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REVIEW ARTICLE

Diagnosis and early management of inborn errors of metabolism presenting around the time of birth

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Abstract
Inherited metabolic diseases often present around the time of birth. They are responsible for some cases of hydrops fetalis and a number of dysmorphic syndromes. Patients with inborn errors may also present at (or shortly after) birth with seizures or severe hypotonia. Most affected babies, however, appear normal at birth and subsequently deteriorate, with hypoglycaemia, acidosis, neurological or cardiac problems, or liver disease. Treatment often involves measures to reduce catabolism and to remove toxic metabolites. It should not be delayed for a definitive diagnosis.

Conclusion: In the newborn period, inborn errors can easily be misdiagnosed as sepsis or birth asphyxia; prompt detection requires vigilance and the early measurement of biochemical markers, such as plasma ammonia.

Key Words: *Encephalopathy, neonatal seizures, hypoglycaemia, hyperammonaemia, dysmorphism liver faliure, cardiomyopathy*

Introduction

Inborn errors of metabolism are individually rare but many disorders are now recognized and a significant proportion of these present during the neonatal period. Many inborn errors are treatable, and delay in initiating treatment can lead to permanent neurological damage. Unfortunately, for most disorders, the early symptoms and signs are non-specific. The aim of this article is to help neonatologists identify those patients who require investigation. Diagnostic tests and management should then be undertaken in collaboration with a specialist unit. In the UK, phenylketonuria is still the only inherited metabolic disease that is routinely sought by newborn screening, though a trial of screening for medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is in progress. A number of countries have introduced extended newborn screening for inborn errors of metabolism. Many disorders, however, present with clinical problems before the screening results are available. Screening has therefore had relatively little impact on the management of inborn errors that present around the time of birth.

Further information about the metabolic disorders mentioned in this article can be found in the relevant chapters of *The Metabolic and Molecular Bases of Inherited Disease* [1]; other references are given for conditions that are not covered by this text or to support specific statements.

Family history

A plan for investigation and management should be devised before delivery in families known to have a metabolic disease, aiming to prevent patients from developing symptoms. Even without a specific diagnosis, undiagnosed neonatal deaths or unexplained severe illness in childhood may provide useful clues to potential problems. Most patients have autosomal recessive disorders and have no affected relatives, but there may still be pointers in the family history, such as consanguinity, which increases the risk of rare

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autosomal recessive disorders. Since some metabolic disorders are X linked, relatives outside the immediate family may be relevant.

Mode and timing of presentation

Inborn errors may present at almost any time and in many different ways, but four circumstances are particularly characteristic: a) before birth, b) at birth, c) sudden death, typically at 2–3 d of age, and d) deterioration after a symptom-free interval.

During pregnancy

Non-immune hydrops fetalis can be caused by a number of inherited metabolic diseases, though these are rarer than chromosomal abnormalities, placental anomalies, congenital infections, skeletal dysplasias and haemoglobinopathies. Patients with hydrops fetalis are generally detected before birth by prenatal ultrasound scanning, as are a number of patients with malformations due to inborn errors of metabolism. Metabolic causes of these problems are listed in Table I.

Women carrying a fetus with a fatty acid oxidation disorder, particularly long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, are at risk of complications during pregnancy. The most frequent complication is HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), but acute fatty liver at pregnancy and prolonged hyperemesis are also recognized [2]. However, the vast majority of women with these complications do not have a fetus with an inborn error [3].

At birth

Metabolic disorders may present at or soon after birth with ascites, dysmorphic syndromes, seizures or severe hypotonia (Table I). Most patients with lysosomal diseases appear normal at birth but, for several disorders, the most severely affected patients are dysmorphic from birth; these conditions are generally those that can also give rise to hydrops fetalis (Table I, footnote). Over recent years, several other dysmorphic syndromes have been found to have a metabolic basis, and more will be elucidated with time. Patients presenting with neurological abnormalities at this age, particularly in patients with congenital lactic acidoses and early-onset fits [4], are often misdiagnosed as perinatal asphyxia. Some of the conditions associated with these fits actually cause seizures *in*

Table I. Inborn errors presenting before or soon after birth.

