

# Metabolic responses to exercise after fasting

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DOHM, G. LYNIS, RICHARD T. BEEKER, RICHARD G. ISRAEL AND EDWARD B. TAPSCOTT. *Metabolic responses to exercise after fasting*. *J. Appl. Physiol.* 61(4): 1363-1368, 1986.—Fasting before exercise increases fat utilization and lowers the rate of muscle glycogen depletion. Since a 24-h fast also depletes liver glycogen, we were interested in blood glucose homeostasis during exercise after fasting. An experiment was conducted with human subjects to determine the effect of fasting on blood metabolite concentrations during exercise. Nine male subjects ran (70% maximum  $\dot{V}O_2$  consumption) two counterbalanced trials, once fed and once after a 23-h fast. Plasma glucose was elevated by exercise in the fasted trial but there was no difference between fed and fasted during exercise. Lactate was significantly higher ( $P < 0.05$ ) in fasted than fed throughout the exercise bout. Fat mobilization and utilization appeared to be greater in the fasted trial as evidenced by higher plasma concentrations of free fatty acids, glycerol, and  $\beta$ -hydroxybutyrate as well as lower respiratory exchange ratio in the fasted trial during the first 30 min of exercise. These results demonstrate that in humans blood glucose concentration is maintained at normal levels during exercise after fasting despite the depletion of liver glycogen. Homeostasis is probably maintained as a result of increased gluconeogenesis and decreased utilization of glucose in the muscle as a result of lowered pyruvate dehydrogenase activity.

glucose; lactate; fatty acids; endurance

WE HAVE BEEN INTERESTED in the metabolic responses to exercise and how they are influenced by various dietary manipulations. In rats, we found that a 24-h fast altered both the metabolic response to exercise and the endurance time to exhaustion (11). Muscle glycogen levels were significantly higher in the fasted rats than in the fed rats at exhaustion despite the fact that the fasted rats had run longer than the fed rats. The muscle glycogen "sparing" observed in the fasted rats was most likely due to greater mobilization and utilization of fat as suggested by the elevated plasma concentrations of free fatty acids and  $\beta$ -hydroxybutyrate (11). These findings seemed consistent with the results of Costill et al. (6), who showed that elevated plasma free fatty acids (FFA) can result in decreased muscle glycogen usage during exercise, and Ivy et al. (23), who demonstrated that increased mobilization of fat can lead to enhanced endurance performance.

In contrast to our findings in rats, Pequignot et al. (28) found that fasting human subjects for 15-h reduced cycling time to exhaustion at 80% of maximum  $\dot{V}O_2$  consumption ( $\dot{V}O_{2\max}$ ). Since the effects of fasting do not

seem to be well understood in exercising humans, we thought it was important to investigate whether fasting alters metabolism in humans in the same manner as observed in rats. Of special interest was the effect of fasting on blood glucose concentration during exercise, since hypoglycemia may be a factor in fatigue. A 24-h fast nearly depletes liver glycogen stores (26), and mobilization of liver glycogen is commonly thought to be the major mechanism for maintaining blood glucose concentration during exercise. Thus, in this study we investigated the effects of a 1-day fast on the metabolic response to prolonged (90 min) running at  $\sim 70\%$   $\dot{V}O_{2\max}$ .

## EXPERIMENTAL METHODS

Subjects were nine physically conditioned male runners who felt they would be able to complete 90 min of treadmill exercise at 70–75% of their  $\dot{V}O_{2\max}$ . The experimental protocol was explained to all subjects, and informed consent was obtained before the experiment was performed. The project was approved by the East Carolina University Policy and Review Committee on Human Research. After the subjects were given a thorough physical examination, they underwent a maximum treadmill test to determine  $\dot{V}O_{2\max}$  as previously described (8). Physical characteristics of the subjects were as follows: age,  $28.7 \pm 1.3$  yr; height,  $175 \pm 2$  cm; weight,  $70.2 \pm 2.0$  kg; percent body fat,  $12.1 \pm 1.1\%$ ;  $\dot{V}O_{2\max}$ ,  $61.4 \pm 1.1$  ml  $\cdot$  kg $^{-1} \cdot$  min $^{-1}$ ; maximum heart rate,  $190 \pm 4$  beats/min.

