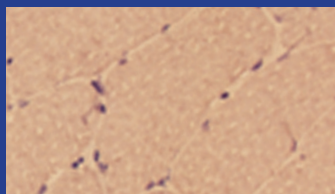
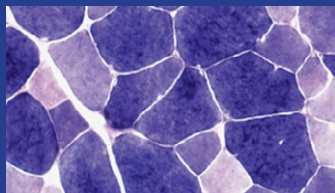


The McArdle Disease Handbook

A guide to the scientific and medical
research into McArdle Disease,
explained in plain English.



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Association for Glycogen Storage Disease (UK) Ltd
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In case of discrepancies between the different language versions of the Handbook, the English version is the original version and will prevail.

Disclaimer

Unless otherwise stated, this Handbook represents the views and opinions of the author, Kathryn Birch, and does not represent the views and opinions of AGSD-UK or Vodafone World of Difference. The purpose of this Handbook is to explain scientific research and knowledge about McArdle disease in layman's language so that it can be understood by people with McArdle disease or those interested in McArdle disease. It is not intended to replace medical advice from your family doctor or specialist. The information provided in this Handbook is correct to the best of the author's knowledge. If you have any doubts about the accuracy of the information in this Handbook, it is recommended that you read the original source (full details in the reference list). Where no definitive information is available, the author has sought to suggest scientific rationale behind anecdotal observations reported by people with McArdle's. It is stated where a theory or opinion of the author is given. Due to the nature of scientific research, current theories and understanding of the science behind McArdle's may change over time and subsequently be proven or disproven. It is recommended that you check the AGSD-UK website frequently to ensure you are reading the most up-to-date version of this Handbook.

Cover pictures

Left: People with McArdle disease can experience severe muscle damage, which is indicated by raised creatine kinase levels. There is a risk of kidney damage so hospitalisation may be required. Stacey Reason and Dan Chambers have both experienced severe muscle damage with creatine kinase levels of over 200,000 IU/L (about a thousand times the normal level).

Right: By working to regain their fitness, creating a high aerobic capacity and learning helpful techniques (like the use of walking poles as shown here) Stacey Reason and Dan Chambers completed the 210 mile "Walk over Wales" in the summer of 2010. Some people with McArdle's cannot achieve these results and remain badly affected, ongoing research is trying to find the answers. Thanks to Stacey and Dan for permission to use their photos.

Centre: McArdle disease is caused by an absence of muscle glycogen phosphorylase. McArdle disease can be diagnosed by muscle biopsy. A chemical reaction is carried out which produces a red/purple colour if muscle glycogen phosphorylase enzyme is present. Muscle biopsy photographs are reproduced by kind permission of Professor Caroline Sewry, Great Ormond Street Hospital, London and RJA Orthopaedic Hospital, Oswestry.

Centre top: Normal muscle showing muscle glycogen phosphorylase enzyme.

Centre bottom: Muscle of a person with McArdle disease showing absence of the enzyme.

Definitions of terms used in this Handbook

In this Handbook, "McArdle person" is used to mean a person who has received a definitive diagnosis of McArdle disease (who has no functional muscle glycogen phosphorylase enzyme in their skeletal muscle cells). McArdle people have two faulty copies of the *PYGM* gene. In a McArdle person, both copies of the *PYGM* gene contain a mutation which prevents functional muscle glycogen phosphorylase being made.

"Unaffected by McArdle's" is used in this Handbook to describe a "normal" person who has no mutations in either copy of the *PYGM* gene. People unaffected by McArdle's have two normal copies of the *PYGM* gene. Normal copies of the *PYGM* gene contain no mutations, and can be used to make functional muscle glycogen phosphorylase. People unaffected by McArdle's have a normal amount of functional muscle glycogen phosphorylase in their muscle cells.

"Carrier" is used to describe a person who has one normal copy of the *PYGM* gene without any mutations, and one faulty copy of the *PYGM* gene which contains a mutation. A carrier is likely to have approximately half the normal level of muscle glycogen phosphorylase. Carriers do not usually have symptoms of McArdle disease.

Further definitions are given where appropriate throughout the Handbook. There is also a glossary at the end of the Handbook for scientific or medical words used frequently in the Handbook which would not be included in a standard English glossary.

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Comments and feedback about this Handbook

To contact the author please visit the AGSD-UK web site at: www.agsd.org.uk and use the "Contact Us" page, choosing "McArdle Disease Handbook".

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Types of Glycogen Storage Disease

- Type 0
- Type I
Von Gierke Disease
- Type II
Pompe Disease
- Type III
Cori Disease
- Type IV
Andersen Disease
- Type V
McArdle Disease
- Type VI
Hers Disease
- Type VII
Tarui Disease
- Type IX

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Glycogen Storage Disease Type V (McArdle Disease)

● Site map of McArdle pages

Also known as myophosphorylase deficiency.

McArdle disease is a rare metabolic disorder which causes muscle pain in everyday activities and exercise. If activity is prolonged despite the pain then muscle damage ensues with the risk of muscle breakdown and kidney failure.

Symptoms are usually apparent during the first decade of life but many people do not manage to obtain a diagnosis until the third or fourth decade. Later in life some people with McArdle disease experience fixed muscle weakness, possibly from cumulative muscle damage. It is important for those with McArdle disease to take regular aerobic exercise such as walking and avoid anaerobic activities such as lifting heavy weights.

Type V summary

Symptoms	Muscle pain on everyday activity and exercise. Fatigue. Fixed contractures with rhabdomyolysis.
Secondary symptoms	Raised urate level. Possible muscle wasting.
Treatment	No specific treatment. Maintain healthy diet, control weight, take gentle aerobic exercise.
Outlook	Good with gentle aerobic exercise and avoidance of anaerobic activity.

Coordinator

The Coordinator for Type V is Andrew Wakelin. You can contact him via the **Contact us** page, or telephone him on 01597 860686.

About the disease

- More about McArdle disease from Dr Ros Quinlivan
- McArdle Emergencies Guidance for patients and information for emergency doctors
- The UK McArdle Clinic multi-disciplinary team
- Support for patients sources of help and information
- NEW The McArdle Disease Handbook - Kathryn Birch - A guide to the scientific and medical research into McArdle Disease explained in plain English
- NEW Information Cards order these handy cards to help explain the disease
- Tips for people with McArdle's - living with the disease

Exercise and McArdle Disease

- Exercise and McArdle disease second wind and the 6 second rule
- NEW Adapting activity understanding how to protect ourselves
- Starting an exercise programme advice for those who are very de-conditioned
- Walking with McArdle's more advanced hints and tips
- Walking with McArdle's - Wales a week's holiday, learn how to best

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Book the date now - Saturday and Sunday 22nd to 23rd October. The Holiday Inn, Telford (Ironbridge). Details here.

Walking with McArdle's - Wales

Follow the blog. Walkers from around the world learn how best to cope with McArdle's and enjoy a week's walking holiday in Snowdonia.

Testimonials.

Daily blog.

Photo gallery.

Full details.

Visit the McArdle Disease pages on www.agsd.org.uk for information and regular updates.

1 Introduction to McArdle disease

McArdle disease is caused by the lack of the muscle glycogen phosphorylase enzyme in muscle cells. This enzyme is a special protein which plays a key role in changing glycogen into glucose in the muscle cells. Glucose can then be used to provide energy to allow the muscle to contract and generate movement. In McArdle people, muscle glycogen phosphorylase does not function. During exercise, the muscle cells of McArdle people use up all their energy and are not able to generate further energy. The short term lack of glucose causes tiredness and stiffness in muscles of McArdle people when they carry out exercise, and can lead to muscle pain and muscle breakdown.

Without muscle glycogen phosphorylase, the glycogen which is stored in the muscle cells cannot be changed into glucose. The glycogen therefore accumulates in the muscle cells, which is the reason why McArdle disease is known as a “glycogen storage disease”.

McArdle disease is named after Dr Brian McArdle, a doctor who published the first medical paper describing his patient who had this muscle disease.

1.1 A brief introduction to McArdle disease

Muscle contractions are required to generate movement. Muscle cells require a source of energy in order to perform muscle contractions. Anaerobic exercise is a short burst of high intensity effort, such as a sprint for a bus. During anaerobic exercise, glucose within muscle cells is broken down to produce ATP. ATP is the source of energy for muscle cells. The breakdown of glucose to produce ATP is called “glycolysis”. However, only a small amount of glucose is present in the muscle cells and this is used up within a few minutes of anaerobic exercise.

Muscle cells also contain much larger stores of glycogen. Glycogen can be converted into glucose by a process called “glycogenolysis”. In people unaffected by McArdle disease, the process of converting glycogen into glucose requires several enzymes, one of which is called “muscle glycogen phosphorylase”.

McArdle disease is caused by the lack of the muscle glycogen phosphorylase enzyme in muscle cells. In McArdle people, muscle glycogen phosphorylase is either absent or not functional. The muscle cells are not able to convert the stored glycogen into glucose. The muscle cells therefore run out of glucose and run out of energy. The short term lack of glucose causes tiredness and stiffness in muscles of McArdle people when they carry out anaerobic exercise (Rommel *et al.*, 2006), but this improves once exercise ceases.

McArdle people must rest until energy (ATP) is produced in the muscle cells by another method such as fatty acid oxidation or until glucose is obtained through the blood from the liver. A period of rest is necessary because these other methods are slower to produce energy than glycogenolysis (the method which normally involves muscle glycogen phosphorylase). Once these other methods begin to replenish the amount of ATP in the muscle cells, McArdle people can continue to exercise. This is known as a “second wind” (Amato, 2003).

However, if McArdle people continue to exercise without rest, the muscle cells use up all the available ATP and have no energy source available. This can lead to breakdown of muscle cells (rhabdomyolysis) and muscle cramps (fixed contractures), both of which cause McArdle people to experience muscle pain. Following rhabdomyolysis, the components of the broken muscle cells are released into the bloodstream. An enzyme normally found in muscle cells called creatine kinase (CK) (also known as creatine phosphokinase (CPK)) is released into the bloodstream following muscle damage. A blood test performed by a family doctor or at a hospital can be used to measure the amount of CK in the blood, which can be used as an indicator of the extent to which muscle damage has occurred. The components of the broken muscle cells are transported through the bloodstream to the kidneys. Myoglobin is another protein released from broken muscle cells. Myoglobin is transported in the bloodstream to the kidneys, where it is removed from the body in the urine, resulting in dark red/cola coloured urine (known as myoglobinuria or proteinuria). A rare, but serious effect of extreme muscle damage is that broken muscle cells may block the filtration system of the kidneys, preventing them working, and resulting in kidney failure (Martin *et al.*, 2001; DiMauro *et al.*, 2002; Quinlivan *et al.*, 2008).

1.2 What is the cause of McArdle disease?

McArdle disease is caused by the absence of the muscle glycogen phosphorylase enzyme (Mommaerts, 1956; Schmid *et al.*, 1959). An enzyme is a protein which has a special function of

changing or breaking down one compound to another. Muscle glycogen phosphorylase breaks down glycogen into glucose-1-phosphate. A mutation in the *PYGM* gene which is responsible for muscle glycogen phosphorylase prevents the production of functional muscle glycogen phosphorylase.

1.3 McArdle disease is one of the family of glycogen storage diseases

There are many enzymes involved in the breakdown of glycogen into glucose. If a mutation occurs in the enzyme which prevents it from functioning, it will result in an inability to break down glycogen and its components to form glucose. Diseases caused by a mutation in an enzyme required to break down glycogen are called “glycogen storage diseases (GSDs)”. The glycogen storage diseases identified to date are listed in Table 1.1. There is further information about the glycogen storage diseases on the AGSD-UK website (<http://www.agsd.org.uk>). The major symptom of every glycogen storage disease is an intolerance to exercise. Glycogen storage is characteristic of all the diseases except GSD 0. Tarnopolsky *et al.* (2006) described McArdle disease as the most common glycogen storage disease.

GSD VIII is caused by a mutation in phosphorylase b kinase. Phosphorylase b kinase is essential for activation of the muscle glycogen phosphorylase enzyme. However, disease symptoms for GSD VIII are not very similar to McArdle disease, possibly because there are difference mechanisms for activation of muscle glycogen phosphorylase in the absence of phosphorylase b kinase (Orngreen *et al.*, 2009).

1.4 Why is it called “McArdle disease”?

McArdle disease is named after Dr Brian McArdle, the British family doctor who first published a paper describing a patient with the disease. In 1951, Dr McArdle described a 30 year old male patient for whom light exercise caused pain in the muscles, and continued exercise led to weakness and stiffness. Pain during exercise would occur in any muscle in the body – the most noticeable being in the arms or legs. The pain would force the patient to stop and rest, but it was noted that after a period of rest, the patient was then able to exercise further. Dr McArdle realised that after exercise the lactate (lactic acid) level of the patient did not increase as expected, and that glycogenolysis was incomplete. He also noticed that the patient’s muscles were very weak even though they had quite a large bulk. His astonishingly perceptive theory was that “it is the... enzyme system that is at fault... it seems... that the patient has a disorder of carbohydrate metabolism... during exercise a change took place in the muscle chemistry which effectively led to a breakdown in glycogenolysis” (McArdle, 1951).

Mommaerts *et al.* (1956) realised that McArdle disease was caused solely by the loss of muscle glycogen phosphorylase, not the loss of any other related enzymes. Schmid *et al.* (1959) took samples of different skeletal muscles from a McArdle person (muscles located between the back and shoulder, middle of the back, and the calf) and found there was a lack of functional glycogen phosphorylase in all of these muscles. He tested the different enzymes involved in the breakdown of glycogen and identified the cause of the disease as the loss of the ability to produce glucose-1-phosphate, because muscle glycogen phosphorylase wasn’t functional.

Glycogen Storage Disease	Alternative name	Deficient enzyme	Gene name
GSD 0		Glycogen synthase	<i>GYS2</i>
GSD Ia	Von Gierke disease	Glucose-6-phosphatase	<i>G6PC</i>
GSD Ib		Glucose-6-phosphate translocase	<i>G6PT1</i>
GSD Ic		Endoplasmic reticulum inorganic phosphate transporter	<i>NPT-I/NPT-II/NPT-III</i> (not fully determined)
GSD II	Pompe disease	α -1, 4-glucosidase and α -1, 6-glucosidase	<i>GAA</i>
GSD III	Cori disease	Debranching enzyme	<i>AGL</i>
GSD IV	Andersen disease	Branching enzyme	<i>GBE1</i>
GSD V	McArdle disease	Muscle glycogen phosphorylase	<i>PYGM</i>
GSD VI (and X)	Hers disease	Liver glycogen phosphorylase	<i>PYGL</i>
GSD VII	Tarui disease	Phosphofructokinase	<i>PFK</i>
GSD IX	Phosphorylase b kinase deficiency	Phosphorylase b kinase (lack of one of the four subunits)	<i>PHKA2</i>
GSD XI	Fanconi-Bickel syndrome	Glucose transporter	<i>GLUT2</i>

Table 1.1 Summary of the glycogen storage diseases identified to date

1.4.1 Other names for McArdle disease

McArdle disease is also known as McArdle's, McArdle syndrome, McArdle's syndrome, Muscle Phosphorylase Deficiency, Myophosphorylase Deficiency, Phosphorylase Deficiency, McArdle Myopathy, McArdle's Myopathy, Muscle Glycogen Phosphorylase Deficiency and Glycogen Storage Disease (GSD) type V. It may be called MacArdle's, but this is incorrect because it is named after Dr Brian McArdle. ("Myopathy" is a general name for muscle disease.)

1.4.2 Other names and abbreviations for muscle glycogen phosphorylase

Glycogen phosphorylase, Phosphorylase, muscle phosphorylase a and b, myophosphorylase, PYGM, GP-M, MGP, alpha-1, 4-glucan orthophosphate glycosyltransferase or EC 2.4.1.1.

1.5 How can I explain my McArdle disease to my friends and family who have never heard of it before?

This is my suggestion of how I would describe it to friends and family who haven't heard of McArdle disease before:

"Your muscles use glucose to provide energy to move. There isn't much glucose in your muscles, so after a couple of minutes of vigorous (anaerobic) exercise, the glucose is all used up. There are also stores of glycogen in the muscle, and there is an enzyme called "muscle glycogen phosphorylase" which normally changes the glycogen into glucose, which gives the muscles more energy to continue to exercise. In people with McArdle disease, this enzyme doesn't work, so the muscles run out of energy and can't get any more. If the McArdle people continue to exercise, the muscles basically "starve" and can be damaged. However, if the McArdle person rests for a short period, the muscles can get energy from glucose in the blood or from other sources, such as fat which is stored in the body. The McArdle person can then continue to exercise"

1.6 The future is promising for people with McArdle disease

The future is positive for McArdle people. In the 60 years since Brian McArdle published the first paper describing McArdle disease, a lot of research into understanding McArdle's has been done (as outlined in this Handbook). There are research groups around the world carrying out research into McArdle's. These range from research into brain functioning by Drs Quinlivan and Edelstyn in the UK, to the investigations into exercise and diet by Drs Vissing and Haller in Denmark and the US, to Prof Howell and colleagues carrying out research to increase the amount of a different form of glycogen phosphorylase (the brain isoform) using a drug called valproate in the McArdle sheep in Australia.

In the shorter term, there are some excellent specialists who are highly knowledgeable about McArdle's and can offer up-to-date advice on diet and exercise for people with McArdle's. The internet has also enabled people with McArdle disease to compare symptoms and advice and to provide support with others around the world through online patient support groups.

Research into improving everyday life with McArdle's is ongoing, including investigating whether other genes (phenotype modulators) may have an effect upon the severity of symptoms. In the longer term, many different avenues for treatment are being considered, including correcting the

expression of muscle glycogen phosphorylase which contains a mutation, or replacing it with the brain glycogen phosphorylase enzyme.

Online resources:

There is information about McArdle disease and the other glycogen storage diseases on the AGSD-UK website: <http://www.agsd.org.uk>

2 Symptoms and diagnosis of McArdle disease

The typical symptom of McArdle disease is pain caused by anaerobic exercise (e.g. repetitive movements, rapid movements or holding a pose). The onset of pain occurs within a few minutes of exercise. If the McArdle person does not stop and rest, then prolonged exercise can cause painful cramps, and red/cola coloured urine may be seen a few hours later.

If a McArdle person interrupts exercise with short rests, they then can get into a “second wind” which will then allow them to continue to exercise for longer. The presence of a “second wind” is unique to McArdle disease, so it can be used by a specialist as a clue to suggest a diagnosis of McArdle disease.

At present, diagnosis is most commonly by muscle biopsy and/or DNA testing. A muscle biopsy is an invasive procedure, but has the advantage that one sample can be used to test for many different muscle diseases. DNA testing is usually targeted to a specific area of the DNA so is more appropriate if McArdle disease is already suspected. DNA testing is highly accurate and becoming more commonly used. DNA is usually obtained from a blood sample, so is minimally invasive.

As McArdle disease is rare, many McArdle people are misdiagnosed before they receive the correct diagnosis of McArdle disease. Diseases which McArdle people are misdiagnosed with can include other muscle diseases, diseases which cause inflammation of the muscles, or chronic fatigue.

2.1 The personal history of symptoms described by a typical McArdle person

A typical McArdle person will have pain which occurs within a few minutes of anaerobic exercise. They will remember these symptoms from childhood. Often they will have struggled in sports lessons at school. Children with McArdle's have great difficulty in carrying out activities such as cross country running if their teacher does not allow them to rest and get into a second wind. Outside of school, many McArdle children and adults will have developed coping mechanisms to allow themselves to rest without other people noticing. These techniques could include frequently pretending to tie up their shoelace, stopping to look in shop windows, or pretending to use a mobile phone. Some McArdle people will have discovered the "second wind" phenomenon; they will have learnt that if they rest when they feel muscle pain, they are then able to continue to exercise for a much longer period of time. Some McArdle people will not have experienced the "second wind" phenomenon, but all are able to experience it if taught (Quinlivan and Vissing, 2007). Most McArdle people will have experienced fixed contractures (stiff, contracted, enlarged muscles), often following more intense exercise. Examples of exercise which is likely to lead to contractures includes intense activity such as running for the bus, repetitive activity such as chewing or peeling potatoes, or an activity where the muscles hold the body in one place for a long time such as squatting or some yoga positions. Some McArdle people will have experienced dark red/cola coloured urine, which is particularly likely after a muscle contracture. Some McArdle people will have attended a hospital emergency department because of the cola coloured urine and contractures. In rare cases, they may have had kidney failure and required dialysis. McArdle people typically find that a very sedentary lifestyle makes it more of a struggle to perform any exercise. They may find that if they keep fit, they are able to do more. However, at the other extreme, intense exercise can make the muscles very painful, forcing the McArdle person to rest for many days while the muscles repair and recover. After this period of time, they may then find that exercise is harder and the muscles feel weaker than before. For most McArdle people, the symptoms remain similar throughout their life, although some muscle weakness may occur as they get older.

The above description is a combination of information published by Quinlivan and Vissing (2007), Lucia *et al.* (2008a) and information from McArdle people provided to me via online discussion groups.

2.1.1 Activities which McArdle people have reported can cause pain/fatigue in muscles:

Here are some examples of activities which McArdle people have said can cause pain or fatigue in muscles (activities are taken from published papers and from internet chat groups and e-mail conversations). This is a brief list, designed to give some examples of the types of activities.

Repetitive movements:	Holding a pose:	Rapid movements:
Chewing (McArdle, 1951)	Squatting or crouching	Running (Lucia <i>et al.</i> , 2008a), such as running for the bus
Using can opener	Standing on tiptoes	Climbing stairs (Lucia <i>et al.</i> , 2008a)
Brushing teeth (Lucia <i>et al.</i> , 2008a)	Lifting a heavy weight, such as carrying a box/bag (Lucia, 2008)	Very brisk walking without pausing to rest (Lucia <i>et al.</i> , 2008a)
Grating cheese or peeling vegetables	Some yoga poses	Cycling fast on a bike

Table 2.1 Activities which cause muscle pain for McArdle people. Taken from published papers (references in brackets) and personal communication with McArdle people (unreferenced).

2.2 Symptoms of McArdle disease

The symptoms of McArdle disease are well characterised, and are summarised below. Exceptions include some reported cases of late-onset symptoms, which are discussed further in section 8.1.3. Differences in severity of symptoms have been reported, and possible explanations are discussed in section 9.

Very common symptoms of McArdle disease (seen in almost all McArdle people):

- Exercise intolerance; muscles becoming tired very quickly and running out of energy (Lucia *et al.*, 2008a).
- Continued exercise causing painful cramps (contractures) (Lucia *et al.*, 2008a).
- Myoglobinuria; dark red/cola coloured urine after intense exercise. Lucia *et al.* (2008a) say that the colour of urine due to myoglobinuria has been described by McArdle people as looking like “cola, marsala, or red wine”.
- Muscle pain during intense exercise will usually have existed since childhood (Quinlivan and Vissing, 2007).
- People with McArdle’s are able to experience a “second wind”; if they exercise gently to warm up, and rest when they feel pain, they will then find that they can exercise for a much longer period. It should be noted that a “second wind” is unique to McArdle disease (Lucia *et al.*, 2008a). (However, some McArdle people do not know how to get into a second wind or do not realise that this is occurring unless guided through it by a family doctor or specialist (Quinlivan and Vissing, 2007)).
- High levels of creatine kinase (CK) in the blood at rest, even when a McArdle person has not exercised intensely for hours or even days. Lucia *et al.* (2008a) say that 100% of McArdle people have average CK levels above 200U/l, and approximately 50% of McArdle people have average CK above 1000U/l. (See section 5.3.2 for further information on creatine kinase.)

- Occasional instances of very high levels creatine kinase (CK) in the blood. (Lucia *et al.*, 2008a define “very high” as being in the region of several thousand U/l.) This is likely to be detected hours or days after the McArdle person has performed an intense exercise.

Less common symptoms of McArdle disease (seen only in some McArdle people):

- Some McArdle people have “fixed proximal weakness”. “Fixed proximal weakness” is found in approximately 33% of people with McArdle disease (Lucia *et al.*, 2008). (It has not been possible to find a definition of “fixed proximal weakness”, but I believe that in this context “fixed” means non-reversible/ permanent, and “proximal” is used to describe the muscles closest to the trunk of the body, such as the shoulder and around the pelvis.)
- A feature rather than a symptom is the fact that some McArdle people find that they are able to exercise more easily if they have had a high sugar/glucose drink or eaten carbohydrates (such as pasta or rice) prior to exercise (Lucia *et al.*, 2008a).

Some of the more severe symptoms which can lead to diagnosis of McArdle disease:

- Kidney (renal) failure due to rhabdomyolysis and myoglobinuria can lead to hospital investigations which result in a diagnosis of McArdle’s (Biller, 2007).
- Muscle pain (myalgia), inflammation (myositis) and damage caused by statins (drugs taken to lower cholesterol) can sometimes lead to hospital investigations which result in a diagnosis of McArdle disease (Biller, 2007).

2.3 Diagnosis of McArdle disease

McArdle disease can be suspected based on a person having the symptoms described above, or if a sibling has already been diagnosed with McArdle disease.

There are several methods used to diagnose McArdle disease. A brief description of each, along with the pros and cons, and limitations is given in Table 2.2. They are not listed in any particular order. An indication of how commonly I believe each method is used to diagnose McArdle’s is also given.

Type of test	How often is this test used to diagnose McArdle's?	Will a positive result definitively diagnose McArdle's?	Notes
Ischaemic/non-ischaemic forearm exercise test	Very commonly used.	No	Use of this test was first described by Dr Brian McArdle and has been in use for about 50 years.
Cycle ergometer exercise test	Sometimes used.	No	Often used by scientists testing the effects of exercise or diet.
Treadmill exercise test	Rarely used.	No	Used predominantly in the UK McArdle's clinic.
Muscle biopsy; staining of slides	Very commonly used.	Yes	Looks for lack of enzyme and excess of glycogen. High success rate at producing a definitive diagnosis. Most invasive method of diagnosis.
Muscle biopsy; enzyme activity test	Rarely used.	Probably not	High risk of inaccurate result. Requires invasive muscle biopsy. Often used by scientists in the past.
DNA/genetic testing	Recently become one of the most common methods.	Yes	High success rate at producing a definitive diagnosis. Not very invasive. Can be prohibitively expensive but likely to become cheaper in the future.
Creatine Kinase blood test	Very commonly used	No	CK is invariably raised in McArdle disease so this simple blood test is a useful first sign that something needs investigating.
Electromyogram (EMG)	Sometimes used.	No	Not diagnostic.
Magnetic resonance spectroscopy (³¹ P MRS)	Rarely used.	No	Principally used by scientists investigating changes which occur in the muscle cells during exercise. Requires complex and expensive equipment.

Table 2.2: Methods to diagnose McArdle disease. An overview of my opinion of how commonly each method is used, whether it produces a definitive diagnosis,

2.3.1 Exercise test

There are three types of exercise test; a forearm test, a cycling test or a treadmill. All three are intended to test whether the body is able to break down glycogen to produce glucose in order to provide the muscles with energy during exercise.

