entrance site through AcetylCo-A then also becomes unavailable.

The data presented strongly suggest that the pathologic processes of dying and B-state transition are related to increased formation of Alanine from BCAA and Pyr. The data are best explained by a major catabolic breakdown of muscle protein with BCAA being used by muscle and with the other amino acids not catabolized by muscle (Pro, Phe, Tyr, Meth) being released into the plasma without subsequent normalization of the plasma levels by the liver. Furthermore, the data strongly suggest that this major catabolic breakdown of muscle protein is not prevented or controlled by exogenous amino acids in septic patients who are dying and/or undergoing a "B" state transition.[11]

Autocannibalism, or the autogenous utilization of one's own muscle for metabolism, is a significant component of the septic process. In septic patients who survive, it is influenced and possibly minimized or controlled by appropriate exogenous metabolic support, assuming the septic focus has been appropriately dealt with and other therapeutic modalities (*e.g.* cardiopulmonary support and antibiotics) have been used to stabilize the host's adaptive responses. In septic patients who expire, however, the autocannibalism procedes unabated by exogenous metabolic support until death ensues. It is apparent that currently available fuels are inadequate to appropriately support this type of altered metabolism. In the absence of the identification of the prime mover, new therapeutic support regimens must employ more appropriate fuels that can be used in septic metabolic failure. One promising fuel is branch chain amino acids; other fuels might include acetoacetate or short and medium chain fatty acids.[5,6,16]

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Discussion

DR. LLOYD D. MACLEAN (Montreal, Quebec): I do not think anyone could accuse Dr. Cerra and his colleagues of oversimplifying the problem but maybe I can for their comments.

Hemodynamic monitoring has been extremely useful in low-flow states, and this includes, of course, the problem we most commonly deal with, that is, hypovolemia and cardiogenic shock. Unfortunately, this approach for sepsis shock has been quite disappointing, and it is difficult to show that meticulous hemodynamic management of septic patients makes much difference.

One can take several directions to get around this. The one we have chosen, or spend most of our time on, is the identification of patients who have decreased host resistance, who might be candidates for septic complications. We try to do another operation, get the patient in better shape with total parenteral nutrition or use some mechanism to make them less likely to become septic, that is, avoid the problem in the first place.

An equally attractive approach is the one we have heard here today, and this is to support specific defects after identifying the metabolic problem.

When we learned that these patients have a decreased oxygen utilization, it was attractive to elevate the Po_2, and, of course, one can do that and not increase the oxygen utilization. High-energy phosphates might be used; this has been done in animals but has not been confirmed in humans. We could provide appropriate substrates to preserve protein; I believe that is what these authors are suggesting.

The present study presents two problems: the effect of exogenous protein on plasma levels of amino acids and the differential protein

utilization. The authors are asking: Is a defect in fuel utilization in the periphery, or is the liver faulty? The authors showed that the level of alanine, which originates in muscle from branched-chain amino acid and lactate, increases in fatal sepsis, and this is not the result of branched-chain amino acid load. Another finding is that the marked increase in amino acid efflux from muscle is more than that needed for hepatic protein synthesis. So the work does strongly point to the periphery. I think the authors are correct, but I do have some questions.

Does the amino acid concentration they are measuring in the plasma reflect flux from muscle? Does not one have to know more about flow and uptake in this setting to really be able to say that the plasma concentration reflects what is coming out of muscle, and not being taken up by liver, for instance?

Can you alter the amino acid concentration with more glucose? I noticed in the paper the amounts of glucose given appeared less, that is, 15–30 kilocalories per kilogram per 24 hours than most of us are using, 30–50 kilocalories per kilogram per 24 hours in this setting.

Can you reverse or in any way ameliorate the cannibalism by giving branched-chain amino acids before the patient reaches what you refer to as the B state, low oxygen uptake the late type of septic shock? If this is the preferred fuel of sepsis, which I believe you point out, how should we be using it clinically at this time?

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): When you have had a chance to study this paper, you will understand it as an extensive and careful study, demonstrating failure of the mitochondria/oxidative metabolism in patients who are destined to die.

I want to supplement from our own studies one or two parts of the metabolic pattern which the authors present.

(slide) Dr. Lloyd MacLean asked the question: Is this a failure of metabolism in the periphery, or is it in the central tissues? Dr. Cerra is depending on blood levels to determine failure of various pathways involved in amino acid metabolism. What is required to be certain is the knowledge of the flux of amino acid from the peripheral tissues, or from infusions to the liver and other central tissues. There they must be removed from the plasma.

We need to differentiate the metabolic pattern in the periphery from that in the central tissues.

