The Heart Beat

Center for Developmental Health Winter 2021-2022

Director's Message

Kent Thornburg, Ph.D.

OHSU and other medical universities have been challenged recently to address deeply rooted racial disparities that put people of color at a great disadvantage over people who are white. We at OHSU are fortunate to have a president who has helped us stand up and articulate our desire to be an institution that treats all people with dignity and respect regardless of race, ethnic background, sexual orientation or disability status. One additional area that we need to address is our view of people who carry excess body fat. These people are often shamed by medical personnel and they often get less attention to their medical needs. In this issue of *Heart Beat*, a scientist in the Center for Developmental Health (CDH), Dr. Jonathan Purnell, explains why such people are unable to change their physiology to become permanently thin. The reason is that the craving for food, derived from signals from the brain, cannot be overcome by will power alone. Knowledge of this fact will, we hope, bring new sympathetic attitudes from health care providers.

OHSU is on the forefront of brain research. Chris Kroenke, a CDH scientist, specializes in viewing the brain using magnetic resonance imaging. MRI is now so common as a diagnostic tool that most people have had one or seen MRI images. Dr. Kroenke is pushing the frontier of imaging of babies before they are born. All the basic structures of the brain are formed at the time of birth. However, the details of how the structures are assembled can depend on parents' genetic backgrounds and, just as importantly, the mother's social environment and diet. Human brain development is likely to become a very hot field in medical practice as anatomic features of the brain during fetal life become linked to brain function after birth.

A new twist on the Covid-19 story is found within this Heart Beat issue. It turns out the conditions that lead to hospitalization and death of people who suffer diabetes and heart disease are derived, in large part, from their developmental roots. This fact also accounts, in part, for the increased vulnerabilities for severe disease in Black and other ethnic populations.

My father loved old books and had some 19th century medical books that I used to read when I was in middle school and high school. One story I won't forget was in a section written to make the case that women should not be subjected to undue stress

(continued on page 5)

You don't get the blame and you don't get the credit: Body weight regulation and obesity

Jonathan Purnell, M.D.

by Jonathan Q. Purnell, M.D.

Our bodies are very good at sensing and responding to changing environs both within and without. Just consider the act of arising from bed in the morning to start our day. To do this without immediately passing out requires near instantaneous detection of a drop in blood pressure by special receptors in our arteries. These receptors send signals through the base of the brain to connect with nerves throughout the body to ensure that heart rate and blood pressure are properly maintained. All these physiologic changes repeat multiple times throughout the day to allow seamless movement from sitting to standing and back again. If our day involves a hike on a high-altitude mountain trail, additional sensors are activated that quicken our breath in compensation for lower oxygen levels, ensure insensible water losses through sweating are minimized, and energy stores are efficiently released so that the added demands of hiking are met and blood sugar levels are maintained.

These are examples of "homeostatic" systems that govern vital life processes. Each of these regulatory mechanisms occur without our awareness and often include overt behaviors. For example, when thirsty after a hike, our drive for water will continue to invade our thoughts until we find water

(continued on page 4)

KNIGHT CARDIOVASCULAR Institute OHSU

What does Covid 19 have to do with heart disease? More than meets the eye.

Your first reaction to this title was likely to remember that the Covid-19 causing virus, SARS-CoV-2, can infect the hearts of patients who have Covid-19. Some such people will have symptoms while combating the heart infection such as a rapid heart rate, palpitations or fatigue. Others may become "long-haulers" and suffer persistent cardiovascular issues long after the acute illness phase has disappeared.

Or you might have been thinking about the rare cases of young adult males who suffered heart muscle inflammation (myocarditis) within days of receiving the second dose of Pfizer or Moderna vaccines. You may remember that young males are six times more likely to suffer a cardiac infection if they contract Covid-19. All of these issues are of high importance to medical scientists and very concerning to our cardiologists who care for Covid-19 patients.

However, there is another connection to heart disease that has not been emphasized in the news media. Heart and blood vessel disease, along with diabetes, obesity and high blood pressure, are conditions that are associated with high risks for hospitalization and death among people who contract Covid-19. You may also know that the numbers of people who suffer these conditions in the US population has been rising over the last three to four decades. In other words, the US population has been becoming increasingly more vulnerable to the harm caused by infectious diseases like Covid-19 and influenza over the last 40 years because of our overall worsening health. Why, you might ask.

