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OUTLOOK MAGAZINE

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# OUTLOOK

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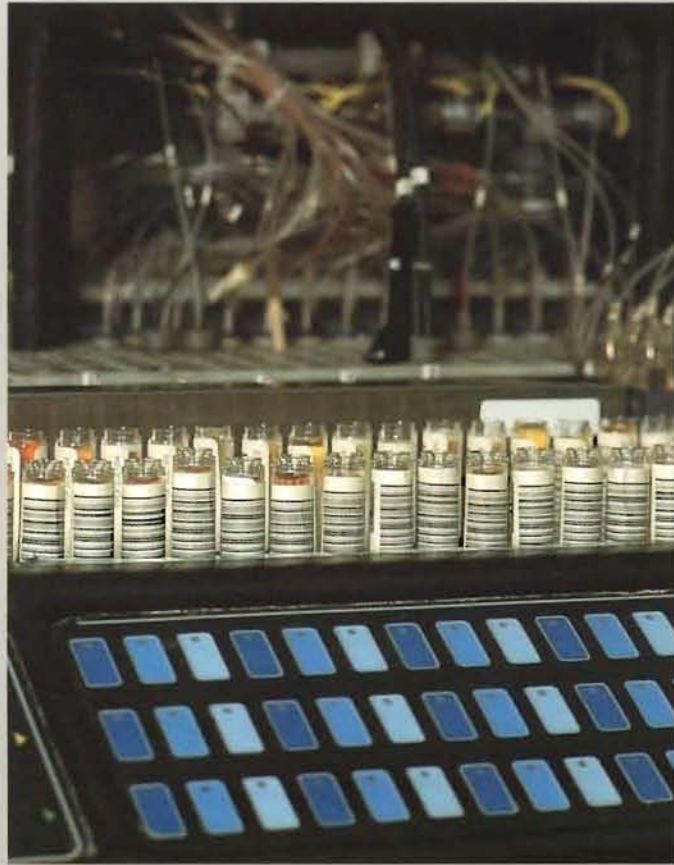
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Indexed



Interferon Trials  
Ripple the Water



*High technology makes it possible for large medical centers to keep up with physicians' demands for rapid, accurate test results. See story, page 10.*

# OUTLOOK

Volume XXIII, Number 3 Fall 1986

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Glenda King Wiman

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Don Clayton

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**Editor**

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Suzanne Hagan

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**Associate Editor**

---

Linda Sage

---

---

**Design**

---

Lee Ann Woolery

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**Photography**

---

Doug Whitaker

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**Circulation**

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Barbara Hebrank

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**On The Cover:**

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For Michael Durand the typical life of a 4-year-old was once disrupted by biweekly surgery to unblock his larynx. But after experimental interferon therapy, he now is free of wart-like growths on his vocal cords. Story begins on page 19. (Cover photo by Louis Rivera, Jr.)

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**CVS: Reborn Partner in Prenatal Testing** 8

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A recently revived experimental screening procedure can detect some birth defects at least six weeks earlier than amniocentesis, allowing problems to be diagnosed in the first, rather than second, trimester of pregnancy.



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**Laboratory Medicine** 10

---

Physicians often find it cheaper to perform lab tests in their offices, yet they also have to worry about not sacrificing quality for the sake of profit or expediency; several laboratory medicine specialists comment on these dilemmas, address the high cost and short-life of high technology, and describe their research.



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**Ubiquitin** 16

---

A protein found in most organisms — from bacteria to humans — turns out to be a member of a family known as the heat shock proteins. Having sequenced its gene — and found some unusual features — scientists would like to know how the protein, ubiquitin, protects cells against stress.



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**Interferons on Trial** 19

---

At Washington University School of Medicine, the protein interferon is helping some patients with kidney cancer and wart-like growths on the larynx. It may also be useful in the fight against childhood leukemia.



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**Wooing Promising Students** 22

---

Discovering and then attracting the most promising graduate-student prospects is a problem all universities ponder. Recent recruitment programs including research internships and targeting top-notch small colleges are working for our Division of Biology and Biomedical Sciences.



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**Newsbriefs:** 2

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---

**Personal Outlook: Howling at the Moon** 26

---

---

**Alumni Report:  
Hagemann Receives Eliot Award** 28

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---

**Class Notes** 29

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---

**Silhouette: Patricia Newton's Progress** 31

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# NEWSBRIEFS



*Joseph Williamson, M.D. '58*

## Sweet News for Diabetics

**D**iabetics — even those who appear to keep their blood sugar levels well-controlled — can be plagued by side effects of their disease. Damage to peripheral nerves and organs such as the kidney, together with growth of new blood vessels in the eye, are among the leading causes of diabetes-induced disability. But a group of new drugs, currently in clinical trials, may prevent potentially lethal developments.

Glucose can be metabolized in several ways, leading to the formation of various end products including the sugar called sorbitol. Although all persons possess the enzyme capable of changing glucose into sorbitol, non-diabetics have low levels of sorbitol because their glucose levels are low. However, diabetics with high blood glucose levels may convert up to 30 percent of the glucose to sorbitol.

Unfortunately, sorbitol isn't easily excreted by cells, and

scientists think that it — or metabolic imbalances associated with it — causes the litany of ills that can plague even the well-controlled diabetic. So reducing or preventing the activity of the enzyme catalyzing the glucose-to-sorbitol reaction may reduce the incidence of tissue damage.

Several drug companies are preparing to conduct human tests of drugs called aldose reductase inhibitors (ARIs). These drugs (Sorbinil and Tolrestat are the most-studied) prevent formation of sorbitol. But there hasn't been an animal model in which diabetes-caused blood vessel changes, equivalent to those in human diabetics, can be induced readily to permit documentation of ARIs' specific effects. Such a model has been developed by Joseph R. Williamson, M.D. '58, professor of pathology at Washington University. New blood vessels formed in the skin of diabetic laboratory animals show the same marked increase in permeability as vessels in human diabetics.

Williamson says that his animal model enables specific changes induced by the diabetic milieu to be documented and studied: "The most characteristic functional abnormality in human diabetic vascular disease," says Williamson, "is that the blood vessels become leaky, so that the serum proteins leak out of the vessels and into the tissue. You see this most dramatically in the eyes of poorly controlled diabetics. They develop proliferative retinopathy — formation of new blood vessels, which are especially leaky — in the eye. But there's never been an animal model in which you could duplicate this phenomenon.

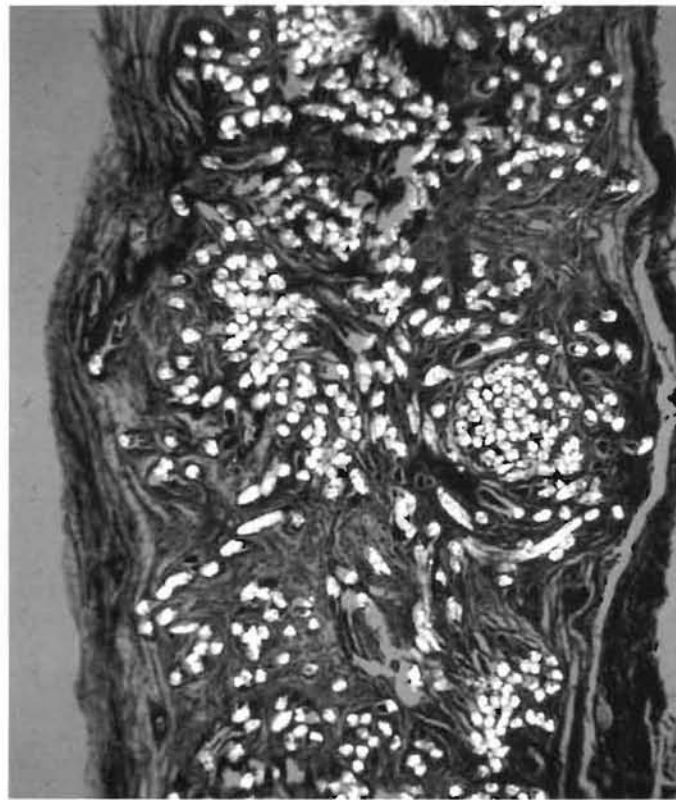
And it's been difficult to show permeability changes in the blood vessels, or structural changes.

"There are an incredible number of metabolic and hormonal imbalances in diabetics," Williamson continues, "and if you don't have some identical functional equivalent in an animal model, then it's virtually impossible to sort out which are important and which aren't. We decided to look at the role of sorbitol metabolism with this model. We tested the ARIs and found that they completely prevented the increase in vascular permeability."

Another contributing factor

to diabetes-induced complications appears to be sex hormones. Pre-pubertal children, even those with poorly controlled blood sugar levels, are spared diabetes' side effects until after puberty.

Williamson was puzzled about how to reconcile these data until he remembered that the sorbitol-creating enzyme was first discovered in the male reproductive tract. "It's reasonable that this enzyme would be modulated by sex steroids, particularly androgens such as testosterone," he says. "This may explain why children are spared the complications of diabetes and suggests that tight



*Joseph Williamson induces new blood vessels to form in rats by slipping a piece of polyester fabric under the skin. The polyester fibers plus collagen fibers form a framework for new vessels, which here appear as circles. Using this technique, Williamson compares vessel formation in healthy and diabetic animals.*

blood sugar control may not be so critical before puberty. After puberty, ARIs may be particularly useful in preventing complications."

In preliminary tests, Tolrestat has not caused worrisome side effects, but Sorbinil has been implicated in serious reactions in a few persons. To Williamson, this means that care needs to be exercised, just as with any drug. "Some persons can't take a common pharmacologic agent like aspirin, either, but it doesn't mean it shouldn't be used. It just means that we have to use caution, just as we do with any drug that's potentially risky."

Charles Kilo, M.D. '59, clinical associate professor of medicine at Washington University, is cooperating in ARI clinical trials being conducted at Barnes and Children's hospitals. He heads the Kilo Foundation, which supports Williamson's research among nearly 20 projects annually funded from its \$600,000 budget.

"An animal model such as the one developed by Dr. Williamson, exhibiting changes similar to what goes on in humans, is a big step forward in testing hypotheses about the mechanism of blood vessel and nerve injury," says Kilo. "And the aldose reductase inhibitors could be the miracle for the diabetic population that insulin's introduction was in 1921. If they delay or prevent blood vessel and nerve damage, there is the potential to greatly reduce the severity of disease in the eye, nerves and kidneys. This could mean a savings of about \$10 million annually in health care and productivity." ■

## Research To Prevent Blindness Provides Becker \$30,000 For Eye Research

**B**ernard Becker, M.D., professor and head of the Department of Ophthalmology, has received a \$30,000 grant from Research to Prevent Blindness (RPB), a voluntary organization committed to the financial support of eye research.

The award is part of an overall 20 percent increase in RPB's nationwide support of eye research, Becker notes, and comes at a time when federal budget cuts are causing concern for the continuity of medical research. During the past 27 years, the Department of Ophthalmology has received \$293,900 in RPB funds. "The significance of these grants cannot be overstated," Becker said. "They provide scientific freedom, and their impact is felt at every level of our research program."

Washington University has one of the world's largest research programs devoted to ophthalmology and visual science. On-going research projects include studies of glaucoma, ocular manifestations of diabetes, abnormal retinal biochemistry and other eye diseases. The university is one of more than 50 medical institutions across the country whose eye research programs are assisted by annual grants from RPB. ■



Gerald Medoff, M.D.

## Respiratory Fungal Pathogen Outwitted

**A** technique that disarms a pathogenic fungus may open the door to vaccines against disease-causing microorganisms that change form when they enter the body.

A team of researchers from the Medical Mycology Center reported recently in *Science* that a chemical called PCMS\* prevents the thread-shaped *Histoplasma capsulatum* from changing into single-cell yeasts. The fungus causes histoplasmosis, a respiratory infection that strikes an estimated 500,000 Midwesterners each year. It normally changes shape when its threads — mycelia — move from soil as dust into the warmer environment of the lungs.

Since only the yeast form causes disease, PCMS renders the fungus innocuous. But it doesn't prevent it from provoking an immune response.

Therefore, inoculations of chemically treated mycelia protect against future infections with virulent *H. capsulatum*, at least in mice, the subjects of the Washington University experiments.

PCMS changes *H. capsulatum* permanently, affecting both the treated cells and their progeny, presumably by altering a gene that directs some crucial stage in the mycelium-to-yeast transition. "We don't know the mechanism, but we are following up on that," says Gerald Medoff, M.D., professor of medicine and head of the division of infectious diseases. "If the transition depended on a plasmid — an extra-chromosomal piece of DNA — and PCMS eliminated that plasmid, that might be one mechanism. Or PCMS might cause a chromosome to rearrange itself."

The altered fungus itself probably will not become a vaccine because inoculation against the usually benign histoplasmosis seems unnecessary. However, it could serve as a model in the development of other vaccines. "There are many parasites, such as the protozoan that causes malaria, that have a phase in a vector, such as a mosquito, and then convert to another phase when they affect humans. So if one could prevent conversion from one phase to another, it might be analogous to what we saw with *H. capsulatum*," says Medoff. ■

\*parachloromercuriphenyl-sulfonic acid



*Shirley Sahrman shows runner Jennifer Shifrin how to properly perform lower abdominal exercises.*

## Shirley Sahrman Receives Physical Therapy Honors

Shirley Sahrman, Ph.D., associate director for research for the program in physical therapy and assistant professor in neurology and physical therapy, has received three of the country's foremost honors in physical therapy.

