Infectious disease-related differences in the adaptation of glucose metabolism to fasting in children and the effect of age
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Chapter 2

Glucose metabolism in children: influence of age, fasting and infectious diseases

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ABSTRACT

This review describes the occurrence of hypoglycemia in young children as a common and serious complication that needs to be avoided because of the high risk of brain damage and mortality. Young age, fasting and severe infectious disease are considered important risk factors. The limited data on the effect of these risk factors on glucose metabolism in children are discussed and compared to data on glucose metabolism in adults. The observations discussed may have implications for further research on glucose kinetics in young children with infectious disease.
INTRODUCTION

Glucose is one of the major fuels to meet the energy requirements of the human body. In the healthy individual the amount of glucose produced is regulated to the need of the body and more in particular to the need of its major user, the brain. Although the brain can also utilize lactate, ketone bodies and certain amino acids, its primary fuel is glucose (1). During fasting more than 90% of its energy is provided by glucose, making the brain highly vulnerable to alterations in the plasma glucose level (2). The child’s developing brain is more susceptible to hypoglycemia compared to the adult brain (3-7). Recurrent hypoglycemia may result in permanent neurological damage (4-6). It is therefore imperative to prevent the occurrence of hypoglycemia in children.

In the fasted state the plasma glucose level is maintained within narrow limits by a delicate balance between endogenous glucose production (EGP) and glucose utilization. The metabolic adaptation of glucose metabolism during fasting differs between children and adults (8). The traditional concept is that children have a limited tolerance of fasting since glycogen stores are less and therefore they are able to maintain a normal plasma glucose level for a fasting period of 12 hours only (9,10).

Starvation is an uncommon event in a healthy child’s life. However, many infectious diseases are characterized by starvation due to disease-induced anorexia as well as by cultural customs and traditional habits in disease (11-13). Hypoglycemia is a frequent but poorly explored feature of severe infectious diseases in children. This review gives an update of the available data on the effect of age and duration of fasting on glucose kinetics. Also differences between adults and children will be addressed to emphasize that data from studies with adult patients cannot be extrapolated to children.

DEFINITION OF HYPOGLYCEMIA

The plasma glucose concentration is the resultant of a tightly regulated balance between EGP and glucose utilization. A disturbance in this balance will lead to hyper- or hypoglycemia. Hypoglycemia in children remains one of the most controversial issues with regard to its definition, the mechanism of adverse effect on the brain, and the practical approach to monitoring, management and treatment (3,14). The definition of hypoglycemia can be based on clinical manifestations, on the range of glucose values measured in epidemiological studies, on metabolic and endocrine counterregulatory responses or on long-term neurological outcome, but none has been entirely satisfactory (15). Hypoglycemia in neonates is often defined as a plasma glucose concentration below 2.5 mmol/L (45 mg/dL) (16), while in older children the threshold of 3.0 mmol/L is often used (17), and in healthy adults 3.9 mmol/L (18), based on the initiation of the counterregulatory response (19). Most studies in infants and children up to 10 years of age show that hypoglycemia is often defined as a plasma glucose concentration below 2.5 mmol/L (45 mg/dL) (16).
age performed in tropical settings (16,20-26) use the WHO definition of hypoglycemia based on clinical and epidemiological data: < 2.2 mmol/L or 40 mg/dL (27).

THE INFLUENCE OF AGE AND FASTING ON GLUCOSE METABOLISM IN HEALTHY HUMANS

Hypoglycemia

Age is a risk factor for hypoglycemia. Studies in both healthy (9) and sick children (20,21,25,26,28) suggest a relationship between age and plasma glucose concentration. In healthy children fasting plasma glucose concentration increases progressively with age. In a study of 28 healthy children, aged 2 to 17 years, plasma glucose concentrations of below 2.7 mmol/l after a 24 hour fast were found only in younger children, while values of all children older than 10 years were in the normal adult range (9). Hypoglycemia is known to be particularly common in the very young children below the age of 3 years (25,27,28).

