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Nourishing America's Preemies Scientists Confront the Challenges of IV Feeding

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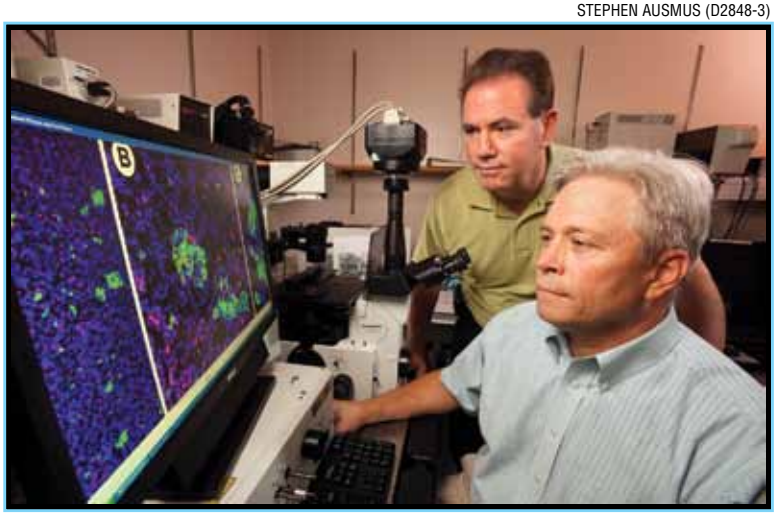

At the Children's Nutrition Research Center in Houston, Texas, ARS physiologist and professor of pediatrics Doug Burrin (left) and associate professor of pediatrics Darryl Hadsell examine a microscope image of pancreatic beta cells obtained from piglets fed by total parenteral nutrition.

Each year, more than a half-million infants are born prematurely in the United States. Many of these preemies, particularly those whose tiny digestive systems are simply too underdeveloped to handle mother's milk or infant formula, may need to be nourished exclusively via intravenous feeding, known as "total parenteral nutrition," or TPN.

TPN solutions, usually administered at the hospital for anywhere from a few days to a month or more, provide essential nutrients broken down into a very basic form. This liquid is gently and continuously infused into the infant's bloodstream, completely bypassing the digestive tract.

"TPN helps save the lives of newborns and supports their growth and development, especially of the brain," says Douglas G. Burrin, an Agricultural Research Service physiologist at the Children's Nutrition Research Center in Houston, Texas, and a faculty member at Baylor College of Medicine, also in Houston.

But preemies who are on TPN for longer than 2 weeks may develop complications that might affect their health later in life. Since 1998, Burrin and colleague Barbara Stoll, who is also with the nutrition center and the college faculty, have worked with teams of scientists in the United States and abroad to discover more about the unwanted side effects of TPN and to develop new, safe, effective ways to prevent these unintended consequences or, at the very least, to minimize their impact.

The TPN-linked problems that their research targets include poor control of blood sugar, slowed growth of the digestive tract, and onset of a constellation of disorders referred to as "parenteral nutrition-associated liver disease."

In these investigations, Burrin and colleagues use piglets as their laboratory animal model.

Why Piglets?

Nutrition researchers worldwide recognize that the pig digestive tract is very similar to that of humans. Also, the size and body composition, that is, the amount of fat and amount of lean tissue, of an infant piglet "are typically comparable to those of a human preemie," says Burrin. "Infant lab mice or newborn lab rats are simply too small for this research."

MARK BOGGESS (D2865-1)

Compared to human preemies, infant piglets are similar in size and body composition and have similar digestive tracts. These healthy piglets are about an hour old.

Does TPN Increase Risk of Insulin Resistance?

In 2005, scientists elsewhere suggested an association between premature birth and increased risk of insulin resistance, a disorder common in type 2 diabetics.

A 2010 study by Burrin, Stoll, and others brought TPN into this picture. Their research provided the first evidence, in a newborn-lab-animal model, of a significant association between TPN feeding and several indicators of insulin resistance.

In people, and in piglets, insulin—a hormone—largely controls the amount of sugar (glucose) in the bloodstream. Insulin is produced exclusively by unique "beta cells" in the pancreas. As it circulates through the body, insulin triggers cells to remove glucose from blood and use it for energy. But resistance to insulin can lead to a buildup of unhealthy levels of glucose in the blood.

Insulin resistance was 40 percent greater in the TPN-fed piglets than in their orally fed counterparts, the scientists found. Also of concern: Proliferation of beta cells was 30 percent less in the TPN piglets.

"The beta cells that you produce during infancy and childhood have to last you a lifetime," says Burrin, "so anything that interferes with normal beta-cell production could be detrimental to your later health. "

GLP-1 Levels: How Important Are They?

Followup research, reported by Burrin, Stoll, and others in 2012, again indicated that insulin

resistance was significantly greater in TPN-fed piglets, compared to piglets that were put on other feeding regimens.

