email: bernadette@navbo.org

ASIP Annual Meeting at Experimental Biology 2002
April 20-24, 2002; E.N. Morial Convention Center in New Orleans
Contact: Tara Zeitner
(301) 634-7130
Fax: (301) 571-1879
Email: tzeitner@pathol.faseb.org

International Society for Analytical Cytology: XXI International Congress
May 4-9, 2002; Town and Country Resort & Convention Center, San Diego, CA
Contact: ISAC Headquarters, 60 Revere Drive, Suite 500, Northbrook, IL 60062 USA
Phone: 847-205-4722, Fax: 847-480-9282
http://www.isac-net.org or E-mail: isac@isac-net.org

(Continued on page 15)
PROTEOMICS 2002: Delivering New Routes to Drug Discovery
(Uncovering Drugable Targets through Analysis and Integration of Protein Science and Technology)
May 6-9, 2002; Philadelphia, PA, U.S.A.
E-Mail:
K-5-728210-4473043-2-261-US1-407B399E@xmr3.com

6th Joint Meeting of The Histochemical Society & Japan Society of Histochemistry & Cytochemistry
July 18-21, 2002; University of Washington, Seattle.
Contact Information: William Stahl, wilstahl@u.washington.edu, Fax: 206-764-2164
Meeting Info: www.histochemicalsociety.org

7th International Symposium on Dendritic Cells
Sept. 19-24, 2002; Bamberg - Germany
Contact: http://www.dc2002.de/

The 9th International Congress on TNF-Related Cytokines Conference
October 30 - November 2, 2002; Hyatt Regency on the San Diego Bay, San Diego, CA
E-Mail: meetings@fliai.org

Association for Molecular Pathology Annual Meeting
November 14-17, 2002; Adam's Mark Hotel, Dallas, TX
Contact: Maricel Herrera, Meetings Manager
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