

# Energy Metabolism in Sepsis:

## Treatment Based on Different Patterns in Shock and High Output Stage

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Studies in seriously septic patients and animals demonstrate that the metabolic pattern of energy production differs not only from that of normal starvation but that significant differences exist between that associated with the usual high cardiac output response and the situation when hypotension and low output are present. In the high output state blood insulin is three times that found in starvation. Blood sugar is normal or high and lipolysis is suppressed. Experimental measurements of limb substrate utilization indicate that oxygen and glucose uptake are the same as in fasting while net fat utilization is almost zero. It is suggested by negative nitrogen balance in patients that the apparent peripheral fuel deficit is satisfied by proteolysis and oxidation of amino acids. When the cardiac output is below the normal basal value the blood insulin is as low or lower than in starvation, probably related to intense catecholamine activity. Peripheral oxygen uptake is not significantly reduced and net fat utilization is normal. Although peripheral glucose uptake is normal, the major portion of it appears to be converted to lactate. The fuel deficit again appears to be satisfied by amino acid oxidation which is reflected by the severe negative nitrogen balance in hypotensive septic patients.

**S**URVIVAL AND RECOVERY from extensive infection is characteristically associated with cardiac indices in excess of 4 L/M<sup>2</sup>/min.<sup>13,35,48</sup> The high cardiac output is in response to a marked reduction to peripheral vascular resistance which appears inappropriate at times.<sup>21,52</sup> The mortality of septic patients who are unable to meet this circulatory challenge and who remain more than transi-

ently hypotensive with cardiac indices below the normal resting output of 2.8 L/M<sup>2</sup>/min has been greater than 70% in various reported series.<sup>13,35,59</sup> Well known metabolic abnormalities also accompany the septic state. Proteolysis and negative nitrogen balance far exceed the values observed in simple starvation.<sup>9,17,22</sup> Mortality from invasive sepsis is high when loss of lean body mass exceeds 30%.<sup>54</sup> Proteolysis during infection appears to be in part related to the extent to which lipolysis is suppressed by high levels of insulin in the blood.<sup>8,43</sup> Paradoxically, a diabetic type of glucose tolerance curve and a resistance to infused insulin are frequently observed in infected and traumatized patients.<sup>30</sup> Lactacidemia is known to occur in the low flow circulatory state, but is also found in certain patients with high cardiac indices.<sup>48</sup> McLean *et al.*<sup>35</sup> suggested that the prognosis of the seriously infected patient is closely related to the blood lactate concentration.

In a series of experiments designed to clarify the relationship of the abnormalities of peripheral energy production and circulation in sepsis O'Donnell *et al.*<sup>40</sup> observed marked metabolic differences between those with high and those with low outputs. Of particular interest was the fact that the blood insulin levels were high in the former and very low in the latter. It is the purpose of this paper to review these data and to demonstrate that similar patterns of metabolism exist in septic man which indicate different forms of metabolic management in the patient who is apparently doing well with a high cardiac output in contrast to the hypotensive patient with

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a relatively low output. When other forms of therapy including fluid replacement, inotropic agents and corticoids have failed in this form of septic shock, restoration of the hemodynamic state has been effected by the administration of insulin in high doses.

### Methods

Cardiac output was measured by indocyanine dye dilution. In the animal experiments hind limb blood flow was determined by the indicator dilution method of Andres *et al.*<sup>1,2</sup> Comparative measurements in four pigs were made to measure the clearance of <sup>133</sup>Xe after injection into leg muscles.

After deproteinization with perchloric acid, the blood concentrations of glucose, lactate, pyruvate, and glycerol were determined by standard enzymatic methods.<sup>4</sup> In the animals these measurements were made in samples of blood obtained simultaneously from both the femoral artery and femoral vein. Free fatty acid (FFA) was determined by the method of Dole and Meinertz.<sup>19</sup> Blood pH and gases were determined by the Instrument Laboratory pH/gas analyzer,\* and blood oxygen content was measured by the Lex-o-Con Instrument.† Radioimmunoassay according to the method of Soeldner<sup>53</sup> was used to measure blood insulin concentration. A porcine insulin standard was employed. In the clinical study, the daily urinary nitrogen excretion was calculated from the volume of a 24 hour urine collection and the nitrogen concentration measured by the micro-Kjeldahl technique.

### Animal Experiments

#### Procedure

Pigs weighing between 35–45 kg were starved for four days being allowed only water. On the fourth day, under halothane inhalation anesthesia, silastic catheters were placed in the carotid artery and in the right atrium through the external jugular vein for systemic hemodynamic measurements. A second set of catheters was placed in the femoral artery and vein by a technique previously described in detail,<sup>40</sup> to measure limb blood flow and obtain blood samples for calculation of the metabolic exchange in the hind leg.

Because of previous observations in this preparation which had disclosed significant alterations of limb blood flow and metabolism during anesthesia, all the animals were allowed to recover fully during the course of several hours prior to performing measurements in the basal state. The pigs are usually docile and remain quietly on the operating table during blood sampling and flow

measurements. In this starved basal state the cardiac output, arterial blood pressure, and central venous pressure were recorded at the same time that blood flow in the hind limb was measured. Blood samples were obtained from the femoral artery and vein. Flow measurements were made in duplicate, and in triplicate if a discrepancy was observed.

Upon completion of these basal measurements the pigs were reanesthetized for laparotomy. Through a mid-line incision a ligature was placed about the cecum at a point approximately 2 cm below the ileocecal valve, which does not produce intestinal obstruction. Approximately 2 cc of pig feces were introduced into the peritoneum near the ligated cecum.

In the postoperative period pigs were given an infusion of 1 of Ringer lactate solution on the day of operation. Thereafter, only water was allowed. On the third postoperative day (seventh day of starvation under a brief halothane anesthesia, catheters were inserted into the femoral vessels of the opposite hind leg to avoid abnormalities caused by clotting or injury to the vessels of the leg which previously had been catheterized. Following full restoration of consciousness the same measurements made in the basal starved state were repeated. At the conclusion of these experiments all of the animals were sacrificed for post-mortem examination.

