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George R. Harrison Spectroscopy Laboratory

Massachusetts Institute of Technology

Research Report:

Detecting cervical cancer early with quantitative spectroscopic imaging

Condon Lau, G. R. Harrison Spectroscopy Laboratory & Dept. of Mechanical Engineering

Early detection is key to reducing cancer related mortality. Treatment procedures are simpler and more effective if cancer is detected at a pre-invasive stage such as dysplasia. In the case of cervical cancer, the American College of Obstetrics and Gynecologists recommends that patients with high-grade squamous intraepithelial lesions (HSIL) receive treatment, typically with the Loop Electrosurgical Excision Procedure (LEEP), to prevent further disease progression. Therefore, it is critical to identify tissue sites with HSIL.

The current practice in cervical cancer screening involves a Papanicolaou smear test (Pap smear). If the Pap smear result is positive, a visual examination of the cervix under magnification (colposcopy) is conducted to guide biopsy, the histopathological examination of which serves as the final diagnosis. Colposcopy and histopathological evaluation, even when conducted by experts, are subject to significant diagnostic variability. A technology that can reduce diagnostic variability by using a quantitative diagnostic scheme while maintaining the ability of colposcopy to examine the entire cervix would present a significant

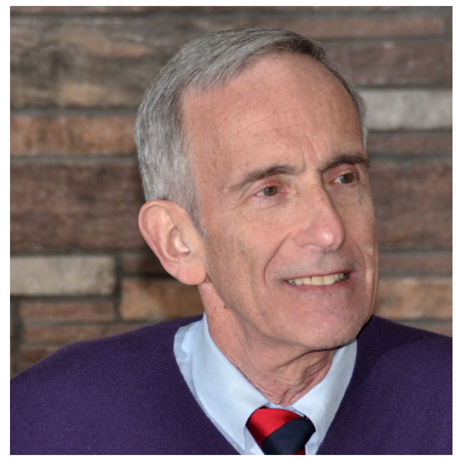
Lau, continues on page 3

Michael Feld to present 2009 Lord Lecture

On April 28, Professor Michael S. Feld will present the 2009 Richard C. Lord Lecture, "Five easy physics pieces: from basic laser science to biomedicine." Feld was born in New York City 1n 1940. He earned all of his degrees at MIT and, following graduation, went up the academic ladder to become Professor of Physics. Today he directs both MIT's George R. Harrison Spectroscopy Laboratory and its Laser Biomedical Research Center. He has received numerous awards, including, most recently, the 2008 Meggers Award of the Optical Society of America, "for major contributions to the foundations of laser spectroscopy, and for pioneering developments in the application of spectroscopy to biomedicine."

Educated as a physicist, Feld did his Ph.D. research in laser spectroscopy. His studies of fundamental interactions of light with matter led, in 1973, to the first experimental observation of superradiance---the collective spontaneous emission of an assembly of excited atoms. It was "a very exciting fundamental advance."

Feld has long been interested in applying science to human needs. In the mid-1980's he began to shift his research to biomedical optics. Much of his work in this field employs physical models of light interacting with biological molecules and tissues.



He seeks to extract information by using such models rather than statistical methods. His research style is to attack problems not by an empirical approach but by exploring and understanding the relevant basic science. "This way of working on problems has been successful for me, though it sometimes goes against the standard approach of biomedical research. I find it gratifying to see former students and their students, and, others adopting this style today."

Feld's students are widely placed in industry and universities in the US and abroad. His students and postdocs have faculty positions at research universities including Duke, Caltech, Northwestern, University of Texas at Austin, Rice, Seoul National University, Tufts, and King Fahd University in Saudi Arabia.

In 1991 Feld pioneered the use of Raman spectroscopy for analysis of biological tissue. This work led to its clinical use in 2006 to diagnose atherosclerosis and breast cancer. In 1998 Feld's group introduced the use of light-scattering spectroscopy to characterize pre-cancerous changes in cells, and in 2001 they combined fluorescence and

Feld, continues on page 2

Also in this issue

Feld, continued from page 1

reflectance spectroscopy to diagnose disease. To make these techniques useful in clinical applications required significant development of novel instruments and spectral probes.

