1 Carbohydrate Ingestion During Prolonged Exercise: Effects on Metabolism and Performance

ANDREW R. COGGAN, Ph.D.
EDWARD F. COYLE, Ph.D.

INTRODUCTION

The effects of ingesting carbohydrates (CHO) during prolonged exercise have interested physiologists since the early part of the 20th century [25, 27, 46, 47]. This interest arises in large part because CHO ingestion provides a means of rapidly altering CHO availability during exercise and, therefore, represents a useful tool for studying the interrelationships between CHO availability, substrate metabolism, and fatigue. Yet despite this long-standing and widespread interest, detailed studies of the metabolic responses to CHO ingestion during exercise are relatively recent. Similarly, it was only in the last decade that it was conclusively demonstrated that ingesting CHO during prolonged exercise can improve performance [38].

The effects of CHO ingestion during prolonged exercise have been reviewed recently by several authors, mostly from the perspective of determining the optimal fluid replacement beverage during exercise [36, 37, 85, 94]. In this chapter, we focus primarily on the metabolic responses to exercise when fed CHO, and develop a model that we believe is useful in understanding how these metabolic effects may be mechanistically linked to enhanced exercise performance. Because early views of substrate metabolism and the possible causes of fatigue during prolonged exercise have had a major impact on research in this area, we begin with a brief historical overview.

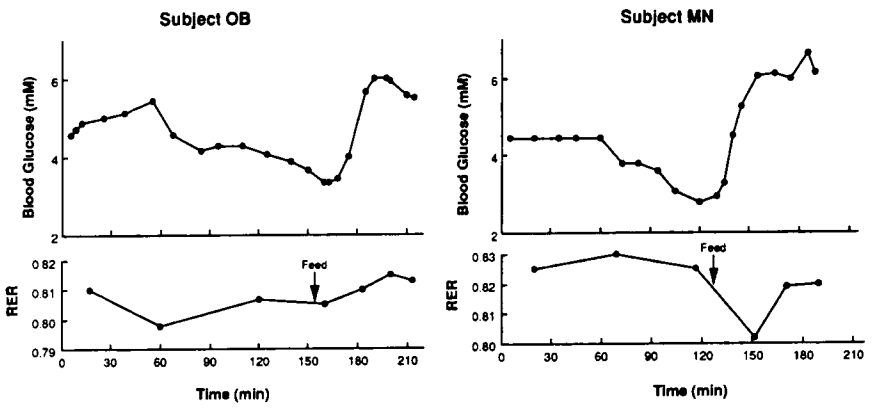
HISTORICAL PERSPECTIVES

At the beginning of this century, studies of exercise metabolism were aimed primarily at defining the fuel(s) used to provide the energy required for muscular activity [6]. These early experiments consisted mainly of determining the respiratory exchange ratio (R) during exercise when CHO availability was increased or decreased by altering a person's

chronic diet [26, 79]. In a few studies, however, CHO availability was increased by having subjects ingest CHO during the exercise itself [25, 27, 46, 47]. As early as 1932, for example, Dill et al. [46] reported that feeding one laboratory dog 20 grams (g) of CHO every hour during prolonged exercise maintained blood glucose levels and enabled the animal to run at 124 meters per minute (m/min) up to a 17.6% grade for at least 13 hours without fatiguing. When the dog was supplied with only water to drink during exercise, however, blood glucose concentrations decreased markedly, and he was able to exercise at this intensity for 3 to 6.5 hours (hr) before tiring. In another experiment, the dog ran for 4.25 hr in the fasted state, which resulted in a decline in blood glucose to 2.6 millimole per liter (mmol/L) coincident with fatigue. The animal was then fed 40 g of CHO during an 8-minute (min) rest period, which increased blood glucose to >6 mmol/L and enabled the dog to run for another 1.5 hr, at which time he was still not exhausted. These observations led Dill et al. [46] to conclude that the limiting factor in the performance of prolonged exercise ". . . seems to be merely the quantity of easily available fuel . . ." in the form of blood-borne glucose. Ingestion of CHO during exercise was therefore thought to delay fatigue by maintaining the availability of this important CHO source for oxidation by the exercising musculature.

In contrast to this view, early studies of exercising humans emphasized the ability of CHO ingestion during exercise to supply glucose for use by the central nervous system (CNS) [16, 17, 27, 58, 86]. As early as 1924, for example, Levine et al. [86] noted that some runners competing in the Boston Marathon became hypoglycemic, showing symptoms of neuroglucopenia such as ". . . muscular twitching . . . nervous irritability, and even collapse and unconsciousness." Performance was reportedly improved when these symptoms were prevented by having these same men consume additional CHO on the day before and during the race the following year [58]. Fifteen years later in 1939, Christensen and Hansen [26] observed in three men that consuming a low CHO diet markedly impaired their endurance during moderate-intensity (≈60–65% oxygen uptake peak [$\dot{V}O_2max$]) exercise. This premature fatigue was accompanied by ketosis, a low rate of CHO oxidation, and hypoglycemia severe enough to result in symptoms of neuroglucopenia. In an attempt to distinguish between these three possible causes of fatigue, Christensen and Hansen [27] performed additional experiments in which two of these men were fed 200 g of glucose at almost complete exhaustion. Glucose ingestion resulted in a rapid increase in blood glucose concentration and relief of the neuroglucopenic symptoms, enabling the men to continue exercising for an additional 60 min (Fig. 1.1). The subjects' R values, however, which were much lower than normal owing to the preceding low CHO diet, changed very little either before or after glucose ingestion (Fig. 1.1). Thus, the initial onset of

FIGURE 1.1
*The data of Christensen and Hansen [27]. Blood glucose and respiratory exchange ratio were measured during prolonged exercise in two men who had been consuming a very low CHO diet. At the point of "almost complete exhaustion" the men were fed 200 g of glucose (denoted by "***Feed***"), and they were able to exercise for an additional hour. In subject O.B., R remained relatively constant before and after glucose ingestion. Interestingly, this is the same subject who was studied by Boje in 1940 [17], and who appears to have been unusually susceptible to hypoglycemia during exercise. In subject M.N., R initially fell and then increased again following glucose ingestion. The response of subject M.N. is similar to our observations shown in Figure 1.6. (Modified from Christensen, E.H., and O. Hansen. IV. Hypoglykamie, Arbeitfähigkeit und Ermudung.* Skand. Arch. Physiol. *81:172–179, 1939.)*



fatigue and its subsequent reversal by CHO ingestion did not appear to be associated with large changes in the rate of CHO oxidation. In another experiment [27], one of these men experienced hypoglycemia and symptoms of neuroglucopenia when exercising 3 hr after ingesting 200 g of glucose, and fatigued prematurely even though R and therefore the estimated rate of CHO oxidation were quite high. Based on these observations, Christensen and Hansen [27] concluded that hypoglycemia must cause fatigue by means of its effects on the CNS, and not by affecting muscle metabolism. A similar conclusion had been reached by Boje in 1936 [16].

With the reintroduction of the muscle biopsy procedure in the 1960s [12], emphasis shifted from blood glucose towards muscle glycogen as the major source of CHO during exercise. Using this technique, muscle glycogen was shown to be depleted after intense exercise performed to fatigue [13, 62]. Dietary manipulations known to affect endurance performance were found to alter preexercise muscle glycogen stores

[14, 57, 75]. In addition, endurance exercise training, which was known to decrease total CHO oxidation and improve exercise performance, was demonstrated to decrease the rate of glycogen utilization [66, 76]. Furthermore, glucose uptake by skeletal muscle during exercise was reported to be minimal [13, 34], and the intravenous infusion of glucose at high rates was found to have little effect on the rate of muscle glycogenolysis [1, 13, 63]. The concept therefore became established that muscle glycogen was the primary CHO source during exercise, and that blood-borne glucose contributed little to the CHO needs of muscle during moderate or intense exercise.

This concept was further reinforced by the notion that CHO ingested during exercise "seems to remain in compartments within an unoxidized glucose pool" [117]. This belief was based on the observation that although carbon-14- (^{14}C) labeled glucose ingested during prolonged exercise at 50–72% $\dot{V}O_2max$ rapidly appeared in the circulation, very little of the ^{14}C label was recovered in expired breath as $^{14}CO_2$ [35, 117]. Because blood glucose in general and ingested CHO in particular were thought to contribute little to the CHO needs of muscle during moderate intensity exercise, CHO ingestion during exercise was assumed to benefit only persons suffering from neuroglucopenia [36].

Despite these earlier views, however, substantial evidence exists indicating that blood glucose is an important CHO energy source during exercise [32]. CHO ingestion during prolonged exercise also has been repeatedly demonstrated to enhance performance, even in persons not suffering from neuroglucopenia [28–30, 38, 41]. Indeed, recent evidence indicates that blood glucose becomes the dominant CHO energy source during prolonged (≥2 hr) exercise, and that, as originally suggested by Dill et al. [46], CHO ingestion improves performance primarily by maintaining the availability and oxidation of this critical fuel [28–30, 41]. The evidence leading to this interpretation is the subject of the present review.

EFFECTS ON METABOLISM

Rate of Blood Glucose Utilization During Exercise When Fasted

In the fasted state, glucose uptake by resting skeletal muscle is minimal, and most of the glucose produced by the liver is used by the CNS [5]. At the onset of exercise, the arteriovenous difference for glucose across the muscle initially decreases and may actually become negative, indicating net glucose release [34, 74, 78, 123]. This free glucose is presumably derived from the hydrolysis of the α minus 1,6-linkages of glycogen by debranching enzyme, or from the hydrolysis of glucose-6-phosphate by the action of nonspecific phosphatases [34, 123]. After the first few min of exercise, however, this glucose release quickly reverts to glucose uptake [34, 123].

The rate of blood glucose utilization during exercise is curvilinearly related to the exercise intensity [77, 123]. During cycle ergometer exercise, for example, glucose uptake by the legs increases from ≈0.05 g/min at rest to ≈0.2, ≈0.4, and ≈0.7 g/min after 40 min of exercise at approximately 25%, 50%, and 75% of $\dot{V}mo_2max$, respectively [123]. Most of the glucose taken up at these intensities is probably directly oxidized; blood glucose utilization can therefore account for roughly one-fourth to one-third of total CHO energy production during the early stages of moderate-intensity exercise [32]. Glucose uptake continues to increase with increasing exercise intensity, with rates as high as 1.4 g/min observed during exercise at ≈100% $\dot{V}o_2max$ [77]. During such high-intensity exercise, however, some of the glucose taken up may accumulate within the muscle, owing to inhibition of hexokinase by glucose-6-phosphate produced by rapid glycogenolysis [77].

