The acute crisis of metabolic imbalance is the most dangerous situation for the patient with maple syrup urine disease (MSUD). It may occur in response to a lapse in good dietary discipline, or to a major trauma or surgery, but in infants and young children it is most often a consequence of infection. This makes it difficult to avoid. Sometimes the first sign of a new viral infection is the characteristic maple syrup odor, a bout of vomiting, or a positive test for ketones in the urine.

We teach parents of our patients with MSUD to test the urine for ketones. A positive test is a strong alert but not a very sensitive index of imbalance.* The most important criterion is the plasma concentration of leucine, which can be very high before ketonuria is evident, so we also teach parents to come in for plasma amino acids at the first inkling that something is wrong. With this disease you do not want to delay treatment. If we catch it early, it is often possible to institute a regimen that reverses the imbalance and keeps the patient out of the hospital.

Quite often the first episode occurs in an infant before diagnosis. The patient is admitted in serious metabolic imbalance. Most of these very young infants are admitted in coma. Similar episodes of imbalance can occur at any age, even in adult life after years of exemplary control. It is important to employ optimal methods of treatment to turn the situation around as rapidly as possible. Cerebral edema is the most dangerous complication of this crisis, but patients may die in coma even in the absence of edema of the brain. We need to do everything we can to prevent neurological damage and developmental delay.

The objective of therapy is to reduce the level of leucine as rapidly as possible. Early approaches to this via exchange transfusion or peritoneal dialysis were ineffective because very small amounts of branched-chain amino acids are removed in these ways. Hemodialysis is more effective, but the thought of undertaking hemodialysis every time an infant came down with an infection, such as, otitis media, is not an attractive prospect.

Our approach is to harness the forces of anabolism [constructive phase of metabolism] to get rid of the extra leucine in the blood by using it to make body protein. To do this we provide energy in the form of intravenous glucose. At the same time, we provide a continuous supply of amino acids minus isoleucine, valine and leucine. In early approaches, we and others supplied these mixtures of amino acids as intravenous solutions. Results were very rewarding. There was a prompt, linear fall in levels of leucine, and clinical manifestations of the crisis receded. We devoted considerable thought to the design of optimal solutions for this purpose, as well as the development of maintenance solutions, which would be useful in a patient who is not in crisis but in need of parenteral therapy over a number of days - as we experienced in one patient with a tonsillecctomy.
This use of intravenous solutions of amino acids remains an excellent approach to the treatment of metabolic imbalance in MSUD. It is particularly useful in a patient with vomiting. It is a mainstay of therapy by doctors Morton and Strauss at the Clinic for Special Children, where the solution is made in their pharmacy. Most institutions do not consider themselves equipped to generate these solutions. We obtained ours commercially, but it soon became evident that costs were prohibitive. The commercial supplier would generate the solution only in a large batch - much more than needed to revive an infant in crisis - and soon all of our hospitals and third parties refused to pay for these solutions. There were timing problems too. A patient admitted in crisis on Friday could seldom get solution before Tuesday. For these reasons we sought another treatment plan.

For ten years now we have successfully used enteral \(\text{[by way of the intestine]}\) solutions to serve the same purpose. This is accomplished by dripping the material very slowly, over 24 hours, through a nasogastric or gastrostomy tube. We have learned to employ the amino acid solutions in minimal volume, and that has been the secret of gastrointestinal tolerance even in patients that have been vomiting. It is possible to employ the same formulas that we use for every day feeding in MSUD, such as, Ketonex or other MSUD formulas. But with all the fat, carbohydrate and minerals that make these preparations so useful for every day use, they hardly meet the prescription of minimal volume. In one of our larger patients, we made a calorie per milliliter solution of a standard formula to provide a dose of 2 g/kg of amino acids, and it came to almost 2½ liters of fluid, hardly what you would like to give a vomiting patient. So we made up our own solutions that contained nothing but amino acids. We tried various mixtures in an attempt to find an optimal mixture. It worked, and we published our experience, with three episodes in 2 patients, in the *Archives of Pediatrics and Adolescent Medicine* (152:593-598, 1998). That published article prompted a request for this current article.

We have had experience with a number of patients, and it is clear that this anabolic therapy is the centerpiece of treatment. We no longer make our own mixtures because Applied Nutrition now supplies such mixes as Complex\textsuperscript{a} Amino Acid Blend. We have learned a few things along the way. Among them is the fact that plasma valine and isoleucine concentrations always drop lower than leucine concentrations during therapy. If you put equal quantities of these branched-chain amino acids into protein, the isoleucine level drops too low, and the patient becomes catabolic \(\text{[destructive phase of metabolism]}\), resulting in elevated leucine levels. Therefore, we supplement with isoleucine and valine.

It is also true that some infections make the patient too catabolic to overcome with this approach. In that situation we add insulin and more glucose to make the patient more anabolic.
and provide protein synthesis. More recently we have been using human growth hormone, a very powerful anabolic agent in this situation. At first we only turned to growth hormone when amino acids plus insulin had not turned things around. More recently I have employed growth hormone earlier and have not needed to use insulin.

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* Editor's note: For many children and adults with MSUD, 2-4 DNPH is a more sensitive home monitoring test to determine leucine elevations. Urine is used for both DNPH and ketone tests. To read more about DNPH, check our web site, www.msud-support.org. In the index, under the topic Medical Treatment, is an article listed with the title "Letter from Dr. Morton (Use of DNPH)."
It was printed in the April 1991 issue of the MSUD Newsletter.