Advancing the understanding and treatment of malnutrition in Africa

Dr. Mark Manary of Washington University in St. Louis, MD and adjunct professor at the USDA/ARS Children’s Nutrition Research Center at Baylor College of Medicine has devoted much of his career to improving the diagnosis and treatment of malnutrition in African children. His two recent studies have helped advance the understanding of this health issue that proves deadly for nearly half a million children annually.

The studies on changes in the intestinal microbiome (the microorganisms that live in the gut) that are related to the development of kwashiorkor, a form of severe acute malnutrition, and on the use of antibiotics in addition to nutritional therapy to treat malnutrition were published in Science and the New England Journal of Medicine, respectively.

“The goal of the research on the intestinal microbiome as it relates to kwashiorkor is to work toward a thorough scientific understanding of what causes children to become malnourished in the first place. This is essential to a future where we can work to prevent malnutrition,” said Manary.

In the first study, twins were recruited shortly after birth from five rural villages in the country of Malawi. A total of 317 sets of twins and three sets of triplets were recruited. They were examined every month for the first three years of their lives for the development of acute malnutrition. Every two to three months, they also provided stool specimens. If any of the children became malnourished, they were treated using standard nutritional

Web-based intervention designed by and for teens is effective

How do you motivate teens to eat a healthy diet and become more active?

Researchers at the USDA/ARS Children’s Nutrition Research Center at Baylor College of Medicine recently showed that when adolescents participated in an eight-week intervention using a website with helpful tools for healthy eating and physical activity designed by their peers, it resulted in higher vegetable consumption and increased physical activity than those who were given fewer tools. Their findings appeared in a recent issue of Health Education Research.

“Teen Choice: Food and Fitness” was designed by researchers after receiving input from teens between the ages of 12 and 17 on what materials they felt would help them be more active and eat healthy. These adolescents offered suggestions including information on what to eat, how much, types of physical activity and more.

“It was interesting to talk to these teens and realize that they wanted to have access to this information all at once and in one place,” said Dr. Karen Cullen, professor of pediatrics at BCM and first author of the study.

After developing a website based on this input, researchers recruited 408 teens for the eight-week web-based intervention. Volunteers were asked questions about their physical activity and eating behavior at the beginning of the study and then asked to log onto the intervention website weekly during the eight-week period. They were asked to select one eating and/or physical activity goal for the week and then report on their progress the following week. They could then choose a new goal for the next week or stay on the same goal.

“The website provided them with information on recipes and other nutritional information, and volunteers were able to watch short videos that showed examples of teens overcoming physical activity or healthy eating challenges.

“This put the teens in control of their own problem solving and goal setting,” said Cullen.

After the intervention, volunteers were asked to complete a final questionnaire.

Volunteers in the control group had access to the same website, but without...
DNA methylation in embryonic stem cells turns genes on

It may be time to revise some textbooks. Practically any molecular genetics textbook will tell you that DNA methylation (the addition of a methyl group or CH3 molecule) is an epigenetic switch that turns off genes. Studies by researchers at the USDA/ARS Children’s Nutrition Research Center at Baylor College of Medicine show, however, that during early human embryonic development, as stem cells start to develop into different cell types and tissues, the DNA in certain genome regions become methylated, turning on important genes involved in development. Stem cells have the flexibility to develop into any cell type in the body. DNA methylation is one of the molecular ‘switches’ that guides their development into specific cell types.

Methylation affects so-called CpG sites in our genomic DNA (a cytosine (C) is followed by guanine (G)). The methylation does not occur at the promoter region (the beginning of the gene), but rather at CpG-dense regions called ‘CpG islands’ at the end of the gene, called the 3’ (3 prime) end, said Dr. Lanlan Shen, associate professor of pediatrics at BCM and senior author of the report in the journal *Molecular and Cellular Biology*.

“This study is the first to document a specific mechanism for how DNA methylation at 3’ CpG islands activates gene expression,” said Shen. Not only that, but by using a computer to analyze their large sets of DNA methylation data, she and her colleagues showed that as stem cells develop and become more specialized tissues and cells, these 3’ CpG islands become more and more methylated.

This methylation regulates the activation of gene transcription (the first step in translating DNA into a blueprint that eventually becomes a protein) via a mechanism that depends on an important developmental transcription factor called CTCF.

“The bottom line of the report is that CTCF-mediated gene activation appears to be used by our cells as a general mechanism...
therapy and additional stool specimens were collected during treatment.

