



Kent Thornburg, Ph.D.

Director's Message

The Center for Developmental Health (CDH) has one primary purpose—to discover the underlying mechanisms by which stressors during development lead to cardiovascular disease and other chronic disorders. The discovery that prenatal stress leads to later disease was made first in human populations. We know that people born with low birthweight or with poor nutrition before birth suffer

more type 2 diabetes and heart disease than the general population. Early skeptics within the scientific community of a developmental cause, including me, became believers only after it was shown that developing organisms - from a mouse to a monkey - adapt to stressors by compromising the structure of their organs and modifying the regulation of their genes. These responses which lead to vulnerability for cardiovascular disease for life are built into our biology.

The discovery that *every stage of development* can be detrimentally affected by stresses came later. Eggs in the ovary can be modified by poor diets in females. Diet and obesity can affect the transmission of disease risk in sperm. Embryos traveling from the ovary to the womb can be

detrimentally affected by maternal diet. Social and dietary stresses can affect the growth of developing organs in the embryo, fetus and infant and lead to disease risk. Studies have suggested that some 50-70 percent of current heart disease can be accounted for by developmental exposures to stressful conditions.

In this issue we highlight work in the CDH that links our understanding of embryo development and an application of the knowledge to implanted embryos in individuals or couples who are infertile. Dr. Chavez is a basic scientist and Dr. Amato, a clinician. They both work toward improving the success of pregnancy assistance techniques by understanding the biological underpinnings of embryo development.

We also highlight the work of Dr. Alkayed because of the amazing discovery of a new receptor that will offer another layer of understanding blood pressure regulation in humans. This is important for two reasons: 1) women who are hypertensive during pregnancy may have offspring with changed heart structure, and, 2) the discovery of Alkayed, Kaul and colleagues may explain why babies born small have high blood pressure as adults.

The CDH offers sincere thanks to our fans. In the age of COVID-19 we are all the more cognizant of why our attention to early life health is so important. You can read this issue of The Heart Beat to understand why.

Microvascular Regulation and Vascular Dementia

We all know that blood vessels deliver blood from the heart to various organs but did you know that these vessels branch into smaller and smaller vessels, the smallest of which are one-tenth the diameter of a hair? If lined up end to end, the large vessels and the microvessels together would stretch 60,000 miles or 2.5 times around the earth. Eighty percent of our vessels are small, microvessels that deliver oxygen and nutrient-rich blood to all organs of the body.

Thus, the health of these microvessels is important in ensuring the function of our heart, brain, eyes, skin and more.

The microvessels are also important in COVID-19, as the blood clots some patients experience are a result of the virus attaching to the inner lining of microvessels, which then activate clotting around the site where the virus attached.

Nabil Alkayed, M.D., Ph.D., professor of anesthesiology and perioperative medicine and director of research at the Knight Cardiovascular Institute (KCVI) at OHSU, made an important discovery when he was a graduate student at the Medical College of Wisconsin. He showed that microvessels in the brain are opened or dilated by EETs (short for lipid molecules called epoxyeicosatrienoates). He has since learned that these vessels are constricted (or narrowed) by other lipids called hydroxyeicosatetraenoates (HETEs), and that both act on the same receptor. This represents a new understanding of the way that microvessels are regulated.

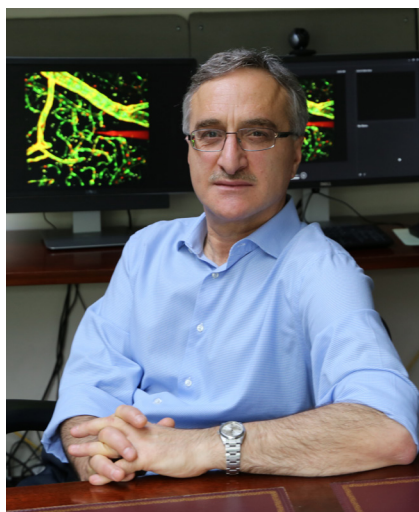
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Microvascular Regulation and Vascular Dementia

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Nabil Alkayed, M.D., Ph.D.

Alkayed grew up in Jordan and attended medical school in Russia at age 17 with a goal to return to the University of Jordan for a residency in neurology. However, it became clear when he returned that he would need a research background to be successful. He was attracted to Ph.D. programs in the U.S. because of the strong scientific programs. While waiting for a research opportunity in neuroscience, the first Iraqi war erupted and all flights and mail to Jordan were disrupted. When the war ended, he received only one offer letter. It turned out the program that accepted him was not particularly strong in neuroscience, but it was one of the best programs in the country for blood vessel biology.