All subjects participated in two counterbalanced trials separated by at least 2 wk, one in the fed condition and one in the fasted state. The treadmill speed for the two trials was determined after the  $\dot{V}O_{2\max}$  test when each subject ran at progressive speeds until he reached a speed producing an  $O_2$  uptake ( $\dot{V}O_2$ )  $\sim 70$ –75% of his  $\dot{V}O_{2\max}$ . That speed was then used in both dietary trials. The subjects were asked to do only a light workout (half the usual training run) 2 days before the trials and to refrain from running the day before the treadmill runs. Diet was carefully controlled for 2 days before each trial as well as on the day of the exercise test. Composition of the diet was controlled by giving the subjects a complete liquid nutrient (Exceed, Ross Laboratories) that contained 15 g protein, 47 g carbohydrate, and 12 g fat per 8-oz. can (355 kcal). From past experience we have found that dietary compliance on this liquid diet is improved if the subjects are given some solid food, and therefore each subject was given five granola bars (Quaker Oats, 150 kcal/8-oz. bar) and enough 8-oz. cans of liquid nutrient

to provide 45 kcal·kg body wt<sup>-1</sup>·day<sup>-1</sup>.

On the day of the fed trial, subjects were instructed to eat one granola bar and one can of liquid nutrient before 9:00 A.M. (2–4 h before exercise). On the day before the fasted trial, subjects were given two-thirds of their usual dietary allotment to consume before 12:00 noon. They were then instructed to ingest nothing but water from 12:00 noon until after exercise test, which resulted in a 23-h fast.

On the days of the trials the subjects reported to the laboratory at approximately 10:15 A.M., a blood sample was drawn (preexercise), and the treadmill runs began at 11:00 A.M. The treadmill speed was predetermined to produce a  $\dot{V}O_2$  that was 70–75% of maximum, and the subjects ran until exhausted (i.e., were unable to continue to run at that pace) or for 90 min, whichever came first.  $\dot{V}O_2$  and  $\dot{V}CO_2$  were determined every 15 min throughout the run using a Beckman Horizon System 2, and heart rate was determined from the electrocardiogram every 5 min as previously described (8). Differentiated ratings of perceived exertion were obtained for legs and cardiorespiratory system, along with an overall rating, every 10 min during the run using the Borg 15-point scale (4). Blood samples were drawn preexercise, every 30 min during the run, immediately after termination of the run, and 30 min after cessation of exercise. It was necessary to have the subjects stop running during blood sampling by venipuncture and blood was usually drawn in less than 1 min.

Plasma was prepared from the blood samples and frozen at  $-20^\circ\text{C}$  until analyzed. Concentrations of the following substances were determined in plasma by referenced methods: glucose (5), lactate (18), FFA (1, 12), glycerol (13),  $\beta$ -hydroxybutyrate (31), and insulin (25).

Data within each trial (across times) were analyzed by a one-way analysis of variance with repeated measures. When significant *F* values were obtained, differences within a trial were determined by a Dunnett's post hoc analysis (32). Statistical differences between trials were determined by paired *t* tests.

## RESULTS

$\dot{V}O_2$  was not appreciably altered during either trial, and there was no difference in the average  $\dot{V}O_2$  between the two trials (Table 1). Subjects were instructed to complete the 90-min exercise bout if possible. However, in the fed trial only four subjects completed 90 min of running and in the fasted trial only one subject was able to finish the bout. Although this experiment was not

TABLE 1. Effect of fasting on percent  $\dot{V}O_{2\text{ max}}$ , exercise time, and perceived exertion

	Fed	Fasted
% $\dot{V}O_{2\text{ max}}$	71.7±1.2	71.8±0.7
Exercise time, min	82.4±2.7	76.1±3.1
Perceived exertion after		
60 min running		
Cardiorespiratory	13.1±0.6	14.3±0.6
Legs	14.6±0.9	15.7±0.6
Overall	13.9±0.6	14.8±0.4

Values are means ± SE for 9 observations.

originally designed to investigate endurance time to exhaustion, the performance of the subjects seemed to indicate a deficit in endurance capacity after a 23-h fast (Table 1). Since perceived exertion has been shown to correlate with heart rate and blood lactate concentration (14), our observation that fasting increased heart rate (Fig. 1) and blood lactate (Fig. 3) also seems consistent with the conclusion that fasting decreases the ability to perform endurance exercise. Decreased endurance capacity after fasting would be in agreement with the result of Pequignot et al. (28) and Henschel et al. (21).

Fasting decreased plasma glucose preexercise (Fig. 2) but glucose increased during exercise in both trials and tended to be somewhat higher in the fasted trial during the exercise bout. Lactate was elevated by exercise in both trials but was significantly higher ( $P < 0.05$ ) in the fasted trial (Fig. 3).