Fasting is considered a major risk factor for hypoglycemia in children. Healthy adults are able to maintain normal plasma glucose levels up to 86 hours of fasting (29). There are gender-related differences in the metabolic response to fasting in adults: plasma glucose concentrations are lower in women than in men after a 38 hour fast (30). During a fasting period of only 24 hours healthy pre-pubertal children show a significant steeper decrease in plasma glucose concentration than adults, and they are not able to maintain a plasma glucose concentration > 3.0 mmol/l (8,31,32). Indeed several studies suggest that fasting is a major factor in the occurrence of hypoglycemia in children and in adults since an association between the occurrence of hypoglycemia and the time since the last meal has been found (20,21,25,26,28,33-35). These studies indicate that young children probably have a higher risk for developing hypoglycemia when fasting compared to older children and adults.

This conclusion is supported by studies on lipolysis and ketogenesis. During fasting lipolysis increases, thereby providing the body with alternative fuel and delaying the occurrence of hypoglycemia. This is reflected by elevation of plasma concentrations of free fatty acids and ketone bodies, e.g. β-hydroxybutyrate and acetoacetate. After 30 hours of fasting plasma concentrations of ketone bodies reach levels in children that are seen in women only after a 3 day fast and that are never seen in men (8,31). This indicates that glycogen stores in children are depleted more rapidly than in adults and thereby their risk of developing hypoglycemia is increased.

In conclusion, young children are more at risk for developing hypoglycemia than older individuals especially in response to fasting.
Glucose production and utilization

Plasma glucose is derived from exogenous supply, e.g. enteral or parenteral nutrition, or from endogenous production. Glucose is produced mainly (~90%) in the liver by gluconeogenesis and glycogenolysis and to a smaller extent (~10%) in the kidney by gluconeogenesis only (36). Glucose can be oxidized and thereby used for energy supply in various tissues, it can be stored as glycogen in the liver and muscle, or stored as triglycerides in adipocytes (figure 1).

During fasting, plasma glucose is dependent on glucose production which consists of glycogenolysis, the breakdown of glycogen, and gluconeogenesis, the production of glucose from lactate, glycerol or several amino acids. Most studies on glucose kinetics in adults are performed after different periods of fasting, up to 86 hours. After an overnight fast EGP in healthy adults is approximately 11 µmol/kg•min (30,37). Prolongation of the fasting period from 16 to 22 hours results in a decline in EGP by ~20% (38) and is further reduced to one-third after 86 hours (10).

In healthy humans EGP decreases from infancy towards adulthood (32,39-64) (table 1). This decrease is related to the ratio of brain weight to body weight. The weight of the human brain increases 3.5-fold from birth (400 g) to adulthood (1400 g) whereas body weight increases more than 20-fold (31) which means a 6-fold decrease in the ratio of brain weight to body weight. Since the brain is a major user of glucose (65), young children meet up to these cerebral demands by producing relatively more glucose in relation to their body weight (17). This relationship of EGP to brain weight is found to be linear throughout life (32).
Studies on EGP in young healthy children can only be carried out during a restricted fasting period for ethical and safety reasons. The first published data are on 35 children aged between 1 month and 14 years after a 8-9 hour fast: mean EGP was 38 ± 1.4 µmol/kg•min in the 1 month to 6 years old and 29 ± 1.5 µmol/kg•min in the 6 to 14 years old children (32). Haymond et al. reported glucose production rates of 5 healthy children aged 4-8 years which declined from 35 to 23 µmol/kg•min after 14 and 30 hours of fasting respectively (56).

In conclusion, EGP is approximately 10-11 µmol/kg•min in adults after an overnight fast and decreases to minimally 4 µmol/kg•min depending on the duration of the fast. No prolonged fasting studies are performed in children or neonates for obvious ethical reasons. EGP ranges from 23-38 µmol/kg•min following short term fasting studies in infants and children. Age dependency of glucose production is the cause of this wide range.

Gluconeogenesis

Gluconeogenesis is the process in which glucose molecules are newly formed from lactate, glycerol or gluconeogenic amino acids, especially alanine and glutamine. In the postabsorptive state the estimated contribution of the gluconeogenic precursors to total glucose production is approximately 15% for lactate (66-70) and 2-4% for glycerol (71) which may increase to 22% after prolonged fasting due to accelerated lipolysis (72). Alanine accounts for 6-12% of glucose production in the postabsorptive state (73-75) and glutamine, the predominant substrate of gluconeogenesis in the kidney, contributes 5-8% (76-78).