So he decided to study blood vessels in the brain and focus on vascular brain diseases, especially stroke. He moved to Johns Hopkins University to work with a nationally recognized, stroke research team that was recruited to OHSU in 2003, and he was part of that recruitment.

Advances in technology allowed Alkayed to investigate the role of EETs and HETEs in vascular brain diseases, such as stroke and vascular dementia. Vascular dementia is a small vessel disease. It is the second most common form of dementia after Alzheimer's disease and appears later in life, usually around 80 years of age.

The microvessels are very delicate and can be damaged by several risk factors including high blood pressure, smoking, poor diet, obesity, stress and diabetes. When the microvessels in the brain are damaged, they can result in vascular dementia. When asked whether damage to the microvessels can be

reversed, Alkayed answered that a good diet, exercise, healthy lifestyle, lack of stress and treatment of any existing disease conditions such as diabetes and hypertension might reverse the damage - although he noted that this reversal needs to be done early, before too much damage is done.

Alkayed believes that EETs and HETEs are important in early development. EETs and HETEs have been shown to regulate vascular development in multiple organs, including brain and heart. The role of nutrition and stress during development are known to be related to brain diseases in the elderly but it is not known whether EETs and HETEs play a role.

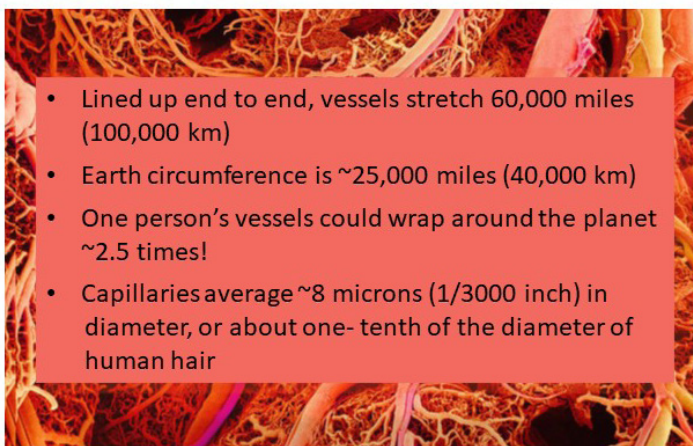
Nearly 29 years after Alkayed's pioneering discovery of EETs, he and his team recently discovered the protein on cells (receptor) that is stimulated by EETs and HETEs molecules. This was a monumental discovery. In order to stimulate an action in a cell, molecules must first bind to a receptor on the surface of the cell. A study of brains from dementia patients showed that those with the highest risk for vascular dementia have a gene mutation for this receptor. He is now working to understand the role of the receptor in stroke and vascular dementia and is optimistic that this discovery will lead to earlier diagnosis and the development of drugs and treatments

for both stroke and vascular dementia.

Alkayed credits all of his mentors since he was a graduate student for helping develop his career and for advancing the field. He also credits the financial support from KCVI leadership, especially Sanjiv Kaul, M.D., professor and founding director of the KCVI, with special acknowledgement to the following individuals who contributed

significantly to the project: Xiangshu Xiao, Ph.D., A. Paul Barnes, Ph.D., Shanthi Nagarajan, Ph.D., Zu-yuan Qian, Ph.D., Jim Cao, Ph.D., Xuehong Liu, Ph.D., and Jonathan Nelson, Ph.D.

The Center for Developmental Health is fortunate to have Dr. Alkayed as a colleague. His discoveries are so important that we suspect they will become instrumental in understanding how the heart and vascular system of babies in the womb become compromised in pregnancies facing nutritional stress that leads to lifelong disease.



- Lined up end to end, vessels stretch 60,000 miles (100,000 km)
- Earth circumference is ~25,000 miles (40,000 km)
- One person's vessels could wrap around the planet ~2.5 times!
- Capillaries average ~8 microns (1/3000 inch) in diameter, or about one-tenth of the diameter of human hair

Coronavirus pandemic and early life origins of underlying conditions

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However, for some reason the dramatically increasing rates of chronic diseases in the U.S., like type 2 diabetes, heart disease, obesity and uncontrolled high blood pressure, have not received the attention they deserve. Why care what term we use for the problem? The word matters because an epidemic of a harmful virus or of opioid use or of vaping captures the national attention. Thus, epidemics matter. Once identified, experts get called to testify. Resources are set aside to combat its spread, programs are established and no one is happy until the culprit is vanquished. None of these efforts have happened to the scale necessary to reverse the current pandemic of COVID-19. Worse, little attention has been paid to the origins of the underlying conditions that lead to disability and death.