Ascites/non-immune hydrops	Dysmorphic syndromes	Seizures/apnoea	Severe hypotonia
Some lysosomal disorders[a]	Peroxisomal biogenesis disorders	Peroxisomal biogenesis disorders	Peroxisomal biogenesis disorders
Erythrocyte enzymopathies[b]	Disorders of cholesterol synthesis[c]	Non-ketotic hyperglycinaemia	Non-ketotic hyperglycinaemia
Pearson syndrome and other respiratory chain disorders [49,50]	Some lysosomal disorders[d]	Congenital lactic acidoses	Congenital lactic acidoses
Neonatal haemochromatosis [21]	Congenital defects of N-glycosylation	Pyridoxine dependency [36]	Congenital defects of N-glycosylation
Congenital defects of N-glycosylation* [51]	Dystroglycanopathies (e.g. Walker-Waarberg syndrome)* [58]	Pyridoxamine 5′-phosphate oxidase deficiency* [37,62]	Dystroglycanopathies (congenital muscular dystrophies)* [58]
Glycogen storage disease type IV* [52]	Congenital lactic acidoses [59,60]	Molybdenum co-factor deficiency	
	Glutaric aciduria type II	Folinic acid responsive seizures* [38]	
	3-hydroxyisobutyryl-CoA deacylase deficiency* [61]		

The aetiology of neonatal haemochromatosis is unclear—it is probably *not* an inborn error.

[a] Lysosomal disorders associated with hydrops fetalis include G_{M1} gangliosidosis, galactosialidosis, infantile free sialic acid storage disease, mucopolysaccharidosis types IV and VII, mucolipidosis types I and II, Gaucher's disease type II, Farber disease, Niemann-Pick disease types A and C, Wolman disease, and multiple sulphatase deficiency [45].

[b] Hydrops fetalis has been associated with deficiencies of glucose-6-phosphate dehydrogenase, glucose phosphate isomerase and pyruvate kinase [46–48].

[c] Smith-Lemli-Opitz syndrome, Conradi-Hunermann syndrome, desmosterolosis and mevalonic aciduria are all disorders of cholesterol synthesis associated with dysmorphism.

[d] Lysosomal disorders associated with dysmorphism from birth include G_{M1} gangliosidosis, galactosialidosis, infantile free sialic acid storage disease, mucolipidosis type II and mucopolysaccharidosis type VII [53–57].

* Particularly rare causes.

utero, but it is unusual for these to be recognized at the time.

Sudden death

Sudden death at 2 to 3 d of age is usually due to a non-metabolic condition, such as sepsis or congenital heart disease [5]. It is important to recognize that defects of fatty acid oxidation may also be responsible, as a result of cardiac arrhythmias [6]. In most cases, autopsy reveals an excess of fat droplets in the liver or heart, but specimens for metabolic tests should be obtained as soon as possible after death, without waiting for the autopsy (Table VI). Under these circumstances, it is particularly important to collect blood spots on a Guthrie card for analysis of acylcarnitines, a specimen for DNA extraction and skin for fibroblast culture.

Deterioration after a symptom-free interval

Most babies with inborn errors are born at term and initially appear to be well but subsequently deteriorate. Typically, this occurs in disorders associated with abnormal metabolites that cross the placenta. Metabolites accumulate following delivery, even in babies who do not receive oral feeds, because catabolism is part of the normal adaptation to postnatal life. The rate of deterioration varies. Understandably, sepsis is usually suspected in the first instance. Other differential diagnoses include neurovascular problems (especially in the preterm), duct-dependent heart disease, drug withdrawal and endocrine problems such as adrenal insufficiency. Ultimately, most patients with inborn errors presenting in this way become encephalopathic, but every effort should be made to identify patients before they are seriously ill if neurological sequelae are to be avoided. For this reason, we recommend some additional investigations at the same time as the septic screen, particularly in term babies. These are listed in Table II.

Table II. Additional investigations to be done at the time of the septic screen.

Blood/plasma	Urine
pH and blood gas	sugars
glucose	ketones
electrolytes and anion gap	
liver function tests	
ammonia [a]	
Guthrie card for amino acids and acylcarnitines [b]	

[a] The interpretation of plasma ammonia concentration is discussed in the section "Hyperammonaemia".
[b] Tandem mass spectrometry allows rapid analysis of amino acids and acylcarnitines in blood spots. Guthrie cards carrying blood spots are a useful resource and should be stored because they can also be used as a source of DNA.