### Results

The average cardiac output in the starved basal state of the sixteen pigs studied was  $3.9 \pm 0.3$  L/M. Three days after the induction of peritonitis, nine of the animals had cardiac outputs in excess of their basal values with an average value of  $5.0 \pm 0.6$  L/M. This group was classified as "high flow." Seven in which the cardiac output was below their basal values had an average of  $2.0 \pm 0.3$  L/M, and were designated as "low flow." Hind limb flow rose from  $2.4 \pm 0.2$  to  $3.1 \pm 0.1$  in high flow and fell to  $1.9 \pm 0.2$  ml/kg body wt/min. Significant differences ( $p < .005$ ) exist between the three groups. In four pigs these changes of flow were reflected very closely by the rate of disappearance of <sup>135</sup>Xe from muscle, indicating that muscle capillary perfusion is directly proportional to limb flow.

The results of these studies are summarized in Table 1. Attention is drawn to the fact that in the septic state the arterial blood insulin concentration of  $41 \pm 9$  uU/ml in the high flow group is significantly greater ( $p < 0.001$ ) than that of the low flow group which was  $14 \pm 5$  uU/ml. Despite this fact, the glucose uptake in high flow was lower but not significantly different from either the basal or the low flow animals. Although the hind limb flow of the low flow group was significantly lower than that of either the "basal" or "high flow" groups, there was no statistically significant difference of hind

\* Instrumentation Laboratories, Lexington, Mass.

† Lexington Industries Corp., Lexington, Mass.

TABLE 1. *Peritonitis (Cecal Ligation)*  
(Values  $\pm$  SEM)

	Basal n = 16	High Flow n = 9	Low Flow n = 7
Temperature ( $^{\circ}$ F)	101 <sup>4</sup> $\pm$ 0.2	102 <sup>8</sup> $\pm$ 0.5	100 <sup>8</sup> $\pm$ 1.2
Cardiac Output (L/M)	3.9 $\pm$ 0.3	5.0 $\pm$ 0.6	2.0 $\pm$ 0.3
Hind Limb Flow (ml/kg body wt/min)	2.4 $\pm$ 0.2	3.1 $\pm$ 0.1	1.9 $\pm$ 0.2
Mean Arterial Pressure (mm Hg)	115 $\pm$ 3.7	103 $\pm$ 4.1	103 $\pm$ 10.8
Hind Limb Resistance (pres/flow)	49 $\pm$ 6	33 $\pm$ 2	53 $\pm$ 4
Arterial Insulin (uU/ml)	10 $\pm$ 4	41 $\pm$ 9	14 $\pm$ 5
Arterial Glucose (uM/ml)	5.6 $\pm$ 0.5	4.0 $\pm$ 0.2	4.6 $\pm$ 0.6
Glucose Uptake* (uM/kg/min)	1.6 $\pm$ 0.3	1.3 $\pm$ 0.3	1.5 $\pm$ 0.4
Arterial Lactate (uM/ml)	1.0 $\pm$ 0.1	0.9 $\pm$ 0.1	1.7 $\pm$ 0.3
Lactate Production* (uM/kg/min)	+1.2 $\pm$ 0.2	+1.2 $\pm$ 0.3	+2.5 $\pm$ 0.6
FFA Arterial (uEq/ml)	.715 $\pm$ 0.8	.398 $\pm$ .07	.462 $\pm$ .03
FFA Uptake or Release* (uMol/kg body wt/min)	-.101 $\pm$ .03	+.067 $\pm$ .04	+.126 $\pm$ .04
Glycerol Release* (uMol/kg body wt/min)	+.042 $\pm$ .011	+.009 $\pm$ .001	+.116 $\pm$ .01
O <sub>2</sub> Uptake* (ml/kg body wt/min)	.15 $\pm$ .03	.14 $\pm$ .03	.12 $\pm$ .01
Arterial pO <sub>2</sub> (mm Hg)	72.36 $\pm$ 2.6	69.5 $\pm$ 7.18	75.2 $\pm$ 7.2

\* Net uptake (-) or release (+) by hind limb.

limb oxygen uptake. Nevertheless, lactic acidemia and lactate production by the hind limb of the low flow group was nearly double ( $p < 0.001$ ) that of either the basal fasting or high flow groups.

Whereas free fatty acids were taken up in starvation at a rate of .042 uM/kg body wt/min, FFA was released in both septic groups. The extent of lipolysis in the limb is indicated by the glycerol release. Approximately 3 M of fatty acid are mobilized from the fat deposits for each mole of glycerol. On this basis the net fatty acid utilization by the limb in starvation was 0.22 uM/kg body wt/min. The high flow group uptake was zero, and the low flow group took up 0.22 uM/kg body wt/min, the same as in the fasted basal animals.

At autopsy large purulent peri-cecal abscesses were present. Culture in every instance revealed mixed enteric flora with coliform organisms predominating.

## Experimental Response to Glucose, Potassium, and Insulin in Peritonitis

### Procedure

To examine the effects of glucose, potassium and insulin on the high output and low output responses to peritonitis, a series of 12 experiments was carried out in exactly the same fashion as described in the previous section. After four days of starvation, silastic catheters were inserted into the jugular vein and carotid artery as well as the femoral artery and vein. When fully conscious, basal measurements were made followed by the induction of peritonitis by cecal-ligation. After three further days of starvation, cannulation of the opposite femoral artery and vein was carried out with a repetition, when fully conscious, of the standard hemodynamic and metabolic measurements. Based upon their responses to peritonitis the pigs were assigned to the high output or low output groups. Thereafter a 50% glucose solution containing glucose 1 g/kg body wt, insulin 1.5 units/kg body wt, and potassium 10 mEq. was infused during a ten minute period into the central venous catheter. Fifteen minutes, thereafter, the circulatory and metabolic measurements were repeated. Two hours later the measurements were again carried out prior to sacrifice of the animals.