What is tested: When a muscle of an unaffected person is exercised vigorously (anaerobic exercise), the free glucose is rapidly used up. Stored glycogen is then broken down by the process of glycogenolysis to produce energy. During glycogenolysis, lactate and pyruvate are produced. In people unaffected by McArdle's, the amount of lactate (lactic acid) and pyruvate should increase 5-6 fold (Dubowitz *et al.*, 2007). Glycogenolysis is required to produce the rise in lactate and pyruvate levels. In McArdle people, the absence of functional muscle glycogen phosphorylase blocks glycogenolysis. McArdle people therefore do not have the expected increase in lactate and pyruvate levels.

In the ischaemic forearm test, a cuff is used to reduce blood flow to the arm. (Ischaemic means to reduce blood flow.) It is performed as an ischaemic test to prevent the blood bringing glucose or fatty acids to the muscle. This ensures that anaerobic, not aerobic, exercise occurs. However, recent studies have shown that similar results with less risk of muscle damage can be achieved with a non-ischaemic forearm test (Niepel, 2004).

Cons of all exercise tests: The level of effort must be below the maximum so that severe complications like rhabdomyolysis and myoglobinuria do not occur (Fernandes, 2006).

Following exercise, increased ammonia levels, increased uric acid levels (see section 13.1 for the relationship between uric acid levels and gout) and increased creatine kinase are often seen (Milunsky, 2010).

Limitations: The exercise tests do not definitively diagnose McArdle disease. An absence of increase in lactate and pyruvate levels indicates a metabolic disease caused by a block in glycogenolysis. Many other glycogen storage diseases prevent lactate production after anaerobic exercise (Lane, 1996). The exercise test does not distinguish whether the person has McArdle disease or another other metabolic disease, for example, another glycogen storage disease such as Tarui disease (phosphofructokinase deficiency) (Abramsky, 2001). Cori disease and Tarui disease can produce flat (not increasing) lactate levels after the forearm test (Biller, 2007).

If a small increase in lactate (1.5-3 fold of resting levels), and a very high increase in ammonia occurs, it may suggest that the person has a disease where a small amount of enzyme is still functional, examples of these diseases would be phosphoglycerate mutase, phosphoglycerate kinase and lactate dehydrogenase deficiencies (Abramsky, 2001).

A different disease called myoadenylate deaminase deficiency (MADD) is another metabolic disease characterised by decreased ammonia production (Lane, 1996). (MADD is discussed further in section 9.3.2.) If a person with MADD exercises, the amount of lactate will increase, and the amount of ammonia will be lower than expected (Lane, 1996; Abramsky, 2001). For this reason, the level of ammonia in the blood (plasma ammonia) is usually measured before and after an ischaemic forearm test (Lane, 1996).

2.3.1.1 Ischaemic or non-ischaemic forearm exercise test

How the ischaemic forearm test is carried out: A pre-test blood sample is taken before the test. A cuff (tight band) is put around the forearm (or occasionally the thigh). The forearm is contracted by squeezing a ball or balloon, or the thigh is contracted at maximum force/strength for one minute or until extreme pain. The cuff is then loosened. Blood samples are taken (for example at 1, 3, 5, and 10 minutes) after exercise. The blood is analysed to determine whether the expected increase in lactate and pyruvate occurs.

After exercise, the amount of lactate in the blood will not increase (Cush, 2005) in McArdle people, but McArdle people will have an increase in ammonia levels in the blood, which can go up to 360-560µg/dl (Lane, 1996). It is important that ammonia levels in the blood rise, as this shows that the person has exercised enough, as an incorrect result could be obtained if the person who is being tested does not exercise with enough effort (Lane, 1996).

Cons of the ischaemic forearm test: The test can lead to muscle damage. Cramping, muscle pain and contracture of the muscle may occur following the test (Cush, 2005) There is a small risk of the severe problem of compartment syndrome (discussed further in section 12.3.2). The risk of compartment syndrome is much lower if the non-ischaemic forearm test is performed. There is also a risk of the test causing severe muscle damage which could lead to kidney failure (see section 5 for further information on rhabdomyolysis and kidney failure). Meinck *et al.* (1982) published a report where a 57 year old McArdle person was asked to perform an ischaemic forearm test. The muscle of the tested forearm was damaged, which resulted in myoglobinuria and raised creatine kinase levels in the blood. The person was placed under medical observation and instructed to drink plenty of fluids. Although kidney failure did not occur, the authors (Meinck *et al.*, 1982) warned that it could be a potential hazardous side effect of the ischaemic forearm test.

How the non-ischaemic forearm test is carried out: A non-ischaemic forearm test (similar to that described above but without use of a cuff) is now recommended. A study by Kazemi *et al.* (2002) found that the non-ischaemic forearm test was able to distinguish McArdle people from unaffected people. The non-ischaemic forearm test is much less likely to cause damage (Niepel, 2004). The ischaemic forearm test can cause a lot of pain and discomfort for McArdle people, whereas the non-ischaemic test produces “almost no discomfort” (Abramsky, 2001).

Cons of the non-ischaemic forearm test: I think that it seems possible that muscle damage could also be a side effect of the non-ischaemic forearm test if the person exercises too vigorously (as described by Meinck *et al.*, 1982 for the ischaemic forearm test).

Pros of both the ischaemic and non-ischaemic forearm exercise tests: It is not very invasive (the only invasive part is taking blood samples). It can be performed with relatively simple equipment.

Cons of both the ischaemic and non-ischaemic forearm exercise tests: If people who don't have McArdle's are very weak or are unmotivated during the exercise test, no increase in lactate and pyruvate may be seen, resulting in an incorrect diagnosis of McArdle disease (Lucia *et al.*, 2008a).

It may produce a positive result in people with other similar diseases which affect glycogenolysis or glycolysis (like some of the other glycogen storage disease).

Only works for children old enough to squeeze the ball/balloon.

It was suggested by Lane (1996) that false negative results could be seen in the rare cases of McArdle people with low levels of functional muscle glycogen phosphorylase, but no experimental data was provided to support this theory.

If both lactate and ammonia increase only a small amount, it suggests that either the person being tested did not put enough effort into the exercise or that the wrong vein was used to sample the blood. The correct vein to use is called the “median cubital vein”, and one example of an incorrect vein to use is the basilica vein (Abramsky, 2001). The blood samples must be assayed quickly, so it is essential that the test is performed at a location near to a biochemistry laboratory (Barnes, 2003).

2.3.1.2 Cycle ergometer exercise test

A cycle ergometer is a static bike commonly found in a gym. Pedalling turns a wheel which runs over a band. The band can be tightened to provide more resistance, making it harder work to pedal and increasing the amount of energy the person needs to move the pedals (energy is measured as Watts (W)).

What is tested: This test measures whether exercise leads to an increase in lactate and pyruvate in the blood. In addition, breathing apparatus is often used to quantify the amount of oxygen used for exercise ($VO_2\text{max}$).

How the cycle ergometer test is carried out: McArdle people have very low work capacities, so the cycle ergometer should be precisely adjusted to provide a low amount of resistance (0-50W). The person begins to pedal gently, with the amount of resistance being increased by 5-10W every other minute. The person being tested wears a type of oxygen mask over their head. This allows measurement of the amount of oxygen they breathe in (oxygen consumption, called VO_2) and the amount of carbon dioxide breathed out (called VCO_2). These two numbers can be combined to produce a VCO_2/VO_2 ratio. A heart rate monitor can be used to measure heart rate. A blood sample is taken prior to exercise, and after exercise to find out the lactate levels in the blood (Abramsky, 2001).

If the blood lactate levels do not rise, it may suggest a diagnosis of McArdle’s or Tarui disease. To determine which of these diseases a person has, the person is asked to briefly exercise at maximum capacity; which is called $VO_2\text{max}$. The person is then asked to exercise at approximately 40% of $VO_2\text{max}$ (Abramsky, 2001). In McArdle people, this level of exercise causes a high heart rate and a high level of perceived exhaustion (it feels like really hard work to pedal) until 8-10minutes into the exercise, when the second wind occurs. At this point (8-10mins into exercise), McArdle people have a dramatic drop in heart rate and it feels much easier to exercise/pedal even though they are pedalling at the same rate as before. It can be further tested by increasing the resistance (making the band tighter so that the person has to pedal even harder). This causes the person’s heart rate to increase. In some experiments, the person is then given intravenous glucose (glucose via a needle and drip in the arm; 50ml of a 50% solution). In McArdle people, the glucose leads to a second “second wind” – the heart rate will drop again, and it will feel easier to pedal again.

These changes in heart rate and second wind are diagnostic of McArdle disease. In Tarui disease, a second wind does not occur, and intravenous glucose makes it harder for the person to exercise (Abramsky, 2001).

To ensure that the person exercised is not working at their maximum level, their pulse rate should be kept below 150 beats/min for adults and 150-180 beats/min for children (Fernandes, 2006).

Pros of cycle ergometer for exercise tests (pros are not specific to testing for McArdle disease):

Keeps person being tested in the same place, so it is easy for them to wear a facemask which is used to monitor the amount of oxygen being breathed in, and amount of carbon dioxide being breathed out. It is also easier to take blood from the person as they are staying in the same place. It is easy to use the cycle machine to accurately quantify the amount of exercise the person is doing (adapted from Cooper and Storer, 2001). For these reasons, a cycle ergometer is often used by scientists testing the effect of diet or exercise on the ability of McArdle people to exercise, for example, Drs Haller and Vissing frequently publish papers using cycle ergometers (e.g. Vissing *et al.*, 2009).

Cons of cycle ergometer for exercise tests (cons are not specific to testing for McArdle disease): If people do not cycle regularly, it may feel strange, and may result in premature leg tiredness if it is an unfamiliar form of exercise (adapted from Cooper and Storer, 2001). Children have to be old enough to be able to cycle.

2.3.1.3 Treadmill test

How the test works: This is similar to the ischaemic/non-ischaemic forearm tests, and also similar to the cycle ergometer test.

What is tested: The treadmill test is used to measure presence of second wind, effect of exercise on heart rate, and to test whether exercise leads to muscle pain. Breathing apparatus can be used to measure the amount of oxygen breathed in and carbon dioxide breathed out (used to calculate VO_2 max) (Perez *et al.*, 2009).

How the treadmill test is carried out: The person being tested walks on a treadmill. The speed of the belt and the slope of the belt (level of inclination) can be adapted so that the person is walking at a speed of 3-5km/h with a pulse rate of 150-180beats/min. The length of time that it takes for the person to become exhausted can indicate which disease they may have. Glycogen storage diseases will make people exhausted more rapidly, whereas diseases caused by defects in fatty-acid oxidation will make people feel exhausted later (Fernandes, 2006).

Pros of the treadmill test: It can be used to test very young children (as soon as they can walk) (Fernandes, 2006; Perez *et al.*, 2009). Everyone is used to walking around, so it is a very natural and familiar way to test (Cooper and Storer, 2001).

Cons of the treadmill test: It can be harder to measure oxygen and carbon dioxide. It is perhaps harder to obtain blood samples.

Note: At the UK McArdle's Clinic the treadmill test was sometimes used by experienced physiotherapists to teach McArdle people how to achieve a second wind, if they had not previously experienced second wind before (personal observation at the clinic while located at the RJAH Orthopaedic Hospital in Oswestry, UK).

2.3.2 Muscle biopsy

What is tested:

A muscle biopsy can be used to test for two things:

- 1) An accumulation of glycogen. McArdle people and people with other glycogen storage diseases (apart from GSD 0) have an accumulation of glycogen within the muscle cells. Unaffected people have a much lower amount of glycogen in their muscle cells.
- 2) An absence of functional muscle glycogen phosphorylase in the muscle cells. Unaffected people have a high level of muscle glycogen phosphorylase in their muscle cells.

How is the muscle biopsy test carried out: The McArdle person is placed under either local or general anaesthetic. A surgeon removes a piece of muscle from one of the large muscles such as the upper arm, thigh, or calf. The piece of muscle is sent to a histology department who will preserve it if necessary, and carry out the necessary tests. To confirm the validity of the test the enzyme must be seen in either an internal control (a blood vessel) or an external control (muscle tissue from someone who is known not to have any muscle disease). The family doctor or specialist should then be sent a report from the histology department outlining the results.

It should be noted that muscle biopsies can either be taken as a needle biopsy (a hollow needle is used to cut and remove a sample of the muscle), or as an open biopsy (a surgeon cuts and removes a small sample of muscle). A needle biopsy is normally smaller than an open biopsy, is likely to cause less damage to the muscle, and have a quicker healing time. A needle biopsy is recommended by Dubowitz and Sewry (Heckmatt *et al.*, 1984; Dubowitz *et al.*, 2007).

Some textbooks recommended that a muscle biopsy be performed in the most symptomatic area (Cush, 2005). However, in theory, I think that it shouldn't matter which muscle the biopsy is taken from, because if a person has McArdle's, muscle glycogen phosphorylase is missing/not functional in all the skeletal muscles of the body. Surgeons usually chose to biopsy the thigh, calf, or bicep because they are large muscles, so it is easier to take a small biopsy without damaging any surrounding tissue.

Cons of the muscle biopsy test: Malignant hyperthermia is an inherited condition whereby some anaesthetic drugs produce an adverse reaction which includes an extreme rise in body temperature (see section 12.3.1. McArdle people are at an increased risk of having malignant hyperthermia-like symptoms which can cause a dangerous reaction to general anaesthetic). It is important to remind/inform your surgeon of this risk prior to surgery. Dubowitz and Sewry (2007) recommend muscle biopsy be performed under local anaesthetic, which reduces risk of side effects like malignant hyperthermia.

Limitations: An inaccurate result may be obtained if muscle biopsy is performed shortly after a period of rhabdomyolysis and muscle damage. If muscle damage has occurred prior to the biopsy being taken, small (immature/regenerating) muscle fibres may be seen which are positive for the phosphorylase stain due to expression of other isoforms of glycogen phosphorylase enzyme (Lane, 1996). (An explanation of the other isoforms of glycogen phosphorylase is given in section 6.5.) Serial sections (pieces of tissue cut from the same muscle biopsy sample) can be stained with antibodies for other immature proteins such as myosin, which will confirm that these fibres are

immature (Dubowitz *et al.*, 2007). It is not possible to distinguish between the different isoforms of glycogen phosphorylase enzyme in the phosphorylase staining test. Testing a muscle biopsy shortly after rhabdomyolysis has occurred is likely to result in a false negative result; a person who really does have McArdle disease will be told that there is nothing wrong with them.

Notes: It should be noted that McArdle disease cannot be diagnosed by skin biopsy. This is because McArdle disease only affects skeletal muscle cells. Skin cells have a different form of glycogen phosphorylase.

It would be advisable to ask/request that the muscle biopsy is stored by the laboratory carrying out the tests (in liquid nitrogen or a -80 freezer as appropriate) until the diagnosis is confirmed. If there are any questions or uncertainty about the diagnosis, the stored muscle biopsy can be used to perform further tests. This eliminates the need for a further biopsy.

2.3.2.1 Staining of slides with slices of muscle

What is tested: Following a muscle biopsy, thin slices of muscle are made and mounted onto thin glass slides. The muscle fibres can be stained to determine the amount of glycogen present. A special stain called the periodic acid-Schiff (PAS) stain (DiMauro *et al.*, 2002; Dubowitz *et al.*, 2007) is used to stain glycogen.

A chemical reaction is carried out to determine whether there is functional muscle glycogen phosphorylase in the muscle fibres (Amato, 2003). Muscle glycogen phosphorylase is used to produce a compound which can be stained to produce the purple/brown colour. If the muscle glycogen phosphorylase is not functional, it will not produce this compound and no colour will be seen.

After staining, the slides with slices of muscle will be examined under a microscope. It is important that the laboratory carrying out these tests performs the same tests on a biopsy from an unaffected person (a “negative control”) at the same time. This removes the possibility of a false negative test if some part of the test does not work correctly.

Pros of the staining of slides with slices of muscle test: If the phosphorylase staining is carried out correctly, it will provide an accurate and specific diagnosis of McArdle disease. An absence of muscle glycogen phosphorylase is diagnostic of McArdle disease. It will work whether the mutation is known or a brand new mutation which has not been identified before. One muscle biopsy can also be used to test for (and exclude) many different muscle diseases.

Cons of the staining of slides with slices of muscle test: It should be noted that an accumulation of glycogen will be seen from almost all the glycogen storage diseases, and therefore is not diagnostic of McArdle disease. The site of the biopsy may be painful until healed and may cause a scar. It is more invasive than any of the other tests.

2.3.2.2 Enzyme activity test

How is an enzyme activity test carried out: It is also possible that the amount of functional muscle glycogen phosphorylase in muscle biopsy sample can be tested in a different way. A biopsy sample is taken as described below. Instead of making thin slices, the sample is homogenised (mashed up),

and a chemical reaction is carried out to measure how much functional muscle glycogen phosphorylase is present (if any). This technique is not used very commonly.

Pros of an enzyme activity test: It may be possible to use it for diagnosis. It may be easier to quantify a very low level of functional glycogen phosphorylase, but with the limitation described below.

Cons of an enzyme activity test: One limitation with this technique is that it will also detect other isoforms of glycogen phosphorylase (which is found in the blood vessels in muscle). These other isoforms of glycogen phosphorylase may produce a false positive result.

I think that there is no advantage of the enzyme activity test over the usual staining of slides with slices of muscle biopsy test.

2.3.3 DNA testing

How is DNA tested for McArdle disease: DNA may be tested in various ways, either looking for specific mutations within a gene using a Polymerase Chain Reaction (PCR) based test, or using genetic sequencing to search the whole genome for mutations.

PCR is a laboratory technique whereby a small amount of DNA can be amplified into a large amount. For the PCR based technique, a DNA sample is first amplified using PCR, and then special proteins called “restriction enzymes” are used to cut up the DNA. Each enzyme will only cut one particular DNA sequence, for example it may cut DNA with the mutation but not DNA with the normal sequence. The sample can then be analysed; if the enzyme has cut the DNA it indicates that it contains the mutation.

Genetic/DNA sequencing is a different modification of a PCR based test which can be used to determine the exact genetic sequence of a gene. This sequence can then be compared to a reference normal sequence and analysed to identify mutations.

How is the DNA test carried out: A blood sample is taken. DNA is prepared from the cells in the blood sample (Tsujino *et al.*, 1993). The DNA is analysed in a laboratory either using the PCR based test or by genetic sequencing.

Pros of both types of DNA test: This is a highly accurate test. It causes very little pain during or after the test. It is minimally invasive.

Pros of the PCR based DNA test: It is relatively cheap once a laboratory has become familiar with the test. It is relatively easy with standard laboratory equipment.

Cons of the PCR based DNA test: A PCR based test will only identify common mutations. It is only useful for populations where a few mutations commonly occur; for example the R50X mutation is very common in the UK and North America. It will not detect a less common mutation or a mutation which has never been detected or reported before. It may be unavailable in some countries.

Pros of genetic sequencing: It can be used to identify any/all mutations, even if they are rare or have never been reported before. Recently, sequencing has become much cheaper, and is in the process of becoming an affordable method of diagnosis. A gene is made up of both coding sequence

(exons) and non-coding sequence (introns), with splicing sequence in between. The splicing sequence should also be tested for mutations as an increasing number of mutations have been found in splicing sequence (explained in further detail in section 3.2.4).

Cons of genetic sequencing: This is currently an expensive test. It may be unavailable in some countries.

2.3.4 Creatine kinase blood test

What is tested: Creatine kinase (CK) (also known as creatine phosphokinase (CPK)) is an enzyme (a special kind of protein) which is usually found within muscle cells. If muscle cells are damaged, then creatine kinase is released from the muscle cells into the blood.

How is the creatine kinase blood test carried out: A blood sample is taken from the patient and sent to a hospital laboratory. The blood is separated into serum (which contains the creatine kinase) and blood cells. A chemical reaction is carried out to measure how much creatine kinase is present in the serum. The amount of creatine kinase in the blood samples is expressed as units per litre of blood (U/l) or international units per litre (IU/l).

Different hospital laboratories may carry out slightly different creatine kinase tests. For each specific test, it is useful to compare the result of your CK test with a reference level for the same test. The reference level is the amount of creatine kinase which would be expected in a person unaffected by McArdle's who has not had any recent muscle damage. Reference levels may vary by age, gender, ethnicity and amount of muscle the person has. As a rough guide, people unaffected by McArdle's have CK levels below 190 IU/L (Quinlivan *et al.* 2010) or 220U/l (Miteff *et al.* 2011). At rest, McArdle people always have raised CK levels, between 200U/l and 1000 U/l (Lucia *et al.*, 2008a). If a McArdle person carries out intense exercise, which leads to rhabdomyolysis (muscle damage), CK levels can rise to "several thousand U/l" (Lucia *et al.*, 2008a). In extreme cases of rhabdomyolysis, McArdle people have anecdotally reported CK levels of hundreds of thousands U/l.

Pros of the creatine kinase blood test: It causes very little pain during or after the test. It is minimally invasive. A high creatine kinase provides an indication that muscle damage has occurred. This can indicate a diagnosis of a muscle disease.

Cons of the creatine kinase blood test: Raised creatine kinase levels are symptomatic of many muscle diseases (including inflammation of the muscles and various muscular dystrophies), so it cannot provide a specific diagnosis of McArdle disease. High levels of creatine kinase may also be seen in people who do not have a muscle disease but who have recently undergone strenuous exercise or muscle injury, for example from a car crash. Table 5.1 in section 5 gives other causes of rhabdomyolysis (muscle damage) which could lead to raised creatine kinase levels in people unaffected by McArdle's.

Note: In McArdle people, the creatine kinase is released from skeletal muscles (such as the muscles in your arms and legs). However, an alternative cause of raised creatine kinase levels can be a heart attack. The heart is a different kind of muscle, but can also release creatine kinase if damaged. If the heart muscle is damaged by a heart attack (also called a myocardial infarction), this can lead to a raised level of creatine kinase. In most cases, a McArdle person will be aware that the raised

creatine kinase levels are probably due to damage of the skeletal muscles. If a heart attack is suspected, medical staff will be able to perform further specific tests.

Rhabdomyolysis and creatine kinase are discussed in further detail in section 5.

2.3.5 Electromyogram (EMG)

What is tested: A muscle contraction occurs when an electrical impulse/signal travels from a nerve to a muscle fibre or a set of muscle fibres. A standard pattern of electrical activity is seen when a person unaffected by McArdle's contracts and relaxes their muscles. A standard pattern of electrical activity is also seen in the muscles when an unaffected person is at rest. Some muscle diseases affect the electrical impulses; either by producing electrical activity when the muscles are at rest, or by reducing the amount of electrical impulses seen (Lane, 1996).

How is EMG test carried out: An electromyogram (EMG) measures this electrical activity within muscles. Surface electrode probes may be placed on the skin next to the muscle being tested or a very fine needle electrode is inserted in the muscle. This probe/electrode is connected to apparatus which measures the electrical impulses in the muscles.

Braakhekke *et al.* (1986) performed the test on McArdle people as follows: Surface EMG was performed on the quadriceps (thigh) muscle. Two electrodes were placed 5cm apart. The electric signal was recorded during exercise. A computer was then used to identify bursts of electrical pulses.

The test detects whether the electrical waves are showing the normal expected pattern. In the McArdle people, an increase in EMG activity was seen during the first 6 to 7 min of exercise, then stabilised. EMG activity did not increase in unaffected people (Braakhekke *et al.*, 1986). An increase in electrical activity was also seen in the bicep muscles of McArdle people during the ischaemic forearm test (Linszen *et al.*, 1990). It has been suggested that as some muscle fibres use up their energy and become unable to contract, the electrical signals increase to stimulate more muscle fibres to help the muscle move/contract in McArdle people (Braakhekke *et al.*, 1986). Unusual EMG readings were seen in approximately half (49%) of McArdle people tested (Darras and Friedman, 2000).

Pros of the EMG test: If surface probes are used then it is non-invasive.

Cons of the EMG test: It has anecdotally been reported to be an uncomfortable test. It does not provide a definitive diagnosis and would just suggest that a person may have McArdle disease. Based upon the figures provided by Darras and Friedman (2000), 51% of McArdle people have normal EMG. If EMG were used to diagnose McArdle's, half the people tested would receive a false negative diagnosis.

Different results may be seen depending which part of the muscle the electrodes are placed on, or which muscle is tested. Different muscles have different combinations of type I and type II fibres, which can affect the EMG measurement.

2.3.6 ³¹P magnetic resonance spectroscopy (³¹P MRS)

This technique is not used routinely, but a few papers report using ³¹P MRS to diagnose McArdle disease. Greutter *et al.* (1990) described the use of ³¹P MRS to diagnose children in a situation where both parents were known to have McArdle disease. Ross *et al.* (1982) also used ³¹P MRS to diagnose McArdle disease. ³¹P MRS has been used by some scientists (such as Martinuzzi, 2007 and also Vorgerd *et al.*, 2000) to investigate the effects of treatments in McArdle people.

What is tested: ³¹P MRS was used by Greutter *et al.* (1990) to study the pH (acidity) within the muscle cells during exercise. In unaffected people, lactic acid is generated in muscles during exercise causing the pH to decrease as the contents of the muscle cells became more acidic. In McArdle people, the pH does not decrease (and may increase slightly; becoming more alkaline) during exercise.

In McArdle people, there is no decrease in intracellular pH after exercise, low resting ATP, and no accumulation of phosphomonoesters (phosphorylated sugars) (Lane, 1996).

How is the test carried out: The person being tested either lies on their back with the thickest part of their calf muscle within the MRS machinery or places their forearm inside the MRS machinery (de Kerviler *et al.*, 1991). The MRS machinery is used to take a reading before exercise. The person is then instructed to move their foot up and down with increasing force or contract their hand/arm using hand grips. The MRS machinery is then used to take another reading.

Pros: This technique is non-invasive (Boesch, 2007). ³¹P MRS can be used to diagnose asymptomatic people with McArdle's (Greutter *et al.*, 1990).

Cons: ³¹P MRS cannot distinguish between other glycogen storage diseases, for example it cannot be used to distinguish between McArdle disease and phosphofructokinase deficiency (de Kerviler *et al.*, 1991). In most cases an ischaemic test is performed, meaning that a cuff is used to reduce blood flow to the limb – this could cause damage in the same way as described for the ischaemic forearm test (section 2.3.1.1). ³¹P MRS is time-consuming and expensive (Lane, 1996). Use of MRS requires access to the specialist MRS equipment and staff trained to use it. The MRS machinery is typically found in hospitals, and some McArdle's clinics may not have the appropriate accessories and setting to perform ³¹P MRS (Boesch, 2007).

2.4 Causes of similar symptoms to McArdle disease (in people who don't have McArdle's)

Muscle pain and fatigue may be caused by many other diseases, some of which are listed below (section 2.5.2).

Muscle damage and rhabdomyolysis (muscle breakdown) can occur in people unaffected by McArdle's and can be caused by many factors (listed in more detail in section 5) including excessive exercise or as a side effect of the use of statins (drugs taken to reduce cholesterol levels).

Blood in the urine could be caused by urinary tract infections (e.g. cystitis). Menstruation (a woman having a period) may also result in blood in the urine.

Some foods, such as beetroot (beets), rhubarb, and blackberries may give urine a red colour. Red coloured urine may also be seen if taking some medicines, such as warfarin or laxatives containing senna.