Fasting appeared to increase the mobilization and utilization of fat preexercise, during the exercise bout, and during recovery. Plasma FFA were elevated preexercise (Fig. 4) and after 30 min of exercise in the fasted trial. However, the FFA concentration rose during exercise in the fed trial, so that there was no significant difference after 60 min of exercise. Plasma glycerol concentrations give an indication of the rate of fat mobilization from adipose tissue and triglyceride lipolysis in muscle. Plasma glycerol rose during exercise in both trials (Fig. 5), suggesting activation of triglyceride lipase. However, plasma glycerol (Fig. 5) was higher in the fasted

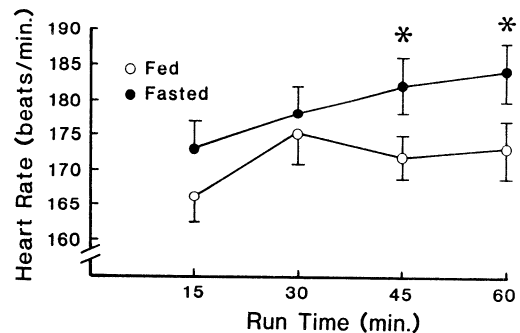


FIG. 1. Effect of fasting on heart rate during exercise. Data points are means ± SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted.

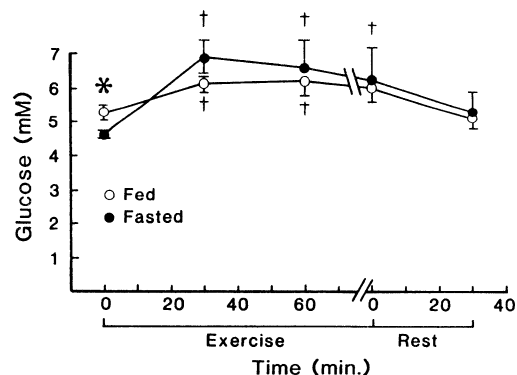


FIG. 2. Effect of fasting on plasma glucose concentration during exercise. Data points are means ± SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted; † significantly different ( $P < 0.05$ ) from preexercise values. Samples for data points at origin of rest period were taken immediately after cessation of exercise (82.4 ± 2.7 min for fed trial and 76.1 ± 3.1 min for fasted trial).

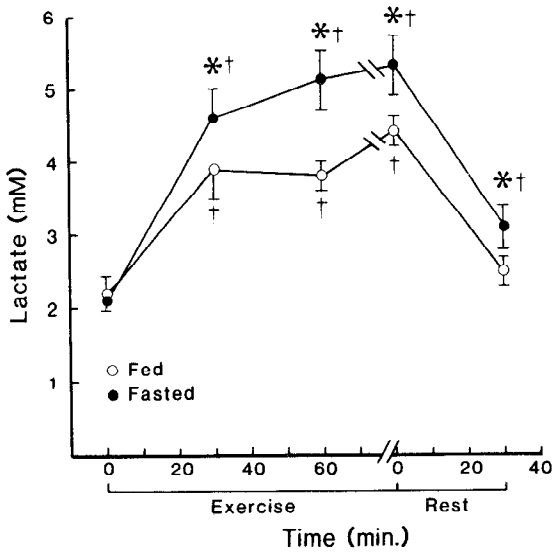


FIG. 3. Effect of fasting on plasma lactate concentration during exercise. Data points are means  $\pm$  SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted; † significantly different ( $P < 0.05$ ) from preexercise values. Samples for data points at origin of rest period were taken immediately after cessation of exercise ( $82.4 \pm 2.7$  min for fed trial and  $76.1 \pm 3.1$  min for fasted trial).