A good example is Raman spectroscopy. This technique was first demonstrated in 1928 by C.V. Raman and has been used widely in industry for decades but never effectively for spectroscopy of biomedical tissue. It was too difficult to implement. "Many difficulties had to be overcome," says Feld. "For one thing, Raman signals were thought to be too weak to be observed at the excitation levels at which you could safely irradiate biological tissue. For another, collection times were much too long for clinical use." In Feld's first experiments with tissue samples it took 30 minutes to collect the Raman spectra, and there was so much background fluorescence that the Raman signals were obscured. But when Feld looked closely at the data, he could recognize definite signals. These results encouraged him to persevere, even when an NIH evaluation committee of Raman experts advised him to terminate the project. Feld recalls, "The committee also thought that even if the Raman signals could be discerned, you'd see nothing but 'Raman grass', weak Raman signals due to the overlap of spectra from numerous molecules in the tissue." Feld managed to convince the committee to let him proceed, and his work laid the foundation for the field of Raman spectral diagnosis of disease; it also encouraged development of CARS and SERS, two forms of nonlinear Raman spectroscopy..

As Feld's Raman research progressed, he and his colleagues realized that data could be collected much more rapidly with CCD detection than with the then standard Fourier transform technology. "We realized," he said, "that CCD detection could collect data at the shot noise level." This was a key insight. Combining CCD detection with other advances, Feld and his team reduced the time for data collection from 30 minutes to one second or less – fast enough for use in clinical situations. Finally, to make the technique useful in clinical situations, they developed a unique type of Raman spectral probe that overcame the large Raman background from the quartz in 3 meters of optical fiber. "The fun of this," he says, "is that we took nothing and made it into something—something that is useful and makes sense."

The fun of this is that we took nothing and made it into something —something useful that makes sense.

"All of my role models were in fundamental physical science, not biomedical science—and that has given me a different perspective," says Feld. "It has sometimes put me at odds with the conventional wisdom of biomedical science, but that has been healthy."

As role models who strongly influenced him, Feld mentions three people in particular—his Ph.D. thesis advisor, Ali Javan, inventor of the helium-neon laser, with whom he worked on problems of fundamental physics; Charles Townes, head of the laser group at MIT, who won the Nobel prize for inventing the maser, the precursor of the laser; and the inspiring Japanese physicist, Koichi Shimoda, with whom Feld worked at MIT in his first year as a grad student.

But even earlier, Feld had found an important mentor in his Uncle George, an electrical engineer who worked in the field of radio and television. "He always talked to me about technical things, and he used his textbooks from City College of New York to introduce me to math concepts years before I learned them in school," says Feld. "He made a huge difference for me, as my father had died at a young age."

Feld feels that he is "paying forward" his uncle's gift of encouragement. One way he does this is by acting on his deeply held beliefs about encouraging under-represented minorities in science. He has graduated five black Ph.D.'s. Feld's first African American Ph.D. student was Ron McNair, who went on to become the first black astronaut scientist and tragically died in the 1986 Challenger accident. "My goals in this area are generally modest," says Feld. "I know I can't change the world, but I feel I can change my own institution." He has worked to effect that change by chairing and co-chairing several committees, including MIT's Martin Luther King committee. His committee developed the Martin Luther King Visiting Professor program, in which up to a dozen minority professors each year come to MIT for 1–2 year visits. More than 60 MLK visiting professors have come to MIT through this program. Feld views this as a temporary measure to fill the current void of the presence of under-represented minority faculty members at MIT. These MLK visiting professors have no obligation to work on minority issues when they come; rather they engage in scholarship and teaching as do any other MIT professors, and thus serve an important function as role models—for both the minority and majority students. "This committee, and the earlier Equal Opportunity Committee, which I also chaired, has played an activist role," says Feld. Each of the four MIT presidents with whom I've worked has warmly welcomed my initiatives in this area." Feld has won three MIT awards for his activist role, including the 2008 Martin Luther King Jr. Achievement Award, given by the MIT Campus Committee on Race and Diversity to honor his "extensive and persistent efforts to make MIT a more open, more welcoming and more harmonious workplace."