### Results

In the high flow/high output group of animals, the cardiac output increased significantly from a basal value

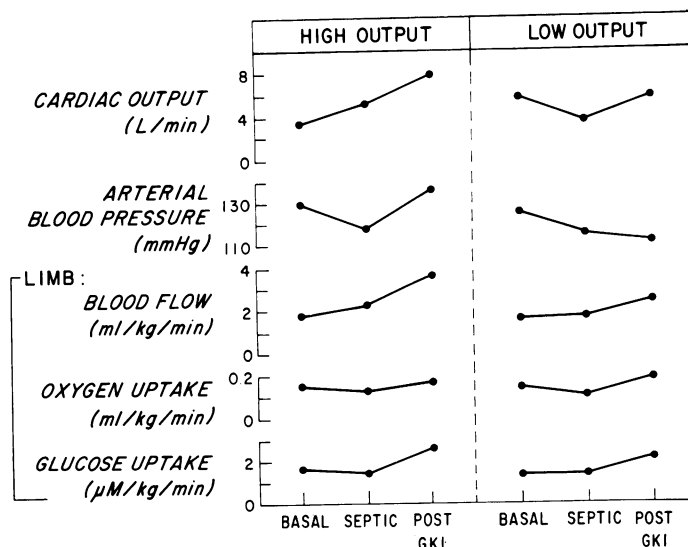


FIG. 1. Hemodynamic and metabolic responses of septic pigs in the high output and low output states to bolus infusion of glucose potassium and insulin. Note the increase of cardiac output and reduction of peripheral vascular resistance in the animals with low cardiac outputs.

TABLE 2. *Peritonitis—Pig: Response to Glucose Potassium and Insulin*  
(Mean Values  $\pm$  SEM)

	High Output n = 5			Low Output n = 7		
	Basal	Septic	Post GKI	Basal	Septic	Post GKI
Cardiac Output ( /min)	3.59 $\pm$ .35	5.20 $\pm$ .95	8.00 $\pm$ 3.3	5.66 $\pm$ .34	3.46 $\pm$ .39	5.56 $\pm$ .79
Art. Pressure (mm Hg)	130 $\pm$ 3	118 $\pm$ 14	136 $\pm$ 19	125 $\pm$ 5	115 $\pm$ 8	110 $\pm$ 18
Pulse Rate (beats/min)	132 $\pm$ 13	160 $\pm$ 16	176 $\pm$ 12	129 $\pm$ 13	145 $\pm$ 13	156 $\pm$ 16
Centr. Ven Pres. (cm H <sub>2</sub> O)	1.3 $\pm$ 2.3	-1.3 $\pm$ 2.6	-2.6 $\pm$ 2.3	1.9 $\pm$ 1.8	-.14 $\pm$ 1.7	1.3 $\pm$ 3.2
Limb Blood Flow (ml/kg body wt/min)	1.8 $\pm$ .3	2.3 $\pm$ .5	3.7 $\pm$ .7	1.6 $\pm$ .4	1.7 $\pm$ .3	2.3 $\pm$ .5
Limb O <sub>2</sub> Consumption (ml/kg body wt/min)	.15 $\pm$ .03	.13 $\pm$ .02	.17 $\pm$ .04	.14 $\pm$ .04	.10 $\pm$ .03	.18 $\pm$ .05
Limb Glucose Uptake ( $\mu$ M/kg body wt/min)	1.6 $\pm$ .03	1.4 $\pm$ .3	2.6 $\pm$ .9	1.3 $\pm$ .5	1.3 $\pm$ .3	2.1 $\pm$ .3

of  $3.95 \pm .35$  to  $5.20 \pm .95$  L/min in the septic state. Limb flow rose from  $1.8 \pm 2.3$  to  $2.3 \pm .05$  ml/kg body wt/min. By contrast the low output group exhibited a reduction of cardiac output from  $5.66 \pm .34$  to  $3.46 \pm .39$  L/min but no change in limb blood flow. Following the administration of glucose, potassium, and insulin the cardiac output of the high flow group rose to  $8.00 \pm 3.3$  L/min while that of the low output group rose from  $3.46 \pm .38$  to  $5.56 \pm .79$ . In both groups there was significant increase of limb oxygen consumption being most marked in the low output group which rose from  $.10 \pm .03$  to  $.18 \pm .05$  ml/kg body wt/min. Limb glucose uptake was also significantly increased in both groups. The data obtained from these experiments are illustrated in Fig. 1 and summarized in Table 2.

### Clinical Observations on the Metabolic and Hemodynamic Response to Infection

#### Procedure

Eighteen septic patients with peritonitis, retroperitoneal abscesses, or extensive gangrene admitted to the Surgical Service of the Boston City Hospital were selected for study. All had wound or abscess cultures containing coliform organisms. No patients known to be diabetic were included in this study. Treatment was in no way altered from that being administered by the attending surgeons except that glucose administration was limited to 100 g/day during the 24 hours in which urine was collected for nitrogen excretion. No oral alimentation or glucose infusion took place for twelve hours prior to blood samples which were drawn to measure: insulin, glucose, free fatty acid, lactate, pH and gases. The patients were divided into "high flow" and "low flow" groups depending upon whether they were normotensive or hypotensive. Patients with mean arterial pressures less than 80 mm Hg were included in the low flow group. If more than one observation was made for any patient, they were accomplished within a period of no more than six hours.

For comparative purposes measurements after an

overnight fast were made in three normal volunteers and in five patients after full recovery.

#### Results

Twenty observations were made in ten patients who were classified in the high flow group with average mean blood pressure of  $110 \pm 12$  mm Hg. Twelve observations were made in eight patients in the low flow group with mean arterial blood pressures of  $70.2 \pm 4$  mm Hg. The data obtained from these measurements are summarized in Table 3. The average cardiac index of the high flow group was 4.6 which is significantly higher than the cardiac indices of the normal or low flow patients which were respectively 2.8 and 2.4 L/min/m<sup>2</sup>. Attention is drawn to the fact that the body temperature of those patients in the low flow state were significantly lower (average 100.6F) when compared with those of the

TABLE 3. *Metabolic Substrates and Urinary Nitrogen Excretion in Fasting and Septic Man*  
(Values  $\pm$  SEM)