The science of Developmental Origins of Health and Disease (DOHaD) is, for the first time, explaining why some people are more vulnerable to acquire heart disease than others and why social circumstance has a powerful association with heart disease.

We now know that people gain predispositions for cardiovascular disease in the earliest years of their lives. People born in poverty or other detrimental social circumstances are influenced by the effects of stressors while developing in the womb and in the first years of their lives. For example, the rate at which a person grew before they were born was determined by a number of factors including their mother's nutrition and her social stress. If they grew slowly before birth and gained weight rapidly after birth, they were likely to have changes in their gene regulation systems (epigenetics) that predispose them for type 2 diabetes, obesity and heart disease as adults.

The racial disparities are enormous. People of color are at high risk for acquiring a chronic disease. They are more likely to suffer from detrimental conditions while growing in the womb and as adults. Because of their social circumstances, women of color often have limited access to nutritious food and an environment that promotes a health lifestyle.

Recent studies show that prepregnancy health is just as important as a healthy lifestyle during pregnancy. The social determinants of health are, perhaps, more important in young men and women than in middle aged adults. Among the most harmful aspects of the social environment are racism, housing insecurity, food insecurity, fear of violence and physical abuse by a spouse or family member. These need to be addressed by all communities.

So, back to the story. The increasing rates of type 2 diabetes, obesity, hypertension and cardiac disease are clearly related to vulnerabilities derived from early life development. Poor diets and powerful social stressors that have increased over the last four decades explain why increasing numbers of people are highly vulnerable to the ravages of a SARS-CoV-2 infection. This vulnerability is the substrate for disease and the reason that many people die from Covid-19.

The Center for Developmental Health within the Knight Cardiovascular Institute has as its mission the discovery of the root causes of disease vulnerability. Unfortunately, we know too little about changing the disease trajectory toward a healthy outcome.

Could we prevent the eventual heart disease in an adult by assessing the disease trajectory in the child? Now is the time to find out.

The Heart Beat

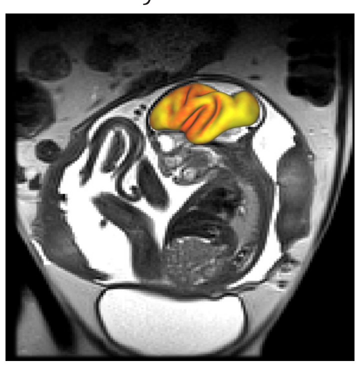
Please contact us by email at heart@ohsu.edu or by phone at 503-494-2382 if you would prefer to receive this newsletter by email or if you would like to receive information about CDH lectures and events.

New Technologies to Understand the Developing Brain

Christopher Kroenke, Ph.D.

By now, many are accustomed to pictures produced by magnetic resonance imaging (MRI) scanners. Christopher Kroenke is a professor in OHSU's Advanced Imaging Research Center and the Oregon National Primate Research Center's (ONPRC) Division of Neuroscience, where he heads the MRI facility. When he gives presentations to Portland-area elementary and middle school students, he is always impressed by the way kids can look at an MR image and recognize the organ being shown, and even appreciate different parts of the kidney, heart, or brain, etc., by the varying brightness levels in the grayscale images. However, Kroenke points out that the reasons *why* some regions of the image are bright, while others are dark, are surprisingly poorly understood – even though the serendipitous pattern allows the viewer to name the object being pictured and radiologists to identify pathology. Kroenke and his team see this lack of knowledge as an opportunity: understanding why these images appear as they do would mean we can interpret the biology that influences them. Such knowledge furnishes new innovations for using MRI to diagnose disease, assess therapeutic efficacy, and characterize normal changes in development throughout the lifespan.

A primary focus of the Kroenke lab involves studying how the brain develops. In particular, during the second half of pregnancy, the fetal brain undergoes dramatic changes in size and shape, and this reflects its functional development. One recent advance in MRI research is improved imaging of moving objects – such as fetal heads. Kroenke and his team are among a number of research laboratories worldwide who utilize MRI to study maturation of the fetal brain in the uterus. One finding is that the patterns of dark to light and light to dark throughout the developing brain change in an extreme, but highly typified manner. But if you ask Kroenke how changes in the appearance of these images relate to the critical neurobiological processes that are likely to be reflected in fetal brain MRI, he will be the first to admit that our current level of understanding is merely the tip of the iceberg.



