Energy pathyways in muscle and the metabolic myopathies

Federico Roncaroli

Neuropathology Unit – Division of Clinical Neuroscience

f.roncaroli@imperial.ac.uk

LEARNING OBJECTIVES

- Describe the bioenergetics of muscle contraction
  - Short-term energy source: role of creatinine phosphate, creatinine kinase and myokinase
  - Intermediate-term energy source: anaerobic glycolysis i.e. the break-down of glucose to lactate and pyruvate and conversion of ADP to ATP (mainly type II fibres that have few mitochondria and many glycogen granules)
  - Long-term energy source: oxidative phosphorylation i.e. aerobic process that generates ATP from fat, carbohydrate and protein (type I fibres are suited to this as thay have many mitochondria and lipid droplets)

- Understand the different types of metabolic myopathy
  - Briefly describe the key types of primary metabolic myopathies i.e. (1) glycogen storage disorders, (2) lipid disorders and (3) mitochondrial disorders (*NB detailed knowledge of individual syndromes is not required*)
  - Describe the common glycogen storage disorder: Myophosphorylase deficiency (also termed: McArdle's syndrome, glycogen storage disorder type V)

DEFINITION OF METABOLISM

- **Metabolism is the set of chemical reactions that occur in living organisms in order to maintain life.**

- **Metabolic processes allow organisms to grow and reproduce, maintain their structures, and respond to their environments.**

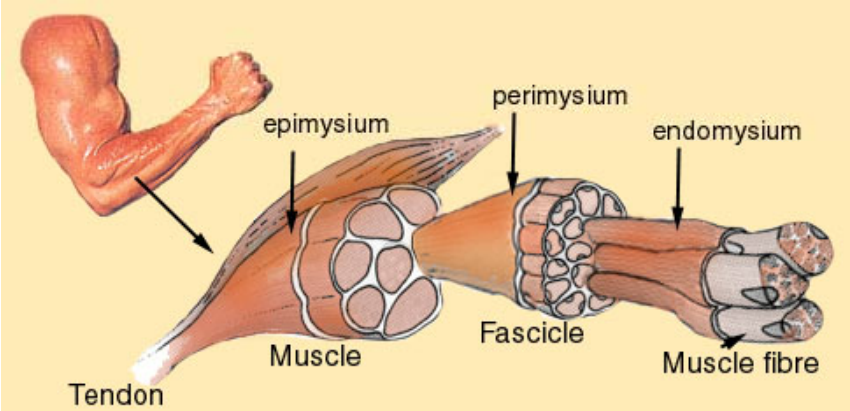
- **Metabolism is divided into catabolism (to break down organic matter) and anabolism (to construct components of cells)**

ESSENTIAL CONCEPTS

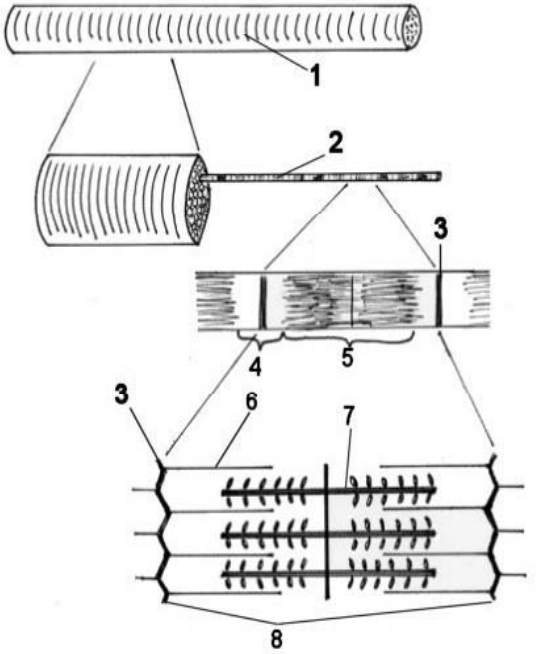
- Energy pathways are aimed to reconstitute ATP from ADP
- Acetyl-CoA is the essential molecule of all pathways
- Muscle fibres need energy for contraction
- Slow and fast twitch fibres have different metabolic requirements
- Slow fibres have high glycogen, high lipids and more mitochondria (run marathons) – fast fibres use OXPHOS (run 100mt)

ENERGY IN MUSCLE FIBRES

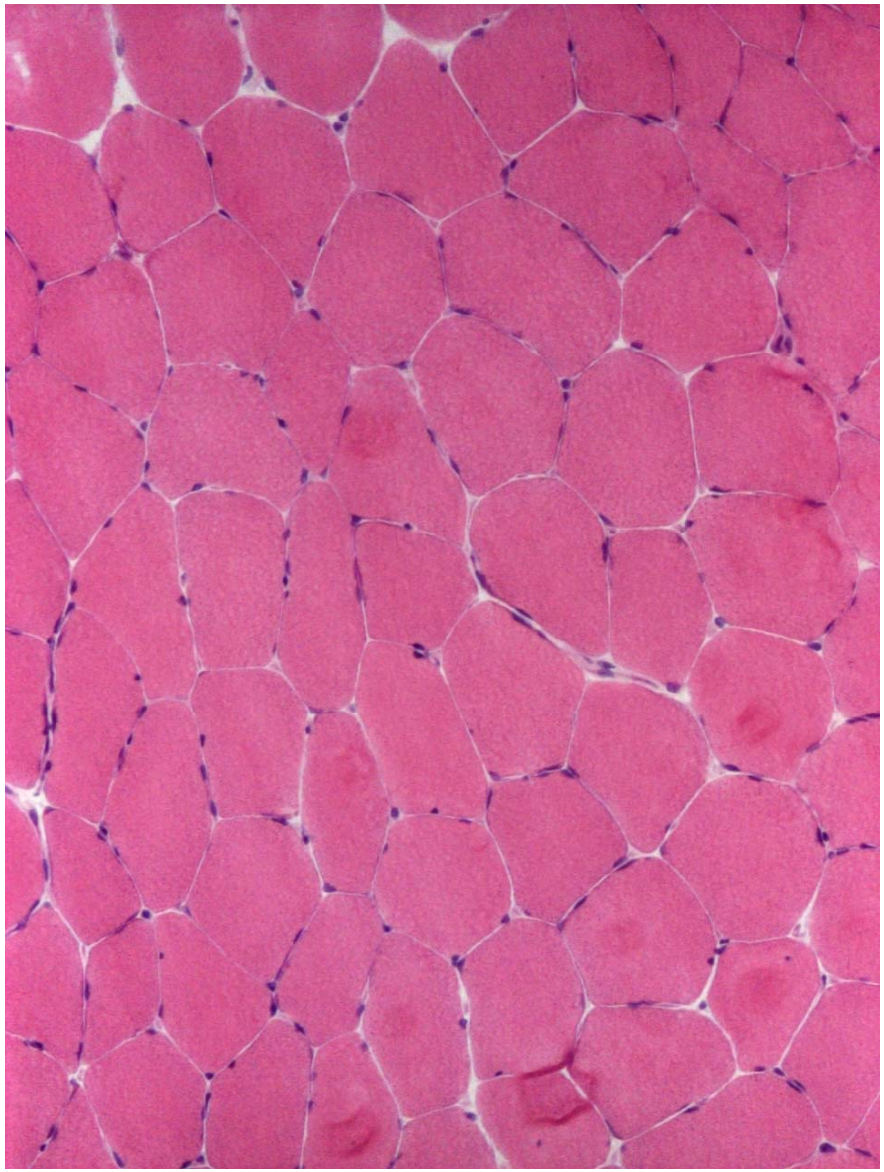
- **ATP/ADP is the immediate source of energy – ADP&ATP binds myosin and allow sarcomeric contraction and release of actin**

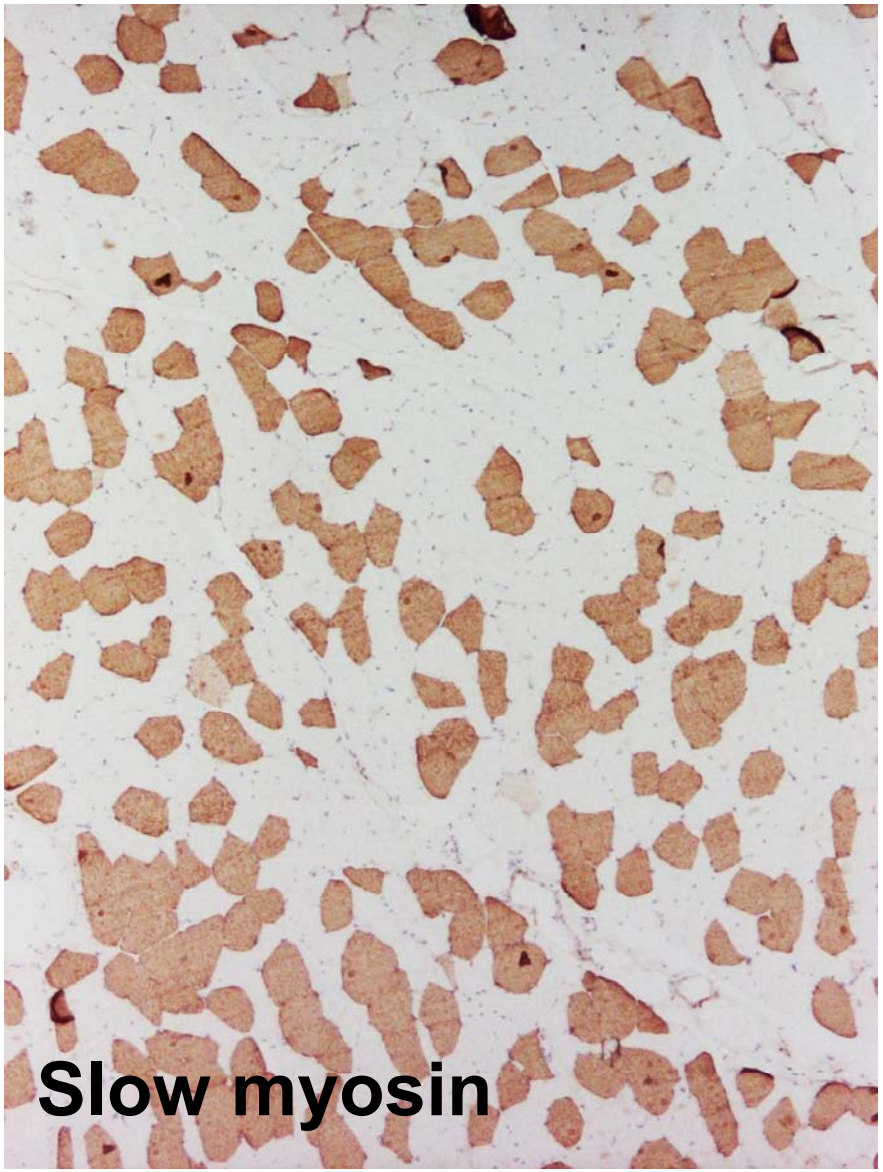


- **Oxidative phosphorylation - Anaerobic glycolysis (use of glucose stored as glycogen – lipids) – Creatine kinase reaction – Adenylate kinase reaction**



NORMAL MUSCLE





SKELETAL MUSCLE SOURCE OF ENERGY

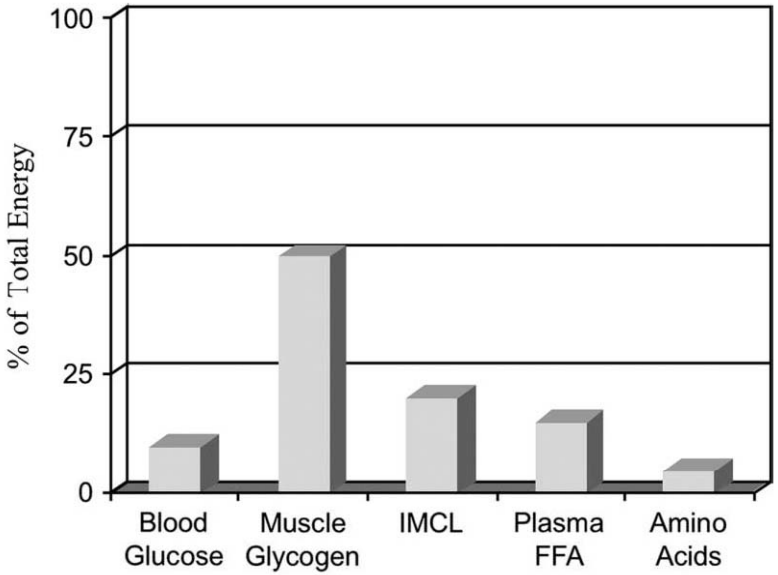


FIGURE 2. The major fuel sources in skeletal muscle during submaximal endurance exercise. Each value is a proportion of the total energy expenditure. FFA, free fatty acids; IMCL, intramyocellular lipids.