The American Physical Therapy Association selected

Sahrman to receive the Marian Williams Award for Research in Physical Therapy, and also named her a Catherine Worthingham Fellow. The University of Southern California's physical therapy department chose Sahrman to deliver its 1986 Viola Robins Lecture.

The Marian Williams Award cites Sahrman for leadership in physical therapy research, and for contributions that have helped bridge the gap between animal and human research in the neurosciences.

Sahrman is one of only six recipients of the award, first

presented in 1965 to recognize individuals who have performed sustained and outstanding basic, clinical and/or educational research pertaining to physical therapy. The award commemorates Marian Williams, Ph.D., whose professional life was dedicated to the promotion of physical therapy through teaching, writing and research.

The APTA's selection of Sahrman as a Catherine Worthingham Fellow recognizes her for national leadership in advancing the science, education and clinical practice of physical therapy. The fellowship was first awarded to former APTA president Catherine Worthingham in 1982.

Sahrman is the second distinguished health scientist to be chosen as Viola Robins Lecturer at the University of Southern California. Viola Robins had served as director of the department and associate clinical professor of physical therapy. In her lecture, Sahrman addressed classification, the categorizing of patients by specific muscle imbalance problems in order to ensure more effective therapy.

Sahrman first joined Washington University in 1959 as a staff physical therapist at the School of Medicine's Irene Walter Johnson Rehabilitation Institute. In addition to her current appointments, she serves as an instructor in physiology at the School of Medicine. She received doctoral and master's degrees in neurobiology, as well as a bachelor's degree in physical therapy, from Washington University. ■

## Where Nerve Meets Muscle

**"N**eural Regeneration: Bridging the Gaps," a feature in the Fall 1984 issue of *Outlook*, described Washington University scientists' research on why brain and spinal cord nerve cells fail to repair themselves after injury. One area being investigated by Gerald Fischbach's group concerns the growing nerve tip and its influences on the muscle it innervates. They know that where the nerve touches the muscle, clusters of acetylcholine receptors assemble. (These receptors enable the muscle to respond to the neurotransmitter acetylcholine by contracting.) But they didn't know whether the receptor clustering was due to formation of new receptors, or whether the nerve caused pre-existing receptors to migrate.

Because of some recent evidence gathered by David Harris, Fischbach suspects that the nerve tip causes new receptor subunits to be synthesized: "The receptor molecule is very complex," explains Fischbach. "It's made up of four subunits. David has been using recombinant DNA probes to measure the capacity of the muscle to synthesize receptor subunits. Our preliminary data suggests that that's probably increased, an effect of the growing nerve tip on the muscle."

Postdoctoral fellow Lorna Role and predoctoral student Richard O'Brien found that nerve has a powerful effect on muscle: Receptor clusters on the muscle are within a few

microns of the growing nerve tip. Says Fischbach: "That's a very high incidence. If you look anywhere else along the course of the nerve, the incidence is much lower. And that leads us to believe that there's something very special about the advancing nerve tip."

Another former student, Ted Usdin, scored an impressive coup. He was able to purify a glycoprotein — a sugar-containing protein — from extracts of chick brain. Using a protocol developed several years ago, Usdin added several new purification steps "and ended up with a molecule purified to homogeneity," says Fischbach, "about a million-fold purification, which is a tremendous feat. Ted found that when this glycoprotein was added to muscle fibers in cul-

ture, it promoted the formation of receptor clusters."

Now, the question to be answered is, is this molecule what growing nerve tips secrete to induce the receptor clusters? Postdoctoral fellow Doug Falls hopes to answer this question by making antibodies to the glycoprotein. "Once we have antibodies," says Fischbach, "we'll see if the glycoprotein is located in the growing nerve tip and if we can use them to block its effects."

Answers to such questions may prove a boon to clinicians trying to treat patients with devastating neurological conditions such as myasthenia gravis or Alzheimer's disease. "There's a long list of possible causes of a disorder like Alzheimer's disease," explains Leonard Berg, M.D., director

of the Alzheimer's Disease Research Center at Washington University. "We don't have enough background information to narrow the list and focus on one or two possible causes.

"It's sensible to look for ways brain cells handle injury and adapt to survive and maintain function. And it's logical to assume that brain cells will fall back to the basic mechanisms of growth and development. Hopefully, those basic biological principles can be studied in relation to a disease like Alzheimer's, to give us some means of palliating the disorder and reducing symptoms until the future, when we find a cure."

Gerald Fischbach, M.D., is head of Anatomy and Neurobiology. ■

## Rough and Clot-Ready

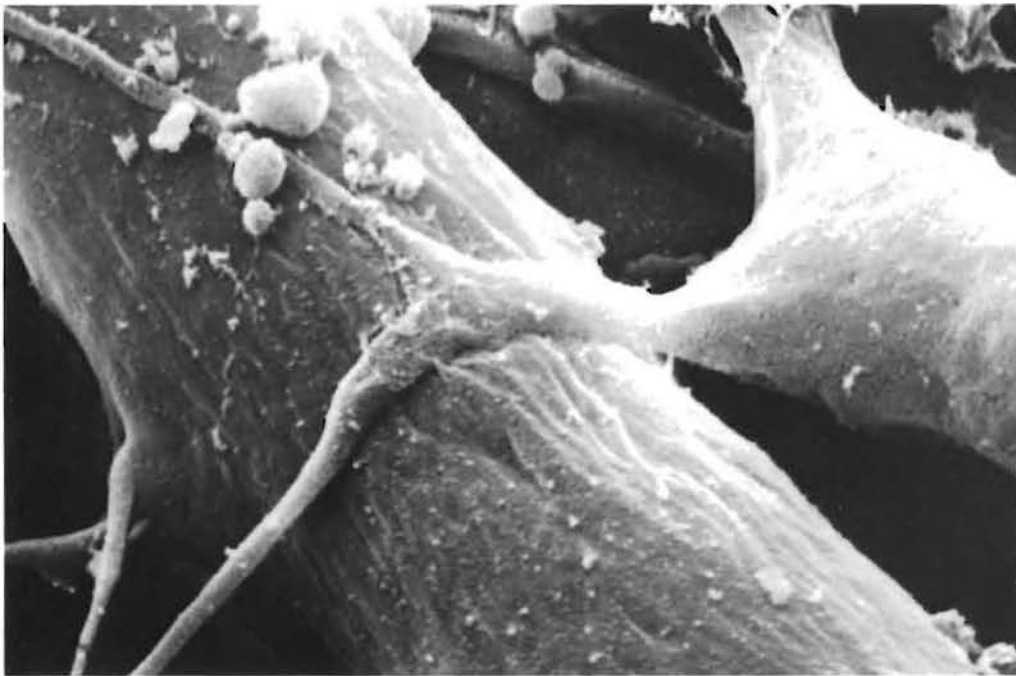
**T**he layer of cells lining blood vessels plays a key role in repair and disease processes. The endothelium, as it's called, consists of a single layer of cells which, under normal conditions, stays smooth. Any roughness or irregularity attracts blood components that lead to the formation of clots.

Yet when blood vessels give off new branches or repair themselves, these lining cells must divide. And in diseases such as atherosclerosis, whatever keeps these lining cells a smooth layer stops working or is overpowered with the development of an atheroma — a mass inside the blood vessel that becomes calcified over time, eventually blocking it.

Researchers have been struggling for years to learn how blood vessels repair themselves and grow, and how these normal processes go awry when conditions like atheromas occur. Now, thanks to research performed at Washington University, there are some clues.

Thomas Deuel's group has found a new protein in endothelial cells. This protein is kin to one on which Deuel has worked for years, a protein called platelet-derived growth factor (PDGF). When secreted into blood, PDGF attracts blood cells and other blood components to the area, and it stimulates cell division.

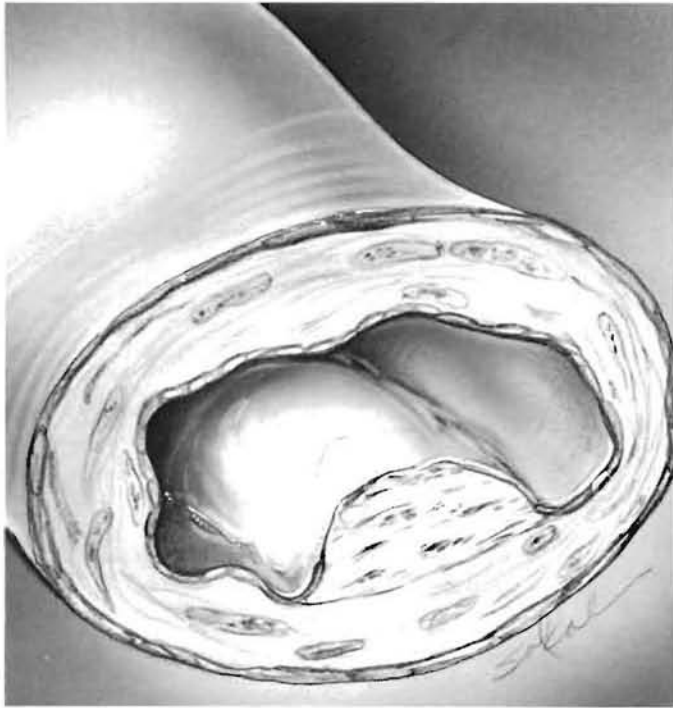
The new protein, which is structurally similar to one of the polypeptide chains comprising PDGF, is manufactured



L. Role

*A microscopic view of a chick neuron (right) and a muscle fiber (left) in culture. A process has grown out of the body of the neuron and forked over the fiber. Information, in the form of chemical signals, can pass between the two cells at such contacts, which are called synapses.*





*Atheromas, like the one in this drawing, form after the disruption of normal processes that repair the linings of blood vessels.*

by the same gene coding for PDGF molecules, report Deuel *et al.* in a recent issue of *Science*. Furthermore, Deuel discovered that this new protein could be found in much higher levels in actively dividing endothelial cells but not in non-dividing cells. Thus, it may play a key role in normal repair processes, and it may be implicated in diseases like atherosclerosis.

"The gene for this PDGF-like protein has been cloned," says Deuel, professor of medicine and biological chemistry and director of hematology/oncology, "and we have cloned a piece of the gene from endothelial cells. We have also developed antibodies to the protein. With antibodies and the DNA probe, we hope to go back and see under what condi-

tions the gene is expressed." Using the protein-specific antibodies and the DNA probe, Deuel's team will examine lesions in the blood vessel wall and try to correlate anatomical changes with the presence of the protein.

"There seems to be a sort of cascade of events that occurs in endothelial cells," summarizes Deuel, M.D., director of the Marilyn Fixman Cancer Center at Jewish Hospital. "On the one hand, these events should lead to a normal regeneration or repair of blood vessels that have been injured. On the other hand, in tumor growth or atherosclerosis, those events are exaggerated or not under the usual regulation and thus contribute to the abnormal situation. But how? That's the question we're trying to answer." ■

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## Urologic Division Dedicates Library in Honor of Elwin Smith

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**T**he Division of Urologic Surgery has dedicated its library in honor of Elwin R. Smith and the Urologic Research Foundation.

Smith, a St. Louis insurance executive, established the Urologic Research Foundation in 1979 to encourage and sustain research in urologic disorders. Since its beginning, the non-profit organization has raised almost a half million dollars, primarily through private individual sources.

"The Division of Urologic Surgery owes a great deal of gratitude to the organizers and supporting members of the Urologic Research Foundation," says William J. Catalona, M.D., professor and chief of the Division of Urologic Surgery. "At a time when governmental funding of medical research has been reduced across the board, funding for research in urology has been stripped to the bone.

"We have been touched by the tremendous support we have received from Elwin R. Smith and the other founders and members of the foundation," he adds. "We dedicate our new library to Mr. Smith and the Urologic Research Foundation in recognition of their efforts on our behalf. We are delighted to honor them in this small way."

Smith, who has been president of the Urologic Research Foundation since its creation, was recently named chairman

of the board. Arnold Schwab is the new president.

Smith's association with Washington University began in 1920 when he was a student in the business school. He graduated in 1924 and received his master's degree in economics in 1926, the same year he formed the Smith Insurance Agency. He continues to be involved in the insurance business with the firm Lawton-Byrne-Bruner. ■

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## Bunge Receives Javits Neuroscience Investigator Award

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**R**ichard P. Bunge, M.D., professor of anatomy and neurobiology, will conduct research for the next seven years with more than \$900,000 in funding from a Javits Neuroscience Investigator Award.

Bunge is the ninth Washington University faculty member to receive a Javits Award since the highly competitive awards program began in October 1983. Award recipients are selected three times each year.

The U.S. Congress gives the awards in honor of Sen. Jacob K. Javits of New York, on recommendation of the National Advisory Neurological and Communicative Disorders and Stroke Council of the National Institutes of Health. Javits was a victim of amyotrophic lateral sclerosis (ALS), more commonly known as Lou Gehrig's

disease. ALS is a degenerative neuromuscular disorder that attacks the nerve cells that control muscles.

The Javits Awards, given to investigators who have submitted regular research grant applications for competitive review, encourage research and research training in communicative and neurological disorders. The prestigious grants provide a seven-year commitment of support to the researchers who receive them.