	Normal 12 Hour Fasting 8 Patients	Septic Semi-Starvation (Glucose 100g/24°)	
		High Flow n = 20 10 Patients	Low Flow n = 12 8 Patients
Cardiac Index (L/min/m <sup>2</sup> )	2.8 $\pm$ 0.4	4.6 $\pm$ 0.8	2.4 $\pm$ 0.3
Mean Arterial Pressure (mm Hg)	93 $\pm$ 14	110 $\pm$ 12	70.2 $\pm$ 4
Rectal Temperature (°F)	99.6 $\pm$ 0.6	102 <sup>a</sup> $\pm$ 0.8	100 <sup>b</sup> $\pm$ 0.6
Blood Insulin (uU/ml)	18 $\pm$ 2	42 $\pm$ 6.4	12 $\pm$ 4
Blood Glucose (uMol/ml)	3.6 $\pm$ 0.8	7.2 $\pm$ 0.5	7.68 $\pm$ 2.3
Blood FFA (uMol/ml)	1.3 $\pm$ .15	0.41 $\pm$ .06	1.176 $\pm$ 0.9
Blood Lactate (uMol/ml)	0.6 $\pm$ 0.1	1.15 $\pm$ .11	2.79 $\pm$ 0.3
Arterial O <sub>2</sub> Tension Breathing Air (mm Hg)	90 $\pm$ 3	65 $\pm$ 6	55 $\pm$ 8
Urinary N (gms/24 hrs)	—	7.4 $\pm$ 0.9	16 $\pm$ 2

n = number of observations

TABLE 4. Clinical Treatment of Low Output Septic State with Glucose, Potassium, and Insulin

Patient	Age	Diagnosis	Bacterial Culture	Condition		Response		Result	Cause
				MAP* (mm Hg)	CO† (L/M)	MAP* (mm Hg)	CO† (L/M)		
1.	67 M	Pelvic peritonitis and phlegmon after endarterectomy	Mixed <i>E. coli</i> predominating	62	2.3	78	9.6	Died 10 d. later	Respiratory failure
2.	71 F	Upper G.I. bleed., Abscess Subphrenic, Pneumonia	<i>E. coli</i> + <i>Proteus vulgaris</i>	58	2.4	73	9.2	Died 3 d. later	Coronary infarct myocardial failure
3.	53 M	Cholangitis, Pancreatitis	Mixed coliform	50	3.5	72	10.2	Died 4 d. later	Respiratory and renal failure
4.	62 M	Peritonitis—perforated cecum, diverticulitis	Mixed enteric <i>E. coli</i> predominating	50	4.1	70	7.4	Recovered	
5.	27 M	Trauma—Hepatectomy Bile peritonitis	<i>E. coli</i>	76	3.1	80	6.7	Recovered	
6.	32 M	Trauma—Hepatectomy Subphrenic abscess—peritonitis	<i>E. coli</i> + <i>A. aerogenes</i>	51	—	76	—	Recovered	
7.	23 M	Trauma—liver laceration Bile peritonitis	<i>E. coli</i>	64	3.5	88	8.7	Recovered	
8.	52 M	Gunshot wound colon and pancreas. Pancreaticomy peritonitis	Mixed coliform	62	2.9	90	—	Died 14 d. later	Respiratory failure
9.	48 M	Duodenal rupture post gastrectomy—subhepatic abscess. Myocardial infarct	<i>E. coli</i> + <i>S. fecalis</i>	58	—	78	—	Recovered	
10.	52 M	Anal carcinoma. Rectal resection. Abdominal abscess	Mixed enteric	48	2.9	71	8.6	Recovered	

\* Mean arterial pressure

† Cardiac output

high flow group which averaged 102.4F. The blood glucose in both groups of patients was approximately twice that of the fasting normal people. However, the average blood insulin in the high flow patients was  $42 \pm 6$  uU/ml compared to  $18 \pm 2$  uU/ml in the normal and only  $12 \pm 4$  pU/ml in the low flow patients. Although lactacidemia was present to some extent in both septic groups, the blood lactate concentration was significantly higher at 2.8 uM/ml in the low flow patients ( $p < .001$ ). The urinary nitrogen excretion of 7.4 g/day in the high flow patients was slightly more than the accepted, normal, fasting value. However, nitrogen excretion in the low flow patients was significantly ( $p < .001$ ) elevated being on the average  $16 \pm 2$  g/24 hours.

### Clinical Response to Glucose, Potassium and Insulin (GKI)

#### Procedure

Ten patients in "septic shock" who were suffering from a variety of serious intraabdominal and pelvic infections with protracted arterial hypotension which did not apparently respond to intravenous fluid, ionotropic agents, or corticoid administration, were treated with GKI. The condition of these patients and their major hemodynamic responses are given in Table 4. Hemodynamic measurements were made and arterial blood samples were drawn for subsequent determination of gasses, insulin,

and blood concentrations of glucose, FFA, and lactate. To sufficient 50% glucose solution to contain 1 g of glucose/kg body wt., were added 1.5 U crystalline insulin/kg body wt., 10 mEq of potassium chloride and 1 g of human albumin. The mixture was infused in a 10-minute period through a central venous catheter. The arterial blood pressure and central venous pressure were followed during the infusion. Within 10 minutes after completion of the GKI infusion, the hemodynamic measurements were repeated and another set of blood samples was obtained. The patient's course was then followed with occasional repetition of the hemodynamic measurements if indicated. In three patients, numbers 2, 4, and 9, the GKI therapy was repeated one or more times in the 24 hours after the initial dose.

#### Results

As shown in Table 4 only one patient died in a shock state several days later following a coronary infarction. Three others died of respiratory or renal complications.

In each instance, the arterial blood pressure response was dramatic and had risen before the end of the GKI infusion. The response of a typical patient is shown in Fig. 2. The cardiac output in every instance had risen within 15 minutes. As shown by the data in Table 5 and Fig. 3, the average cardiac output increased from  $3.0 \pm 0.3$  to  $8.6 \pm 0.5$  L/M. During the infusion there was no significant change of CVP in any patient, but at the