Diffusion MRI results are encoded in the fetal rhesus macaque brain model. Neural circuit development is relatively immature in yellow compared to orange areas.

Kroenke's graduate studies were at Columbia University where he used nuclear magnetic resonance (NMR) to study molecular dynamics. Importantly, much of the theory behind MRI is common to NMR.

As a postdoctoral scholar, he joined the Biomedical Magnetic Resonance Laboratory (BMRL) at the Washington University Department of Radiology, where he was able to apply his expertise in molecular dynamics toward a class of MRI techniques termed "diffusion MRI," which encodes image intensity with properties of water diffusion within the tissue being studied. At the BMRL, Kroenke contributed to the interpretation of diffusion-weighted MRI images of the properties of the cells being imaged.

In the developing brain, as cells form functional circuits, they change their shapes. Developing neurons (nerve cells) grow specific structures for receiving signals from other neurons and structures for transmitting signals. The changes in size and shape of the developing brain result from the network of neuronal processes growing into an intricate arbor of branches to facilitate neural connections.

Many reports have shown that in brains of individuals affected by neurodevelopmental disorders such as Autism Spectrum Disorders and Fetal Alcohol Spectrum Disorders, branch patterns are less elaborate than expected. A line of thinking that has guided much of the work in the Kroenke laboratory is that perhaps diffusion MRI can be used to identify characteristics of these neurodevelopmental disorders.

Although many neurodevelopmental disorders cannot be cured, the developing brain is more responsive to intervention than it is later in life. Kroenke and colleagues are attempting to determine the earliest time *in utero* that MRI might detect abnormal brain developmental patterns in the context of fetal alcohol exposure in pregnancy (for example, prior to pregnancy awareness). In preclinical studies they have identified a pivotal point in pregnancy when fetal brain structures are large enough to be studied by MRI, and at this time, region-specific differences between alcohol exposed and non-exposed fetuses are observed. Ongoing work will characterize the behavioral consequences of these differences.

As MRI becomes more common in detecting abnormalities in pregnancy, you can be certain that Kroenke and his team will be at the forefront.

Body Weight Regulation and Obesity (continued from page 1)

to replenish what we lost. We may think we can control these internal biological signals, but the reality is they control us.

Historically, body weight has been considered by both the public and medical community as a personal choice. This presumes that every moment of every day we know how many calories we are burning and are capable of determining the exact amount contained within a mixed meal, which is consumed intermittently, to maintain weight balance. Obviously, none of these presumptions are true.

The study of body weight regulation and the health complications of living with obesity began in earnest at the turn of the 20th Century. Autopsy studies of patients who presented with unregulated, voracious hunger revealed lesions (most commonly from locally growing tumors) in an area of the brain that regulates appetite (fullness and hunger) and how many calories we burn in a day.

It was not until laboratory techniques were developed that could isolate hormones, proteins, and other circulating factors that the regulation of body weight could be understood. It is now known that the signals to the brain conveying sensations of fullness (satiety) and hunger are generated by the stomach and intestine in response to the presence and absence of food availability, respectively. Indeed, the gastrointestinal tract secretes over 100 known hormones and is considered the largest endocrine organ in the body.

Two key concepts important to understanding weight regulation are that the abundance of these fullness factors in the blood and suppression of the hunger hormone, ghrelin, are determined by the calories consumed during the meal. This is how our brains know how many calories we eat—and it is these internal signals that govern whethre we put down our forks and feel satisfied or decide it is time to have a snack or prepare a meal. We do not control these signals. They control us.

Fat cells complete the feedback loop to the brain by secreting another hormone, called leptin, in proportion to the amount of fat we carry. Leptin binds to the neurons in the brain that receive satiety and hunger signals from the gut, governing our food intake and energy expenditure to maintain body weight typically within a five-pound (two kilogram) range of what the brain thinks of as "normal."

Unwanted weight gain followed by establishment of a new, higher body weight set point occurs when the brain develops a resistance to leptin. Although the mechanisms causing a resistance to leptin are poorly understood, twin and family studies have established that much of what determines our adult weight is inherited.