2.5 Other diseases which have similarities to McArdle disease

Many McArdle people are misdiagnosed with a different disease before they are correctly diagnosed with McArdle disease. Pavic *et al.* (2003) carried out one study on McArdle people diagnosed between 1962 and 2002, and found that one third of these people had at least three muscle biopsies before the correct diagnosis was made. The authors described some of the reasons why family doctors struggle to diagnose McArdle disease. They say that muscle cell damage caused by McArdle disease may lead to inflammation. A muscle biopsy may therefore look the same as other type of inflammatory muscle disease (for example, polymyositis). Also, they said that if muscle damage had caused the muscle cells to die (cell death due to damage is called necrosis), it may not be possible to see if glycogen storage has occurred.

Many people with McArdle disease are not diagnosed until adulthood, although most have experienced symptoms from childhood (Quinlivan *et al.* 2007; Quinlivan *et al.* 2010). It may be harder for children to obtain a diagnosis of McArdle disease. In part, this may be because muscle pain caused by exercise may be misdiagnosed as “growing pains” in children with McArdle disease. Diagnosis of McArdle disease in children is discussed further in section 8.2.2.1.

2.5.1 Some of the diseases which McArdle people have been misdiagnosed with before getting a proper diagnosis of McArdle’s

There are a few published cases of McArdle people who were initially misdiagnosed with another disease. It is likely that most cases are not published because cases of misdiagnosis are not considered to be of interest to the medical community!

2.5.1.1 Polymyositis

O’Brien *et al.* (1998) reported two cases of men with McArdle’s who had been misdiagnosed with an inflammatory myopathy, thought to be idiopathic polymyositis (idiopathic polymyositis is muscle inflammation with no known cause). These men were aged 50 and 62, and did not report the classic symptoms of McArdle disease; they said that they had had relatively late onset of symptoms. They had both been prescribed immunosuppressants, which is a treatment for idiopathic polymyositis. They were later shown to have no muscle glycogen phosphorylase enzyme activity in their muscle biopsies. Paradas *et al.* (2005) reported a woman with McArdle’s who had been misdiagnosed with polymyositis, and treated with steroids, prior to diagnosis of McArdle’s.

2.5.1.2 Refractory dermatomyositis

Gómez-Cerezo *et al.* (2008) reported a case of a 25 year old woman who was misdiagnosed as having refractory dermatomyositis (refractory dermatomyositis is inflammation of muscles and skin which does not respond to treatment). As well as McArdle’s symptoms of muscle weakness and high CK level (93728 U/l), she had skin lesions on both arms, which led to diagnoses by three independent family doctors that she had dermatitis. She was treated with prednisolone (a steroid), 60 mg/day of prednisone, 150 mg/day of azathioprine and 7.5 mg/week of methotrexate which

appeared to reduce the CK level. A later biopsy showed absence of muscle glycogen phosphorylase, confirmed by genetic identification of the mutations in the *PYGM* gene.

2.5.2 Other muscle diseases with similar symptoms to McArdle disease

Sometimes people are suspected of having McArdle disease but actually have another, similar disease. A very brief list of some of the diseases which have similar symptoms to McArdle disease is given in Table 2.3.

2.6 McArdle disease was considered a possible diagnosis for a patient with chronic pain in the television series “House”

The challenges of correctly diagnosing a patient with McArdle disease is mentioned in the television series “House”. (“House” is produced and distributed by Universal Playback.) “House” is a hospital drama which stars Hugh Laurie as Dr Gregory House, a consultant who specialises in diagnosing patients whom no other consultants have been able to successfully diagnose. In series 5, the episode called “Painless” focuses upon the diagnosis of a patient in chronic pain. One suggestion by the medical team assisting House is that the patient may have McArdle disease.

Information about McArdle’s is mostly described in an accurate way in this programme. In the programme, the family doctors hypothesise (guess) that the patient’s pain could be caused by McArdle disease, which they correctly described as a glycogen storage disease. The patient is experiencing chronic pain throughout his body. (Chronic/permanent pain is reported by some patients with McArdle’s, see 9.4). In the programme, they say that there are muscle cells in the wall of the intestine, which could lead to pain (I am not sure that this statement is correct. The intestine is made of smooth muscle, which is unaffected by McArdle disease and therefore would not be painful. However, it is possible that there is skeletal muscle overlaying the intestine, which would be affected by McArdle’s and could be painful.) They correctly propose to test whether the patient has McArdle disease using the ischaemic forearm test (this is a commonly used method to diagnose McArdle’s, and is discussed further in section 2.3.1.1). They take blood from the patient while he is undergoing the ischaemic forearm test and monitor the level of lactate in the blood. The medical team tell the patient’s wife that McArdle’s can be treated with gene replacement therapy and lifestyle changes. (At present gene replacement therapy is not available as a treatment for McArdle’s, although it is being investigated by scientists as a potential therapy, see section 16. Lifestyle changes such as regular gentle aerobic exercise are recommended as a good treatment for McArdle’s, see section 4.2.2.) So overall, most of the information about McArdle disease given in this episode is correct, or almost correct.

The popularity of this programme should mean that many more people will now have heard of McArdle disease and will have learnt a little about the disease.

General name for the group of diseases	Brief description	Examples of some of the specific diseases in each group
Glycogen storage diseases	Characterized by glycogen storage (apart from GSD 0)	Tarus disease, Pompe disease
Lipid storage diseases	A group of inherited metabolic disorders in which harmful amounts of fatty materials called lipids accumulate in some of the body's cells and tissues.	Gaucher disease, Fabry disease
Muscular dystrophies	A group of muscle diseases (usually inherited) which usually lead to muscle weakness in various different muscles of the body.	Duchenne muscular dystrophy, Limb-girdle muscular dystrophy
Myositis	Myositis is a general term for inflammation of the muscles. Many of these are considered to be caused by autoimmune conditions and are treated with immunosuppressant drugs. In many cases these muscle diseases are not inherited.	Polymyositis
Mitochondrial myopathies/ Disorders of fatty acid metabolism	Muscle diseases caused by defects in the mitochondria. Mitochondria are a part of the cells which play an important role in producing energy. These are inherited diseases caused by the lack of function of an enzyme which is needed to break down fatty acid to provide energy in muscle cells.	Carnitine palmitoyltransferase I deficiency (CPT I), Carnitine palmitoyltransferase II deficiency (CPT II), Medium-chain acyl coenzyme A dehydrogenase deficiency (MCAD), Short chain acyl coenzyme A dehydrogenase deficiency (SCAD)
Chronic fatigue syndrome	The primary symptom is extreme tiredness and fatigue. It may also include muscle pain and feeling ill after exercise. The cause is not known, although it can sometimes begin after a virus or infection. It is not believed to be an inherited disease.	Chronic fatigue syndrome/ ME/Post viral fatigue syndrome

Table 2.3 Other muscle diseases with similar symptoms to McArdle disease.

Online resources and recommended reading:

There is information about McArdle disease and the other glycogen storage diseases on the AGSD-UK website: <http://www.agsd.org.uk>

There is information about McArdle disease and other muscle diseases, including muscular dystrophies on the Muscular Dystrophy Campaign (MDC) website: http://www.muscular-dystrophy.org/about_muscular_dystrophy/conditions

Inborn metabolic diseases: diagnosis and treatment by John Fernandes, Jean-Marie Saudubray, Georges Van Den Berghe, John H. Walter (*For a brief description of each disease ; Google free books*)

3 The genetics of McArdle disease

McArdle disease is caused by the lack of functioning muscle glycogen phosphorylase enzyme. Enzymes are a special kind of protein. A gene is the piece of DNA that provides the instructions which the cell uses to produce a protein. Each gene has a unique name, and the gene for muscle glycogen phosphorylase is called “*PYGM*”. McArdle disease is caused by mutations in the *PYGM* gene. Different mutations in this gene can have different effects, which can include creating a shortened version of the enzyme, or a mixed up version of the enzyme with the wrong components. In almost all cases, this leads to a complete absence of functioning muscle glycogen phosphorylase.

The precise mutations which an individual has are usually determined by their ethnic background, for example, one mutation found in Japanese people is not found in British people.

McArdle disease is inherited in a recessive way. This means that both parents must be carriers of a faulty copy of the *PYGM* gene, in order for the child to inherit two faulty copies of the gene. Parents who are carriers of a faulty copy of the *PYGM* gene will not have symptoms of McArdle disease and will probably be unaware that they are carriers. There is a 25% chance that a child will have McArdle disease if both parents are carriers. In practice, this means that when a child is born with McArdle’s disease they are usually the first person in the family to be affected. The inheritance of McArdle’s is not affected by gender; so men and women are equally likely to inherit McArdle disease. In a situation where one parent has McArdle disease, but the other does not, all the children will be carriers of McArdle disease. Carriers do not usually have symptoms of McArdle disease. Different scenarios for the inheritance of McArdle disease are discussed in more detail in this Chapter.

3.1 Genes, messenger RNA and protein

3.1.1 Genes are used to make messenger RNA, which is used to make protein

Although this may seem complicated, a basic understanding of genes, messenger RNA (mRNA), and protein is important to understand how mutations in the *PYGM* gene lead to McArdle disease.

Proteins are essential within the body. They help to make up the structure of the body and control most of the processes of the body. The body is able to use genetic information to make almost all the protein it requires. Each gene contains the genetic information (the genetic code) which the body can use to produce a particular protein. The *PYGM* gene encodes the genetic information for the cell to make muscle glycogen phosphorylase. Muscle glycogen phosphorylase is an enzyme. An enzyme is a special kind of protein which is able to change one thing to another. For example, muscle glycogen phosphorylase is able to change glycogen into glucose-1-phosphate. Glucose-1-phosphate is then broken down by several other enzymes, eventually producing glucose.

Genes are made up of DNA sequences. DNA is made up of chemical compounds called “nucleotides”. There are four nucleotides in DNA, which are cytosine (C), thymine (T), and guanine (G) and adenine (A). Different genes each have a unique order or sequence of nucleotides. It is possible to use special techniques and machinery (a process known as “genetic sequencing”) to determine the nucleotide/DNA sequence. In the *PYGM* gene, the genetic information which encodes muscle glycogen phosphorylase is made up of 2,523 nucleotides (Burke *et al.*, 1987; Kubisch *et al.*, 1998; DiMauro *et al.*, 2002). The DNA sequence of the *PYGM* gene was first published by Burke *et al.* in 1987.

Genetic information is contained in chromosomes. Chromosomes are basically a string of genes. Humans have 23 pairs of chromosomes. There are 22 chromosomes which are unrelated to gender; these are called “autosomes”. The X and Y chromosomes are the “sex chromosomes” which determine gender. Men have one X and one Y chromosome and women have two X chromosomes. The *PYGM* gene which encodes muscle glycogen phosphorylase is located on chromosome number 11. Chromosome 11 is an autosome (this is why McArdle disease is not related to gender and both men and women can have McArdle disease). The chromosomes are located within the nucleus of cells (a special compartment in the cell).

Proteins are made in another area of the cell called the endoplasmic reticulum (ER), which is basically the protein-making-factory. However, the protein-making-factory (ER) is located in a different area of the cell to the nucleus. As outlined above, the gene has the information which the cell needs to make proteins. However, each gene is contained within a chromosome (which is relatively large), so the gene cannot be taken outside of the nucleus to the ER. In order to solve this problem, a temporary copy of the gene is made. This copy is called mRNA (which stands for messenger RNA). The mRNA is a copy of the DNA sequence of the gene, which is made in the nucleus. The mRNA is very small, and is able to move from the nucleus to the ER. The mRNA is then used to produce the protein. A very simple analogy would be to baking a cake. The chromosome is like a cook book with different recipes on each page. Each gene is like a recipe. You need the recipe at home so that you can bake the cake in your kitchen. But the recipe can't be taken away from the library (a gene can't leave the nucleus). If a photocopy is made of a page with one recipe, that is like mRNA. You can then take the recipe home and put it in your kitchen (mRNA can be transported

from the nucleus to the ER). The recipe is used to make a cake in your kitchen at home (mRNA is used to make protein in the ER). But the photocopy is easily destroyed (mRNA does not last long in the cells).

In the ER, the mRNA is translated to produce protein. A component of the protein-making-factory (ER), called ribosomes, makes the protein by joining together amino acids in a long chain. Amino acids are the building blocks of proteins. The ribosomes use the code in the mRNA to determine in what order to put the amino acids. The mRNA is translated in triplets; three nucleotides are translated to identify one amino acid. These triplets are known as “codons”. For example, in muscle glycogen phosphorylase, the first three nucleotides (ATG) encode an amino acid called methionine (the single letter code for methionine is “M”). (The situation is slightly more complicated than this because the first amino acid is removed from the muscle glycogen phosphorylase protein during the process of making it functional. This is discussed further in section 17.5.1.7.)

There are 20 amino acids which can each be written as a single letter code. Each amino acid has a different chemical structure. Within the protein, amino acids can interact together to make complex structures which are necessary for the protein to function as an enzyme. In some proteins (including muscle glycogen phosphorylase), the order of the amino acids is very important for the protein to be able to function correctly. The order of the amino acids is known as a “protein sequence” or “amino acid sequence”. The protein sequence for muscle glycogen phosphorylase begins “MSRPLSDQEKRRKQISVRGLAGVENVTE...”. Muscle glycogen phosphorylase is 842 amino acids long (Kubisch *et al.*, 1998).

3.2 Mutations in the *PYGM* gene prevent production of functional muscle glycogen phosphorylase enzyme and cause McArdle disease

McArdle disease is caused by the lack of functional muscle glycogen phosphorylase in muscle cells. Almost all known mutations result in a complete lack of functional muscle glycogen phosphorylase. It is possible that some mutations may still result in the production of muscle glycogen phosphorylase, but that it is not able to fold into the correct shape or to function as an enzyme and therefore it cannot break down glycogen into glucose-1-phosphate.

There are several types of mutations in the *PYGM* gene which prevent production of functional muscle glycogen phosphorylase. These are illustrated in Table 3.2 and explained more fully below.

Type of mutation	An example of how each mutation affects the translation of mRNA into protein. (The sentence represents <i>PYGM</i> mRNA.)	Effect on protein production
Correct <i>PYGM</i> mRNA with <i>no mutation</i>	The sentence can be read correctly.	Protein is made correctly.
Mutations:	Premature stop codon leads to nonsense-mediated decay of the mRNA (no sentence is seen).	No protein is made.
	Premature stop codon (a full stop is introduced between "s" and a")	Shortened protein is made.
	Missense mutation (the "s" is changed to a "p")	Protein has incorrect sequence.
	Frameshift (the "s" is removed/deleted):	Protein has incorrect sequence.
	Splice site mutation (the space before the "s" is removed)	Protein has incorrect sequence.

Table 3.1 An example of how different types of mutation disrupt the reading frame using the sentence "The cat saw the rat", which represents *PYGM* mRNA with the triplet codons. The person reading the sentence (you!) represents the ribosome which has to decode the mRNA. The effect of the mutation upon protein production is also given.

3.2.1 Stop codons

Stop codons occur naturally at the end of the gene and, during translation of mRNA, signal to the ribosome that it has got to the end of the instructions to make a particular protein. However, mutations which introduce stop codons in the wrong place, for example halfway through a gene, interrupt the instructions. Mutations which introduce stop codons in the wrong place are also known as “premature stop codons”, “premature termination codons”, “nonsense mutations,” or “nonsense codons”. In a protein sequence, stop codons are indicated by an “X”. An example of how this would be written in a protein sequence would be “R50X”. “50” indicates that it is amino acid number 50 in the protein sequence; arginine (single letter code R) is the original amino acid, which has been replaced by a premature stop codon, as are shown by “X”. Mutations which introduce premature stop codons can have several effects: nonsense-mediated decay of mRNA or production of a non-functional protein.

3.2.1.1 Nonsense-mediated decay destroys mRNA containing some premature stop codons

Some premature stop codons make the mRNA highly susceptible to being destroyed before it can be used to make a protein. mRNA which has a premature stop codon could lead to production of a protein which is too short. The body has a surveillance system in place to identify mRNA which has mutations. mRNAs containing certain premature stop codons are specifically identified and then destroyed by a process called “nonsense-mediated decay”. It has been suggested that the benefit of nonsense-mediated decay is to prevent the production of proteins which could potentially be bad for the cell due to the mutations they encode (Frischmeyer and Dietz, 1999). (For example proteins with an incorrect sequence or which are too short may not fold correctly, and may instead clump together and stop the cell working properly.)

Several premature stop mutations are known to cause nonsense-mediated decay in mRNA encoding muscle glycogen phosphorylase in McArdle people. Experimentally, if nonsense-mediated decay is taking place, then it is possible to identify a premature stop codon mutation in the gene/genomic DNA, but no mRNA will be detected. To date (August 2011), nonsense-mediated decay has been shown to occur to *PYGM* mRNA with the premature stop codon mutations R50X, L5VfsX22, Q73HfsX7, E125X, N134KfsX161, W388_V390delinsSfsX33, R491AfsX7 and D534VfsX4 (Bartram *et al.*, 1993; Nogales-Gadea *et al.*, 2008; Sohn *et al.*, 2008). Each of these mutations results in no muscle glycogen phosphorylase being made. I think that other premature stop codon mutations which lead to nonsense-mediated decay will be identified in the future.

3.2.1.2 A non-functional protein may be made

Not all mRNA with mutations is destroyed by nonsense-mediated decay. The body is not always able to recognise mutations. If the body does not identify a mutation, then mRNA which contains a mutation is produced in the nucleus, and transported to the ER where it is used to make protein. However, the protein will not have the correct sequence as it will contain the mutation. If the mutation was a stop codon, the protein will be too short. Both ends of the muscle glycogen phosphorylase amino acid sequence are very important for muscle glycogen phosphorylase to form the correct shape and be functional. It is not functional if the protein is too short because of a premature stop codon. For example, at present, the premature stop codon nearest the end of the *PYGM* gene is C784X (Rubio *et al.*, 2007). Muscle glycogen phosphorylase is 842 amino acids long, so

the C784X mutation results in a protein which is missing 58 amino acids. It is therefore missing approximately 1/14th of the protein. Removing this number of amino acids stops muscle glycogen phosphorylase being functional.

3.2.2 Missense mutations

Missense mutations change the code of the gene so that the code for one amino acid is replaced by the code for a different amino acid. The ribosome will not know that a missense mutation is present in the mRNA, and will include the wrong amino acid in the protein. Some proteins are able to function even if the wrong amino acid is present, but others are not able to function. Missense mutations (which result in the wrong amino acid being included in the protein) can make the protein form the wrong shape (or misfold). In some cases, the cell will recognise that the protein is the wrong shape, and will destroy it. As of August 2011, 61 missense mutations have been identified which prevent muscle glycogen phosphorylase from being able to function (Table 3.2).

An example of how a missense mutation would be written in a protein sequence would be G205S, where “205” indicates that it is amino acid number 205 in the sequence (the numbers start at 1), that “G” (single letter code for glycine) was the original amino acid, and “S” (single letter code for serine) indicates that the missense mutation has changed the DNA sequence so that it now encodes serine.

3.2.3 Frameshift mutations

Frameshift mutations occur if nucleotides are added to or removed (deleted) from the gene, which causes the ribosome to misread the amino acid sequence specified by the mRNA. Misreading of the amino acid sequence leads to the production of a protein which doesn't have the right sequence of amino acids, and is not able to function in the normal way. Frameshift mutations change the way in which the ribosome reads the amino acids sequence, and often this results in a premature stop codon. An example of how this would be written would be: L5VfsX22. This indicates that amino acid number 5 was originally L (single letter code for Leucine), and “fs” indicates that a frameshift mutation has now occurred. “22” means that after misreading 22 amino acids, a premature stop codon (shown by “X”) has been introduced.

3.2.4 Splice site mutations

Genes are slightly more complicated than already described. Basically, genes are composed of coding regions (called exons) which are used to make mRNA and encode the sequence for making proteins, and non-coding regions (called introns), which are not used to make protein. During the process of making mRNA, mRNA is first made which includes both the exons and introns. However, splicing then takes place. During splicing, introns in the mRNA are removed. The exons are then joined together at “splice sites”. It is possible to have a mutation at the splice site. This can disrupt the removal of introns or prevent the joining of exons so that the mRNA sequence is no longer correct. It will therefore not be possible to use this mRNA to produce functional protein.

Splice site mutations can cause McArdle disease. Fernandez-Cadenas *et al.* (2003) described a McArdle person with a splice site mutation (K608K) in the muscle glycogen phosphorylase gene. When the mRNA was studied closely, it was shown that this mutation caused major changes the way in which the mRNA was spliced and was read by the ribosome. Garcia-Consuegra *et al.* (2009) identified a nucleotide change c.529-8 g> a in the splice sequence of intron 4 which caused retention

of 6 nucleotides in the coding region of intron 4, which would lead to the insertion of two amino acids in the coding region. However, there are a few very rare cases where mutations in splice sites still result in production of a very low level of functional enzyme (see section 9.1.3).

3.2.5 Theoretical possible outcomes of various mutations

There remains a lack of published data on whether having a specific mutation has an effect on whether the mRNA can be detected and if there is any muscle glycogen phosphorylase present. Different amounts of muscle glycogen phosphorylase mRNA and protein have been reported by researchers, but in many cases the specific mutation was not known. The flowchart shown in Figure 3.1 is my own theoretical explanation of what may cause the different amounts of mRNA and protein which have been reported in published papers.

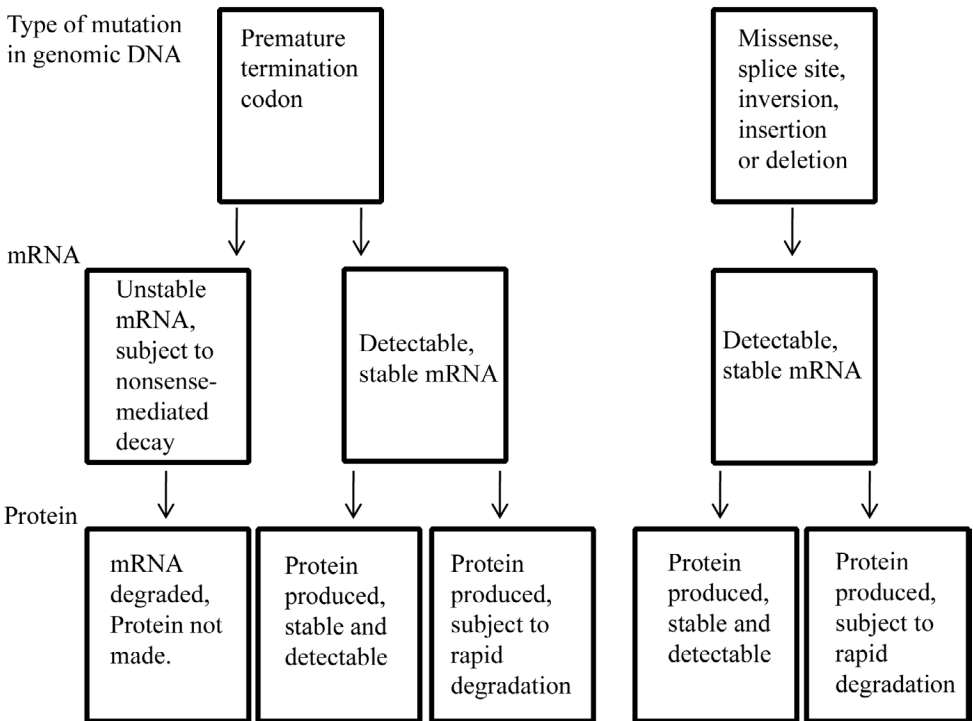


Figure 3.1 Flowchart illustrating theoretical explanations for the possible effects of different mutations in the *PYGM* gene upon stability of mRNA and production of protein (Wright, 2009).

PYGM mRNA containing a premature stop codon may be subject to nonsense-mediated decay, and degraded, preventing translation of the amino acid sequence. If mRNA with a premature stop codon is not subject to nonsense-mediated decay, the protein may be stable and detectable, or it may be unstable and quickly destroyed by the cell. Other mutations, such as missense, splice site, insertion, inversion or deletion mutations are likely to lead to detectable, stable mRNA unless they introduce a premature stop codon which causes nonsense-mediated decay. These mRNAs may result in either

stable, detectable protein being produced, or unstable protein which is quickly broken down by the cell. Mechanisms to identify and destroy incorrect proteins are known as protein degradation pathways. The variable outcomes illustrated in Figure 3.1 have been demonstrated by studies of muscle glycogen phosphorylase from McArdle people. Normal levels, reduced levels, or a complete absence of muscle glycogen phosphorylase protein have been reported in McArdle people (although in all these cases the protein is non-functional).

3.2.6 How many of these mutations have been identified in the *PYGM* gene so far?

Currently 137 mutations in the *PYGM* gene have been found which cause McArdle disease (reviewed in Wright, 2009). Mutations found in the *PYGM* gene have included missense, premature stop codons, splice site, insertion, inversion, and single base deletions (summarised in Table 3.2). These are located throughout the muscle glycogen phosphorylase amino acid sequence rather than just occurring in particular areas of the gene.

3.2.6.1 Most of the mutations are specific to particular ethnic groups

The locations of the mutations within the *PYGM* gene depend on the ethnic background of the person. The most common mutation amongst Caucasians in Europe and North America is the R50X mutation in exon 1 (DiMauro *et al.*, 2002). This occurs when an arginine (CGA) is mutated to the premature stop codon mutation (TGA). The R50X mutation is the cause of McArdle disease in 81% of British McArdle people, between 63% (DiMauro *et al.*, 2002) and 75% (Tsujino *et al.*, 1995) of US McArdle people, 56% of German McArdle people, and 32% of Italian and Spanish McArdle people (DiMauro *et al.*, 2002; Quintans *et al.*, 2004).

Type of mutation	Number of locations identified to date for mutation within <i>PYGM</i> gene
Loss of start site	2
Premature stop codon: (of which: known to be subject to nonsense-mediated decay)	15 (2)
Missense	61
Deletion of one or more amino acid(s) (of which: deletion of a single amino acid)	6 (5)
Splice site or intronic mutations	20
Silent polymorphism	3
Insertion/deletion	3
Frameshift: of which: (resulting in a premature stop codon) (known to be subject to nonsense-mediated decay)	27 (13) (6)
Total number of mutations identified to date	137

Table 3.2 Summary of mutations in the coding sequence and splice sites of the human *PYGM* gene known to cause McArdle disease (correct as of August 2011).

Other mutations appear to be specific to ethnic groups. For example, the single codon deletion 708/709 has only been found in Japan. Other ethnic mutations include R270X and R602Q, which were found in two unrelated Yemenite-Jewish families (Hadjigeorgiou *et al.*, 2002).

Until recently, no McArdle people had been identified in some ethnic groups. Quinlivan *et al.* (2010) recently described a Pakistani McArdle person where both copies of the *PYGM* gene had a newly discovered single base pair deletion in exon 1 (c.14delT) which resulted in a premature stop codon (pL5RfsX20). A Korean person who had a novel single codon deletion (p779delE) plus the R50X mutation was described by Sohn *et al.* (2008). Several cases of people where McArdle disease was caused by both copies of the *PYGM* gene having the V456M mutation in exon 11 have been described; this mutation was found in a Moroccan baby (Mancuso *et al.*, 2003), in a Latin American person born in Ecuador (Fernandez-Cadenas *et al.*, 2007), and in people from Tunisia and Algeria (Aqaron *et al.*, 2007).