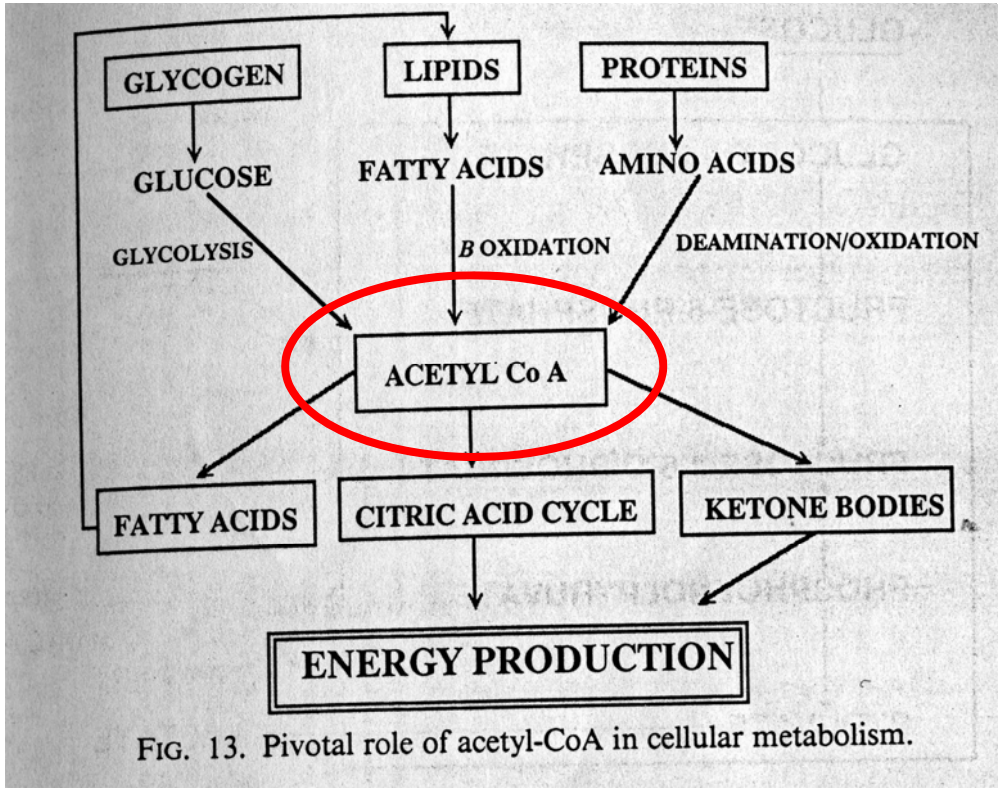
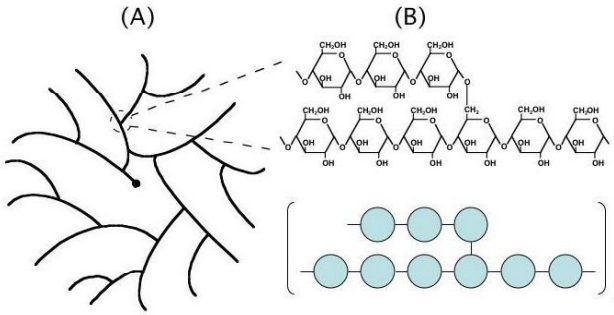


FIG. 13. Pivotal role of acetyl-CoA in cellular metabolism.

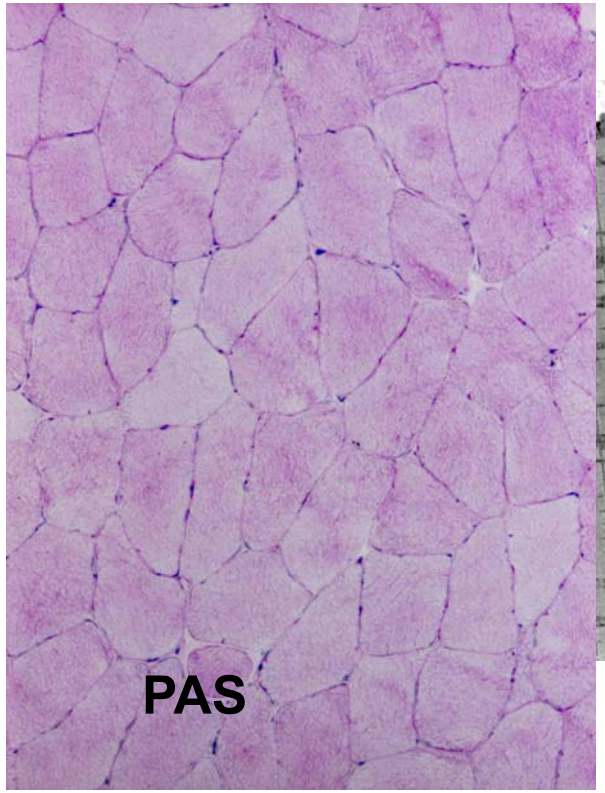
GLYCOGEN



Readily available source of energy when there is demand of glucose

Stored predominantly in muscle and liver

Synthesised from glucose by Glycogen synthase

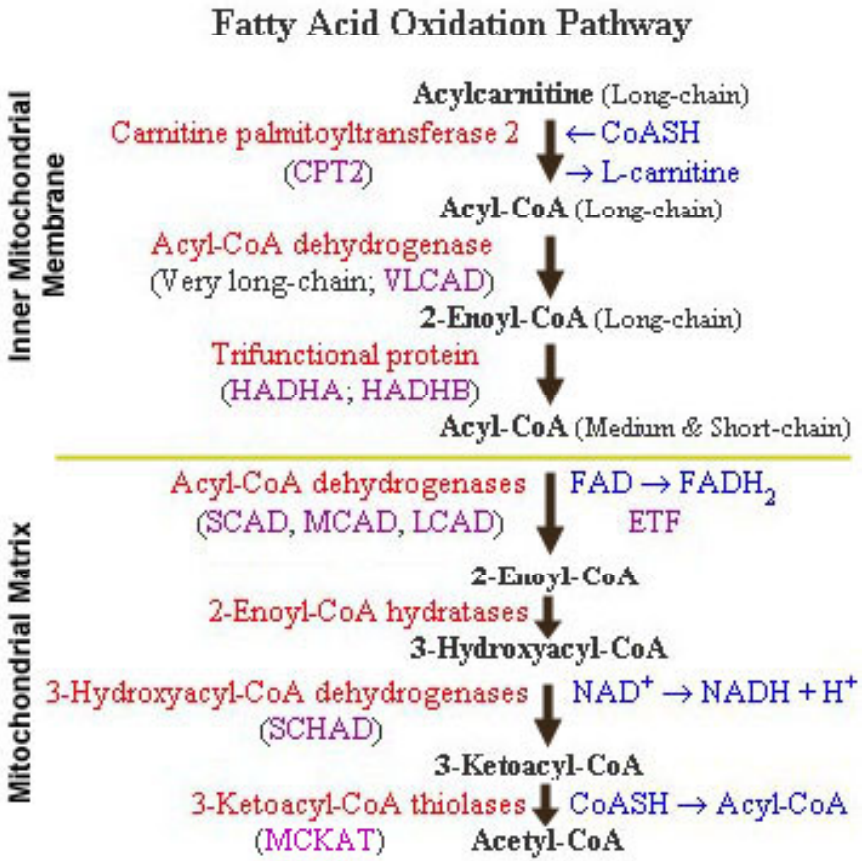


PAS

Electron microscopy

LIPIDS

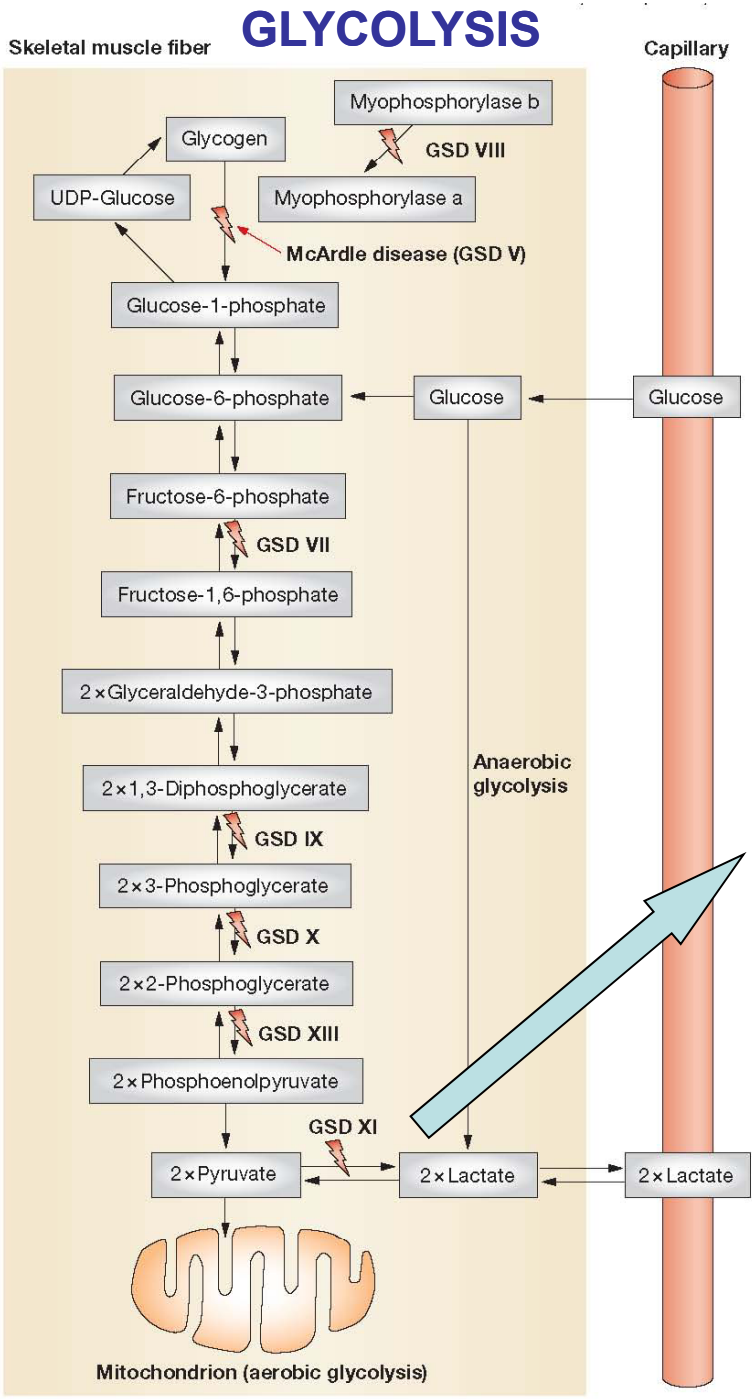
- Free fatty acid are released from adipose tissue by lipases
- They are the major source of energy for muscle after long exercise when glycogen is exhausted
- Their hydrolysis produces Acetyl-CoA to feed the Krebs cycle and produce ATP



ENERGY PATHWAYS

ADP ⇄ ATP

GLYCOLYSIS



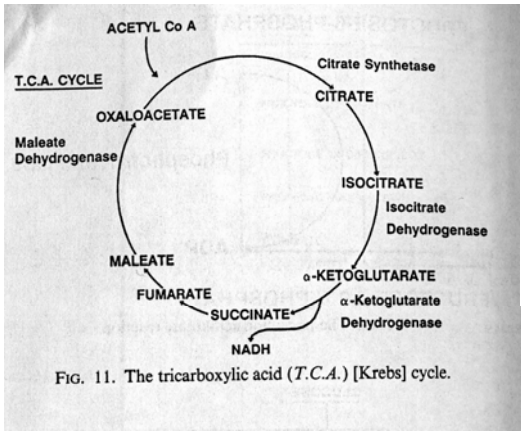
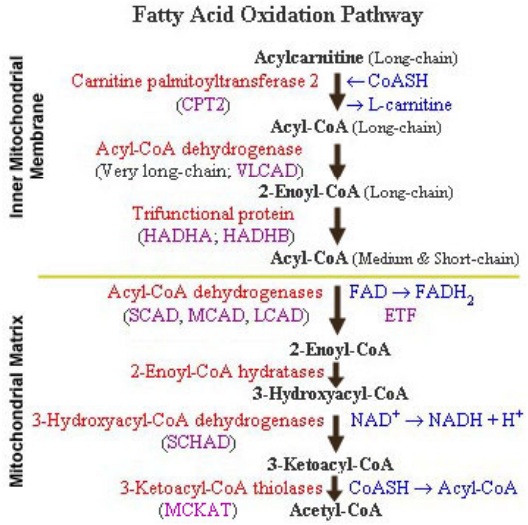
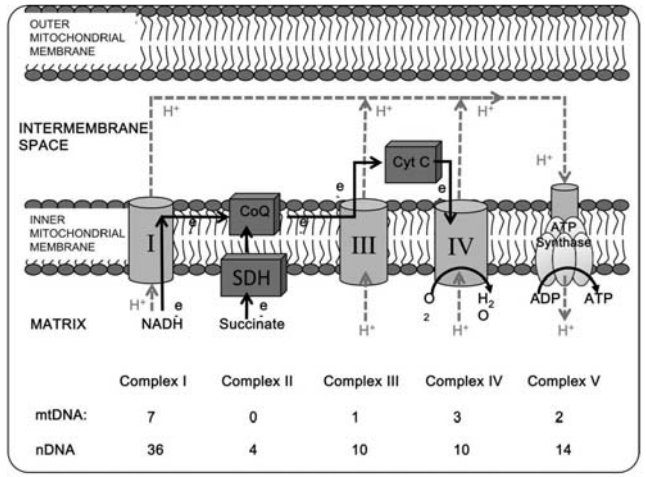


FIG. 11. The tricarboxylic acid (*T.C.A.*) [Krebs] cycle.