For all of Feld's scientific and social accomplishments, the effort that got him the most attention was his lecture-demonstrations on the physics of karate. Ron

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GEORGE R. HARRISON SPECTROSCOPY LABORATORY
Director: Michael S. Feld
Assoc. Director for Scientific Coordination: Robert W. Field
Associate Director: Kamran Badizadegan

The Spectroscopy Laboratory houses two laser research resource facilities. The MIT Laser Research Facility provides shared facilities for core researchers to carry out basic laser research in the physical sciences. The MIT Laser Biomedical Research Center, a National Institutes of Health Biomedical Research Technology Center, is a resource center for laser biomedical studies. The LBRC supports core and collaborative research in technological research and development. In addition, it provides advanced laser instrumentation, along with technical and scientific support, free of charge to university, industrial, and medical researchers for publishable research projects. Call or write for further information or to receive our mailings.
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Feld, continued from page 2

McNair had introduced him to karate and invited him and his 8 year old twin sons to join a karate club McNair had started at his church near MIT. As Feld recalls, "Then someone at MIT called to invite me to give a Christmas lecture on the physics of karate. 'Sure, I said. As soon as I got off the phone, I was gripped with terror—I realized that I had just agreed to give a lecture on a topic I knew nothing about! Motivated by fear, I began a crash research program, including taking strobe movies of karate strikes. Fortunately, we managed to get our act together and did well, and so we were invited to give presentations at two annual meetings of the American Association for the Advancement of Science, the first in Washington DC and the second the following year in Denver. In the course of our research we wrote a 1979 *Scientific American* article, 'The Physics of Karate.' There was worldwide press interest in all this."

It's not limits of technology that hold us back; it's limits of peoples thinking.

Feld says that people often ask him what technological limitations hold back advances in the field of biomedical optics. "This question misses the point," he says. "It's not limits of technology that hold us back, but limits in people's thinking. We need to better understand basic science. A case in point: Today, one of the most important problems in biological tissue imaging is our inability to see deeply into tissue. People have been misled by diffusion theory to think that light cannot propagate through turbid tissue. Light propagation through tissue should be viewed as a wave phenomenon rather than a succession of bullet-like photons." Feld believes that E-field based wave techniques can overcome the current limitations. "CT with visible light may thus be possible!" he says.

Feld symposium June 27, 2009

Plans are being made for a symposium to honor the work and achievements of Michael Feld. The event will be held on the MIT campus in the Stata Center on June 27. The symposium will feature talks by friends, colleagues, and former students and post-doctoral associates.

Ramachandra Dasari is the local coordinator. You can get in touch with him at rrdasari@mit.edu. More details will be coming soon. Keep the date open.

Feld Fest

Lau, continued from page 1

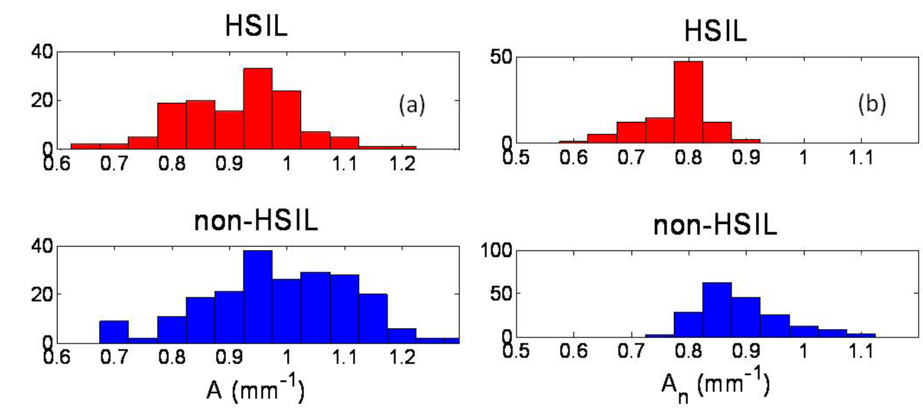

Fig. 1. Histograms of regular A (a) and normalized A (b) spectroscopy parameters measured from HSIL and non-HSIL sites in the cervical transformation zone.