In addition to increasing with greater exercise intensity, the utilization of blood glucose also increases as the duration of exercise increases. For example, glucose uptake by the legs during cycle ergometer exercise at ≈60% $\dot{V}o_2max$ increases almost 40% between 40 and 90 min of exercise [4]. Rates of blood glucose utilization of over 1.2 g/min have been observed at the end of exercise to fatigue at 67% $\dot{V}o_2max$ [21]. Even very intense, intermittent exercise, which is normally thought to rely primarily on muscle glycogen as a CHO source, eventually results in marked increases in glucose turnover. In two subjects, for example, Hultman [63] observed that splanchnic glucose release increased from 0.4–0.6 g/min early in exercise to 0.9–1.1 g/min at fatigue (≈60 min). In both cases, the arterial blood glucose concentration remained constant, indicating that these high rates of splanchnic glucose production were matched by equally high rates of peripheral glucose utilization.

This increase in blood glucose utilization with time partially compensates for, and may be related to, a steady decrease in the rate of muscle glycogenolysis [32]. Because blood glucose utilization increases over time as muscle glycogen utilization decreases, blood glucose utilization represents a progressively increasing proportion of total CHO oxidation [41]. As indicated above, during the first hour of exercise at ≈60–70% $\dot{V}o_2max$, blood glucose utilization represents only about one-fourth of total CHO oxidation [4, 21, 41, 72]. Late in exercise when muscle glycogen is low, however, blood glucose appears to account for almost all of the CHO being oxidized [21, 28, 41]. However, blood glucose utilization may actually decrease during the later stages of prolonged moderate intensity exercise because of a decrease in blood glucose concentration that results from a decrease in splanchnic glucose production [4, 28, 41].

Blood glucose utilization also increases with time during low-intensity exercise. During prolonged cycle ergometer exercise performed at 30% $\dot{V}o_2max$, glucose uptake by the legs does not plateau until after 90 min

of exercise [2]. Nevertheless, fat remains the primary source of energy for skeletal muscle during prolonged, low-intensity exercise [2]. Like moderate-intensity exercise, leg glucose uptake may decrease during the later stages of lower intensity exercise because of a decrease in blood glucose concentration [2].

Substantial data therefore indicate that blood glucose represents a very important source of CHO for exercising skeletal muscle, especially when muscle glycogen stores become depleted during prolonged, moderate-intensity exercise. The contribution of blood glucose to CHO oxidation by muscle may be limited, however, by a decrease in blood glucose concentration late in exercise [2, 4, 28, 41]. This decrease in blood glucose may be prevented by ingesting sufficient amounts of CHO. The effects of such CHO ingestion on blood glucose and muscle and liver glycogen utilization during exercise are considered below.

Rate of Blood Glucose Utilization During Exercise When Fed CHO

During low-intensity exercise (30% $\dot{V}O_2$max), CHO ingestion results in increased blood glucose and insulin concentrations [3]. As a result of this hyperglycemia and hyperinsulinemia, the rate of muscle glucose uptake is up to twofold greater compared to the rate observed during exercise in the fasted state [3]. At the same time, adipose tissue lipolysis is decreased, as indicated by lower plasma free fatty acid (FFA) and glycerol concentrations [3] and a slower rate of plasma FFA turnover [24]. As will be discussed subsequently, muscle glycogen utilization does not appear to be affected by CHO ingestion during exercise. The net result of these metabolic changes is a decreased reliance on adipose tissue (and possibly intramuscular) triglycerides and an increased reliance on blood glucose as the source of energy during exercise, leading to an increase in R [3, 9–11]. Nevertheless, the rate of blood glucose utilization does not exceed that observed during more intense exercise performed in the fasted state [3].

CHO ingestion during moderate intensity exercise (50–75% $\dot{V}O_2$max) tends to produce less marked alterations in substrate metabolism. The insulin response to CHO infusion or ingestion during moderate-intensity exercise is suppressed compared to that observed during low-intensity exercise, probably because of greater sympathetic nervous system inhibition of insulin secretion. Consequently, insulin levels are the same or only slightly higher than those observed during exercise in the fasted state [28–30, 38, 41, 69]. The increases in plasma FFA and glycerol concentrations during exercise are blunted, but not to the same extent as observed following CHO ingestion during low-intensity exercise [38, 41, 69]. Plasma FFA or muscle triglyceride utilization have not been directly determined during moderate-intensity exercise when fed CHO. However, these small differences in plasma FFA and glycerol concentrations, along with little or no difference in R, at least during

the first several hours of exercise [38, 41], suggest that the rate of fat oxidation is not greatly affected.

The effects of CHO ingestion on blood glucose metabolism during moderate-intensity exercise also have not been studied directly in humans. As described under "Historical perspectives," early studies that attempted to calculate blood glucose oxidation by feeding subjects ^{14}C-labeled glucose during exercise at 50–72% $\dot{V}O_2$max surmised that very little blood glucose was oxidized under these conditions [35, 117]. This notion was based on the observation that, although up to two-thirds of circulating glucose was derived from the ingested glucose load, <10% of the ^{14}C label was recovered in expired CO_2 during the first hour of exercise following glucose ingestion. However, CO_2 produced by cellular respiration enters the body's bicarbonate pools, which turn over relatively slowly, even during exercise [31, 115, 127]. This limited recovery probably primarily reflects the slow passage of the $^{14}CO_2$ through these pools, not a limited rate of blood glucose oxidation. This interpretation is supported by the observation that, irrespective of the size, timing, or type of ^{14}C-labeled CHO load, the recovery of $^{14}CO_2$ during exercise follows a similar time course [10, 35, 117], which lags well behind the appearance of the label in the blood [35, 117]. Again, considerable data indicate that blood glucose is an important CHO source during moderate-intensity exercise performed in the fasted state. Thus, these studies using ^{14}C-glucose [35, 117] undoubtedly greatly underestimated the extent to which blood glucose is oxidized when CHO are ingested during moderate-intensity exercise.

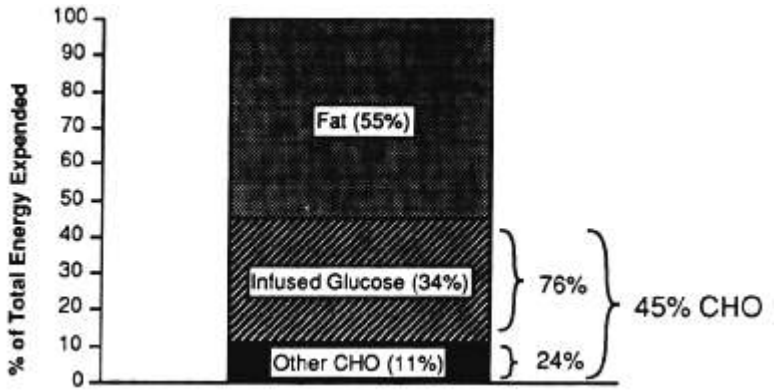
In contrast, studies that have attempted to measure the oxidation of exogenous CHO by feeding exercising subjects CHO sources that are naturally enriched with carbon-13 (^{13}C) [56, 80, 87, 88, 104–108] have overestimated the rate of oxidation by up to 75% [105]. Because the ^{13}C enrichment of CHO is greater than that of fats [71, 112], an increase in the relative contribution of CHO oxidation to total CO_2 production (i.e., an increase in R) due either to exercise or to CHO ingestion, or both, will result in an increase in $^{13}CO_2$ production from endogenous CHO sources [8, 31, 112, 126]. Indeed, recent data indicate that, when subjects are fed naturally labeled CHO during exercise, up to one-half of the increase in $^{13}CO_2$ production arises from endogenous substrates, not from the ingested CHO load [105]. This increase in endogenous $^{13}CO_2$ production when fed CHO during exercise is not accounted for by measuring the breath $^{13}CO_2$ enrichment at rest prior to exercise, and is only partially accounted for by measuring the $^{13}CO_2$ enrichment in breath during exercise in the absence of CHO ingestion. This may explain why, under otherwise almost identical experimental conditions, the apparent recovery of the label in expired CO_2 during exercise is much greater when subjects ingest CHO sources labeled with ^{13}C [56, 80, 87, 88, 104–108] rather than ^{14}C [10, 35, 117]. Similarly, production

of $^{13}CO_2$ from endogenous sources may explain why over 50 g of ingested ^{13}C-labeled sucrose are apparently "oxidized" during 4 hr of moderate-intensity exercise, despite the simultaneous ingestion of a potent α-glucosidase inhibitor to block hydrolysis and therefore absorption of the sucrose in the small intestine [56]. Estimates of the rate of exogenous CHO oxidation during exercise obtained using this technique therefore require quantitative reevaluation. Furthermore, these studies have provided no information on the effect of CHO ingestion during exercise on the oxidation of endogenous blood glucose.

The effects of CHO ingestion during moderate-intensity exercise on blood glucose utilization remain uncertain. In the absence of direct data, we attempted to estimate this indirectly by measuring muscle glycogen utilization in subjects fed CHO throughout moderate intensity exercise; any additional CHO oxidized was assumed to represent blood glucose [41]. Because these estimates are indirect, they must be viewed as only a first approximation. Nevertheless, the results of this study suggested that blood glucose utilization initially increased similarly during exercise at 70–75% $\dot{V}O_2$max when fasted or when fed CHO, reaching ≈1 g/min after ≈2 hr of exercise. After this time, blood glucose utilization appeared to decrease during exercise in the fasted state, owing to a decline in blood glucose concentration. When fed CHO throughout exercise, however, estimated blood glucose utilization continued to increase with time, so that after ≈3 hr of exercise, it appeared to account for almost all of the CHO being oxidized. Blood glucose must have been oxidized at ≈2 g/min late in exercise to support the observed rate of total CHO oxidation. Most of the blood glucose being oxidized was presumably derived from the ingested CHO load (i.e., ≈340 g of maltodextrins during ≈4 hr of exercise), because previous studies have demonstrated that up to two-thirds of circulating glucose originates from the exogenous CHO load when much smaller amounts (10–42 g) of CHO are ingested during exercise [35, 117].