Patterns of deterioration

Most babies with inborn errors who deteriorate after an initial period of health fall into one or more of five categories. These are:

1. unexplained hypoglycaemia
2. disorders of acid–base status
3. neurological deterioration
4. cardiac disorders: cardiomyopathy and arrhythmias
5. acute parenchymal liver disease

The disorders that may be responsible for these problems are listed in Table III. Whilst some babies may have a characteristic odour (e.g. maple syrup urine disease, isovaleric acidaemia), these are uncommon and unfortunately seldom diagnostically useful. It is also important to note that other problems may co-exist with inborn errors. Thus, galactosaemia predisposes to Gram-negative sepsis [7], and cerebral or pulmonary haemorrhage may be the terminal event in urea cycle disorders [8].

Hypoglycaemia

There are many causes of hypoglycaemia in neonates, and the majority of neonates with low blood glucose concentrations do not have a primary metabolic or endocrine disorder. Nevertheless, well-grown term babies with severe, prolonged or otherwise unexplained hypoglycaemia should be investigated for an underlying metabolic or endocrine cause (Table III). The course of the hypoglycaemia may provide important clues. Hyperinsulinism should be suspected if the child has recurrent severe hypoglycaemia or if glucose requirements necessary to maintain normoglycaemia are high [9]. Hypoglycaemia associated with metabolic acidosis suggests an organic acidaemia or defect of gluconeogenesis (glycogen storage disease type 1 or fructose 1,6-bisphosphatase deficiency). The possibility of adrenal or pituitary insufficiency [10] or a defect of fatty acid oxidation [6] should be considered in patients with hypoglycaemia and cholestatic jaundice.

Acid–base disorders

Acid–base disorders are common in sick neonates; most commonly they have a mixed respiratory and metabolic acidosis. In babies presenting with grunting and dyspnoea, however, two findings may provide useful clues. First, a persistent metabolic acidosis,

Table III. Metabolic disorders associated with various patterns of deterioration.

Hypoglycaemia	Acid–base disorders	Neurological deterioration	Cardiac disorders	Parenchymal liver disease
Endocrine disorders	Metabolic acidosis	Hyperammonaemia	Disorders of fatty acid oxidation [6]	Respiratory chain disorders [22–24]
Disorders of fatty acid oxidation	Organic acidaemias	Organic acidaemias	Respiratory chain disorders [14–16]	Neonatal haemochromatosis [21]
Glycogen storage disease type I	Congenital lactic acidoses	Maple syrup urine disease	Congenital defects of glycosylation* [17,18]	Galactosaemia
Fructose 1,6-bisphosphatase deficiency	Fructose 1,6-bisphosphatase deficiency	Disorders of fatty acid oxidation [6]	Pompe disease* [20]	Tyrosinaemia type 1
Respiratory chain disorders	Ketolysis defects	Congenital lactic acidoses	Some other forms of glycogen storage disease* [64,65]	Disorders of fatty acid oxidation [6]
Organic acidaemias	Respiratory alkalosis	Peroxisomal disorders		α-1-antitrypsin deficiency
Hereditary fructose intolerance* [27]	Hyperammonaemia [11]	Non-ketotic hyperglycinaemia		Niemann-Pick type C
		Molybdenum cofactor deficiency		Bile acid synthesis defects*
		Remethylation defects* [63]		Hereditary fructose intolerance* [27]

Neonatal haemochromatosis has been included since its aetiology is unclear, although it is probably *not* an inborn error. Endocrine causes of hypoglycaemia have been mentioned since they are common and require urgent diagnosis and management.
* Particularly rare causes at this age.

particularly if associated with ketosis and normal tissue perfusion, may suggest an organic acidaemia or a congenital lactic acidosis. Second, a mild respiratory alkalosis, in patients who are not being ventilated, is highly suggestive of hyperammonaemia [11]. This is often associated with irritability and even stridor, and is a valuable pointer to many inborn errors (Table IV). It should be emphasized that these acid–base changes are not specific. Patients with organic acidaemias can be alkalotic [12], and those with urea cycle disorders may be acidotic. The latter is particularly likely if the diagnosis has been delayed, since hyperammonaemia leads to vasomotor instability and collapse, emphasizing the value of assessing the acid–base status at an early stage of the illness.