clinical advancement. Furthermore, if this technology is inexpensive and easy to use, it could improve cervical cancer prevention in developing countries where medical infrastructure is lacking compared to developed countries.

Recent research in the Spectroscopy Laboratory has focused on extending quantitative spectroscopy from contact-probe[1,2] to wide-area quantitative spectroscopic imaging (QSI) for detection of HSIL in the cervix. In this project, we train and evaluate QSI's ability to quantitatively detect HSIL in patients referred for LEEP. Specifically, we investigate if per-patient normalization improves spectroscopic contrast between HSIL and non-HSIL (less severe disease or normal tissue) by possibly reducing normal inter-patient variability. Using the measured spectroscopy changes, we train QSI to produce diagnostic maps showing the locations of HSIL. These maps are compared to pathology to determine the ability of QSI to detect HSIL.

We had previously developed a QSI system for early cancer detection with reflectance and fluorescence spectroscopy capabilities.[3] In brief, QSI illuminates a 1-mm diameter region of the cervix with visible and 337-nm light and collects reflectance and fluorescence spectra returning from a concentric 2-mm diameter region over the visible wavelengths. The measured spectra are fit to light propagation and fluorescence models to extract the amounts of native scatterers, absorbers, and fluorophores present. Once the measurement is complete for one region, raster scanning is used to interrogate another 1-mm diameter region until a 2.1-cm by 2.1-cm area is examined. This method is free of cross-talk.The total acquisition time is 80 seconds. After the spectra are processed (offline), we obtain maps of six spectroscopy parameters: A (reduced scattering coefficient in mm^{-1} at 700 nm); B (wavelength dependence of reduced scattering coefficient); [Hb] (total hemoglobin concentration in mg/mL); α (fraction of hemoglobin carrying oxygen); Coll (collagen concentration in A.U.); and NADH (NADH concentration in A.U.). These 21 x 21 pixel maps show the value of a spectroscopy parameter at multiple points on the cervix. Per-patient normalized parameter maps (A_n, B_n, $[Hb]_n$, α_n, $Coll_n$, and $NADH_n$) are subsequently obtained by dividing every pixel of a regular parameter map by the average value of parameters measured from the normal squamous epithelium of the same patient.

The QSI system is used to examine 30 LEEP patients recruited for the study. During a measurement, 5% acetic acid is first applied to the cervix. The QSI system is positioned at the correct orientation and distance (22.5 cm) from the patient and data

Lau continues on p. 6

Seminar on

MODERN OPTICS AND SPECTROSCOPY

Spring 2009

March 3 Ji Ung Lee, University of Albany
Optical spectroscopy of individual carbon nanotube p-n diodes

March 10 Roderic Pettigrew, National Institutes of Health
The emerging field of molecular theranostics

March 17 Laura Kaufman, Columbia University
Role of the probe in single-molecule experiments on supercooled liquids

March 24 Condon Lau, MIT
Detecting cervical dysplasia with quantitative spectroscopic imaging

March 31 Barry Masters, MIT
C. V. Raman: discovery of the effect and attribution of credit

April 7 Gautham Nair, MIT
Many-body processes in colloidal semiconductor nanocrystals

April 14 David Blank, University of Minnesota
Thiophene photophysics: oligomers, dendrimers, and polymers

April 21 Hootan Farhat, MIT
Electron-phonon interactions in carbon nanotubes studied by Raman spectroscopy

April 28 ***18th Annual Richard C. Lord Lecture:***
Michael Feld, MIT
Five easy physics pieces: from basic laser science to biomedicine

May 5 Daniel Nocera, MIT
Sunlight in a drop of water

Tuesdays, 12:00 - 1:00 p.m., Grier Room (34-401)

Refreshments served following the seminar

Sponsored by the George R. Harrison Spectroscopy Laboratory, the Department of Electrical Engineering and Computer Science, and the School of Science, MIT.