3.2.7 What caused the first mutation in the *PYGM* gene?

It is not known what caused the first mutation in the *PYGM* gene. The body has to copy all the DNA (including the *PYGM* gene) to produce egg and sperm cells. If this copying process introduces an error into the *PYGM* gene in an egg or sperm cell which is then used to conceive a baby, the mutation in the *PYGM* gene will also be inherited. Mutations occur relatively frequently in the human genome, but often have no effect or mild effect. In general, natural selection removes mutations which have a lethal effect, but recessive mutations often remain at low frequency in populations. It is highly likely that mutations in the *PYGM* gene and McArdle disease have been occurring for thousands of years, long before Dr Brian McArdle published his paper describing the condition in 1951.

3.3 How is McArdle disease inherited?

3.3.1 One copy of each gene is inherited from each parent

During conception, each person will inherit one set of chromosomes from their mother and one set of chromosomes from their father. They will inherit a copy of the *PYGM* gene from each parent – giving a total of two copies of the *PYGM* gene in each person.

To continue the analogy to baking a cake with a cook book which was used earlier (section 3.1.1); each person will have one set of books from their mother and one set from their father. Both the chromosome (book) from the mother and chromosome (book) from the father will have a gene (recipe e.g. the *PYGM* gene) for each protein (e.g. muscle glycogen phosphorylase). So each person will have two copies of the gene (*PYGM*) which contains the genetic information for muscle glycogen phosphorylase.

3.3.2 What are the combinations of normal and faulty copies of the *PYGM* gene which can occur?

People unaffected by McArdle's have two normal copies of the *PYGM* gene. The normal copy of the *PYGM* gene is used to produce functional muscle glycogen phosphorylase which works normally in muscle.

Carriers have one normal copy of the *PYGM* gene, and one faulty copy of the *PYGM* gene. They do not usually have symptoms of McArdle disease (see section 9.1.1). The faulty copy of the *PYGM* gene cannot produce any functional muscle glycogen phosphorylase, but the normal copy of the *PYGM* gene is able to produce functional muscle glycogen phosphorylase. Carriers have approximately half the amount of functional muscle glycogen phosphorylase compared to people unaffected by McArdle disease (see section 9.1.1), and this is enough enzyme to allow the muscle to work normally.

McArdle people have mutations in both their copies of the *PYGM* gene. These mutations may be different in each copy of the *PYGM* gene. Neither of the mutant copies of the *PYGM* gene can be used to produce functional muscle glycogen phosphorylase (for rare exceptions see section 9.1.3). McArdle people do not have any functional muscle glycogen phosphorylase in their muscles – and therefore have McArdle disease.

3.3.3 Methods of inheritance

3.3.3.1 Recessive disease versus dominant disease

McArdle disease is a recessive disease which means that a person must inherit two faulty copies of the *PYGM* gene in order to have McArdle disease. In the case of a recessive disease, carriers do not have any symptoms of the disease as they have one normal copy and one faulty copy of the gene.

In a dominant disease, carriers do have symptoms. Just one faulty copy of the gene is sufficient to have all the symptoms of the disease even though the carrier has one normal copy of the gene. An example of a dominant disease is malignant hyperthermia (which is discussed further in section 12.3.1).

Although there has been at least one paper suggesting that McArdle's had been inherited in a dominant or pseudo-dominant way, this was incorrect, and was due to the combination of an asymptomatic carrier parent with a McArdle parent who had both the R50X and a novel mutation which was not discovered until later (Tsujiro *et al.*, 1993; Isackson *et al.*, 2005).

3.3.3.2 Autosomal disease versus sex-linked disease

McArdle disease is an autosomal disease. This means that inheritance is unrelated to gender, and men and women are equally likely to have McArdle's.

Sex-linked inherited diseases usually occur due to a mutation in a gene which is located on the X chromosome. If the disease is sex-linked and recessive, women are much less likely to have the disease as they have two X chromosomes. Even if the faulty copy of the gene is located on one of their X chromosomes, they are likely to have a normal copy of the gene on their other X chromosome. Men only have one X chromosome, so if they have a mutation in a gene on that chromosome, they have no "back-up" gene on their second X chromosome. Men are much more likely to have sex-linked inherited diseases than women. Haemophilia is an example of a sex-linked recessive disease where men are affected much more frequently than women.

3.3.3.3 Genetics nomenclature

In the following examples, upper case "M" is used to represent the normal copy of the *PYGM* gene for muscle glycogen phosphorylase. Lower case "m" is used to represent the faulty copy of the

PYGM gene. There is no standard one letter code used to represent *PYGM*, so I have chosen to use the letter “m”. However, the use of upper and lower case as described above is standard practice in genetics.

Information about a person’s genotype (information about which copies of the *PYGM* gene they have) can therefore be written as follows:

A McArdle person would be written as “mm”

A carrier would be written “Mm”

A person unaffected by McArdle’s would be written “MM”.

Humans have two copies of the *PYGM* gene. A baby will inherit one copy from the mother and one copy from the father. This is achieved because during the production of egg and sperm (known as gametes) in the parents, only one of the two copies of the *PYGM* gene go into each. (The actual mechanism for egg and sperm production is a little more complicated than this, and involves a few extra steps before this part, but this is the important part and is sufficient to understand inheritance.) If the parent is unaffected by McArdle’s (MM), the gametes will be either “M” or “M”, so the child can only inherit “M”. If the parent is a carrier (Mm), the child could inherit either M” or “m”. If the parent has McArdle’s (mm), the child could only inherit “m”. When the parents have a baby, the possible outcomes can be illustrated by a diagram, known as a Punnet square (invented by Mr Punnet!). The chances for each subsequent child are exactly the same and are not altered by whether any previous child had McArdle’s, was a carrier, or was unaffected.

3.3.4 How many people have McArdle disease or are carriers of a mutation in *PYGM*?

McArdle disease is a rare disease. It has been estimated that the frequency of people with McArdle disease is approximately 1 in 100,000 (Applegarth *et al.*, 2000; Haller, 2000; Tarnopolsky, 2006; Beynon *et al.*, 2002). The number of people who are carriers is also low. It has been suggested that the number of people who are carriers for McArdle disease is between 1 in 66 (Tarnopolsky, 2006) and 1 in 158 (Isackson *et al.*, 2005). Examples of how McArdle disease is inherited are outlined below. Because McArdle disease is so rare, a McArdle person or a carrier is most likely to have a partner who is unaffected by McArdle’s. For completeness, several different scenarios are described.

3.3.5 Examples of how McArdle’s is inherited

As McArdle’s is inherited in an autosomal manner, the possible outcomes are unaffected by whether the parent with McArdle’s is the mother or father. Please assume that parents are not related in the following examples. A different pattern of inheritance might be seen if the parents were closely related, which is explained further in section 3.3.6.

The examples show the chances of having a child with McArdle’s, depending upon whether the parents were unaffected, carriers or have McArdle disease themselves. For a pair of parents, the likelihood of a child having McArdle’s is exactly the same for the every subsequent child as the first child. For example, in the case of a carrier parent plus a carrier parent, as illustrated in Table 3.1, the first child has a 25% chance of having McArdle’s. If the same parents have a second child, this child will also have a 25% chance of having McArdle’s. All subsequent children will each have a 25%

chance of having McArdle's. Some families may have no children with McArdle's, some families may have some children with McArdle's and some unaffected children, and yet other families may have all children with McArdle's – but in each case the risks were the same.

NOTE: The following information is based upon theoretical methods of inheritance. It is not intended to replace genetic counselling. Medical advice/genetic counselling should be sought if you would like to discuss or further understand the way in which McArdle's is inherited or the chances of having a child with McArdle's.

3.3.5.1 Neither of my parents had symptoms of McArdle's, but I have McArdle's

It is likely that both parents were carriers (each parent had one normal copy of the *PYGM* gene and one faulty copy of the *PYGM* gene). Carriers of the faulty copy of the *PYGM* gene do not usually have symptoms of McArdle disease. In order for the child to have McArdle's, the child must have inherited a faulty copy of the *PYGM* gene from each parent – resulting in two faulty copies of the *PYGM* gene and no normal copies.

Carrier parent (Mm) plus carrier parent (Mm):

If both parents are carriers, there is a 25% (1 out of 4) chance that the child will be unaffected, a 50% (2 out of 4) chance that the child will be a carrier, and a 25% (1 out of 4) chance that the child will have McArdle's.

		Father (Mm, carrier)	
		Sperm cells have:	
		M	m
Mother (Mm, carrier) Egg cells have:	M	MM (unaffected)	Mm (carrier)
	m	Mm (carrier)	mm (McArdle's)

Figure 3.2 A punnet square illustrating the possible outcomes when a father who is a carrier (Mm) has a baby with a mother who is also a carrier (Mm). There is a 25% (1 out of 4) chance that the child will be unaffected (MM), a 50% (2 out of 4) chance that the child will be a carrier (Mm), and a 25% (1 out of 4) chance that the child will have McArdle's (mm).

3.3.5.2 I have McArdle disease and my partner does not; will my children have McArdle disease?

The parent with McArdle disease will be homozygote for the mutation; will have two faulty copies of the *PYGM* gene. There are two possible situations for the partner. The partner could be unaffected (have two normal copies of the *PYGM* gene), or could be a carrier.

McArdle's parent (mm) plus unaffected parent (MM):

The only possible outcome is that the child is a carrier (Mm). There is a 4 out of 4 (100%) possibility that the child will be a carrier. This is the most commonly occurring situation, and results in a child which is a carrier and does not have any symptoms of McArdle's.

		Father (mm, McArdle's) Sperm cells have:	
		M	m
Mother (MM, unaffected- has two normal copies of the <i>PYGM</i> gene) Egg cells have:	M	Mm (carrier)	Mm (carrier)
	M	Mm (carrier)	Mm (carrier)

Figure 3.3 A punnet square illustrating the possible outcomes when a father who has McArdle's (mm) has a baby with a mother who is unaffected (MM). The only possible outcome is that the child is a carrier (Mm). There is a 100% (4 out of 4) chance that the child will be a carrier.

McArdle's parent (mm) plus carrier parent (Mm):

There is a 2 out of 4 (50%) chance that the child will be a carrier, and a 2 out of 4 (50%) chance that the child will have McArdle's. None would avoid receiving at least one faulty copy of the *PYGM* gene. There is a 50% chance that both the parent (the father in this example) and the child will have McArdle's. This can be the explanation when McArdle's appears to run in families and to be passed down the generations. This doesn't happen very often because McArdle's is relatively rare.

		Father (mm, McArdle's) Sperm cells have:	
		m	m
Mother (Mm, carrier) Egg cells have:	M	Mm (carrier)	Mm (carrier)
	M	mm (McArdle's)	mm (McArdle's)

Figure 3.4 A punnet square illustrating the possible outcomes when a father who has McArdle's (mm) has a baby with a mother who is a carrier (Mm). There is a 50% (2 out of 4) chance that the child will be a carrier (Mm), and a 50% (2 out of 4) chance that the child will have McArdle's (mm).

3.3.5.3 My partner and I both have McArdle's

This is a very unusual situation, but is included for completeness. If both parents have McArdle's, they must both be homozygous for the mutation; must have two faulty copies of the *PYGM* gene.

McArdle's parent (mm) plus McArdle's parent (mm):

There is a 4 out of 4 (100%) chance that the child will have McArdle's.

		Father (mm, McArdle's)	
		Sperm cells have:	
		m	m
Mother (mm, McArdle's) Egg cells have:	M	mm (McArdle's)	mm (McArdle's)
	M	mm (McArdle's)	mm (McArdle's)

Figure 3.5 A punnet square illustrating the possible outcomes when a father who has McArdle's (mm) has a baby with a mother who also has McArdle's (mm). There is a 100% (4 out of 4) chance that the child will have McArdle's (mm).

3.3.5.4 I am a carrier of McArdle disease. Will my children have McArdle disease?

The answer depends on whether your partner has any faulty copies of the *PYGM* gene. A person who is a carrier could have a partner who either

- a) has McArdle's (see Figure 3.4),
- b) is a carrier (see Figure 3.2),
- c) is unaffected – see below.

Carrier parent (Mm) plus unaffected parent (MM):

There is a 2 out of 4 (50%) chance that the child will be unaffected, and a 2 out of 4 (50%) chance that the child be a carrier.

		Father (MM, unaffected)	
		Sperm cells have:	
		M	M
Mother (Mm, carrier) Egg cells have:	M	MM (unaffected)	MM (unaffected)
	M	Mm (carrier)	Mm (carrier)

Figure 3.6 A punnet square illustrating the possible outcomes when a father who has is unaffected (MM) has a baby with a mother who is a carrier (Mm). There is a 50% (2 out of 4) chance that the child will be unaffected (MM), and a 50% (2 out of 4) chance that the child be a carrier (Mm).

3.3.5.5 My grandmother/grandfather/aunt/uncle has McArdle disease

Having a grandparent or aunt/uncle with McArdle's may suggest that you could be a carrier. It will not be possible to determine this without a genetic test (or possibly a muscle biopsy to accurately quantify the amount of muscle glycogen phosphorylase, as carriers usually have approximately half the amount of muscle glycogen phosphorylase compared to unaffected people). Unless family members have had children together, the chances of a carrier having a partner who is also a carrier is relatively unlikely. It is therefore unlikely that you would have a child which has McArdle's. For

this reason, I suspect that many family doctors would not be interested in performing tests to determine if you are a carrier.

3.3.6 Consanguineous parents; why are they more likely to produce a child with an inherited disease?

Consanguineous means that the parents are closely related family members. Examples of this could be two siblings or first cousins having children together. There are many different recessive diseases which a parent could have, but if a child has unrelated parents, it is unlikely that both parents will be carriers of a faulty copy of the same gene. If the child inherits only one faulty copy of a gene, it will be a carrier, and will usually not have any symptoms. In contrast, siblings or cousins are more likely to be carriers of a faulty copy of the gene for the same recessive disease, or even for faulty copies of genes for several different recessive diseases. This may result in their child having one or multiple inherited diseases.

Mancuso *et al.* (2003) reported a consanguineous marriage, which resulted in the birth of a baby that had McArdle disease and also mitochondrial DNA depletion syndrome (see section 8.1.1). These are both autosomal recessive diseases. It is likely that both parents were carriers for both of these diseases, and the child inherited several diseases.

Recommended reading:

Basic Genetics: Textbook and Activities By Ahmed Abouelmagd, Hussein M. Ageely (*Google free books*). (*For general information about inheritance. There are many other complicated patterns of inheritance, so focus on "autosomal recessive inheritance".*)

4 Exercise, muscle contractions, and contractures (muscle cramps)

Anaerobic exercise is when a short burst of high intensity exercise occurs, for example, running for a bus. For McArdle people, more than a few seconds of this type of intense exercise can cause muscle damage, and lead to muscle cramps (contractures). For McArdle people, the saying “No pain, no gain” does NOT apply. If pain is felt, then McArdle people should stop exercising and rest. However, after a rest, energy is provided to the muscles from a different source. This creates a “second wind” which enables McArdle people to exercise further. More effort is required to move around a heavier body, so McArdle people are recommended to maintain a healthy weight and avoid being overweight.

Muscle contractures are painful muscle cramps, which can last several hours or days. At present, the scientific reason for this pain is not known. The only recommended treatment for contractures is rest. McArdle people have anecdotally reported the following home treatments: use of cool/ice packs, heat packs, strong painkillers and massage. There is no published information on any of these home treatments, and some of these treatments (like massage) could lead to further damage to the muscles. Pain can serve as a warning to protect the muscle from further damage so McArdle people should be warned that the use of strong painkillers could lead to the muscle being used, which could cause further damage.

4.1 Types of exercise

Exercise can basically be divided into two classes; aerobic and anaerobic.

4.1.1 Anaerobic exercise

Anaerobic exercise occurs when energy is produced in the muscle cells without using oxygen. This occurs when the blood is not able to supply enough oxygen to the muscle cells for aerobic exercise to occur (Sleamaker and Browning, 1996). Anaerobic exercise is usually when a short burst of high intensity exercise occurs. An example of this would be fast sprinting, like running for a bus. The energy for muscle cells to move during exercise is usually provided by a combination of aerobic and anaerobic exercise. However, the first 10 to 30 seconds of exercise are solely anaerobic (Sleamaker and Browning, 1996).

Initially, free glucose in the muscle cells is used to provide energy for movement. However, this is used up within the first few minutes of exercise. In people unaffected by McArdle's, energy is then produced by glycogenolysis. This is the chemical reaction where stored glycogen is broken down to produce glucose, which is used to generate Adenosine Triphosphate (ATP). Muscle glycogen phosphorylase is essential for this chemical reaction in muscle cells. Because muscle glycogen phosphorylase is not functional, McArdle people cannot utilise this energy source.

4.1.2 Aerobic exercise

Aerobic exercise takes place when oxygen is supplied in the bloodstream to the muscles. Taking a breath of air pulls the air into the lungs. The lungs are made up of lots of alveoli which are tiny sacks. The surfaces of the alveoli are covered in lots of blood vessels. Oxygen from the air binds to haemoglobin in the red blood cells. Haemoglobin, with oxygen bound to it, is then pumped around the body to many places, including the muscles. In the muscles, oxygen is taken from the haemoglobin in the blood vessels into the muscle cells. The oxygen is then combined with sources of energy such as free fatty acids in chemical reactions which generate ATP (energy). Aerobic exercise is defined as exercise for a minimum of ten minutes (Sleamaker, 1996). An example of aerobic exercise would be walking on a road or treadmill for 20 minutes.

4.2 Exercise recommendations for McArdle people

4.2.1 Anaerobic exercise or static muscle contractions should be avoided

Strenuous exercise must be avoided as it can lead to muscle damage, muscle cell breakdown and possible kidney failure. Lucia *et al.* (2008a) recommend McArdle people to avoid exercise that induces severe pain, and in particular to avoid static muscle contractions. Static muscle contractions (also called isometric contractions) are those which are required to hold something in one place for a long time, such as holding the body in one place for a long time by squatting, or holding a heavy bag or weight for a long time.

Andrew Wakelin, McArdle's Coordinator for AGSD-UK, suggests a "six second rule" (see Box 4.1). This suggestion is based upon the experiences of McArdle people, but has not been scientifically proven.

The six second rule:

"To avoid damage when doing something of maximum intensity it is a good idea to time 6 seconds by saying to "One thousand, two thousand..." up to six. If the task is not completed by 6, stop or put it down. Take a break, let the muscles recover and try again later."

Box 4.1 The six second rule as suggested by Andrew Wakelin. (Taken from www.agsd.org.uk.)

4.2.2 Moderate aerobic exercise and conditioning improves symptoms of McArdle's

The breakdown of fatty acids and amino acids, and the release of glucose from the liver, provide the energy for the second wind. In the second wind, energy is produced using oxygen for oxidative phosphorylation, and is therefore aerobic. McArdle people are able to continue to exercise aerobically for a long period of time using fatty acid oxidation to provide energy (Quinlivan and Vissing, 2007).

Exercising regularly (but gently) improves aerobic conditioning. Aerobic conditioning is the ability of the lungs to take in more oxygen, and the ability of the heart to pump blood round the body. Aerobic conditioning improves the supply of glucose, fatty acids, and oxygen to the muscles via the bloodstream, and also improves the ability of the mitochondria to utilise sources of energy (Vissing and Haller, 2003; Quinlivan and Vissing, 2007; Quinlivan *et al.*, 2008). Warming up prior to exercise will improve blood supply to the muscles, and can aid the transition to "second wind" (Haller, 2000).

Low level warm-up (Amato, 2003) and regular light aerobic exercise can speed the beneficial transition to second wind from anaerobic to fatty acid oxidation in McArdle people (Quinlivan *et al.*, 2008). Perez *et al.* (2008) described a 9 year old boy with McArdle disease who presented with severe myalgia (muscle pain), muscle weakness, myoglobinuria, and elevated creatine kinase after exercise. He was recommended to consume 20g of carbohydrate before exercise, and to carry out age-appropriate exercise. One year later, his fitness had improved, he was able to exercise and perform ordinary activities, and had almost normal serum creatine kinase levels. He had not had any further acute clinical episodes (such as myoglobinuria).

Haller *et al.* (2006) investigated whether aerobic conditioning (regular aerobic exercise) could improve the ability of McArdle people to exercise. The training programme for eight McArdle people was as follows: they were trained on a cycle ergometer for 30-40 minutes, four days a week, for 14 weeks. They exercised at an intermediate rate, not the hardest they could do. The authors found that after this period of training, the participants were able to carry out more exercise, take in more oxygen (which is needed to produce energy during the second wind), and their heart was able to pump blood more efficiently. They also found that levels of some of the enzymes involved in producing energy (called "citrate synthase" and " β -hydroxyacyl coenzyme A dehydrogenase") had increased. The participants did not have pain, cramps, and the level of creatine kinase in the blood did not rise during the exercise – which suggested that the exercise was not causing muscle damage. The participants were still able to achieve a second wind in the same way as before the training programme. The authors concluded that moderate aerobic exercise was a way to increase the ability of McArdle people to exercise. The training programme improved the ability of the heart to pump blood around the body, which increased the amount of energy sources which could be taken by the blood to the muscles.

Other researchers have also described positive results of aerobic training for McArdle people. Quinlivan and Vissing (2007) describe unpublished data by Portero *et al.*: Portero *et al.* carried out a trial where four McArdle people performed aerobic exercise for 30-45 minutes three times a week for eight weeks. The authors said that the results showed an improvement in the amount of oxygen taken into the body, an increase in the amount of glucose carried in the blood to the muscle cells, and increase in the ability to exercise and the length of time which exercise could be carried out, and also a reduction in the CK levels in the blood. Quinlivan and Vissing (2007) also describe an unpublished study by Zange *et al.*, who studied two McArdle people who carried out aerobic training daily for 12 weeks. Following the training programme, these McArdle people also had “an improvement in strength without any significant adverse effects. There were no episodes of pain or cramping.

4.2.3 Being overweight can make McArdle people find it harder to move around

A large number of McArdle people are overweight. Quinlivan *et al.* (2010) reported that 71% (32 of 45) of the McArdle people seen at the UK McArdle Clinic were clinically overweight, with a body mass index (BMI) greater than 26. This is not surprising when you remember that in the past, McArdle people were advised to avoid exercise. And also that in the past, McArdle people were advised to have a sugary drink before exercise. If a sedentary lifestyle is combined with consuming a lot of sugar, it is likely to lead to weight gain. The advice to McArdle people is now different; moderate exercise is recommended (see section 4.2.2), and although a sugary drink can be of use in certain circumstances, it obviously has to be used in moderation (see section 7.1.6.2). McArdle’s experts are now keen to ensure McArdle people are warned about this disadvantage of a sugary drink. “When informing people with McArdle disease about such treatment [sugary drinks before exercise], family doctors should stress the importance of restricting its use to avoid unintentional weight gain” (Vissing and Haller, 2003).

For people unaffected by McArdle disease, the ways in which they can maintain a healthy weight include a balanced diet, and regular exercise. For McArdle people, there is some debate about what the balance of carbohydrate and protein in the diet should be (see section 6.6), but it remains the case that if you consume more calories (more food or energy) than you use, then this will result in weight gain. Energy from food is used up in everyday life (walking around or doing housework) in addition to during exercise.

For anybody (whether they have McArdle’s or not), being overweight leads to an increased risk of other serious health problems such as heart disease and cancers of the breast, colon, and prostate (source: <http://www.nhs.uk/Livewell/loseweight/Pages/Whyyourweightmatters.aspx>). In addition to these risks, a disadvantage of being overweight for a McArdle person is that it may make it harder to exercise (Amato, 2003). A heavier body weight increases the amount of work which the muscles have to do in holding the body upright and in moving around. This is more likely to lead to muscle damage (rhabdomyolysis and muscle pain) if the muscles are unfit or unconditioned.

4.3 Muscle contraction and relaxation

A very simplified description of a muscle cell is that it is like a bag of liquid. The liquid is called the cytoplasm or sarcoplasm. Inside this bag, are small compartments, one of which is the sarcoplasmic reticulum (SR). The sarcoplasm has a very high concentration of potassium, and the SR has a high

concentration of sodium. The sodium has a very important role as it is used to transmit a nerve impulse to stimulate muscle contraction.

Muscle contractions are stimulated by nerve cells. The area where a nerve meets a muscle is called the “neuromuscular junction”. In order for a muscle to contract, a compound called “acetylcholine” is released from the nerve. This passes through the neuromuscular junction and binds to the end of the muscle. When acetylcholine binds to the muscle, it opens special channels which let sodium move from the SR into the sarcoplasm and allow potassium to move in the opposite direction. As the amount of sodium begins to increase in the sarcoplasm, adjacent channels begin to open, causing a ripple effect along the length of the muscle cell.

The amount of sodium within the sarcoplasm quickly increases. This triggers calcium channels release of calcium from the SR into the sarcoplasm, where the calcium binds to troponin (a component of muscle). The presence of calcium binding to troponin stimulates the myosin and actin (two main proteins in muscle) to pull against each other, causing muscle contraction. Energy (in the form of ATP) is also required for myosin and actin to create a muscle contraction.

A muscle contraction occurs when there is a high concentration of sodium within the sarcoplasm, and a high concentration of potassium in the SR. If further acetylcholine was released from the nerve, there would be no sodium available to flow through the special channels into the sarcoplasm. Calcium could not be released, and the muscle would not be able to contract.

In order to prepare the muscle so that it is ready to contract again, the sodium must be returned to the SR, and the potassium must be returned to the sarcoplasm. There is a sodium-potassium pump and also a calcium pump in the muscle cell. The sodium-potassium ATPase pump uses ATP to provide the energy to move sodium to the sarcoplasmic reticulum, and potassium into the sarcoplasm. In addition to enabling the transmission of nerve impulses, the sodium-potassium ATPase pump also maintains a high concentration of sodium in the SR which keeps the right amount of water within the cell. If the sodium stopped being pumped out, water could move into the cell by a process called “osmosis”, and this could cause the cells to swell.

After a muscle contraction has occurred, the calcium ATPase pumps use ATP to provide the energy to pump calcium from the sarcoplasm to the SR. This removes calcium from the troponin, which results in relaxation of the muscles (Martonosi, 2000). In people unaffected by McArdle’s, the calcium is all pumped back into the sarcoplasmic reticulum within 30 milliseconds, causing the muscles to relax (Alberts *et al.*, 1994).

4.3.1 Muscles require energy (ATP) to contract and to relax during exercise

Muscle contractions require energy. Food is the initial source of energy. Food is digested in the digestive system then transported in the blood to the muscle cells where it is further broken down by several different mechanisms to release energy (as ATP). The muscle cells require ATP to contract. Muscle contractions are needed to carry out all forms of exercise. However, in McArdle people, the lack of muscle glycogen phosphorylase means that muscles are not able to use ATP produced from the breakdown of glycogen into glucose.