Table IV. Causes of neonatal hyperammonaemia.

Inherited disorders	Acquired
Disorders of the urea cycle	Any severe illness
Organic acidaemias	Birth asphyxia [68]
Disorders of fatty acid oxidation [6]	Total parenteral nutrition [69]
Pyruvate carboxylase deficiency*	Herpes simplex [25]
Hyperornithinaemia* (HHH syndrome and OAT deficiency) [66,67]	Transient hyperammonaemia of the newborn* [70]
Mild hyperammonaemia is common in many other inborn errors	

* Particularly rare causes.

Neurological deterioration

This is probably the most common presentation. Conditions that present in this way include organic acidaemias, urea cycle defects, maple syrup urine disease, fatty acid oxidation defects, congenital lactic acidoses, and any of those conditions that may present with fits or hypotonia at birth (see Tables I and III). The rate of deterioration varies considerably, depending on the nature and severity of the defect. Some patients may have only a very brief phase when they appear well and, in these, it can be difficult to distinguish the illness from birth asphyxia. Others may appear well for several days with a much more gradual deterioration. Two-thirds of patients with non-ketotic hyperglycinaemia develop symptoms within 48 h of birth [13]. Urea cycle disorders and branched-chain organic acidaemias typically present between 12 and 72 h of age, whereas maple syrup urine disease usually presents later in the first week. Early signs of encephalopathy are non-specific, such as poor feeding, lethargy, vomiting, abnormalities of tone or irritability, once again emphasizing the need for vigilance and for strategies that will detect

biochemical markers at an early stage if diagnostic delays are to be avoided. Later problems may include drowsiness, fits, hiccups, myoclonus, apnoeic episodes, marked hypotonia, irritability with cycling movements and coma. Cerebral oedema may lead to a bulging fontanelle, and brainstem swelling may be responsible for the vasomotor instability observed.

Cardiac disease: cardiomyopathy and cardiac arrhythmias

Some patients with long-chain fatty acid oxidation disorders or respiratory chain defects (including Sengers and Barth syndromes) present with cardiomyopathy or arrhythmias shortly after birth or later in the neonatal period [6,14–16]. Neonates with congenital defects of glycosylation sometimes have pericardial effusions [17] or, more rarely, cardiomyopathy [18]. Cardiomegaly is also a feature of congenital hyperinsulinism [19]. Pompe disease occasionally presents during the neonatal period, but most patients develop symptoms later (median age 1.6 mo) [20].

Acute parenchymal liver disease

These patients present with jaundice, coagulopathy and hepatomegaly (sometimes with splenomegaly and ascites). Metabolic causes are summarized in Table III. In the first week it is important to consider neonatal haemochromatosis [21] and mitochondrial respiratory chain disorders [22–24], though the latter may present at any age. Galactosaemia typically presents in the first or second week of life, and tyrosinaemia may also present from this age onwards. Alpha-1-antitrypsin deficiency, Niemann-Pick disease type C and bile acid synthesis defects usually present after 3 wk of age, predominantly with cholestasis. Non-metabolic causes of liver failure may mimic inborn errors: disseminated herpes simplex can cause severe hyperammonaemia [25], and in cases of haemophagocytic lymphohistiocytosis there may have been an affected sibling [26]. Hereditary fructose intolerance only presents in neonates if fructose is given [27]. Crigler-Najjar syndrome, the main disorder of bilirubin metabolism presenting at this age, causes *unconjugated* hyperbilirubinaemia. Peroxisomal biogenesis disorders generally present with dysmorphic features or neurological problems rather than liver disease. Renal tubular abnormalities commonly accompany metabolic liver disease, and cataracts may be seen in galactosaemia and mitochondrial disorders.

Management

For some disorders, such as Zellweger syndrome, supportive care is all that can be offered. Fortunately, treatment is possible for many inborn errors, and the principles are outlined in Table V. General neonatal intensive care is essential, and in some conditions this may be all that is needed (e.g. phototherapy $\pm$ exchange transfusion in erythrocyte enzymopathies). In other conditions, treatment to minimize catabolism and remove toxic metabolites is required. These measures can start before a precise diagnosis is known; indeed, this is vital if the outcome of these inborn errors is to improve. The outcome of many inborn errors presenting at this age is highly dependent on the speed with which the diagnosis is suspected and treatment started.