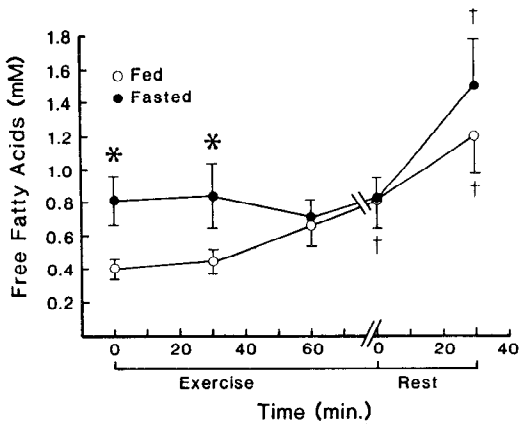


FIG. 4. Effect of fasting on plasma free fatty acid concentration during exercise. Data points are means  $\pm$  SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted; † significantly different ( $P < 0.05$ ) from preexercise values. Samples for data points at origin of rest period were taken immediately after cessation of exercise ( $82.4 \pm 2.7$  min for fed trial and  $76.1 \pm 3.1$  min for fasted trial).

trial at all times of exercise and recovery (but not preexercise). Plasma  $\beta$ -hydroxybutyrate concentrations (Fig. 6) were higher in the fasted trial preexercise, during exercise, and recovery, an indication of increased conversion of fatty acids to ketone bodies in the liver. Another measure of fat utilization is the respiratory exchange ratio (RER). The lower RER ( $P < 0.05$ ) in the fasted trial (Fig. 7) at 15 and 30 min of exercise suggests greater fat utilization. However, the RER in the fed trial declined during exercise, so that after 45 min there was no statistically significant difference between the two trials.

Plasma insulin was decreased by fasting (preexercise, Fig. 8). However, exercise caused insulin to decrease in the fed trial resulting in only a very small difference between the two trials during exercise.

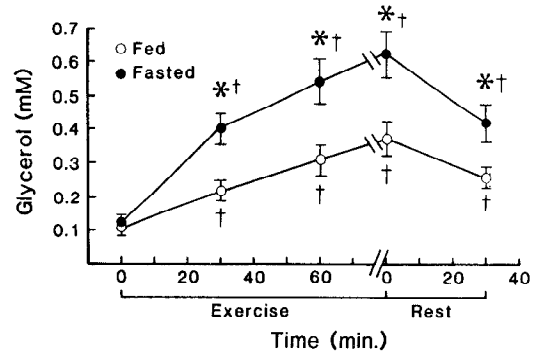


FIG. 5. Effect of fasting on plasma glycerol concentration during exercise. Data points are means  $\pm$  SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted; † significantly different ( $P < 0.05$ ) from preexercise values. Samples for data points at origin of rest period were taken immediately after cessation of exercise ( $82.4 \pm 2.7$  min for fed trial and  $76.1 \pm 3.1$  min for fasted trial).

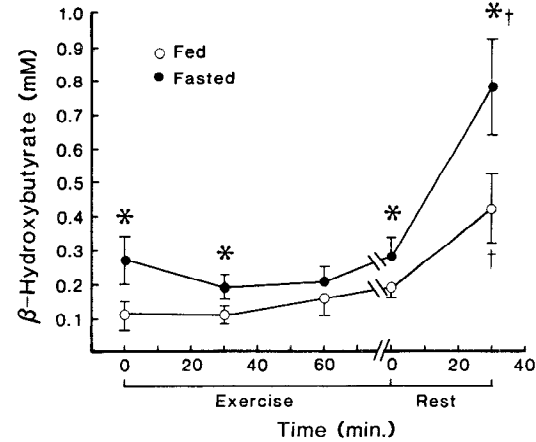


FIG. 6. Effect of fasting on plasma  $\beta$ -hydroxybutyrate concentration during exercise. Data points are means  $\pm$  SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted; † significantly different ( $P < 0.05$ ) from preexercise values. Samples for data points at origin of rest period were taken immediately after cessation of exercise ( $82.4 \pm 2.7$  min for fed trial and  $76.1 \pm 3.1$  min for fasted trial).

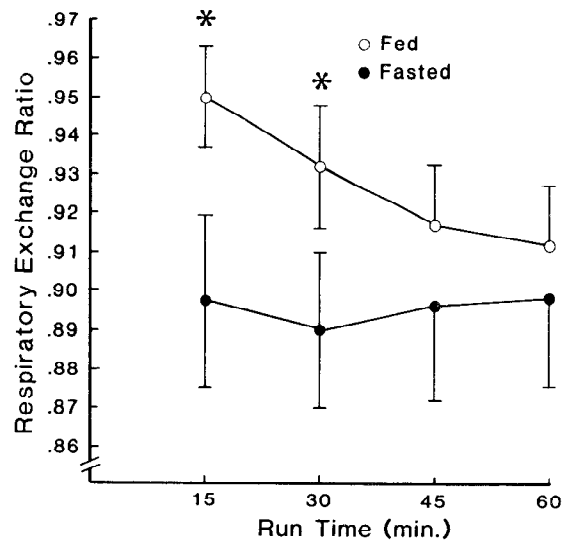


FIG. 7. Effect of fasting on respiratory exchange ratio during exercise. Data points are means  $\pm$  SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted.