OXIDATIVE PHOPHORYLATION

METABOLIC MYOPATHIES – General concepts

- **Genetically determined heterogenous group of disorders characterised by anomalies of energy production**
- **Disease secondary to defects in glycogen, lipid, adenine nucleotide and mitochondrial metabolism**
- **Usually infantile and adult forms – Infants are usually more severely affected**
- **They usually present with muscle disfunction induced by exercise or rhabdomyolysis & may become mildly symptomatic during childhood and emerge late in life (*"I have never been good at sport")***

TABLE 2. Clinical Signs, Symptoms, and History Suggesting Metabolic Myopathies

Clinical Feature	Possible Disorder
Signs and symptoms	
Pigmenturia	GSDs, FAODs, some mitochondrial disorders
Muscle weakness	GSDs, FAODs, mitochondrial disorders
Myalgias/cramps with endurance sports	FAODs, mtDNA defects, AMPD1 deficiency
Myalgias/cramps with power/sprint sports	GSDs, AMPD1 deficiency
Symptoms triggered by fasting or superimposed illness	FAODs, mtDNA defect
Nausea/vomiting with exercise	GSDVII, mtDNA defect
Encephalopathy	FAODs, mitochondrial disorders
Respiratory failure	Pompe disease, mtDNA defect
Cardiac arrhythmias	Pompe disease, FAODs, mitochondrial disorders
Seizures	FAODs, mitochondrial disorders
Sudden infant death	FAODs, mitochondrial disorders
System involvement	
Multiple system involvement	mtDNA defect, FAODs
Peripheral neuropathy	GSDIII, FAODs, mitochondrial disorders
Hemolytic anemia	GSDIX (PGK deficiency)
Sideroblastic anemia	MLASA (mitochondrial disorder)
Mental retardation	FAODs, mitochondrial disorders
Failure to thrive/growth retardation	FAODs, mitochondrial disorders
Cardiomyopathy	Pompe disease, FAODs, mitochondrial disorders
Endocrinopathy	FAODs, mitochondrial disorders
Vision and hearing	Mitochondrial disorders
Family history	Phosphorylase b kinase, GSDIX
X-linked	mtDNA
Maternal	mtDNA deletions
Sporadic	Twinkle and polymerase gamma mutations
Autosomal dominant	Most FAODs (eg, CPT II) & GSDs (eg, Pompe disease), AMPD deficiency, several mitochondrial disorders (MNGIE, polymerase gamma mutations, SCO2 deficiency, etc.)
Autosomal recessive/consanguineous	mtDNA

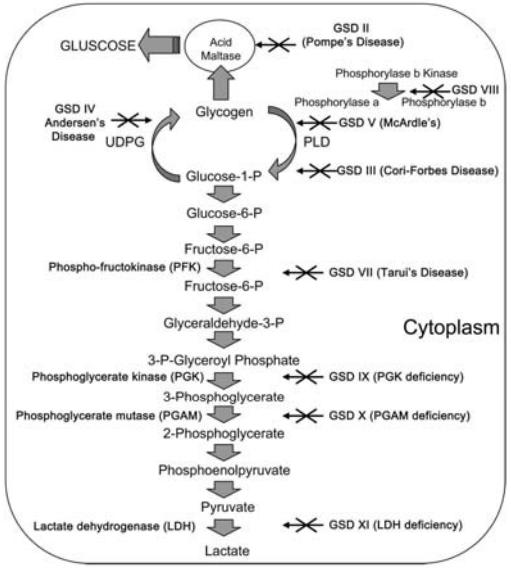
MLASA, mitochondrial myopathy and sideroblastic anemia; SCO2, synthesis of cytochrome *c* oxidase.

GLYCOGENOSES

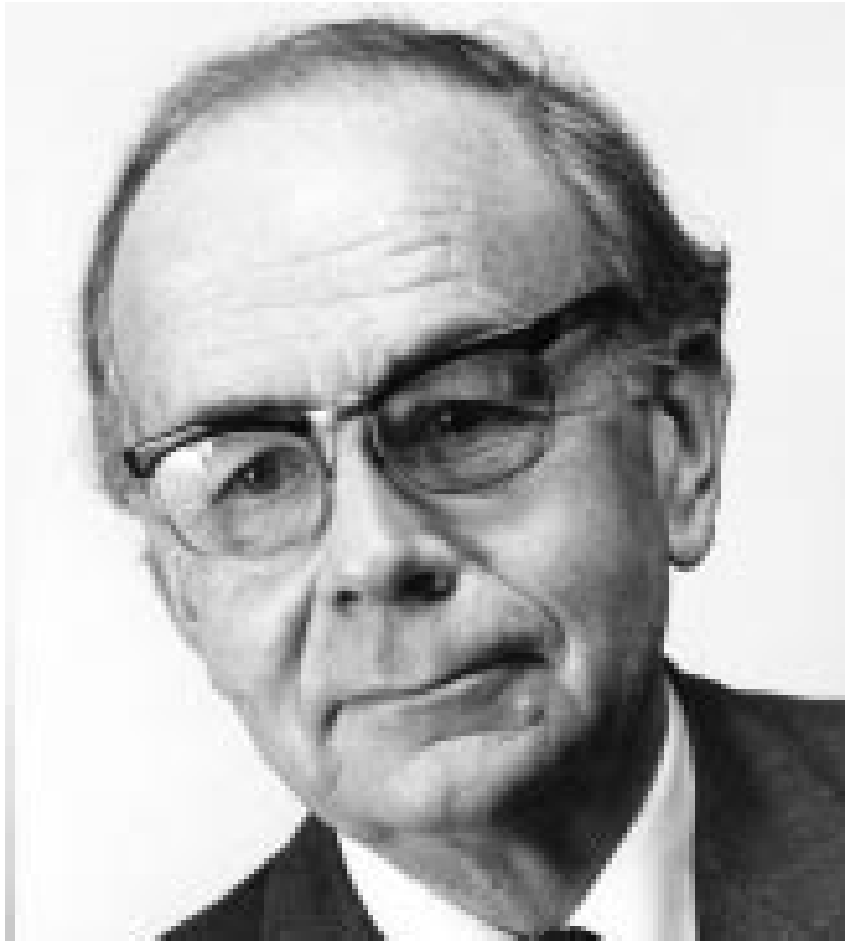
- **Autosomal recessive (but glycogenosis IX and IXa)**

TABLE 17.1 *Features of glycogenoses that affect muscle*

Type	Enzyme deficiency	Eponymous or other names	Clinical features	Other tissues/systems affected
Type II	α-1,4-Glucosidase (acid maltase)	Pompe's disease	(a) Severe form: resembles SMA (b) Milder forms: resemble LGMD	Heart, nervous system, leukocytes, liver, kidneys
Type III	Amylo-1,6-glucosidase (debrancher enzyme)	Forbes' disease Cori's disease	Infantile hypotonia Mild weakness	Hepatic hypoglycaemia, ketosis, leukocytes, heart
Type IV	Amylo (1,4 → 1,6) transglucosidase (branching enzyme)	Amylopectinosis	Usually no muscle symptoms, muscle wasting in some	Liver, heart
Type V	Myophosphorylase	McArdle's disease	Exercise intolerance, cramps, fatigue, myoglobinuria	None
Type VII	Phosphofructokinase	Tarui's disease	Exercise intolerance, cramps, fatigue, myoglobinuria	Haemolytic anaemia
Type VIII	Phosphorylase *b* kinase		Exercise intolerance, muscle stiffness, muscle weakness	Liver, heart
Type IX	Phosphoglycerate kinase		Exercise intolerance, cramps, fatigue, myoglobinuria	Haemolytic anaemia, CNS
Type X	Phosphoglycerate mutase		Exercise intolerance, cramps, fatigue, myoglobinuria	
Type XI	Lactate dehydrogenase		Exercise intolerance, cramps, fatigue, myoglobinuria	

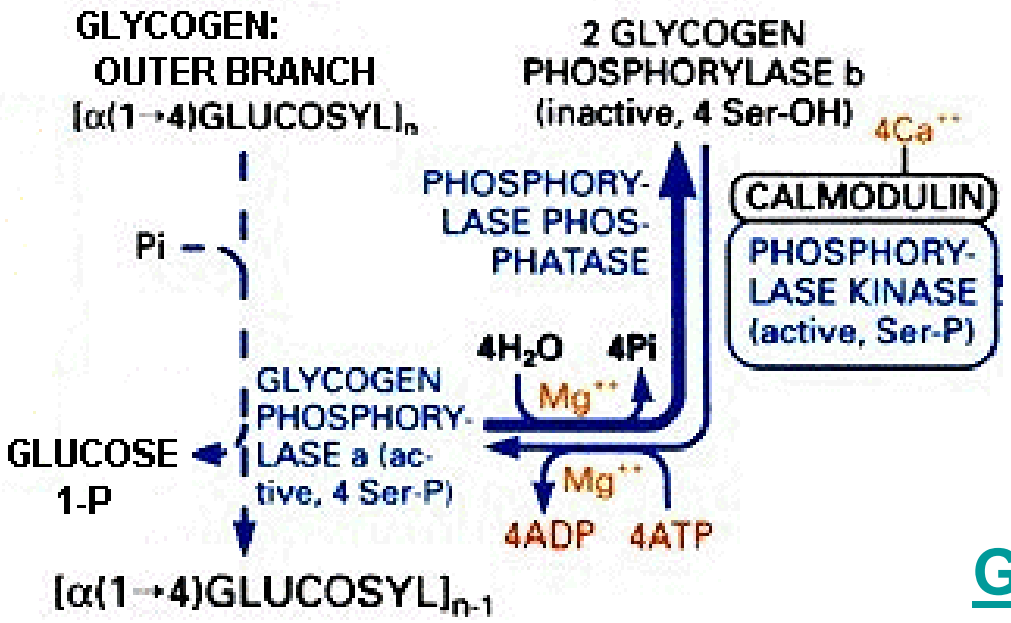


MYOPHOSPHORYLASE DEFICIENCY



Dr Brian McArdle 1911-2002

- Described the disease in 1951 in a 33 yr-old man with stiffness after exercise
- Discovered the use of scopolamine for treating seasickness in soldiers in the II World War
- Worked at the National Institute, Great Ormond Street, Brompton, Cambridge and Guy's Hospital



Glycogen phosphorylase

Removes glucose residues from α-(1,4)-linkages within glycogen molecules

Product of reaction: Glucose-1-phosphate.