Within muscle cells (and other cells in the body), energy is stored in bonds between adenosine and phosphates. Up to three phosphates can be attached to adenosine, and the names of the

compound will change accordingly (see Table 4.1). When the bond between a phosphate and the adenosine is broken, energy is released. For example, adenosine triphosphate (ATP) is converted into phosphate (denoted as “Pi”) and adenosine diphosphate (ADP), releasing energy. This release of energy can be used for many purposes, including driving a calcium pump, as described in paragraph 4.4.1.

Number of phosphates attached to adenosine	Name of the structure
1	Adenosine monophosphate (AMP)
2	Adenosine diphosphate (ADP)
3	Adenosine triphosphate (ATP)

Table 4.1 Names of the structure depends on how many phosphates are bound

In order to function, the calcium pumps and the sodium-potassium pumps require ATP. Glucose within the muscle cells is used to produce ATP. Muscle cells contain a small amount of glucose, which is rapidly used up during intense exercise. Glycolysis is the process where muscle glycogen phosphorylase and other enzymes convert glycogen stored in the muscle cells into glucose which is used to produce ATP. In people unaffected by McArdle’s, it has been estimated that about 20% of the ATP used by a muscle cell during exercise is produced by glycolysis (Conley et al., 2001). In McArdle people, this ATP cannot be made, and it would be expected the cells would temporarily run out of ATP during exercise. Once the second wind occurs, the muscle cells can receive glucose from the liver and fats in the bloodstream, both of which can be used to produce ATP.

4.3.2 Muscle contraction and relaxation in McArdle people

Most of the published studies have looked at the effect of excessive exercise upon the muscle of McArdle people. I was not able to find any studies which looked at the ATPase pumps, or calcium, sodium and potassium within the muscles of McArdle people who are exercising for only a short period of time, or aerobically. I think that the assumption is that when McArdle people are exercising aerobically, muscle contraction and relaxation is basically the same as in people unaffected by McArdle’s.

4.4 Muscle pain can occur if McArdle people exercise anaerobically

It is not known why intense exercise causes pain for McArdle people. For people unaffected by McArdle’s, one theory is that lactic acid (lactate) produced in muscle cells during intense exercise causes pain. Lactic acid is produced during glycolysis (the process where glycogen is used to produce glucose and then energy). The lactic acid makes the cells become more acidic, and this stimulates the nerves, creating pain sensations. McArdle people are unable to produce energy by glycolysis, and do not produce lactic acid during exercise. A study by Malucelli *et al.* (2005) showed that in McArdle people, the pH does not become more acidic (and may instead become slightly more alkaline) during exercise. This suggests that muscle pain in McArdle disease is not caused by lactic

acid. Since McArdle people feel pain after intense exercise, some scientists claim that this disproves the theory that lactic acid causes muscle pain, but at present it is not known whether the cause of muscle pain in McArdle people is the same as in people unaffected by McArdle's.

4.4.1 The phrase “No pain, no gain” does NOT apply to McArdle people

For people with McArdle's, pain is felt in the muscles when the muscle cells run out of energy. This pain is a way of the body telling you to stop exercising and rest. After a rest, energy should then be provided by the second wind and it should then be possible to exercise further. Continuing to exercise once pain is felt could lead to muscle damage. Lucia *et al.* (2008a) describe the severe pain which is felt during exercise as a “self-protective mechanism”, and say that if a McArdle person continues to exercise once pain occurs then it could increase the risk of muscle damage, myoglobinuria and kidney failure. For McArdle people, the saying “no pain, no gain” does NOT apply and could have dangerous consequences!

4.5 A muscle contracture (cramp) can occur if McArdle people continue to exercise anaerobically after pain is felt

4.5.1 A contracture is a muscle cramp without nerve electrical signals

Muscle contractures (cramps) are a well-known phenomenon in McArdle people following intense exercise (Rommel *et al.*, 2006; Lucia *et al.*, 2008a and many other publications). Contractures cause the muscles to go hard, to swell up, and it becomes very difficult to move or relax the muscle. Contractures can occur if the muscles are exercised intensely, and if the McArdle person continues to exercise once pain is felt.

From a medical point of view, a contracture is a particular kind of muscle cramp which occurs in the absence of nerve electrical signals (which could be detected with an EMG). The physiological contractures which occur in McArdle people should not be confused with another unrelated medical condition also called “contractures” that can occur where connective tissue such as joint capsules or ligaments can gradually change and become shortened. The stiffness of physiological contractures experienced by McArdle people are physiologically different to stiffness caused by rheumatic arthritis or old age.

4.5.2 What causes muscle contractures?

The biochemical reason for contractures is still not properly understood (Lucia *et al.*, 2008a). At present, the most common theories are that contractures occur when one or both of the sodium-potassium ATPase pumps or the calcium ATPase pumps stop working. Swift and Brown (1978) studied two McArdle people. They used radioactivity to see what happened to the bone and muscle during contractures. They found unusual results, because the muscles became labelled in a way which suggested that calcium was involved in contractures. The authors suggested that either the exercise caused muscle damage which led to accumulation of calcium in the muscles (during contracture), or that certain small capsules in the muscle cells (called sarcoplasmic reticulum) were unable to pump the calcium back into them after activity, so that the calcium remained in the main part of the cell (the cytoplasm/sarcoplasm). This may be the research that led Quinlivan and Vissing (2007) to say that contracture is caused by “inhibition of calcium ATPase”.

If the sodium stopped being pumped out, water would diffuse into the cell by a process called osmosis, and this could cause the cells to swell. I wonder if this leads to the swelling of muscle cells observed by McArdle people during contracture, but haven't found any published evidence to support this theory.

ATPase pumps require energy in the form of ATP. If there is insufficient ATP, the pumps cannot work. The pumps can also be inhibited (prevented from working) by a build-up of waste products such as ADP. These theories are explained in further detail below:

4.5.2.1 Theory one: A lack of ATP prevents the ATPase pumps from working

During intense exercise, free ATP within the muscle cell is quickly used up. In people unaffected by McArdle's, muscle glycogen phosphorylase converts glycogen into glucose, which can then be used to produce ATP. In McArdle people, the muscle cells are not able to convert glycogen into glucose, and are not able to produce ATP. In a McArdle person, during exercise, calcium will flow from the SR into the sarcoplasm of the muscle cell, which stimulates a muscle contraction. Normally, ATP in the muscle cell would then be used to power the calcium ATPase pump which will move calcium from the sarcoplasm into the SR. Once the calcium is returned to the SR, the muscle cell will be ready to receive a signal from a nerve and generate a contraction. However, in McArdle people, because the muscle glycogen phosphorylase is not functional, glycogen cannot be made into glucose. This produces a lack of ATP. Without ATP, the ATPase pump is unable to function. At this point in time, there is a high concentration of sodium within the sarcoplasm, and a high concentration of potassium in the SR. If further acetylcholine was released from the nerve, there would be no sodium available to flow through the special channels into the sarcoplasm. Calcium could not be released, and the muscle would not be able to contract. It is likely that a lack of ATP would prevent both the sodium-potassium ATPase pump and the calcium ATPase pump from working.

As early as 1968, a research group including Dr Brian McArdle initially suggested that it could be "depletion of ATP giving rise to a contracture similar to rigor mortis" (Gruener *et al.*, 1968). Studies by Gruener *et al.* found that "there was little or no reduction in the ATP level of muscle in contracture", which was later confirmed by Lewis *et al.* (1985), Lewis and Haller (1986) and Lofberg *et al.* (2001). These studies have shown that the levels of ATP in the muscles of McArdle people only decrease slightly during exercise (the decrease is similar to that seen in people unaffected by McArdle's), suggesting that contractures are not caused in the same way as rigor mortis.

4.5.2.2 Theory two: The ATPase pumps are inhibited by ADP and Pi

An alternative hypothesis is that the compounds produced when ATP is used for energy could stop the ATPase pumps from working. When ATP is used to produce energy for muscle contraction, it is broken down into Pi and ADP. Lewis and Haller (1986) said that exercise would lead to an increased amount of Pi and ADP in muscle cells. They state that accumulations of Pi and ADP are known to inhibit the sodium-potassium ATPase and the calcium ATPase.

4.5.3 McArdle people have fewer sodium-potassium pumps

Haller *et al.* (1998) found that McArdle people have fewer sodium-potassium pumps than people unaffected by McArdle's. In a study of six McArdle people, Haller *et al.* found that McArdle people had approximately a third fewer sodium-potassium pumps. As described above, the sodium-potassium pumps play an essential role in returning sodium to the SR so that the muscle is ready to

contract as soon as it is stimulated by a nerve. It is likely that when gentle exercise is performed, the sodium-potassium pumps of McArdle people are able to function sufficiently to allow muscle contraction to occur. However, when McArdle people perform intense exercise, the pumps may not be able to function fast enough, and the muscle will not be able to contract in response to a signal from the nerve. Even if the sodium-potassium pumps are able to function at normal speed, the reduced number of pumps would increase the time taken for the muscle to return the sodium to the SR and potassium to the sarcoplasm. This may increase the time taken for the muscle to be ready to respond to a signal from a nerve which stimulates a contraction.

Haller *et al.* (1998) also observed that after exercise, the concentration of potassium in the blood rose much higher in McArdle people compared to people unaffected by McArdle's. He suggested that the body might release more potassium into the blood in an attempt to compensate for the sodium-potassium pumps not functioning fast enough.

Information from studies of people unaffected by McArdle's are that potassium levels in the blood increase in proportion to the amount of exercise being performed (Medbo and Sejersted, 1990). Regular training appears to increase the total number of sodium-potassium pumps in the muscle cells. It seems likely that following exercise, sodium-potassium pumps remove potassium from the blood and from the area between cells and return the potassium to the sarcoplasm. It has been found that regular aerobic exercise increases the amount of exercise McArdle people can do (see section 4.2.2). If aerobic training leads to an increase in the number of sodium-potassium pumps, this may contribute to the positive effect of aerobic exercise for McArdle people.

4.5.4 Treatment for contractures

Contractures occur if a McArdle person continues to exercise or to use a muscle after pain is felt. Exercises that can lead to contracture can include moving exercise (such as running) or static exercise (such as squatting). A list of some of the types of exercises that can lead to muscle pain and contracture is given in Table 2.1. If possible, it is best to avoid producing a contracture.

It is not known why contractures cause pain. A muscle, for example a leg muscle, is composed of many muscle cells, which group together to form muscle fibres. If some of the muscle fibres cramp and shorten, they may pull against other muscle fibres which are not cramping. Mense *et al.* suggested that as the cramping fibres pull away from the non-cramping fibres; this may stimulate the nerves, thereby creating pain signals.

There is very little published information on how to treat contractures once they have occurred. Mense *et al.* (2001) say that contractures are "relieved by rest". McArdle people have anecdotally reported the following home treatments; use of cool/ice packs, heat packs, strong painkillers, gentle massage. There is no published information on any of these home treatments, and some of these treatments (like massage) could lead to further damage to the muscles. Pain can serve as a warning to protect the muscle from further damage, and the use of strong painkillers could lead to the muscle being used, which could cause further damage.

IMPORTANT: Contractures may be accompanied by rhabdomyolysis (muscle breakdown), which can lead to increased creatine kinase levels and myoglobinuria. Severe muscle damage may lead to kidney failure, which can be fatal. (See section 5 for further information.) In the event of severe muscle damage, medical attention should be sought.

Recommended reading:

Serious training for endurance athletes by Rob Sleamaker, Ray Browning, 1996 (*Information about different types of exercise.*)

Biology: Concepts and Applications Without Physiology By Cecie Starr, Christine A. Evers, Lisa Starr (*An easier explanation of the role of the calcium, sodium and potassium pumps, see page 85.*)

Essential medical physiology By Leonard R. Johnson, John H. Byrne (*A more complicated explanation of the role of the calcium, sodium and potassium pumps.*)

Muscle pain: understanding its nature, diagnosis, and treatment By Siegfried Mense, David G. Simons, I. Jon Russell, 2001

5 Muscle damage causes raised creatine kinase levels and myoglobinuria

Most McArdle people experience muscle pain after a few minutes of intense exercise, and should stop and rest until the pain is no longer felt. If McArdle people continue to exercise after pain is felt, muscle damage may occur. “Rhabdomyolysis” occurs when muscle damage causes the breakdown of skeletal muscle cells. There are many special proteins and compounds within muscle cells, including creatine kinase (CK) and myoglobin, which are released into the bloodstream when muscle damage occurs.

The amount of CK in the blood can indicate how much muscle damage has occurred. In a blood sample higher CK indicates more muscle damage. However, McArdle people have higher CK levels than unaffected people even if they have not carried out recent strenuous activity, so it is important to know what is normal for each McArdle person so that very high levels can be recognised.

The broken parts of the muscle cells (CK, myoglobin and other compounds) go into the bloodstream. The kidneys act like sieves, and after muscle damage has occurred the myoglobin is filtered from the blood and leaves the body in the urine. Myoglobin causes urine to have a red/cola colour. For some people, the change in urine colour is the first indication that muscle damage has occurred. McArdle people who are experienced at dealing with their symptoms will treat mildly coloured urine by drinking plenty of fluids. If it is the first time that a McArdle person has coloured urine, or it is darker than usual, it is important to seek medical attention because they may be at risk of kidney failure. If the muscle damage is severe, the broken parts of the cells may clog up kidneys and lead to kidney failure. Urgent medical attention should be sought if you are unable to urinate, as it could indicate kidney failure. Kidney failure can be fatal, but early treatment usually allows kidney function to be restored.

5.1 Rhabdomyolysis and acute kidney failure

Rhabdomyolysis occurs when muscle damage leads to the breakdown of skeletal muscle cells. Muscle cells are like a balloon which is filled with water and lots of little components, including creatine kinase and myoglobin. When muscle damage occurs, the components are released. The broken parts of the muscle cells and the components go into the bloodstream, and then pass through the kidneys. The kidneys act like sieves, and filter these broken parts from the blood. The smaller bits, like myoglobin, pass out in the urine – producing dark red/brown coloured urine known as myoglobinuria. (An alternative name for myoglobinuria is proteinuria.) If the muscle damage is severe, the parts of the cells may clog up the kidneys. Kidney failure occurs if the kidneys become clogged and are unable to function.

The kidneys also play an important role in keeping the correct concentration of several compounds including potassium, sodium and calcium (called “electrolytes”) in the bloodstream. The kidneys ensure that the concentration of potassium and calcium is maintained. If kidney failure occurs, the kidneys are no longer able to maintain the correct concentrations of electrolytes.

If a small amount of rhabdomyolysis occurs, the person may feel fine, but may have raised CK levels. It is most likely to lead to weakness and pain in the affected muscle(s) and dark urine. If a very large amount of rhabdomyolysis occurs, it could lead to extremely high CK levels in the blood, electrolyte imbalances, acute renal failure, and the formation of blood clots in blood vessels (Huerta-Alardín, 2005).

5.2 Causes of rhabdomyolysis

5.2.1 Causes of rhabdomyolysis in people unaffected by McArdle disease

There are many causes of rhabdomyolysis in people unaffected by McArdle’s. These are outlined in Table 5.1. It is likely that these may also increase the chance of rhabdomyolysis in McArdle people, and would be best avoided.

5.2.2 Causes of rhabdomyolysis in McArdle people

In McArdle people, rhabdomyolysis is most likely to be caused by excessive exertion during exercise. This can occur if a McArdle person continues to exercise once pain is felt.

Some drugs have the side effect of rhabdomyolysis in people who are unaffected by McArdle’s, and recently, some of these have been found to also increase the risk of rhabdomyolysis in McArdle people. For example, the cholesterol lowering drugs known as statins have been reported to increase the likelihood of rhabdomyolysis in McArdle people. See section 12.1 for a list of drugs which may cause rhabdomyolysis in McArdle people.

Voduc *et al.* (2004) recommend that McArdle people should be advised to avoid dehydration (dehydration is the lack of water and lack of essential salts like potassium), and to seek medical attention if they have dark urine.

<p>Causes of rhabdomyolysis in people unaffected by McArdle disease</p> <p>Immobilisation: if a person lies motionless for a long period of time this can compress (and damage) the muscle. E.g. if an elderly person has a fall or a stroke and then remains in one position for a long time, or if a person is drunk and lies motionless for a long time.</p> <p>Surgery: if a surgical procedure is performed in an improper position or a tourniquet is used for a long period of time.</p> <p>Extreme physical exertion, especially in conditions of high temperature and humidity.</p> <p>Hypokalemia (when potassium levels in the blood are lower than they should be) increases the risk of rhabdomyolysis during strenuous exercise. Diuretics are drugs which increase the rate of urine production and can lead to depletion of electrolytes such as potassium. Abuse of diuretics may lower potassium levels, making athletes more likely to develop rhabdomyolysis during strenuous exercise.</p> <p>Any condition which produces major electrolyte losses and dehydration (such as severe diarrhoea, vomiting, or bulimia) could lead to rhabdomyolysis.</p> <p>Electric shock and lightning strikes.</p> <p>Hyperthermia including malignant hyperthermia (see section 12.3.1 for more information on malignant hyperthermia): A symptom of malignant hyperthermia is an extreme rise in body temperature, leading to excessive sweating, which can reduce potassium levels. Neuroleptic malignant syndrome is a reaction to antipsychotic drugs like butyrophenones, phenothiazines and thioxanthenes. This can lead to hyperthermia, muscle rigidity, and rhabdomyolysis.</p> <p>Heat stroke: where people have a core body temperature above 40.5 °C.</p> <p>Hypothermia (being very cold or frozen) can reduce the blood flow to the muscles, reducing the amount of glucose and energy available for movement.</p> <p>Freezing of muscle cells can breakdown and damage the cells.</p> <p>Recreational drugs such as cocaine and LSD (D-lysergic acid diethylamide). Cocaine can cause rhabdomyolysis by having a toxic effect on muscle cells; prolonged use can limit the amount of blood flow to the muscles, and by inducing coma and immobility for a long time.</p> <p>Prescribed drugs. Statins are some of the most widely prescribed drugs in the United States. Statins are well known to have the side effect of rhabdomyolysis. Rhabdomyolysis may be triggered by statins within a short period of commencing the drug, or many years later. Statins can also cause inflammation of the muscles (myositis), causing pain, and weakness of the muscles.</p> <p>Excessive amounts of alcohol, either binge drinking or alcohol abuse, can lead to pain and swelling of the muscles.</p> <p>Eating excessive quantities of liquorice (often found in sweets), which has a component that reduces levels of potassium in the kidney.</p> <p>Infections including influenza, Epstein-Barr virus, herpes simplex virus, HIV, sepsis, legionella infection, bacteria pyomyositis (bacterial infection of the skeletal muscles).</p> <p>Metabolic diseases including McArdle disease, Tarui disease, phosphoglycerate mutase deficiency, and carnitine palmitoyltransferase deficiency.</p>
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Table 5.1 Causes of rhabdomyolysis in people unaffected by McArdle’s (summarised from Huerta-Alardín, 2005).

5.3 Symptoms of rhabdomyolysis

5.3.1 General symptoms

General symptoms are feeling ill, fever, increased heart rate (tachycardia), nausea and vomiting. The early complications include an increased level of potassium in the blood (hyperkalemia), very low levels of calcium in the blood (hypocalcaemia), elevated liver enzymes, cardiac dysrhythmias and cardiac arrest, while the late complications include acute renal failure and clotting of blood in the blood vessels (called “disseminated intravascular coagulation”).

5.3.2 Raised creatine kinase levels in the bloodstream

Creatine kinase (CK) is also known as creatine phosphokinase (CPK). CK levels in the blood can be used as an indicator of muscle damage because the amount of CK released into the blood is approximately proportional to the amount of muscle damage; the more muscle cells that are damaged during exercise, the higher the amount of CK will be released from the damaged cells into the blood. Normal CK levels in men unaffected by McArdle’s are 50–500 U/l, although those of women are often 25% lower (Cush, 2005). In people unaffected by McArdle’s, raised CK level above 5000 U/l indicates severe muscle injury, and suggests an increased risk of kidney failure (Huerta-Alardín, 2005). An increase in CK due to rhabdomyolysis will occur within 12 hours of the onset of muscle injury. The CK level will reach a peak in 1–3 days, and begin to decrease 3–5 days afterwards. The peak CK level may indicate the likelihood of kidney failure (Huerta-Alardín, 2005). In McArdle people, the CK levels can rise to “several thousand U/L, indicating marked rhabdomyolysis after intense exercise” (Lucia *et al.*, 2008a). (This is known as “hyper-CK-emia”).

CK is determined in a laboratory using a sample of blood (further information on CK tests is provided in section 2.3.4). A blood sample will usually be taken from a vein in the arm or hand, and it will take a period of time for the CK to be transported from the small blood capillaries in the damaged muscles (for example the leg muscles) and into the veins in the arms where the blood is taken. If frequent blood samples were taken after a McArdle person carried out intense exercise, it would be expected that the amount of CK in the blood would gradually increase, reach a plateau (a maximum) and then begin to decrease as the kidneys begin to remove the CK (and other proteins) from the blood and they will leave the body as waste (for example, in the urine).

In people unaffected by McArdle’s, CK levels also increase (but to a lower level) if muscle damage occurs during exercise. Garrett and Kirkendall (2000), say that that the maximum level of CK usually occurs 2 to 4 days after exercise. However, different types of exercise produce a maximum CK level at different times after exercise. Garrett and Kirkendall (200) say that for people unaffected by McArdle’s, “downhill walking results in a maximal serum CK level at 24 hours, whereas biceps curls ... or leg resistance exercises attained a maximal CK value at 3 or 4 days after exercise”. Resting CK levels vary depending on gender, age, ethnicity, the size of muscles and general fitness for people unaffected by McArdle’s (Brancaccio *et al.* 2007), and I imagine that similar variations apply to McArdle people.

Although many scientific papers quote the CK levels in McArdle people when resting or after intense exercise, I was not able to find any papers which tracked the changes in CK level during the hours and days after exercise. Anecdotally, it has been suggested that for a McArdle person, the amount

of CK in the blood reaches the maximum amount approximately 24 hours after muscle damage, and then reduces by 30% to 50% in each 24 hours thereafter.

5.3.2.1 McArdle people always have raised CK levels, even at rest

McArdle people always have raised CK levels, even at rest. All (100%) of McArdle people have CK levels above 200 U/l at rest (Lucia *et al.*, 2008a). Lucia *et al.* found that approximately half (approximately 50%) of McArdle people have CK levels above 1000 U/l at rest. In a study of 45 McArdle people, Quinlivan *et al.* (2010) reported that the average CK level was 2,471 IU/l. Anecdotally, the CK levels at rest which are “normal” for a McArdle person seem to vary from person to person. If you have a CK test, it is important to inform the family doctor or medical professional that you have McArdle’s. It is also useful to know your “normal” CK range.

5.3.3 Myoglobinuria (blood in the urine)

It can be useful to quantify the amount of myoglobin in the blood and urine as a measure of the amount of muscle damage which has occurred. Although the amount of myoglobin in the blood can be measured, CK levels remain higher in the blood for longer than myoglobin levels. (The half-life of CK is 1.5 days).

Myoglobinuria (blood in the urine) can cause the urine to be a colour ranging from “pink-tinged, to cola-coloured, to dark black” (Huerta-Alardín, 2005). The red-brown colour is usually seen when the myoglobin concentrations in urine are above 300mg/l. A urine dipstick can be used to test for myoglobinuria. The dipsticks are designed to detect haemoglobin (at concentrations of 0.3mg/l), but should also detect similar concentrations of myoglobin (Huerta-Alardín, 2005).

IMPORTANT: Urgent medical attention should be sought if you are unable to urinate, as it could indicate kidney failure (Greenberg, 2005).

5.3.4 Treatment of rhabdomyolysis:

In order to protect the kidneys, the person will need vigorous hydration (Huerta-Alardín, 2005). The main treatment is aggressive fluid replacement with saline (water containing salts), usually delivered via an intravenous drip. The amount of urine which is passed will probably be measured to determine how much fluid is passing through the kidneys. A catheter may be inserted into the urethra to achieve this, or you may be asked to urinate into a cup/bedpan or other measuring device. The quicker rehydration is achieved, the lower the risk of kidney failure.

Mannitol and bicarbonate are often given after saline has been given. Mannitol may reduce the amount of cell injury, may reduce the amount of heme (a component of hemoglobin) which is left in the tubes of the kidneys (heme deposits are bad for the kidneys), and also may help to keep the tubes of the kidney open (is a renal vasodilator). Sometimes other diuretics such as furosemide are given to try to encourage the flow of liquids through the kidneys. After rhabdomyolysis, a large amount of acidic urine may pass through the kidneys. Acidic urine may be damaging to the kidneys. Bicarbonate would help to neutralise the acidic urine, and could help to reduce the level of damage. However, there is not very much clinical evidence for use of bicarbonate or mannitol, and just the use of saline alone seems to have an equal result (Huerta-Alardín, 2005).

Even if immediate treatment is given, some people may have kidney failure (acute renal failure). The treatment for acute renal failure is an intravenous drip to provide the correct amount of fluid, to make sure the acidity is correct, and to add any electrolytes (such as potassium or calcium) which are required. Dialysis may be needed to remove urea and potassium, which are released during muscle damage. It is very important to correct the concentration of potassium in the bloodstream as hyperkalemia can lead to cardiac arrest (the heart stopping).

At the most extreme, advanced life support (airway, breathing and circulation) may be required.

IMPORTANT: Kidney failure can be fatal, but early treatment usually allows kidney function to be restored. The Muscular Dystrophy Campaign recommends that you get prompt medical help if you have any of the symptoms which could indicate kidney failure, such as myoglobinuria, swollen and tender muscles, or flu-like symptoms (source: http://www.muscular-dystrophy.org/about_muscular_dystrophy/conditions/124_mcardles_disease).

5.3.5 McArdle people are at an increased risk of rhabdomyolysis, raised creatine kinase levels and kidney failure

McArdle people are at an increased risk of muscle damage (rhabdomyolysis) when they exercise. McArdle people always have raised creatine kinase levels, even at rest, which may suggest that even a small amount of movement is producing a small amount of muscle damage. McArdle people should stop exercising when they feel muscle pain. Continuing to exercise once severe pain is felt could result in muscle damage and potential kidney failure. Lucia *et al.* (2008a) reported that when McArdle people continued to exercise despite feeling severe pain, myoglobinuria occurred in about half (50%) of McArdle people, with a quarter (25%) suffering from renal failure, which required hospital treatment.

Recommended reading:

Bench-to-bedside review: Rhabdomyolysis – an overview for clinicians by Ana L Huerta-Alardín, Joseph Varon and Paul E Marik *Crit Care*. 2005; 9(2): 158–169. (*This paper is the source for most of the information given here about rhabdomyolysis in people unaffected by McArdle's.*)

McArdle disease: what do neurologists need to know? Alejandro Lucia, Gisela Nogales-Gadea, Margarita Pérez, Miguel A Martín, Antoni L Andreu and Joaquín Arenas. (*For information about CK levels which are normal for McArdle people and rhabdomyolysis in McArdle people.*)

6 Sources of energy in muscle cells

Energy for muscle contractions originally comes from food. During digestion in the stomach and intestine, food is broken down into smaller units; for example, carbohydrates are broken down into simpler compounds, including glucose. Glucose released during digestion is carried by the bloodstream around the body. Muscle cells take up glucose from the blood, and within the muscle cell, most of the glucose is bound together to form a compound called glycogen. Glycogen is the main way in which carbohydrates are stored in muscle cells.