Lester Wolfe Workshop in Laser Biomedicine

Stem Cells See the Light

Stem cell research has become a hot topic in biomedical research for several reasons, including: a change in federal funding policy, their enormous potential in regenerative medicine, fundamental discoveries in developmental biology, and their role in cancer progression and metastasis. This workshop will highlight the role that biomedical optics can play in imaging, tracking, measuring and destroying various classes of stem cell.

Bone Marrow Hematopoietic Stem and Progenitor Cells Go Live: Tracking HSPC/niche Interactions at Single Cell Resolution
***Cristina Lo Celso**, PhD, Instructor in Medicine, Massachusetts General Hospital (MGH) Center for Regenerative Medicine*

Therapeutic and Diagnostic Stem Cells for Cancer Therapy
***Khalid Shah**, PhD, Neurobiologist, Assistant Professor, Harvard Medical School, Laboratory for Molecular Neurosciences and Imaging, MGH Center for Molecular Imaging Research*

Cancer Stem Cells Evade Photodynamic Therapy
***Janet Morgan**, PhD, Department of Dermatology, Roswell Park Cancer Institute, Buffalo, NY*

Tuesday, April 21, 2009
4:00 - 6:00 PM
Massachusetts General Hospital
Richard B. Simches Research Center, Room 3110
185 Cambridge Street, Boston
(located in Charles River Plaza next to Whole Foods Market and CVS)

Sponsored by the G. R. Harrison Spectroscopy Laboratory, MIT; MGH Wellman Center for Photomedicine; Harvard—MIT Division of Health Sciences and Technology; and CIMIT (Center for Integration of Medicine and Innovative Technology).

Lau, continued from pg.3

Fig. 2. The red squares are pixels identified by QSI to have HSIL. All other pixels are either non-HSIL or have no spectroscopy data due to specular reflection or foreign objects. The white line is the disease map showing the location of HSIL.

are taken. After the QSI scan, the patient proceeds with the scheduled LEEP. The resulting specimen is independently evaluated by three pathologists, the gold standard of this study, to determine the location of any HSIL. These are charted on a disease map.

Figure 1 plots histograms of A and A_n measured at pixels corresponding to HSIL and non-HSIL sites. We see that the difference between HSIL and non-HSIL is greater when normalized parameters are used. Trying all combinations of regular and normalized parameters, we find A_n alone best distinguishes HSIL from non-HSIL, and the addition of other parameters is insignificant. HSIL can be distinguished from non-HSIL with 89% sensitivity and 83% specificity (leave-one-out cross validated) if a threshold of $A_n = 0.83$ is applied.

HSIL regions on a cervix are primarily identified by thresholding the A_n parameter map. Figure 2 shows a region identified by QSI as having HSIL, which is in good agreement with the disease map. The results show QSI can quantitatively and accurately map HSIL on the cervix. As a result, it has strong potential to improve upon the current cervical cancer screening and diagnosis procedures. Furthermore, the fact that only A_n, the normalized reduced scattering coefficient at 700 nm, is needed to detect HSIL suggests that a significantly simpler and less expensive instrument based on a red laser pointer and an optical power meter will suffice. This could enable QSI to improve early cancer detection in developing countries where cervical cancer is a significant health problem and where conventional methods of screening are impractical.

To follow up on these promising results, further studies will be conducted to validate these findings and test the effectiveness of a simplified instrument in clinics here in the United States and in low resource countries.