Bunge is Beaumont-May Institute of Neurology Scholar in Anatomy at the School of Medicine. His grant will allow detailed studies of the biology of the Schwann cell, the predominant helper-cell to the nerve fibers of the peripheral nervous system. The responsibilities of the Schwann cell include production of myelin, the insulating material of peripheral nerve fibers, and production of extracellular matrix materials. The Schwann cell is affected in several human diseases, including neurofibromatosis and Guillain-Barre syndrome, and is believed to be a key cell in fostering peripheral nerve regeneration. ■

## Thomas Named W.K. Kellogg Foundation National Fellow

**J** Regan Thomas, M.D., assistant professor of otolaryngology, is one of 40 outstanding American professionals named to Group VII of the W.K. Kellogg Founda-

tion's Kellogg National Fellowship Program.

The Kellogg program provides each fellow with a three-year, \$30,000 grant that funds a study project outside the fellow's field of expertise. The foundation also will host educational programs in the United States and Latin America for the fellows. Group VII members will address leadership development, focusing on such issues as the changing American family, agricultural and environmental resources for the future, and international interdependence.

Thomas is on staff at Barnes and Jewish hospitals, sponsoring institutions of the Washington University Medical Center. Before joining the Washington University faculty in 1983, he was clinical assistant professor of otolaryngological surgery at the University of Missouri Medical Center.

He received the doctor of medicine degree from the University of Missouri School of Medicine in 1972. Thomas trained in surgery at Yale University and in otolaryngology at the University of Missouri School of Medicine, and also completed a fellowship in facial plastic surgery at Northwestern University School of Medicine.

He is currently vice president of the American Academy of Facial Plastic and Reconstructive Surgery. He is also a member of the American Academy of Otolaryngology-Head and Neck Surgery, the American Board of Otolaryngology, the American College of Surgeons, the American Medical Association's Committee on the Young Physician, and the St. Louis Metropolitan Medical Society. ■

## Rice Named Pew Scholar in the Biomedical Sciences

**C**harles M. Rice, Ph.D., virologist and assistant professor of microbiology and immunology, has been chosen as one of 20 Pew Scholars in the Biomedical Sciences by the Pew Memorial Trust of Philadelphia.

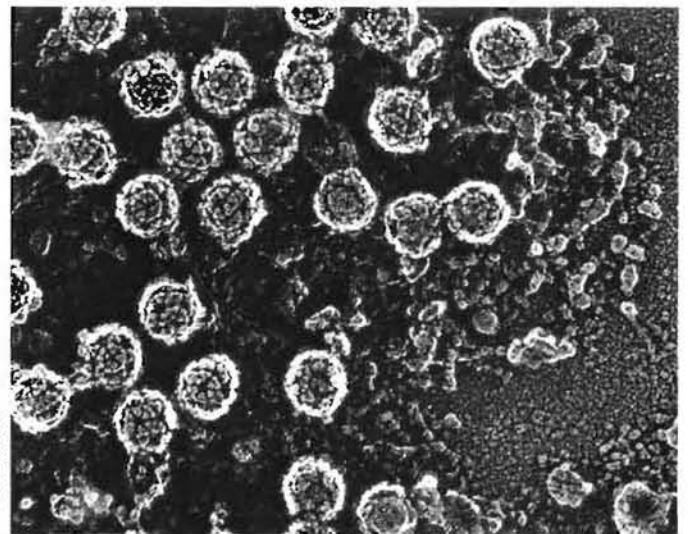
The 1986 Pew Scholars, junior faculty members at 17 medical schools and research institutes in the United States, were selected in recognition of their promising work in basic science or clinical research. Each of the scholars will receive a total of \$200,000 over the next four years to encourage research for the advancement of human health.

Rice's work, much of it done while he was a fellow at the California Institute of Technol-

ogy in Pasadena, uses recombinant DNA technology to unravel the molecular details of how viruses reproduce. This technology opens up new avenues for the design and propagation of live vaccine strains against RNA viruses, including yellow fever virus, Rice explains. Also, he says, it should allow researchers to explore the possible use of these viruses as transmitters for the cytoplasmic expression of foreign genes in animal cells.

The goal of the Pew Memorial Trust is to establish a network of outstanding, innovative researchers who are likely to become future leaders in the scientific community. The Pew Scholars Program is administered at Yale University School of Medicine, and winners are selected by a 13-member national committee.

Rice joined the Washington University faculty earlier this year. He received a Ph.D. in biochemistry from the California Institute of Technology in 1981. ■



John Heuser

*Sindbis viruses, one type of RNA virus that Rice is studying, bud through the outer membrane of a chick embryo fibroblast cell.*

# CVS: Reborn Partner In

BY TONY DIMARTINO

After deciding that there must be more to life than an MBA and a walletful of platinum credit cards, Nina — well-established in her career at 37 — is pregnant for the first time. There's a one-in-100 chance that her child will be born with a birth defect.

Liane lost her first child three years ago to Tay-Sachs, a fatal brain disease. She's now eagerly expecting her second child. But there's a one-in-four chance that this baby will also be born with Tay-Sachs.

Nina's age and Liane's genetic history mark their pregnancies as high risk. Both women are worried about their unborn children: are they developing normally, or do they have genetic deformities that will cause severe birth defects, impaired quality of life, or even death?

Currently, many high-risk mothers-to-be wait anxiously until disorders in their unborn children can be detected with amniocentesis. This prenatal diagnostic test analyzes cells from the fluid surrounding the fetus. Amniocentesis can identify many birth defects, but cannot be performed until enough amniotic fluid has formed — at least the 15th week. Results may take two more weeks while the siphoned cells multiply into a sample large enough to study.

But with an experimental screening procedure called CVS — chorionic villus sampling — being tested at the School of Medicine, results of cell analysis can be obtained as early as the ninth week of pregnancy. That's at least six weeks earlier than amniocentesis.

"The overwhelming advantage of CVS over amnio is early diagnosis," says

James P. Crane, M.D., director of the genetics division in Washington University's obstetrics and gynecology department. "If no birth defect is found, CVS provides earlier reassurance to frightened parents who might have considered ending the pregnancy."

If a problem is diagnosed, Crane says, CVS allows parents more time to prepare for a handicapped child or, if the defect is severe, to end the pregnancy much earlier.

"Early termination is safer for the mother both physically and psychologically," explains Crane, who also serves as director of obstetrics and gynecology at Jewish Hospital. "And first trimester detection of abnormalities also paves the way for fetal therapy, which may one day enable us to treat and correct defects before birth."

Fourteen other U.S. medical centers are examining CVS' safety and reliability under a Food and Drug Administration protocol. In March, Washington University made the first national presentation of preliminary CVS evaluation results. The study was described in a poster session at a meeting of the Society for Gynecological Investigation in Toronto.

The researchers attempted to assess the safety of CVS by comparing first trimester miscarriage rates in 116 high-risk women who underwent CVS to miscarriage rates in 75 high-risk women who did not have CVS.

There was one miscarriage among the controls and two among the CVS group. "One [CVS] miscarriage was due to a weak cervix that dilated prematurely, totally unrelated to the CVS procedure," says Crane. "The other case is still under investigation."

Crane's group concluded that CVS did not significantly increase risk of miscarriage. "We've now done almost 200 CVS procedures," says Crane. "We've had four more miscarriages since the meeting in Toronto, but none of them appears to be procedure-related. CVS is potentially as safe as amnio."

The recent study did not compare amnio and CVS head-to-head, but data available worldwide shows that CVS seems safe. Crane cautions that no definitive comparisons can be made until many more CVS procedures — perhaps 30,000 to 40,000 — are completed. Statistics are being collected at the 15 U.S. centers and others abroad as the CVS evaluation continues.

"So far, our diagnoses have been 99 percent accurate, and there's every indication that CVS will eventually prove to be as reliable as amniocentesis," says Heidi Beaver, M.P.H., a genetics associate. "We're just waiting for more patients to be referred so more diagnoses can be attempted."

Amniocentesis can identify about 200 abnormalities. CVS currently can detect about 100 disorders, but the procedure's diagnostic range could increase.

Even so, CVS will never completely replace amniocentesis because it can't detect neural tube defects — spina bifida and other spinal column disorders, which are indicated by high levels of alpha-fetal protein in the amniotic fluid. Also, some uteri are positioned in such a way as to make it difficult to obtain an adequate sample of villus tissue.

CVS, performed at Jewish Hospital, takes only 30 minutes, can be done without anes-

# Prenatal Testing

thetia and costs about \$750, roughly the same as amniocentesis. "Like amnio, CVS is relatively painless," Beaver explains. "In terms of discomfort, I'd compare amnio to a blood test and CVS to a Pap smear."

The CVS procedure begins with an ultrasound examination to determine the embryo's location and age. A thin, flexible catheter is guided through the cervix to an area between the uterine lining and the chorion — a layer of tissue that surrounds the embryo and eventually becomes the placenta. A syringe is attached to the catheter, and a sample of chorionic villi — tiny, hairlike projections — is withdrawn. About one one-thousandth of the chorion is removed.

These cells can be examined almost immediately. Not so with amniocentesis. Collected through a hollow needle inserted through the abdominal wall into the amniotic sac containing the fetus, fetal cells are so scarce in the amniotic fluid that they must multiply for at least two weeks in laboratory cultures. The delay means that amniocentesis results often are not known until after the 20th week of pregnancy, well into the second trimester.

Genetics associate Beaver says CVS will remain experimental until more centers present their studies and the FDA is satisfied that use of CVS catheters is safe.

At least four different catheters are being tested, says Lillian Yin, Ph.D., director of the FDA's Office of Device Evaluation. "It is hard for us to estimate when CVS will be available to the general public. Research centers are sending their statistics on fetal loss to the catheter companies, which in

turn will send them to us for review when enough data has been compiled."

Both amniocentesis and CVS are considered invasive procedures and pose a risk of complications that might lead to miscarriage. They are recommended only when women will be 35 or older at the time of delivery; when women have had a previous child with a chromosome abnormality such as Down syndrome; or when women or their mates are carriers of a chromosome translocation, a sex-linked disease such as hemophilia or muscular dystrophy, or a biochemical disease such as Tay-Sachs.

CVS isn't new. In the late 1960s, about the same time amniocentesis was being developed, Scandinavian researchers showed that chorionic villus tissue could be used for prenatal diagnosis. But the miscarriage rate was high at that time, and the procedure was overshadowed by the early success of amniocentesis.

It wasn't until the early 1980s that CVS — improved by refined ultrasound techniques and availability of thin catheters that made cervical dilation unnecessary — began to catch on. The procedure was championed by British and Italian researchers and sponsored in the United States by investigators at Jefferson Medical College in Philadelphia, the University of California at San Francisco, Michael Reese Hospital in Chicago, and the Washington University team in St. Louis.

Within the next 10 to 15 years, experts predict that first-trimester CVS will enable doctors to diagnose potentially fatal birth defects early enough to treat them before birth. Many genetic disorders are caused by



*Using a dissecting microscope, research technician Nanette Fyan separates chorionic villus tissue from maternal tissue. The villus tissue is cultured overnight to generate cells for chromosome analysis. Sau Wai Cheung, Ph.D., standing, is the director of the cytogenetics laboratory at Barnes Hospital, where the cells are prepared and analyzed. Results of chorionic villus sampling can indicate the presence or absence of certain birth defects as early as the ninth week of pregnancy.*

a lack of some vital enzyme or substance. In Tay-Sachs disease, for example, an enzyme deficiency causes the abnormal accumulation of fatty substances in brain cells. By the second trimester, when amniocentesis finally diagnoses Tay-Sachs, brain damage has already occurred. "Early warning that all is not well within the fetus may eventually lead to treatment that will compensate for any dangerous excesses or deficiencies," says Crane.

Experts predict, however, that CVS will raise as many questions as it answers and pose hard ethical choices. Although the ultimate aim of early genetic screening is fetal therapy, ability to discover problems currently outstrips ability to solve them and may continue to do so for many years. Interpreting genetic messages adds fuel to the abortion debate.

"We're not pro-abortion," says Crane. "But many high-risk parents who've experienced the agony of watching their helpless child suffer and die will tell you that they'd rather not go through it again." ■



# Laboratory Medicine

## *Matters of Technology and Technique*

BY SUZANNE HAGAN

**T**he matchbook-sized clear plastic device looked like a miniature Pachinko machine. But Kim Walton wasn't playing games. Instead, Walton — a technician in the clinical chemistry lab at Barnes Hospital — was preparing to test a few drops of serum using a state-of-the-art machine called "Vision."

Walton uses this Abbott Laboratory device to analyze either whole blood or serum. First, the sample is centrifuged through the Pachinko-like maze of the sample holder; then, at the appropriate location, a pre-measured reagent automatically mixes with the centrifuged sample. Depending on which reagent is packaged into the sample holder, Vision measures the concentration of blood-borne substances like cholesterol, glucose and uric acid. Soon, technicians may use the personal-computer-sized device to assay



*In the clinical chemistry lab at Barnes Hospital, Jay McDonald (standing) studies test results generated by medical technologist Robert Roggeman. Roggeman operates the Parallel Analyzer, which performs 28 different tests and can make 7,800 analyses per day. This machine will soon be replaced by an even more sophisticated piece of equipment.*

*Left: The Vision System is a laboratory device that calculates and prints out the concentrations of blood components, such as proteins or electrolytes. Just two drops of blood from a finger prick are sufficient for each analysis.*

blood concentrations of theophylline and creatinine. And in the future, Vision will be able to measure concentrations of drugs such as phenobarbital and phenytoin, as well as natural components like iron, calcium, albumin and bilirubin.

The Pachinko-like sample holder isn't the only innovation in state-of-the-art equipment. The Kodak Company has created a blood chemistry machine that uses samples applied to film disks. Technology is the watchword.