These data suggested that when blood glucose concentration is prevented from decreasing during the later stages of moderate-intensity exercise, blood glucose may be oxidized at much higher rates than previously believed possible. To test this hypothesis, we [28] measured whole-body glucose disposal late in exercise using the euglycemic clamp technique [45]. After prolonged exercise that led to muscle glycogen depletion and a decline in blood glucose concentration, glucose was infused intravenously at the rate required to restore and maintain euglycemia while the subjects performed additional exercise. These experiments demonstrated that whole-body glucose disposal averaged 1.13 g/min late in exercise. If completely oxidized, the infused glucose could account for three-quarters of total CHO oxidation under these conditions [28] (Fig. 1.2). It is probable that blood glucose oxidation constituted nearly 100% of total CHO oxidation during glucose infusion,

FIGURE 1.2
Estimated substrate utilization during the final 30 minutes of exercise at ≈70% $\dot{V}O_2$max, when glucose was infused intravenously at the rate required to maintain plasma glucose concentration at ≈5 mmol/L. The relative contributions of fat (55%) and CHO (45%) to total energy expenditure were determined from the mean R value (i.e., 0.84). The rate of total CHO oxidation (i.e., 1.50 g/min) was also determined from R and $\dot{V}O_2$. Exogenous glucose was assumed to be oxidized at the infusion rate required to maintain euglycemia (i.e., 1.13 g/min), and could account for 76% of total CHO oxidation and 34% of total energy expenditure. The rate of oxidation of other CHO sources (i.e., 0.37 g/min) accounted for 24% of total CHO oxidation and 11% of total energy expenditure. This probably reflects primarily the oxidation of endogenous blood glucose, because muscle glycogen concentration did not change during glucose infusion. (Reprinted with permission from Coggan, A.R., and E.F. Coyle. Reversal of fatigue during prolonged exercise by carbohydate infusion or ingestion. J. Appl. Physiol. *63:2388–2395, 1987.)*



because muscle glycogen concentration did not decrease during this time despite a high rate of total CHO oxidation (i.e., 1.50 g/min). This additional glucose (i.e., 0.37 g/min) would presumably be derived from residual hepatic glycogenolysis or gluconeogenesis, or both, which are not determined by the euglycemic clamp technique [45].

To test this hypothesis further, in a recent pilot experiment we measured plasma glucose turnover and oxidation using a primed, continuous infusion of [U^{-13}C]glucose in one well-trained cyclist exercising for 2 hr at 70–75% $\dot{V}O_2$max when fed CHO throughout exercise [A. R. Coggan, D. M. Bier, and J. O. Holloszy, unpublished observations]. By priming the bicarbonate pools with $NaH^{13}CO_3$ and by infusing the [U^{-13}C]glucose at a relatively high rate (≈50 μmol/min), it was possible to achieve a plateau in breath $^{13}CO_2$ enrichment

during the final 30 min of exercise that was approximately 100 times greater than any potential increase from exercise or CHO ingestion alone [31, 126]. It was therefore possible to accurately quantify glucose oxidation under true steady-state conditions. The results of this experiment indicated that the rate of plasma glucose oxidation during the 90–120 min period of exercise exceeded 1 g/min, which could have accounted for about one-half of the total CHO being oxidized at this time. Although representing only a single subject, these direct measurements of the rate of blood glucose oxidation after 1.5–2 hr of moderate-intensity exercise when fed CHO agree very well with prior indirect estimates derived from the measurement of $\dot{V}O_2$, R, and muscle glycogen concentration [41]. These measurements also agree reasonably well with the rate of whole-body glucose disposal determined after 3 hr of exercise using the euglycemic clamp technique [28].

Obviously, additional experiments will be required to more accurately quantify the rate of blood glucose utilization during moderate-intensity exercise when subjects are fed CHO, especially during exercise of >2 hr duration. In particular, it will important to compare these rates of blood glucose utilization during exercise when fed CHO to rates observed during exercise in the fasted state. More information also is needed on the contribution of ingested CHO to the total glucose pool during exercise. Nevertheless, the available data support the conclusion that blood glucose can be oxidized at very high rates during prolonged, moderate-intensity exercise when fed CHO, and that at least some of this glucose is derived from the ingested CHO load. As developed later in this chapter, it is this ability of CHO ingested during exercise to maintain or increase blood glucose availability and oxidation late in exercise that apparently results in the improvement in exercise performance.

Effect of CHO Ingestion on Muscle Glycogenolysis During Exercise

An important question is whether ingesting CHO during exercise, by maintaining or increasing blood glucose availability and oxidation as previously described, slows the rate of muscle glycogenolysis. This possibility was first raised by the experiments of Hultman and coworkers [1, 13, 63], who reported that the intravenous infusion of glucose at up to 3.5 g/min decreased net glycogen degradation during intermittent exercise by ≈20%. This decrease in glycogen utilization was not statistically significant when only 2 to 6 subjects were studied [1, 63], but did achieve statistical significance ($P < 0.001$) when a total of 10 men were tested [13]. Similarly, Ehrenstein et al. [49] reported that, although intravenous glucose infusion during 8 hr of intermittent cycle ergometer exercise at 30% $\dot{V}O_2$max did not result in a statistically significant decrease in the amount of muscle glycogen utilized, differences in muscle glycogen utilization between the control and glucose

infusion trials were inversely related to differences in blood glucose concentration ($r = -0.62$; $P < 0.01$). These observations, along with the observation that less muscle glycogen was used when glucose was infused into exercising rats [7], led us to hypothesize that CHO ingestion during exercise improves performance by slowing the rate of muscle glycogen degradation [38, 39]. However, subsequent direct measurements of muscle glycogen utilization during exercise with and without CHO feedings, both by us [41] and by others [53, 55, 61, 91, 100], have indicated that this hypothesis is incorrect. Nevertheless, some authors have concluded that CHO ingestion during exercise does indeed exert a glycogen-sparing effect [15, 23, 50, 60, 113]. The evidence for and against this hypothesis is considered in detail below.

In apparently the first study to directly examine the effects of CHO ingestion on muscle glycogen use during exercise, Hargreaves et al. [60] reported that feeding subjects 43 g of sucrose every hour during 4 hr of intermittent cycling exercise decreased net glycogen degradation in the vastus lateralis from 126 ± 5 (X ± S.E.) to 101 ± 10 mmol glucosyl units/kg wet muscle ($P < 0.05$). Interpretation of these results is confounded, however, by the fact that muscle glycogen concentration was significantly higher prior to the placebo trial compared to the CHO feeding trial. In fact, when the data are reanalyzed excluding the four subjects with the largest intertrial difference in pre-exercise glycogen stores (20–63% higher prior to their placebo trial), the difference in glycogen utilization between trials is almost completely eliminated. Thus, the apparent sparing of glycogen in this study appears to be an artifact of the higher pre-exercise glycogen concentration in the placebo trial.

Soon after, Bjorkman et al. [15] measured muscle glycogen concentration and performance time in moderately trained men exercising to fatigue at 68% $\dot{V}O_2max$ when fed a placebo, glucose, or fructose throughout exercise. Muscle glycogen concentration decreased similarly in all three trials. However, because the time to fatigue was significantly longer during the glucose feeding trial, the researchers concluded that glucose ingestion decreased the rate of glycogen degradation during exercise. Simard et al. [113] reached a similar conclusion when glycogen degradation was expressed relative to the distance skated during a hockey match. Yet when muscle glycogen is measured in serial biopsies throughout exercise with and without CHO ingestion, no difference in the rate of glycogen utilization is observed [41]. The apparent sparing of muscle glycogen reported by Bjorkman et al. [15] and Simard et al. [113] therefore appears to be due to the greater quantity of exercise made possible by ingesting CHO during exercise, and not to a decrease in the actual rate of glycogenolysis.

Brouns et al. [23] also concluded recently that CHO ingestion during exercise decreases the utilization of muscle glycogen. In these experiments, however, muscle glycogen concentration was measured at rest

on one day, and after exercise four days later. In the interim, the subjects (highly trained cyclists) performed two bouts of very strenuous exercise, and ingested extra CHO not only during the exercise itself but also between exercise bouts. It is impossible to determine from this design whether the higher glycogen level observed after exercise when consuming a CHO supplement was caused by a decrease in the rate of glycogen utilization during exercise, or was the result of higher preexercise glycogen levels from an accelerated rate of glycogen resynthesis between exercise bouts.

Definitive evidence of glycogen sparing would require demonstrating that, when preexercise muscle glycogen concentration and the duration of exercise are the same, postexercise muscle glycogen concentration is significantly higher when fed CHO during exercise. To date, in at least seven studies muscle glycogen concentration has been measured before and after exercise of the same duration, performed with and without CHO supplementation during exercise [41, 50, 53, 55, 61, 91, 100]. In six of these studies [41, 53, 55, 61, 91, 100] in which a total of 85 subjects were examined, CHO ingestion had no effect on the decrease in muscle glycogen during exercise. In contrast, Erickson et al. [50] reported that muscle glycogen utilization was significantly reduced when five trained cyclists ingested 70 g of glucose during 90 min of exercise at 65–70% $\dot{V}O_2$max. These results, however, like those of Hargreaves et al. [60], appear to be due to higher preexercise muscle glycogen levels in the control trial, rather than a decrease in the rate of glycogen utilization when fed CHO during exercise.

A review of the literature indicates that CHO ingestion during continuous, moderate-intensity exercise does not reduce the utilization of muscle glycogen. In contrast, some evidence suggests that intravenous glucose infusion during exercise may decrease the rate of muscle glycogenolysis [7, 13, 125]. These studies, however, have generally provided glucose at rates that produced significant hyperglycemia, therefore possibly resulting in a greater impetus to decrease muscle glycogenolysis during exercise.

To address this possibility, we recently measured muscle glycogen utilization in eight men during 2 hr of continuous exercise at 73% $\dot{V}O_2$max, when glucose was infused throughout exercise at a rate which elevated and then maintained blood glucose at 10.8 ± 0.4 mmol/L [42]. This required the infusion of glucose at an average rate of ≈2 g/min. Despite this high rate of glucose infusion and an increase in blood insulin concentrations during the second hour of exercise to 20–25 μU/mL, muscle glycogen degradation was unaffected (glycogen utilization averaged 76 ± 7 mmol glucosyl units/kg wet muscle during the control trial vs. 75 ± 8 mmol glucosyl units/kg wet muscle during the glucose infusion trial). Thus, increasing blood glucose to ≈10 mmol/L during

continuous exercise at 70–75% $\dot{V}O_2$max does not reduce utilization of muscle glycogen in humans.

Nevertheless, the decline in muscle glycogen during exercise appears to be attenuated in men when the exercise is intermittent and glucose is infused at higher rates that result in greater hyperglycemia [13]. This may be the result of stimulation of glycogen resynthesis, which may occur either during rest periods between exercise bouts or even during exercise itself [19, 33, 49, 65, 68, 81–83, 118]. However, in glycogen-depleted men fed large amounts of CHO during mild exercise, net glycogen accumulation occurs only in Type II fibers, and not in Type I fibers [82]. Thus, glycogen synthesis during exercise following CHO ingestion appears to occur primarily in resting muscle fibers within the exercising muscle, rather than in exercising muscle fibers themselves. It therefore seems unlikely that CHO ingestion during continuous, moderate-intensity exercise could decrease net muscle glycogen utilization by inducing glycogen synthesis, because most muscle fibers are recruited during this type of exercise [120]. Net glycogen sparing due to glycogen synthesis during exercise may still be a possibility, however, when subjects are fed CHO during low-intensity or intermittent exercise.

Effect of CHO Ingestion on Hepatic Glycogenolysis and Gluconeogenesis During Exercise

In contrast to the lack of effect of CHO ingestion during exercise on muscle glycogen metabolism, hepatic CHO metabolism appears to be affected by CHO supplementation during exercise. Liver glycogenolysis has been shown to be reduced when exercising rats are infused with glucose during mild exercise [7]. Furthermore, the uptake of gluconeogenic precursors by the splanchnic bed has been shown to be greatly reduced when men ingest CHO during low-intensity exercise [3]. These effects are probably mediated by the accompanying hormonal responses of CHO ingestion during low-intensity exercise (i.e., increased insulin and decreased glucagon and epinephrine concentrations [3]).