Compared to the COVID-19 crisis, chronic disease rates are less alarming to news media, government officials and most medical organizations. Perhaps because there is no organism to blame and strategies for reversal are complex. The chronic disease epidemic has risen slowly by comparison to the usual standards of an influenza epidemic, but rapidly if viewed across human history. Nationally, the prevalence of type 2 diabetes has increased some 10 fold in the past 50 years. In Oregon, type 2 diabetes has more than tripled over the last three decades. Such a rapid rise in prevalence of a chronic disease is unlikely to have been seen previously in human history. By that standard, the condition has emerged so rapidly, it has taken us by surprise. It must now be placed in the epidemic category and associated with words like “crisis” and “urgent.” In reality, the chronic disease epidemic is truly a pandemic because, although the U.S. is among the leaders, countries across the globe are suffering similar increases in these conditions.

The CDH, within the OHSU Knight Cardiovascular Institute, has a focus that is different from most research centers. It joins its sister center, the Center for Preventive Cardiology, and the OHSU Moore Institute in addressing the nutritional underpinnings of chronic diseases. The CDH research ranges from the subcellular to the population levels. Its scientists focus on investigating the root causes of disease, ranging from a system-level, like the cardiovascular system, to the cellular and the molecular levels. CDH scientists study how eggs and sperm carry epigenetic messages that cause offspring to be

vulnerable to disease and how poor maternal diets can permanently change blood vessels in offspring even before birth. There are dozens of ways that the CDH is gathering the evidence for specific causes of chronic disease.

As of this writing, COVID-19 has caused over 250,000 deaths in the U.S. in just nine months. That number will surely double before the pandemic subsides. Vaccines

will likely slow the pandemic in the next 12 months. However, chronic diseases will keep on killing people unnecessarily. Currently, in the U.S., cancer causes about 600,000 deaths per year and

cardiovascular disease some 850,000. These deaths are related to the vulnerability set in early life.

While the CDC has stated that smoking is the leading cause of preventable death, in reality, poor nutrition is by far the leading cause of preventable death. Poor nutrition is the primary reason that people are vulnerable for virtually all the chronic diseases listed above. In a survey of 195 countries, published this year in the journal, *Lancet*, poor nutrition was cited as the leading cause of death worldwide. High calorie malnutrition (calorie rich, nutrient poor diets) during the reproductive years, underlies the increasing rates of chronic disease in the U.S.

In Oregon, as well as nationally, we need a two-pronged approach to halt the chronic disease epidemic that we now face. 1) Invest heavily in understanding the

biological causes of disease so that specific remedies can be applied to slow or stop the disease process. 2) Improve access to nutrition in every community. This will require community action across the state.



We have been asking the question, “When will we as Oregonians decide to end chronic disease?” If never, the epidemic will continue unabated. Life expectancy will continue to decrease. Our hospitals will overflow as our pocketbooks dwindle. If now, we can invest in the health of our state and show that the current epidemic, which has reached crisis level, can be reversed.

We know the primary culprit. We should be driven to action by this epidemic. Now is the time.

*When will we as Oregonians
decide to end chronic disease?
Now is the time.*

Forty Years of In Vitro Fertilization: Clinical Application

In vitro fertilization (IVF) is one of the biggest breakthroughs in medicine of the last century, for which British Scientist Dr. Robert Edwards was awarded the Nobel Prize in 2010. Since the first IVF baby was born in 1978, there have been over eight million babies born worldwide as a result of IVF. It is responsible for 1-3 percent of births globally. IVF has allowed us to study the preimplantation embryo in vitro (in a Petri dish), something that wasn't possible before. We now have 40 years of data on birth outcomes allowing us to compare children born through IVF to spontaneously-conceived children.

Paula Amato, M.D., professor of obstetrics and gynecology, cares for patients with infertility, polycystic ovary syndrome and menopausal issues. Her research interests include understanding stem cells, hormone interactions and environmental impacts on reproductive health. The science of reproduction and connecting with individuals and families who have trouble conceiving were her inspirations to pursue a career in reproductive endocrinology and infertility.

About one in eight couples in the U.S. have infertility. The causes of infertility can involve issues with the female partner, the male partner, or both. The most common causes in women are disorders of ovulation such as polycystic ovary syndrome, age-related infertility, tubal disease and endometriosis. Exposure to certain

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Paula Amato, M.D.