During exercise, any free glucose in the muscle cells are quickly used up. In people unaffected by McArdle's, muscle glycogen phosphorylase begins to unbind the stored glycogen. This releases glucose, which can be used to provide energy for movement. In McArdle people, this enzyme does not function, so when the muscle cells quickly use up any free glucose within the cell they run out of energy. The lack of energy prevents movement and causes pain and muscle damage. McArdle people should rest if pain is felt. This rest period enables the body to provide energy from other sources; fats and proteins from digested food can be broken down to produce energy. Muscle cells can also use glucose which is produced by the liver, and carried from the liver to muscle in the bloodstream. These energy sources do not require muscle glycogen phosphorylase, so they can be used to provide energy in the muscle cells of McArdle people. Both of these methods are slower to provide energy than muscle glycogen phosphorylase, which is why the McArdle person has to rest before continuing to exercise. The energy provided by these sources produces the "second wind" effect, which enables McArdle people to continue to exercise.

Many studies have been carried out to see which diet is best for McArdle people, but there is no obvious consensus at the moment. It seems likely that protein, carbohydrate and fat are all required by McArdle people. Some protein is probably required to rebuild muscles which get damaged, and also as a source of energy. Carbohydrates are the primary source of energy for muscle cells. Simple carbohydrates such as sugar can quickly be digested and begin providing energy to muscle cells, whereas complex carbohydrates will provide a slower release of energy. Fat is a source of energy which is used to generate the second wind, but artificially

increasing the amount of fat in the body does not seem to increase the ability to exercise.

Having a sugary drink before exercise can provide glucose to the muscle cells through the bloodstream, which can make it easier for McArdle people to exercise. However, McArdle people should be careful about having sugary drinks too often as there is a risk of becoming overweight.

6.1 Methods of producing energy in muscle cells of people unaffected by McArdle's

Muscle cells need ATP (a form of energy) to contract and relax, as described in section 4.3. Energy originally comes from food. Protein, carbohydrates, and fats are eaten as part of the diet. During digestion, these are each broken down into smaller units; fats are broken down into fatty acids and glycerol, proteins are broken down into amino acids, and carbohydrates are broken down into sugars.

6.1.1 Storage, release and breakdown of carbohydrates to produce energy

Carbohydrates are often stored as glycogen in the body and about 75% of the total body glycogen is stored in muscle. At rest, glucose entering the muscle from the blood is converted to glycogen, and very little is used to produce ATP. The primary source of ATP at rest is fatty acid oxidation (described below). Fatty acid oxidation is an aerobic process which supplies 85% of energy needs (Berg *et al.*, 2008).

When exercise begins, muscle cells need energy to contract and relax. During the first few moments of intense exercise, free glucose in the muscle is used to provide energy. In people unaffected by McArdle's, glycogenolysis then takes place. Glycogenolysis is the breakdown of stored glycogen into glucose. Muscle glycogen phosphorylase is one of the key enzymes involved in this process.

The glucose produced by glycogenolysis is then used in glycolysis. Glycolysis occurs in the cytoplasm/sarcoplasm. During glycolysis, glucose is broken down into pyruvate. Glycolysis is able to produce ATP without requiring oxygen (it is therefore anaerobic). During glycolysis, ATP, NADH, and pyruvate are produced.

Pyruvate is then moved from the cytoplasm into the mitochondria. Pyruvate is then converted into acetyl CoA. Acetyl CoA is then broken down further by the citric acid cycle.

6.1.2 Storage, release and breakdown of fats to produce energy

Fats in food are digested in the intestine, and transported around the body, to the muscles and other locations. They are converted to free fatty acids in the muscles, or stored in special cells in the body called adipose tissue. When energy is needed, fatty acids can be released from the adipose tissue. A high level of glucagon (see section 6.2.3) is one of several triggers for the cells to release fatty acids, but insulin can inhibit the release of fatty acids. Free fatty acids released from the adipose tissue can be taken by the blood to the muscle cells.

Fatty acids are broken down in the mitochondria by a process called "fatty acid oxidation or beta (β)-oxidation". Fatty acid oxidation produces NADH, FADH₂, and Acetyl-CoA. Acetyl-CoA is broken down further in the citric acid cycle to produce more NADH, FADH₂ and ATP. NADH and FADH₂ are then broken down further to produce more energy.

If a very high amount of fatty acid oxidation occurs (particularly in the liver), very large amounts of Acetyl-CoA are produced. This is called ketogenesis, and can result in the production of ketone bodies. If fat is the main/only source of energy, then muscle will use these ketone bodies to produce energy, and will leave any glucose in the blood so that it can be transported to and used by the brain. These fats can be broken down further in the citric acid cycle.

6.1.3 Breakdown of proteins to produce energy

Proteins are more important for use as building blocks to build, strengthen, and repair the body, rather than a source of energy. However, some amino acids released from proteins during digestion can be taken in the blood to the muscle cells. These amino acids can be broken down in the citric acid cycle.

6.1.4 Acetyl CoA from carbohydrates, fats and proteins can be broken down in the citric acid cycle

The citric acid cycle is also known as the tricarboxylic acid (TCA) cycle or the Krebs cycle. Acetyl CoA is produced from the breakdown of carbohydrates, fats, and proteins as described above. In the citric acid cycle, acetyl CoA is broken down to produce NADH, FADH₂ and carbon dioxide. NADH and FADH₂ are then used to produce ATP by oxidative phosphorylation.

6.1.5 NADH and FADH₂ from the breakdown of carbohydrates, fats and proteins is used to produce ATP by oxidative phosphorylation

NADH is produced by the breakdown of carbohydrates, fats, and amino acids. FADH₂ is also produced from the breakdown of fats and amino acids. The breakdown of NADH and FADH₂ is a process called oxidative phosphorylation. (It is called “oxidative” because it requires oxygen and it therefore aerobic.) Both NADH and FADH₂ are “supercharged” with hydrogen, which can be used to power a process called the electron transport chain, which produces lots of ATP.

6.2 Glucose from the blood is an important source of energy for muscle cells

6.2.1 Glucose is transported from the blood into muscle cells

Muscle cells require energy (ATP) to contract and relax. Glucose is used as a source of energy, and is broken down by muscle cells to release ATP.

GLUT-4 is a special protein (called a “transporter”) which takes glucose from the blood into muscle cells. At rest, insulin can bind to GLUT-4, and stimulate (make) the GLUT-4 transporter take up glucose from the blood into the muscle cells. During exercise, GLUT-4 is stimulated in a different way, possibly by calcium and Pi (the role of calcium and Pi in exercising muscle is discussed further in section 4.3).

6.2.2 Excess glucose is stored as glycogen

If there is an excess of glucose in the blood (more than is needed), it can be taken up by the muscle cells and converted to glycogen by a process called “glycogen synthesis”. Glycogen can then be stored in the muscle cells until energy is needed (for example, during exercise). In people unaffected by McArdle’s, when this energy is needed, a group of enzymes including muscle glycogen phosphorylase are used to convert glycogen into glucose, and use the glucose to produce energy. McArdle people are able to store glucose as glycogen as normal, but are not able to convert the glycogen back into glucose. This results in increased stores of glycogen in the muscle cells of McArdle people. This is why McArdle disease is known as a “Glycogen Storage Disease” (GSD).

6.2.3 Insulin and glucagon are two hormones which maintain the right amount of glucose in the bloodstream

The human body needs a constant amount of glucose in the bloodstream. This is achieved using the hormones insulin and glucagon, both of which are produced by the pancreas. Insulin and glucagon work in opposite directions to lower and raise the levels of glucose in the blood.

If blood glucose levels are high, this stimulates islet cells within the pancreas to release insulin into the blood. Insulin then has an effect on several cells including muscle cells, red blood cells, and fat cells. These cells respond to insulin, and absorb glucose out of the blood. This lowers the level of glucose in the blood to the normal amount. As the amount of glucose in the blood gets lower, less insulin is produced.

Insulin can stimulate GLUT-4 to take glucose from the bloodstream into the muscle cells and stimulate glycogen synthesis. Insulin can also stimulate the body to convert excess glucose into fats for storage.

In the opposite manner, if blood glucose gets low (for example between meals or during exercise), more glucagon is produced by the pancreas; this affects many cells, especially the liver. Excess glucose is stored as glycogen in the liver (as well as the muscles), and glucagon stimulates liver glycogen phosphorylase to convert glycogen into glucose, which is then released into the bloodstream (Biesalski, 2005).

Diabetes is the inability to control the level of glucose in the blood. Diabetes and McArdle disease are discussed further in section 13.4.

6.3 In people unaffected by McArdle's, enzyme activity of muscle glycogen phosphorylase is controlled to maintain the right amount of glucose within the cell

In people unaffected by McArdle's, the enzyme activity of muscle glycogen phosphorylase is strictly controlled in order to maintain the correct amount of glucose within the cell. The function of muscle glycogen phosphorylase is to help to breakdown glycogen into glucose to provide energy for muscle contractions. But it is also important that muscle glycogen phosphorylase can be inactivated so that it does not continue this process when the muscles are at rest, which would lead to an excess of glucose in the cell. Muscle glycogen phosphorylase can be activated and inactivated an infinite number of times. (A very basic analogy would be to say that the activity can be turned on and off like a light switch.) There are several layers of control of the activity of muscle glycogen phosphorylase, which includes the physical structure of the enzyme, and also the presence of ligands and cofactors. These are very complicated, so only a brief explanation is given below.

6.3.1 Muscle glycogen phosphorylase is made of several identical subunits which require the presence of phosphate

As described in section 3.1, ribosomes use *PYGM* mRNA as a template to assemble amino acids into a chain (also known as polypeptide chains). Initially, two of these chains bind together; this is called a "dimer" (shown in Figure 6.1). The dimer is often known as "phosphorylase b". A dimer is not the right shape for enzyme activity. Several steps are needed to make the dimer the right shape. Several compounds (such as ATP) bind to the chains of the dimer, and another enzyme called

phosphorylase b kinase adds a phosphate to each chain in the dimer. The presence of these phosphates encourages the polypeptide chains of the dimer to change shape and to bind together with another dimer. The four polypeptide chains are together known as a “tetramer”. The tetramer is often known as “phosphorylase a” (Barford and Johnson, 1992; Johnson, 1992). The tetramer is now ready to be activated.

Protein phosphatase 1 can work in the opposite way to phosphorylase b kinase. Protein phosphatase 1 can remove the phosphate. This makes the tetramer fall apart, back into dimers. Insulin can stimulate protein phosphatase 1 to remove the phosphate (Johnson, 1992).

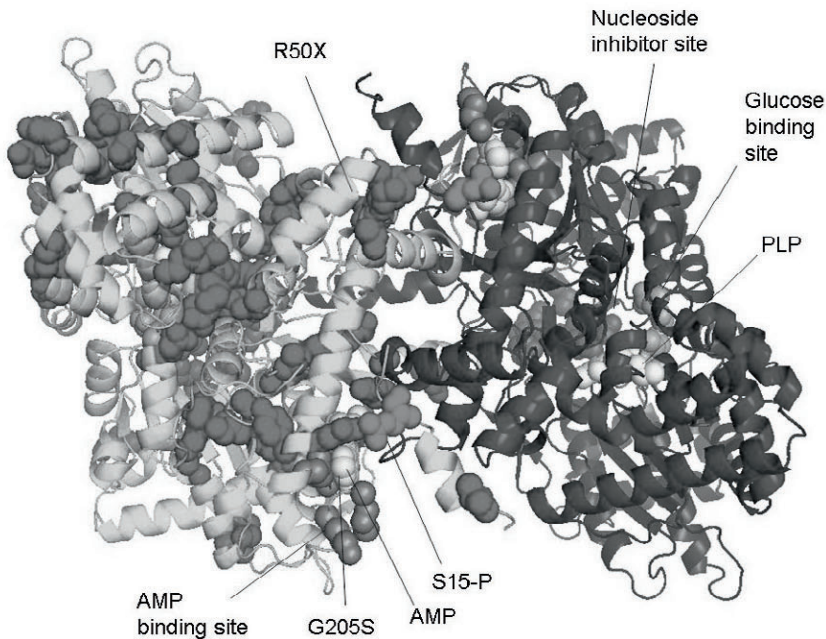


Figure 6.1 3D model of human muscle glycogen phosphorylase a, shown as a dimer of a green and a blue polypeptide chain. Locations of important sites are shown by colour with the atoms of the side chains shown as spheres. AMP is shown in aquamarine, the AMP binding site is shown in sky blue, serine-15 is shown in magenta, nucleoside inhibitor site is shown in purple, glucose binding site is shown in orange and PLP binding site is shown in yellow. All known mutations are shown in red in the green polypeptide chain, with R50X and G205S (not visible) labelled. Picture created using the PyMol program using file 1z8d.mmol from EBI website (based on PDB ID 1z8d; Lukacs *et al.*, 2006).

6.3.2 Muscle glycogen phosphorylase activity is controlled by ligands and cofactors

Muscle glycogen phosphorylase does not always need to be active. Activity is most needed during exercise when energy is required. The activity of muscle glycogen phosphorylase is under strict control (Mutalik and Venkatesh, 2005). Special compounds called ligands bind to binding sites spread over the enzyme. Ligands are used to control the speed at which muscle glycogen phosphorylase breaks down glycogen (Johnson, 1992). These sites have names like “catalytic side”, “active site”, “and nucleoside/AMP inhibitor site”. When glycogen binds to the active site, it can be

broken down into glucose-1-phosphate (which is then broken down by other enzymes into glucose). Muscle glycogen phosphorylase also has a cofactor, which is needed for it to be active. The cofactor is called pyridoxal-1-phosphate (PLP) and is produced from vitamin B6. PLP attaches onto muscle glycogen phosphorylase near to the catalytic site (Johnson, 1992; Klinov and Kurganov, 2001).

6.3.3 The levels of glycogen may affect the activity of muscle glycogen phosphorylase

During activation of muscle glycogen phosphorylase, having some glycogen nearby helps to increase how active muscle glycogen phosphorylase can be. However, abnormally high levels of glycogen may reduce muscle glycogen phosphorylase activity. Schliselfeld *et al.* (2002) compared the amount of glycogen and phosphorylase activity between unaffected mice and mice genetically modified to have increased amounts of glycogen in their muscles. They found an inverse relationship between mouse muscle glycogen phosphorylase activity and the muscle glycogen content. The unaffected mice had 52% greater muscle glycogen phosphorylase activity. If the same applied in humans, this could mean that even if a McArdle person had a very low level of muscle glycogen phosphorylase enzyme activity (see section 9.1.4); it may be inhibited by high levels of glycogen in the muscle cells.

6.4 How is energy produced in the muscles of McArdle people?

6.4.1 Glycogen cannot be broken down into glucose to provide energy for exercise

In McArdle people, at rest, carbohydrates are stored as glycogen within the muscle cells. At rest, energy is provided to the muscle cells primarily by fatty acid oxidation (section 6.1.2).

During exercise, free glucose within the muscle cells is used up within a few minutes. Normally, stored glycogen would then be broken down into glucose to provide the muscle cells with energy. However, in McArdle people, the lack of functional muscle glycogen phosphorylase means that this cannot take place. Muscle cells of McArdle people are not able to break down glycogen into glucose.

If McArdle people continue to exercise, they will feel muscle pain and tiredness as the muscle cells run out of energy. This indicates that the McArdle person should stop exercising. If they continue to exercise, rhabdomyolysis (muscle damage) and contractures (see section 4.3) may occur.

However, after about 10 minutes, taking brief rests as required, the pain and tiredness will reduce and McArdle people can continue to exercise with minimal pain or no pain for a long time. This is the second wind phenomenon. The second wind occurs because the muscles begin to get energy from different sources; glucose from the liver and free fatty acids from adipose tissue (Vissing and Haller, 2003).

6.4.2 Other mechanisms provide the energy needed for the second wind

If McArdle people rest for a few minutes, the muscle cells will begin to produce energy by the break down of fatty acids and amino acids. Fatty acids will be released from body stores of adipose tissue into the bloodstream and taken to the muscle. The fats will be broken down by fatty acid oxidation, citric acid cycle, and oxidative phosphorylation. These processes will generate ATP (energy). Amino acids can also be broken down by the citric acid cycle and oxidative phosphorylation to produce ATP. Since these processes require oxygen, McArdle people begin to breathe more heavily, which

increases the amount of oxygen in the bloodstream and this oxygen is then taken to the muscle cells (Hilton-Jones, 2001).

In addition, glucose is also released from the liver and transported in the bloodstream to the muscle cells. This glucose can then be broken down by glycolysis to generate pyruvate and NADH. Pyruvate is broken down further in the citric acid cycle to produce NADH and FADH₂. NADH and FADH₂ are both used to generate energy by oxidative phosphorylation.

Although some McArdle people may not have experienced a second wind, McArdle's specialists agree that all McArdle people are capable of it (Quinlivan and Vissing, 2007).

During an ischaemic forearm test (see section 2.3.1.1), a cuff is placed around the arm or leg to restrict blood flow. Restricted blood flow is called "ischaemia". This reduces the amount of glucose and free fatty acids able to get into the exercising muscle, and prevents the muscle from getting a second wind.

6.4.3 The production of energy by other mechanisms is not as efficient in McArdle people

Normally, the breakdown of glucose (which has been produced from glycogen), generates pyruvate. McArdle people don't produce as much pyruvate, and this has a knock-on effect which reduces the ability of McArdle people to produce energy by oxidative phosphorylation. The result of this decreased rate of oxidative phosphorylation is that the amount of oxygen consumed (the amount of oxygen used to produce energy) is reduced in McArdle people (Haller *et al.*, 2006).

6.4.4 The way in which the body of a McArdle person responds to exercise

During exercise, the heart increases the number of contractions per minute. This increases the pulse rate and the heart rate. Porte *et al.* (1966) were the first to test the effect of exercise on cardiopulmonary system and to find an accelerated heart rate response is usually seen. When exercising, the heart rate of McArdle people increases much more steeply than people unaffected by McArdle's. This may be so that the blood can pump more oxygen from the lungs to the muscle, and also so that the blood can carry more glucose from the liver to the muscles.

During exercise, muscles breakdown fuel sources (such as carbohydrates and fats) and generate waste products (such as potassium, phosphate, lactate and carbon dioxide) (described further in section 5). As the amount of these waste products increases, it stimulates nerves in the exercising muscles. These nerves are linked up with nerves which run throughout the body (called the sympathetic nervous system). Stimulation of nerves in exercising muscles in turn leads to stimulation of the sympathetic nervous system. Sympathetic nerves cause the heart to beat faster, producing an increase in heart rate. (In addition, muscle pain can also stimulate the sympathetic nervous system.) (Information from Voduc *et al.*, 2004; and Khan, 2005).

McArdle people also breathe more heavily in response to exercise. If a person breathes in and out more than is expected, this is known as "hyperventilation". However, McArdle people do not use as much oxygen as expected. This can be measured as VO₂ max.

6.4.4.1 VO_2 max / VO_2 peak

McArdle disease appears to have an effect upon the rate of breathing by causing hyperventilation (breathing faster or deeper than usual) and also upon the amount of oxygen which is used by the body.

Air that is breathed into the lungs contains several kinds of gas, including oxygen and carbon dioxide. Air that is breathed in has more oxygen and less carbon dioxide. In the lungs a lot of the oxygen travels into tiny blood vessels and binds to red blood cells. This oxygen is carried around the body, to many locations, including the muscles. The oxygen is then used in chemical reactions with fuel sources such as fat or carbohydrate. These chemical reactions produce energy, and produce carbon dioxide as a waste product. The carbon dioxide is carried by the red blood cells back to the lungs. The air that is breathed out has more carbon dioxide and less oxygen. It is possible to accurately measure how much carbon dioxide and oxygen is breathed in and out. This can be used to calculate how much has been used for the chemical reactions in the muscles.

In order to determine VO_2 max, the person being tested wears a type of oxygen mask over their head. This allows measurement of the amount of oxygen they breathe in (oxygen consumption, called VO_2) and the amount of carbon dioxide breathed out (called VCO_2). These two numbers can be combined to produce a VCO_2/VO_2 ratio. When the person exercises at maximum capacity, and has the maximum oxygen uptake, this is called VO_{2max} . When a person is doing aerobic exercise with the maximum possible effort, the VO_2 max is determined by the capacity of the heart, lungs and blood to transport oxygen to the muscles, and the use of oxygen by the muscles during exercise (Heyward, 2006).

In exercise tests, a McArdle person may be asked to exercise at approximately 40% of VO_{2max} . In McArdle people, this level of exercise causes a high heart rate and a high level of perceived exhaustion (it feels like really hard work to pedal) until 8-10 minutes into the exercise, when the second wind occurs (Abramsky, 2001).

Some types of exercise cause a peak rather than a maximum rate of oxygen use. VO_2 peak is the highest rate of oxygen consumption.

Absolute VO_2 is the actual amount of oxygen used for leg or arm cycle ergometer. Relative VO_{2max} is used to determine how good the cardio respiratory (heart, lungs and blood) fitness is (Heyward, 2006).

Many studies report that the amount of oxygen used is reduced in McArdle people compared to unaffected people. Hagberg *et al.* (1982) showed that McArdle people had hyperventilation in response to exercise, but did not use as much oxygen as expected. (Oxygen is used to produce energy in muscle cells, but if some oxygen is breathed out, not as much is being used as expected.) Some research suggested that the result of this decreased rate of oxidative phosphorylation is that the amount of oxygen consumed (VO_{2max} ; the amount of oxygen used to produce energy) is less than half the amount of people unaffected by McArdle's. VO_{2max} was on average 14 ml x kg⁻¹ x min⁻¹ in McArdle people compared to 37.7 ml x kg⁻¹ x min⁻¹ in unaffected people (Haller *et al.*, 1985).

Although it has been reported that the amount of oxygen (VO_2) used by McArdle people may be less than unaffected people, this may have been difficult to measure because there are big differences between the amount of exercise McArdle people can do compared to unaffected people (Dochartaigh, 2004). Dochartaigh *et al.* suggested that if the amount of exercise was kept similar, it would become clear that the VO_2 would be higher in McArdle people than unaffected people. They found that the amount of oxygen used (VO_2) and amount of carbon dioxide breathed out (VCO_2) were both higher in McArdle people. The authors suggest that McArdle people may use more oxygen because more oxygen is needed to produce energy from the breakdown of fats than the amount of oxygen needed to breakdown carbohydrates. Riley *et al.* (1993) had also seen that the amount free fatty acid in the blood was increased during exercise and suggested that the use of fat to produce energy could explain the unusual breathing patterns (like hyperventilation) seen in McArdle people.

6.4.5 How would having a sugary drink before exercise increase the amount of energy available for the muscles of McArdle people?

A sugary drink (sucrose dissolved in water) would be quickly digested (broken down into glucose and fructose) and absorbed into the bloodstream. The glucose will be carried to the muscle cells. The glucose could then be used by the muscle cells to produce pyruvate by the process of glycolysis, and this pyruvate could then be used to produce energy. Having a sugary drink a couple of minutes before exercise seems to put the glucose into the bloodstream faster than the liver is able to. In the liver, glycogen which is stored in the liver must be converted to glucose (by liver glycogen phosphorylase), before the glucose can be released into the bloodstream.

6.4.5.1 A sugary drink may inhibit the second wind

There is evidence that having a very high level of glucose in the blood may inhibit the transition to second wind. Having a sugary drink (or a glucose infusion given intravenously) will lead to a very high level of glucose in the blood. Vissing *et al.* (1992) tested the effect of a glucose infusion on McArdle people. They found that a glucose infusion raised glucose levels (hyperglycaemia) and raised insulin levels (hyperinsulinemia) in the bloodstream. They also found that the glucose infusion reduced the normal increase in glucose production (release of glucose from the liver), and reduced the amount of free fatty acids released in the bloodstream. The heart rate also did not increase as much as is usually seen in McArdle people during exercise. This may suggest that a sugary drink is most useful for very short term exercise, but not very useful for prolonged exercise.

6.4.6 The amount of some other enzymes may be increased in the muscle cells of people with McArdle's to compensate for the lack of muscle glycogen phosphorylase

It has been found that the amount of some proteins is increased in people with McArdle's, possibly to compensate and try to make up for the lack of muscle glycogen phosphorylase. Robertshaw *et al.* (2008) found that people with McArdle's had more phosphofructokinase (PFK) enzyme than people unaffected by McArdle's. There are many enzymes involved in the many steps glycolysis (the breakdown of glucose to release energy as ATP). Glycolysis is the process where glucose is broken down to release energy in the form of ATP. There are many steps in this process, and PFK is one of several enzymes involved in the breakdown of glycogen.

Robertshaw *et al.* (2008) also found that people with McArdle's had more glucose transporter 4 (GLUT-4) protein level than people unaffected by McArdle's. GLUT-4 is involved in taking glucose from the blood into the muscle cells (GLUT-4 is discussed further in section 6.2.1). The authors suggested these changes may occur in the cells of people with McArdle's to increase the amount of glucose taken from the bloodstream into the muscle cells, and that this may explain why oral sucrose can alleviate symptoms during exercise.

Muscle α 2 AMP-activated protein kinase (α 2AMPK) is an enzyme which is involved in the production of energy in many different ways. When muscle cells exercise and begin to suffer from a lack of energy, AMPK becomes more active and helps to increase the amount of energy available for the muscle cell by increasing muscle glucose uptake, and stimulating fatty acid oxidation. Nielsen *et al.* (2002b) found that during exercise, an increase in muscle α 2AMPK activity was seen in McArdle patients but not in unaffected people. This result may suggest that the body of a McArdle person will try to overcome the lack of muscle glycogen phosphorylase by increasing the activity of a different enzyme.

When there are excess levels of glucose in the body, for example when digestion of a meal results in the release of lots of glucose, it is converted into glycogen so that it can be stored until needed. Glycogen synthase is an enzyme which helps to convert glucose into glycogen. (By producing glycogen, glycogen synthase works in the opposite manner to muscle glycogen phosphorylase.) During exercise, glycogen synthase activity was decreased in McArdle people, and increased in unaffected people. Glycogen synthase activity appears to be increased by glycogen breakdown, and decreased by AMPK activation (Nielsen *et al.*, 2002b).

6.5 Non-muscle isoforms of glycogen phosphorylase breakdown glycogen into glucose-1-phosphate in other areas of the body

Mammals have three very similar forms of glycogen phosphorylase within their body. The DNA sequence and the amino acids which make up these enzymes are very similar, and for this reason these enzymes are known as "isoforms". Each isoform is expressed predominantly in the respective tissue; brain, muscle or liver (Newgard *et al.*, 1988). The muscle and brain isoforms have greater similarity to each other than to the liver isoform (Hudson *et al.*, 1993). The human brain isoform is slightly longer, so that it is 862 amino acids long, compared to 846 for the human liver isoform and 841 for the human muscle isoform. Each gene is located on a different chromosome. The *PYGB* gene for the brain isoform is located on chromosome 20, the *PYGL* gene for the liver isoform is located on chromosome 14, and the *PYGM* gene for the muscle isoform is located on chromosome 11 (Newgard *et al.*, 1988; Glaser *et al.*, 1989). There are control regions located next to each gene to control the location within the body where each isoform is produced. All three isoforms; brain, muscle and liver glycogen phosphorylase break down glycogen into glucose-1-phosphate.