The effects of CHO ingestion on hepatic glucose metabolism during moderate-intensity exercise are less certain. However, it appears that ingested CHO can at least partially replace the liver as the source of glucose entering the circulation. For example, glucose ingested during exercise at 50–72% $\dot{V}O_2$max has been demonstrated to supply up to two-thirds of the circulating glucose pool [35, 117]. Because the total glucose mass increases only slightly following CHO ingestion during moderate-intensity exercise (as indicated by relatively small increases in blood glucose concentration), these observations suggest that hepatic glycogenolysis or gluconeogenesis, or both, must be reduced. Similarly, glucose infusion during moderate-intensity exercise has been demonstrated to at least partially suppress glucose production in both rats [125] and humans [51, 73]. When hepatic glycogen stores become

depleted late in exercise, ingested CHO will represent almost the sole source of blood glucose supply, because the rate of gluconeogenesis in exercising humans seems to be limited to at most 0.2–0.4 g/min [2, 4], and appears to be suppressed by CHO ingestion [3].

EFFECTS OF PERFORMANCE

Early Evidence That CHO Ingestion May Aid Performance

As previously discussed, during the 1970s it was generally believed that CHO ingestion during prolonged exercise would be of little benefit to performance except in persons suffering from neuroglucopenia [36, 117]. This was true despite preliminary attempts to address this question that suggested otherwise [22, 59, 69, 93]. For example, in 1972 Green and Bagley [59] fed subjects either a placebo or a total of 230 g of maltodextrins before and during a ≈2.5 hr canoeing race. CHO ingestion before and during exercise increased blood glucose concentration above preexercise levels, whereas blood glucose decreased moderately (by 1–1.5 mmol/L) during exercise when fed the placebo. CHO ingestion also permitted the athletes to maintain their pace during the final ≈30 min of the race; during the same time in the placebo trial they were forced to reduce their pace by ≈10–15%. The average difference in overall performance time in this study, however, was very small (2%) and not statistically significant.

In a follow-up study, Brooke et al. [22] reported that blood glucose concentration and the rate of CHO oxidation were well maintained during 3 to 4 hr of cycling at 67% $\dot{V}O_2$max when trained cyclists ingested 90 g of CHO in the form of either maltodextrins or rice pudding plus sucrose every 20 minutes during exercise. In contrast, both blood glucose concentration and the rate of CHO oxidation declined when the subjects consumed a low-energy drink or nothing at all during two other trials. These authors reasoned that ". . . muscle glycogen must be reduced considerably and the only way of maintaining such a high CHO participation is by use of the blood glucose." These observations and this interpretation are generally supported by our more recent findings [28, 41], as discussed below. In addition, Brooke et al. [22] reported that the "work time cut-off" averaged 148 ± 13 min when completely fasted, 180 ± 19 min when fed the low energy drink ($P < 0.10$ vs. fasted), 200 ± 16 min when fed rice pudding plus sucrose ($P < 0.01$ vs. fasted), and 214 ± 14 min when fed maltodextrins ($P < 0.01$ vs. fasted; $P < 0.05$ vs. the low energy drink). Interpretation of these results is confounded because the subjects' performance time appears to have been defined by a decrease in R or blood glucose, or both, below a certain level, rather than by the inability of the subjects to continue exercising. Furthermore, $\dot{V}O_2$ varied considerably between

and within trials, suggesting that the exercise intensity may have been inadequately controlled. Despite these limitations, this study [22] suggested that CHO feedings during prolonged exercise could potentially delay fatigue, and that this was associated with the maintenance of blood glucose concentration and the rate of CHO oxidation.

A further indication that CHO ingestion may improve endurance performance was provided by Ivy et al. [69], who had trained cyclists attempt to maximize their average power production during 2 hr of exercise on a hydraulically braked cycle ergometer. The cyclists ingested ≈13 g of maltodextrins immediately prior to and every 15 min during the first 90 min of exercise during one trial, whereas they ingested a placebo at these time points during another trial. CHO ingestion did not significantly affect the average power produced during the entire 2 hr of exercise. During the last 30 min of exercise, however, when fed CHO the subjects were able to increase their power output during this time period when fed the placebo. It was not specified whether these differences in power output late in exercise were statistically significant.

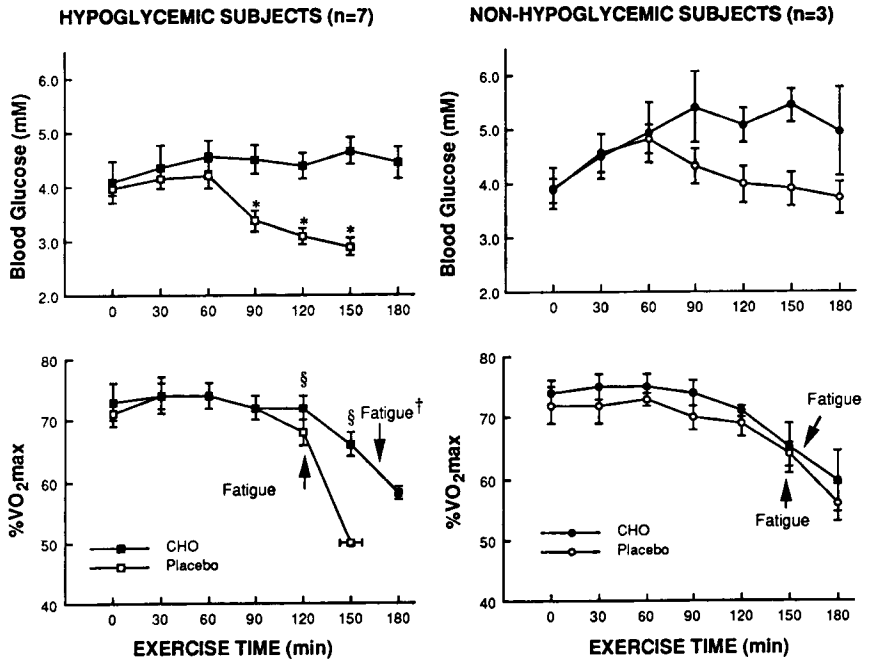
In contrast, Felig et al. [52] observed only small (+7 to +13 min), insignificant increases in time to fatigue during cycle ergometer exercise at 60–65% $\dot{V}O_2$max when subjects ingested either 10 g or 20 g of glucose instead of a placebo every 15 min during exercise. The subjects in this study, however, were not experienced cyclists and showed great variability in their exercise performances owing to motivation or learning effects. This variability may have obscured any potential improvement in performance as a result of ingesting CHO during exercise.

Studies by the Authors

Green and Bagley [59], Brooke et al. [22], and Ivy et al. [69] suggested, but did not prove, that CHO ingestion may potentially enhance performance during prolonged (≥2 hr) moderate-intensity exercise. To address this question, we had experienced cyclists exercise at ≈74% $\dot{V}O_2$max for as long as possible on two occasions [38]. When the subjects were no longer able to maintain this exercise intensity, they were permitted to reduce their exercise intensity to the highest level they could maintain for at least another 10 min. Fatigue was defined as the time when they were forced to reduce their exercise intensity by 10% of $\dot{V}O_2$max below their initial level (i.e., from ≈74% $\dot{V}O_2$max to ≈64% $\dot{V}O_2$max). Both trials were performed after an overnight fast in order to minimize the acute effects of the last meal on exercise metabolism [40, 92]. During one trial, the subjects ingested 1 g of maltodextrins/kg body weight in a 50% solution after 20 min of exercise, and an additional 0.25 g of maltodextrins/kg body weight in a 6% solution after 60, 90, and 120 min of exercise. During another trial, they received equal volumes of an artificially sweetened and flavored placebo.

CHO ingestion significantly delayed fatigue by 23 min (i.e., from 134

FIGURE 1.3
*Blood glucose concentration and exercise intensity during prolonged exercise by ten cyclists receiving either a placebo or CHO feedings throughout exercise. The seven subjects who became hypoglycemic (blood glucose < 3 mmol/L) during exercise when fasted were able to exercise significantly longer when fed CHO throughout exercise (i.e., 159 ± 6 min CHO vs 126 ± 3 min Placebo; † P < 0.001). Fatigue was not delayed in the three subjects who did not demonstrate a significant decrease in blood glucose concentration during their placebo trial (i.e., 153 ± 14 min CHO vs 150 ± 9 min Placebo). * Blood glucose concentration significantly (P < 0.05) lower than before exercise as well as significantly lower than CHO. § Exercise intensity significantly higher during CHO. (Reprinted with permission from Coyle, E.F., J.M. Hagberg, B.F. Hurley, W.H. Martin, A.A. Ehsani, and J.O. Holloszy. Carbohydrate feedings during prolonged strenuous exercise can delay fatigue.* J. Appl. Physiol. *55:230–235, 1983.)*



± 6 min to 157 ± 5 min; P < 0.01) for the entire group of 10 subjects. However, as shown in Figure 1.3, this effect was evident only in the seven subjects who experienced a decline in blood glucose concentration to below 3 mmol/L during their placebo trial; in these subjects fatigue was delayed by an average of 33 min (i.e., from 126 ± 3 min to 159 ± 6 min; P < 0.001). This decrease in blood glucose was associated with symptoms of neuroglucopenia in only two of these persons, whereas

the other five subjects complained primarily of severe weariness in the exercising muscles as the cause of fatigue. Fatigue was not delayed in the three subjects whose blood glucose concentration did not decline during their placebo trial (Fig. 1.3). To our knowledge, this was the first study to conclusively demonstrate that CHO ingestion during exercise can delay fatigue and improve performance in people not suffering from neuroglucopenia. Furthermore, this effect appeared to be due to prevention of a decline in blood glucose to levels which, although not associated with symptoms of neuroglucopenia in most of the subjects, apparently contributed to local muscular fatigue during the latter stages of prolonged exercise. At the time, however, we incorrectly interpreted these observations to suggest that CHO ingestion during prolonged exercise improves performance by delaying muscle glycogen depletion [38, 39].

To test this hypothesis, we first measured muscle glycogen concentration in the vastus lateralis before and after 105 min of cycling at 71% $\dot{V}O_2$max with and without CHO ingestion throughout exercise. No differences in glycogen utilization were observed [41]. Thinking that CHO feedings may spare muscle glycogen only late in exercise, we next obtained muscle biopsies from another group of cyclists at rest, after 120 min of exercise at 71% $\dot{V}O_2$max, and at fatigue during both a placebo and a CHO ingestion trial [41]. Fatigue occurred after 181 ± 11 min of exercise when fed the placebo, whereas fatigue was delayed ($P < 0.01$) until 241 ± 20 min when fed CHO throughout exercise (i.e., 1 g of maltodextrins/kg body weight in a 50% solution after 20 minutes of exercise and 0.4 g maltodextrins/kg body weight in a 10% solution every 20 min thereafter). As shown in Figure 1.4C, however, the decline in muscle glycogen concentration during exercise was again similar both with and without CHO ingestion, with the additional 60 ± 16 min of exercise made possible by CHO ingestion accomplished without a further decrease in muscle glycogen.