Quantifying the contribution of gluconeogenesis to total glucose production is possible with techniques using stable isotopes (79). Using the deuterated-water method, the contribution of gluconeogenesis to total glucose production in healthy adults has been estimated at 47% after 14 hours, 67% after 22 hours and 92% after 42 hours of fasting (80). The absolute rate of gluconeogenesis is more or less constant, indicating that the decrease in EGP is solely due to a decrease in glycogenolysis. In healthy lean and obese pre-pubertal children and adolescents gluconeogenesis contributes 50-60% to EGP after an overnight fast, comparable with healthy adults (57,59,60).
During the first 86 hours of fasting EGP is not dependent on precursor supply in healthy adults, unless precursor supply drops more than 50%, a value in general not reached during this period (10). Studies measuring gluconeogenesis in non-fasted premature infants show that the availability of gluconeogenic substrates is not impaired (81). In conclusion, during short term fasting the contribution of gluconeogenesis to EGP increases and is comparable in adults and older children. Since absolute gluconeogenesis is constant, the decline in EGP is merely caused by decreased glycogenolysis.

Glycogenolysis and glycogen content

Glycogen is a glucose polymer which is stored mainly in the liver and muscle. The kidney does not store glycogen (82-84). Glycogenolysis or glycogen breakdown is the process of debranching glucose polymers to glucose. The liver is the major contributor to plasma glucose derived by glycogenolysis since myocytes lack glucose-6-phosphatase which dephosphorylates glucose-6-phosphate, an obligatory conversion enabling glucose to leave the cell and enter the blood (85). The glucose formed by breakdown of glycogen in muscle tissue is used as fuel supply for the myocyte itself.

Quantification of glycogen stores can be done by liver biopsy (86) but its use in humans for research purposes is limited for practical and ethical reasons. In vivo measurement of liver glycogen content by using $^{13}$C- nuclear magnetic resonance spectroscopy (NMR) is an alternative method (87). Data on the NMR technique in young children are scarce, partially because of its practical limitations since especially the younger children need to be sedated or narcotized. Furthermore, measurements using the NMR technique require equipment that is available in only a few centres in the world (79). The available data are mainly confined to non-fasted young children with disorders of carbohydrate metabolism (88-90).

A study in pre-pubertal children with type 1 diabetes mellitus reports that their ability to replenish glycogen stores after an overnight fast was as good as in healthy controls (91). Direct measurements with $^{13}$C NMR in adults show that liver glycogen stores decrease concomitantly with the decrease in glycogenolysis (87,92). These data indicate that glycogenolysis and liver glycogen content are correlated during fasting (93). As mentioned earlier, in healthy adults, EGP decreases with ~20% between 16 and 22 hours of fasting, which could not be contributed to a decrease in gluconeogenesis (94,95). The decline is explained by a decrease in glycogenolysis, as was shown in healthy adults using the $^{13}$C NMR technique: glycogenolysis accounts for 45 % of total glucose production during the first 6-12 hours of fasting (92), for 30% after 23 hours (96) and for 4% after 68 hours of fasting (87). A limitation of the NMR method is that it may underestimate the contribution of glycogenolysis to glucose production, since hepatic gluconeogenic flux into glycogen and glycogen turnover persist during fasting. Thus the contribution of glycogenolysis to glucose production is greater than the measured net glycogen loss (97).

Since the liver biopsy and NMR technique cannot readily be used in children, data on liver glycogen and glycogenolysis in children have to be derived from indirect sources.
A non-invasive approach to test the ability to release glucose from glycogen stores in young children is to measure the increase in EGP and plasma glucose concentration after a bolus glucagon, a method that is often used in clinical practice (98-101). In adults the response of EGP to a glucagon bolus is considered an indicator of glycogen content. The response of plasma glucose concentration to a glucagon bolus has been measured in healthy children aged 2-6 years after a 24 hour fast and showed that an increase in plasma glucose concentration of at least 50% in 30 min after the glucagon bolus is considered normal (102). However, these results have to be interpreted with caution because a subnormal response of plasma glucose concentration to glucagon is not always indicative of impaired glycogenolysis. Since a change in the plasma glucose concentration is not necessarily a good parameter for a change in EGP, more insight in glucose kinetics must be obtained by combining the glucagon test with stable isotope studies (103). This technique was used to measure EGP in response to glucagon in (preterm) infants (104-107) and in adults (97,108-110) showing a 4.5 fold and 9-fold increase in EGP respectively. In children merely case reports have been published on this subject (111,112).