Forty Years of In Vitro Fertilization: Basic Science Advances



Shawn Chavez, Ph.D.

Many will remember the excitement and fascination felt around the world when the first baby conceived by in vitro fertilization (IVF) was born over 40 years ago. While the rate of IVF procedures has increased over the last couple of decades, the overall success rate of about 35 percent has not.

Shawn Chavez, Ph.D., associate professor, Oregon National Primate Research Center (ONPRC), hopes her work will improve the success rate of IVF by learning which embryos have the highest chance to result in a healthy birth.

Chavez began her college education with a goal to become a physician. However, a volunteer marine science project and an undergraduate course in which sea urchin eggs were fertilized and followed during development in the lab, piqued her interest in developmental biology and genetics.

Soon after Chavez graduated, her mother became ill with a rare cancer, from which she has since recovered. The time spent at the hospital supporting her mother made her realize that being a physician was not her calling. Instead of medical school, she entered a graduate program at Yale University where she studied placental apoptosis (a process leading to cell death). In some maternal medical conditions, cell death in the placenta

can reduce the nutritional support the baby receives.

After receiving her graduate degree, Chavez joined the lab of a well-known stem cell biologist at Stanford University where she studied human embryos and the use of time-lapse imaging to distinguish embryos with a high developmental potential from those that are unlikely to implant.

Chavez came to OHSU primarily with a background in human studies and did not originally see non-human primate research in her future. However, she says she gets the best of both worlds at the ONPRC. The non-human primates she studies are genetically close to humans and share both the timing of key developmental events and the typical percentage of embryos that reach the implantation stage (when the embryo buries itself in the womb and pregnancy begins). Her funded research translates to human health.

According to Chavez, as individuals, humans are not very successful at reproducing. Only 30 percent of known cases of copulation and ovulation result in a baby. This means that 70 percent of embryos or fetuses are lost during pregnancy. She is trying to determine whether these losses are due to defects of the embryo, the placenta, or a combination of factors.

Between 50 and 80 percent of human embryos have at least one chromosomal abnormality during the earliest stages of cell division. About 90 percent of inherited chromosomal abnormalities come from the egg, and the abnormality rates increase as a woman ages. Women are now waiting longer to have families so another of Chavez's goals is to understand how to

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IVF: Clinical Application *(continued from page 4)*

industrial chemicals, environmental pollutants and radiation can also affect fertility. In about 15 percent of cases, the cause of infertility is unexplained.

Among women who have an unassisted pregnancy and who know they are pregnant, the miscarriage rate is about 10-20 percent, depending on maternal age (higher as women get older), while the rate among assisted fertilization is around 30-50 percent.

During IVF the ovaries of a woman are stimulated to produce eggs at a stage ready for ovulation. The eggs are extracted from the body via a small surgical procedure involving inserting a needle through the vagina into the ovaries. The eggs are then fertilized in vitro (in the Petri dish) by injecting an individual sperm into each egg or by letting the sperm fertilize the eggs on their own. The embryos are then cultured in the Petri dish for approximately five days and one embryo is transferred into the uterus through the cervix where it hopefully implants in the lining of the uterus to initiate a pregnancy. The remaining embryos can be frozen for use at a later time in case the first attempt is unsuccessful.

The success rate of IVF has increased markedly over the last few decades in part due to improvements in culture conditions which allow us to mimic conditions in vivo (in the body) and culture the embryos to the blastocyst stage (day five or six after egg retrieval).

In IVF, the health of the embryo is evaluated primarily by a grading system based on its appearance. It is also possible to genetically test the embryos (preimplantation genetic testing) to assess whether they are chromosomally normal. In the companion article in this issue of The Heart Beat, Dr. Chavez discusses the issues surrounding assessment of healthy embryos.

There are limited data on long term outcomes in children born from IVF. Evidence shows that children conceived from assisted reproductive technology (ART) have detectable differences in blood pressure, body composition, and glucose homeostasis - as well as a slightly higher risk of birth defects and certain genetic abnormalities. It can be difficult to determine whether these differences are due to the actual ART procedures or to the problems that caused the infertility in the first place. The good news is that the risk of adverse outcomes is small. Remember, millions of healthy babies would not have been born if it were not for IVF!

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IVF: Basic Science Advances *(continued from page 4)*

overcome the effects of maternal age. It is also known that mothers eating high fat diets have more problems with eggs that result in abnormal fetuses.