(slide) This slide compares the rates of protein breakdown, protein synthesis and oxidation of glucose and leucine in normal fasting human muscle when incubated with the metabolism of incubated muscles from septic patients. The huge protein breakdown rate in the septic muscle is not present in the normal muscle despite a slightly greater rate of protein synthesis. When we compare the glucose oxidation in the normal muscle, it is almost the same as in the septic muscle, but it turns out that the septic muscle is oxidizing much more leucine. This is an important difference.

(slide) Now, what about the central tissues? If we look at the CO_2 production from leucine in normal and septic states, there is really no difference. (slide) However, if we look at the use of the amino acids in the central tissues, we find that the protein synthesis from leucine supplied from the periphery is ever so much larger in the septic state than the normal.

(slide) Turning to clinical studies, here are the blood levels of patients with liver failure who died compared with the levels of those who lived. My results show several things in common with Dr. Cerra's findings. The alanine and methionine levels were higher in patients who subsequently died. The production rates show that there is not a great difference. Actually patients who died had lesser releases from the periphery. However, the difference in the clearance rates shows that there are dramatically different values between patients who lived and patients who died. The clearance of the amino acids produced in the periphery demonstrated as being most significant in this fasted group of patients was that of the aromatics Dr. Cerra mentioned as well as methionine and cystine in the sulfur-containing group of amino acids. There are several, including proline and ornithene, that are not cleared as fast in patients who are going to die. Knowing the flux and clearance rates it is then possible to confirm many of Dr. Cerra's conclusions.

For this reason, I believe these studies are valuable and begin to give us an idea of why people die of sepsis. Obviously the best treatment is to eliminate the septic stimulus or toxic agents that interfere with the metabolic pathways by draining an abscess or removing gangrenous tissue. Failing that, energy metabolism and protein synthesis must be supported by maintenance of the circulation and other vital functions as well as by supplying the metabolic substrates that can still be used.

DR. STANLEY M. LEVENSON (Bronx, New York): It's too bad that Dr. Wilmore's paper early this morning and Dr. Cerra's paper late this afternoon were separated in time, since they are so closely related. It would have been useful to have them juxtaposed so we could have discussed them together. Despite all the seemingly complicated regression equations that Dr. Cerra showed his last two diagrams put it all in perspective for us, and made a lot of sense. Usually, when data fit well-established biochemical principles or mechanisms one gets a certain sense of reassurance.

There are some points that I would like to emphasize: the studies by Cerra, Border, McMenamy and their colleagues were done in desperately ill patients who were receiving on the average what looks to me as limited nutrient intake. That doesn't mean that there were not some patients who might have received more liberal (? adequate) intakes but when one looks at the mean caloric intake, it was relatively low, and, similarly, the mean protein intake was relatively low. So some of the patients, then, were studied on what many of us would consider inadequate nutrient intakes. Similarly, Cerra and his associates point out that their patients received no fat. The possibility exists, then, that there was some fatty acid deficiency, which further complicates the situation. They point out also that the patients received no insulin, and this, too, has to be considered in evaluating their observations. Nevertheless, I think that their clear demonstration of the changes in the most critically ill patients in the rate and degree of transformation—using the word loosely—among the various branched chain amino acids valine, leucine, isoleucine, to alanine is very important and casts additional light on our understanding of the metabolic changes in skeletal muscle and liver which occur after serious injury and sepsis, matters of which our understanding is still incomplete despite the number of studies carried out for many many years.

DR. FRANK B. CERRA (Closing discussion): We cannot imply any kind of flux from the plasma levels we measured.

The question about altering the amino acid concentrations with more glucose is an interesting one and relates to Dr. Levenson's comments on the amino acid and caloric loads. Those means are misleading because they include the 40 interventions in which no glucose or amino acids were given.

The patients who received amino acids alone and survived had a mean load of approximately 60 g per body surface area; that is confusing. By normalizing to body surface area, instead of kilogram, we did not use the usual nomenclature; it was done so we could relate everything back to oxygen consumption.

Worked out mathematically, the upper limit is about 2.5 g/kg/day. The same concept relates to calorie load.

If you select out the appropriate groups and do the subset analysis, it would be difficult to say you could change anything in the amino acid profile by giving increased loads of glucose. That is a fixed relationship. Remember that the septic process has progressed quite far in these patients.

The mean insulin level in this group of patients is approximately 85 microunits. They have a sufficient amount of insulin. The subject of hormonal balance is interesting, but a discussion of that topic would not be appropriate at this point because of time commitments.

Dr. McLean, obviously there is a second purpose in this study, and that is to set the stage for the next series of fuel evaluations. The first of which is the branched-chain protocol, which in effect has been started with a 50% branched-chain solution. It is too early to discuss those results.

There are some results in the literature, from Dr. Fischer and Dr. Freund, but not enough data at this point to make meaningful comments.

We are also looking at other forms of fuel, such as acetoacetate, at the same time getting at the flux question by doing arteriovenous differences across selected organs and using heavy isotope analysis.