

## Director's Message: Celebrating the Future of OHSU Heart Research

These are exciting times at OHSU. On July 1, 2013, the Heart Research Center joined the newly formed Knight



*Kent Thornburg, Ph.D.*

Cardiovascular Institute with a new name — the Center for Developmental Health. The Institute was made possible through a generous gift from Phil and Penny Knight. The momentum of the HRC, which is now in its 20<sup>th</sup> year, will not be lost. Instead, it will join the outstanding new research programs of the Knight Cardiovascular Institute, thus fulfilling the hopes and dreams of scientists, staff and community volunteers who have made the HRC successful. From now on the newly formed institute will bring cutting edge clinical service, research and training to Portland. HRC friends and fans can join the celebration of a new chapter in OHSU's heart history. I could not be more pleased.

The gift from the Knights will be distributed in roughly three ways: 1) clinical services will be enhanced; 2) research infrastructure will be strengthened both on the OHSU Portland campus and on the west campus, and 3) support the launching of specific new research programs. The reincarnation of the Heart Research Center in the form of the Center for Developmental Health will continue to raise its support from community funds.

This newsletter begins with both a sad note and a thrilling optimistic note. The sad message is that our colleague, David Barker, M.D., Ph.D., FRS, died unexpectedly in August. Please see our tribute to Dr. Barker inside. On a bright note, Albert Starr, M.D., offers a message that is steeped in hope for the eradication of cardiovascular disease. Heart and blood vessel disease remains the number one killer of all human beings on earth. Dr. Starr suggests that eradication will be driven by the 21<sup>st</sup> century biological discoveries embedded in the genome.

The steady decline in US deaths from cardiovascular disease since 1968 is a triumph of modern medicine to be sure. But we must not rest on our laurels. Hospitalizations from heart disease and heart failure have steadily increased as death rate declined. This fact, along with the increase in type 2 diabetes among children suggests that heart disease is on the rise and that the consequences of poor diets and stress will drive increases in the foreseeable future. The American Heart Association predicts that the current generation of children will live shorter lives than their parents. Furthermore, the costs to society associated with heart disease, which exceed some \$1.5 billion per day, could become financially unbearable.

The time has come for the medical community to join forces in an all-out effort to eradicate cardiovascular disease before it cripples our economy and disables millions more people.

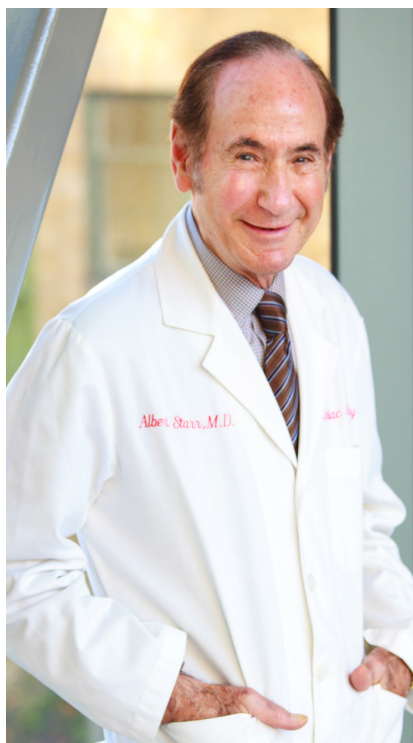
The new frontier in medicine will be personalized disease prevention based on the biological propensities of individuals for acquiring the disease. We know that some people are vulnerable for heart disease because of inadequate nutrition or stress in early life. These people have coronary arteries that are unable to withstand the attacks of oxidized fats that cause coronary arteries to become clogged. Nutritious food will be the new medicine. Prevention research and therapy will be a high priority for the new Knight Cardiovascular Institute. Twenty years of research in the Heart Research Center have built the foundation for exciting new discoveries in the new institute.

As the Heart Research Center becomes the Center for Developmental Health, the Knight Cardiovascular Institute will be on the forefront of discovering how early life malnutrition leads to heart disease and how genes are involved. As a result of the foresight of heart directed philanthropy in Oregon, you can expect to see a constant flow of new and exciting treatments and therapies from OHSU scientists that will save the lives of Oregonians.



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Albert Starr, M.D.

## Understanding & Preventing Disease

by Macy Guppy

Albert Starr, M.D., calls the times we live in “the century of biology.”