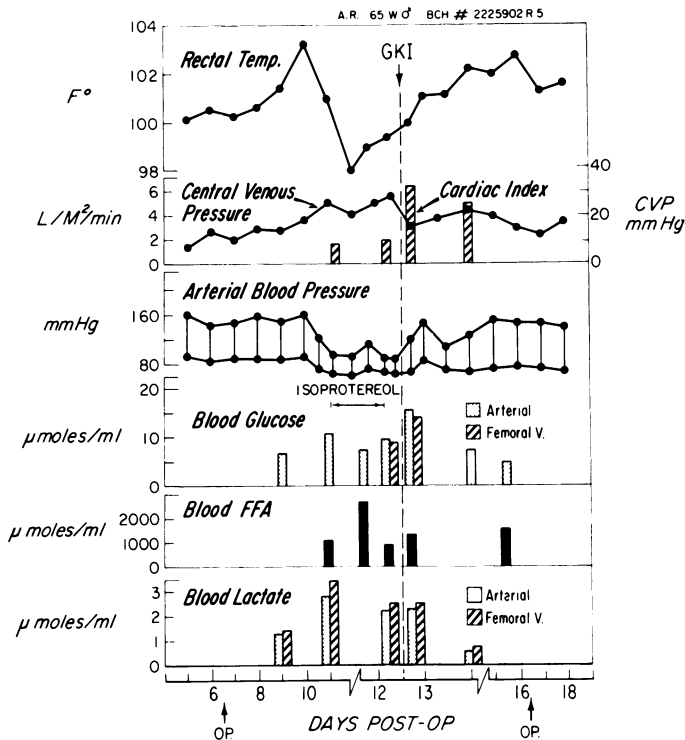


FIG. 2. The clinical course of a severely septic patient who exhibits the metabolic responses associated with both high and low cardiac outputs. Also illustrated are the circulatory and metabolic effects of glucose, potassium, and insulin in the low output shock state. This man who underwent bilateral iliac endarterectomy required reexploration on the sixth postoperative day because of hemorrhage from an arterial suture line. He became infected with coliform organisms present by blood culture. Becoming hypotensive on the tenth day, he did not respond to isoproterenol. On the twelfth day, GKI was administered with a prompt rise of cardiac output and body temperature. A pelvic abscess was drained on the sixteenth day. Because of progressive bronchopneumonia he died of respiratory failure on the twenty-second postoperative day.

time of the second hemodynamic measurement the average had fallen from 14 to 9 cm H<sub>2</sub>O. In five patients in whom pulmonary wedge pressure measurements were available through a Swan-Ganz catheter, there was a decrease from 16 to 12 mm Hg.

The rectal temperature rose in five of the seven people in whom it was recorded before and after GKI. Although the blood glucose was high ( $8.7 \pm 1.3$  uM/ml) prior to the infusion, in four patients the average insulin concentration was only 12 uU/ml. Subsequently after GKI blood glucose rose to  $16.3 \pm 3.1$  uM/ml while insulin increased to  $230 \pm 56$  uU/ml. Simultaneously the blood FFA fell from 971 to 432, and blood lactate from 2.6 to 1.9 mM/ml. The latter decrease is not significant. These responses are shown in Fig. 4.

Although the average value for arterial oxygen tension rose from 89 to 109 mm Hg while breathing a 40% O<sub>2</sub> respiratory mixture, the reduction of pulmonary shunt was probably more apparent than real because of the increase of mixed venous pO<sub>2</sub> which in four patients,

on the average, rose from 28 to 36 mm Hg. Arterial pH and pCO<sub>2</sub> both increased slightly.

## Discussion

The circulatory response to severe infection anywhere in the body is characterized by low peripheral vascular resistance accompanied by high cardiac output. In potentially lethal situations such as general peritonitis, the average cardiac output in patients, who are apparently doing well from a metabolic standpoint, averages 60% or more above the normal basal value.<sup>12,35,51</sup> On the other hand, oxygen consumption or metabolic rate seldom are elevated by more than 30 to 40%.<sup>32,48</sup> Other metabolic abnormalities including proteolysis of moderate to severe degree<sup>17,34</sup> differentiate this hyperdynamic circulatory state of major sepsis from the economic metabolic pattern of starvation.<sup>8,42</sup> Normally in the absence of cardiovascular failure the blood flow and cardiac output, through reflex arcs involving the autonomic nerves and the endocrines, are regulated by the sum total of the vascular resistances in the organs supplied by the systemic circulation according to their metabolic requirements.<sup>26</sup> If for any reason the cardiovascular system is unable to satisfy the elevated circulatory demand imposed upon it by major sepsis an intense sympatho-adrenal discharge is manifested by marked tachycardia and vasoconstriction.<sup>12</sup> The result frequently is progressive deterioration of energy production accompanied by lactic acidemia and metabolic acidosis leading to death.<sup>21,48</sup> That the metabolic utilization of fuel substrates in the peripheral tissues varies according to changing peripheral

TABLE 5. Clinical Response to Glucose, Potassium, and Insulin in Low Output Septic State  
Values  $\pm$  SEM

	Pre GKI	Post GKI
<i>Hemodynamic</i>		
Cardiac Output (L/min)	$3.0 \pm 0.3(8)$	$8.6 \pm 0.5(7)$
Pulse (beats/min)	$124 \pm 4 (10)$	$115 \pm 4 (10)$
Mean Arterial Pres. (mm Hg)	$59 \pm 7 (10)$	$76 \pm 4 (10)$
Centr. Venous Pres. (cm H <sub>2</sub> O)	$14 \pm 3 (8)$	$9 \pm 2 (8)$
Pulm. Wedge Pres. (mm Hg)	$16 \pm 3 (5)$	$12 \pm 2 (5)$
<i>Metabolic</i>		
Rectal Temperature (°F)	$100.6 \pm 0.6(7)$	$101.2 \pm 0.5(7)$
Blood Glucose (uM/ml)	$10.2 \pm 2.3(8)$	$16.3 \pm 3.1(6)$
Lactate (uM/ml)	$2.6 \pm 0.8(6)$	$1.9 \pm 1.1(6)$
FFA (uM/ml)	$971 \pm 124(7)$	$432 \pm 78 (6)$
Blood Insulin	$12 \pm 3 (4)$	$230 \pm 56 (4)$
<i>Blood Gases</i>		
Resp. O <sub>2</sub> Gas Mixture (%)	$40 \pm (7)$	$40 \pm (7)$
Arterial pO <sub>2</sub> (mm Hg)	$89 \pm 12 (8)$	$109 \pm (8)$
Arterial pCO <sub>2</sub> (mm Hg)	$35 \pm 3 (7)$	$38 \pm 4 (7)$
Hydrogen Ion (pH units)	$7.41 \pm .03(10)$	$7.44 \pm .04(9)$
Urine Output (ml/br)	$18 \pm 6 (6)$	$61 \pm 14 (6)$

