Discussion

Dr. Watts R. Webb (Syracuse): I think there are several things of imortance here. Exactly why does one group fall into the low output, and the other fall into the high output syndrome? Is it just a matter of cardiac failure? Dr. Clowes is using what Sodi-Polaris described as a polarizing solution of the glucose-potassium and insulin. Many of us have been using this for many years in heart failure cases of one kind or another, such as after cardiac surgery or for preservation of the heart for transplantation or in ischemic arrest at surgery. With this he is converting many of the animals who were definitely in cardiac failure into a normal or high cardiac output state, and then their metabolism seems to return toward normal. Is the deficit, then, one of insulin or of oxygen delivery or of cardiac failure?

The oxygen uptake in the leg appears to be comparable in all the states, which makes one wonder if the oxygen uptake in the leg actually reflects the oxygen uptake in the total body. With a cardiac index only about one-third of normal, it seems unusual that it should be reflective of the total body uptake.

We have seen some very interesting situations in patients with extreme hyperdynamic states as a result of massive sepsis, and in these we have seen a cardiac output in the range of 301 per minute with blood pressures of 180/0. We and our cardiac consultants were fully convinced that the patients had developed an acute SBE and had overwhelming, acute aortic regurgitation. In fact, one of them had cardiac catheterization before any of us would be convinced that this did not represent aortic insufficiency.

I would like to ask Dr. Clowes, then: Is the hypodynamic state merely a late stage of the hyperdynamic state, or is it just a reflection of cardiac failure?

And I would ask if glucose oxidation is blocked primarily by an oxygen deficit, or is this a manifestation of something more specific than a lack of insulin? Does the insulin blood level actually reflect the amount of insulin that's being secreted?

Dr. Boyd W. Haynes, Jr. (Richmond): While reading the abstract it occurred to me that some of the data that we have collected in the burn patient might provide further insight into the problem. I'm sure the audience recognized, George, that this is almost a unified field theory, and that you have added a significant in-depth understanding to the total problem of cellular and cardiovascular function in sepsis.

(Slide) If you look at the hemodynamic response of the burn patient immediately following his injury, you see that there is at first a low cardiac output which in time progresses in an almost straightline fashion toward excessive outputs.

Measuring cardiac output up to two weeks or three weeks, one finds supernormal cardiac outputs, often 15 liters/min. As all of you are aware, the burn patient's wound is his major problem, and infection occurring progressively is primarily responsible for the hyperdynamic state.

At the same time, in following the increasing outputs, we observed alterations in carbohydrate metabolism too, much as Dr. Clowes has told you, in that often these patients had quite elevated blood glucose levels; and more recently we have observed that in the extremely seriously ill burn patient their blood cholesterol levels are extraordinarily low, which is not characteristic of all burn patients, but of the more severely burned.

(Slide) Finally, these data were collected from three patients whom we studied in extremis and at a time when blood volumes were normal or supernormal, the mean blood pressures were all low. You will note that the cardiac indices in at least one of those patients were quite good—5.3 l/sqm./min.—in a situation characterized by circulatory collapse.

The addition of vasopressor—Levophed—improved the blood pressure somewhat, but didn't significantly improve cardiac output.

Dr. William R. Drucker (Charlottesville): Dr. Clowes and his associates are to be congratulated for continuing to do something that I believe is tremendously important in the field of studies of shock and sepsis; and that is, they are attempting to provide a correlation of basic biochemical, metabolic data with the physiological changes that occur. By this means, they provide for those of us who are responsible for taking care of patients, through the physiological information, clues as to how to monitor and keep an eye on what's happening to the patient, and through the biochemical data give us a better understanding of the rationale for the various therapeutic modalities that we choose to employ, in addition to—as an adjunct to—the basic modalities, such as surgery or re-infusion of volume or giving antibiotics or draining an abscess, and so forth.

In this particular instance, Dr. Clowes is providing some very firm data which, if one follows his logic and will agree with his interpretation, lends strong support to the idea that one under rare occurrences—but there are rare occurrences when one is justified in supplementing the therapeutic regimen by the infusion of glucose and insulin.

I find this a dangerous concept, because of the dangers of giving insulin and the hypoglycemic shock that it can cause, which may be lethal, particularly in very sick and aged patients. However, my understanding is that Dr. Clowes reasons as follows: that these patients he has studied relate very much to the pigs that he used in his laboratory, and he can get similar data from the laboratory to what he finds in man; that there is a similar oxygen consumption in the fasting state as there is under the two kinds of sepsis, with a high output and a low output from the heart.

I'm a little concerned, and would like Dr. Clowes to make one comment as to how, with the presence of fever, one finds the same oxygen consumption. But on the basis of the fact that there are no changes in oxygen consumption, Dr. Clowes moves ahead and says, if I understand him correctly, that one must find some other substrate to explain the rise in lactic acid; and he jumps to carbohydrate, which is the most logical cause.

Well, then, if carbohydrate is being converted to lactic acid, under which circumstance it does not use oxygen, what is using the oxygen? Dr. Clowes postulates that it's protein, and this seems to me a very sensible postulate. But then I'm a little bit concerned as to why, having developed this beautiful argument, he turns right around and says the insulin and glucose infusion that he gives works by some effect on a membrane rather than by a restoration of the very metabolic defect that he has been able to demonstrate so nicely.