[1] *Tunnell et al., "Instrumentation for Multi-modal Spectroscopic Diagnosis of Epithelial Dysplasia," TCRT, Vol. 2, 2003.*

[2] *Georgakoudi et al., "Trimodal spectroscopy for the detection and characterization of cervical precancers in vivo," AJOG, Vol. 186, 2002.*

[3] *C.C. Yu et al., "Quantitative spectroscopic imaging for non-invasive early cancer detection," Optics Express, Vol. 16, 2008.*

Badizadegan new Spec Lab Associate Director

On March 23rd Dr. Kamran Badizadegan became Associate Director of the Harrison Spectroscopy Laboratory where he has been Principal Research Scientist since 1997. In appointing him Associate Director, laboratory Director Michael Feld noted that "Kamran's breadth of experience in basic science, engineering, and medicine has been an invaluable asset to the Spectroscopy Laboratory and the LBRC."

Badizadegan adds his new duties as Associate Director, to his work as Associate Professor of Pathology at Harvard Medical School, head of pediatric pathology at MGH, and as a faculty member of the Harvard-MIT Division of Health Sciences and Technology. He has a BS in Chemical Engineering from MIT and an MD from the Harvard-MIT Division of Health Sciences and Technology.

Badizadegan replaces Dr. Ramachandra Dasari as Associate Director. Dasari will continue to be the chief fiscal officer of the Spectroscopy Laboratory and leader of the vibrational spectroscopy group. "I am pleased to see Kamran take on more leadership within the laboratory, and I am happy to help him any way I can to smooth his transition into his new position."

Dr. Kamran Badizadegan

Dresselhaus wins Vannevar Bush award

Adapted from Patrick Gillooley, MIT News Office, March 9, 2009

The National Science Board has named Institute Professor Mildred Dresselhaus as the 2009 recipient of the Vannevar Bush award, which annually recognizes an individual who, through public service activities in science and technology, has made an outstanding "contribution toward the welfare of mankind and the nation."

The award, established in 1980, commemorates Bush's unique contributions to public service; it also has a unique tie-in with MIT, as Bush was an influential professor, Vice President and Dean of Engineering at the Institute, and later an advisor to several U.S. presidents.

Dresselhaus said the award was a "total surprise," but noted that it not only honors her work, but that of all MIT faculty.

"Ever since I've been here—and I've been here for my whole career—we've been strongly influenced by service not only to MIT but the whole country; it's part of what MIT stands for, we're indoctrinated with this, and we feel good about this," she said. "It's an honor to receive this award … Vannevar Bush is somebody really special at MIT, and someone special in the nation."

A native of the Bronx, Dresselhaus received her PhD from the University of Chicago, and began her MIT career at the Lincoln Laboratory studying superconductivity; she later switched to magneto-optics, carrying out a series of experiments that led to a fundamental understanding of the electronic structure of semi-metals, especially graphite.

Among the criteria, used select award candidates are distinguished public service activities in science and technology; pioneering exploration, charting and settling new frontiers in science, technology, education and public service; and demonstration of leadership and creativity that have helped to shape the history of advancements in science, technology and education in the United States.

Other members of the MIT community who have won the award include former presidents Jerome B. Wiesner and James R. Killian Jr..

Dresselhaus will receive the Vannevar Bush medal at a black-tie dinner and ceremony on May 13, at the U.S. Department of State in Washington.

Wilk, continued from Back Page

eudiometer, observed the electrically-induced fluorescence, and wondered if it might be related to the well-known phosphorescence that resulted from heating.

There certainly was some connection, since exposure to the electrical spark revived the glow, and the glow got brighter the more the crystal was exposed to the sparks. But the color of the glow from heating was green, while the glow caused by heating changed from blue-green to pink to white.

Johann Wilhelm Ritter (1776-1810)

Different specimens, obtained from different areas, glowed with different colors when heated or treated with sparks. But again, the colors generally weren't the same. Pearsall dutifully recorded them all, describing the colors. Had spectroscopy been invented, he would undoubtedly have recorded the wavelengths.