MYOPHOSPHORYLASE DEFICIENCY – CLINICAL FEATURES

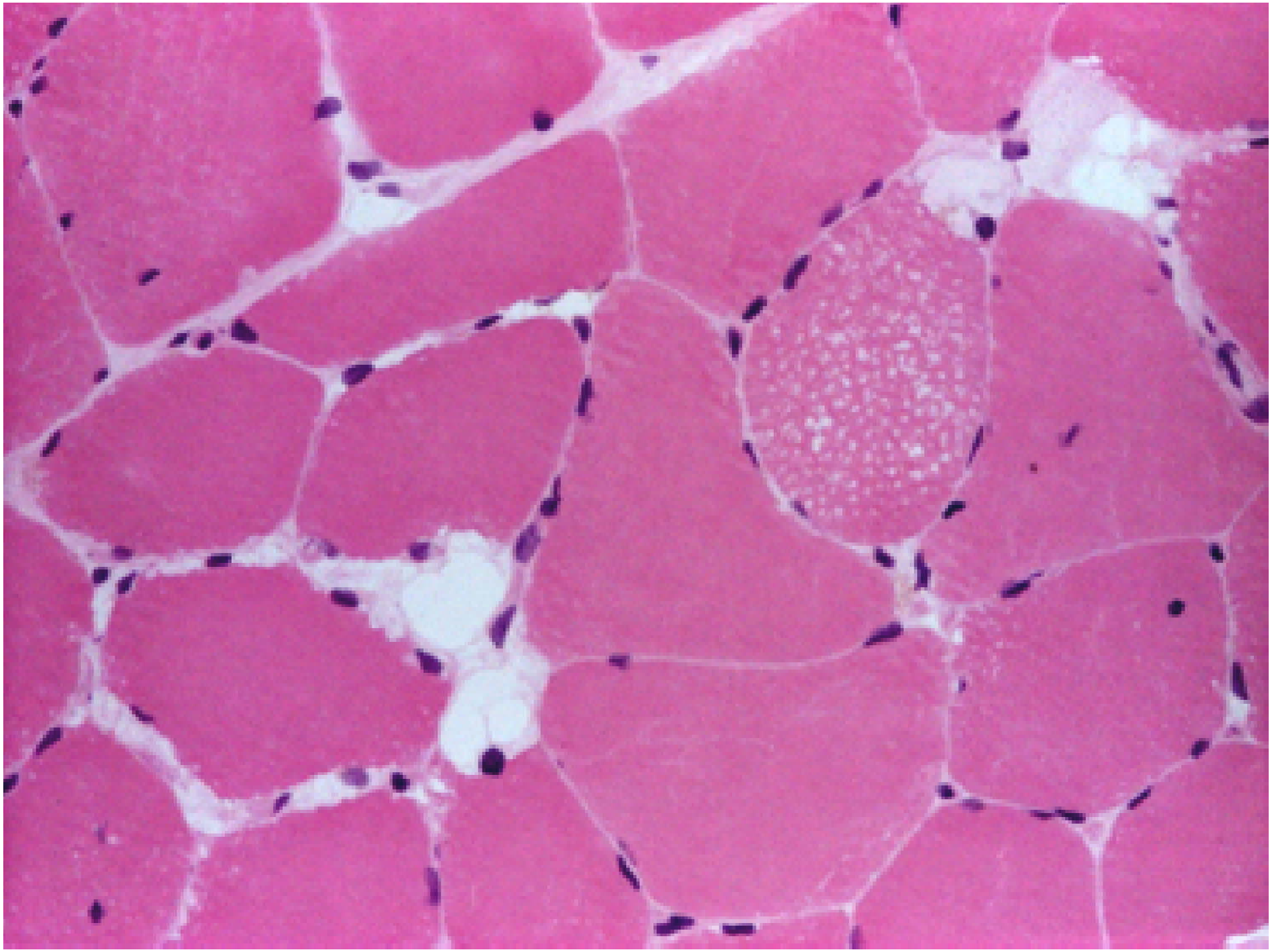
- Exclusively myopathic
- Presents with cramps and myoglobinuria following exercise – fixed weakness
- Double wind phenomenon (typical – ability of resume exercise after 10 min of rest)
- No respiratory impairment

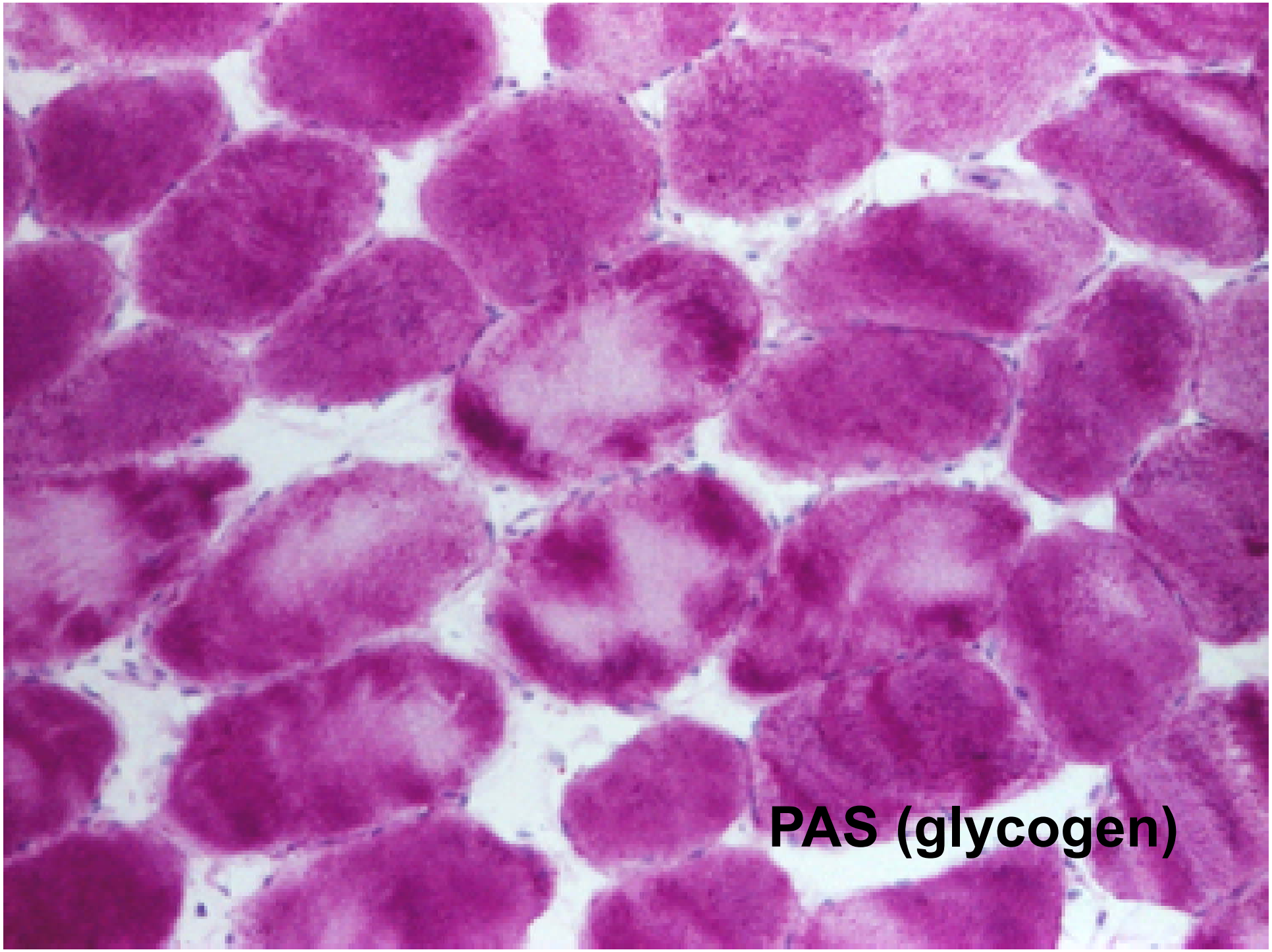
MYOPHOSPHORYLASE DEFICIENCY - GENETICS

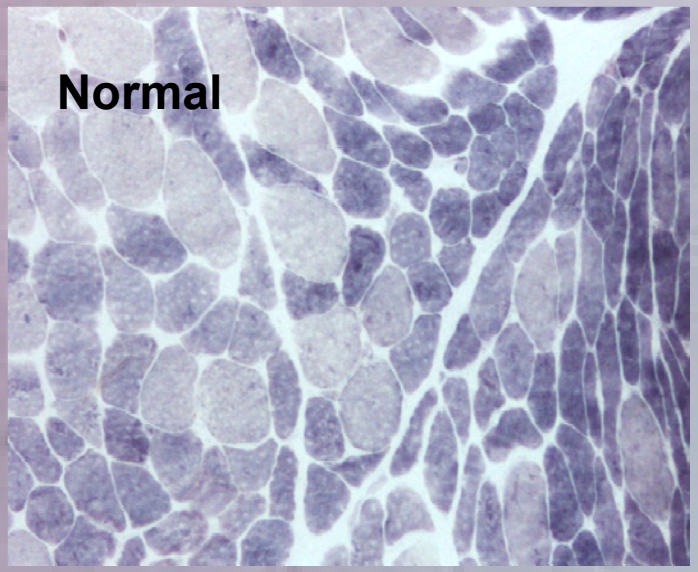
- *PYGM* gene – 11q13
- Autosomal recessive
- 80 known types of mutation
- Common stop codon mutation in exon 1 (nonsense Arg49)
- No protein expression or unstable protein
- Manifesting heterozygotic or asymptomatic carriers

MYOPHOSPHORYLASE DEFICIENCY - PATHOLOGY

- Often subtle changes – can be missed
- Subsarcolemmal vacuoles
- Subsarcolemmal glycogen accumulation
- No phophorylase activity at histology




PAS (glycogen)



Myophosphoryalse

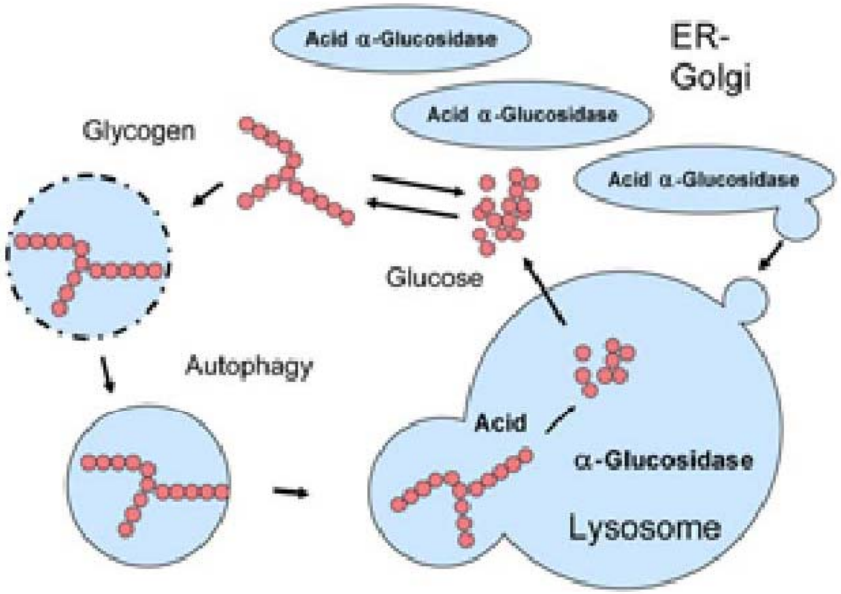
ACID MALTASE DEFICIENCY

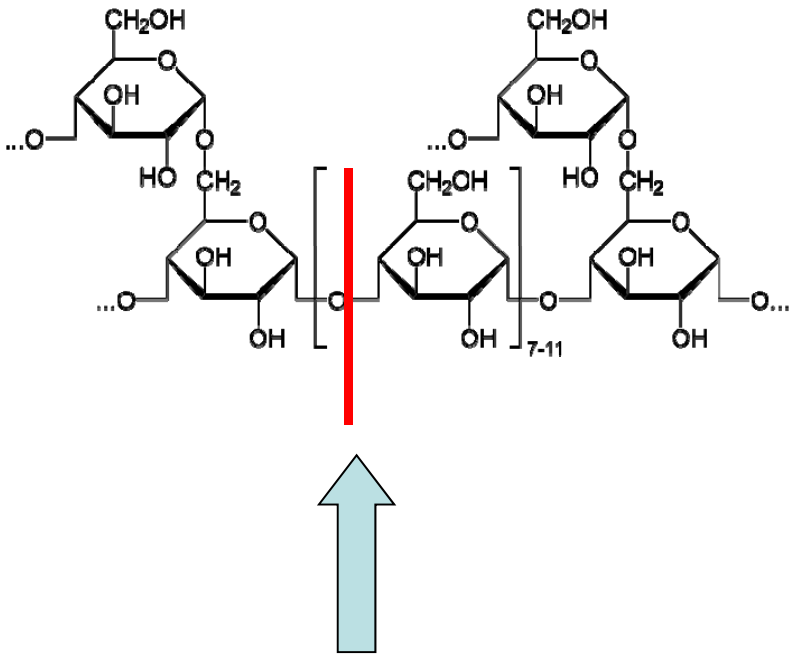
- **Synonyms: Pompe's disease; glycogenosis type II; alpha-glucosidase deficiency**

- **First reported by Johannes C Pompe in 1932 – Post-mortem of a seven-month-old infant who died suddenly from a disease associated with the accumulation of glycogen in many tissues**