Now, perhaps the time of observation was too short to be able to show any change in these metabolic alterations, but I would ask Dr. Clowes: After the infusion of his glucose and insulin in his pigs, and in the humans, was he able to show an increased consumption of glucose in the periphery? He began to show that in his next-to-last slide, I believe, but I didn't get a clear answer to that.

Is there an increased consumption of glucose? And is there a reduced utilization of the protein? Or do we have to fall back on some effect of insulin on the membrane? If that is so, do we have any data in terms of electrocardiographic changes, in the electrolyte shifts, that would help support the idea that insulin in this particular instance is acting not through its provision of substrate, namely glucose, for metabolism, but by some specific effect on membrane potentials?

Dr. George H. A. Clowes: (Closing discussion): I very much appreciate the penetrating remarks of the discussors concerning this fascinating relationship of energy metabolism to the state of the circulation during the stress of sepsis. Their thoughts provoke more questions than can possibly be answered at the present state of our knowledge.

To consider a very major problem posed by Dr. Webb, "Why do animals or patients fall into the high and low output group?" As we and others have pointed out before, the high cardiac output is the normal state of affairs for the seriously septic patient. Further, as in normal life, cardiac output is determined by circulatory demand which in turn is established by the total peripheral vascular resistance. Whether the low resistance encountered in sepsis is caused by the presence of metabolites secondary to metabolic abnormalities, as suggested by the data presented today, or whether it be due to circulating peptides and other vasodilator substances, the fact remains that the mortality is very high among those in whom the cardiovascular system is unable to satisfy

the high circulator demand. Then it is that catecholamine activity and vasoconstriction occur. A vicious cycle is established. Acidosis increases, and now, we see that circulating insulin is reduced in contrast to the high output state. In short, I believe that the low output state is an end stage of circulatory failure into which a patient may slip for a variety of causes: hypovolemia, reduced venous return, elevated pulmonary vascular resistance, heart failure, metabolic failure, or by other mechanisms which may suggest themselves. Unless the vicious cycle is broken by correcting one or more of the abnormalities, death will ensue. We are simply pointing out that hypoinsulinemia is a secondary abnormality due to the "shock state" of low output sepsis which can be corrected.

Dr. Haynes' data confirm these views on the high cardiac output demands in sepsis. He adds another aspect to the problem, and that is the extra caloric expenditure and secondary high circulatory demand in burns. Because of the huge heat loss, about one-half K calorie per ml of evaporated water, the metabolic rate is often grossly elevated. Again death occurs if the cardiovascular system does not satisfy the very high circulatory requirements. However, I would question his use of Levophed to stimulate the flagging circulation. Vasoconstriction is not what is needed, rather B adrenergic stimulation of the myocardium. Therefore, a drug such as isoproteronol, in my view, would be more appropriate to help break the vicious cycle of failing circulation. Perhaps in burns with circulatory insufficiency insulin, glucose, and potassium might be tried when all other corrective measures have failured.

How insulin works on the failing myocardium under these conditions, I don't know. There seems little doubt that it does, since output rose while atrial pressures fell after its administration. Most of the research on the effects of insulin on the heart have been concerned with how it affects the ischemic and hypoxic myocardium. There it can be demonstrated that insulin raises ATP production by increasing both glucose uptake and lactate production. We have no evidence that hypoxia did or did not play a roll in the myocardial performance of the low output patients or pigs. One can only speculate that either the metabolism was rapidly altered to increase energy production, or insulin produced an immediate change on the myocardial membrane to permit greater polarity and other ionotropic effects.

Several important points were raised by Dr. Drucker. What the role of fever may be in establishing oxygen requirement in the leg we don't know, but it must be elevated, since the metabolic rate of the body as a whole rises 7% for each 1° F. elevation of temperature. He makes the point that oxygen supply may be sufficiently limited, that in the presence of an augmented demand, lactate would be produced. Only in the low flow state do we find the leg producing lactate. This occurs despite the absence of a significant reduction of oxygen uptake. There are several explanations. First, my colleague, Dr. Thomas Ryan, has shown that contrasting with the normal fed and fasted situation in the septic state pyruvate dehydrogenase activity (PDH) of skeletal muscle is severely reduced. Since PDH is rate limiting a large potion of pyruvate cannot be converted to acetyl CoA of oxidation in the Krebs cycle. Pyruvate then can only be converted to lactate. Second, in the low output state fat uptake by the limb is great which alters the redox potential and also increases the lactate-pyruvate ratio. Thus, despite an apparently normal glucose uptake induced by catecholamines it is being inefficiently utilized anerobically. Oxygen apparently is used to oxidize fat, yet calculations show a fuel deficit in skeletal muscle in both the high and low output states of sepsis, more pronounced in the latter. It is tempting to speculate that the fuel deficit in the skeletal muscle which appears to be the only tissue not responding normally to insulin during sepsis may fall back on proteolysis and oxidation of branched chain amino acids. Alanine, arginine and other amino acids released by muscle proteolysis might then stimulate the secretion of glucagon, as suggested by Rocha, to induce greater hepatic glucogenesis, and further insulin secretion. This offers a pretty explanation for the well known phenomenon of proteolysis after trauma and sepsis.