Pearsall found that colorless fluorite, which did not glow at all when heated, could be given the ability to glow if exposed to several sparks from the spark container. "In this case, the property was conferred upon a substance which probably never possessed it previously," Pearsall wrote.

He found that exposing the fluorite to sunlight did *not* cause the fluorite to glow when subsequently heated, even when exposed as long as eight months.

So what was happening? Pearsall lacked many pieces of the puzzle and much of the equipment that might have helped. One thing he was undoubtedly doing was exposing the crystals to bursts of ultraviolet light. Passage of electricity through the air breaks down the gases, and these rapidly recombine with emission of photons. The main constituent of air is nitrogen, and the characteristic bluish color of sparks, be they static electricity sparks made by scuffing your feet on the rug and touching a doorknob, or by using a Tesla coil, or by a bolt of lightning, is mainly due to the recombination of ionized nitrogen. This produces a series of peaks centered around 360 nm, spaced about 20 nm apart. These long wavelength UV peaks are sufficiently energetic to induce many effects.

Pearsall later tried other substances – crystals such as apatite, lime carbonate, cuttlefish "bones", mother of pearl, scallop shells, oyster shells, marble. You get the feeling he was simply throwing whatever he had at hand into the *eudiometer* and seeing what happened.

But he kept coming back to fluorite, noting the changes in different-colored fluorite from all over the world. Eventually, he found something very interesting. He could produce color in previously uncolored fluorite by exposing it to enough sparks. "…there appears every reason to conclude that the colour induced is the effect of structure alone," he wrote (and not of impurities in the crystal).

Pearsall was correct —ultraviolet light (and higher energy photons) are well-known for their ability to produce defects, and in particular the defects called color centers that can have absorption bands in the visible. Some of them act very much like square-well potentials with trapped electrons, and they really are structures without impurities that produce color. Crystals with colors due to defect centers have long been known – smoky quartz is one, and the blue potassium chloride of Northern Africa described by Herodotus is another, but as far as I am aware Thomas Pearsall was the first to create such color centers by deliberate irradiation of colorless crystals by exposure to what was (although he did not know it) ultraviolet radiation.

References

Thomas J. Pearsall, *The Journal of the Royal Society of Great Britain* 1830, pp.77-83; and 1831, pp. 267-281

Lewis R. Koller, *Ultraviolet Radiation,* 2nd ed., Wiley, 1965; pp. 1-5

James A.R. Samson, *Techniques of Vacuum Ultraviolet Spectroscopy,* Wiley, 1967; pp. 1-4

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James Burke, *Connections*, Simon & Schuster, 1978; pp. 177-179

Karl Przibram, *Irradiation Colours and Luminescence*, Pergamon Press 1956

Awards, awards—congratulations!

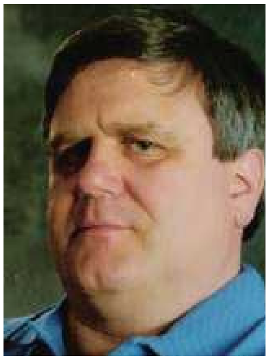
Dan Nocera was recently honored by the American Chemical Society for his work in the field of chemistry. Nocera, the Henry Dreyfus Professor of Energy and professor of chemistry, won the ACS Award in Inorganic Chemistry, which recognizes and encourages fundamental research in the field of inorganic chemistry.

Alexander van Oudenaarden is among 16 scientists nationwide to receive the 2008 Pioneer Awards from the National Institutes of Health for their "pioneering -- and possibly transforming -- approaches to major challenges in biomedical and behavioral research." The Pioneer Award program is designed to support individual scientists of exceptional creativity at any career level. Van Oudenaarden, the W.M. Keck Career Development Professor in Biomedical Engineering and a Professor of Physics, will explore the role of random variables in gene expression during cellular development and specialization.