In addition, the study suggested that reduced production of GLP-1 (glucagon-like peptide 1), a hormone secreted in the digestive tract, may help explain the difference in insulin resistance among the research piglets.

Previous research has shown that GLP-1, a "gut hormone," circulates through the body and helps lessen insulin resistance. It belongs to a class of hormones known as "incretins." Their insulin-regulating role, dubbed the "incretin effect," has led to development of synthetic incretins now used in treatment of type 2 diabetes.

Says Burrin, "We found that plasma levels of GLP-1 were significantly lower in the TPN piglets than in any of the other piglet groups. That makes sense, given that there was no food in the TPN piglets' digestive tracts to stimulate secretion of GLP-1.

"We are continuing to investigate GLP-1 in our research because we think there's much more to be learned about it in the context of preventing or reducing insulin resistance in TPN infants."

Small Doses of Bile Acid May Blunt Liver Disease

Gut hormones were also key in a study of a potential new approach to preventing parenteral nutrition-associated liver disease (PNALD).

PNALD is an umbrella term that encompasses several conditions, including cholestasis, which results from a buildup of excess bile acids in the liver, and steatosis, which—as its "fatty liver" nickname implies—occurs when there is too much fat in the liver.

There is no well-established, science-based cure for PNALD. In severe cases, this disease can lead to liver failure and the need for a liver transplant—a major surgery that, though not new, is still regarded as having considerable risks.

A team of Burrin, Stoll, and coinvestigators showed that giving newborn TPN-fed piglets a very small dose of a natural bile acid three times a day helped combat PNALD.

The acid, CDCA (chenodeoxycholic acid) is one of the major bile acids that are produced in the liver, then secreted—via the gall bladder and bile duct—into the upper digestive tract to help the body digest fat.

According to Burrin, the CDCA study is the first to demonstrate the use of small doses of this bile acid, delivered directly to the upper digestive tract, to control PNALD in a newborn-lab-animal model.

TPN piglets that were given CDCA had significantly lower levels of serum bilirubin, a biomarker of cholestasis, than did the TPN-fed piglets that were given a placebo. In addition, levels of serum bile acids, which are another biomarker of cholestasis, and levels of liver triglycerides, an indicator of steatosis, were nearly normal in the CDCA-treated TPN piglets.

The team also found that CDCA stimulated growth of mucosa, the inner lining of the intestine. That is significant. Explains Burrin, "TPN often has the exact opposite effect: It can lead to atrophy of the mucosa." The shriveling and shrinking of the intestine that result can diminish the body's ability to digest and absorb nutrients.

The researchers are now taking a closer look at the basic mechanisms responsible for the beneficial effects of the CDCA regimen. CDCA's ability—as shown in mice—to indirectly induce secretion of key gut hormones such as GLP-2 (glucagon-like peptide 2) and FGF19 (fibroblast growth factor 19) "may provide an explanation for some of our piglet findings," Burrin says.

For example, previous research, including that by Burrin and Stoll, has shown that GLP-2 boosts growth and proliferation of intestinal mucosal cells in piglets and in adult humans. In this newer study, reported in 2012, three factors—GLP-2 levels, better mucosal growth, and CDCA treatment—appeared to be interrelated. That's because TPN piglets that were treated with CDCA had higher levels of GLP-2 in their plasma. Those same piglets had better mucosal growth than the other TPN piglets.

FGF19 may also be an important part of the picture. In mice, FGF19 has the protective effect of suppressing production of bile acids in the liver, in response to signals sent from specialized bile-acid-sensing cells in the gut. CDCA-treated TPN piglets had healthier bile acid levels, and more FGF19 in their plasma, than did the other TPN-fed piglets.

Piglets that were not on a TPN regimen had the highest plasma FGF19 levels. "We regard this finding as strong evidence that TPN suppresses secretion of FGF19, which results in disruption of normal regulation of bile acids. We think this suppression is a key piece of the puzzle of why and how TPN can cause liver disease."

Burrin and Stoll, along with Teresa A. Davis, Darryl L. Hadsell, and David D. Moore, all of the nutrition center research staff and Baylor College of Medicine faculty, and other collaborators, have documented their TPN findings in peer-reviewed articles in the *Journal of Nutrition,* the *American Journal of Parenteral and Enteral Nutrition,* the *American Journal of Physiology: Gastrointestinal and Liver Physiology,* and other scientific publications. The American Society for Parenteral and Enteral Nutrition, the National Institutes of Health, the American Liver Foundation, and ARS funded the studies.—By **Marcia Wood,** ARS.

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Research instructor of pediatrics Barbara Stoll (left) and assistant Liwei Cui fill parenteral nutrition bags with formulas to nourish infant piglets.