“The 20th century was the century of astrophysics; this is the century when we will understand genetic elements at the molecular level,” he said. “This will lead to true understanding of diseases, which will allow us to conquer most of them.”

In other words, before we can truly prevent disease,

we have to understand it. He sees the pace quickening toward that goal, pointing to the example of the Encyclopedia of DNA Elements (ENCODE) project of the National Human Genome Research Institute within the National Institutes of Health. The ENCODE catalog of more than 15 trillion bytes of raw data is like Google Maps for the human genome. The ENCODE data is rapidly becoming a fundamental resource for researchers to help understand how genes influence human biology and disease.

Dr. Starr predicts we are on our way to eradicating disease, with cardiovascular disease making the biggest strides. In the first half of the 20th century, the public’s health dramatically improved and life expectancy increased due to the development of antibiotics and immunizations, which led to improved medical care.

During the second half of the 20th century, Dr. Starr played a major role in OHSU’s pioneering cardiovascular program. In 1958, he performed Oregon’s first open-heart surgeries and the state’s first heart transplant. Starr partnered with engineer Lowell Edwards to invent the world’s first artificial human heart valve in 1960. Before that invention, most patients with rheumatic heart disease and other valve disorders died.

These inventions and those that followed coincided with an enormous drop in mortality from cardiovascular disease and led to numerous advances. Starr sees development of cardiac assist devices, or artificial hearts, as key. “Heart transplantation is held back because

only 2,000 hearts are available each year, but 200,000 are needed,” he said. “There is no way we can fulfill that need without artificial hearts.”

He also sees progress in nonsurgical methods to implant devices such as the transarterial aortic heart valve replacement. “The risk of surgery is too great for 25 percent of patients who need it. They are too ill to have the operation. So being able to replace this valve without surgery is extremely important,” he said.

Dr. Starr also notes that ambulatory monitoring devices, portable monitors for various body functions that send information to the patient’s physician, will respond to the physician’s directions in the future.

After the dynamics of disease are thoroughly understood, he looks toward a day when scientists will be able to build living body structures such as muscle and heart valves. He thinks the biggest breakthrough in the 21st century will be replacing a heart with a mechanical device that does not use a pulse or heart valves to keep the person alive. The device would consume less energy and be much smaller than the average human heart.

OHSU researchers such as those profiled in this issue are playing important roles in preventing and treating heart disease and strokes. Starr also points to the stroke prevention research of Mary Stenzel-Poore, Ph.D., which will soon be applied to humans.

In September 2012, Dr. Starr was appointed chairman of the newly minted Knight Cardiovascular Institute. Sanjiv Kaul, M.D., head of OHSU’s Cardiology Division, is the chief executive officer. The institute’s mission is to accelerate new prevention, diagnostic and treatment strategies coming from research and take them into patient care as quickly as possible.

The \$125 million gift from Nike founder Phil Knight and his wife, Penny, establishes the institute and gives OHSU the impetus to confront the whole spectrum of cardiovascular disease, from prevention to regeneration of tissue after a heart attack.

Dr. Starr’s involvement strengthens the interface between industry and OHSU as partners in developing drugs and devices. “It’s the magic of collaboration when people have common goals,” Starr said. “For example, when engineers from device companies rotate through OHSU for brief visiting professorships, scientists and engineers understand each other better, resulting in better products.”

With the Cardiovascular Institute’s goals to speed up science’s advances to prevent heart disease, this renowned surgeon finds himself in an unusual yet welcome role: “I’m working to put myself out of business,” he said.



## A Tribute to David J.P. Barker, M.D., Ph.D., FRS (1938-2013)

by Kent Thornburg, Ph.D.

The OHSU campus was deeply saddened by the recent news that our colleague, David J.P. Barker, M.D., Ph.D., FRS, died on August 27, 2013. Dr. Barker had just finished his tenth year as an adjunct faculty member in the Department of Medicine at OHSU and as a member of the Heart Research Center. He and his wife, Jan, shared their time between Portland and their home in southern England, where Dr. Barker was a Professor of Medicine at the University of Southampton.

Dr. Barker became famous for his discovery that chronic diseases like heart disease, high blood pressure, type 2 diabetes and obesity are caused more from poor nutrition in early life than from a “bad” gene code that people inherit from their parents. While controversial at first, it became clear to the international scientific community that early life nutrition is important for life long health, something farmers have recognized for a hundred years.