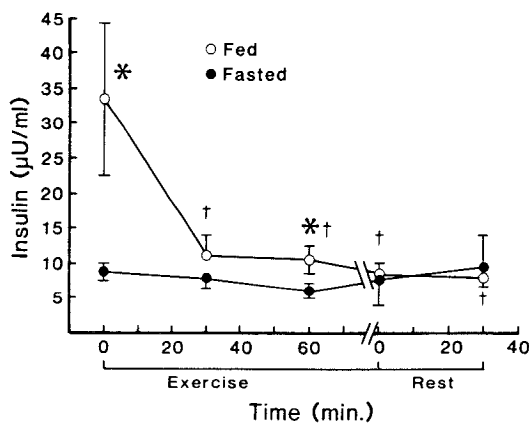


FIG. 8. Effect of fasting on plasma insulin concentrations during exercise. Data points are means  $\pm$  SE for 9 observations. \* Significant difference ( $P < 0.05$ ) between fed and fasted; † significantly different ( $P < 0.05$ ) from preexercise values. Samples for data points at origin of rest period were taken immediately after cessation of exercise ( $82.4 \pm 2.7$  min for fed trial and  $76.1 \pm 3.1$  min for fasted trial).

## DISCUSSION

During the first half of the exercise bout, fasting caused a much greater utilization of fat as a fuel as evidenced by higher plasma concentration of FFA, glycerol,  $\beta$ -hydroxybutyrate, and lower RER in the fasted trial. However, as duration of exercise progressed fat became a greater portion of the energy expenditure in the fed subjects, so that the difference in RER,  $\beta$ -hydroxybutyrate, and FFA between fed and fasted were less apparent. These findings are in general agreement with those of other investigators (2, 3, 15–17, 24).

Hormones play a very large role in controlling mobilization of energy fuels during exercise. The lower insulin concentrations in fasted subjects (Fig. 8) and the antilipolytic action of insulin are consistent with greater fat utilization observed in the fasted trial. The drop in insulin during exercise is likely a regulatory adaptation to increase fat utilization, as reflected in the declining RER in the fed subjects. Pequignot et al. (28) investigated plasma catecholamine concentrations in fed and fasted subjects during exercise ( $80\% \dot{V}O_{2\max}$ ) and found that both epinephrine and norepinephrine were higher in the fasted subjects after 15 min of exercise. This change in catecholamines would also increase lipolysis.

The increase in plasma glucose in the fasted trial (Fig. 2;  $4.6 \pm 0.1$  mM preexercise to  $6.9 \pm 0.5$  mM after 30 min of exercise) was an unexpected finding in light of the fact that a 24-h fast nearly depletes liver glycogen stores (26). However, our results are in general agreement with those of Coyle et al. (7), who observed that plasma glucose was higher in fasted than fed subjects during the first 40 min of exercise at  $70\% \dot{V}O_{2\max}$ , and the findings of Björkman and Eriksson (3), who observed an increase in blood glucose ( $2.96 \pm 0.17$  mM at rest and  $3.64 \pm 0.27$  mM after 20 min at  $60\% \dot{V}O_{2\max}$ ) in subjects that had fasted for 60 h.

The increase in plasma glucose that occurs at a time when liver glycogen is depleted seems to suggest that peripheral glucose utilization may be decreased during exercise in the fasted subjects. This conclusion is supported by the findings of Rennie and Holloszy (30) and

Randle et al. (29), that provision of FFA to cardiac and skeletal muscle decreases the uptake and oxidation of glucose. Thus a reciprocal relation between blood glucose and fatty acids exists such that, during fasting, fat mobilization and utilization are increased and blood glucose is conserved. This seems to be substantiated by the results of Minuk et al. (24), who found that the rate of disappearance of glucose during exercise was decreased from  $12.2 \pm 1.4$  to  $8.6 \pm 1.0$  g in obese subjects who had fasted for 2 wk.