Yet these days, it's not only samples that are bouncing around in search of equilibrium. Physicians are pulled in one direction by manufacturers touting the latest in "foolproof" technology to equip their office laboratories; in another by the knowledge that many laboratory tests should be done in a hospital or commercial setting outside the physician's private office; and in yet another by the changing reimbursement policies for laboratory tests.

Some experts point to this as evidence that current trends are leading away from centralized laboratory facilities and that more tests will be done in physicians' offices, at patients' bedsides, and at home. Others point to the fact that many prominent teaching hospitals are only just beginning a task that Barnes Hospital set about 17 years ago: dissolving individual labs and moving them to one central facility, gaining efficiency as well as consistently strict quality control standards.

"I think that there has been a lot of talk about decentralization of laboratory facilities," admits Leonard Jarrett, M.D. '62, Flexner Professor and chairman of the Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine. "But the reality is not as great as the talk."

Jarrett says that this "trend" is mythical because of two basic reasons: the rigid quality control standards mandated by law,

**“Physicians are pulled in one direction by manufacturers touting the latest in “foolproof” technology to equip their office laboratories; in another by the knowledge that many laboratory tests should be done in a hospital or commercial setting outside the physician’s private office...”**

and the fact that there are few tests suitably easy to be done outside an accredited laboratory. One exception, he says, is glucose monitoring: "Blood glucose is measured by diabetics who are highly motivated, they really want to take care of that blood chemistry equipment. And they get information within an acceptable range to be able to make their decisions. Is it really highly accurate and precise? No. The instrument they're using is not as good as the ones in a clinical laboratory. But it's good enough for them to make sensible decisions."

Jarrett speaks with authority. Winner of the Ernest Cotlove Award, given by the Academy of Clinical Laboratory Physicians and Scientists, he led the effort in 1969 to centralize Barnes Hospital's laboratory facilities. Only now, he says, are other major academic hospitals like Massachusetts General and Brigham and Women's following suit. Why? "Profit. DRGs are not reimbursing like they used to," says Jarrett. "There used to be all these little fiefdoms,

with people doing their own tests, and it was profitable. They can't do this now; the hospital loses money, and they don't run 24 hours a day or abide by quality control.

"My staff just ran an educational program for physicians who want to do their own laboratory testing," he continues. "Even though it was well-attended, most of the physicians walked out with the realization that they really didn't want to get into it, once they were told what the legislation in the state of Pennsylvania requires for quality control."

But Pennsylvania is one of few states that have rigid quality control standards mandated by law. A bigger factor, some experts say, is the changing reimbursement pattern. Now the incentive is for private physicians to perform tests in the office instead of sending them out. And added to this are the growing numbers of instruments

that make many tests easy to perform. Which way should the private practitioner turn?

#### MISSING LINK

"One advantage of performing tests in the physician's office is that the person performing the test knows the patient and could relate the test result back to the patient better than we can," says Patrick Murray, Ph.D., associate professor of medicine and pathology at Washington University and codirector of microbiology in laboratory medicine. "The same thing would apply to a patient who's performing a test at home to monitor glucose or detect organisms in urine. The patient might pick up a slight change that we would consider insignificant.

"On the other hand, particularly for tests performed with instruments, you may be misled by the simplicity of the testing procedure. You may not know when that test is accurate unless the appropriate quality control tests are performed. With our volume

of tests, we can financially justify running a large number of quality control tests. In a physician's office, where maybe only eight or nine tests are performed each day, it's very difficult to justify spending the money required for quality control."

"Training in the elements of quality assurance and quality control is missing in most independent setups," says Jack Ladenson, Ph.D., professor of medicine and pathology, "and this is the key weakness if untrained people are doing the work. It's not that you can't learn how to pipette or put a dipstick into a sample. But how do you know that what you're doing is working right? That requires some concepts of statistics and quality assurance, which I think is the real missing link in non-hospital-based labs."

Ladenson, who is president of the American Association for Clinical Chemistry and director of clinical chemistry in the division of laboratory medicine, points out that in a laboratory like Barnes', 10 to 30 percent of samples tested aren't from patients; in one way or another, they are related to assuring quality.

"When you leave that out, eventually you're asking for problems," he points out. "We look at the total picture of 'quality' — is the test being done accurately, precisely, rapidly enough; is it the right test; should there be additional tests — these are the key components of the job we do."

So it's this no-win situation that has many clinicians confused. Fortunately, a Physician Outreach Program is available through Barnes Hospital. "This program is designed for us to help physicians in their office do as many tests as they can do well in their office, with our help and quality control," says Jay M. McDonald, M.D., professor of pathology and medicine and director of the division of laboratory medicine. "And we can help them determine what tests they shouldn't do. We will do them very competitively. We can offer them other assistance because we have all the hospital information in one package and can transmit all kinds of information from the hospital to help them practice medicine. Our goal is not to do their work, but to help them do the work themselves and do it right."

## How Laboratory Medicine Came to be

Laboratory medicine at Washington University is a clinical division that weds pathology to medicine; practitioners carry appointments in both departments. Within the scope of laboratory medicine, headed by Jay McDonald, are sections in microbiology, clinical chemistry, blood bank, hematology/hemostasis, and immunology/HLA (human lymphocyte antigens).

What gives rise to a new academic specialty like laboratory medicine? According to Leonard Jarett, who was the first to head the new division at Washington University, the normal process of instituting a new specialty worked backwards: "Typically, a specialty grows and becomes strong in the community because of what's at the medical school. Laboratory medicine went the other way — it started out in the community and then came back to the medical school.

"At academic centers, internists, surgeons and others often did individual tests in their labs with no coordinated effort. They were not usually interested in

residency training, teaching, quality control or the consultative role that laboratory physicians and scientists now play. Thus, at academic centers, laboratory medicine is distinct from anatomic pathology. Furthermore, laboratory medicine reflects a more academic and scholarly approach than that found in traditional clinical pathology."

Washington University was one of the first academic medical centers to establish a division of laboratory medicine. Jarett, who now chairs the Department of Pathology and Laboratory Medicine at the University of Pennsylvania, says that Washington University's program in laboratory medicine "is unequivocally number one in the country."

He says that nationally, laboratory medicine is in its "... preteen period. Future developments in the field will depend on what happens in the medical centers in Boston and at Johns Hopkins. If those places develop strong academic programs, we will jump immediately from our preteen period to young adulthood." ■



*Sample holders in the Vision System, which separates whole blood into cells and plasma and then mixes a correct amount of plasma with reagents.*





*Jack Ladenson has developed an assay for an enzyme that appears in serum after a myocardial infarction. He uses monoclonal antibodies to measure the enzyme. Right: This close-up shows how the Parallel Analyzer got its name.*

### FINE-TUNING DIAGNOSIS

Typically, private practitioners have office laboratories that perform microscopy and other tests. Many still send some of their tests out to commercial and hospital laboratories. Nevertheless, they want to do what can be done in-house to increase profits and speed turnaround time, yet they're aware that quality control could be a problem. So a Physician Outreach Service, such as the one provided by Barnes Hospital, is often just what the doctor ordered.

One of the private practitioners who's found this service helpful is John William Campbell, M.D. '77, FHS, now a specialist in infectious diseases at the Grant Medical Clinic in St. Louis. Campbell, who was chief resident in medicine, says that he occasionally comes across patients whose infections are difficult to diagnose. "Sometimes the culturing techniques may be difficult, or the blood tests fall into the gray zone of interpretation," says Campbell.

Campbell says he plans to use the outreach service to help train the Grant Clinic staff, which already has more training than

is typical: One of the clinic's physicians' assistants has training in medical technology. Says Campbell: "We do all the routine things most laboratories do — blood counts, sedimentation rates, urinalyses, blood potassium levels. But most of our culturing is still sent out."

But there are limitations to what such a consultancy can do, and the principal problem is that it's really the patient who tells the story, not the bodily fluids: "We're only consultants," McDonald says. "We can't palpate the abdomens, we can't look in the eyes, and we can't take the histories."

Quality control isn't just an issue with private physicians doing their own tests, says McDonald. It's a major problem in many hospitals, too: "In some hospitals, there are untrained persons doing what seem like the simplest tests, and they're making errors. One of the things we're setting a priority on nationally is to make sure that the practice of laboratory testing does not deteriorate because untrained persons are performing tests."

To alleviate this, McDonald is participating in a national task force that is looking at the problem of quality control in glucose monitoring. "How do you monitor glucose and do it effectively?" he muses. "That's the question we're trying to answer. Can it be done well by nurses, or do you need to limit the number of persons who do it? I don't think it has to be done necessarily by registered medical technologists; it just has to be done by persons who've been trained or retrained."

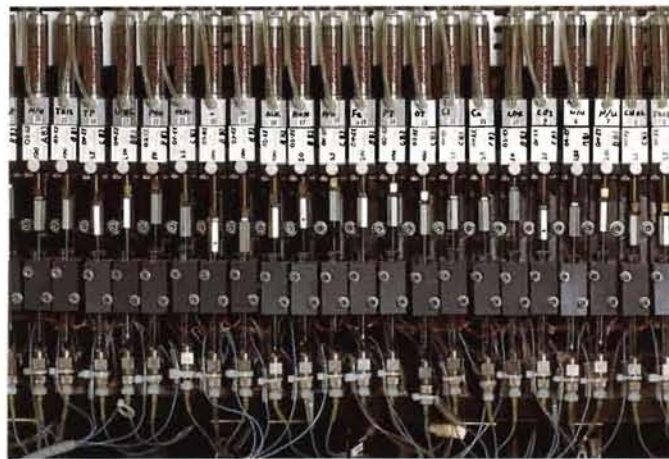
The task force on glucose monitoring, organized by the American Diabetes Association, will result in a consensus report. McDonald says that the answers obtained here will help determine the way quality control issues for other types of such tests are handled: "You have to establish criteria for analytical excellence."

Another group that establishes performance standards for a wide range of laboratory tests is the NCCLS — National Committee for Clinical Laboratory Standards — a group in which Ladenson and Murray are active.

Ladenson and others have worked with manufacturers like Abbott and Ames to evaluate chemical analyzers' performance. "In some cases," says Ladenson, "the machines perform well. In others, the precision is not what can be achieved in a laboratory like the one at Barnes. In many cases, it makes sense to do these measurements in the physician's office, while the patient waits to find out if the medication they're on needs adjustment. The major drugs that can be monitored with in-office devices are theophylline, digoxin and the anti-convulsant drugs. So these are the tests most companies are trying to develop."

Added to the push by manufacturers to sell physicians office laboratory equipment is the additional incentive to test in-house because of the changing reimbursement pattern. If a clinician gets reimbursed by Medicare, for example, then the laboratory doing the test must be the laboratory that bills Medicare. "This is different than before," says Ladenson, "because then, a physician who collected a sample could bill Medicare for the test yet arrange for another laboratory to do it at a lower charge. Now, there's an economic incentive for clinicians to do these tests in their own offices, since the cost of performing the test is generally less than what Medicare will pay."

The realm of home tests is also growing, and more manufacturers are trying to cash in on a lucrative market. But Murray, who chairs the Clinical Microbiology Division of the American Society for Microbiology, is skeptical of how useful to consumers many of these home tests will be: "I was at an FDA meeting in Washington recently," he says, "and saw a home diagnostic test for gonorrhea. What was especially disturbing to me was that this is a test being marketed for persons who have signs of urethritis."



“
One of the things that we're setting a priority on nationally is to make sure that the practice of laboratory testing does not deteriorate because untrained persons are performing tests.”

They are instructed to test their urethral exudate, and within seconds the test results are available. If the test is positive, the package insert recommends that they see a physician. But what the manufacturers neglect to say is that patients should also see a physician if the test is negative because urethritis is not normal.

"I think the real burden is on the FDA to determine which tests are really appropriate for home use. This particular test had already been licensed for males, and the company wanted to expand its use to females. In fact, it shouldn't have ever been licensed. It's not a precise indicator of the gonorrhea micro-organism, and a negative test result in a symptomatic patient should not dis-

courage the patient from seeking necessary medical care."

### ADVANTAGES OF ACADEME

An academic entity like laboratory medicine, born of a union between pathology and medicine, is more than machine monitoring. In addition to the instruction all students receive in laboratory medicine, there is a vigorous research program. The division currently has nearly \$1.8 million in annual funding for 32 research projects.

Says Ladenson: "We are developing monoclonal antibodies for measurement of isoenzymes, which are the different forms of an enzyme. The reason we monitor enzymes is usually to assess the extent of cell death. If we have specificity in that measurement, then we can begin to make much better predictions of the cell or organ involved."

Ladenson's research team is working on one of the enzymes, creatine kinase, that's a marker for cardiac cell death in myocardial infarction. They have developed an assay specific for only the enzyme CK-MG, found predominantly in the heart. This assay is based on a unique monoclonal antibody they

developed that recognizes only the isoenzyme CK-MB among the three isoenzymes of creatine kinase known to exist. Besides being very precise diagnostic tools, these tests will help probe the mechanisms of these enzymes, thus adding to the fund of basic science knowledge.

But this research is only one aspect of what laboratory medicine is all about: "We have to dispel the notion that the laboratory is a black box," says Ladenson, "where you put a sample in, a number comes out, and the whole process works through some sort of miracle. Without knowledge of the process, you're just pushing a lot of numbers. And that's not information, it's just data."

# Warming up to Ubiquitin

BY SUZANNE HAGAN

The gender of our offspring is not something we primates leave ungoverned; sex chromosomes called "X" or "Y," nestled among the other 22 in sperm, determine whether we buy pink or blue booties. Some turtles and lizards, however, do things differently. The sex of their offspring depends solely on the temperature caressing their clutch of leathery eggs. For map turtles, very low (20 C) or high temperatures (31 C) induce femaleness; mid-range temperatures produce male offspring.