Number of observations in parentheses

**CLINICAL SEPSIS: LOW OUTPUT STATE  
EFFECTS OF GLUCOSE, POTASSIUM AND INSULIN  
HEMODYNAMIC RESPONSES**

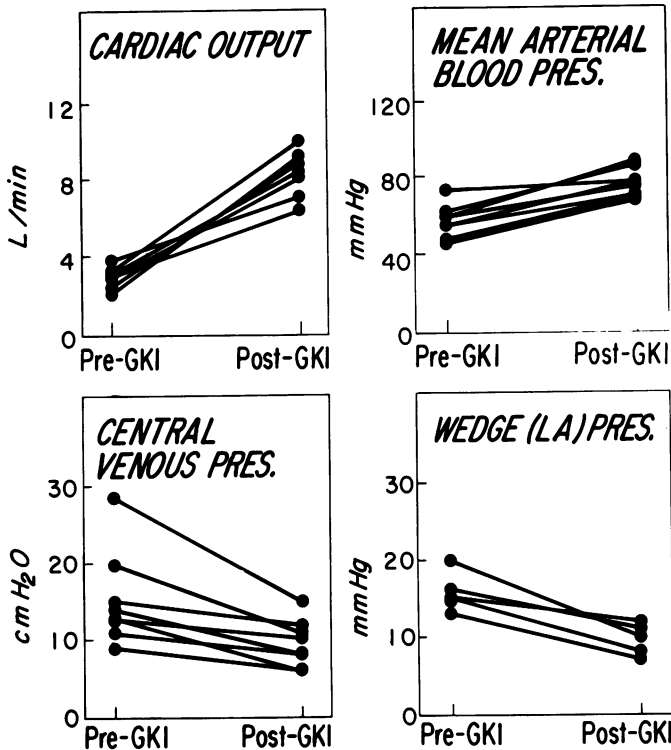


FIG. 3. The early hemodynamic responses of hypotensive septic patients to treatment with glucose, potassium, and insulin.

vascular resistances and blood flows under these normal fasting and septic conditions is clearly shown by these experimental and clinical observations. At the same time the demonstrated metabolic alterations engendered by an insufficient low cardiac output response may further impair the function of the cardiovascular system, thus, establishing a vicious cycle of progressive circulatory failure and shock.

Since the demonstration of a continued demand for a high cardiac output in sepsis<sup>12,21</sup> in which there is lacking the proportionate increase of oxygen consumption found in health,<sup>32,34</sup> speculation has existed regarding the cause for the apparently inappropriate peripheral vasodilation. Based upon clinical and experimental observations a variety of explanations have been put forward. Reduction of the arterial-mixed venous oxygen difference in the face of high cardiac outputs prompted Siegal *et al.*<sup>52</sup> to consider the possibility of open anatomical arterio-venous shunts. The clearance rate of intramuscularly injected Xenon correlates with changes in measured limb flow rates and cardiac outputs during sepsis,<sup>60</sup> making the presence of anatomical shunts unlikely. Thus, the high

or low blood flow in the limbs of the septic pigs must reflect the capillary perfusion rate.

Circulating vasodilator substances activated by endotoxin or tissue injury at the site of infection have been shown to exist.<sup>28,33</sup> Among those observed to be present in the blood during sepsis are the kinins,<sup>15</sup> thrombin,<sup>41</sup> fibrinopeptides,<sup>3</sup> and substances released from platelets which include serotonin, prostaglandins, adenosine triphosphate, and histamine in some species.<sup>45</sup> However, clear cut evidence is lacking of continuing activity of these agents throughout the prolonged period of vascular resistance which remains until the septic process is brought under control.

Alternatively, metabolic abnormalities of muscle or other tissues have been proposed as causes for the peripheral vasodilation. Hypoxemia is common in septic patients,<sup>11</sup> yet hyperbaric oxygen has proven of no significant benefit.<sup>35</sup> Reduction of 2, 3 Diphospho-glycerate in erythrocytes of patients in septic shock was reported by Miller *et al.*<sup>38</sup> The shift of the oxyhemoglobin dissociation curve to the left appeared as a possible mode of producing tissue hypoxia which would result in lactate production and vasodilation. Yet the limb oxygen con-

**CLINICAL SEPSIS: LOW OUTPUT STATE  
EFFECTS OF GLUCOSE, POTASSIUM AND INSULIN  
METABOLIC RESPONSES**

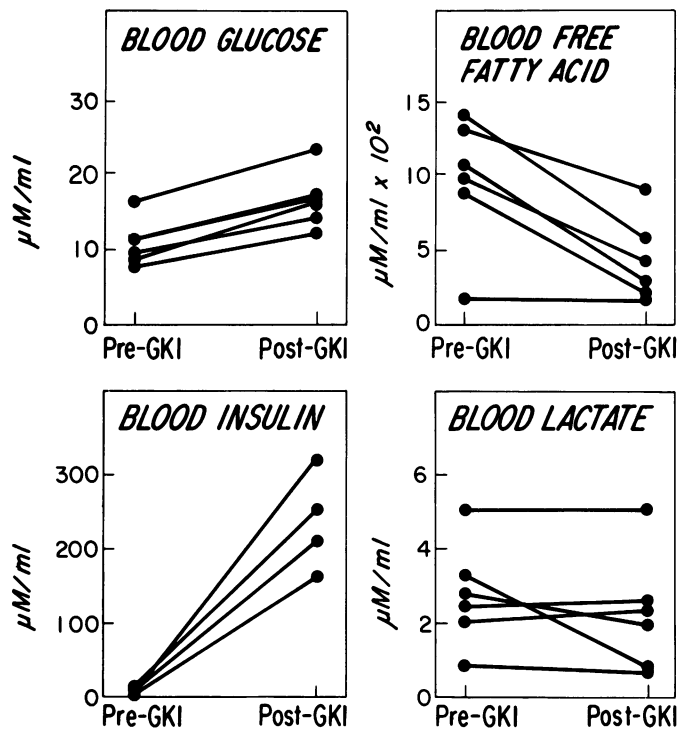


FIG. 4. The early metabolic responses of hypotensive septic patients to treatment with glucose, potassium and insulin as reflected by blood concentrations of insulin, glucose, free fatty acids and lactate.