The rate of total CHO oxidation was also similar during the first 2 hr of exercise in both trials (Fig. 1.4B). However, CHO oxidation began declining during the third hour of the placebo trial, at a time when muscle glycogen was low and blood glucose concentration was also declining (Fig. 1.4C and 1.4A). Blood glucose concentration and the rate of CHO oxidation eventually fell to 2.5 mmol/L and to <1.4 g/min, respectively, at the time of fatigue. Thus, the lowering of blood glucose during the latter stages of prolonged strenuous exercise appeared to play a major role in the development of muscular fatigue. Fatigue under these conditions was clearly preceded by a decline in CHO oxidation, which in turn was preceded by a decline in blood glucose to approximately 2.5–3.0 mmol/L.

In contrast, when blood glucose was maintained at 4–5 mmol/L through CHO ingestion, the high rate of CHO oxidation required by

FIGURE 1.4
Metabolic responses to prolonged cycling at 71% $\dot{V}O_2$max when fed a placebo or CHO every 20 minutes during exercise. **Panel A:** *Plasma glucose concentration.* **Panel B:** *Total CHO oxidation estimated from $\dot{V}O_2$ and R.* **Panel C:** *Glycogen concentration in the vastus lateralis muscle, reported both graphically and numerically.* * *Significantly lower ($P < 0.05$) than CHO. (Reprinted with permission from Coyle, E.F., A.R. Coggan, M.K. Hemmert, and J.L. Ivy. Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate.* J. Appl. Physiol. *61:165–172, 1986.)*

exercise at 71% $\dot{V}O_2$max (≈2 g/min) was also maintained, and the subjects were able to exercise strenuously for an hour longer (Fig. 1.4A & B). As described above, muscle glycogen concentration was already low after 3 hr of exercise and appeared to contribute little to this maintenance of CHO oxidation and exercise tolerance (Fig. 1.4C). It appears that other CHO sources, presumably blood glucose, were able to largely replace muscle glycogen in providing CHO for oxidation during the latter stages of exercise.

We reasoned that, if a decline in plasma glucose during prolonged, glycogen-depleting exercise contributes to fatigue by limiting CHO oxidation, it should be possible to increase CHO oxidation and reverse fatigue late in exercise under these conditions by restoring euglycemia. To test these hypotheses, the study illustrated in Figure 1.5 was performed. On three separate occasions, we had trained cyclists first exercise to fatigue at 70% $\dot{V}O_2$max after an overnight fast [28]. This required about 170 min and resulted in a reproducible decline in plasma glucose concentration (to 3–3.5 mmol/L) and in R (to 0.81) at fatigue (Exercise Bout 1, Fig. 1.5). In each trial, the subjects attempted to perform further exercise at the same intensity after a 20-minute rest period when one of three treatments was applied (Exercise Bout 2, Fig. 1.5).

In one trial, the subjects ingested a placebo solution at the end of Exercise Bout 1. Although plasma glucose concentration increased slightly during the rest period, plasma glucose decreased again during further exercise, and the subjects were able to tolerate only 10 ± 1 min of additional exercise (Fig. 1.5). The rate of CHO oxidation, as reflected by R (Fig. 1.5), did not increase from that observed at the end of Exercise Bout 1.

During a second trial, the subjects ingested 3 g of maltodextrins/kg body weight at the end of Exercise Bout 1. This initially increased plasma glucose concentrations and R during Exercise Bout 2 above the levels observed at fatigue in Exercise Bout 1 (Fig. 1.5). Plasma glucose concentration and R were not maintained, however, declining progres-

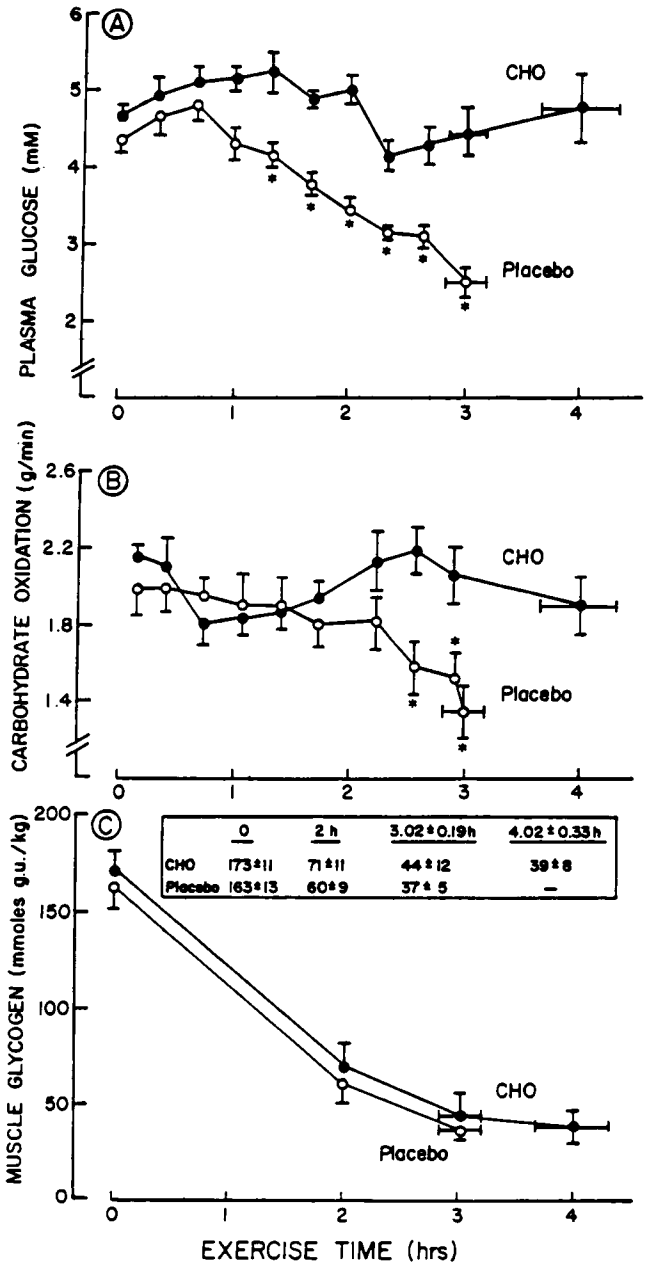
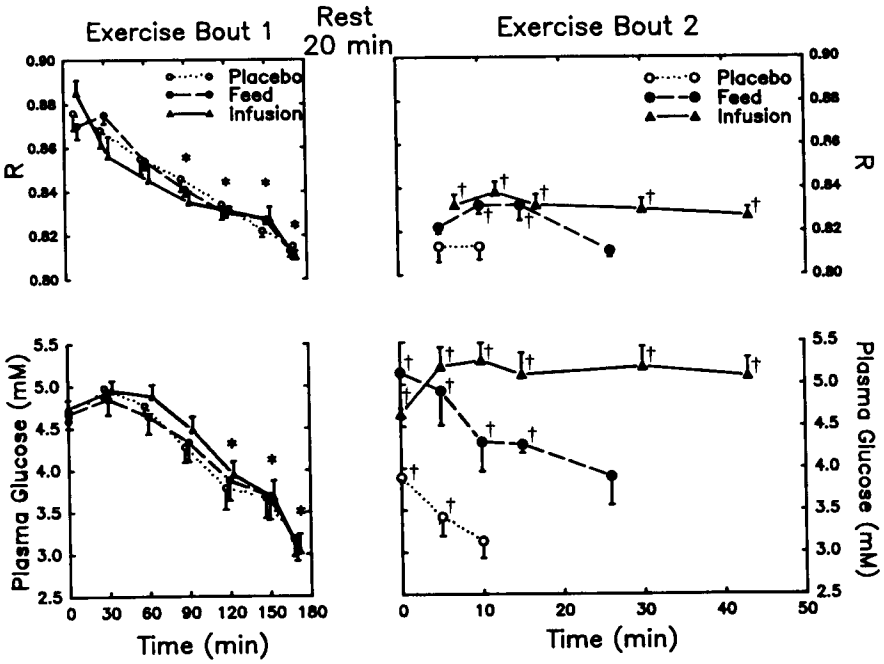

A
PLASMA GLUCOSE (mM)
CHO
Placebo
B
CARBOHYDRATE OXIDATION (g/min)
CHO
Placebo
C
MUSCLE GLYCOGEN (mmoles g.u./kg)
0 | 2 h | 3.02±0.19h | 4.02±0.33h
CHO 173±11 | 71±11 | 44±12 | 39±8
Placebo 163±13 | 60±9 | 37±5 | –
CHO
Placebo
EXERCISE TIME (hrs)

FIGURE 1.4

FIGURE 1.5
*Plasma glucose and R during prolonged cycling at 70% $\dot{V}O_2max$. During three trials, the subjects first exercised to fatigue while drinking only water (Exercise Bout 1). They then attempted to perform additional exercise at this intensity (Exercise Bout 2) after ingesting a placebo and resting 20 minutes (Placebo), after ingesting 200 g of maltodextrins and resting 20 minutes (Feed), or after resting 20 minutes and while glucose was infused intravenously at the rate required to maintain plasma glucose at ≈5 mmol/L (Infusion). The subjects were able to exercise significantly longer when glucose was infused (43 ± 5 min; P < 0.01) or when fed CHO (26 ± 4 min; P < 0.05) in comparison to when fed the placebo (10 ± 1 min). * Significantly lower (P < 0.05) than the initial value during Exercise Bout 1. † Significantly higher (P < 0.05) than the value observed at fatigue of Exercise Bout 1.*



sively until the subjects again fatigued, which occurred after 26 ± 4 min (P < 0.05 vs. placebo) (Fig. 1.5).