Heat, then, could be considered sexy because of its strange and wonderful effects on amphibians' eggs. But the story doesn't stop there. Across the realm of biology — from primitive, one-celled organisms to complex creatures like amphibians, birds and mammals including humans — the application of a stressor such as heat brings about profound changes within cells.

Too much heat, of course, can be fatal to cells, congealing their proteins into a useless glob. Cancer cells seem to be particularly sensitive, which is why hyperthermia is part of oncologists' armamentarium. But non-fatal amounts of heat applied to normal cells stimulate the production of what are known as the heat shock proteins (HSPs). We don't know whether HSPs cause sexual differentiation in map turtles, ordaining that one clutch of eggs will be primarily female or male baby turtles. Exactly how the HSPs

protect cells and enhance their survival is unknown.

The effects of heat shock were first described about 25 years ago. Exposure to heat produced marked changes in fruit fly chromosomes.

During the next 15 years, the phenomenon was defined; new RNAs and new proteins, called HSPs, were identified. Yet the heat-induced changes in fruit flies were thought to be an interesting but isolated anomaly. But in the late 1970s, research in the field of heat shock proteins took off. When exposed to heat, cells of most organisms, from bacteria to humans, displayed these unusual proteins.

Because their structure is identical, or nearly so, from one species to another, HSPs were believed to play an integral role in all cells. Yet their actual function remained a mystery.

No one is sure how many HSPs exist, but their number is probably small. In chicken cells, four major HSPs have been identified. Three are known simply by their subunit molecular weights: HSP-90, HSP-70 and HSP-24. But the fourth, ubiquitin (so named because of its ubiquitous distribution from species to species), wasn't even known to be a heat shock protein until a few years ago.

Like so many important scientific discoveries, ubiquitin's identity as a heat shock protein was serendipitous. Ursula Bond, a predoctoral student in the laboratory of

Milton J. Schlesinger, Ph.D., was treating cells with heat to see what new proteins might be induced.

Rather than looking at the new proteins themselves, she examined the messenger-RNA that carries instructions for their manufacture.

"When I started to analyze the m-RNA present in the cells after heat shock," says Bond, "I found several RNAs that were induced. When I sequenced one of them, I found it coded for ubiquitin. That was the first time anybody had shown that ubiquitin was a heat shock protein."

Ubiquitin, a 76-amino acid protein, had first been described in 1975. Because of its widespread distribution among species, and the fact that its amino acid structure is nearly identical from species to species, ubiquitin was thought to play an important role in cells. But just how important is only beginning to be understood.

"Ubiquitin is needed for all cells to go through their cycle of cell division," says Schlesinger, professor of microbiology and immunology. "We think that ubiquitin's importance lies in its association with proteins known as histones, which are molecules that interact with DNA in a highly organized structure. It's been known for many years that about 15 percent of histones have ubiquitin attached to them. This attachment occurs only during a portion of the cell growth cycle. When the cell gets ready to



*Predocctoral student Ursula Bond discovered that ubiquitin formation is induced as temperature rises, making it a member of a still-mysterious family of proteins called heat shock proteins. Ubiquitin was so named due to its presence in a wide variety of species.*

divide, these ubiquitinated histones release their ubiquitin. Apparently, as soon as the ubiquitin is released from the histone, the chromatin condenses into a form that is ready for cell division."

Besides its functions in the cell nucleus, ubiquitin plays a second role. It serves as a marker, tagging proteins that need to be broken down. "The way the system works," remarks Schlesinger, "is that there's a set of enzymes that recognize ubiquitin. In the presence of ATP, these enzymes can activate ubiquitin. The activated ubiquitin is then attached to proteins destined for disposal. A single protein can get many ubiquitin molecules attached to it."

The remainder of this cellular protein-digesting scheme is unknown in detail, says Schlesinger, but it too is dependent on ATP. "Most cellular protein-digesting activities we're familiar with occur in compartments — there are protein-digesting enzymes on

the membranes of the Golgi secretory system, and in lysosomes and mitochondria. But the ATP/ubiquitin system may be the only protein-digesting system present in the cytoplasmic part of cells."

In addition to its functions in cell division and protein breakdown, ubiquitin has a third role: It has been found on "homing receptors." These are structures on the surfaces of lymphocytes enabling them to "home in on" and bind to tiny veins in the lymph organ from which they originated — their first "home."

"We really don't know whether the ubiquitin found on these homing cell receptors is acting as a modulator of the receptor structure," says Schlesinger. "It could be affecting the receptor's function, as it does for histones. Or if many molecules of ubiquitin are present, it could be a mechanism for eliminating the receptor from the cell surface."

Heat shock proteins like ubiquitin are produced in response to several forms of stress, including heat. In some way, the application of this stress triggers the so-called "promoter" region that governs the activity of genes coding for the heat shock proteins. In fact, HSPs like ubiquitin have a unique promoter region, the so-called "Pelham box," named for its Cambridge discoverer, Hugh Pelham.

"So there are two criteria that I consider for any heat shock protein," summarizes Schlesinger. "It is inducible after heat or some other stress is applied to cells. And its production is governed by the Pelham box promoter region."

"We've shown that the gene coding for ubiquitin has all of the characteristics of a heat shock gene," says Bond. "It has the Pelham box. And you can see this gene expressed when you give the cell several forms of stress."

Bond has just sequenced the gene for ubiquitin in chicken cells. This may be the first complete sequence of the gene for ubiquitin.

"It's a very simple gene, made up of multiple copies of the protein-coding sequence placed in tandem to each other," says Bond. "And that makes it really unique. Also, it has an intron — an intervening sequence of base pairs, not part of the protein code — at one end. That was a surprise because normally heat shock genes don't contain introns."

The important roles played by HSPs generally, and ubiquitin in particular, are only just beginning to be understood, for the ways that HSPs help cells tolerate stress remain a mystery.

"Shortly after we began studying HSPs," says Schlesinger with a grin, "a colleague warned that we might be 'hunting the snark.' I think that's unlikely. There's plenty of evidence to indicate that we'll soon know what heat shock proteins do." ■

**Editor's Note:** For further information, see "Ubiquitin Moves to the Cell Surface," *Science Magazine*, 231, 21 February 1986, 796-7.



# INTERFERONS *on TRIAL*

BY LINDA SAGE

*Lorraine Luebbert of Creve Coeur, Missouri, has a new lease on life. In July 1985, her doctor diagnosed kidney cancer and predicted death within two months. But seeking a second opinion, Lorraine had the kidney tumors removed and entered an experimental interferon program at Washington University. She still has the cancer, in the form of metastatic growths on the pancreas. But she is still alive to enjoy her grandchildren.*

Corrine Durand of Galesburg, Illinois, doesn't have to look up the date of her son's first interferon treatment — December 19, 1983, is engraved on her mind. In the previous six months, Michael had undergone laser surgery every two to three weeks for recurrent growths on the larynx. Each operation lasted over an hour and cost \$3,500 to \$4,000. But with regular injections of interferon, the intervals between surgery lengthened and then the growths disappeared. Michael is now a healthy 4-year-old and has needed neither surgery nor interferon since June 1985.

In clinical trials, there may be only a few such success stories, but each provides hope during the long hours of research that follow. At Washington University, there is hope among clinicians who are testing the antiviral and antitumor properties of the interferons, a family of proteins that have just become widely available.

In the division of pediatric otolaryngology, an interferon is on trial in the treatment of recurrent respiratory papillomatosis, the viral disease that afflicted Michael Durand. In the division of urologic surgery, urologists are testing two types of interferon against renal cell adenocarcinoma, the kidney cancer that has stricken Lorraine Luebbert. And pediatric oncologists will see if an interferon can combat relapses of

the most common childhood leukemia, acute lymphoblastic leukemia.

### Papillomas

Recurrent respiratory papillomatosis (RRP) begins most often in children between the ages of 12–24 months, though it can occur at any age. Only 1,500 cases are diagnosed in the United States each year, but RRP can be devastating for those affected. A carbon dioxide laser can safely remove most of the growth from the larynx, windpipe or nasal part of the pharynx, but some infected tissue usually remains and the tumor grows back. If it is on the vocal cords, the first symptom is hoarseness. But as it proliferates, like the top of a miniature cauliflower, it can completely close off the airway — a tiny 5mm in diameter in a small child. Children need an average of 13 operations to clear them of the disease, but some patients make hundreds of trips to the operating room. And for parents, there is the constant worry about the timing of the surgery. “The most traumatic thing is that you don’t know how far [the disease] has gone,” says Connie Durand. “You live on pins and needles.”

Inevitably, she and her husband once misjudged the extent of the papilloma. One night they found Michael bouncing in his crib as he struggled for air. He had developed stridor, the noisy respiration typical of a blocked airway, and he needed immediate surgery.

Other than interferon, there is little help for patients like Michael. Radiation therapy is ineffective and may convert the benign growths into malignant tumors. Chemicals applied directly to the vocal cords and courses of antibiotics, steroids or chemotherapeutic agents (such as 5-fluorouracil) are also of little use.

In 1978, a Swedish physician who was treating a woman with interferon for cervical cancer noted that the plantar warts on the woman’s feet disappeared. Reasoning that plantar warts are closely related to laryngeal warts, he gave interferon to seven children with respiratory papillomas. In 1981, he reported that most of the children had improved dramatically.

Clinical trials began at Washington University in early 1982, when Harlan Muntz,



Louis Rivera, Jr.

*Michael Durand with his mother, Corrine, at their home in Galesburg, Illinois.*

M.D. '77, assistant professor of otolaryngology and pediatrics, entered a study using interferon provided by Burroughs Wellcome. In July 1985, assistant professor of otolaryngology and pediatrics Rodney Lusk, M.D., joined the Washington University staff, bringing experience of two other types of interferon under investigation. Lusk had previously participated in the study at the University of Iowa.

The Burroughs Wellcome trial is one of two carefully controlled studies to assess the effectiveness of interferon against RRP. It involved 66 patients who previously required laser surgery at least every two months. Twelve of the patients were from Washington University.

The patients were divided into two age-matched groups. After their last laser treatment, half the patients were randomized into a six-month trial of interferon, and the other half continued to have laser treatments. At the end of the six months, the two groups were crossed over.

Only the data for the first six months have been analyzed. Among the 33 patients treated with interferon during that time period, three responded completely and 15 had partial remissions, whereas none of the patients in the control group improved.

Though heartened by these findings, Lusk is not ecstatic: “Interferon is not going to be a panacea for RRP,” he says. “It is effective in some children but not in all. That may have something to do with the

type of virus since there are several subtypes, some much more severe than others.”

At present, the Burroughs-Wellcome trial is expanding to include RRP patients who require surgery every three to nine months. “Since interferon seems to be effective in a certain percentage of patients,” says Muntz, “less severely affected ones may also benefit. We’ll be doing mostly adults because it’s a problem for them to take off from work every few months to go to the hospital. And between times, they have significant hoarseness and symptoms of airway obstruction.”

### Kidney Cancer

Although RRP can be a major trauma, it is rarely fatal. Not so with renal cell adenocarcinoma, which kills about 8,000 Americans each year, mostly men over 40. The only treatment is early detection and removal of the affected kidney. But diagnosis is rarely made in time because the disease is symptom-free in its early stages. If a tumor grows large enough to cause problems, metastases inevitably occur. Then, there is no effective treatment because the cancer is resistant to all forms of chemotherapy.

Previous studies showed that gamma interferon has some activity against renal cell adenocarcinoma. For example, the protein inhibited the proliferation of kidney cancer cells in tissue culture and slowed the growth of human kidney tumors transplanted into mice. And in preliminary clinical trials,

about one-third of patients made some type of response to interferon.

William Catalona, M.D., professor of surgery (urology), Timothy Ratliff, Ph.D., research associate professor of surgery (urology), and surgery resident M'liss Hudson, M.D., began to test gamma interferon on 14 patients, including Lorraine Luebbert, in August 1985. Their studies were part of a Biogen trial with interferon produced by recombinant DNA technology.

Of the 14 patients, six received only progesterone, the approved but largely ineffective treatment for renal cell adenocarcinoma. The other eight received gamma interferon. CT scans at six-week intervals revealed that three of the test patients had responded, though one later relapsed. (Failure of the tumors to grow larger was considered to be a response.)

"There are two potential mechanisms of action," says Ratliff. "One is direct inhibition of cell growth by interferon. The other is interferon's ability to augment the immune response. It activates cells that attack and kill tumor cells. It also enhances tumor cells' expression of proteins that the immune cells recognize."

Now Catalona, Ratliff and Hudson are taking part in a new multicenter study sponsored by Schering-Plough. The patients will receive gamma or alpha interferon alone or together. The hope is that the latter will be more effective. In tissue cultures of kidney cancer cells, the two interferons halve the rate of cell proliferation when combined at concentrations where neither is effective alone. The duo also decreases the growth of human kidney tumors implanted into mice.

But Ratliff is tempering his optimism. "These drugs are just experimental," he says. "We can't offer them to patients as treatment. We are just trying to develop new approaches for the use of interferons, and we hope that this study will provide us with better results than we have gotten in the past."

