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Discussion

Dr. Timothy S. Harrison (Ann Arbor, Michigan): I would like to emphasize two aspects of their data which I consider particularly important.

The first deals with the observation that beta adrenergic receptor blockade eliminates the hypermetabolism of burned patients. This establishes that the hypermetabolic response to the burn injury is, in fact, mediated by the catecholamines, something which has been strongly suggested but not conclusively proved up until this time.

The second point of emphasis is that in burn patients in whom catecholamines are exhausted, there is insufficient precursor, these formerly hypermetabolic patients will, in fact, die. This is a definable source of burn mortality, and one which can be influenced favorably as Goodall and more recently, Dr. Wilmore have shown, by the administration of the appropriate precursor, dopamine or its equivalent.

If I may, I will show one slide briefly, (slide) which is a photomicrograph of the myocardium, and shows here a focal necrosis. This type of lesion can be produced by catecholamines in any species in which it is attempted.

This lesion also, interestingly enough, has been found in pheochromocytoma patients in a recent study from the Mayo Clinic. This particular section represents none of these situations, however, but, in fact, is the myocardium of a hypermetabolic burn patient with prolonged catecholamine hypersecretion. This patient died! These lesions were described, about 20 years ago, by Dr. Carl Moyer before this Association. He felt confident that this was a source of major burn mortality about which very little could be done. We feel the catecholamine hypersecretion was implicated strongly in this patient's death. Therefore, with a hyperreactive adrenergic nervous system one can define another source of burn mortality about which very little has been done therapeutically.

In the past 20 years nothing has altered the mortality from major thermal burns. I think insights such as those provided by the work described this afternoon will enable us to be more effective toward these patients than we have been up until now.

Dr. George H. A. Clowes, Jr. (Boston): Are the catecholamines really the factor that pushes the metabolic rate? Alternatively, are they just one of several that participate? The endocrines that we really have to worry about are insulin, glucagon, the catecholamines and perhaps the tissue injury factor.

We do know that such a thing exists in burns. We can prove that an inappropriate vasodilation takes place in an experimental animal, if one takes a fraction of the plasma from a burn patient or other animal and infuses it into a leg. We can see that vasodilation occurs then.

This is just an example of the kind of huge cardiac output that is required for a burn patient to maintain his equilibrium and to satisfy his metabolic requirements.

(Slide) This is a case studied some time ago, when we were making an attempt to measure catecholamines in the plasma. As you know, that's a very unsatisfactory type of measurement, and we have never emphasized it much, but this one tends to illustrate the point. The patient started with high cardiac output, when his cardiac output decreased, and his catecholamines started to rise in the plasma at that time. Was the elevated plasma catecholamine to enable him to maintain a high cardiac output that would satisfy the high circulatory requirements or was it to maintain a high metabolic rate?

If we look at the matter of insulin, it does rise in the high-output state, but in a shock state, a low cardiac output, it tends to be low, as shown by Hebert and many others, as well as ourselves in the septic shock state.

The glucagon part of the picture, I think, is purely secondary. It's a stimulator of more carbohydrate production in the liver, and plays a major role, but probably does not influence the periphery, where the metabolic control appears to lie, as I pointed out previously.

The difference between those patients who did not respond and the seriously septic patients that had low metabolic rates compared to the others may be related to the action of endotoxin. Recently we have been able to show by animal experiments that the endotoxin model really does not resemble the typical clinical septic state. It poisons the liver, if you like, and glucose production falls off very rapidly. The animal does not deteriorate until the circulating glucose has fallen to low levels. I simply throw this out because the septic patients may have been suffering from some such phenomenon.

It does seem to me that this particular piece of work has proven beyond any question the value of the warm ambient atmosphere, and that the metabolic rates—when you examine the paper, you will see that they are distinctly lower to maintain core temperature at the higher ambient temperatures. Therefore, I think we have to take exception to Dr. Codwell's statement.

The only other point I would make is that whatever the tissue injury factor is, it may play a role in altering the responsiveness of the hypothalamus, where heat regulation takes place. We know that these people tend to be alkylotic—in other words, the respiratory system is overly sensitive to CO_2—and I think that probably herein lies this change of core temperature regulation.