sumption was not significantly reduced below that in the basal starved state in either the high output or low output septic pigs. The oxyhemoglobin dissociation of these animals, when arterial and venous  $pO_2$  values were compared with blood oxygen contents appeared little changed from those in the basal state. Being under control of several hormones which vary as the degree of circulatory stress, it is not surprising to find the significant differences in the metabolism of energy production exhibited by the patients and animals in this study. Those endocrine secretions of greatest metabolic importance under these conditions probably are: insulin,<sup>5,8</sup> glucagon,<sup>46,61</sup> the catecholamines,<sup>44</sup> and possibly the glucocorticoids. Insulin, the only one actually measured in the blood during these observations, was strikingly different in the high flow and low flow septic states. At the same time evidence of "insulin resistance"<sup>62</sup> further complicates the control of metabolism under these septic conditions. Cahill<sup>9</sup> has defined insulin as "the overall fuel control in mammals." The blood insulin concentration being high in the fed state, it suppresses glycogenolysis and lipolysis and promotes glycogenesis, deposit of fat in adipose tissue and the synthesis of protein. In the starved state, the reverse is the case as observed in starved animals (Table 1) and in fasted humans (Table 3). Blood insulin is low while free fatty acids (FFA) are high. Glucose for supply to the nervous system and certain other tissues is dependent upon proteolysis in muscles, etc. and diamination of alanine in the liver for gluconeogenesis which appears to be in part a function of glucagon.<sup>36,62</sup>

Paradoxically, in the starved septic pigs with high cardiac outputs in which all available glycogen had been exhausted, the average blood insulin concentration was 41 uU/ml despite the presence of blood glucose in the normal range. The situation was similar in the high output septic patients, who had received no glucose or oral alimentation for twelve hours before blood samples were drawn. Their average blood insulin value was 42 uU/ml. Despite the four-fold increase of arterial insulin in this group of septic starved animals, the glucose uptake by the extremities remained unchanged. This is evidence of an "insulin resistance" in the periphery, for normally glucose uptake is proportional to concentration of blood glucose and insulin. Possibly herein lies part of the explanation for the pseudodiabetes described by Howard<sup>30</sup> in Korean battle casualties. However, in this group free fatty acids (FFA) in the blood were low both in patients and pigs. In the animals, lipolysis, as indicated by glycerol release, was reduced. When the balance of glycerol and FFA release from the limb are considered, the net utilization of fat by the extremity is nearly zero in this septic starved group with high flows. This situation differs significantly from the basal state and reflects the normal antilipolytic action of insulin.

Thus, it appears that whereas muscle is resistant to insulin in sepsis, adipose tissue continues to respond normally. This concept is born out by studies conducted by Ryan *et al.*<sup>49</sup> in which it was observed that the insulin sensitive pyruvate dehydrogenase is low in muscle during infection but rises in fat as it normally does when stimulated by insulin.

Since glucose and oxygen uptake are unchanged and fat is not available for peripheral oxidation by muscles, a net deficit in energy fuel must exist. That this deficit is made up by oxidation of branched chain ketogenic amino acids derived from intracellular protein is suggested by the moderate elevation of urinary nitrogen excretion in the high flow septic patients and by a similar finding of 13.1 g/24 hours in the series studied by Duke *et al.*<sup>22</sup> This view is supported by Fleck and Munro's findings that the nitrogen excretion during a negative balance arises principally from muscle protein catabolism.<sup>23</sup>

The situation in regard to the blood insulin concentration as well as the availability and uptake of fuel substrates in the extremity is very different in the low flow septic animals and patients who are unable to meet the high circulatory requirements. Here the blood insulin remains in the low range found in fasting and starvation. Doubtless this is due to the intense sympatho-adrenal discharge as indicated by tachycardia and the significant rise of vascular resistance in the legs of the animals and in the peripheral vessels of the patients.<sup>16</sup> Catecholamine concentrations as high as 75  $\mu\text{g/l}$  have been observed in the low flow circulatory response to sepsis contrasting with the more normal values of 10  $\mu\text{g/l}$  in the high flow state.<sup>12</sup> Insulin secretion is reduced by alpha-adrenergic stimulation,<sup>49</sup> and in shock states insulin secretion is low.<sup>10,29</sup> However, the glucose uptake stimulated by catecholamines in the low flow pigs remains normal. Based upon the fact that two lactate molecules are derived from one glucose molecule during glycogenolysis it would appear that the major portion of the glucose taken up by the limb is converted to lactate. Since the oxygen uptake is only slightly and insignificantly reduced under these conditions, it appears that it is being utilized for the oxidation of fat. Low insulin levels favor lipolysis which is further stimulated by the presence of catecholamines. Calculation of the net fat uptake by the leg is essentially the same as that in starvation. Although fat is probably being oxidized, the conversion of the glucose to lactate means that only 2 ATP equivalents, very little energy, is being derived from glucose under these conditions. Thus, a rough estimate of the fuel deficit indicates that it is even greater than that encountered in the high flow state. That protein catabolism is in part making up for this and is reflected in the negative nitrogen balance amounting to 16 g/day in the low output septic patients.

Regarding the lactic acidemia in both groups of septic



patients and the elevated production of lactate in the legs of the low flow septic pigs, low tissue oxygen tension due to poor perfusion has generally been cited as the cause.<sup>31</sup> However, in the animals oxygen uptake by the limb did not differ significantly from the starved state. The increased concentration of fatty acids may shift the equilibrium between NAD and NADH, favoring the conversion of pyruvate to lactate.<sup>24</sup> Schumer *et al.*<sup>50</sup> and Drucker *et al.*<sup>20</sup> have suggested that an anaerobic type of block occurs in the aerobic oxidation of glucose after shock or endotoxemia. That this concept in shock may also be true in sepsis is the observation of reduced muscle pyruvate dhydrogenase (PDH), the enzyme complex in the energy producing pathways required for the conversion of pyruvate to acetyl CoA for aerobic oxidation in the tricarboxylic acid cycle. Comparing the activity of PDH in the diaphragms of fed, starved, and starved septic rats with induced peritonitis, a decrease approximately to one half was found in starvation, as expected in the presence of low insulin values. However, the septic animals had PDH values of nearly one quarter that of the fed state despite the high blood insulin values.<sup>49</sup>