Hence, we no longer "blame" patients for developing obesity any more than we blame patients for developing diabetes or hypertension, two other prominent chronic diseases that are strongly influenced by inheritance. This also means that those of us who remain in a healthy weight cannot claim to be "special" since protection against unwanted weight gain is also determined by our inheritance.

Even so, there is still plenty of influence on expression of obesity by the environment. Advances in technology and market-driven production of unhealthy foods interact with our inherited predispositions to push the body weight set point ever higher. Unfortunately, like other chronic diseases such as hypertension and diabetes, once obesity becomes manifest, lifestyle changes alone are not sufficient to fully restore this physiology back to a healthier weight. No matter how much patients with obesity are told to "eat less and move more," the brain will defend the higher body weight set point against caloric deprivation and increased expenditure just like it did at the lower, healthier weight.

Environmental influences on our susceptibility to obesity reach all the way back to the womb. Both animal models and observational studies in humans provide a strong scientific basis for in-utero exposures from maternal obesity to program a future increased risk for developing obesity and its metabolic complications in the fetus. Knowing this increases the urgency to combat the obesity epidemic, for what is needed is a dual approach that involves both prevention and management of the chronic disease of obesity. Preventing obesity will be the greater challenge but will have the bigger impact for future generations. This will require taking our scientific knowledge and partnering it with educational programs to combat obesity bias by both the lay public and within the medical community, ensuring adequate supply of nutritious foods to everyone, and establishing policies that reverse unhealthy environments and their detrimental impact on our health, especially for our youth and in women of childbearing age.

Save the Date: May 12, 2022: David J.P. Barker Memorial Lecture

The Impact of the Dutch Hunger Winter on Lifetime Health

You may recall from a previous newsletter that ***Tessa Roseboom, Ph.D.***, professor of Early Development and Health at the University of Amsterdam, was scheduled to present the Barker Memorial Lecture in 2020. Due to the Covid-19 pandemic, her visit has been rescheduled to May 2022.

Tessa Roseboom, Ph.D.

Roseboom has received international recognition for her studies on the health effects of the Dutch Hunger Winter during early development. The Dutch kept detailed health records, enabling her to follow the children who were in their mothers' wombs during the famine. Her studies found that children who were conceived during that winter have increased risk of heart disease, high blood pressure and hospitalization as adults and higher lifetime rates of obesity. She is now studying the effects on the next generation.

The impact of the German occupation of The Netherlands continues to this day. You may recall from your history class that the occupation began in 1940 and lasted until May 1945 when Allied troops arrived to liberate the people of The Netherlands. In September of 1944 the exiled Dutch government called for a railway strike to slow the German Army. Germany retaliated by cutting off the country's food supply, thus the winter of 1944-45 is known as the Dutch Hunger Winter. Rations fell below 1000 calories per day by November and were as low as 500 calories per day by April. Sadly, about 20,000 Dutch people died during the winter. Food supplies were immediately reestablished when the Allied troops arrived. Because the exact dates of the famine are known and the population had good nutrition before and after the hunger winter, it is possible to study the effects of famine on the health of the population including those who were in the womb at the time.

Roseboom is translating this knowledge into more effective care and advice for pregnant women in developed and developing countries. Her goal is to ensure that every child gets a good start in life, thus improving the health of future generations.

The OHSU Knight Cardiovascular Institute has invited Dr. Roseboom to deliver the 2022 Barker Memorial Lecture on May 12, 2022. Dr. Roseboom will discuss differences in long term outcomes depending on the pregnancy trimester during the famine and how the diets of pregnant women affect their children and grandchildren for life.

Dr. Roseboom will also present the keynote lecture for the OHSU Moore Institute's Oregon Nutrition Day on May 13, 2022.

Please email heart@ohsu.edu if you would like more information on these events.

Director's Message (continued from page 1)

during pregnancy because of adverse effects on the child. To prove the point, the physician author recited a case where a pregnant woman was terribly frightened by a wolf. Subsequently her child was born with a birthmark in the shape of the wolf's profile on the child's leg. The author linked cause and effect. I was very entertained by the story. It was so farfetched that I concluded that people who believe that a mother's stress experiences somehow affect their offspring were nothing short of superstitious. Now that I have seen the evidence over 30 years, it is clear that a mother's social environment can have long lasting detrimental effects on her offspring. While a frightening experience might not cause a birthmark, the author was right. Stress during pregnancy can be harmful to offspring.