In conclusion, measurements of glycogenolysis and glycogen stores in adults indicate that glycogenolysis and liver glycogen content are correlated during fasting. The decline in EGP during fasting is explained by a decrease in glycogenolysis ranging from 45 to 4% depending on the duration of the fast. The use of techniques to quantify glycogen stores in young children is limited and can best be done by combining the glucagon test with stable isotope studies: however, definitive data in children supporting this conclusion are scarce.

GLUCOSE METABOLISM IN MALARIA AND OTHER INFECTIOUS DISEASES

Hypoglycemia in infectious diseases

In children with infectious diseases such as severe falciparum malaria, hypoglycemia is a common and serious complication (113-116). Hypoglycemia occurs more frequently in children (up to 34%) (20,26,27,114,116) than in adults (8%) with malaria (117). Hypoglycemia is an important feature in children with malaria, because it predicts mortality (118,119). The mortality rate increases four- to six-fold in children with malaria complicated with hypoglycemia (20,118,119): 20-30% of the children admitted with malaria and suffering from hypoglycemia do not survive (120) compared to a mortality rate of 3.8% in normoglycemic children (20). Thus hypoglycemia is considered to be one of the major outcome predictors in children with severe malaria. The pathogenesis of hypoglycemia in malaria is still incompletely understood although several possible mechanisms have been identified. Increased glucose consumption by the malaria parasites is considered to be a contributing factor. Parasitized erythrocytes consume up to 30-75 times the quantity of glucose that non-infected cells require (121).
Its contribution to total human glucose need however is thought to be relatively modest, since the glucose demand of the severely ill patient is far greater than that of the parasites: glucose clearance rates increase 40-70% in severe malaria (122-124) and only 20% in non-severe malaria (35,125). Another well-known contributing factor is hyperinsulinemic hypoglycemia as a complication of quinine and quinidine in malaria treatment since quinine stimulates insulin release \textit{in vivo} (126,127).

Hypoglycemia does not only occur in children with malaria but is also seen in children with other infectious diseases, such as pneumonia and diarrhea, both in tropical (20,21,24,25,28,113,115) and in western countries (128,129). In a Kenyan study hypoglycemia occurred frequently in children with malaria (8.4%), but also in pneumonia (3.9%) and diarrhea (5.5%) (20). In Tanzanian children the frequency of hypoglycemia was similar in malaria (5.2%) and in other serious infectious illnesses (11.2%) (21), as was the case in Nigerian children where hypoglycemia occurred in 6.4% of children with malaria, sepsicaemia and pneumonia (28). The mortality rate of children with other infectious diseases is similar to that of children with malaria (table 2). Therefore hypoglycemia may not be a disease-specific symptom but may be regarded as a serious metabolic complication in acute severe infections in young children (20,21,25,28,115,130-132).

In conclusion, hypoglycemia is a common and serious complication in young children with malaria and other infectious diseases and markedly increases mortality rates.

**Glucose production and uptake in infectious disease**

Hyperglycemia is a common finding in sepsis and other acute infections (133), caused by an imbalance between alterations in glucose tissue uptake and glucose production (134-137). In septic adult patients EGP is doubled compared to healthy subjects (138,139). However, the increase in EGP does not invariably lead to hyperglycemia. Plasma glucose concentrations are sometimes within the normal range despite increased glucose production rates in patients with sepsis (140) and in adults with falciparum malaria (124,125). Infection with \textit{Plasmodium falciparum} results in an increase in EGP in adult patients with both non-severe and severe falciparum malaria (33,123,125,141). In adults with non-severe malaria EGP increases by 20% and plasma glucose concentrations are higher (but in the normoglycemic range) compared to healthy controls (125,141). In adults with severe malaria and adults with cerebral malaria EGP is doubled and plasma glucose concentration is approximately 40% higher than in healthy controls (124,123). In pregnant women, infection with \textit{Plasmodium falciparum} results in a 35% higher EGP after an overnight fast but the plasma glucose concentration is comparable with healthy pregnant controls (33).