His discovery came from a careful examination of birth and death records of the same people in England. He found that people born on the low end of the birthweight scale died more often of heart disease than people at the high end. He theorized that people who were smaller were more prone to get the disease because of slow growth before birth. Thus low nutritional flow from the mother to the baby in fetal life led to a high risk for not only heart disease but also for other so-called diseases of aging that are becoming more common in American society.

The Barker theory changed the world’s view of chronic disease. It is now clear that the diseases that are the most costly in terms of human suffering and medical cost are related to the food culture in which people find themselves. In many cultures, and even in Oregon, the nutrition of women is highly neglected. The world now thinks differently about the origins of disease and about the care of girls and young women who will bear the children of the next generation.

Dr. Barker received many accolades including notable awards. He was cited by royalty in the U.K. and Thailand. He was made a Fellow of the Royal College of Physicians, the Royal College of Obstetricians and Gynaecologists and the Royal College of Paediatrics and Child Health. He became a Fellow of the Royal Society and of the Academy of Medical Sciences in 1998. He received the Prince Mahidol Prize in 2000, the Danone International Prize for Nutrition in 2005, and the Richard Doll Prize in Epidemiology in 2011.

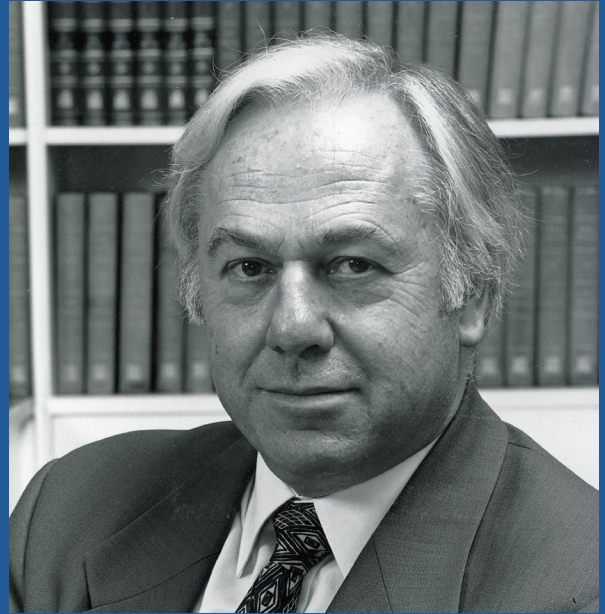
In 2003, Dr. Barker retired as director of the Medical Research Council’s (NIH equivalent) Epidemiology Unit and moved to Oregon to join forces with scientists in the OHSU Heart Research Center and the Division of Cardiology to understand the biological mechanisms whereby low nutrition in early life can lead to high risk for disease in later life.

During the decade of his presence in Oregon, the HRC “developmental origins” program grew in size and national stature. Dr. Barker obtained funding from the National Institute of Aging to investigate how early life growth influences the aging process and longevity. He also participated in the National Institute of Child Health and Human Development funded program studying how the placenta influences the development of the heart.

David Barker was proud to be an Oregonian and he will be more remembered by his Oregon friends for his quick wit, his English sense of humor and his love for Oregon wine than for being an international superstar. Local Barker fans in the Heart Research Center send their love and admiration to his family.

His powerful influence on OHSU will remain for decades to come. Without giants today, there will be no giants of tomorrow.

Dr. Barker’s family requests that memorial donations be made to the Barker Foundation. The Barker Foundation website is located at <http://www.thebarkerfoundation.org/>.



**David J.P. Barker, M.D., Ph.D., FRS**

*Innovator, physician, scientist, humanitarian and founder of the Barker Theory and the Developmental Origins of Health & Disease Branch of Science*

## Developmental Origins of Hypertension

Susan Bagby, M.D. is an expert in hypertension (high blood pressure) and has spent her 40+ year career treating hypertensive patients, teaching medical students and residents to diagnose and treat hypertension, and studying the mechanisms of high blood pressure development.

Dr. Bagby, along with many of her colleagues who are studying the developmental origins of chronic disease, believes that susceptibility to developing high blood pressure when exposed to lifestyle risk factors is determined early in life by conditions present in the womb or in early infancy – the first 1000 days. Investigators world-wide have learned that poor nutrition in early development creates risk in later life for not only high blood pressure, but also obesity, diabetes, stroke and coronary heart disease. Poor nutrition of a fetus in early development can be due not only to mother's diet during pregnancy, but also to the nutritional state of a mother's body prior to pregnancy.