6.5.1 Muscle glycogen phosphorylase

Muscle glycogen phosphorylase is the only form of glycogen phosphorylase produced by skeletal muscles (except see 6.5.4). In people unaffected by McArdle's, muscle glycogen phosphorylase is able to breakdown glycogen to glucose-1-phosphate to provide a source of energy for muscle contractions. In the skeletal muscle of McArdle people, there is no (or very little) muscle glycogen phosphorylase, leading to McArdle disease. Brain glycogen phosphorylase and liver glycogen

phosphorylase have not been found in adult skeletal muscle, as shown by the lack of a positive phosphorylase stain in a muscle biopsy from a McArdle person (section 2.3.2). Adult skeletal muscle contains the genes for brain and liver glycogen phosphorylase, but they are “turned off” so that they are not used to produce enzyme. It has been suggested that a potential therapy for McArdle disease could be to use drugs to “turn on” these genes, leading to the production of brain or liver glycogen phosphorylase in skeletal muscle (see section 16.3.1).

6.5.2 Brain glycogen phosphorylase

Brain glycogen phosphorylase is a form of glycogen phosphorylase which is found in smooth muscle (such as the stomach wall, wall of the intestine, wall of the bladder, probably the wall of the womb). Brain glycogen phosphorylase is also found in the brain and in the heart.

6.5.2.1 The brain isoform is also known as the foetal isoform

Historically, it was believed that the brain isoform was the only isoform of glycogen phosphorylase expressed in a foetus (a foetus is the name for a baby in the womb prior to birth). However, some researchers disagree. Newgard *et al.* (1991) found that the *Pygm* mRNA was the predominant mRNA of rabbit foetal muscle and that *Pygb* mRNA was barely detectable. “Thus, our studies of phosphorylase mRNA in the rabbit provide no evidence for general predominance of the brain isoform in foetal tissues, or for isoform ‘switching’ from the brain to the liver or muscle forms during development, as has been suggested by others”(Newgard *et al.*, 1991). Walker (2006) found there to be a gradual decrease of the brain isoform and a concurrent gradual increase of muscle isoform over time in the sheep foetal muscle and sheep neonatal (newly born) skeletal muscle. By 15 days after birth, there was only a trace of the brain isoform in the sheep muscle.

6.5.2.2 Mutations in brain glycogen phosphorylase have not been reported

No humans have been reported who have mutations in *PYGB* gene which encodes brain glycogen phosphorylase. If the brain isoform is also the predominant foetal isoform, mutations in the *PYGB* gene may be lethal and prevent development and survival of the foetus.

6.5.3 Liver glycogen phosphorylase

Liver glycogen phosphorylase is a form of glycogen phosphorylase which is found in smooth muscle and in many locations where brain glycogen phosphorylase is also found. Liver glycogen phosphorylase has been found in the liver, intestine, and bladder.

6.5.3.1 Mutations in liver glycogen phosphorylase cause Hers Disease

Hers Disease/Glycogen Storage Disease VI is caused by mutations in the *PYGL* gene (Burwinkel *et al.*, 1998).

6.5.4 After muscle damage, regenerating immature muscle produces brain and/or liver isoform

Mature skeletal muscle cells produce only muscle glycogen phosphorylase. However, after muscle damage has occurred, muscle cells divide to produce new cells to replace the damaged cells. These newly dividing cells are called “regenerating” or “immature”. Immature muscle cells produce other forms of glycogen phosphorylase which are not the muscle isoform. At present, it is not clear if this is just the brain isoform, just the liver isoform, or both.

6.5.5 A brief discussion about the three isoforms of glycogen phosphorylase

It hasn't been possible to definitively state which isoforms of glycogen phosphorylase are found in which tissues. In some cases the available literature is contradictory. This may be because different detection methods have different levels of sensitivity, so some may detect a form of the enzyme which others do not (for example, methods which detect mRNA may be able to detect much smaller amounts of mRNA than methods which detect protein). It should also be noted that much of this information is not based upon humans and is instead based on studies of other mammals such as rat, rabbit, and sheep.

To summarise published information, it seems that two general statements could be made about the isoforms of glycogen phosphorylase:

Brain and liver glycogen phosphorylase are often found in the same locations; smooth muscle such as bladder, and intestine.

Brain and liver glycogen phosphorylase are not found in the same location as muscle glycogen phosphorylase. Muscle glycogen phosphorylase is not detected in bladder or intestine. Brain and liver glycogen phosphorylase are not found in skeletal muscle.

6.5.6 Non-muscle isoforms of glycogen phosphorylase spare the smooth tissue and organs of the body from symptoms of McArdle disease

Only limited studies have been performed upon McArdle people to find out which isoforms of glycogen phosphorylase are expressed in which tissues. My opinions of the expression of different isoforms in the body of a McArdle person are given in Table 6.1.

Part of the body of a McArdle person	Comments in relation to McArdle disease
Brain	Glycogen phosphorylase in the brain of a person unaffected by McArdle disease is approximately 50% brain glycogen phosphorylase and 50% muscle glycogen phosphorylase. In a McArdle person only brain glycogen phosphorylase is present. This does not appear to have a major effect upon the functioning of the brain. It has been suggested that it may have a small effect upon the functioning of the brain but further studies are needed to prove this (see section 10.2).
Skin	I believe that skin cells express either brain or liver glycogen phosphorylase (or both). They are unaffected by the absence of muscle glycogen phosphorylase in McArdle disease.
Heart	Glycogen phosphorylase in the heart of a person unaffected by McArdle disease is approximately 50% brain glycogen phosphorylase and 50% muscle glycogen phosphorylase. In a McArdle person only brain glycogen phosphorylase is present. This does not appear to have any effect upon the functioning of the heart (see section 13.5).
Lungs	These are composed of smooth muscle and express both brain and liver glycogen phosphorylase. They are unaffected by the absence of muscle glycogen phosphorylase in McArdle disease.
Digestive system: Intestine, digestive tract, bladder, liver, kidney	These are composed of smooth muscle and express either brain or liver glycogen phosphorylase (or both). Muscle glycogen phosphorylase has been found in the kidneys of rats unaffected by McArdle disease. These organs do not seem to be affected by the absence of muscle glycogen phosphorylase in McArdle disease.
Reproductive system: uterus, testis, probably ovaries	These are composed of smooth muscle and express either brain or liver glycogen phosphorylase (or both). Brain glycogen phosphorylase has been found in the testis. They are unaffected by the absence of muscle glycogen phosphorylase in McArdle disease.

Part of the body of a McArdle person	Comments in relation to McArdle disease
Skeletal muscles of the entire body: biceps, triceps, quadriceps, calves and many others.	These are composed of skeletal muscle. In a person unaffected by McArdle disease they would express muscle glycogen phosphorylase. In a McArdle person no glycogen phosphorylase is present, leading to symptoms of McArdle disease.
Nervous system: spinal chord and nerves	These express either brain or muscle glycogen phosphorylase (or both). There is no information about whether the lack of muscle glycogen phosphorylase has any effect upon the nervous system of McArdle people.

Table 6.1 The expression of different isoforms of glycogen phosphorylase in the body of a McArdle person and the effect upon symptoms of McArdle disease. Based upon limited published information (summarised from information reviewed by Wright, 2009) and my opinion.

6.6 The balance of protein, carbohydrate and fat in the diet

In the search for an effective treatment for McArdle's, many researchers have looked at diet. Changing the balance between the amount of protein, carbohydrate, and fat in the diet is a cheap and easy approach to try to improve the amount of energy available to the muscles. There is not a consensus between McArdle's specialists over what the balance of protein, carbohydrate, and fat in the diet should be, and several different theories have been suggested. Reasons why each diet has been recommended for McArdle people are given below. Some clinical trials to try to prove these theories have been carried out, and there are likely to be further trials in the future.

There is already much information available about balanced diet and healthy eating for the general population, such as the information on the NHS website. The purpose of this chapter is to consider whether diet may play a role in improving the supply of energy to the muscles and reducing McArdle's symptoms.

6.6.1 The role of protein, carbohydrate and fat in McArdle's

Protein is used as the main component to build and maintain cells in the body. It has been suggested that McArdle people may need an increased amount of protein to repair muscle cells due to repeated muscle injury (Quinlivan *et al.*, 2008). The body can also breakdown protein into amino acids, which can be used as a source of energy (see section 6.1.3), but this is a slow release form.

Carbohydrate is principally used to provide energy. Simple carbohydrates such as sugar, glucose, fructose are quickly digested and provide a rapidly available source of energy. Complex carbohydrates such as bread or pasta can take longer to digest, and provide a slow release of energy.

Fat is a source of energy. Free fatty acids are a source of energy during the second wind. Theoretically, a high fat diet may increase the amount of free fatty acids available.

6.6.2 Research into whether the balance of protein, carbohydrate and fat in the diet affects McArdle people

Slonim and Groans (1985) had a theory that a diet rich in protein and adequate in carbohydrate would meet the protein requirements caused by the ongoing muscle injury and increased muscle regeneration that are typical of this condition. Slonim and Groans (1985) studied one McArdle man who was fed either glucose, protein (broiled beef) or had an intravenous injection of fructose. The man was exercised into the second wind, and then tested to see how long he could exercise before becoming exhausted. He was able to exercise for longer after the protein meal than after having glucose or fructose. Kushner (1990) and Maclean (1998) each tried giving McArdle people protein (branched-chain amino acids) supplements, but it was not shown to have any benefit (see section 7.1.1.2).

Jensen *et al.* (1990) compared one McArdle man who was fed either a diet of 15% protein, 42% fat and 43% carbohydrate, or a high protein diet of 28% protein, 29% fat and 43% carbohydrate. He was able to exercise for longer following the high protein diet. They also tested the man following an intravenous infusion of amino acids (proteins). They found that giving protein intravenously did not improve the ability to exercise.

There are several criticisms of the studies by Slonim *et al.* (1985) and Jensen *et al.* (1990). The first criticism is that they were single case studies – they only looked at one person. The second criticism is that they were not blinded – the people could see what food they were eating, and did not have a placebo. Much larger studies with many more McArdle people would be needed to produce scientifically valid results (see section 17.6 for more details about how the best clinical trials are carried out). As mentioned by Quinlivan *et al.* (2008), a further criticism of the high protein diet is that there are no published randomised controlled trials.

Andersen and Vissing (2008) carried out a crossover open study of seven McArdle people. They had either a carbohydrate or protein rich diet for 3 days. Their ability to exercise and the amount of exercise they were able to do was compared before and after this diet. Each person was tested after each diet. The results were that on the carbohydrate diet, the participant's heart rate was lower and the participants felt it was easier to exercise than on the protein rich diet. Participants had a "25% improvement in maximal oxidative work capacity on the carbohydrate versus the protein diet". The authors concluded that "the carbohydrate diet not only improves tolerance to everyday activities, but will probably also help to prevent exercise-induced episodes of muscle injury in McArdle disease."

Vorgerd and Zange (2007) tested a ketogenic diet. This was diet with a high level of fat, and a restricted level of carbohydrate in this case, 80% fat, 14% protein, (and I calculate there would be approximately 6% carbohydrate). Vorgerd and Zange (2007) tested a single McArdle person (a 55 year old man) with this ketogenic diet for one year. The participant had improved muscle symptoms and his ability to exercise was increased between three and ten times what it had been before the trial. However, no visible changes in muscle energy metabolism were seen within the muscle cells using ³¹P MRS (see section 2.3.6 for explanation of ³¹P MRS).

Orngreen *et al.* (2009) investigated whether the bodies of McArdle people compensate for not being able to break down glycogen by instead using more fat to provide energy. They studied whether fat was used to provide the muscles with energy in 11 McArdle people. Orngreen *et al.* (2009) found that total fat and free fat acids were used more to provide energy during exercise, and carbohydrates were used less to provide energy, in McArdle people. They found that during the start of the second wind, fat was used more to provide energy, but if more free fatty acids were given, it did not increase the ability to exercise even further. They conclude that their results suggest that the bodies of McArdle people do use fat to provide energy during prolonged, low intensity exercise, and this may partially compensate for not being able to produce glucose from glycogen in the muscle cells. They also suggest that energy produced using fat could be important in producing the energy for the second wind. However, they think that there may ultimately be a limit, so that increasing the amount of fat does not keep leading to increases in energy.

Andersen *et al.* (2009) also investigated the role of fat in providing energy during exercise for McArdle people. They studied ten McArdle people. They compared the amount of exercise the participants were able to do when given either nicotinic acid (which prevents the breakdown of fat to produce energy) or gave a 20% "Intralipid" infusion (free fatty acids). They compared these to a placebo (isotonic sodium chloride solution – basically a salt solution at the same concentration as found in the body) and also glucose. Each of these treatments was given as an intravenous injection. They compared the effect on the heart rate during exercise. As predicted, they confirmed that

giving an Intralipid injection increased the amount of free fatty acid in the blood, and that nicotinic acid reduced the levels of free fatty acids by about half. “Heart rate was significantly higher during exercise in the Intralipid infusion and nicotinic acid trials compared with the placebo and glucose infusion trials, an effect that was observed before and after the people had experienced the second wind phenomenon.” They concluded that although free fatty acids are an important source of energy for muscles of McArdle people during exercise, artificially increasing the levels of free fatty acids above those normally present does not lead to an increased ability to exercise. They suggest that the lack of breakdown of glycogen into glucose (caused by the lack of muscle glycogen phosphorylase in McArdle people) may have knock-on effects which reduce how much energy can be made from the free fatty acids. Fat is made into energy by a series of reactions called the “tricarboxylic acid cycle”, and Andersen *et al.* suggest that methods to improve these reactions will be necessary if researchers want to develop a therapy whereby McArdle people could use more fat to produce energy.

6.6.3 Comments on these trials

The research published to date (described above), suggests that protein, carbohydrate and fat are all required by McArdle people. It is likely that some protein is required to rebuild muscles which get damaged, and also as a source of energy, but studies by Andersen and Vissing (2008) suggest that a high carbohydrate diet enables McArdle people to exercise more easily than a high protein diet. Although free fatty acids are required to produce energy by oxidative phosphorylation in order to generate a second wind, research by Orngreen *et al.* (2009) and Andersen *et al.* (2009) suggests that having a very high level of free fatty acids in the blood does not enable oxidative phosphorylation to produce any more energy than usual. This data could suggest that a high fat diet would not be of benefit to McArdle people, and that a balanced diet with a normal level of fat would be sufficient.

One criticism of all the trials of different diets is that the participants were not blinded; they knew which diets they were being given and would have been able to work out whether they had received the high fat, high carbohydrate or high protein diets. The participants may have had preconceptions that one diet would help them exercise better and this may have had an effect subconsciously. However, this effect becomes reduced as the number of participants increases, as they are unlikely to all have the same preconceptions.

IMPORTANT: It is important to obtain medical advice before commencing an unusual diet such as those described above. This is because without appropriate advice, you may not get all the essential nutrients that are required, which could lead to a deficiency that could have negative effects on the body. Vogerd and Zange (2007) say for a diet such as the ketogenic diet “very careful calculation of nutrient composition has to be combined with very restrictive and demanding medical and nutritional supervision”.

6.6.3.1 The importance of not over-eating

Protein, fat, and carbohydrates each contain calories. Calories are a measure of energy, which is needed for many body processes, including providing energy for exercise. Calories are burnt by exercise, but also in everyday activities. An excessive amount is consumed if more calories are eaten than calories used by the body, and this can lead to weight gain. It is important for McArdle people to try to avoid becoming overweight (see section 4.2.3).

Recommended reading:

Most of the information about the production of energy in muscle cells in people unaffected by McArdle's is based upon Molecular Biology of the Cell by Alberts et al., 2007. This is a university undergraduate degree level textbook, and therefore quite complicated. The textbook can be read online for free: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=mboc4>

A good source of reliable information on healthy eating and a balanced diet (not specific to McArdle people) is the NHS website: <http://www.nhs.uk/Livewell/Goodfood/Pages/Goodfoodhome.aspx>

7 Dietary supplements which have been considered for McArdle's

McArdle people, specialists and scientists have all suggested that taking supplements could theoretically improve McArdle's symptoms by providing an alternative source of energy for the muscle cells, or by helping the body to work more efficiently. Supplements are foods, vitamins or minerals which are eaten, drunk (or injected) in addition to your usual diet. Some scientific trials have been performed to see whether taking certain supplements enable McArdle people to exercise more easily. However, there are criticisms of many of these studies, which are explained in more detail in this chapter. Medical advice should be obtained before commencing use of a supplement.

There are a couple of supplements which studies suggest do improve the ability of McArdle people to exercise, but they can also have some disadvantages. A sugary drink before exercise improves the ability of McArdle people to exercise. But it may temporarily prevent a second wind, may cause weight gain, and is not suitable for unplanned exercise or for McArdle people with diabetes. Studies suggest that taking a low amount of creatine as a supplement may help to provide energy to muscle cells and the enable McArdle people to exercise more easily. However, taking a high amount of creatine as a supplement can cause McArdle people to feel an increased amount of muscle pain when exercising.

Studies suggest that supplements which do not improve the ability of McArdle people to exercise include: amino acids, branched-chain amino acids, vitamin B6, dantrolene sodium, and ribose. A study on whether verapamil helped McArdle people to exercise was inconclusive.

Anecdotally, some McArdle people have considered taking other supplements including other vitamins and other amino acids. However, these supplements have not been tested in clinical trials, and there is no clinical evidence that they could treat McArdle's.

Descriptions of supplements which it has been suggested may help McArdle's are given below. Please note that the inclusion of a supplement in this list DOES NOT indicate that it is a recommended treatment for McArdle's! In order to provide the reader with a comprehensive overview, the following chapter includes information on supplements which have been shown to be effective, to have no effect or a negative effect, and for which there is limited information. A brief description of the medical/scientific reason for these supplements is given. And the results of any trials are also given.

7.1 Supplements which have been tested as possible treatments for McArdle's

7.1.1 Amino acids

7.1.1.1 Amino acids (given intravenously)

What it is: Amino acids are the simple building blocks of proteins.

Form of the supplement: Intravenous (injected in solution into a vein).

Reason why it might help McArdle's: Amino acids are used to build proteins for body growth and maintenance. Amino acids can also be used as a fuel to provide energy for movement. Exercise can lead to rhabdomyolysis (muscle damage) in McArdle people. McArdle people may have a high requirement for amino acids which are used to build and repair muscle damage.

Results of clinical trials: Jensen *et al.* (1990) tested a McArdle man following an intravenous infusion of amino acids (proteins). They found that giving protein intravenously did not improve the ability to exercise. Criticisms of these studies are discussed in section 6.6.2.

7.1.1.2 Branched-chain amino acids (BCAAs)

What it is: BCAAs are made up of branched chains of amino acids; a form of proteins which are medium complex.

Reason why it might help McArdle's: proteins are broken down by the citric acid cycle and used to produce energy by oxidative phosphorylation (see section 6.1). BCAAs may provide "an alternative energy source for exercising muscle" (Kushner and Berman, 1990), and therefore help McArdle people exercise more easily.

How is it taken: orally as a supplement to the usual diet

What were the results of clinical trials: Kushner (1990) studied three McArdle people before treatment. They gave them a short term treatment: they tested whether 300mg of BCAAs per kg of body weight, consumed 45-60 minutes before exercise had any effect. They also gave them longer term treatment: one and two months of having 300mg of BCAAs per kg of body weight daily. They measured muscle strength and how quickly muscles became tired. Neither the short term nor long term treatment had any positive effect.

Maclean (1998) also tested BCAAs, and found that the ability to exercise was worse when taking the supplement.

7.1.2 Vitamin B6

What it is: B6 is a vitamin.

Form of the supplement: A powdered sachet made up in water as a drink (used by Beynon *et al.* as described in the report by Quinlivan *et al.*, 2008)). B6 is also available as a tablet.

Reason why it might help McArdle's: B6 is used to produce PLP. PLP is usually bound to muscle glycogen phosphorylase. However, not all B6 is bound to muscle glycogen phosphorylase. Beynon *et al.* (1996) suggested that in people unaffected by McArdle's, the PLP bound to muscle glycogen phosphorylase could serve as a way of buffering the body if the amount of vitamin B6 obtained from the diet varies from day to day. For McArdle people, the lack of muscle glycogen phosphorylase may reduce the amount of PLP available. Their theory was therefore that unless enough B6 is obtained from the diet, McArdle people may suffer from a B6 deficiency.

Results of clinical trials: Pheonix (1998) studied a McArdle person who had been taking 50mg of vitamin B6 daily for two years. The ability of the participant was compared when he was given either vitamin B6 or a placebo. He did not know which he was receiving. He felt less well when given placebo, but it did not seem to affect the strength of the muscles.

Quinlivan *et al.* (2008) described an unpublished trial of vitamin B6 by Beynon *et al.* Muscle strength was measured, and the amount of B6 in the body was also measured. No significant difference was seen with the B6 treatment compared to placebo treatment. It should be noted that the data from Beynon *et al.* is unpublished and therefore has not been subjected to peer review or approved for publication by other professionals in the field.

Izumi *et al.* (2010) described a McArdle woman who was treated with a vitamin B6 supplement (90mg per day) for two months. Compared with before, her CK level decreased, an ischaemic forearm test produced a rise in lactate level and she felt that her muscles became tired less quickly after treatment. However, I suspect that this woman did not have typical McArdle disease. The authors report that she had a low level of enzyme activity, but they did not perform genetic testing. I wonder if this woman had an unusual mutation which resulted in a small amount of functional muscle glycogen phosphorylase. Studies suggest that even a small amount of functional enzyme can make a large difference to the severity of McArdle symptoms (see 9.1.3). Further studies on McArdle people with typical symptoms of McArdle disease (such as a complete absence of functional muscle glycogen phosphorylase) would be required to determine the effect of vitamin B6 supplements.

7.1.3 Creatine

What it is: Creatine is a compound which is found naturally in muscle cells. It can be made by the body from the amino acids L-arginine, glycine, and L-methionine.

Form of the supplement: capsule/tablet

Reason why it might help McArdle's: Muscle cells contain both creatine and phosphocreatine, and the balance of each is used to control the levels of ADP and ATP within the muscle cells. This helps to maintain a supply of ATP for energy, and also to control the level of ADP, which can have an effect upon the speed of some energy producing reactions in the body. Creatine supplements had

previously been found to improve the ability to do intense exercise in people unaffected with McArdle's and also people with mitochondrial myopathies (see section 2.5.2).

What were the results of clinical trials: Vogerd (2000) carried out a double blind crossover trial where McArdle people were given either a low dose creatine (150mg of creatine per kg of body weight for one week, followed by 60mg of creatine per kg of body weight for four weeks) or a placebo. They showed that McArdle people were able to exercise more easily after taking the creatine. Vogerd *et al.* (2002) then went on to compare high dose (150mg of creatine per kg of body weight) to low dose (60mg creatine per kg of body weight). When taking high dose creatine, the McArdle people reported that they felt muscle pain more frequently during exercise and the level of pain was higher.

Low dose creatine appeared to help McArdle people to exercise more easily. Vogerd (2002) felt that "An effective [creatine] dosage without adverse effects may be between 60 and 150 mg/kg daily", but that further trials were necessary.

It was not possible to determine how creatine improved the ability to exercise as treatment did not increase creatine levels in the muscles. It was therefore possible that creatine was having a different, albeit positive effect upon the body (Vogerd and Zange, 2007).

7.1.4 Cornstarch (such as the commercially available "Glycosade")

What is cornstarch: Cornstarch is a source of carbohydrate.

Form of the supplement: powder made into a drink for oral use.

Reason why it might help McArdle's: Cornstarch is not likely to help McArdle's. It is used to treat several other Glycogen Storage Diseases (GSDs). Cornstarch is useful for other GSDs where the main problem is either storing glycogen in the liver, or releasing this glycogen from the liver into the blood - this is important as it helps the body keep the right amount of sugar in the blood between meals. In McArdle people, the liver form of the glycogen phosphorylase enzyme works perfectly well, so the body is able to store excess sugar as glycogen in the liver, and then convert it back into glucose which can be released into the blood when needed.

Although there have been one or two suggestions published by family doctors that cornstarch might help McArdle's (in a similar way to a sugary drink), the view of the experts seems to be that cornstarch is NOT likely to help. A sugary drink can help, as the sugar is very rapidly absorbed through the stomach/intestine into the blood, and can quickly get to the muscle cells where it is needed (quickly in this case would be sometime between 5 mins and 2 hours). In contrast, cornstarch takes much longer to absorb and for the body to break it down into sugar (Sweetman, 2009).

McArdle people don't need cornstarch to provide energy as they would get this from the food they usually eat. If you tried drinking/eating cornstarch just before exercise, the sugar from the cornstarch would not be released until a long time after you had finished exercise, and would not provide any sugar for the muscles during exercise. Having cornstarch might be more like eating extra food in addition to your normal meals, and might be more likely to result in becoming overweight - which is not recommended for McArdle's.

What were the results of clinical trials: There has been one published study of cornstarch plus vitamin B6 by Sugie *et al.* (2003) however, I wasn't able to read it as it was in Japanese! The abstract said that it was an open trial - which means that the participants knew if they were having the treatment or not - which is much less scientifically/medically useful. In addition, the abstract suggests that the McArdle people were given both cornstarch plus B6 - which isn't very useful because it wouldn't have been possible to tell which (if either) was producing a positive result.

It may be that no other trials of cornstarch have been performed because most researchers have decided based on the science that it would be unlikely to help, and therefore not bothered testing it.

7.1.5 Dantrolene sodium

What it is: Dantrolene sodium is a chemical compound.

Form of the supplement: It can be given orally (as in the trial by Poels *et al.*, 1990) or into the vein by intravenous injection. A total of 150mg (given as three doses of 50mg) was given to participants in the trial by Poels *et al.* (1990).

Note: An intravenous injection of dantrolene sodium can be used as a treatment for malignant hyperthermia (Sweetman, 2009)(see section 12.3.1).

Reason why it might help McArdle's: Dantrolene sodium is a muscle relaxant, which works directly on the skeletal muscles (Sweetman, 2009). It was thought that dantrolene sodium might induce or improve the second-wind (Poels *et al.*, 1990). There was also a case report that dantrolene sodium prevented rhabdomyolysis caused by exercise, in a person who had rhabdomyolysis and whose muscles quickly became tired during exercise (Haverkort-Poels *et al.*, 1987). However, this person had NOT been diagnosed with McArdle's. The researchers may have hoped that dantrolene sodium would have a similar positive effect on McArdle people.

Results of clinical trials: Poels *et al.* (1990) carried out a double-blind placebo-controlled study. High doses led to the side effects of tiredness, dizziness, and muscle weakness. Surface EMG results showed that after treatment, the muscles of McArdle people responded differently as they became tired during exercise. However, the overall conclusion was that "None of the patients experienced beneficial effect of dantrolene sodium medication" (Poels *et al.*, 1990).