This point will be driven home by Dr. Tessa Roseboom from The Netherlands who will be visiting in May 2022. She will give a lecture on the long-term transgenerational effects of the WWII Dutch Hunger Winter on people who were in the womb during the starvation period in 1944-1945.

Scientists have to change their minds often based on new evidence. I have been changing my views based on changing evidence for my whole career.

Science Policy Can Be Confusing (continued from page 8)

showed that dairy fats taken in moderation are not as harmful as once thought. We once thought that all fats were harmful. Thus, the dogma of the '60s warning of the harms of butter have been softened. Another example is the benefit of the Mediterranean diet that has been shown protective against heart disease by several independent studies. A key feature of the Mediterranean diet is the inclusion of olive oil.

Olive oil is now known to be a "healthy" oil that has cardioprotective properties and interacts with the microbiome. The gut microbiome, the sum total of all the bacteria living inside the human intestine, is another aspect of our new understanding of diet and heart health that has changed. Over the past several years, there has been increasing evidence that compounds in red meat interact with intestinal bacteria. Certain species of bacteria in the normal intestine are able to convert L-carnitine, which is found in high concentrations in red meat, into trimethylamine (TMA) . After TMA is formed in the intestine, it travels to the liver where it is oxidized to form TMAO-- which is detrimental to blood vessels and the clotting mechanism. Chronic exposure to excess TMAO can lead to heart disease, stroke, and chronic kidney disease. The interesting part of this story is that **cold-pressed extra virgin olive oil** contains a substance that inhibits the generation of TMA by the bacteria in the gut. Now we all have an excuse to incorporate this special olive oil into our salads and other dishes. We have known for decades that diets dominated by red meat consumption lead to elevated risks for cardiovascular disease. Large amounts of saturated fats found in fatty red meat add another risk to those who eat red meat on a regular basis. With the new TMAO discovery, we now understand the association between red meat consumption and adult onset disease risk a bit more.

One mystery is how each of us acquired our unique microbiome. We have some answers but not a complete answer. It is known that babies pick up and swallow helpful bacteria as they travel through the birth canal. Mothers also pass on bacteria through their saliva and from their skin and nipples. A recent discovery is fascinating. Only three years ago we believed that human milk was sterile as it was manufactured by glands in the breast. However, recent data have shown that human breast milk contains bacteria similar to the bacteria in the mother's intestinal microbiome. Exactly how a mother's bacteria reach the milk glands has not been determined. These helpful bacteria "seed" a baby's intestine so that it can better digest food. This discovery adds more evidence to explain how breast-fed babies get an important boost in life.

The Center for Developmental Health (CDH) was formed to find the early life causes of cardiovascular and metabolic diseases. OHSU has a long history of making important contributions to our understanding of heart disease. One of our tasks is to understand the diets of women across the state among all ethnic groups. Perhaps we will discover how red meat consumption affects babies in the womb. We seek support for this effort. We began this discussion by stating that science policy can be confusing. Another task of the CDH is to present scientific information in every day language so that everyone can understand it and live the healthiest life possible.

CDH Seed Grant Program

We are pleased to once again offer seed grants to CDH scientists. In the past, seed grants awarded to Heart Research Center scientists provided the preliminary data required for our scientists to receive national funding for their quest to understand the causes of heart disease. Over the years, our $200,000 investment in seed grants brought in more than $18 million in national funding.

<u>We are now working to raise $50,000 in order to continue this program to stimulate new research projects</u>, especially for our early career scientists who are establishing research programs. These funds will help determine how gene functions are altered during development and put our children on a trajectory for good health for life.

We hope you will join our quest to learn more about the primary caues of heart and blood vessel disease. Please use the enclosed envelope or visit our website at www.ohsu.edu/heart if you are able to make a gift. Your gift of any amount will help an early career scientist make a discovery of the early causes of heart disease.

YES! I support the mission of the Center for Developmental Health.

Online donations can be made at www.ohsu.edu/heart.