A second important phenomenon linked to poor growth in the womb is accelerated growth in childhood; evidence in human studies shows that when accelerated childhood growth follows undernutrition in the womb, it increases the later-life risk of hypertension, as well as the risk of other chronic diseases.

Enhanced arterial contraction in response to stress in children is a well-established risk factor for high blood pressure later in life. This might suggest that prenatal calorie restriction could reduce high blood pressure risk in children subjected to poor fetal growth. However, calorie restriction might also lead to a profound stunting of body weight and height. This suggests the need for much more sophisticated understanding of growth regulation and how it is modified by undernutrition during development before we can recommend therapeutic interventions in affected children. It also points to the fact that primary prevention will be much more effective than attempting to intervene after the fact.

There is another form of malnutrition known as 'high-calorie malnutrition' that is a result of nutrient-poor high-fat/high-calorie diets. Affected offspring exhibit many of the same chronic-disease risks as those following undernutrition. However, in the case of maternal obesity and/or maternal high-fat/high calorie diet, offspring grow fast in infancy, rather than later in childhood. Offspring of obese mothers are at increased risk of developing hypertension, obesity and diabetes during childhood. This sets the stage for a vicious cycle: girls born to obese moms will likely be obese during their pregnancies, leading to transgenerational transmission of obesity and associated chronic diseases. It is this process that may well account for the marked rise in maternal obesity now appearing in the United States and Europe.

This transgenerational transmission of disease applies to many of the diseases associated with poor fetal nutrition, emphasizing the importance of improving nutrition of girls, mothers-to-be, and pregnant women.



*Susan Bagby, M.D.*



*Michael Shapiro, M.D.*

## Preventing Heart Disease *by Macy Guppy*

One-half of all heart attacks and sudden cardiovascular death occur as unheralded catastrophic events in previously asymptomatic individuals.

Yet many of those susceptible to these events don't realize their risk. OHSU cardiologist and imaging expert Michael Shapiro, M.D., thinks we can change that by

better identifying those at risk for adverse cardiac events.

Dr. Shapiro is the medical director of OHSU's Heart Disease Prevention Program. He is concerned with both primary and secondary prevention of heart disease, preventing first events and keeping patients from having recurring heart problems.

For decades, the Framingham Heart Study (FHS)

has guided physicians' diagnosis of their patients' risk for cardiovascular events. Since 1948, FHS followed three generations of predominantly white males in order to identify common risk factors for heart disease.

Although the Framingham Heart Study is useful in establishing a 10-year risk profile for a first cardiovascular event in large populations, it performs less well in predicting risk in individual patients. It also fails to provide risk information beyond the 10-year window. Individuals, particularly middle-aged patients, often have a low 10-year risk but a high lifetime risk for cardiovascular disease.

In general, the Framingham Risk Score works reasonably well at the extremes. In other words, people identified at low or high risk with this algorithm generally are at that predicted risk. However, the largest sector of the U.S. adult population falls in the intermediate risk category and this turns out to be a very heterogeneous

*(continued on page 5)*

## Stress, Society and Chronic Disease *by Macy Guppy*

Developmental origins research findings can be a pathway to thinking differently about when and how disease occurs and, importantly, about the collective decisions we can make as communities to affect the causes of disease, according to Liana Winett, DrPH.

Dr. Winett, a research associate professor at Portland State University's School of Community Health, studies how health and health policy are portrayed in our culture and media. She believes developmental origins of health research outcomes can help move the conversation toward the major role that "deep enduring social stress, in addition to poor nutrition" plays in many people's lives and health.



Liana Winett, DrPH.

"Chronic and pervasive stress can predispose us to disease," she said. "The difficult circumstances in which many people live, work and learn get under their skins in ways we have not understood before now." The chronic stress of those ongoing circumstances and the structural factors that cause them set people on a lifelong path of poor health and, strikingly, have a cascading effect on the health of subsequent generations. They can biologically predispose us, our children and even our grandchildren for disease. "The good news," Dr. Winett said, "is that there are things we can do as communities to change these outcomes for the better."

Although the first thousand days after conception are most important to a baby's lifelong disease outlook, the nutrition and stress experienced by the generations before the baby is born are also key. Center for Developmental Health Director Kent Thornburg, Ph.D., calls this the "100 years of nutritional flow."