Table V. Management of a suspected metabolic disorder.

Stop any "toxic" nutrient	e.g. protein, galactose
Give high-energy intake	usually glucose, orally or intravenously
Neonatal intensive care	correct tissue perfusion, dehydration, acidosis, hypothermia, anaemia, etc.
Treat hyperammonaemia	sodium benzoate, sodium phenylbutyrate, arginine
Dialysis	haemofiltration/haemodialysis or peritoneal (bicarbonate based)
Insulin	to control hyperglycaemia and reduce catabolism
Vitamins	e.g. biotin, hydroxocobalamin or pyridoxine
Specific therapy	e.g. carnitine, glycine for isovaleric acidaemia

First, any nutrient that may have precipitated the illness, such as galactose or protein, should be stopped and a high-energy intake given either orally or intravenously. In this group of patients, the need to provide adequate glucose may require use of concentrated solutions through a central line (or possibly relaxation of the usual fluid restrictions, with diuretics or even dialysis if necessary). It is usual to give just glucose, although fat emulsions have been used in some disorders to increase energy intake [28]. With high rates of glucose infusion, blood glucose concentrations should be monitored. If hyperglycaemia (>12 mmol/l) and/or glycosuria are a problem, insulin may be given cautiously: although some patients with metabolic disorders are insulin resistant, some neonates are very sensitive to small doses. Insulin has the additional advantage of promoting anabolism [29]. Growth hormone has also been advocated to promote anabolism [30], though as yet there is no evidence that it improves outcomes. Acidosis, electrolyte disturbances, dehydration and hypothermia should be corrected, and vigilance is necessary for sepsis or other complications.

Sometimes it is impossible to control the metabolic derangement solely by these means. Moreover, neurological damage is often related to the concentration and the duration of exposure to toxic metabolites such as ammonia or leucine (in maple syrup urine disease).

Toxic metabolites should therefore be removed as quickly as possible, which often requires some form of dialysis; this will also correct other problems, such as acidosis and fluid overload. Peritoneal dialysis was used in the past, but many studies have now shown that higher clearances can be achieved using extracorporeal blood purification [31]. In theory, the optimal technique is haemodialysis since this can achieve the highest clearances. Haemodialysis devices are now available with relatively small extracorporeal volumes, and their haemodynamic effects can be minimized by pre-filling the systems with blood [31]. The choice of haemodialysis, haemofiltration or haemodiafiltration is, however, partly dependent on local considerations. Haemodialysis only has higher clearances at high blood flow rates, which require the placement of adequately sized catheters [31]. Ideally, the dialysis should be continuous to avoid rebound accumulation of toxic chemicals, but this requires the availability of adequate numbers of skilled staff. It is also possible that extremely rapid changes in electrolyte and metabolite concentrations might lead to excessive fluid shifts and further complications.

Hyperammonaemia

The interpretation of plasma ammonia concentration can give rise to difficulties. Whilst normal values in neonates are less that 65 μmol/l [32], any sick neonate may have values up to 180 μmol/l. Values greater than 200 μmol/l suggest a metabolic disorder [33] and should be investigated urgently. Severe hyperammonaemia (>500 μmol/l) is a very serious complication of many inborn errors, and the outcome is poor [11], although it may be improving with aggressive treatment [34]. Nevertheless, before proceeding, it is essential to inform the parents about the risk of neurological impairment, the likelihood of further hyperammonaemic episodes and the need for complex treatment throughout life.

Haemodialysis or haemofiltration should be instituted as soon as possible in patients with severe hyperammonaemia or rapidly rising concentrations. In addition, it is customary to give arginine, sodium benzoate and sodium phenylbutyrate. The latter two drugs are conjugated to glycine and glutamine, respectively, and the products are excreted, thereby creating an alternative pathway for nitrogen excretion [35]. There are, however, few data concerning the conjugation of these compounds in the newborn period, and it is probably sub-maximal (C. Bachmann, pers. comm.). Virtually all studies have involved patients with urea cycle defects, but it may be difficult to distinguish patients with organic acidaemias at the time of presentation. Some have advocated more conservative regimens until the diagnosis is known but, fortunately, what little evidence is available suggests that the drugs are safe and effective in organic acidaemias [12].