The remaining chromosomal abnormalities occur during early cell division and are just as frequent as errors inherited from the egg. Chavez is looking at new ways to diagnose the abnormalities in embryos before they are placed in the womb with IVF. Most studies



of early abnormalities have been based on visual observation, but appearances don't always tell the story. An embryo that looks good can have genetic abnormalities and one that does not look perfect can be fine. The

cadence in which early embryonic cells divide is more important than appearances in determining which embryos will result in successful births.

Embryos that incur a chromosome abnormality in the later stages of cell division can have a mixture of normal and abnormal cells, and are called mosaics. Until recently, mosaic embryos were not considered suitable candidates for IVF transfer. However, a 2015 New England Journal of Medicine article reported that in a group of women that only had mosaic embryos available, 50 percent of the mosaic embryos that were transferred resulted in a live birth. Scientists are still learning what makes one mosaic embryo succeed and another fail. Chavez identified at least one mechanism whereby an embryo that has a highly abnormal cell, senses that it is abnormal and blocks it from dividing. In this way, the cell is prevented from developing.

Chavez wants to understand how the placenta is formed and how events before and during implantation, through the first trimester, impact offspring after birth. In collaboration with Lucia Carbone, associate professor and director of the Epigenetics Consortium, Knight Cardiovascular Institute, and others, Chavez is beginning to study the embryo to fetal transition and early placental development using single-cell and epigenetic approaches. It is not yet understood how embryo or placental health affects adult health but Chavez suspects that the environment in which the early embryo forms, sets the stage for later chronic disease. Work from other laboratories supports this idea.

Chavez is passionate about her work and notes that the best perks are having a great group of collaborators and being able to do research that can't be done in the human world but that can be used to improve human health.

Okonomiyaki

From The new Heart Protection Kitchen cookbook, this recipe is an easy and kid-friendly way to eat more vegetables—turn them into savory Japanese pancakes.

Okonomi means “to one’s liking,” and *yaki* means “grill,” so you can use whatever vegetables you like or have on hand for this dish.

The egg substitute provides plenty of low-cholesterol protein if you want to keep it vegetarian, or add leftover cooked chicken, fish, or shrimp for a bigger protein boost.

Dairy-free, QUICK, VEG

Prep time: 15 minutes

Cook time: 15 minutes

Ingredients

- 1 2/3 cups whole wheat flour
- 1/8 tsp baking soda
- 5 to 6 cups thinly sliced vegetables, such as cabbage, onion, mushrooms, bean sprouts, green pepper, carrot, and/or spinach
- 6 Tbsp liquid egg substitute
- 1 Tbsp finely chopped ginger
- 3 oz cooked chicken, fish, or shrimp (optional)

Optional toppings*

- Bonito flakes (see Note)
- Thinly sliced scallions
- Dried seaweed flakes
- Okonomiyaki sauce

Method

In a large bowl, whisk flour and baking soda. Add vegetables, 1 3/4 cups water, egg substitute, ginger, and optional protein, if using, and stir until thoroughly combined. It should have the consistency of thick pancake batter, though if a thinner batter is desired, add an additional 1/4 cup water.

Preheat a griddle over high heat. Pour batter onto the hot griddle and cook for 5 to 6 minutes, until golden brown. Carefully flip over and cook for another 5 to 6 minutes or until cooked through and golden.

To serve, slice into 6 wedges. If using, garnish each wedge with bonito flakes, scallions, seaweed flakes, and/or okonomiyaki sauce. Serve immediately.

Note: Bonito flakes are made from skipjack tuna that has been dried and shaved into long, pinkish-tan curls or flakes. A 2-tablespoon serving contains no sodium or fat. Bonito flakes can be found in Asian markets, well-stocked supermarkets, or online.

*Optional ingredients are not included in the nutrition analysis for this recipe.

Contributor: P. Barton Duell, M.D.



Nutrition Facts

6 servings per container

Serving size 1/6 of pancake (1 wedge)

Amount per serving

Calories 210

% Daily Value*

Total Fat 1g 1%

Saturated Fat 0g 0%

Trans Fat 0g

Cholesterol 0mg 0%

Sodium 75mg 3%

Total Carbohydrate 41g 15%

Dietary Fiber 9g 32%

Total Sugars 2g

Includes 0g Added Sugars 0%

Protein 11g

Vitamin D 0mcg 0%

Calcium 45mg 4%

Iron 3mg 15%

Potassium 214mg 4%

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

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New Cookbook from the OHSU Center for Preventive Cardiology

The Heart Protection Kitchen is a collection of 100 mouthwatering recipes designed to prevent and reverse heart disease. Cowritten by the director and dietitian of Oregon Health & Science University's (OHSU's) Center for Preventive Cardiology and based on their innovative cooking program of the same name, this cookbook teaches readers to prepare delicious meals that are quick, affordable, healthy, and perfectly balanced to protect the heart.