These findings indicate that peripheral glucose uptake is sometimes increased in adult patients with certain infectious diseases. This may be the result of increased tissue insulin sensitivity. Under healthy conditions, insulin inhibits hepatic glucose production by decreasing both gluconeogenesis and glycogenolysis and stimulates peripheral glucose uptake (142-144). In most critically ill adult patients with sepsis and other acute infections,
glucose metabolism is disturbed, resulting in hyperglycemia and insulin resistance rather than hypoglycemia (133,137,144-146). Insulin resistance is defined as the relative inability of insulin to increase glucose uptake and utilization end/or to suppress glucose production (147) and typically presents with hyperglycemia despite “normal” or increased insulin levels (148), although during infections seemingly low insulin levels have been reported (149). During illness, these alterations in glucose metabolism may differ in children compared to adults (150). For instance, in children with meningococcal sepsis and shock, hyperglycemia and inadequate low insulin levels were found which is compatible with an insufficient insulin response (151,152), whereas in children with meningococcal sepsis without shock insulin resistance was found (151). This is in contrast with adults in whom normal or high insulin levels were found under those circumstances (153,154). It is not clear whether children and adults can reduce insulin production as an adaptive response to severe disease or whether this is a direct effect of a specific critical illness (153).

Data on glucose kinetics in children with acute infectious diseases are scarce. There are four studies that report on glucose production rates in children, all with malaria. Glucose production rate in Ghanaian children with severe malaria aged 11 months to 10 years after a 9 hour fast was 56 µmol/kg•min (155), 2 to 5 times higher than in fasted adults with severe malaria (123,124) and approximately twice the production in fasted children with non-severe malaria (156). The other three studies (156-158) report on Kenyan children with uncomplicated malaria and measured glucose production rates of 27 to 30 µmol/kg•min in children 2-10 years after 14-23 hours of fasting. Compared to healthy children these values are in the normal range for age (table 1).

Although data are limited and contradictory, glucose metabolism in children with malaria seems to be regulated differently than in adults. Severity of infection may be of influence on EGP although a possible correlation between EGP and glucose concentration was not investigated in the children with severe malaria (155). In children with uncomplicated malaria a correlation between EGP and glucose concentration was found (157), indicating that hypoglycemia may be caused by limited glucose production capacity. This
is in contrast with adults in whom peripheral uptake is more important (124,125). In adults with malaria peripheral glucose demands may increase considerably because of accelerated tissue metabolism (122,123), although there also is evidence of tissue insulin resistance in both uncomplicated and severe malaria (124). In conclusion, the limited data in children with malaria suggest that EGP is an important determinant of plasma glucose concentration, indicating that hypoglycaemia may occur as a result of impaired EGP. This is in contrast with adults in whom EGP is often increased during severe illness with glucose concentrations in the normoglycemic range suggesting that peripheral uptake of glucose is facilitated.

Gluconeogenesis in infectious disease

Only one study measured endogenous glucose production and gluconeogenesis in children under five years of age with an infectious disease: in Kenyan children aged 2 to 6.5 years with non-severe malaria fractional gluconeogenesis was 73% after 8 hours of fasting (156). In comparison: gluconeogenesis contributed for ~87% of glucose production in Vietnamese adults with uncomplicated malaria after a seven hour fast (125) and for ~75% in pregnant women with uncomplicated falciparum malaria after a 24 hour fast (33). In adults with cerebral malaria EGP was completely (100%) derived from gluconeogenesis after a 20 hour fast (123). These findings indicate that in adults with malaria the contribution of gluconeogenesis to glucose production increases with severity of disease (159) and makes impaired gluconeogenesis as a cause of hypoglycemia in adults with malaria unlikely. Studies measuring gluconeogenesis in children 2-7 years of age with uncomplicated malaria after a 15 hour fast (156) show that the availability of gluconeogenic substrates is not impaired in contrast to what was previously thought (160).

In conclusion, the only study in young children on gluconeogenesis in malaria reports a 73% contribution of gluconeogenesis to EGP after a short term fast. In adults with malaria this contribution varies from 75-100%.

Glycogenolysis in infectious disease

One single study reports on the response of plasma glucose concentration to a bolus glucagon in children with a chronic infection: normoglycemic well-nourished pre-pubertal HIV-infected children had a low response of plasma glucose concentration to glucagon (4%) in comparison to age-matched healthy controls (91%) after a 15 hour fast, but stable isotopes were not used in this study (161).