During a third trial, glucose was infused intravenously throughout Exercise Bout 2 using a syringe pump. The rate of glucose infusion was adjusted every 5 min during exercise to maintain plasma glucose concentration at ≈5 mmol/L. Restoration and maintenance of euglycemia in this manner increased and maintained R above the levels observed at fatigue during Exercise Bout 1 (i.e., 0.84 vs. 0.81; Fig. 1.5),

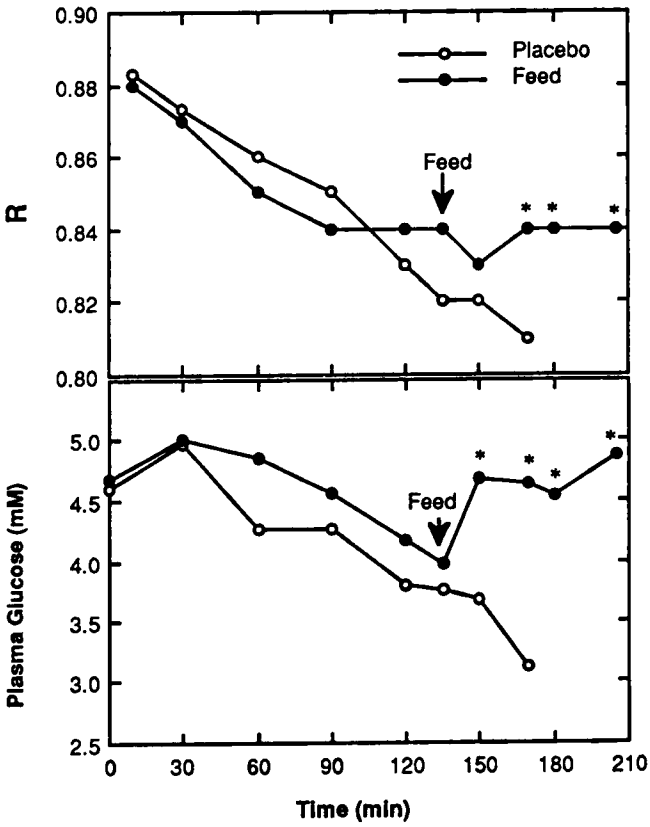
although R was still lower than observed at the beginning of Exercise Bout 1, when muscle glycogen was probably still high. Infusion of glucose also allowed the subjects to complete an additional 43 ± 5 min of exercise ($P < 0.01$ vs. both placebo and CHO ingestion at fatigue) (Fig. 1.5). As previously described, glucose had to be infused at over 1 g/min in order to maintain plasma glucose concentrations at ≈5 mmol/L. Because insulin concentrations remained low and muscle glycogen concentration did not change, the infused glucose was probably oxidized at this same high rate.

Finally, in a fourth trial, the subjects were provided with a single large CHO feeding (3 g maltodextrins/kg body weight) during Exercise Bout 1 after 135 min of exercise [30]. This large CHO load reversed the gradual decrease in plasma glucose and R values (Fig. 1.6), similar to glucose infusion or CHO ingestion at fatigue. Unlike ingesting CHO at fatigue, however, ingesting CHO late in exercise was able to maintain plasma glucose and R during additional exercise, thereby delaying fatigue by 36 ± 10 min ($P < 0.01$).

The above observations form the basis for our model regarding the mechanism by which CHO feedings improve performance during prolonged intense exercise [41]. This model is summarized in Figure 1.7, which depicts the relative contributions of muscle glycogen and blood glucose to energy production during prolonged strenuous exercise when fasted or when ingesting CHO throughout exercise. The percent of total energy derived from CHO oxidation was determined from R. The contribution of muscle glycogen has been estimated using the rate of decline in glycogen measured in the vastus lateralis [41] and by assuming that this reflects the response in a total of 10 kg of muscle. The difference between the rate of total CHO oxidation and muscle glycogen utilization presumably reflects primarily the oxidation of blood glucose. Although the relative contributions of muscle glycogen and blood glucose to total CHO oxidation vary depending on the muscle mass that is used in these calculations, the pattern of response (i.e., steadily decreasing reliance on muscle glycogen and steadily increasing reliance on blood glucose) remains the same.

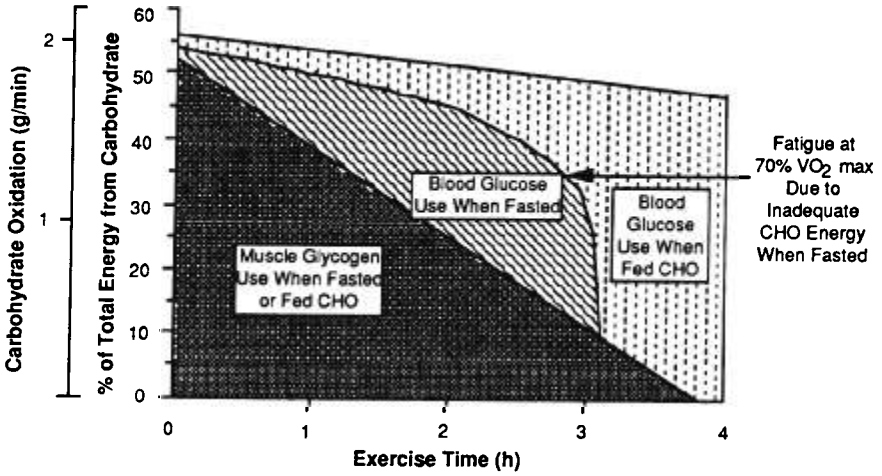
We interpret Figure 1.7 as follows. During the initial ≈2 hr of exercise at ≈70% $\dot{V}O_2max$, substrate utilization is generally similar both with and without CHO ingestion, although the ingested CHO may partially or completely replace hepatic glycogenolysis or gluconeogenesis as the source of blood glucose [3, 35, 117]. When no CHO is consumed, blood glucose concentration decreases late in exercise, at a time when muscle glycogen is already low. This decline in blood glucose apparently prevents glucose oxidation from increasing sufficiently to offset the reduced contribution of muscle glycogen, resulting in fatigue due to an inadequate rate of CHO oxidation. CHO ingestion, by maintaining blood glucose at 4–5 mmol/L during the latter stages of exercise, allows

FIGURE 1.6
*Plasma glucose and R during prolonged cycling at 70% $\dot{V}O_2max$. The subjects ingested either a placebo or 200 g of maltodextrins after 135 minutes of exercise ("Feed"), which was approximately 30 minutes before the anticipated time of fatigue during the placebo trial. The subjects were able to exercise significantly longer when fed CHO compared to when fed the placebo (205 ± 17 vs 169 ± 12 min; $P < 0.01$). * Significantly higher ($P < 0.05$) during Feed. (Reprinted with permission from Coggan, A.R., and E.F. Coyle. Metabolism and performance following carbohydrate ingestion late in exercise.* Med. Sci. Sports Exerc. *21:59–65, 1989.)*



for a progressive increase in blood glucose oxidation to the point where it supplies nearly all of the CHO energy required during exercise. As previously discussed, substantial evidence exists that blood glucose can contribute a major proportion of the CHO energy required during prolonged moderate-intensity exercise. Indeed, when blood glucose

FIGURE 1.7
The authors' model of the percentage of energy and the absolute rate of CHO oxidation derived from various sources during prolonged cycling at 70–75% $\dot{V}O_2max$ when fasted or when fed CHO throughout exercise. The rate of muscle glycogen utilization during exercise is the same when fasted or when fed CHO. As the duration of exercise increases, progressively less energy is derived from muscle glycogen and progressively more is derived from blood glucose. During the first 2 hours of exercise, substrate utilization is generally similar when fasted or when fed CHO. However, fatigue occurs after 3 hours of exercise when fasted owing to an insufficient rate of CHO oxidation as a result of a decrease in blood glucose concentration. CHO ingestion prevents this decrease in CHO oxidation by maintaining blood glucose availability and allowing blood glucose oxidation to increase to the point where it accounts for almost all of the CHO being oxidized. Therefore, over the course of 4 hours of exercise when fed CHO, muscle glycogen and blood glucose each contribute approximately one-half of the CHO energy and thus should be considered as equally important substrates. Estimated blood glucose oxidation when fed CHO does not distinguish between endogenous and exogenous sources of glucose. For example, during the first 2 hours of exercise, it is likely that ingested CHO partially replaces endogenous blood glucose. (Reprinted with permission from Coyle, E.F., A.R. Coggan, M.K. Hemmert, and J.L. Ivy. Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. J. Appl. Physiol. *61:165–172, 1986.)*



concentration is maintained by CHO ingestion, muscle glycogen and blood glucose each contribute approximately one-half of the CHO energy during prolonged exercise and, therefore, should be considered as equally important substrates. Thus, it appears that CHO ingestion during prolonged exercise improves performance primarily by main-

taining blood glucose oxidation at sufficiently high rates late in exercise, as suggested over 50 years ago by Dill et al. [46].

Recent Studies by Others

The model developed above may explain many observations regarding the effects of CHO ingestion on exercise performance. For example, most studies that have reported that CHO ingestion during exercise improves performance have also observed that blood glucose concentration and the rate of total CHO oxidation gradually decrease during exercise performed without CHO supplementation after an overnight fast, but are maintained at higher levels when fed CHO throughout exercise [5, 22, 28–30, 38, 41, 48, 53, 59, 60, 69, 70, 90, 91]. This model may also explain why CHO ingestion during exercise fails to improve performance under certain conditions. CHO ingestion during exercise does not appear to be of benefit to individuals who, in the absence of CHO supplementation, are able to maintain adequate blood glucose concentrations [15, 38, 48]. CHO ingestion during exercise also appears to have less of an effect on performance when the exercise bout is $\leq$2 hr in duration [69, 89], probably because CHO availability usually does not become limiting during this time. If body CHO stores are reduced prior to the onset of exercise, however, CHO supplementation has improved performance during exercise of shorter duration (i.e., 60 min) [99].

Similarly, CHO ingestion also often has been ineffective in improving exercise performance during prolonged running [100, 110, 111]. This may be because blood glucose concentration does not appear to decrease as readily during prolonged running as it does during prolonged cycling [cf. 32 for discussion]; consequently, there may be less of a need for supplemental CHO. Williams et al. [124] observed, however, that blood glucose concentration decreased to $\approx$3.5 mmol/L and R fell to 0.86 by the end of a 30 kilometer (km) treadmill run when subjects were provided with only water to drink, whereas glucose ingestion throughout exercise maintained blood glucose at $\approx$5 mmol/L and R at 0.89–0.90. Consistent with the model developed above, the subjects were able to run significantly faster during the final 5 km when ingesting glucose.

In apparent conflict with this model, several recent studies have reported that CHO ingestion during exercise improves performance even when blood glucose availability and total CHO oxidation do not appear to have been especially limited during the placebo or control trial [43, 44, 90, 91, 95–97]. However, in all of these studies the improvement in exercise performance due to CHO ingestion was associated with a higher blood glucose concentration and a greater rate of total CHO oxidation, as predicted by the model. In addition, performance in these studies was defined as the ability to increase the exercise intensity above the control level, and not as the ability to

maintain a given exercise intensity for a longer period of time. Although blood glucose availability and total CHO oxidation may not have been limiting at the exercise intensity that the subjects were able to tolerate in the fasted state, they were apparently insufficient to support exercise at a higher intensity. When fed CHO during exercise, however, the increase in glucose availability and oxidation apparently permitted the subjects to increase their exercise intensity. We interpret these results to indicate that the effects of CHO ingestion during exercise are probably related more to relative changes in CHO availability and oxidation, rather than to some absolute level of blood glucose or CHO oxidation per se.