Randle and co-workers (29) have investigated the biochemical basis for the carbohydrate-sparing effect of fatty acids (the glucose fatty acid cycle) and found that the primary regulatory site resides in the pyruvate dehydrogenase (PDH) complex (29). PDH exists in an inactive phosphorylated form and an active nonphosphorylated form, and these forms are interconverted by a specific PDH kinase and a PDH phosphatase that are associated with the enzyme complex. PDH kinase is activated by acetyl-CoA and NADH and inhibited by ADP, CoA,  $NAD^+$ , pyruvate,  $Ca^{2+}$ , and  $Mg^{2+}$ , whereas PDH phosphatase is activated by  $Ca^{2+}$  and is inhibited by acetyl-CoA and NADH, so that an increase in intramitochondrial  $Ca^{2+}$  (as during exercise) would increase PDH activity but increases in the acetyl-CoA/CoA and NADH/NAD ratios (as during increased utilization of fatty acids) would lead to deactivation of PDH (29).

Since fasting before exercise leads to muscle glycogen sparing in rats (11) and in human subjects (7), it seems likely that conservation of carbohydrate may be a result of an altered response of muscle PDH to exercise after fasting. Hagg et al. (19) and Hennig et al. (20) found that muscular contraction activated PDH but that the activation was blunted in fasted rats. In addition, we recently found that the conservation of muscle glycogen in fasted rats was well correlated with the reduced activation of muscle PDH (27). Fatty acid oxidation generates intermitochondrial acetyl-CoA, which can activate PDH kinase, which would in turn phosphorylate and deactivate PDH (29). Decreased pyruvate oxidation in muscle of fasted subjects could thus lead to glycogen sparing.

The higher plasma lactate concentrations in the fasted trial may be yet another manifestation of the regulation of carbohydrate metabolism during periods of enhanced fat utilization. Elevated plasma lactate is due to a faster rate of production by muscle and/or decreased extraction of lactate by gluconeogenic tissues such as liver. Björkman and Eriksson (3) found that splanchnic uptake of lactate was increased twofold in 60-h-fasted subjects compared with subjects fasted overnight. Since plasma lactate was higher in the fasted trial, the rate of lactate production must have been increased to an even greater extent than the increase in lactate removal. Both exercising and nonexercising muscles may be involved in increased lactate production, since it is likely that plasma catecholamine levels were higher in the fasted trial.

A mechanism to explain the increased lactate production in the fasted trial may involve decreased activation of PDH during exercise. If PDH is activated to a lesser extent than is glycogen phosphorylase in the fasted exercised group, then pyruvate would be produced at a

faster rate than it could be metabolized to acetyl-CoA. A surplus of pyruvate, linked to an increased NADH/NAD ratio that would be expected from increased fatty acid oxidation, could lead to an accelerated rate of lactate formation in exercising muscles of fasted subjects.

Changes in the concentration of blood glucose occur in response to changes in the rate of glucose production and/or the rate of glucose utilization. The results of Minuk et al. (24) indicate that glucose utilization is decreased during exercise after fasting, whereas the report of Björkman and Eriksson (3) shows that fasting increased the rate of gluconeogenesis during exercise. The rate of gluconeogenesis is controlled both by the rate of delivery of substrates to the liver and by hormonally stimulated covalent modification of several regulatory enzymes in the gluconeogenic pathway (22). The elevated concentrations of lactate and glycerol give ample evidence for increased availability of gluconeogenic substrates during exercise in the fasted subjects. We previously investigated (9) the regulation of gluconeogenesis during exercise and found that changes in the hepatic concentration of fructose 2,6-bisphosphate was one of the primary regulatory mechanisms operating during exercise. Since the hormonal milieu is probably more conducive to activation of gluconeogenesis in the fasted state, these changes are undoubtedly important for increasing glucose production in fasted subjects during exercise.

A 1-day fast increases fat mobilization and utilization in humans during exercise similar to increases observed in rats. However, in contrast to rats, fasting did not improve endurance in human subjects and may even have a deleterious effect on exercise performance. We can only speculate why fasting increases endurance in rats but not in humans. It may relate to a greater capacity to oxidize fatty acids in rat muscle and thus a greater ability to conserve muscle glycogen. Another possibility is that the conditioned human subjects had already increased their capacity to mobilize and oxidize fatty acids because of prior training, whereas the rats were untrained and were able to increase the capacity to utilize fatty acids during exercise when fasted. Intensity of exercise may also be a factor in whether fasting will increase endurance, since the untrained rats ran at a low intensity that allowed them to run 2–5 h. Whatever the explanation, these data demonstrate that fasting does not improve endurance in human subjects running at 70%  $\dot{V}O_{2\text{ max}}$ .

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