- **In 1963, H.G. Hers and his co-workers link the basis of Pompe disease to an inherited absence or shortage of enzymes present within the compartment of the cell known as the lysosome, making Pompe disease the first to be classified as a lysosomal storage disease (LSD).**

Pompe Center
ErasmusMC Rotterdam





Defect of acid 1-4 alpha glucosidase (GAA) - Chr 17q25.2-q25.3

Lysosomal enzyme

Hydrolyses linear α1-4 glucosidic linkages on carbohydrates – Catalytic site: Asp-518

ACID MALTASE DEFICIENCY – Clinical features

- Disease incidence: Overall: 1 in 40,000 to 50,000 live births
- Symptoms depends of type of mutation – present when enzyme activity is below 30%
- Muscle weakness and respiratory impairment – severe in infants
- Common cardiac involvement

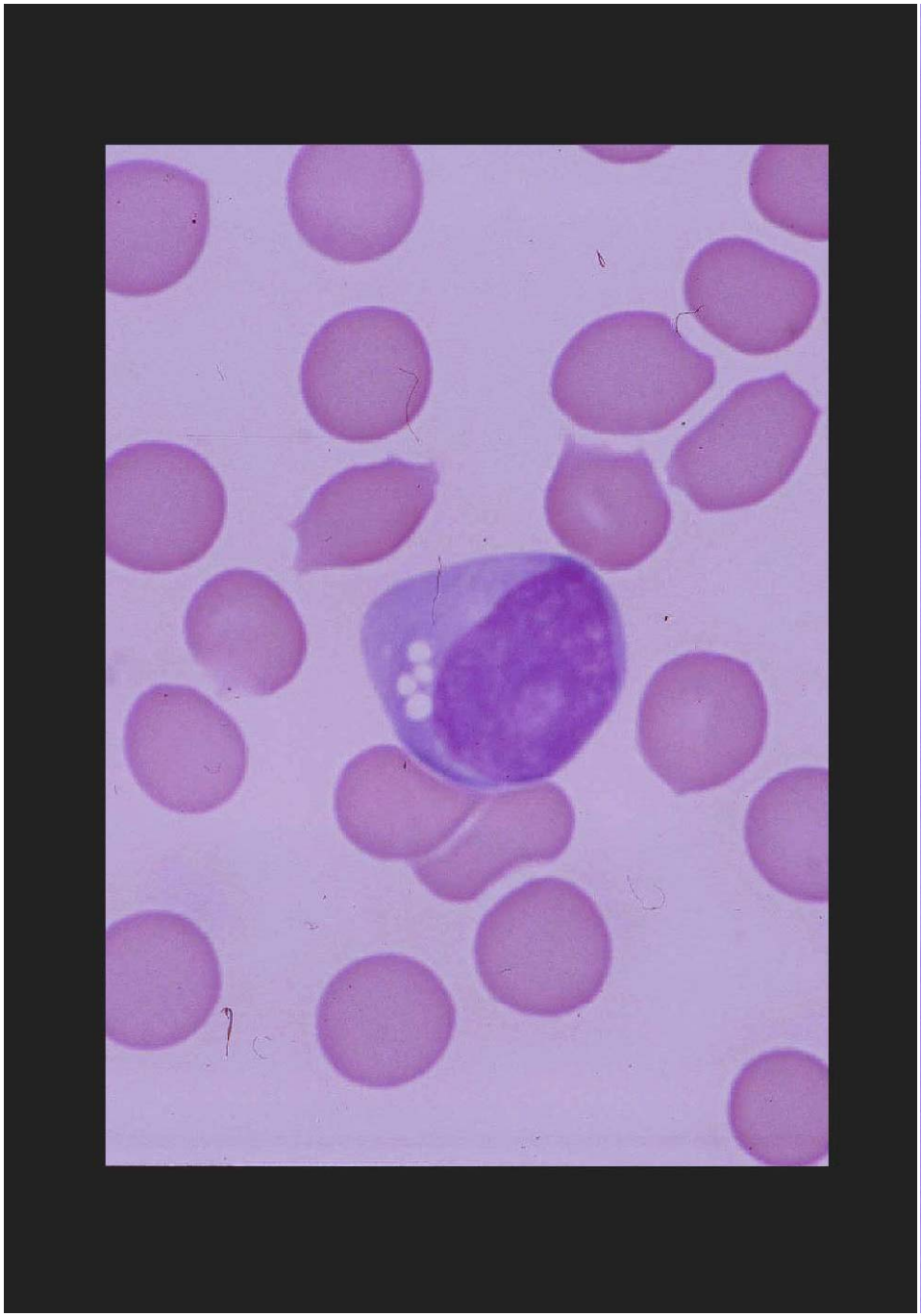
ACID MALTASE DEFICIENCY – Molecular and genetics

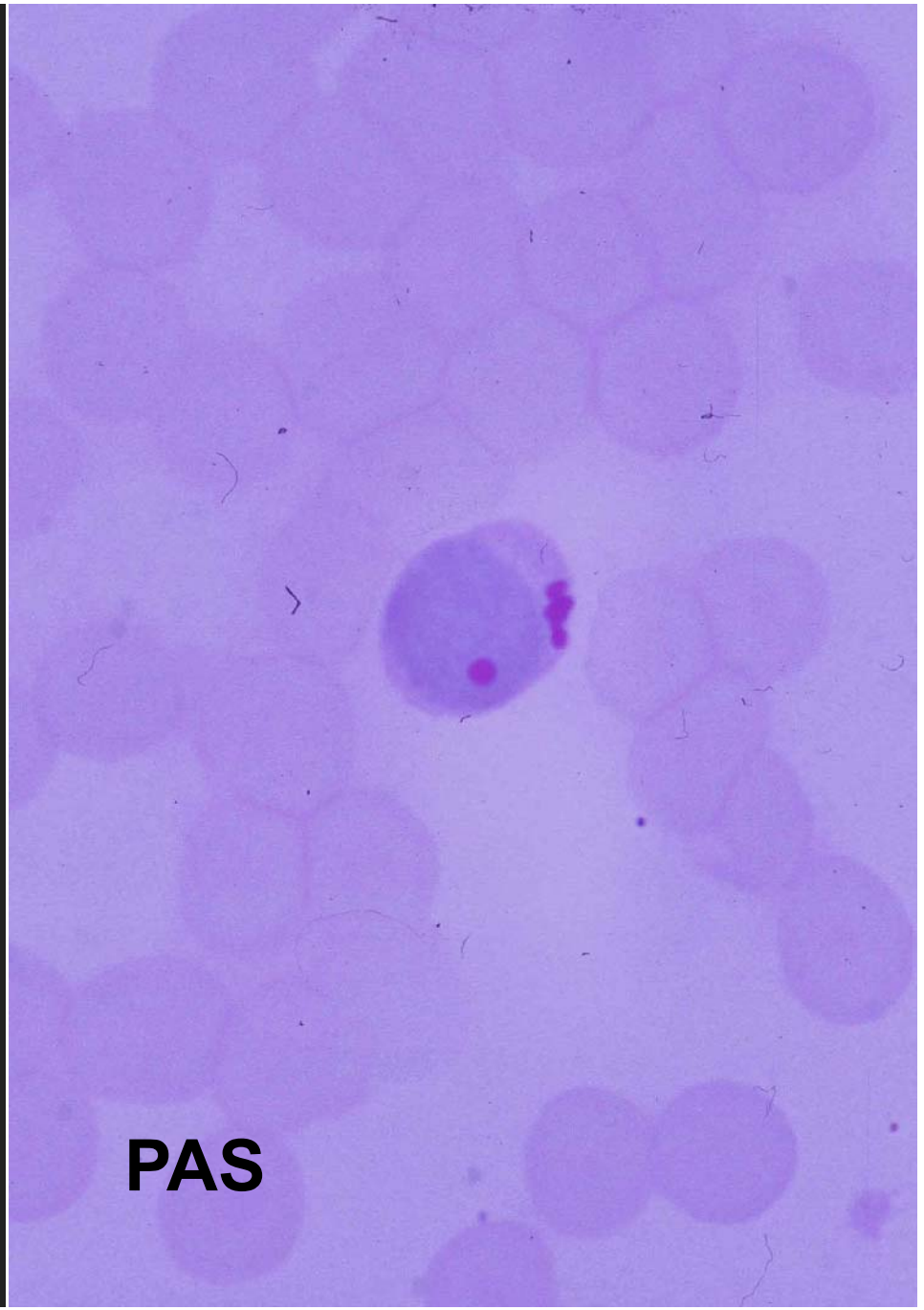
Mutation: 180 mutation identified (Lancet – 2008)

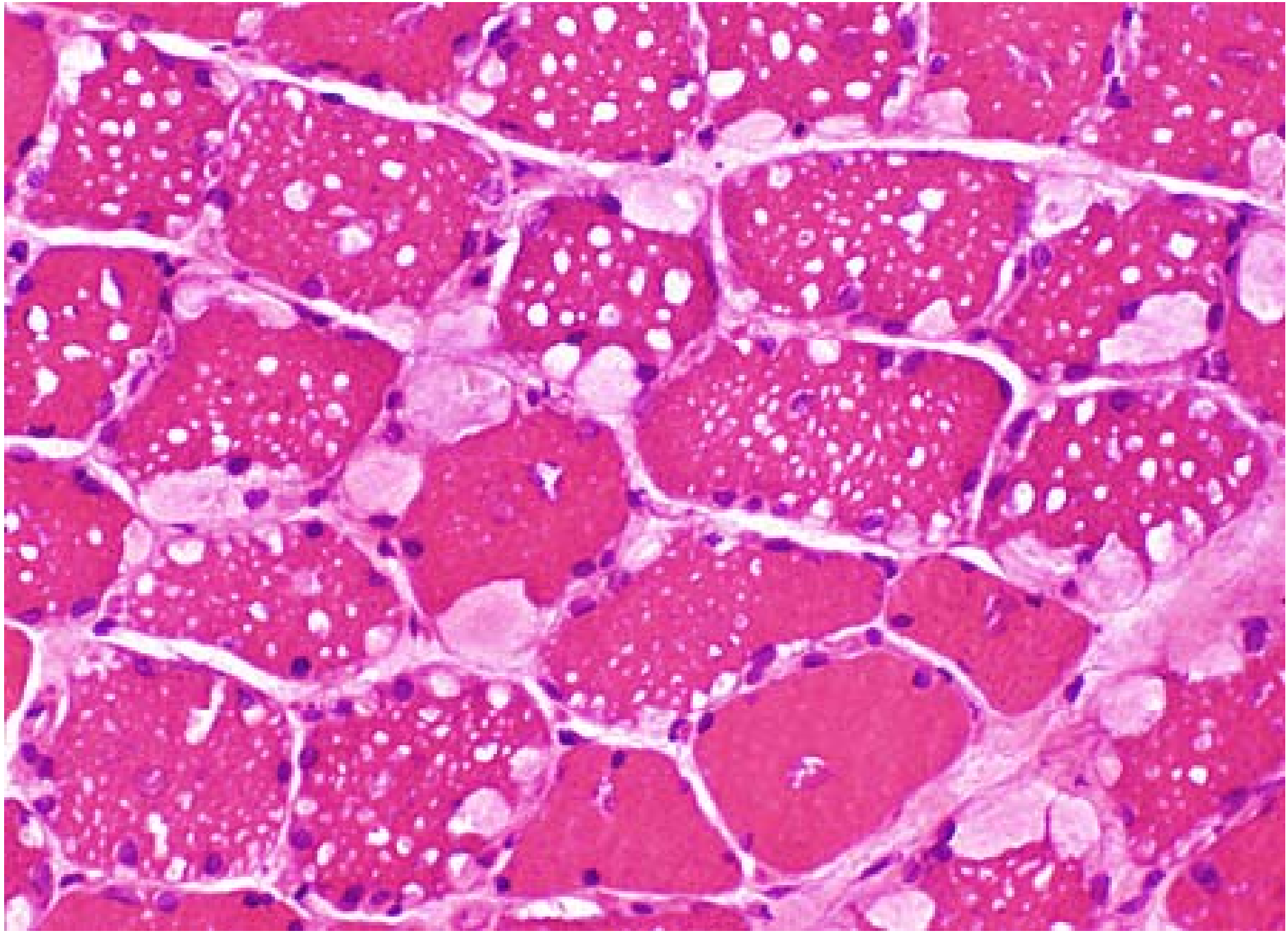
- Enzyme protein absent: Most infantile disease
- Enzyme protein & activity proportionately reduced: Adult onset
- Enzyme protein present but has little catalytic activity: May occur in infants, children or adults
- Abnormal enzyme maturation & transport
- Trp481Arg: Absent catalytic activity; Normal synthesis & posttranslational modification
- Some mutations prevent protein secretion