### Childhood Leukemia

Unlike the struggle against kidney cancer, the fight against childhood leukemia has been one of the success stories of the last decade. Fifteen years ago, only 20 percent of children with acute lymphoblastic

When alpha interferon was first described in Britain in 1957, it was dubbed "imagimon" by scientists who doubted its existence. But today, we have tangible proof of its reality. Large quantities can be prepared, either from a line of abnormal white cells or through recombinant DNA technology. Copies of interferon genes inserted into cultured cells such as bacteria make the cells push out high concentrations of the protein into the medium.

The greater availability of the interferons has led to numerous clinical trials and, recently, to commercial availability. In March, Britain's Committee on Safety in Medicines approved the sale of alpha interferon for the treatment of hairy cell leukemia, an adult cancer. And in June, the Food and Drug Administration licensed Hoffman-LaRoche and Schering-Plough to sell alpha interferon in the United States for the same purpose.

The interferons promise to treat a much wider range of conditions than hairy cell leukemia, however. Recent studies have shown that interferons can protect cultured cells from the AIDS virus, control genital warts and alleviate the pain and inflammation of rheumatoid arthritis. Moreover, nasal sprays of interferon halt the spread of rhinoviruses, the most common of the common cold viruses.

Neither the antiviral nor antitumor activities are fully understood. But interferons are known to inhibit cell growth and cell division, modulate differentiation and alter cell surfaces. They also activate part of the immune system. ■

leukemia (ALL) were alive five years after diagnosis. But thanks to new methods of chemotherapy developed in the mid-1970s, 55 to 60 percent of the 2,000 new cases diagnosed in the United States each year survive for more than five years. And most of those patients are cured because relapses after four years are rare.

However, the Pediatric Oncology Group, an organization of childhood cancer treatment centers, is rooting for the 40 percent that succumb to ALL. At highest risk are black children and males of all races who are less than three years old and over six years old, have high white cell counts at initial diagnosis and rearranged or defective chromosomes in the abnormal white cells. If the cancer cells are derived from the precursors of T-cells, which form in the thymus gland, the outlook is worse than for non-T-cell leukemia.

The pediatric oncologists will take part in a clinical trial funded partly by the National Cancer Institute. The study will determine if interferon can help children who relapse after chemotherapy and an initial remission. "If you have a cancer that relapses in spite of state-of-the-art therapy and high cure rate, you are in trouble," says Vita Land, M.D., associate professor of pediatrics and one of the five Washington University pediatric oncologists involved in the study. "Then it becomes ethical to introduce a new therapy."

The patients will receive seven days of alpha interferon treatment followed by standard chemotherapy. The latter usually brings a child into a second, temporary remission, and interferon therapy will continue periodically during that time.

Interferon is active against ALL cells in culture and in animals. Also, it has helped adults with ALL or a closely related cancer of the lymph glands. "However, children aren't necessarily little adults," cautions Land. "Just because interferon seems to have activity in adult leukemia doesn't mean that it will work in kids."

Clinical trials with experimental drugs such as interferon are carefully evaluated by both federal and university personnel. The ALL protocol was approved by the Food and Drug Administration and the National Cancer Institute in March 1986 and by the Human Studies Committee of Washington University School of Medicine's Institutional Review Board in May. If the therapy proves very effective, the next stage would be a controlled trial with newly diagnosed patients. So as with the RRP and kidney cancer trials, the verdict will not be in for a while. But there is hope among the jury. ■



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# WOOLING

## Promising Students

### RHODES

### Hits The

### ROAD

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BY CANDACE O'CONNOR

**A**s a promising biology student at St. Olaf College, Sarah Bronson hadn't quite decided whether she'd go on to graduate school. Then she spent last summer as one of 15 undergraduate research interns in Washington University's Division of Biology and Biomedical Sciences, and her summer experience resolved all her doubts. This fall, she's a brand-new predoctoral student working in molecular immunology. Her early reaction to the program? "It's even better than last summer," she says happily.

This kind of success story is a tribute to Washington University's recruitment program, one of the most active among universities. With tools such as the summer

research internship, the aim is to attract top-notch students to Ph.D. and M.D./Ph.D. programs in the graduate division. And this effort has been extremely effective, yielding a bumper crop of fine students like Sarah Bronson. In recent years, for example, applications from small liberal arts schools — a special recruiting target — have increased five-fold.

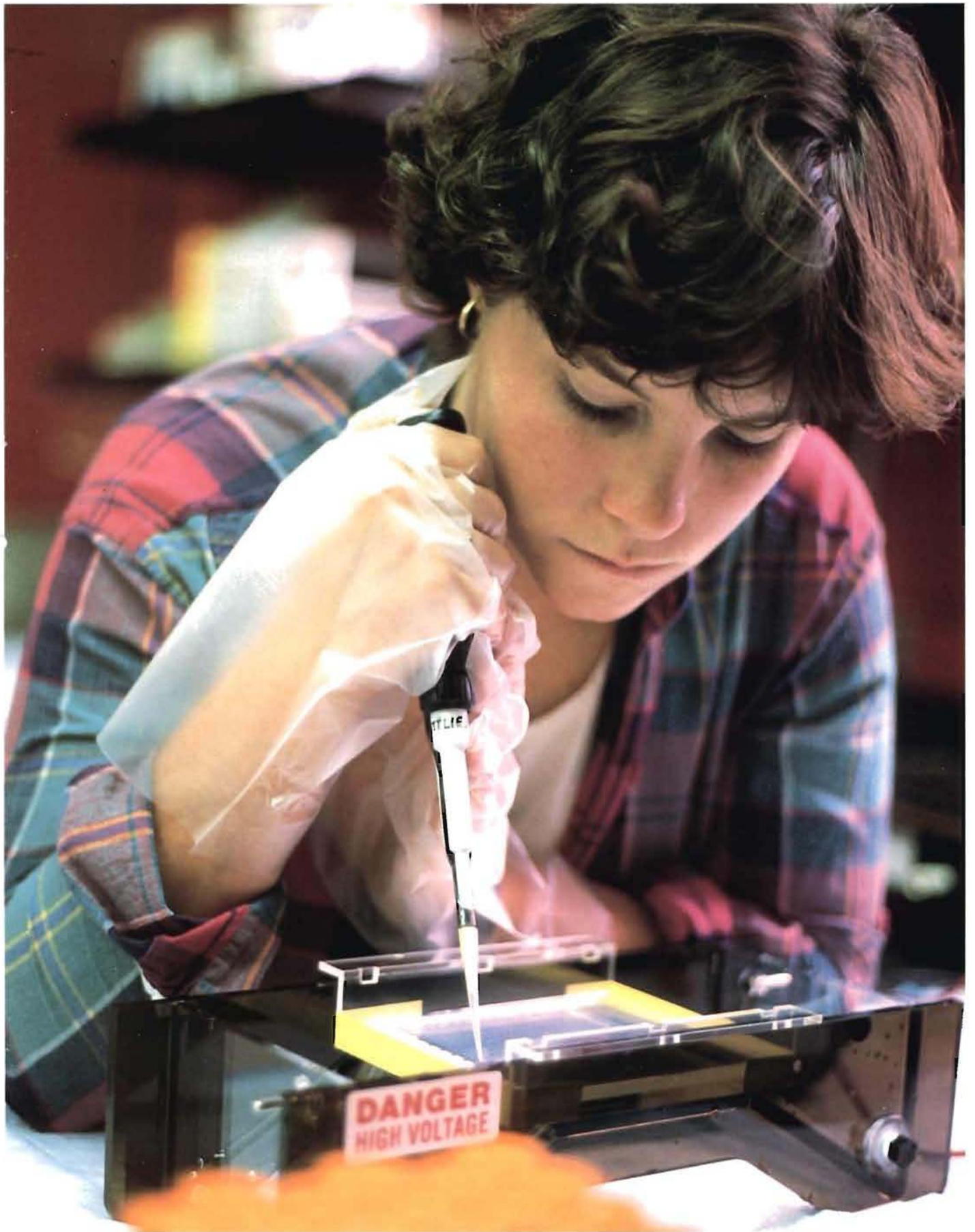
"The quality of our applicant pool is better than ever," says Carl Rhodes, Ph.D., research associate professor of biological

chemistry, associate director of the division and director of graduate training. "When we offer admission to top students, they may instead choose Princeton, MIT or Stanford. The competition for the best students is now greater, so the percentage

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*Kathy Buchanan, a promising undergraduate at Colorado College, Colorado Springs, had the chance to test herself in research and "a graduate study atmosphere" during her summer work at Washington University. Excellent small schools such as Colorado College have been targeted by the School of Medicine as a source of prospective graduate students.*

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we are able to enroll may not be as high. But in the end we will have better students."

Reaching these students requires year-round work by Rhodes, who heads the recruitment effort, and his four-member staff.

In late summer, they mail more than 1,000 posters and brochures to every major biology and chemistry department in the country. Within weeks, Rhodes is airborne, visiting some 25 campuses. Each year, he adds new schools to his itinerary; last fall, he made his first stops at Bates, Bowdoin, Colby and Trinity (Texas). His goal is to meet students and cement ties with sympathetic advisers, usually faculty members whose active research programs entice students interested in graduate work.

While most science faculty at these schools already know Washington University, the students may not. "The joke I use in speaking with them is that we're neither six blocks from the White House nor on Puget Sound," he says. "The fact is, though, that a lot of them don't know where we are."

They may also have misconceptions about graduate work. During his visits, Rhodes often gives a "neutral" seminar, explaining what students should look for in a Ph.D. program and what admissions committees will expect: "All sorts of things come up. Students may not realize how well qualified they are for graduate school. Sometimes they don't even know they can receive tuition and a stipend for their graduate work. They think they'll have to borrow the money."

At some schools, Rhodes also finds that he's a new phenomenon. Though Princeton is beginning to initiate a similar program, other graduate institutions just don't do Washington University's kind of personal recruiting at the graduate level. A genial and energetic man with a strong concern for students, Rhodes has clearly provided some of the impetus for this major recruiting effort. When he arrived three years ago after administrative posts at NIH and Stanford, the time seemed right: A rush of new faculty and a one-to-one faculty/student ratio were extremely attractive. After a lapse during the Nixon administration,

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**"Frankly, we get lots of requests by recruiters to give seminars, but we honor very few of them. Carl Rhodes' seminar, though, is extremely helpful to the students."**

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federal funding — primarily NIH training agents — was available.

Since then, Rhodes has gained solid respect for his work, says Ted R. Johnson, Ph.D., head of the Biology Department at St. Olaf College: "Frankly, we get lots of requests by recruiters to give seminars, but we honor very few of them. Carl Rhodes' seminar, though, is extremely helpful to the students."

Even though he travels to big schools like the University of Washington and Cornell, Rhodes says that recruiting from them can be difficult. There may be more than 1,000 undergraduates in the biological sciences at one of the larger schools; advising is often done on an alphabetical basis. He prefers to concentrate on small liberal arts colleges. Traditionally, they have a high percentage of science majors who go on to do well in research. They also have an excellent track record here: since 1978, some 25 percent of division graduates have come from small colleges.

These schools also supply the undergraduates for Washington University's summer internship. Since 1982, when three biology students came from Kalamazoo College, the program has grown to a maximum of 15 students per summer, drawn

from various colleges. These students, usually incoming seniors highly recommended by their own science professors, spend three months here working on a research project.

"The idea is to give them a view of graduate work at a large institution," says Rhodes. "But you might ask what's in it for us? We hope that when they go back, they will tell other students about the experience they had here," Rhodes says.

One of last summer's group is Michael Kyzer, a chemistry major from Hendrix College in Arkansas. After working in the laboratory of Maynard V. Olson, Ph.D., associate professor in the Department of Genetics, Kyzer is enthusiastic about his experience. "It's wonderful. I'm surprised they've allowed me to do so much independently." He plans to tell other Hendrix students about his summer internship. Will he apply here for graduate study? "Definitely," he says.

In recruiting students to summer and graduate programs, Rhodes says, the reputations of the divisions' 230 faculty members play an important part. "If we didn't have a good faculty, it wouldn't matter what I did. We wouldn't attract anyone," he says.

The innovative Washington University graduate program is also a strong selling point. In 1973, the Division of Biology and Biomedical Sciences was organized as a consortium of seven medical school departments, plus the Department of Biology on Hilltop campus. Rather than traditional concentrations along departmental lines, the new division offers five interdisciplinary programs: Molecular Biology and Biochemistry, Cell and Integrative Biology, Plant Biology, Population Biology, and Neural Sciences.

The 220 graduate students in the division, which is now directed by Daniel Hartl, professor and head of genetics, still enjoy a sense of freedom unmatched at most institutions. During their first year, they can readily switch from one program to another. They can also rotate among two or three labs to see where personalities and research interests best mesh.

This openness is a boon to recruiting, says Johnson of St. Olaf College, who last year sent three of his four top students to



*Carl Rhodes, associate director of biology and biomedical sciences, discusses research progress with an undergraduate research intern, Jeff Zachs. In a program conceived by Rhodes, promising undergraduates receive research experience and familiarity with Washington University through summer internships.*

the division. "In many graduate schools, students come to work with a specific adviser or in a designated area. At Washington University, they can shift around. For our students, whose interests may not be focused yet, this is a great advantage."

Julie Hatch, a St. Olaf graduate and fourth-year student, used that freedom to pin down her own research interests. She stayed in her third rotation, working in the laboratory of Susan E. Cullen, Ph.D., associate professor of genetics and microbiology and immunology. Now, she enjoys the spirit

of cooperation that exists between programs. "There's a lot of interaction between departments. I'm interested in cell biology, but I hear what's going on in pathology and other areas," Hatch says.