This problem is magnified for communities that experience long-term stress from unemployment, poor

working conditions, inadequate education, racism, poverty and other systemic factors. "For example," Dr. Winett said, "recent research shows that for each year of education, life expectancy increases by 1.5 years." Our built

infrastructures can also make it much harder to access healthy foods and to be physically active.

For our society to become healthier, we need to eliminate or mitigate these long-term stressors and level the playing field for all communities. Dr. Winett sees Portland as an excellent idea incubator for this. "Portland already has a systemic lens in its urban design, health policies and social structures," she said. "We are primed to make decisions that help alleviate the burden on communities that are disproportionately affected by stressors." She uses the example of how difficult it is to access healthy food if a person has to take two buses across great distances at the end of a long workday in order to buy fresh food. "We can shape our communities so that everyone has access to healthful, nutritious foods."

To expand the developmental origins of health and disease conversation in Oregon and continue research, Bob's Red Mill founders donated \$25 million to establish the OHSU Bob and Charlee Moore Institute for Nutrition & Wellness. Its aim is to reduce the prevalence of chronic diseases across the lifespan in current and future generations by promoting healthy, nutrient-rich diets based on whole-foods in early life. Ultimately, developmental origins of health and disease is a fundamental equity issue, Dr. Winett said. It refocuses the spotlight on how our biological health is affected through many generations by the structural impediments to a healthy life. "Together, we can sculpt our communities so that everyone can be healthier," she said.

## Preventing Heart Disease *(continued from page 4)*

group. "For this group, you need more information that can only be gained from additional testing," said Dr. Shapiro. "Because of the Framingham's inadequacies, many people identified as intermediate risk may have a significant burden of atherosclerosis (fatty plaque build-up in the heart arteries) and not know it."

Atherosclerosis testing (for example, CT scans for coronary artery calcium scoring) for this group will help physicians define their patients' risk and help motivate individuals to change based on the evidence of disease they see when looking at actual pictures of their arteries.

"The vast majority of coronary artery disease is related to poor lifestyle habits," he said. "There could be dramatic changes in behavior if people have hard evi-

dence of how the disease is affecting them.

For those trying to prevent recurring cardiovascular disease events, Dr. Shapiro notes that statin drugs are commonly prescribed but only provide a 25 to 40 percent reduction in risk. The majority are still at high risk for heart attack or death. To decrease this residual risk, Dr. Shapiro and OHSU researchers are testing new drugs added to statins that can potentially lower risk significantly. However, the timeline for getting these drugs to consumers is unknown.

New drugs and state-of-the-art imaging techniques hold much promise both for those who know they are at risk for a cardiovascular event and for those who are unaware of their risk but who may be susceptible.

## Exercise to Prevent and Treat Disease *by Macy Guppy*



*Jim Chesnutt, M.D.*

Jim Chesnutt, M.D., medical director of OHSU's March Wellness and Fitness Center, said that being active is at least as important as paying attention to the other risk factors for heart disease and stroke.

"But it's also the hardest to do," he said. "Exercise is a vital sign of wellness, like blood pressure and weight management," he said. "People need to

engage in wellness and fitness at their own pace and with a variety of assistance levels."

To help Oregonians learn these skills, the OHSU March Wellness and Fitness Center models how to prevent and treat disease. "As far as we know, there isn't any other program like the OHSU Medical Exercise Program in the Northwest that integrates exercise and wellness into the overall health care system," Dr. Chesnutt said.

There is very good evidence that exercise is effective not only in treating disease but in preventing illness. The center researches exercise outcomes in programs it offers for those trying to prevent disease as well as for cardiovascular rehab patients and those with diabetes and cancer.

Prevention is a key component. The center offers pre-diabetes classes to get people who may be at risk for diabetes started in adopting a healthier lifestyle.

But finding time and flexing schedules to add exercise is hard to do. Dr. Chesnutt applauds companies that give incentives for employee fitness. Research is already showing its benefits. For example, OHSU is gathering data on its own employee wellness program. There is strong evidence that employees who participate are experiencing benefits that include lower blood pressure and sugar levels, heightened fitness and weight loss.

Dr. Chesnutt said it's important to focus as much on fitness as on weight loss. "Fitness is as or more important than weight as an indicator of wellness," he said. The center follows the FITT principle in how to achieve best results from exercise: F = Frequency of exercise; I = Intensity of exercise; T = Type of exercise; T = Time.

We need to find the right combination of these elements and gradually increase all of them, he said. "Ten minute bouts of exercise are just as beneficial as longer ones. It's important that exercise fits into our schedules."