Inability of the cardiovascular system to satisfy the elevated circulatory demand encountered in sepsis can be specifically attributed to certain well documented phenomena. Reduced blood volume secondary to translocation of water and protein into the edema fluid and the interstitial space may reduce venous return, particularly during the onset of infection.<sup>12,35</sup> Peripheral pooling in the splanchnic bed of man appears unlikely.<sup>57</sup> Right heart failure secondary to elevated pulmonary vascular resistance is recognized in the early phase of interstitial pneumonitis and later when bronchopneumonia develops.<sup>11,14</sup> Clear cut evidence for left heart failure in sepsis is lacking except that experimentally myocardial depressant factors have been described.<sup>33,57</sup>

However, the low blood insulin values in the animals and patients with reduced cardiac outputs probably plays a role in the establishment of myocardial insufficiency as shown by the marked response to the infusion of glucose, potassium, and insulin (GKI). That is phenomenon is not associated with an increase of blood volume by the 50% glucose infusion was demonstrated by a series of preliminary experiments in septic pigs in which only a very moderate rise of cardiac output occurred in response to administration of the glucose solution. The high blood glucose level attained cannot be the major responsible factor either, as shown by the patient whose course is reproduced in Fig. 2. The hypotensive patients (Table 5) already had the very high blood glucose concentration which averaged 10.2 uM/ml.

That insulin itself played a major role in converting the low output to that of the high output state is indicated by the responses shown in Figs. 1 and 3 as well as by the

data in Tables 2 and 5. In the four patients in whom blood insulin measurements were made, the blood insulin rose on the average 200% from the lower average of 12 uU/ml. The decline of both right and left atrial pressures as cardiac output went up nearly three-fold leaves little doubt that the myocardium was stimulated to greater contractility. At the same time the total peripheral vascular resistance declined in both patients and animals. Thus, it appears that catecholamine stimulation must have been reduced in the peripheral vasculature. Except for the facts that limb oxygen uptake was not significantly altered and glucose uptake rose only slightly as limb flow rose in the pigs, little can be said concerning the effects of insulin on the peripheral metabolism. However, as shown by Fig. 2 a single treatment with GKI produced a lasting clinical improvement in which lactacidemia and production of lactate as indicated by leg A-V differences were reduced.

The mechanism by which cardiac function is improved by GKI is not explained by the data available from this study. It is recognized that in hypoxic states the myocardium responds favorably to glucose potassium and insulin.<sup>39</sup> Glucose transport and glycolysis are enhanced to produce ATP and other high energy phosphate bands by the conversion of glucose to lactate with significant improvement in ventricular performance (56). Henderson *et al.*<sup>27</sup> have demonstrated that high circulating levels of free fatty acids depresses myocardial contraction for a variety of possible reasons including reduction of enzyme activity or by binding calcium. Whether there is an improvement of metabolic activity or a restoration of cell membrane potential per se mediated by insulin directly, remains to be clarified in the septic state.

### Conclusions

To explain the apparent abnormalities of fuel substrate utilization in the metabolism of energy production during severe infection and to correlate these findings with the circulatory behavior, the hypothesis is proposed that certain of the phenomena observed in the high output septic state may be protective mechanisms to prevent the hypoinsulinemia associated with cardiovascular insufficiency which characterizes the low output state. It is clear from many clinical and experimental observations that a high cardiac output in response to the low peripheral vascular resistance evoked by major sepsis is essential to survival and recovery. The rise of cardiac output and fall of peripheral resistance of the hypotensive patients and animals after GKI is evidence that reduced insulin under these conditions may play a role in producing the low flow state.

The metabolic pattern in the hyperdynamic circulatory state contrasts dramatically with that found in the economic utilization of endogenous protein for energy in the starved state. Blood insulin is elevated in the starved

septic patients and animals to three fold that in normal starvation. The resistance of muscle to insulin observed in these studies of septic pigs appears to be related to proteolysis within the muscle cell to satisfy the energy fuel deficit which is occasioned by low fat and ketone availability associated with the normal lipogenic response of adipose tissue to the elevated blood insulin. Since only branched chain ketogenic aminoacids can be oxidized in the cell, the other amino-acids which are released, principally alanine, must be transported to the liver for deamination and conversion to glucose. Gluconeogenesis is a well documented function of glucagon.<sup>36,61</sup> If, as suggested by Rocha *et al.*,<sup>46</sup> the pancreatic alpha cells are stimulated to secrete glucagon by elevated blood concentration of alanine, an explanation is offered for blood glucagon concentrations as high as  $409 \pm 129$  pg/ml found by his group and others<sup>37,58</sup> in the presence of infection. In turn, the beta cells of the pancreatic islets respond to the elevated glucose concentration in the blood thus leading to the high insulin levels observed in the high output septic animals. This series of responses may be conceived of as a protective mechanism to assure adequate glucose and insulin for its transport into the cells and for continued function of the vital nervous and cardiovascular system.

Blackburn *et al.*<sup>5,6</sup> have shown that in the high output state, the starved septic state, the hyperinsulinemia and the prolonged severe proteolysis with the attendant wasting can be averted or ameliorated by infusion of an isotonic solution of aminoacids instead of glucose. The stimulation of insulin secretion is reduced. Lipolysis is inhibited to a lesser degree. With the greater availability of free fatty acids and ketones energy production becomes less dependent upon endogenous protein. The pattern of fuel utilization thus more closely approaches the normal pattern of simple starvation in which endogenous fat serves as the principal fuel source. Experience now indicates that negative nitrogen balances of as much as seven grams per day can be corrected by this regimen. This is very different from the treatment of the low output septic shock situation in which high doses of insulin with sufficient glucose and potassium to protect against hypoglycemia and hypokalemia have been shown to restore cardiovascular competence.

If for any reason continued high cardiac output fails during the septic course, the resulting circulatory insufficiency results in sympatho-adrenal activity leading to a suppression of insulin secretion as occurs in shock of other types.<sup>29</sup> Low blood insulin concentration, even in the absence of hypoxemia, appear to affect the myocardium adversely. The mechanism of this phenomenon in sepsis is not clear at the moment. However, it is apparent that a vicious circle is thereby established. With decreased perfusion and further catecholamine secretion, insulin secretion is further depressed, and presum-

ably myocardial insufficiency progresses. Suffice to say that restoration of the high blood insulin levels typical of the high cardiac output state by treatment with glucose 1 g/kg body weight, regular insulin 1.5 U/kg body weight, and 10 mEq of potassium has been demonstrated effectively to return cardiovascular function to a condition in which the essential high output can be maintained.

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