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Checks should be made payable to OHSU Foundation and mailed to Center for Developmental Health, Oregon Health & Science University, 3030 S. Moody Avenue, Mail Code MDYMI, Portland OR 97201.

Salmon with Whole Grain Red Rice and Quinoa

Recipe shared by Kent Thornburg

Serves 4 people

Ingredients:

½ cup red rice
½ cup quinoa
1 T olive oil
1 8-oz can petite diced Italian tomatoes, chopped with juice included
¾ cup chopped roasted red peppers
2 T low sugar ketchup (without high fructose corn syrup)
2-4 cups precooked salmon in small pieces
3 T dried dill
1 t salt
parmesan cheese
low sodium soy sauce

Wash and cook quinoa (1/2 cup grain and 1 cup water) in sauce pan for 15 minutes after it begins to boil. Let cool for at least 5 minutes before touching it.

Wash 1/2 cup red rice, add 1 t olive oil and 1 cup water; mix and cook for 15 minutes in pressure cooker or on stove according to package directions. Add remaining olive oil, mix gently and let cool.

Mix rice and quinoa gently with a fork until thoroughly mixed. Gently fold in tomatoes, peppers, ketchup, salmon, dill, salt and a dash of low sodium soy sauce. Heat in oven or microwave and serve with shredded parmesan cheese.

Variations:

- Omit salmon and cheese for vegan option
- Can use red or white quinoa
- Add any of the following:
- 1 T salsa
- Small can chopped olives
- Chopped fresh tomato when in season

Nutrition:

Salmon is a highly nutritious food that supplies essential anti-inflammatory omega 3 long chain fatty acids as well as many vitamins including B-12 and is a great source of protein.

Quinoa has low glycemic index, is a good source of fiber, is a complete protein (all essential amino acids), is gluten free, and contains phosphorus, copper, iron and zinc as well as folate.

Red Rice (Oryza) has a low glycemic index, is a good source of fiber, contains iron, magnesium, zinc, Vit B6 (pyridoxine) and contains more antioxidants than other types of rice, anthocyanin in particular. Red rice contains monacolin K, a substance that helps lower cholesterol with a drug like action. Women who are pregnant should check with a dietician before eating red rice.

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OHSU

Center for Developmental Health
Mail code: MDYMI
3030 S. Moody Avenue
Portland, OR 97201

More Information:

Kent L. Thornburg, Ph.D.,
Interim Director,
OHSU Knight Cardiovascular Institute;

Lisa Rhuman,
Director of Operations,
OHSU Center for Developmental Health

tel: 503-494-2382
email: heart@ohsu.edu
web: www.ohsu.edu/heart

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Science Policy Can Be Confusing

The relationship between heart disease and diet is complex and confusing. No wonder. Eggs were once bad for you and now they are OK. Policies and health related recommendations change depending on our state of knowledge as new discoveries push the edge of understanding heart and blood vessel disease.

The fact that scientific recommendations gradually change over time is frustrating. But we should all be thankful. We live in a society where scientific discoveries are at the forefront of thinking every day. It takes some adjustment and patience to ride the waves of knowledge. Scientists have to change their minds now and then. For example, people opposed to Dr. Anthony Fauci, our country's chief virologist, have pointed out that he did not advise mask wearing early in the pandemic but later changed his mind. Changing his mind was seen as a fatal flaw. Why did he change his mind? Because after his original and logical advice, scientists discovered how SARS-CoV-2, the virus that causes Covid-19, was being transmitted. Once it was known that the virus is carried through the air on droplets that could be filtered by a mask, it became clear that masks were useful in slowing the spread of the virus. Clinical trials have now shown that masks are effective barriers to infection.

We can be thankful for two things: 1) scientific studies were able to determine the primary way in which the virus is transmitted and, 2) we have a national leader who was willing to say that his advice was wrong once contrary evidence was known. The nature of science requires paying attention to the massive stream of new information that arrives in scientific journals every day.

Back to nutrition. The advice landscape regarding diet, nutrition and risk for cardiovascular disease has changed in recent decades. For example, we learned that trans fats, the by-product of processing oils with excessive heat, are harmful to blood vessels and affect the coronary arteries that supply oxygenated blood to the beating heart muscle. This finding resulted in policies that ban trans fats in food products. Other studies

(continued on page 6)