The genetic material in the stool specimens was examined, allowing researchers to develop a complete genetic picture of all the bacteria in the intestinal tracts of the children in the study. These genetic pictures were compared and contrasted among children with kwashiorkor, children with marasmus (another form of severe malnutrition), children with moderate malnutrition, and children who had not become malnourished.

It was especially interesting and informative to compare the bacteria make-up of children who became malnourished to their healthy twin, Manary noted.

The stool specimens were then transplanted into healthy mice, and researchers observed what happened when the mice received the microbiome from healthy children compared to when they received the microbiome from children with kwashiorkor. The mice that were given the stool transplants from children who had kwashiorkor lost weight, but then gained weight and developed more normal intestinal bacteria when given therapeutic nutritional feedings.

“Taken together, these results strongly suggest that the intestinal microbiome plays an important—but not exclusive—role in the development of kwashiorkor,” Manary said. “For children in Malawi and other places who are at high risk for kwashiorkor, this suggests that nutritional therapy alone may not be enough to keep them healthy. Extensive work is still needed, including identifying which bacteria specifically are important and by which immunological, metabolic, inflammatory and infectious pathways.”

Manary noted that even in the best therapeutic feeding programs for children with severe malnutrition, some 15 percent will not recover and as many as 10 percent will die. The use of antibiotics in addition to nutritional therapy has been suggested as a possible form of treatment but there was little clinical evidence to support its use.

In a second study, Manary and his research colleagues sought to test the effectiveness of antibiotics in addition to nutritional therapy. The study was conducted at 18 different village malnutrition clinics in six districts in rural southern Malawi. Children in the study were randomly selected to receive one of two antibiotics (amoxicillin or cefdinir) or placebo in addition to standard nutritional therapy. They returned to the clinic every two weeks for follow-up to measure their recovery. A total of 2,767 children were enrolled in the study over 15 months.

“The results were indeed very significant and surprising,” Manary said. “Most remarkably, the death rate was lowered by about 40 percent among children who received antibiotics.”

New malnutrition guidelines are forthcoming from the World Health Organization that support the use of antibiotics for patients with severe malnutrition.

There are logistical and financial challenges to getting these medications to rural health centers, just as there are challenges in getting therapeutic foods to these sites, Manary noted.

“But by proving their effectiveness in a rigorous clinical trial and by having these results vetted and accepted by the WHO, this will hopefully become an accepted standard of care, which will motivate governments and aid agencies to include funds for this life-saving therapy as they do for other therapies for high-burden diseases,” he said.

The study on intestinal microbiome was supported by funds from the Bill and Melinda Gates Foundation and the National Institutes of Health.

The study on antibiotic treatment was supported by a grant from the Hickey Family Foundation, a cooperative agreement with the Academy for Educational Development Food and Nutrition Technical Assistance 2 project (through the Office of Health, Infectious Diseases, and Nutrition, Bureau of Global Health, and Food for Peace, United States Agency for International Development), and the National Institutes of Health.

Malnutrition advances CONTINUED FROM PAGE 1

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Volunteers

Houston-area residents are invited to participate in the following nutrition research projects designed to help CNRC scientists learn more about the nutritional needs of children. Free parking is provided. Financial compensation is provided for most studies, and transportation may be available.

For more information on any CNRC study call Marilyn Navarrete, 713.798.7002, or e-mail rilynn@bcm.edu.
Web-based intervention  

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The role model videos and the goal setting tools. They could print a goal sheet to use on their own.

Researchers found that those in the intervention group ate more vegetables than those in the control group. Both groups increased their amount of physical activity and recorded less television watching time.

Both the control and intervention group gave high ratings to the website, and researchers documented a 75 percent log-on rate for both groups over the eight-week period.

DNA methylation  

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for regulation of gene expression during differentiation,” said Dr. Robert Waterland, associate professor of pediatrics at BCM and a member of the faculty of the Children’s Nutrition Research Center, as is Shen.

The finding is particularly important for shedding light on the complex roles of DNA methylation during mammalian development, and should lead to refinement of the ‘textbook’ view of this epigenetic modification.

Others who took part in this work include Da-Hai Yu, Miao-Hsueh Chen, Govindarajan Kunde-Ramamoorthy, Laguna M. Nosanvih and Manasi Gadkari, all of BCM, Carol Ware of the University of Washington in Seattle; and Jiexin Zhang of the University of Texas MD Anderson Cancer Center.

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