There appears to be an upper limit, however, to the exercise intensity that can be supported by the oxidation of blood glucose. We have observed that when trained cyclists are fed CHO throughout exercise that alternates every 15 min between 60% and (initially) ≈85% $\dot{V}O_2$max, after 2.5 hr of exercise the subjects were forced to reduce their exercise intensity to ≈75% $\dot{V}O_2$max [29]. This was accompanied by a reduction in total CHO oxidation to ≈2 g/min. Similarly, Davis et al. [43] observed that, even when fed CHO throughout exercise, after ≈2 hr of exercise at ≈75% $\dot{V}O_2$max, subjects are unable to increase their exercise intensity above this level during an additional ≈30 min of exercise. Although blood glucose can apparently be oxidized at much higher rates than previously believed possible, it still does not appear to able to supply all of the CHO energy required to support very intense, steady-state exercise [29]. When endogenous CHO stores are not depleted, however, increasing the availability of blood glucose by means of CHO ingestion during exercise may still supplement these existing stores sufficiently to increase CHO oxidation [18, 99] and to enhance performance during very high intensity exercise [53, 60, 99].

PRACTICAL APPLICATION

Type of CHO

Studies that have directly determined the effects of ingesting glucose compared to maltodextrins or sucrose during exercise, either alone or in combination, have found little difference among these CHO in their ability to maintain blood glucose concentration and CHO oxidation or to improve performance [22, 88, 97, 103]. Apparent exceptions to this conclusion have been observed in studies in which the amount as well as the type of CHO ingested have been altered [84, 89, 119]. This similarity in response between maltodextrins, sucrose, and glucose is probably related to the fact that all three types of CHO deliver glucose into the circulation at similar rates.

Maltodextrins have become a popular form of CHO for inclusion in

sports drinks. The gastric emptying rate of maltodextrins (in g of CHO/min) is generally similar to that of glucose [20, 67, 98, 103], although it has been reported that a 5% solution of maltodextrins may initially empty from the stomach at a slightly faster rate than a similar glucose solution [54]. Because maltodextrins are rapidly hydrolyzed in the small intestine and absorbed as glucose, it is not surprising that the metabolic responses to maltodextrin ingestion are similar to that of glucose. However, the osmolality of a maltodextrin solution is only approximately one-fifth that of an equally concentrated glucose solution, so that the ingestion of maltodextrins results in somewhat smaller gastric secretion and volume [54, 103]. Probably the major difference is that maltodextrins are not very sweet tasting; solutions containing $\geq$10% CHO are therefore more palatable for most people. In support of this, Rehrer et al. [109] have observed that cyclists expending 20 MJ of energy per day voluntarily ingest enough of a supplemental maltodextrin solution to maintain energy and nitrogen balance, but do not ingest enough of a 50% fructose solution. It seems likely that the cyclists became prematurely satiated when consuming the 50% fructose supplement because of the excessively sweet taste.

In contrast to these other sugars, the ingestion of fructose during prolonged exercise apparently does not improve performance [15, 97]. This may be a result of its slower rate of absorption from the gut and subsequent conversion to glucose in the liver. Fructose tends to result in lower blood glucose and insulin concentrations and lower rates of CHO oxidation in comparison to other types of sugars [15, 87, 88, 97]. Alternatively, the failure of fructose ingestion to improve performance may be due to the gastrointestinal distress that often accompanies the ingestion of large amounts of fructose [97].

Liquid Versus Solid CHO

Although at least two studies have compared the metabolic and performance effects of ingesting water plus CHO in solid form (i.e., candy bars) versus those of an artificially sweetened placebo drink during prolonged, intermittent exercise [53, 60], no direct comparisons between solid and liquid forms of CHO appear to have been performed. Because ingested CHO will be in a liquid or semiliquid state when leaving the stomach, however, and because an additional purpose of feeding during exercise is to supply the water needed to maintain hydration, there appears to be little reason to anticipate any physiological advantage to solid forms of CHO. Solid forms of CHO may be preferred by some exercising individuals, however, for reasons of satiety.

Timing of CHO Ingestion

In addition to using different types and forms of CHO, researchers also have employed a wide variety of CHO supplementation schedules

in studies in which the influence of CHO ingestion during exercise has been examined. The performance criteria as well as the training status of the subjects have also varied greatly from study to study. Direct comparisons among these various studies regarding the optimal timing of CHO ingestion during exercise are therefore difficult to make. However, as previously described, we have used four different means of supplying supplemental CHO during exercise to fatigue at 70–75% $\dot{V}O_2max$ [28, 30, 41]. The subjects in all of these studies were well-trained cyclists, and, in many cases, a single subject has been studied using three or even four of these treatments. Summarized in Table 1.1 are our observations of the additional length of time (in min) that exercise could be tolerated by each subject (1) when CHO was ingested throughout exercise, (2) when CHO was ingested 30 minutes prior to the anticipated time of fatigue, (3) when glucose was infused intrave-

TABLE 1.1
Comparison of the Length of Time (in min) that Fatigue is Delayed During Exercise at 70–75% $\dot{V}O_2max$ by Various Means of CHO Supplementation

	Treatment			
Subject Number	*CHO Ingestion Throughout Exercise*[a]	*CHO Ingestion 30 min Before Fatigue*[b]	*Intravenous Glucose Infusion at Fatigue*[c]	*CHO Ingestion at Fatigue*[d]
1			33	27
2		41	60	29
3		43	53	44
4		52	30	29
5		50	27	21
6		**−13**	50	21
7	**149**	46	47	11
8	63			
9	60			
10	47			
11	40			
12	36			
12	21			
X ± S.E. of all	60 ± 16	37 ± 9	43 ± 5	26 ± 4*
X ± S.E. without data shown in bold	45 ± 6	46 ± 2	43 ± 5	26 ± 4*

* Significantly less than all other treatments.
[a] Data from Coyle et al. [41]. Subjects ingested 1 g CHO/kg body weight after 20 minutes of exercise and 0.4 g CHO/kg body weight every 20 minutes thereafter.
[b] Data from Coggan and Coyle [30]. Subjects ingested 3 g CHO/kg body weight 30 minutes before the anticipated time of fatigue.
[c] Data from Coggan and Coyle [28]. After the subjects exercised to fatigue and then rested for 20 minutes, they resumed exercising while glucose was infused intravenously at the rate required to maintain plasma glucose at ≈5 mmol/L.
[d] Data from Coggan and Coyle [28]. After the subjects exercised to fatigue, they ingested 3 g CHO/kg body weight, rested for 20 minutes, then resumed exercising.

nously after fatigue had already occurred, or (4) when CHO was ingested after fatigue had already occurred. On average, little difference existed in the time that fatigue was delayed when the subjects were supplemented with CHO using the first three approaches. In fact, when two seemingly spurious individual responses in Table 1.1 are eliminated, all three methods of CHO supplementation appear to be able to delay fatigue by ≈45 min. Because fatigue is delayed just as much when CHO supplementation is withheld until late in exercise as when CHO is ingested throughout exercise, these observations support the concept that fatigue is delayed as a result of maintaining blood glucose availability and oxidation late in exercise, when muscle glycogen is low, and is not caused by a sparing of muscle glycogen throughout exercise.

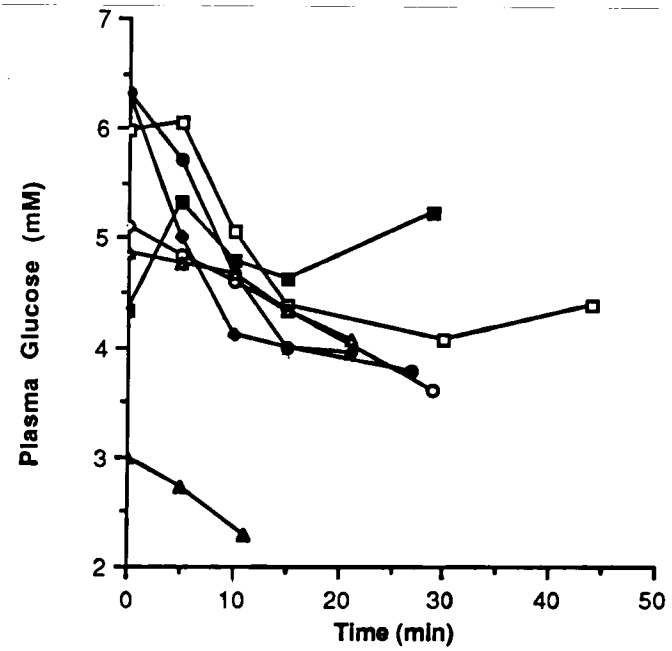
Nevertheless, as illustrated in Table 1.1 and Figures 1.5 and 1.8, CHO feeding at fatigue is usually not effective in restoring and maintaining blood glucose concentration or exercise tolerance [28, 116]. Individual subjects differed widely, however, in the extent to which CHO ingestion at fatigue was able to restore and maintain plasma glucose concentration and exercise tolerance. Several of the subjects were able to maintain euglycemia and a high rate of CHO oxidation for an additional 30 to 45 min of exercise after the large CHO feeding and 20 min of rest, whereas plasma glucose concentration and the rate of CHO oxidation decreased progressively during exercise in others (Fig. 1.8). On the other hand, CHO ingestion and 20 min of rest did little to raise plasma glucose concentration in some fatigued persons, the response of one of whom is shown in Figure 1.8. These results suggest that CHO ingested after fatigue has occurred may not be absorbed into the blood rapidly enough to match the rate at which glucose is removed from the circulation (i.e., at ≈1 g/min; see below).

Although it is possible to postpone CHO supplementation until later in exercise, and still delay fatigue, it is also possible to delay CHO ingestion too long, and fail to enhance performance. It is also important to keep in mind that these results apply to continuous exercise performed at 70–75% $\dot{V}O_2$max. As previously discussed, it is theoretically possible that CHO supplementation at high rates throughout intermittent or low-intensity exercise may potentially promote glycogen resynthesis in resting muscle fibers [33, 49, 65, 82]. Under these conditions, CHO ingestion throughout exercise may prove more beneficial to performance than ingesting CHO only late in exercise. This has yet to be demonstrated experimentally, however.