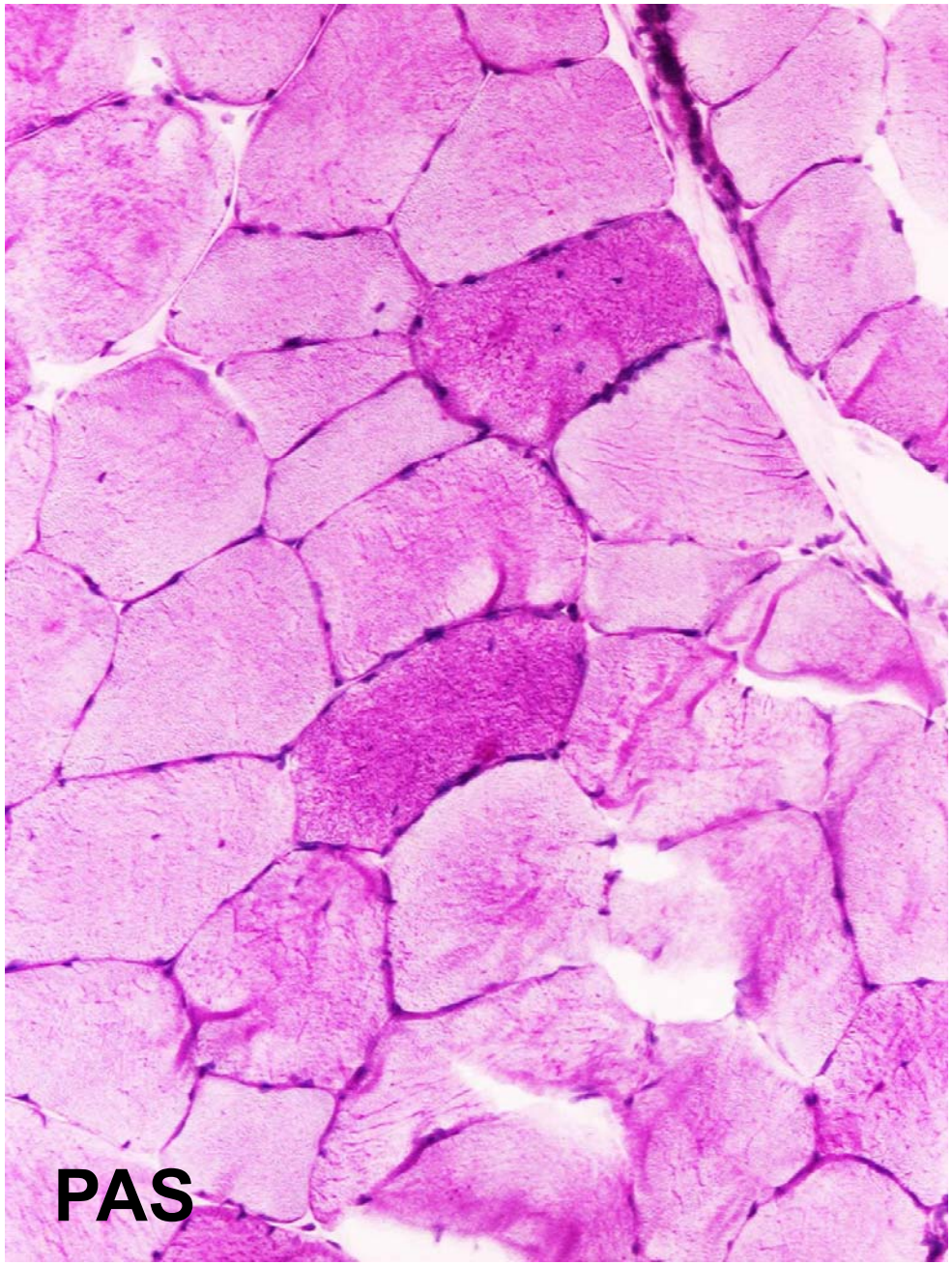
ACID MALTASE DEFICIENCY - Pathology

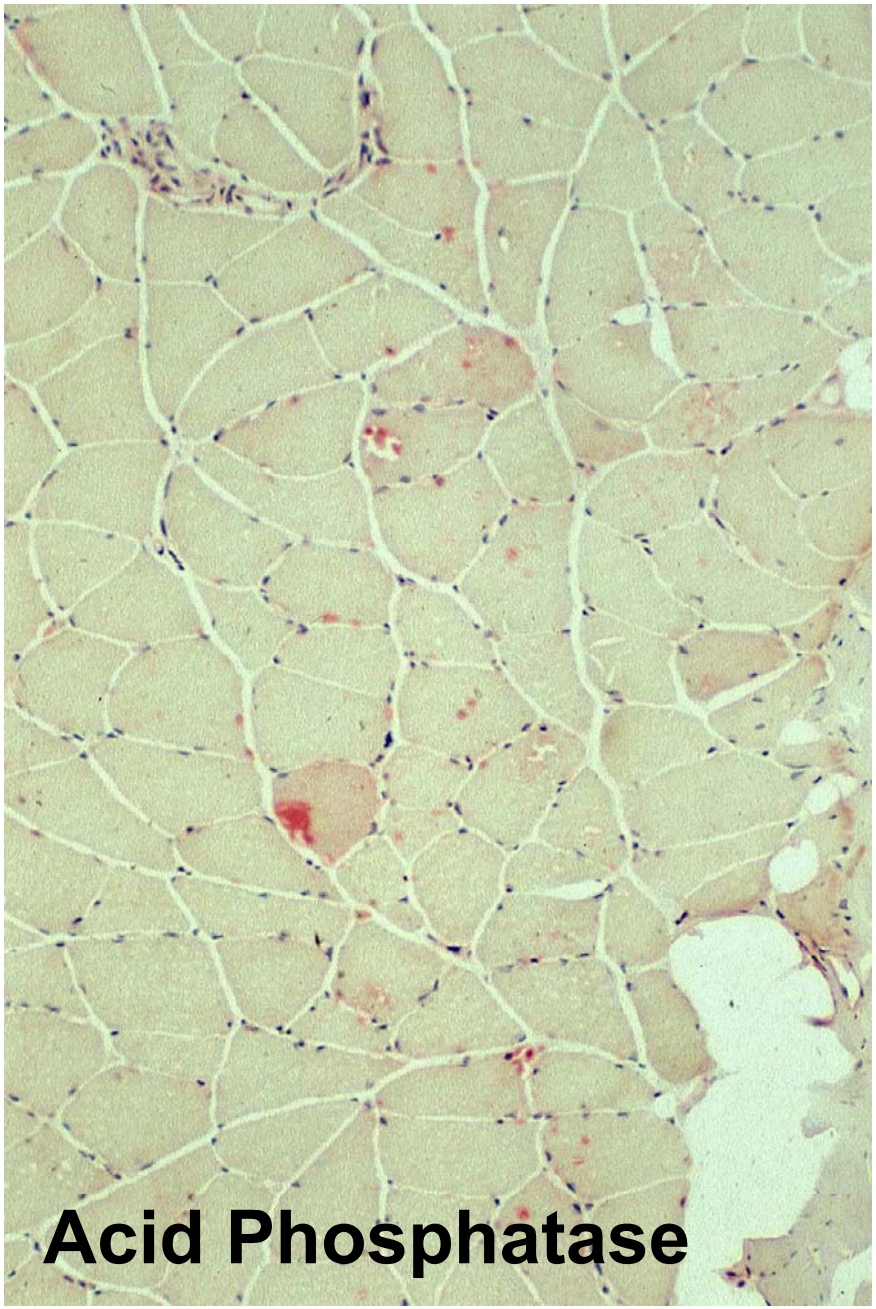
- Widespread accumulation of glycogen (positive in white blood cells)
- Vacuolar myopathy in children (accumulation of glycogen)
- Subtle changes in adults – often normal biopsy or mild, non-specific changes
- Increase in acid phosphatase activity (lysosomes)
- Focal expression of MHC class I antigen (misdiagnosed as possible myositis)
- EM can be informative (membrane-bound glycogen; within lysosomes)