The Washington University graduate division is not for everyone. One summer student discovered his true vocation during his stay — and is now in a Lutheran seminary. And those who wish to apply will find that the school is highly selective. Last year, of 450 applicants, only 85 were offered admission and 44 finally came.

But Rhodes hopes that, through the various aspects of his recruiting program, he can reach those students who would benefit by a Washington University graduate education. Mike Kyzer is convinced. "I plan to go back to Hendrix with many, many positive things to say. The Washington University faculty is supportive and knowledgeable in many fields. Students can pursue their own interests and not just become satellites of an investigator. For a graduate student, it's a very attractive place to get an education." ■

# Howling at the Moon

## *The Unnatural History of the Movement Against Animal Experimentation*

Seventy years ago, infectious diseases stalked the land with far greater certainty of death than AIDS does now. Everyone could experience Mimi's hopeless agony as she slowly expired from consumption (tuberculosis) in Puccini's "La Bohème." Surgical procedures that we now take for granted were still being developed and perfected; little could be done to stem the usually fatal course of post-operative infection.

Progress in medical care is a testament to human imagination, the dedication of health care professionals, and society's ability to solve important problems. Studies using animals as research subjects have sharpened considerably the effectiveness of health care and broadened the scope of its services. Experiments on animals have led to corneal transplants (rabbits; *Am. J. Ophthalmol.* 34 (1951): 142), immunization against polio (chimpanzees; *Am. J. Hyg.* 51 (1950): 85), removing blood clots (dogs; *Circulation* 72 (1985): 18), treatment of diabetes (dogs; *J. Lab & Clin. Med.* 7 (1922): 251), and the spectacular rise of cardiovascular surgery (dogs; *JAMA* 128 (1945): 189). Better diagnosis, treatment and prevention have immeasurably improved the lives of humans and our animal brethren.

Despite many spectacular advances, the future of scientific medicine is threatened in the name of "animal rights." Laboratories at the University of Pennsylvania Medical

School were raided on the 1984 Memorial Day weekend. Sixty hours of videotapes documenting experiments for a head injury project were stolen by ALF (Animal Liberation Front). Soon afterward, PETA (People for the Ethical Treatment of Animals) distributed a slick video, "Unnecessary Fuss," extracted from the stolen tapes. The PETA video, narrated by Ingrid Newkirk, is not pretty. It would turn the stomach of anyone not familiar with the tragedy of head injury and its devastating effects. Yet these stomach-churning experiments are one of the few hopes the victims and their families have.

Last summer, in response to intense political pressure, then-Secretary of Health and Human Services Margaret Heckler suspended federal funding for the Penn research. Subsequent raids on laboratories throughout the country have often been followed by surprise inspections of animal facilities and research laboratories by the National Institutes of Health (NIH). Early this year, all federal funds awarded to Columbia University were withheld for six months after such an inspection, no doubt further providing positive reinforcement for animal rights activists.

Now, the NIH itself is under attack. PETA accuses the NIH of mishandling the care of a group of monkeys seized several years ago from a Silver Springs, Md., laboratory. The activists have enlisted

Congressional support in pressuring the NIH to turn the animals' care over to a private sanctuary.

The response of individuals in the biomedical community to these challenges has been slow, weak and poorly organized. Is this because we believe that the problem will go away? If history tells us anything, it is that this belief is patently absurd.

The animal rights movement is not new; it sprang up in eighteenth-century England and America as a radical offshoot from humane societies. Then, as today, humane societies provided essential services, such as caring for and disposing of stray dogs and cats. Antivivisectionists, as the radicals were then called, attempted to abolish animal experimentation and, failing that, to regulate it into oblivion.

Antivivisectionists in the 1800s assumed that all animal experimentation was painful and cruel. They also accused scientists of being immoral atheists and questioned the validity of scientific progress. Boldly political tacticians, antivivisectionists had "cells" located in cities. These vigorous, well-financed, political organizations recruited supporters, published pamphlets and won over influential clergy and politicians. Their efforts were rewarded by the Cruelty to Animals Act of 1876, which is still the basis for regulation of animal experimentation in England.

As early as 1867, attempts at similar legislation began in the United States. The leaders of American medicine organized strong, successful opposition to the Congressional bills of 1896 and 1900. Their case was bolstered by the demonstrated value of animal research in surgical antisepsis (published by Lister in 1867, based on his direct observations on inflammation in experimental animals), antitoxin treatment for diphtheria (introduced by Behring in 1893, after he and Kitsato demonstrated that serum from animals exposed to diphtheria toxin protected other animals from the disease), and other discoveries that improved the health of humans and animals. Re-emerging in cyclical fashion throughout this century, the animal rights movement has gained renewed strength.

Historians have examined the movement with a dispassionate eye. They note that antivivisection agitation preceded animal experimentation in English and American medical schools. In the historians' view, concern over animal welfare masked ulterior motives. Under the powerful rallying cry of antivivisection seethed other concerns: nationalism, political expression for unfranchised women, and difficult-to-articulate problems like the displacement, squalor and suffering brought on by the industrial revolution.

Since the concept of animal rights is not new, nor is the sensitivity to animal suffering, it is not clear whether ulterior motives underlie the present resurgence opposing animal experimentation and harvesting of animals for food, clothing and sport.

On the *Today* show of July 18, 1985, PETA's Newkirk commented: "If it [animal experimentation] were such a valuable way [to gain knowledge] we should have eternal life by now." This refrain is strikingly similar to one made by antivivisectionist Matthew Woods in 1900: Given the number of experiments on the brain done up to that time, he said, the insane asylums of Washington, DC should be empty.

Indeed, most of the current strategies are strikingly similar to those of antivivisectionists: publicize, misrepresent, find supportive "medical friends" and attempt to limit funds for biomedical research. Even



*Thomas A. Woolsey, M.D.*

more ominous are the breaking into, the theft from and the destruction of laboratories, and the direct threats on the lives of working scientists.

Those who advocate the cessation of animal experimentation have the right to express themselves. But how humane is to deprive of hope victims of senile dementia, stroke and cancer — problems that affect a growing proportion of our population with almost unbearable immediacy? Answers can only come after years of intensive study on experimental animals. It is clearly in our interest to adopt alternatives to animal experimentation — models — when these models more quickly lead to the right answers. But at present, there are no suitable experimental models that can be substituted for animal experimentation in research on senile dementia, stroke and cancer.

Scientists are not inhumane, immoral monsters who delight in torturing helpless

creatures. On the contrary, we have that exceptionally deep respect for all of life, including human, that can only come from years of intensive study. As health professionals, we feel a deep sense of responsibility to those we serve. I believe that part of that responsibility is making sure, to paraphrase Dr. Mary Putnam Jacobi in 1900, that "knowledge is not dominated by ignorance." The record is clear; careful, well-thought-out experiments on animals have vastly improved veterinary practice and medical care. Such work can make, and has made, the difference for their well-being and ours. ■

**Thomas A. Woolsey, M.D.**

*Professor, Anatomy and Neurobiology and Cell Biology and Physiology  
George H. and Ethel R. Bishop Scholar  
in Neuroscience in Neurology and Neurological Surgery  
Professor of Neurology and Neurological Surgery*

# THE ALUMNI REPORT

## Hagemann Receives Eliot Award

**P**aul O. Hagemann, M.D. '34, clinical professor emeritus of the Washington University School of Medicine, has received the prestigious William Greenleaf Eliot Society Award.

William Van Cleve, president of the Eliot Society, presented Hagemann with a silver and marble replica of the sculpture "The Search," designed by Heikki Seppa, professor of art at the university.

Hagemann, an active participant in alumni affairs, is a life member of the Eliot Society. He has served on the university's Alumni Board of Governors and now is vice chairman in charge of the Planned Giving Committee. Hagemann was a key person in the development of the planned giving program and has established an endowed scholarship in the School of Medicine. His leadership in the Medical Center Alumni Association began early when he served as chairman of the fifth reunion of his class of 1934.

Marvin Levin, M.D. '51, professor of clinical medicine, who served both his residency and internship under Hagemann, calls him an "astute and caring" physician. "He had a good relationship with his patients," recalls Levin. "He set a good example for his students, interns and residents."

The Eliot Society is an organization of university alumni and friends. The society is named after the university's founder, the Rev. William Greenleaf Eliot. Each year the society honors an individual who has given outstanding service to the university, chosen by an anonymous committee of the society's members. Last year's award recipient was



*Paul O. Hagemann, M.D.*

Zane E. Barnes, chairman and chief executive officer of Southwestern Bell Corp.

Hagemann is a graduate of the Washington University College of Arts and Sciences and received his medical degree from the university's School of Medicine. After his internship at New York Hospital, he became an assistant resident at New Haven Hospital in Connecticut, where he was a Sterling Fellow in the research department. He returned to the Washington University Medical Center in 1937 to work as a resident at Barnes Hospital. He later joined the faculty of the School of Medicine as an instructor in medicine.

By 1944 he was serving as assistant professor of clinical medicine and director of the Barnes Hospital laboratories when his service with the U.S.

Army took him to Los Alamos with the Manhattan Project. Hagemann was part of the team that monitored the first atomic explosion in New Mexico. He later traveled to Hiroshima, Japan, to evaluate residual radiation in that area.

Hagemann returned to his private practice and teaching responsibilities at the School of Medicine in 1946. He was later appointed chief of medicine at St. Luke's Hospital and established the training program there that serves as Washington University's Postdoctoral Primary Care Training Program in Internal Medicine.

He has served as a Diplomate of the American Board of Internal Medicine, and was given the Distinguished Alumni Award at Founders Day in 1983 and the School of Medicine's Alumni/Faculty Award in 1984.

### CLASS NOTES

#### '30s

**Tom F. Whyne, M.D. '31**, is professor emeritus at the University of Kentucky College of Medicine. He is writing a history of preventive medicine in World War II and directing a program on the Oral History of Medicine in Lexington and Fayette County, KY.

**Robert A. Wise, M.D. '36**, is professor of public health and occupational medicine at the University of Texas School of Public Health, and clinical professor of internal medicine at Baylor College.

**O. Elliott Ursin, M.D. '36**, served in the U.S. Army Medical Corps for 32 years, and received a distinguished service medal. After retirement, he attended the University of Oslo for one semester, and then was medical director of a nursing home in San Antonio.

#### '40s and '50s

**Lawrence W. O'Neal, M.D. '46**, is chairman of the Department of Surgery at St. John's Mercy Medical Center in St. Louis and professor of clinical surgery at St. Louis University.

**Ann DeHuff Peters, M.D. '46**, is clinical professor of pediatrics at the School of Medicine, University of California at San Diego. She was president of the American Orthopsychiatric Association in 1981.

**Harry S. Jonas, M.D. '52, FHS**, dean of the University of Missouri-Kansas City School of Medicine, has been named

president of The American College of Obstetricians and Gynecologists (ACOG).

As a private practitioner in Independence, MO, from 1956 until 1975, Jonas delivered more than 7,000 babies. He became full-time professor of obstetrics and gynecology at the University of Missouri-Kansas City School of Medicine, and chairman of the OB/GYN department at Truman Medical Center, the University's teaching hospital. Since 1978 he has been dean of the medical school.

Jonas was instrumental in the successful passage of a public bond issue which built the teaching hospital for the medical school. Truman Medical Center is a public hospital serving a large number of indigent patients, including many who are high-risk obstetrical patients.

He has held many positions with state, regional, and national OB/GYN societies. For the past 25 years he has been an active member of ACOG. He chaired the College's Health Care Commission, which studies and makes recommendations on those issues facing practitioners of obstetrics and gynecology. He chaired ACOG's Missouri Section and the South Central District and was a member of the national Committee on Professional Liability. For the past year, he served on ACOG's executive board as the president-elect.

He is chairman of the Obstetrics Section of the Southern Medical Association, a board member of the Truman Medical Center, past member of the Governor's Task Force on Rape Prevention, and past president of the Kansas City Gynecological Society.

He has served four terms as a member of the regional screening panel of the President's Commission of White House Fellowships. A member of several professional societies, he has authored a number of scientific journal articles and textbook contributions.

Jonas completed his OB/GYN residency at Barnes-St. Louis Maternity and St. Lukes hospitals.

**Jean A. Chapman, M.D. '53, FHS**, of Cape Girardeau, MO, a specialist in internal medicine and allergy, has been elected to Fellowship in the American College of Physicians (ACP).

Chapman received a B.S. degree from Southeast Missouri State College in Cape Girardeau in 1949, and an additional B.S. in medicine with an M.A. in Anatomy from the University of Missouri in 1951. After completing his M.D., he went on to become a medical resident at St. Louis City Hospital on the Washington University Service.

**Daniel M. Divack, M.D. '56**, is an obstetrician and gynecologist in private practice with appointments at Long Island Jewish Hospital and the State University of New York at Stony Brook.

**Havner H. Parish, M.D. '56**, retired after 25 years of private practice in urology. He lives in Pittsboro, NC, is a pilot and plays the bassoon.

**Morris Reichlin, M.D. '59**, received the 1986 Provost's Research Award from the University of Oklahoma Health Sciences Center. A professor of medicine in the OU College of Medicine, Reichlin was one of two recipients of the annual award, which recognizes per-

sonal achievement in original research. His interests center on the immunological aspects of arthritis and the improvement of diagnostic procedures for certain immunological diseases, particularly systemic lupus erythematosus and polymyositis, an inflammation of the muscles.

**Raymond G. Schultze, M.D. '59**, became administrative vice-chancellor and director of UCLA Medical Center



**Raymond G. Schultze, M.D.**

on September 1. He has been the center's director since 1980. The combined appointment links responsibility for management of the 711-bed center with administrative functions for the campus.