Jing Kong is among the latest recipients of a National Science Foundation CAREER award. Prof. Kong, the ITT Career Development Assistant Professor of Electrical Engineering, received her B.S. degree in chemistry from Peking University in 1997 and her Ph.D. in chemistry from Stanford University in 2002, when she joined MIT. She uses the facilities of the G. R. Harrison Spectroscopy Laboratory to characterize the helicity of carbon nanotubes.

A Bit of the Old Ultraviolets

Stephen R. Wilk



The discovery of ultraviolet light is attributed to J.W. Ritter in 1801. He was following in the footsteps of John Herschel, who had noted that thermometer placed in the region of a solar spectrum beyond the red caused the mercury to rise, thereby proving the existence of *infra-red* rays. Ritter looked for responses at the opposite end of the scale, beyond the violet. Nothing had resulted from placing a thermometer here, but Ritter placed paper that had been soaked in silver chloride there. It had been known for almost two centuries that silver chloride turned black on exposure to light, so he clearly hoped to be able to detect any unseen light with this aid. He did.

Three years later Thomas Young, that indefatigable searcher for evidence of the wave nature of light, proved that the unseen rays would interfere with each other, recording the interference pattern on silver chloride paper, and thereby proving that ultraviolet was, indeed, a wave phenomenon.

In 1814 Joseph Fraunhofer began his work on the solar spectrum. He observed the characteristic dark lines caused by absorption against the blackbody background, named them, and measured their wavelengths. They extended down to just below 300 nm. Beyond this point his glass prisms absorbed the ultraviolet radiation, although this was not known for many years. In 1842 George Gabriel Stokes replaced the glass prism with a quartz one and extended the range to 183 nm. About the same time, John William Draper took a daguerreotype of the solar spectrum, and Leopoldo Nobili and Macedonio Melloni developed the thermopile to record unseen wavelengths, and Alexandre-Edmond Becquerel photographed the UV. And so studies of the wavelengths of the light began.

But the only good source of UV light was the sun, and nobody was using that for investigative work. Mercury discharge lamps didn't become available until the end of the nineteenth century, and there were no powerful UV sources until the early twentieth century. So studies on the effects of ultraviolet light were comparative latecomers.

Or were they? While researching my thesis, I stumbled across a series of experiments involving ultraviolet irradiation of materials that were carried out twelve years before that magic year 1842. This UV irradiation caused changes in ionization states and induced defect formation in crystals, which suggests pretty high levels of ultraviolet radiation. How was this possible at as early a date as 1830?

It was the work of Thomas J. Pearsall (1805-1883), a Laboratory Assistant at the Royal Institution between 1827 and 1832. He assisted Michael Faraday and William Fox Talbot, working on chemical and electrical experiments, writing on manganese solutions and one of the first papers on the toxic biological effects of lead. He may be the same Thomas J. Pearsall who was much later the Secretary of Birkbeck College at the University of London, from 1863-1866.

In 1830, Pearsall was conducting experiments on the effects of electricity on a form of fluorite called *chlorophane*. This form of fluorite would emit light when heated. After heating, it lost this ability. Pearsall found that, if he placed a sample of the fluorite in a glass tube or in a chamber in a hollowed-out piece of ivory into which two electrodes protruded, then made a spark fly between the electrodes by hooking them up to a Leyden jar, the fluorite would glow during the discharge. It would also glow when heated again. Whatever the heating did to the mineral, the discharge apparently undid it.

It's an odd experiment, and Pearsall never says what inspired it. It feels very much like the sort of experiment that might have been done thirty years earlier, when Alessandro Volta invented his *eudiometer*, a glass container in the form of a pistol with two wires coming in through the side and having a slight gap between them. Volta used to fill the vessel with various gases, cork the top, and apply a Leyden jar to the leads to create a spark. Volta found that swamp gas produced a very satisfying "pop" as it burned, expanded, and blew out the cork. Here was Pearsall still experimenting with the same device three decades later, in an era when Faraday had moved beyond such simple spark experiments. I suspect that Pearsall just tried out the fluorite in his home-built

Wilk continues on p. 7

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