Early-onset fits

There is increasing evidence that the outlook is improved if early-onset fits can be controlled quickly. Investigations should include plasma and CSF amino acids, plasma very-long-chain fatty acids, plasma urate, blood and CSF lactate, and urine sulphite. The genetic basic has recently been identified for pyridoxine dependency [36], the commonest cause of vitamin-responsive seizures. All patients should have a trial of pyridoxine (100 mg), which can be given intravenously or enterally, preferably with EEG monitoring. Full resuscitation facilities must be available as patients may collapse after the first dose. If there is no response, pyridoxal phosphate (30 mg/kg) should be given enterally [37] followed, if necessary, by folinic acid (3 mg/kg) [38].

Specific therapy

Once the diagnosis is known, any specific therapy should be given in conjunction with a specialist centre. Organic acids are excreted in part bound to carnitine. Carnitine concentrations are usually low in organic acidaemias, particularly during episodes of neonatal decompensation. Carnitine supplementation increases the excretion of carnitine esters [39] and, for this reason, carnitine is widely used in organic acidaemias, although there is no firm evidence that it improves the outcome. In isovaleric acidaemia, glycine plays an important role in promoting metabolite excretion, and supplements should be given in combination with carnitine [40]. Use of carnitine in fatty acid oxidation defects is controversial, since long-chain acylcarnitines may have toxic effects [41], although this is disputed. Branched-chain free amino acid mixtures should be given as early as possible in maple syrup urine disease [42]. Tyrosinaemia type 1 sometimes presents with acute liver failure in the neonatal period, and the use of Nitisinone (NTBC) may be life saving [43].

Mega-vitamin therapy

Many enzymes require co-enzymes derived from vitamins for enzyme activity, and disorders are well recognized in which pharmacological doses of precursor vitamins will increase the enzyme activity. For this reason, it is a common practice to give large doses of many vitamins or co-factor precursors. Administration of vitamin B_{12} and biotin is probably justified because vitamin-responsive methylmalonic acidaemia and holocarboxylase synthetase can present in the

newborn period. The justification for many other vitamins is doubtful, particularly since vitamin-responsive forms of inborn errors tend to be milder than other forms and, therefore, seldom present in the neonatal period.

Continuing management

It is important to recognize that the emergency treatment outlined is nutritionally incomplete and, if used for a prolonged period, may exacerbate catabolism, leading to poor metabolic control and frank malnutrition. Balanced feeds should be introduced as soon as possible.

Even with the most aggressive therapy, a number of these children will die. It is essential to take appropriate specimens immediately *post-mortem* (Table VI), since otherwise it may not be possible to establish a diagnosis. A conventional autopsy seldom provides many clues.

Conclusions

Progress with the treatment of inborn errors has been slower than progress on their biochemical and molecular bases. Nevertheless, outcomes are improving with the use of dialysis and drugs to promote the removal of toxic metabolites, coupled to measures to minimize catabolism. Early intervention is crucial, however, if neurological sequelae are to be avoided. This requires constant vigilance and routine measurement of biochemical markers, such as ammonia, at an early stage in patients with suspicious presentations.

The management plan outlined here is largely based on personal experience rather than published evidence. There are no clinical trials that document prospectively the presentation and outcome of inborn errors presenting in the newborn period. Some information is available from highly inbred communities such as the old order Amish [44], but for the general population such studies would require enormous numbers (more than 10^6 babies for most disorders) to obtain meaningful results.

Table VI. Specimens to be taken in the event of death when metabolic disease is suspected.

Plasma	heparinized, separated and deep frozen
Blood spots	on filter paper for acylcarnitines
Urine	deep frozen in a plain tube
Sample for DNA	blood anticoagulated with EDTA and deep frozen (other specimens may be suitable)
Skin for fibroblast culture	taken with sterile precautions into medium and stored at 4–8°C—NOT frozen
Liver	snap frozen for histochemistry/enzymology
Muscle and other tissues	as indicated—snap frozen for histochemistry/enzymology

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