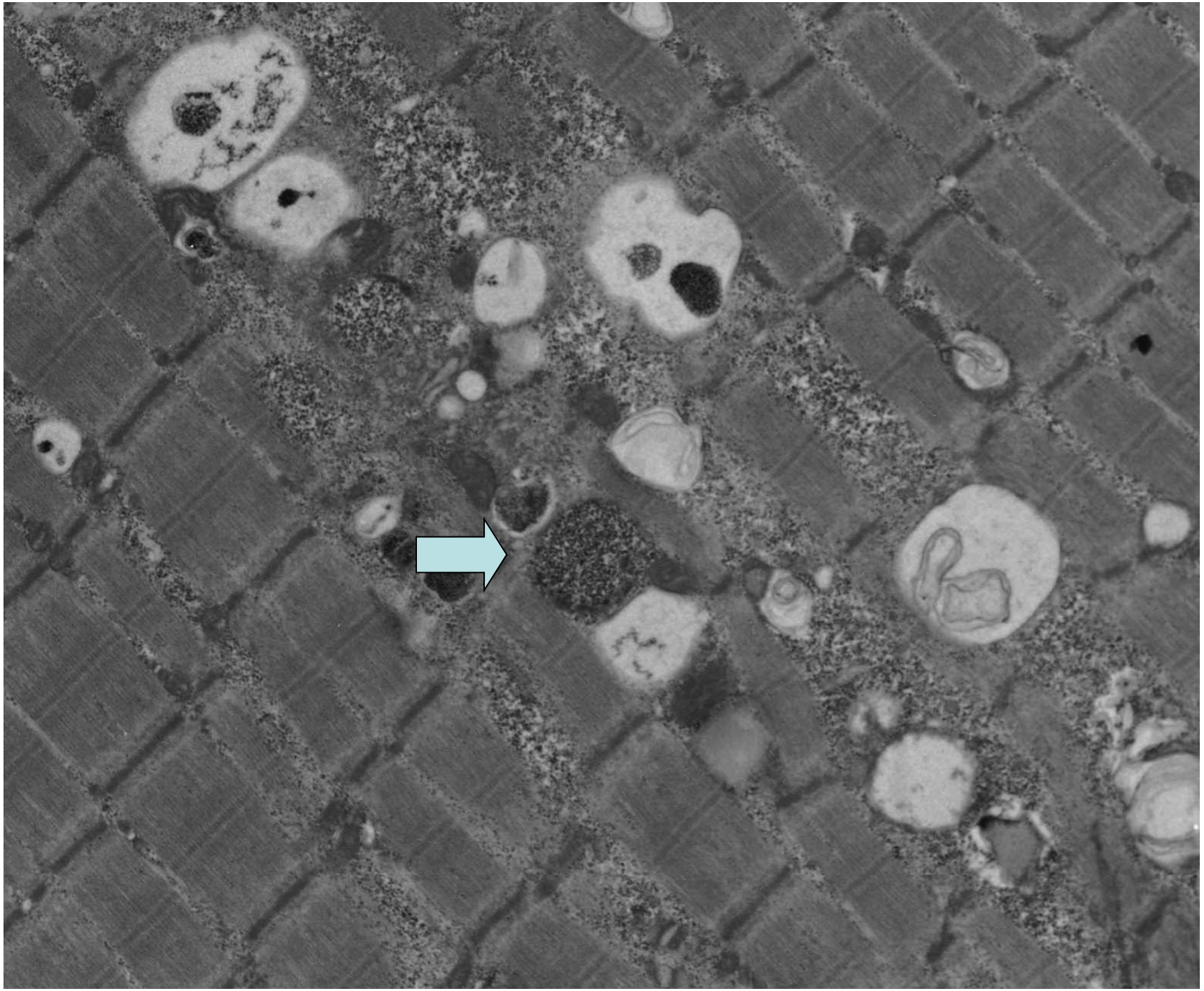



PAS




PAS


Acid Phosphatase



The NEW ENGLAND JOURNAL of MEDICINE

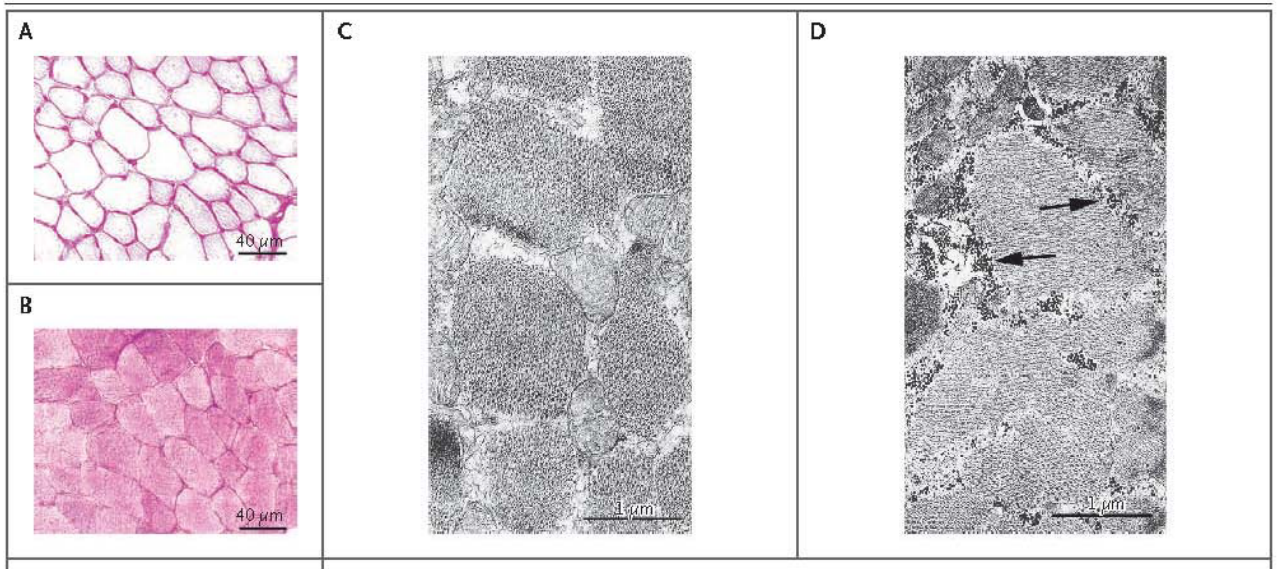
BRIEF REPORT

Cardiomyopathy and Exercise Intolerance in Muscle Glycogen Storage Disease 0

Gittan Kollberg, Ph.D., Már Tulinius, M.D., Ph.D., Thomas Gilljam, M.D., Ph.D., Ingegerd Östman-Smith, M.D., Ph.D., Gun Forsander, M.D., Ph.D., Peter Jotorp, M.D., Anders Oldfors, M.D., Ph.D., and Elisabeth Holme, M.D., Ph.D.

SUMMARY

Storage of glycogen is essential for glucose homeostasis and for energy supply during bursts of activity and sustained muscle work. We describe three siblings with profound muscle and heart glycogen deficiency caused by a homozygous stop mutation (R462→ter) in the muscle glycogen synthase gene. The oldest brother died from sudden cardiac arrest at the age of 10.5 years. Two years later, an 11-year-old brother showed muscle fatigability, hypertrophic cardiomyopathy, and an abnormal heart rate and blood pressure while exercising; a 2-year-old sister had no symptoms. In muscle-biopsy specimens obtained from the two younger siblings, there was lack of glycogen, predominance of oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal.



LIPID STORAGE MYOPATHIES

Result from defects of transport or beta-oxidation or endogenous triglycerides catabolism

Table 2 Disorders of lipid metabolism affecting muscle [12,13]

Defect	Associated clinical features	Laboratory features
Disorders causing reversible muscle symptoms: exercise intolerance, myalgia, myoglobinuria		
CPT II deficiency	Late-onset form limited to muscle Onset typically young adults	Carnitine levels moderately reduced or normal Mutations in *CPT II* gene
VLCAD deficiency	Late-onset form limited to muscle	Increased serum long-chain acylcarnitines: normal/low free carnitine Dicarboxylic aciduria on fasting/exercise Mutations in *VLCAD* gene
Trifunctional protein (LCHAD) deficiency	Hypoglycaemia, coma, hepatomegaly, cardiomyopathy, muscle weakness, peripheral neuropathy, retinopathy Usually presents infancy/childhood	Increased serum long-chain 3-hydroxy-acylcarnitines Dicarboxylic aciduria
Disorders causing progressive myopathy and persistent weakness		
Primary muscle carnitine deficiency	Restricted to muscle. Onset typically second or third decade	Low muscle carnitine, normal plasma carnitine Normal acylcarnitine : free carnitine ratio No dicarboxylic aciduria
Primary systemic carnitine deficiency	Cardiomyopathy, hypoketotic hypoglycaemia, coma, anaemia Onset usually in first decade	Low plasma and muscle carnitine Normal acylcarnitine : free carnitine ratio No dicarboxylic aciduria Reduced carnitine transport in skin fibroblasts. Mutations in gene encoding OCTN2
Riboflavin-responsive MADD	Weakness may fluctuate Frequently affects neck flexors/extensors	Glutaric aciduria type II Low muscle MCAD and SCAD activity Mutations in gene encoding ETF : QO
MCAD deficiency	Hypoketotic hypoglycaemia, coma, Reye-like syndrome Onset usually at age of 12–18 months	Low plasma and muscle carnitine Increased acylcarnitine : free carnitine ratio Medium-chain dicarboxylic aciduria Increased FFA : ketone ratio and ammonia during attacks Mutation 329 lysine to glutamine in 90% (1p31)
SCAD deficiency	Hypoglycaemia, vomiting, seizures, developmental delay Onset usually infancy	Increased serum butyryl-carnitine Increased urine ethylmalonic acid Mutations in SCAD encoding gene

Lipid storage myopathies

Claudio Bruno[a] and Salvatore DiMauro[b]

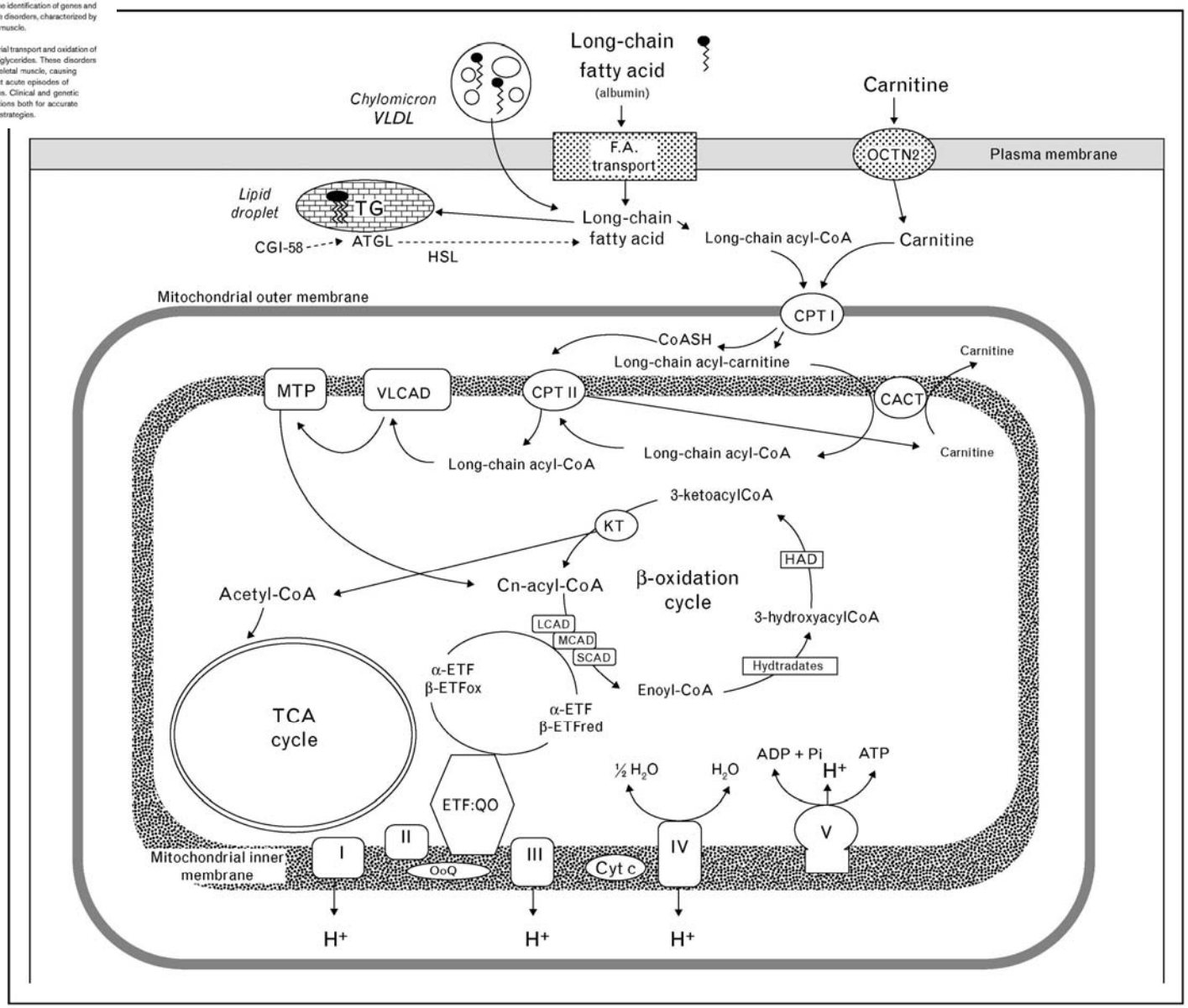
[a]Muscular and Neurodegenerative Diseases Unit, Giannina Gaslini Institute, Genova, Italy and [b]Department of Neurology, Columbia University Medical Center, New York, New York, USA

Correspondence to Dr Claudio Bruno, MD, Istituto Giannina Gaslini, Largo G. Gaslini 5, I-16147 Genova, Italy
Tel: +39 010 5636756; fax: +39 010 3538265; e-mail: claudiobruno@ospedale-gaslini.ge.it

Current Opinion in Neurology 2006, 21:601–606

Purpose of review
The aim of this review is to provide an update on disorders of lipid metabolism affecting skeletal muscle exclusively or predominantly and to summarize recent clinical, genetic, and therapeutic studies in this field.
Recent findings
Over the past 5 years, new clinical phenotypes and genetic loci have been described, unusual pathogenic mechanisms have been elucidated, and novel pharmacological approaches have been developed. At least one genetic defect responsible for the myopathic form of CoQ10 deficiency has been identified, causing a disorder that is allelic with the late-onset riboflavine-responsive form of multiple acyl-coenzyme A dehydrogenation deficiency. Novel mechanisms involved in the lipolytic breakdown of cellular lipid depots have been described and have led to the identification of genes and mutations responsible for multisystemic neutral lipid storage disorders, characterized by accumulation of triglyceride in multiple tissues, including muscle.
Summary
Defects in lipid metabolism can affect either the mitochondrial transport and oxidation of exogenous fatty acid or the catabolism of endogenous triglycerides. These disorders impair energy production and almost invariably involve skeletal muscle, causing progressive myopathy with muscle weakness, or recurrent acute episodes of rhabdomyolysis triggered by exercise, fasting, or infections. Clinical and genetic characterization of these disorders has important implications both for accurate diagnostic approach and for development of therapeutic strategies.