Schultze holds the B.A. and M.D. from Washington University. He served his internship and residency at UCLA.

In 1965, he returned to Washington University as a United States Public Health Service Postdoctoral Fellow, and was also appointed to the faculty as instructor and then assistant professor of medicine.

Returning to UCLA in 1969, he became assistant professor

of medicine. He was promoted to associate professor in 1973 and to professor in 1978.

Within the Department of Medicine at UCLA, Schultze has served as chief of the division of nephrology, executive vice chairman and acting chairman. He was associate dean for administration in UCLA School of Medicine from 1979 to 1986.

**William I. Goettman, M.D. '58**, was inducted into Wittenberg University's Athletic Hall of Honor.

Goettman was co-captain, Most Valuable Player, All-Ohio Athletic Conference and All-Ohio for the 1952 and 1953 basketball seasons at Wittenberg. He set what was then a school single-game scoring record with 38 points against Ohio Wesleyan. Goettman was also a standout tennis player, holding the number one spot in singles and serving as captain of the doubles team.

A Danforth Scholar, Goettman served 12 years as team physician for the Tigers' athletic squads. He was a chair of the Tiger Fund during "The Campaign for Wittenberg" that raised over \$20 million.

## '60s and '70s

**John T. Crosson, M.D. '61**, is associate professor in the Department of Laboratory Medicine and Pathology at the University of Minnesota. His hobbies include tennis, music and running, and he has completed four marathons.

**Phillip E. King, M.D. '61**, is associate clinical professor in radiology at West Virginia University Medical School. He



also has a private practice and appointments at several hospitals.

**Carl Mitchell, M.D. '61**, is in private practice in Nashville, TN, and is clinical assistant professor of medicine at Vanderbilt University and the University of Tennessee.

**Gordon W. Philpott, M.D. '61**, is professor of surgery at Washington University School of Medicine. His hobbies are fishing, photography and vegetable gardening.

**Shigemi Sugiki, M.D. '61**, is associate clinical professor of ophthalmology at the University of Hawaii School of Medicine. He also has appointments at Kuakini, Straub and St. Francis hospitals and the Queen's Medical Center. This year he became president of the Hawaii Ophthalmological Society. He is also an instructor in aikido.

**H. Michael Jones, M.D. '66**, a specialist in pathology and nuclear medicine, is in solo practice in Henderson, NC. He also heads a recruitment program that has tripled the number of physicians in his rural area.

**Donald R. Kirks, M.D. '68**, currently professor of radiology and pediatrics at Duke University Medical Center, has been appointed chairman of the Department of Radiology at Children's Hospital Medical Center, Cincinnati, OH, and professor of radiology and pediatrics, University of Cincinnati College of Medicine, effective September 1, 1986. The 330-bed pediatric institution is the largest children's

hospital in the United States. Approximately 70,000 pediatric imaging examinations (conventional diagnostic x-ray, ultrasonography, computed tomography, nuclear medicine, digital radiography, angiography, interventional procedures, magnetic resonance imaging) are performed annually.

Kirks, chief of the section of pediatric imaging in the Department of Radiology, has been at Duke University Medical Center since 1978. He is secretary of The Society for Pediatric Radiology and chairs the pediatric radiology program for the Radiological Society of North America. As member of the Executive Committee of the Association of University Radiologists, Kirks is editor of *Pediatric Radiology*, associate editor of *Radiology*, reviewer for the *American Journal of Roentgenology*, and examiner for the American Board of Radiology.

Dr. Kirks has published over 250 abstracts, scientific papers, review articles, and textbook chapters during his 14 years in academic pediatric radiology. His textbook, *Practical Pediatric Imaging: Diagnostic Radiology of Infants and Children*, was published by Little, Brown and Company in 1984. He received the John Caffey Award of The Society for Pediatric Radiology in 1979 and the William F. Barry, Jr. Resident Teaching Award of the Department of Radiology at Duke University Medical Center in 1985.

Kirks, a native of Ft. Worth, TX, received his B.A. from Rice University in 1964 and

M.D. from Washington University School of Medicine in 1968. After a medicine internship at Parkland Memorial Hospital in Dallas, Kirks completed a residency in diagnostic radiology at the University of California, San Francisco Medical Center and a fellowship in pediatric imaging at The Hospital for Sick Children in Toronto. He was a staff pediatric radiologist at Children's Hospital Medical Center, Oakland, CA, and Children's Medical Center, Dallas, TX, before joining the Department of Radiology at Duke University.

**Roger Warnke, M.D. '71**, is associate professor of pathology at Stanford University School of Medicine.

**Darwin C. Jackson, M.D. '76**, an obstetrician and gynecologist, has appointments at Washington University School of Medicine and Barnes, Jewish and Deaconess hospitals in St. Louis. His awards include Teacher of the Year, 1983-84 from the Department of Obstetrics and Gynecology, and Outstanding Young Men of America, 1985.

## FORMER HOUSE STAFF NOTES

**William Kaufman, Ph.D., M.D., FHS**, of Stratford, Connecticut, presented his paper "Niacinamide Improves Mobility in Degenerative Joint Disease" before the Biochemistry and Pharmacology Section of the 152nd Annual Meeting of the American

Association for the Advancement of Science held recently in Philadelphia.

**Leo A. Whiteside, M.D., FHS**, was named a member of the Board of Directors of the American Academy of Orthopedic Surgeons at the association's recent annual meeting in New Orleans.

Whiteside is chief of orthopedic surgery and director of the biomechanical lab at DePaul Health Center, Bridgeton, MO. He is research assistant professor of orthopedic surgery at Washington University.

Born in Pampa, Texas, Whiteside has a B.S. from the University of Oklahoma and an M.D. from the University of Texas, where he was honored by Alpha Omega Alpha when he received the Student Research Award in 1968 and 1969.

Whiteside is a member of 16 medical associations and is also editor of *Clinical Orthopedic and Related Research* and *The Journal of Arthroplasty*.

**Medical Center Alumni  
Association**  
Box 8049  
660 S. Euclid  
St. Louis, MO 63110

**Donald Sessions, M.D. '62**  
*President*

**Jack Siefkas, Director**  
Medical Alumni and Development  
Programs

**Kellie Semler, Director**  
Medical Alumni Programs

**Ruth Moenster**  
*Secretary*

## Patricia Newton's Progress

**P**atricia A. Newton, M.D. '75, travels through life with giant strides that would make Paul Bunyan proud. At the age of 40, this Baltimore psychiatrist has already packed more into her career than most people would by retirement.

"I knew when I was 8 that I wanted to go into medicine," she says. "They gave me a nurse's cape, but I didn't want that. I wanted a black bag with a stethoscope in it."

None of Pat Newton's progress could surprise those who knew her as the spirited, high-achieving, determined and somewhat unorthodox daughter of scholar-educators in her native Tuckerman, Ark. After all, this is the young woman who as a child broke a gift doll because she preferred cowboy guns.

The diminutive doctor-to-be won a third-degree black belt in karate, went in for weight lifting and aerobics, excelled in Spanish and piano, hated math, played basketball as a 5'2" forward, became the only pre-med member of the school touring choir and refused to leave that group, even though a faculty member worried that she was trying to do too much.

Always an excellent student, she graduated from high school at 15 — just as her mother, then living in St. Louis, had done 20 years earlier. Before entering medical school, she obtained her bachelor of science degree in pre-medicine from the University



*Patricia Newton, who graduated from the School of Medicine in 1975, is now president of an international behavioral science management consulting firm in Baltimore, and assistant professor of psychiatry at Johns Hopkins University.*

of Arkansas in Pine Bluff, and graduated *magna cum laude* from Vanderbilt University with her master's in molecular biology. While still in school, she worked as a microbiologist for the state of Tennessee.

After receiving her medical degree, she became a resident in psychiatry, then chief resident and instructor in clinical psychiatry at Washington University School of Medicine.

Her next stop was Baltimore, where she took a second master's degree, this one in public health from Johns Hopkins School of Hygiene and Public Health. She then joined the staff of Provident Hospital where, as psychiatrist-in-chief, she instituted pioneer programs for the rehabilitation of the chronically mentally ill. She spurred the hospital's sponsorship, together with the National Institute of Mental Health, of the first Baltimore International Congress of Transcultural Psychiatry. The Congress brought exchange scientists from all over the world, more than 600 participants from 25 nations.

Newton has resigned that hospital post to concentrate on her other professional interests, but she remains an innovative leader in the mental health area. President and medical director of Behavioral Medicine Associates, Inc. in Baltimore, she is editor of that organization's health information and educational service, president of Newton-THOTH, Inc., an international behavioral science management consultant firm, and on the faculty of Johns Hopkins University as assistant professor of psychiatry.

Her research centers on the effects of medical electrical acupuncture in stress management and in chronic pain.

Honor has followed closely on the heels of achievement. As a distinguished Marylander in medical science, she was appointed to the Governor's Task Force on

Alzheimer's Disease in Maryland and to the State Advisory Council on Mental Hygiene. In 1983, *Baltimore Magazine* cited her as one of the city's "100 most influential women." *Essence*, the nation's only black women's lifestyle magazine, chose her as "Woman of the Year in Health and Medicine" in 1985 in commemoration of the 15th anniversary of the publication honoring black women who have made outstanding contributions to American society.

A love of scholarship and education, in whatever field, was as much a part of her heritage as is her name. Her father, McKinley Newton, was her high school principal in Tuckerman; her mother, the former Bernice Jones, was on the faculty and coached basketball. They now live in Little Rock, where her father is vice chancellor of Philander Smith College. Both are graduates of Pat's alma mater in Pine Bluff.

"I studied science and math with Dad and English with Mother. She was one of the pioneer women's basketball coaches. It was tough having her as a coach. I didn't get any breaks," says Newton.

In Newton's high school days in Arkansas, she developed a special interest in drama and later parlayed that interest into a theater group for her patients.

"This started when I was head of psychiatry at Provident. We were looking for a way to give chronically mentally ill patients a way of rehabilitation.

"While I was lecturing at the University of West Indies, I ran across a doctor who was director of the Jamaican Psychiatric Services. He had trained in Edinburgh and had begun to rehabilitate chronic patients using the European technique called sociodrama."

Adapting the technique to her own hospital population, she developed a highly successful program for her patients: "They toured the area and played at Johns Hopkins and several other hospitals. They developed their own bank account and a couple of them got jobs in theater arts, on stage crews and similar work.

"This takes the chronically ill patients, gets them out of the regressive arena so they are able to interact and socialize and go out and get jobs. It's a form of social reintegration, helping to prevent relapse because

they can better manage and manipulate their environments.

"It was not a substitute for medication. It was run as an adjunct to help people re-socialize. From that group we developed a research program to carry those people forward. The state of Maryland developed something called psychosocial rehabilitation including job training for the mentally ill, and this patient group had all the skills to take full advantage of that program," explains Newton.

Even though her work with the chronically mentally ill sparks a missionary zeal, Newton also is concerned with those who

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*One of her great concerns — even though she is unmarried with no children of her own — is the problem of youth suicide*

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are not so disabled enough to be institutionalized but who are, nevertheless, buffeted by the tensions of modern society.

"In my private practice, we have a multi-specialty, doing a lot of prevention such as stress reduction, weight control and smoking cessation. We still treat the typical psychiatric patient, but my whole emphasis is on behavioral change and prevention."

One of her greatest concerns — even though she is unmarried with no children of her own — is the problem of youth suicide, a symptom of society's late 20th-century ills.

"Generations ago, there were not so many drugs available, not as much disintegration of the family," she says, as she considers the causes of human stress.

"There is so much more divorce today,

more single parents, and a lot more for children to get exposed to. We have a society that believes in instant gratification. We have a lot more violence, more child abuse, spouse abuse, teenage pregnancies — and suicide. According to the Youth Suicide Prevention National Committee, 500,000 persons between the ages of 15 and 24 try to kill themselves every year; 5,000 succeed."

Is there a cure, or, at least, a palliative? Her answer comes swiftly. "It has to start with re-education. I think it's too late for many of our children. I think we will have to change the structure of education.

"Children are having to make adult decisions long before they have adult mentality. They are exposed to material things without any kind of value system. Coupled with that is the threat of the present competitive environment. Jobs are being taken away. People are getting out of school while functionally illiterate."

The answer, she says, "should come from the family, but the family isn't there anymore. The only other place is the school system and groups of parents lending a hand in some kind of collective support system. If we don't do something, we will have a society of animals. None of us will be safe."

How does she maintain her own sanity? And how can others? "First of all," she says with a laugh, "I thank God for good genes. I was fortunate enough to have parents who were not overly protective but did protect me from certain things. I had a good family support system that was caring and loving and believed in allowing children to develop normally.

"The other side of this is that I have seen every kind of bad human behavior, and it all comes to a very common denominator — many of these people are not loved and nurtured."

She stresses the importance of "having the nurturance of good friends and family and the sanity to know that when things are overwhelming, you can give them up. And, remember, a little cry never hurts. We have to accept our own limitations and be able to let go and move on to the next level without feeling guilty about it. Only God is perfect." ■



*A chance to conduct research under the direction of internationally recognized scientists can help undergraduates make career choices and entice them to select Washington University for graduate study. See story, page 22.*

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Tony Cracchiolo

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*During orientation week, this year's 120 freshmen had a chance to get acquainted at a buffet supper at St. Charles Wine Garden. The annual freshmen welcoming party, which is sponsored by Washington University Medical Center Alumni Association, follows a bus tour of St. Louis.*

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