Dr. Chesnutt and OHSU have been involved in larger public health efforts to influence a better environment for

wellness in our state. "We are focused on helping everyone – not just our own patients – improve their fitness by increasing exercise and healthy habits," he said. OHSU's sports medicine program has been active in promoting physical activity and nutrition by helping develop the statewide Oregon Physical Activity and Nutrition Program called Healthy Active Oregon.

## Murdock Scholars Program

The M.J. Murdock Charitable Trust has renewed funding for the HRC/CDH scholars program which is directed by Samantha Louey, Ph.D., and provides research experience in OHSU labs for bright undergraduate students in their junior year.

More than 150 students from Oregon colleges and universities have graduated from the program. Many have gone on to successful careers as faculty members in colleges, universities and research organizations. The program has become one of the most highly regarded undergraduate research programs in the Northwest.

Students spend one summer plus part of the academic year working under the mentorship of highly recognized OHSU scientists. They also attend classes

related to professional development and are required to write their findings in a thesis and present their findings at a statewide meeting. We are thankful to the M.J. Murdock Charitable Trust for investing in this valuable program.



*Murdock scholars, mentors and staff, June 2013*

## Treating Atherosclerosis

*continued from page 8*

"If we catch it then, we can reverse the process," he said. "If we have the technique to image vulnerable individuals in their early 20s, we can use that information to treat them with newer anti-inflammatory and anti-oxidant drugs that are best suited to interrupting disease at an early or intermediate stage." This could help them avoid a catastrophic heart event decades later.

The microbubble approach to molecular imaging technique is safe, inexpensive, fast and accessible, according to Lindner. Microbubbles can also help physicians customize therapy and deliver drugs to the site.

If this technique comes to pass and is widely accepted in medical practice, Dr. Lindner may someday be able to say, "Yes, we can and are curing atherosclerosis."

## YES! I support the mission of the Heart Research Center/Center for Developmental Health.

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We appreciate the generosity of our thoughtful donors. Below is a list of recent memorial & honorary donations:

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Joanie & Bruce Chambers

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## Treating Atherosclerosis Before it Begins

*by Macy Guppy*



*Jonathan Lindner, M.D.*

"In my 20 years of practice, I've never cured anyone of atherosclerosis," said OHSU cardiologist and imaging expert Jonathan Lindner, M.D. "Bypass, stents and other devices and drugs slow down or somewhat reverse the disease, but they don't prevent or cure it."

However, Dr. Lindner hopes research from his investigational laboratory will make it possible to identify and, eventually, treat the disease before it starts in earnest. Animal studies show that atherosclerosis can be detected long before plaque builds up. By leveraging this information on the early stages of what will become aggressive atherosclerosis, it is possible to halt the progression of disease prior to major complications that manifest as stroke and heart attack in patients. He and other researchers at OHSU, including Scott Chadderdon, M.D., and Brian Davidson, M.D., are exploring the clinical potential of treating atherosclerosis at an early stage.

The idea is to use molecular imaging to show the early stages of atherosclerosis by detecting inflammation of the blood vessels' lining or tiny blood clots that can form early in the plaque development. "Our only chance to cure heart disease is to catch it early," Dr. Lindner said.

Using ultrasound and "smart" microbubble technology imaging, it is possible to also identify oxidative changes of the blood vessels. Oxidation triggers the acceleration of atherosclerosis. However, oxidative injury goes on for years or even decades without symptoms. By imaging the oxidative stress in the blood vessel walls, it becomes possible to intervene decades before a patient would develop symptoms of coronary artery disease and allow therapy at a stage where disease can be modified.

*continued on page 6*

## Program Project Grant Continues

The National Institute of Child Health and Human Development (NICHD) will continue to invest money in the Heart Research Center/Center for Developmental Health (HRC/CDH) to discover the root causes of cardiovascular disease.

It is well known that the flow of nutrients from a mother to her fetus determines the risk for heart disease when her baby becomes an adult. The role of poor nutrition before birth as a cause of heart disease and other chronic diseases is on the top ten list for the Institute. The NICHD will invest about \$7 million in a program project grant designed to determine how the baby communicates its nutritional needs to its mother during pregnancy.

This project was first funded in 1998 and now will continue until 2018. It serves as the cornerstone of research programs within the HRC/CDH. OHSU has a long track record of providing expertise in the area of pregnancy and fetal development.