ne of selected metabolic pathways of fatty acid transport and oxidation

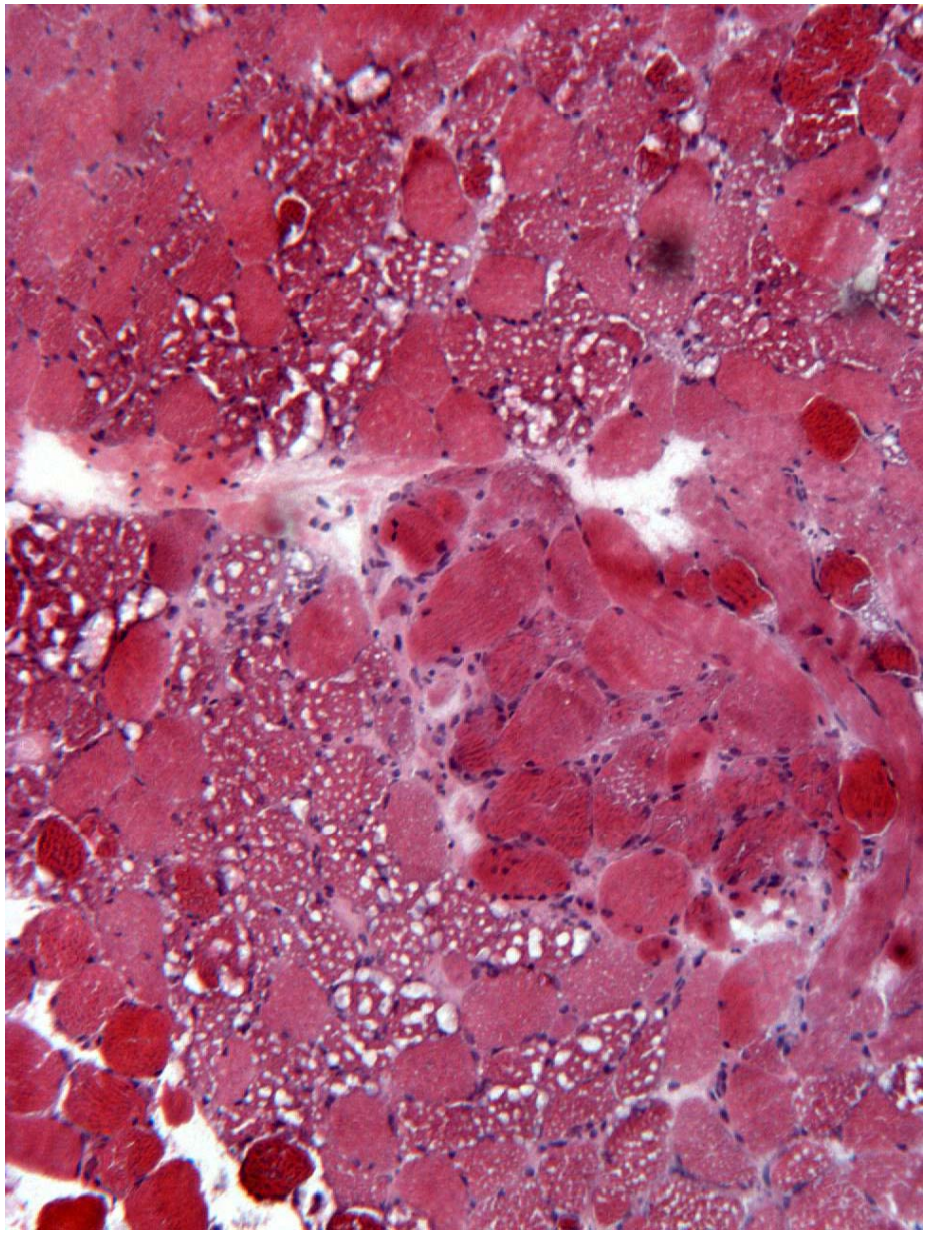


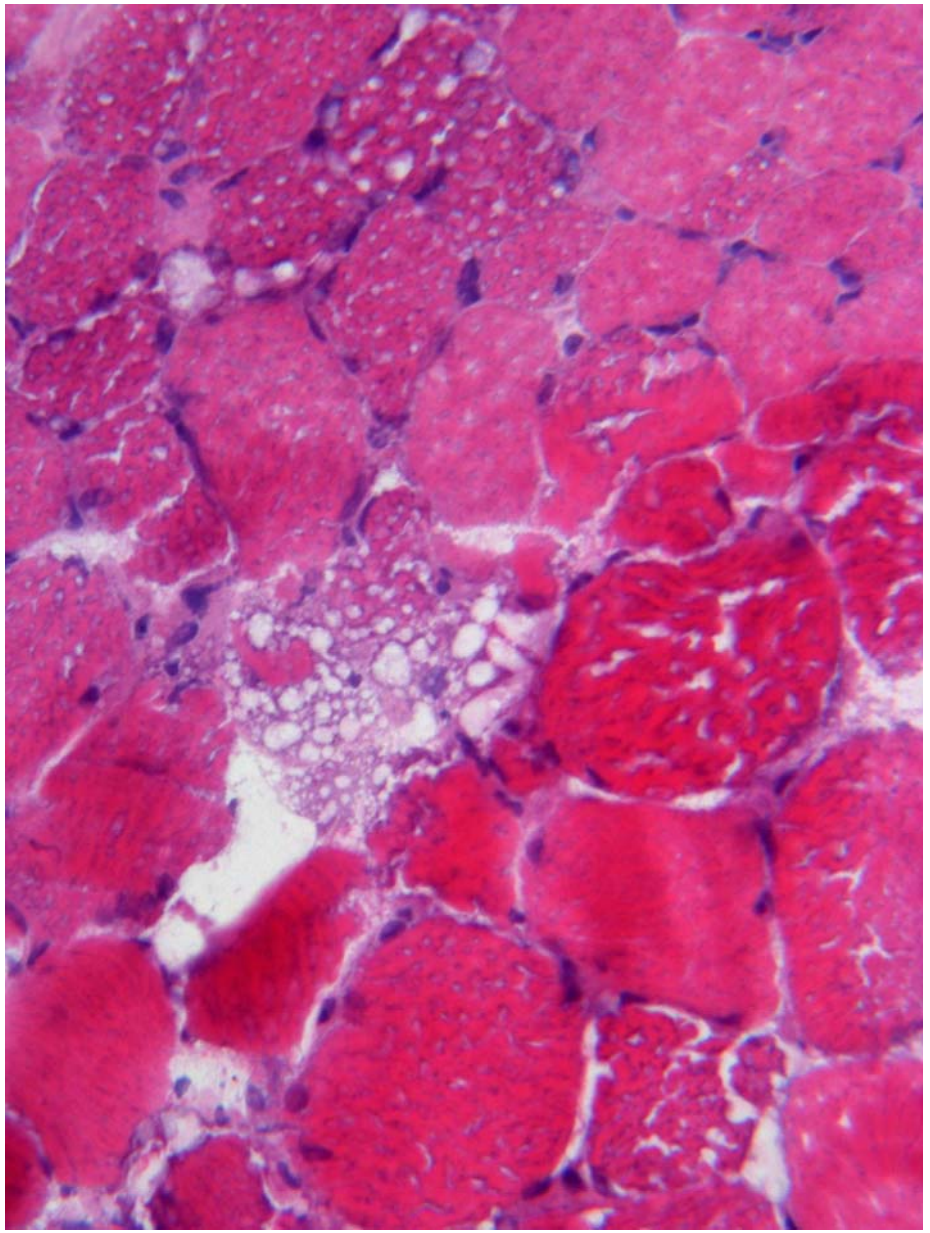
LIPID STORAGE MYOPATHIES – CLINICAL FEATURES

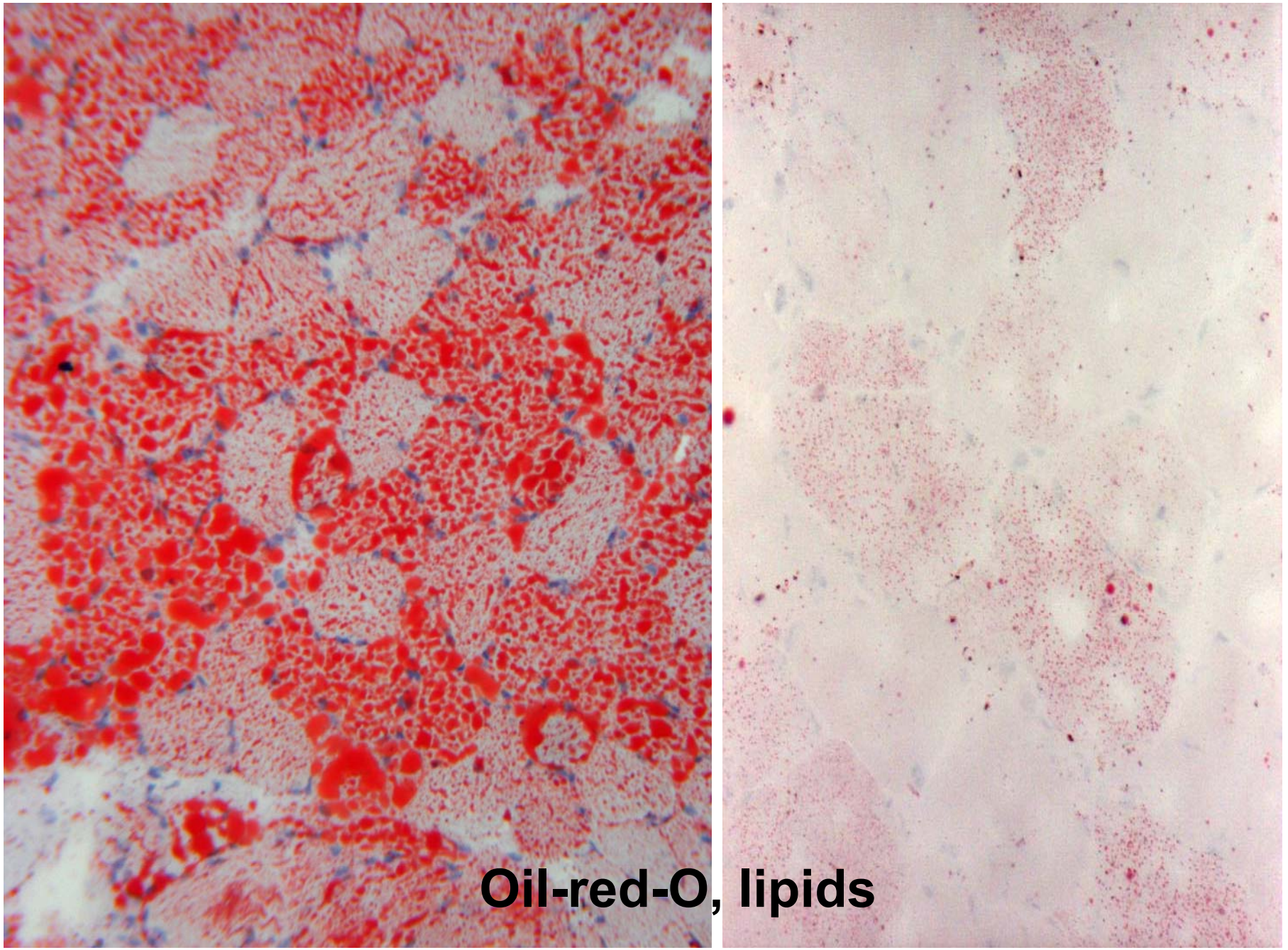
- Uncommon conditions – incidence unknown
- Infants and adults; often misdiagnosed
- Various clinical presentation: progressive myopathy with muscle weakness or recurrent episodes of rhabdomyolysis - Intolerance to exercise

LSM - PATHOLOGICAL FEATURES

- **Muscle biopsy often normal or with mild, non-specific changes (***i.e. disorders of endogenous FA catabolism***)**
- **Accumulation of lipid droplets (***bigger and more numerous than normal muscle***)**
- **Fibre necrosis in some patients presenting with rhabdomyolysis**






Oil-red-O, lipids

REFERENCES

Review Article

Journal of CLINICAL NEUROMUSCULAR DISEASE

97

Volume 10, Number 3
March 2009

Metabolic Myopathies: Update 2009

Brian A. van Adel, MD, PhD, and Mark A. Tarnopolsky, MD, PhD, FRCPC†*

Metabolic myopathies: a guide and update for clinicians

Marian L. Burr[a], Jonathan C. Roos[b] and Andrew J.K. Östör[c]

[a]Arthritis Research Campaign (arc)-Epidemiology Unit, Stopford Building, The University of Manchester, Manchester, [b]Department of Medicine, University of Cambridge, Cambridge and [c]Department of Rheumatology, School of Clinical Medicine, University of Cambridge, Cambridge, UK

Correspondence to Andrew J.K. Östör, Department of Rheumatology, School of Clinical Medicine, University of Cambridge, Cambridge, CB2 2QQ, UK
Tel: +44 1223 217457;
e-mail: andrew.ostor@addenbrookes.nhs.uk

Current Opinion in Rheumatology 2008, 20:639–647

Purpose of review

The present review will focus on the clinical features, and recent advances in the investigation and treatment, of metabolic muscle disease. The aim is to present a summary of this vast and complex topic emphasizing key points of relevance to nonspecialists in the field. Salient examples from each category will be highlighted to illustrate characteristic features and potential sources of diagnostic confusion. The general approach to management will then be outlined.

Recent findings

Awareness of these diseases has grown over recent years, as has appreciation of their variable clinical presentation. Many of the precise genetic and biochemical abnormalities underlying these conditions have been elucidated and novel enzyme defects continue to be discovered. Perhaps the greatest progress, however, has been made in the management of disease. Advances in tandem mass spectrometry techniques have facilitated the introduction of nationwide neonatal screening programmes for a large number of metabolic disorders. Enzyme replacement in Pompe disease has proved successful, improving outcome in a hitherto untreatable condition. Progress towards gene therapy, perhaps the ultimate goal, has been made in animal models.

Summary

Although individually rare, the metabolic myopathies together constitute a significant group of disabling and potentially life-threatening disorders. Appropriate investigations, timely treatment and genetic counselling are paramount to ameliorate the short and long-term consequences of disease.

Keywords

carnitine palmitoyltransferase II deficiency, glycogenoses, lipidoses, McArdle disease, metabolic myopathy

Curr Opin Rheumatol 20:639–647

1040-8711

http://neuromuscular.wustl.edu/