Rate of CHO Ingestion

Based on the rate of intravenous glucose infusion required to restore and maintain blood glucose availability and CHO oxidation late in

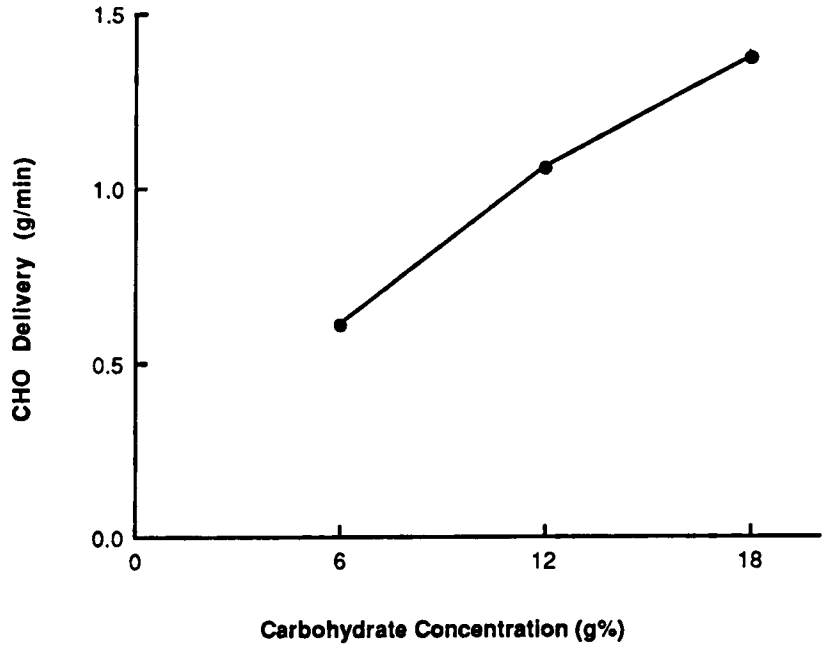
FIGURE 1.8
Plasma glucose concentration in individual subjects during Exercise Bout 2. As shown in Figure 1.5, the subjects first exercised to fatigue at ≈70% $\dot{V}O_2max$ (Exercise Bout 1), then ingested 200 g of maltodextrins and rested 20 minutes before performing Exercise Bout 2. Note the variation between subjects in their ability to maintain plasma glucose concentration during Exercise Bout 2 as well as differences in their time to fatigue. (Reprinted with permission from Coggan, A.R., and E.F. Coyle. Reversal of fatigue during prolonged exercise by carbohydrate infusion or ingestion. J. Appl. Physiol. *63:2388–2395, 1987.)*



exercise [28], trained cyclists need to ingest sufficient supplemental CHO to supply the blood with exogenous glucose at approximately 1 g/min late in exercise, at least during continuous exercise at 70–75% Vo_2max. Because fatigue is delayed by ≈45 min, this amounts to a total of ≈45–60 g of glucose. As discussed above, it does not appear to be critical whether this demand is met by ingesting small amounts of CHO throughout exercise or by ingesting larger amounts late in exercise. To ensure that 45–60 g of exogenous glucose are readily available late in exercise, however, it seems that large amounts of CHO must be ingested.

It is clear that the two most important factors determining the rate at which a CHO solution is emptied from the stomach are the CHO concentration and the volume of solution ingested [20, 54, 67, 90, 109].

FIGURE 1.9
The average rate of emptying of CHO from the stomach during 2 hours of exercise when ingesting 600 mL/h of solutions containing 6, 12, and 18 g of CHO/100 mL (g%). *(Reprinted with permission from Mitchell, J.B., D.L. Costill, J.A. Houmard, W.J. Fink, R.A. Robergs, and J.A. Davis. Gastric emptying: influence of prolonged exercise and carbohydrate concentration.* Med. Sci. Sports Exerc. *21:269–274, 1989.)*



Mitchell et al. [90] have clearly demonstrated that when 600 mL of solution are ingested per hour, the rate of CHO delivery to the small intestine during exercise increases in proportion to the CHO concentration (Fig. 1.9). Figure 1.9 also indicates that it is possible to empty CHO from the stomach at ≥1 g/min when solutions containing ≥12% CHO are consumed. This agrees with our observations that by ingesting 400 mL of a 50% maltodextrin solution approximately 30 min before the time of fatigue when fasted, subjects were able to exercise an additional ≈45 min (i.e., ≈75 min beyond the time of ingestion) [30]. Presumably the presence of this large volume of concentrated CHO was able to provide CHO to the intestines at ≥1 g/min late in exercise. Therefore, if CHO supplementation is withheld until late in exercise, it appears that sufficient volumes (≥400 mL/h) of relatively concentrated (10–50% CHO) solutions should be ingested.

In the majority of studies in which CHO ingestion throughout exercise was shown to improve performance, subjects were provided with 25–60 g of CHO/h [15, 29, 38, 41, 60, 69, 70, 95–97, 124]. Although the extent to which this ingested CHO replaces endogenous blood glucose oxidation, is stored, or remains unabsorbed is not known, it does appear that these rates of supplementation have been sufficient to provide the additional 45–60 g of CHO required to maintain blood glucose oxidation late in exercise. Neither the minimal nor the optimal rate of CHO ingestion throughout exercise needed to improve performance has been systematically determined. It is likely that these rates will differ depending on the criteria used to assess performance. It should also be recognized that there are substantial intraindividual differences in the quantity of CHO required to maintain blood glucose availability and oxidation during prolonged exercise. As indicated previously, some subjects are apparently able to exercise for prolonged periods without evidence of a decrease in blood glucose concentration [15, 38, 48], whereas other individuals appear to rely on blood glucose to a greater extent during exercise [31] and are therefore particularly susceptible to a decline in blood glucose concentration.

UNANSWERED QUESTIONS

Although the model developed in this chapter appears to explain the mechanism by which CHO ingestion during exercise enhances performance, a number of unanswered questions remain. For example, the model we have presented predicts that, during prolonged exercise in the fasted state, the ability of the exercising muscles to resynthesize adenosine triphosphate (ATP) becomes insufficient when CHO availability decreases late in exercise. There is evidence to support this hypothesis [21, 64, 101, 102]. Presumably, CHO ingestion throughout or late in exercise enhances performance by maintaining or restoring the rate of ATP production. However, this latter hypothesis has yet to be verified experimentally.

It is also not certain whether CHO ingestion during exercise enhances blood glucose utilization only during the later stages of exercise, by merely maintaining blood glucose concentration, or whether CHO ingestion increases blood glucose utilization throughout exercise. It is theoretically possible, for example, that the small differences in insulin and FFA concentrations that result from CHO ingestion during moderate-intensity exercise cause an increase in glucose oxidation throughout exercise, which contributes to the enhancement in exercise capacity. An argument in favor of this possibility is the fact that fructose ingestion throughout exercise, which maintains blood glucose concentration but has less of an effect on insulin or FFA levels than does the ingestion of

glucose, maltodextrins, or sucrose, fails to improve performance [15, 97]. An argument against this hypothesis is that CHO ingestion throughout exercise at 70–75% $\dot{V}O_2$max appears to have very little effect on substrate utilization during the first 2 to 2.5 hr of exercise, when blood glucose concentrations are similar to those observed in the fasted state, even though insulin and FFA concentrations differ [38, 41]. Furthermore, subjects who do not show a decrease in blood glucose concentration during prolonged exercise at 70–75% $\dot{V}O_2$max performed in the fasted state do not appear to benefit from CHO feedings [15, 38, 48, 110, 111]. This is true even though changes in insulin and FFA in response to CHO ingestion in these subjects are similar to those in men who do benefit from CHO ingestion [38]. Finally, CHO ingestion or infusion late in exercise increases blood glucose concentration and total CHO oxidation and enhances performance without measurably altering insulin or FFA concentrations [28, 30]. Nevertheless, the possibility remains that very small but physiologically significant changes in insulin and FFA may contribute to the maintenance of CHO oxidation and the enhancement of performance as a result of CHO ingestion during exercise.

Perhaps the most important remaining question concerns the cause of fatigue during exercise when blood glucose concentration is maintained by feeding CHO during exercise. Based on R values, although the estimated rate of CHO oxidation is low, it does not appear to decrease prior to fatigue when receiving CHO supplementation (Fig. 1.7). This could be interpreted to suggest that, because CHO availability is not limiting, other causes of fatigue have emerged. Many possibilities exist, including depletion of muscle potassium [114], a decrease in force-generating capacity at the myofibrillar level [122], or fatigue of neural origin [121]. Alternatively, Figure 1.7 raises the possibility that, although relative contribution of muscle glycogen to energy production is small during the hours prior to fatigue, fatigue during exercise when fed CHO occurs at the same general time that this contribution becomes zero. It is therefore possible that, although blood glucose appears to be able to supply almost all of the CHO required during moderate intensity exercise, some small but critical requirement for muscle glycogen exists. If so, CHO availability may indeed eventually become limiting even when fed CHO throughout exercise, even though this limitation is too small to be manifested by changes in R.

Further experimentation will obviously be required to answer these questions. The point of such speculation, however, is to emphasize that this experimental model could be helpful in designing future studies of the causes of fatigue during prolonged exercise. CHO ingestion during exercise, by providing a means of altering CHO availability, will continue to be a useful tool in attempting to answer these questions.

SUMMARY

It is well recognized that energy from CHO oxidation is required to perform prolonged strenuous (>60% $\dot{V}O_2$max) exercise. During the past 25 years, the concept has developed that muscle glycogen is the predominant source of CHO energy for strenuous exercise; as a result, the potential energy contribution of blood glucose has been somewhat overlooked. Although during the first hour of exercise at 70–75% $\dot{V}O_2$max, most of the CHO energy is derived from muscle glycogen, it is clear that the contribution of muscle glycogen decreases over time as muscle glycogen stores become depleted, and that blood glucose uptake and oxidation increase progressively to maintain CHO oxidation (Fig. 1.7).

We theorize that over the course of several hours of strenous exercise (i.e., 3–4 h), blood glucose and muscle glycogen contribute equal amounts of CHO energy, making blood glucose at least as important as muscle glycogen as a CHO source. During the latter stages of exercise, blood glucose can potentially provide all of the CHO energy needed to support exercise at 70–75% $\dot{V}O_2$max if blood glucose availability is maintained. During prolonged exercise in the fasted state, however, blood glucose concentration often decreases owing to depletion of liver glycogen stores. This relative hypoglycemia, although only occasionally severe enough to result in fatigue from neuroglucopenia, causes fatigue by limiting blood glucose (and therefore total CHO) oxidation.

The primary purpose of CHO ingestion during continuous strenuous exercise is to maintain blood glucose concentration and thus CHO oxidation and exercise tolerance during the latter stages of prolonged exercise. CHO feeding throughout continuous exercise does not alter muscle glycogen use. It appears that blood glucose must be supplemented at a rate of $\approx$1 g/min late in exercise. Feeding sufficient amounts of CHO 30 minutes before fatigue is as effective as ingesting CHO throughout exercise in maintaining blood glucose availability and CHO oxidation late in exercise. Most persons should not wait, however, until they are fatigued before ingesting CHO, because it appears that glucose entry into the blood does not occur rapidly enough at this time. It also may be advantageous to ingest CHO throughout intermittent or low-intensity exercise rather than toward the end of exercise because of the potential for glycogen synthesis in resting muscle fibers. Finally, CHO ingestion during prolonged strenuous exercise delays by approximately 45 minutes but does not prevent fatigue, suggesting that factors other than CHO availability eventually cause fatigue.

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