Despite the lack of direct measurements, the susceptibility to hypoglycemia in children with malaria is often ascribed to impaired glycogenolysis as a result of diminished glycogen stores (21). This hypothesis seems to be supported by a study in adults with malaria who showed a subnormal response of plasma glucose concentration to glucagon (117). However, this is contradicted by a study in adults with uncomplicated malaria who were fasted for 22 hours. In these patients the decrease in the rate of decline of glycogenolysis was slower than in healthy controls, despite a much lower rate of glycogenolysis in the
malaria patients, indicating that the regulation of glycogenolysis in malaria is not dictated by glycogen content, but is driven by the necessity to maintain euglycemia (162). This means that impaired glycogenolysis is unlikely to be a causative factor in the occurrence of hypoglycemia in malaria in adults. It also suggests that malaria itself does not cause glycogen depletion which is supported by the finding that hepatic glycogen is often still present in hypoglycemic adult malaria patients (117).

The mechanism by which hypoglycemia in children with malaria occurs remains uncertain. The limited available data suggest that in children glucose production is an important determinant of plasma glucose concentration. Although glucose production measured in children with malaria is not impaired during relatively short durations of fasting (up to 23 hours), longer periods of fasting may result in declining glucose production thereby increasing the risk of hypoglycaemia. Since gluconeogenesis does not seem to be impaired in malaria the decline in glucose production in children may indeed be caused by decreased glycogenolysis due to diminishing liver glycogen content. This, and whether glycogen content is influenced by different infectious diseases during fasting, remains to be investigated.

In conclusion, the cause of hypoglycemia in young children with malaria remains uncertain. Impaired EGP as a result of decreased glycogenolysis due to diminished liver glycogen stores is presumed the reason, but studies in children are lacking.

SUMMARY

Hypoglycemia in children is a common and serious condition that needs to be prevented because of the high risk of brain damage and mortality. Young age, prolonged fasting and severe infectious disease are well-recognized risk factors for the occurrence of hypoglycemia in children. Young children are more at risk for developing hypoglycemia than older children and adults, especially in response to fasting. EGP decreases from infancy towards adulthood and this decrease is related to the ratio of brain weight to body weight. The contribution of gluconeogenesis to EGP increases during short term fasting and is comparable in adults and older children whereas absolute gluconeogenesis is constant indicating that the decline in EGP is caused by decreased glycogenolysis. Estimation of glycogen stores in young children can be done by combining measurements of the response of EGP to a bolus glucagon with stable isotope studies however, data in children are scarce.

Young children with infectious diseases, who develop hypoglycemia, have a 4- to 6-fold risk of dying. This increased risk is recognized in several epidemiological studies in children with various infectious diseases, of which malaria, pneumonia and diarrhea are particularly common. Several assumptions are made in these studies as to the underlying cause of hypoglycemia, e.g. impaired gluconeogenesis as a result of limited precursor
supply or enhanced glycogenolysis resulting in rapid depletion of glycogen stores. However, very few studies with direct measurements of glucose kinetics in children are performed in order to support or refute these assumptions. The limited data in children with malaria suggest that EGP is a determinant of glucose concentration indicating that hypoglycaemia may occur as a result of impaired EGP. This is in contrast with adults since in adults with malaria EGP is increased but plasma glucose concentrations may be in the normoglycemic range indicating that peripheral glucose uptake is facilitated. Studies in adults show that EGP increases in malaria and that gluconeogenesis is the main contributor to total EGP, making it unlikely that hypoglycemia in malaria is caused by impairment of gluconeogenesis. Such conclusion cannot readily be made for children, since only one study reports on gluconeogenesis in young children with malaria. Whether hypoglycemia in young children with malaria is caused by impaired EGP as a result of decreased glycogenolysis due to diminished liver glycogen stores remains to be investigated.

To understand and thereby being able to anticipate on the occurrence of hypoglycemia in young children, further research on glucose kinetics in these children is mandatory. In particular, studies in adults cannot be extrapolated to children, because glucose metabolism during fasting and severe infections seems to be differently regulated between adults and children. These studies should focus on young children under five years of age with infectious diseases during a period of prolonged fasting. Special reference should be given to measurements of glycogenolysis and liver glycogen content.
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