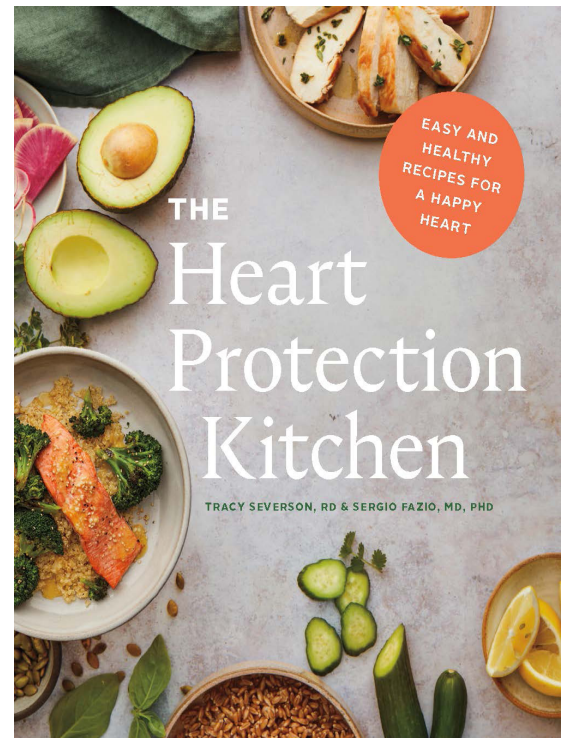
From a kale Caesar salad to chicken cacciatore to decadent brownies, each recipe includes prep and cook times, symbols for special dietary requirements, and a nutritional chart to help readers track their intake.

Moreover, the book includes a comprehensive introduction with heart-healthy information, strategies for meal planning, and tips for healthy cooking.

The Heart Protection Kitchen is an indispensable cookbook for home cooks who want simple, healthy, and flavorful dishes.

Tracy Severson, R.D., and Sergio Fazio, M.D., created the Heart Protection Kitchen, an acclaimed food program at OHSU, with the goal of helping patients reduce heart disease by improving their diets. The service has inspired countless patients with a team of doctors, a nutritionist, and award-winning chefs teaching them how to cook delicious, heart-healthy meals.

This cookbook is a collection of those recipes, from our kitchen to yours and is available from online retailers including Powells.com and Amazon.



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 lectures and events at the Center for Developmental Health.



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Coronavirus pandemic and early life origins of underlying conditions

The Centers for Disease Control and Prevention (CDC) defines *epidemic* as "... an increase, often sudden, in the number of cases of a disease above what is normally expected in that population..." and a *pandemic* as "an epidemic that has spread over several countries or continents, usually affecting a large number of people." Thus, the COVID-19 epidemic in the U.S. is part of a global crisis, warranting the pandemic title. COVID-19 is the disease caused by the Coronavirus known as Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2).

The word *epidemic* is usually associated with the spread of an infectious agent, like influenza, but is increasingly used to indicate a rapidly spreading fad or condition. For example, a recent NBC News headline read, "Vaping illness epidemic shows no sign of slowing."

In the U.S., the severity of COVID-19 is associated with preexisting, underlying conditions. In addition to old age, the CDC lists cancer, chronic kidney disease, chronic lung disease, weakened immune system, obesity, serious heart conditions, type 2 diabetes and sickle cell anemia as the most important underlying conditions that portend a severe infection. This list of chronic conditions is highly important for two reasons:

1) It explains the disparity in severity of illness and death among different ethnic groups. American Indian, Alaska Native, Black or African American, Hispanic and Latinx all have hospitalization rates that are nearly five times higher than in whites. Mortality is nearly twice as high among Black Americans. Why? These groups have much higher rates of the underlying conditions outlined by the CDC.

2) The underlying conditions that predispose severe COVID-19 cases are known to have their roots in early life development. Recent data show that in addition to the lungs, COVID-19 can lead to organ damage in the heart, brain and gastrointestinal tract. These organs are already weakened in people who were exposed to stressful conditions in their early life.

The OHSU Center for Developmental Health (CDH) studies the biological links between early life conditions and later life outcomes. For example, the links between nutrition before birth and heart disease risk could not be clearer.

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