Now, it also may be that these burned people, with their inappropriate vasodilation, are unable to constrict their skin vessels the way a normal individual does, and therefore they require a greater heat production and circulation.

Dr. Douglas W. Wilmore (Closing discussion): As we studied these patients at multiple ambient temperatures—21, 25 and 33 C—we realized that patients decrease their metabolic rate as the room temperature increased.

However, this is a similar response seen in normal man with a decrease in metabolic rate as ambient temperature increased from 21 to 33.

Barr and associates compared 22 with 32 ambient temperature and our data are comparable and show a decrease in metabolic rate when meansured in the 33 C environment. Comparing temperatures of 21 C with 33 C move patients across their critical temperature. Normal man responds at 21 by increasing his metabolic rate, and this is a normal response to cold.

Our studies demonstrate that cool temperature accentuates or accelerates the hypermetabolic response to injury. At no time does the warm ambient temperature return metabolism down to normal levels, and this is comparable with the data from other investigators, showing that the metabolism never returns to normal by caring for these patients in a warm environment.

Burn patients are internally warm, and not cold. Their core temperature is 38–39 C and their skin temperature at 25 ambient is two degrees warmer than normal man. They are not surface cooling in the classic sense, but are internally warm.

Dr. Harrison and Dr. Clowes and Dr. Levenson all pointed out some of the interesting and interrelating factors that have to do with the entire metabolic response in injured man. Thank you very much for your comments. There is no question that the metabolic response is closely related to the circulatory response, and some of the limitations that we see in the ability to generate additional heat may be rate limited by circulation.

Dr. Levenson asked about the change of heat balance and heat transfer and, we have studied these patients and measured radiation conduction, convection and evaporation. By altering room temperature and not changing metabolism or core temperature, we are essentially changing routes of heat transfer from the body.

The temperatures of the burned skin are slightly cooler than the temperatures of the nonburned skin, but still skin temperatures in thermally injured man are a degree or so warmer than what is found in normal man.

How is metabolic rate in traumatized men altered with food intake? Coleman and DuBois fed patients with typhoid fever and noted that the specific dynamic action of food in hypermetabolic infected patients was reduced. This decrease in effect or impact of feeding is similar to the response we observe in burn patients.

The final question posed by Dr. Levenson and Dr. Clowes, is: What is the hypothalamic lesion which directs the metabolic response to injury?

Our patients shiver in a warm ambient temperature. Our patients ask to be warm. If we put them in the environmental chamber and allow them to control the ambient temperature, they make it warm, much warmer than the comfort temperature selected by normal men.

These patients are more comfortable in a warm environment. The metabolic effect that we provide is not that great, but they are more comfortable. They select higher set ambient temperatures, proportionally to the size of their injury, and they are comfortable with an elevated core and skin temperature.

These are men resting in a warm room with a core temperature of 38 or 39 and a skin temperature of 36, and they are comfortable.

If we study the patients in a cooler environment they will shiver at central and mean skin temperatures above set points for normal man, in that their temperature center has been reset upward.

What causes the adjustment in central temperature set point? Dr. Clowes commented about a tissue injury factor; and, indeed, one of the tissue injury factors being discussed more and more is the prostaglandins. Prostaglandins counteract many of the effects of catecholamines. Our data demonstrate that burn patients have an increased perfusion out to the surface; these patients cannot vasocontrict and insulate like normal men. When they are placed in the cool environment, they cannot prevent their heat from coming to the surface.

Prostoglandins or other hormones of toxins may cause this vasodilatation in the wound and exert additional central effects, such as an effect is on the temperature center.

We have topically anesthetized burn wounds; we have placed spinal anesthesia blocks in people with bilateral leg burns; we have given large doses of aspirin—and none of these techniques or maneuvers reduce the hypermetabolic response to injury in our short term studies. This is truly a reset in the hypothalamus.

Finally, we don't know whether the afferent input from the wound is nervous or whether it's hormonal. We hope to determine this and alter the input or adjust the set point in injured man. This approach will allow great therapeutic potential not only for injured man, but also for countless other metabolic problems.