7.1.6 Sugar

7.1.6.1 Ribose

What it is: Ribose is a simple sugar. Ribose comes in two forms, one of which is D-ribose.

Form of the supplement: D-ribose dissolved in water as a drink

Reason why it might help McArdle's: Ribose has several functions in the body. It is part of riboflavin, which is a building block of two components involved in aerobic energy metabolism. Ribose is also used to make ATP the energy source for muscle contraction. Ribose is usually obtained from the diet or by making it from glucose (Kreider, 2009)

It has been suggested that giving ribose supplements to people unaffected by McArdle's (particularly athletes), may help to increase the amount of ATP available in muscle cells. Initial studies suggested

that ribose supplements did appear to help people with either myoadenylate deaminase deficiency (see section 2.3.1) or coronary artery disease (Kreider, 2009). Steele *et al.* (1996) thought that D-ribose could be used by the body to produce ATP in McArdle people.

Results of clinical trials: Several studies have been carried out in people unaffected by McArdle's to see if ribose supplements help them exercise for longer, but in general they did not have much effect. Steele *et al.* (1996) gave McArdle people D-ribose. There was no significant difference in ability to exercise before or after treatment. Participants didn't like taking the ribose. Steele *et al.* (1996) said that it did not appear to benefit McArdle people.

7.1.6.2 Sucrose (glucose)

What is sucrose: Sucrose is a form of sugar.

Reason why it might help McArdle's: Sucrose is rapidly split into glucose and fructose within the muscle cells. This process does not require muscle glycogen phosphorylase. Glucose and fructose can be used in glycolysis to provide energy (Fernandes, 2006). This reduces the need to breakdown glycogen into glucose – which requires muscle glycogen phosphorylase and does not occur in McArdle people (Fernandes, 2009). Having a sugary drink just before exercise can increase the level of glucose in the blood. Glucose in the blood can be transported and taken into the muscle cells, and used to produce energy for exercise. This source of glucose should prevent muscle cells running out of glucose, and reduce symptoms of McArdle's which are normally induced by exercise; such as muscle pain and cramps.

Form of the supplement used in the trials: sucrose powder dissolved in water to produce a drink.

What were the results of clinical trials: Vissing and Haller (2003) gave McArdle people 660ml of a drink containing either 75g of sucrose or artificial sweeteners (as a placebo). Drinking sucrose increased the level of glucose in the blood, and made exercise easier for the McArdle people. The McArdle people who were given glucose had a lower heart rate and felt that exercise was easier compared to when they had the placebo. Exercise was done 30-40 minutes after drinking the sucrose. The exercise was a stationary bicycle (ergometer) which was cycled for 15 minutes.

Andersen, Haller and Vissing then followed this up in 2008 with the following experiment. McArdle people were given either; 75 g of sucrose or a placebo 40 minutes before exercise, or 37 g of sucrose or a placebo 5 minutes before exercise. People were tested with each on different days but did not know which treatment they had each day. The results were that having either 75g or 37g of sucrose made exercise easier for McArdle people. However, taking of sucrose five minutes before exercise had a longer lasting positive effect than taking sucrose 40 minutes before exercise. The author's conclusions were "This study shows that 37 g of sucrose ingested shortly before exercise has a marked and prolonged effect on exercise tolerance in patients with McArdle disease. This treatment is more convenient for the patients and saves more calories than the currently recommended sucrose treatment."

7.1.6.3 The pros and cons of drinking a sugary drink before exercise

Pros: 37g of sucrose in a sugary drink, taken 5 minutes prior to exercise has been shown to make exercise easier for McArdle people (Andersen *et al.*, 2008). It is a quick, easy, and cheap treatment.

Cons: Having a sugary drink before exercise is a short term treatment, and can lead to weight gain (Amato, 2003; Quinlivan *et al.*, 2008). (Weight gain and McArdle's is discussed further in sections 4.2.3 and 6.6.3.1.) It is not helpful if the exercise is unplanned (Quinlivan *et al.*, 2008) (for example, you suddenly have to run for a bus). Sugar isn't a suitable treatment for McArdle people who have diabetes (Quinlivan *et al.*, 2008).

It has been suggested that sucrose may prevent or slow down the second wind. High levels of sucrose may prevent utilisation of fatty acids as a fuel for prolonged exercise (Amato, 2003). (See 6.4 for a further description of how energy is produced in second wind.)

7.1.7 Verapamil

What it is: Verapamil is a chemical compound.

Form of the supplement: It can be given orally as a tablet, or by intravenous injection.

Reason why it might help McArdle's: Verapamil is a calcium-channel blocker. It slows heart rate and is used to treat angina. I think that treatment with verapamil was proposed as a way to reduce the increased heart rate which is usually seen in McArdle people when they exercise. (I am not sure if the authors knew why it might work since they say "mechanism of action of the drug in such cases is unclear".)

Results of clinical trials: Participants were asked to exercise at home and to keep a diary of the amount of pain experienced, to test the effect of the treatment on exercise. But none of the people tested recorded enough information in their diaries. "None of the patients with McArdle disease responded to verapamil" (Lane *et al.*, 1984).

7.2 Supplements which have not been tested to see if they are effective in McArdle's

There are several supplements which McArdle people have mentioned in online chat groups. These supplements have not been tested in clinical trials, and there is no clinical evidence that they could treat McArdle's.

Many of these supplements are involved in the breakdown of fatty acids. Fatty acids can be broken down to produce energy, which provides energy for the second wind. This is an alternative method to produce energy than glycolysis (the breakdown of glycogen to glucose). I imagine that people would take these supplements in the hope of improving the second wind phenomenon. However, there is no clinical evidence for taking any of these supplements.

These supplements include:

7.2.1 Vitamins

(Note: for vitamin B6, see section 7.1.2).

B12 Vitamin B12 is a water soluble vitamin essential for the brain and nervous system, and also in formation of blood. It is also involved in production of fatty acid and energy.

Biotin is a water soluble B complex vitamin. Biotin contributes to breakdown of fatty acids and the amino acid leucine. Biotin is also involved in gluconeogenesis.

Vitamin D is a fat soluble vitamin. Its principal role is bone growth and maintaining bone strength.

7.2.2 Amino acids

(Note: for branched-chain amino acids, see section 7.1.1.2).

L Alanine – an amino acid

L Carnatine – made from a compound of several amino acids. Carnatine is involved in breaking down of fatty acids to produce energy.

7.2.3 Coenzyme Q-10 (CoQ₁₀; also known as ubiquinone or ubidecarenone)

CoQ₁₀ is a naturally occurring compound that is involved in generating energy (ATP) during aerobic respiration (Sweetman, 2009). Coenzyme Q-10 (CoQ₁₀) is also known as ubiquinone or ubidecarenone. There is no published data or any published hypotheses that CoQ₁₀ supplements are of any benefit to McArdle people. The only relevant mention of CoQ₁₀ was in conjunction with statin treatment (see 12.1.1 for further discussion of statins). Statins can reduce the levels of CoQ₁₀ in the blood (Sweetman, 2009). It was hypothesised that taking CoQ₁₀ at the same time as statins may protect muscles against damage caused by the statins. However, research to date has been inconclusive. Molyneaux *et al.* (2008) describe a trial they carried out: People unaffected by McArdle disease took a statin (called simvastatin) with or without CoQ₁₀, but there was no significant difference in the amount of muscle damage seen in the two groups.

CoQ₁₀ supplement is mentioned as an aside in report by Kono *et al.* (1984). They were testing the effect of glucagon on a McArdle woman, aged 26 years old. She had been taking CoQ₁₀ supplements for the past year and had felt these had led to improvement of her symptoms. The authors did not test whether CoQ₁₀ had any effect on McArdle's symptoms.

There have been no clinical trials of CoQ₁₀ supplements as a treatment for McArdle disease.

7.2.4 Medical advice should be obtained before commencing use of a supplement

IMPORTANT: All supplements should be discussed with your family doctor before you begin taking them.

Medical advice should be obtained before commencing use of a supplement. This is for a variety of reasons. An excessive level of some supplements may restrict absorption of other nutrients or vitamins, leading to a deficiency. Some supplements can interact with prescription or herbal medicines/drugs. It is possible to overdose on some supplements, especially those which are fat soluble, and this could have health risks.

Recommended reading:

Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V)
Quinlivan R, Martinuzzi A, Schoser B. (2010) *Cochrane Database of Systematic Reviews* (It is also useful to search online and see if there is an updated version.)

Exercise & Sport Nutrition: Principles, Promises, Science, & Recommendations, 2009, by Richard B. Kreider, Brian C. Leutholtz, Frank I. Katch, Victor L. Katch (*Useful general information on several of the supplements described above.*)(Google free books)

8 The effect of age on the symptoms of McArdle disease

Symptoms are not usually seen in babies with McArdle's, although one case of a toddler with McArdle's has been reported. McArdle children under the age of 5 years old often do not have classic McArdle symptoms and many have no difficulty with exercise. Despite having no classic McArdle symptoms, young McArdle children are likely to have high creatine kinase (CK) levels in the blood. In a child who is suffering from muscle pain or difficulty with exercising, high resting CK levels in the blood may be the first indication to suggest a possible diagnosis of McArdle's. From around the age of 5 years and onwards, McArdle children usually experience the classic McArdle symptoms of muscle pain, muscle cramps, myoglobinuria, and difficulty with exercise. These typical symptoms of McArdle disease continue to be seen in older childhood, adolescence and adulthood.

Over the age of 40, some McArdle people have muscle wasting and weakness in the arms and trunk of the body. The reasons for muscle wasting and weakness are not yet known, but may be a normal part of ageing, as it is usual for muscle wasting and weakness to occur in older people unaffected by McArdle's. McArdle people do not usually become severely handicapped or need to use a wheelchair. McArdle disease does not appear to affect lifespan, and there are several published reports describing elderly McArdle people aged 70-80 years old.

Some older papers have reported rare forms of McArdle disease including a rare fatal infant form and a late-onset form. These papers were published many years ago before all the modern tests were available, and it is therefore not possible to find out whether there is a scientific explanation for these, such as a second disease which was fatal. Recent studies of large numbers of McArdle people have only described the classic form of McArdle disease, and I believe this to be the only form of McArdle's.

8.1 Are there several forms of McArdle's?

Historically it has been suggested that there may be several forms of McArdle disease, which I have summarised these below as four forms. 1 to 3 are outlined by Roubertie *et al.* (1998) and 3 and 4 are outlined by Papadimitriou *et al.* (1990):

1. a rare fatal infant form
2. a milder form with delayed motor milestones, limb muscle weakness and high CK
3. a classic form, which begins in childhood, with symptoms of difficulty in exercising, and normal CK levels alternate with acute episodes of exercise intolerance
4. a late-onset form which begins in adult life and leads to progressive muscle weakness

Each of these forms is discussed in more detail below. Personally I believe that only the classic form is genuinely McArdle disease. It should be noted that no cases of the rare fatal infant form or milder form have been reported in the last ten years. A criticism of the papers which reported these two forms is that they were performed before genetic testing for McArdle disease was possible. The papers also do not make it clear if a second disease was tested for or excluded. A great difficulty with these cases is that it is likely that no samples remain, so it is not possible to carry out further tests on samples from these people to determine if they had been misdiagnosed.

If only the classic form is genuinely McArdle disease, there is a risk that the other forms are perpetuated by published papers repeating old theories until they appear to be fact. I suspect that modern clinicians and experts on McArdle disease now also believe that only the classic form is McArdle disease, as there is no mention of any of the other forms in the recent papers published about McArdle's (such as papers by Quinlivan and Vissing, 2007; and Lucia *et al.*, 2008a). In my opinion, if a survey of all McArdle people was conducted, 98% of them would have the classic form. A possible explanation for the remaining 2% would be that they either have double trouble (see section 9.6.1) or have been misdiagnosed and actually have another similar muscle disease (see section 2.5).

8.1.1 A rare fatal infant form:

There have only been three cases reported (Roubertie *et al.*, 1998). Two of these died at 13 weeks and 16 days respectively. All three of the cases suffered from respiratory failure (i.e. were not able to breathe). But there were other unusual factors. One of the children had general weakness, one was quadriplegic (not able to move any limbs), and one was a child from consanguineous parents. (Consanguineous means that the parents were highly related e.g. brother and sister, or first cousins. See section 3.3.6.) One possible explanation for these unusual cases of infant fatality is that the child inherited McArdle disease and also inherited a second recessive disease (this is known as double trouble, see section 9.6), and it was the effect of the second disease which was fatal.

It is well known that consanguineous parents often lead to an increased likelihood of the child having a recessive disease. There is a report of an infant girl who died at 5 months of age. She had mutations in both copies of the *PYGM* gene and also in both the copies of the deoxyguanosine kinase (*dGK*) genes (Mancuso *et al.*, 2003). Her Moroccan parents were related (they were first cousins). Deoxyguanosine kinase is an enzyme involved in producing energy in the mitochondria,

with the genetic information also provided by mitochondria. Mitochondrial DNA depletion syndrome (caused by lack of deoxyguanosine kinase), is usually fatal. This child had liver failure, which is not seen with McArdle disease, but is commonly seen with mitochondrial DNA depletion syndrome. The mutation in the deoxyguanosine kinase (dGK) gene was a 4bp deletion of GATT at 763. It is relevant to note that Salviati *et al.* (2002) had reported a child with this mutation, who did not have McArdle's, who began to have symptoms at the age of 2 months, and died at the age of 5 months. It is frustrating that Mancuso *et al.* (2003) did not mention this in their paper, and instead suggested that the 5 month old child may have died from the fatal infant form of McArdle's. In my opinion it is much likely that it was the mutation in the deoxyguanosine kinase (dGK) which was fatal.

It is also possible that a child with McArdle disease could die of a completely different cause, which may not be inherited. There is a case of a 3 month old child with McArdle disease who died of sudden infant death syndrome (SIDS) (el-Schahawi *et al.*, 1997). Unlike the other children mentioned above who died shortly after birth, her parents did not notice any muscle weakness. SIDS occurs to adults and children unaffected by McArdle disease, and the cause of SIDS is still not known (Shaffer, 2009). El-Schahawi *et al.* (1997) suggest that McArdle disease could be a predisposing factor for SIDS. But I disagree as a single case of a McArdle's child who died from SIDS is not sufficient evidence to suggest that the SIDs and McArdle disease could be related.

8.1.2 A milder form with delayed motor milestones, limb muscle weakness and high CK

There have only been two cases of this reported (Roubertie *et al.*, 1998). One child had delayed motor milestones (took longer to crawl/sit up/walk than most children), limb muscle weakness and high CK levels. The fact that it is mentioned in only two published reports suggests that delayed motor milestones are not typical symptom of McArdle disease. Therefore a possible explanation is that this child did not have McArdle disease, and it was as case of misdiagnosis. These symptoms are all characteristics of other muscle diseases such as congenital myopathy with type 1 fiber predominance (CMT1P) (Na *et al.*, 2006) or Duchenne muscular dystrophy (Dubowitz and Sewry, 2007).

8.1.3 A late-onset form which begins in adult life and leads to progressive muscle weakness

There are several explanations for this. One explanation is that this is seen in carriers of McArdle's who have a second muscle disease. If the second muscle disease makes the muscles weaker, this may trigger symptoms of McArdle disease. An example of this could be the case described by Papadimitriou *et al.* (1990) who described a man who developed McArdle's symptoms at the age of 30 years, and who was a carrier (he had 25% functional muscle glycogen phosphorylase). (Further details about this case are given in section 9.7.)

A second explanation is if a McArdle person had managed to have a lifestyle which was ideal for McArdle's, and had avoided symptoms without even knowing they had McArdle's. For example, an office worker would not have needed to do intense activity on a daily basis. They may not notice McArdle's symptoms until their muscles begin to grow weaker as part of getting older. Tunzun *et al.* (2002) said that "Many life-long [McArdle's] sufferers are finally diagnosed in their 50's and 60's. It is now believed that many cases may go unnoticed." Makary *et al.* (2008) reported a man who was

diagnosed with McArdle's at the age of 65 years old. His symptoms seemed to have got slightly worse with age, but he did not seem to have had any contractures or severe symptoms. He was not diagnosed until he had treatment with Lipidor (a statin), which seems to have made his McArdle's symptoms worse. Harris *et al.* (1985) reported a woman who was diagnosed with McArdle's at the age of 71 years. She had myoglobinuria, and had muscle breakdown when having very little exertion. She had high CK levels (Harris and Dowben, 1985). She had led a sedentary lifestyle. She had no functional muscle glycogen phosphorylase in her muscles. Her parents were first cousins (consanguineous parents, see section 3.3.6). Her mother had severe muscle cramps when she exercised, and her sister had very high CK and muscle cramps after strenuous exercise (Harris and Dowben, 1985). It is unusual to have several family members (mother, sister, and niece) all with symptoms of high CK and muscle cramps. Wolfe *et al.* (2000) described a man who was diagnosed with McArdle's at the age of 73. He had no history of exercise causing muscle cramps, muscle pain, or myoglobinuria. He had creatine kinase levels which were elevated, serum lactate did not rise when he did an ischaemic forearm test and he had vacuolar myopathy with no functional muscle glycogen phosphorylase.

A third explanation could be that the symptoms were present, but that the McArdle person did not consult a family doctor, or that a family doctor did not recognise the symptoms. As McArdle disease is relatively uncommon, some family doctors may not realise that their patient has McArdle's. The difficulties that patients may find in obtaining a diagnosis are discussed further in section 10.3.2.

Apart from the suggestions given above, I find it hard to explain how late-onset could occur, since McArdle people will have had a lack of muscle glycogen phosphorylase since a baby, and therefore I would expect symptoms to have been present since childhood.

8.2 The classic form

In this classic form of McArdle's, the principle symptoms are difficulty with exercise, and relatively normal CK levels between acute episodes of exercise intolerance.

8.2.1 The classic form of McArdle's from baby to toddler

Ito *et al.* (2003) claimed to have found the youngest clinically diagnosed patient with McArdle disease confirmed by muscle biopsy, in a 14 month old girl. She was admitted to hospital because of repeated high CK levels of 5340 U/l, 17,700 U/l and 10,170 U/l as well as a fever (pyrexia). She was diagnosed with McArdle's after a muscle biopsy showed an absence of muscle glycogen phosphorylase, although it was noted that there was no obvious glycogen storage in the muscle cells. Other muscle diseases were ruled out. This McArdle's girl offered a rare opportunity to get a recent history of a McArdle's baby, and the authors provide many useful details about the baby and her growth. The baby was born "at term after an uneventful pregnancy". "She was capable of visual tracking and social smiling within 2 months of birth, head control at 4 months, sitting unsupported at 6 months, rolling at 6–7 months, walking with support by 12 months, and walking unaided at 13 months." She was beginning to speak at the age of 14 months. Both her development and her physical growth were standard for her age. This McArdle's girl did not demonstrate any of the delayed motor milestones described in the milder infant form (section 8.1.2).

8.2.2 The classic form of McArdle's in childhood

A summary of published reports of McArdle's children is provided in Table 8.1. Several criticisms could be made of the information presented in this section. There is a lack of data as at present, very few studies of children with McArdle's have been performed. Further studies are needed to determine whether the children studied are representative of McArdle's in childhood. As some of these publications are up to 30 years old, the mutations were not identified in some cases, and did not have the benefit of the knowledge of McArdle's which has been gained since then.

If we assume that the information in Table 8.1 is reliable, it may be possible to draw some conclusions about children with McArdle's. From the very limited information available, it could be suggested that up to the age of 5 or 6, children do not have as many symptoms of McArdle's. However Perez *et al.* (2009) found that a 4 year old child had a raised resting CK (2656 U/l) despite being asymptomatic. Since children may not be able to speak clearly or have a wide vocabulary until the age of 5, one possibility is that children under 6 years old are able to experience McArdle symptoms, but are not able to put them into words. It is possible that younger children have a slightly different metabolism (for example newborn babies have brown fat which provides a source of energy), and this may explain why some children do not appear to have McArdle symptoms. Perez *et al.* suggested that children may get energy from other methods rather than glycogenolysis.

Typical symptoms of classic McArdle's in children from birth to the age of 5 or 6 onwards (summarised from Table 8.1):

- May be completely asymptomatic, with no physical signs of McArdle disease
- Do not have delayed motor milestones
- May have raised resting CK levels

Typical symptoms of classic McArdle's in children from the age of 5 or 6 onwards to adulthood (summarised from Table 8.1):

- Difficulty in exercising
- Raised resting CK levels
- Muscle cramps
- Muscle pain
- Myoglobinuria
- Extreme exertion (chopping wood or swimming) can cause myalgia (muscle pain), myoglobinuria, and potentially kidney failure.

These symptoms, summarised in Table 8.1, and the anecdotal reports from McArdle adults recollecting their childhood, I think strongly suggest that the classic form is the most common and "normal" childhood form of McArdle's.

However, children with McArdle's also sometimes do not have the same symptoms as adults, as the second wind may be less noticeable or absent (Perez *et al.*, 2008; Perez *et al.*, 2009) and some McArdle's children are able to sprint. Perez *et al.* (2009) reported that child C had a second wind phenomenon, but that the other three McArdle's children (A, B and D) had a much less noticeable second wind than is usually seen in McArdle's adults. Perez *et al.* (2008) reported that the child H (aged 8-9) did not experience "second wind" – he didn't feel the early tiredness, rapid heart rate, or breathlessness which adult McArdle people get before the second wind begins. Perez *et al.* (2009) noted that the second wind phenomenon may not have been seen if the children were not asked to exercise hard enough when tested. They also noted that the heart rate of the youngest child (child A) during exercise was not as high as would have been expected, suggesting that the child was not exercising enough to trigger the second wind response. Williams *et al.* (1985) made the surprising observation that two of the McArdle's children (J and K) "were able to sprint well for short distances without discomfort", but unfortunately the authors did not give measurements of the distances.

8.2.2.1 Diagnosis of children with McArdle's

Based upon the information available, this suggests that raised CK levels in children under the age of 6 (even in the absence of other symptoms of McArdle's) could indicate that they may have McArdle's.

For children above the age of 6, most of the symptoms (outlined above) are similar to those experienced by McArdle's adults.

Since children with McArdle's do not seem to have all the classic symptoms seen in adults, it is recommended that a high CK level when resting should be the first clue that a child has McArdle's, and this should be followed by genetic testing (rather than muscle biopsy) if at all possible (Perez *et al.*, 2009).

Child	Age (years)	Gender	Method of diagnosis/ PYGM mutations	Symptoms	Publication
A	4	Male	R50X homozygous.	Did not complain of any symptoms of McArdle's, but had a high resting CK (2656U/l). Child A was able to run around and keep up with his friends in physical education classes, and the amount of oxygen he needed during exercise (his VO ₂ peak) was normal for his age and gender. (A and B were siblings.)	(Perez et al., 2009)
B	12	Female	R50X homozygous.	Struggled to exercise since the age of about 6 onwards. Resting CK 829 U/l. (A and B were siblings.)	(Perez et al., 2009)
Unaffected	6	Female	Carrier of McArdle disease (the faulty PYGM gene had the R50X mutation).	Resting CK level was 99 U/l. (Unaffected sibling of A and B.)	(Perez et al., 2009)
C	14	Male	No functional muscle glycogen phosphorylase in muscle biopsy. Mutations not known.	Struggled to exercise since the age of about 6 onwards. Resting CK was 2855U/l.	(Perez et al., 2009)
D	17	Female	R50X homozygous.	Struggled to exercise since the age of about 6 onwards. Resting CK was 1500 U/l	(Perez et al., 2009)
E	5	Not stated	Diagnosed by 31 ^P MRS - the pH in the muscle cells did not fall below 6.94 during exercise.	Did not appear to have symptoms. (NOTE: The lack of McArdle symptoms might have been due to the child being too young to describe symptoms of muscle pain, or if one or both parents were misdiagnosed the child might have in fact only been a carrier.) (Both parents had McArdle's. E and F were siblings.)	(Gruetter et al., 1990)

Child	Age (years)	Gender	Method of diagnosis/ PYGM mutations	Symptoms	Publication
F	9	Not stated	No muscle glycogen phosphorylase in muscle biopsy.	Reported having muscle cramps since the age of 5. (Both parents had McArdle's. E and F were siblings.)	(Gruetter <i>et al.</i> , 1990)
G	8	Male	Low levels of functional muscle glycogen phosphorylase.	He had been performing quite vigorous exercise (chopping wood). He was admitted to hospital with myoglobinuria and muscle pain. Myoglobinuria had led to kidney failure. He also had a CK level of 33,766 U/l. He required dialysis to treat the kidney failure.	(Delibas <i>et al.</i> , 2008)
H	8	Male	No functional glycogen phosphorylase in muscle biopsy. R50X homozygous.	From the age of 5, the boy had had general muscle pain, muscle weakness and struggled to exercise. At the age of 8 he was admitted to hospital with severe muscle pain (myalgia), muscle weakness, myoglobinuria, hyperthermia and high creatine kinase levels (4270 U/l) after swimming.	(Perez <i>et al.</i> , 2008)
I	8	Female	No functional muscle glycogen phosphorylase in muscle biopsy.	Symptoms of exercise intolerance since the age of 4 (difficulty walking uphill). CK of 1500 IU/l and 3234 IU/l following contraction of fingers.	(Williams and Hosking, 1985)
J	10	Female	No functional muscle glycogen phosphorylase in muscle biopsy.	Slow walking (particularly uphill), which caused leg cramps. CK initially 7548 IU/l. No rise in blood lactate occurred when an ischaemic forearm test was performed.	(Williams and Hosking, 1985)
K	10	Female	No functional muscle glycogen phosphorylase in muscle biopsy.	Difficulty walking, needed frequent rests. No rise in blood lactate occurred when an ischaemic forearm test was performed. CK level was 6501 U/l.	(Williams and Hosking, 1985)

Child	Age (years)	Gender	Method of diagnosis/ PYGM mutations	Symptoms	Publication
L	12	Male	No functional muscle glycogen phosphorylase in muscle biopsy. An accumulation of glycogen.	Described as an atypical case. CK ranged from 127 U/l to 11,520 U/l (normal was up to 70 U/l). Symptoms did not change between the ages of 12 and 15. "Lazy since early childhood. Persistent mild muscle weakness. Never had cramp or muscle pain."	(Chiado-Piat <i>et al.</i> , 1993)
M	12	Male	No functional muscle glycogen phosphorylase in muscle biopsy, and reduced amount of phosphorylase was seen in enzyme activity test. Enzyme activity was 0.32U/g (normal was 25.1-37.0U/g).	Rapid walking caused muscle fatigue from the age of 6 onwards. However, able to get into second wind. Had myoglobinuria twice. Cycling caused muscle pains. Ischaemic forearm test caused a contracture. However, a small rise in lactate was seen from 0.86 to 1.07mmol/l.	(Sengers <i>et al.</i> , 1980)
N	8	Male	R50X homozygous.	Exercise caused myoglobinuria.	(Kristjansson <i>et al.</i> , 1994)
O	12	Male	Diagnosed by genetic analysis.	Muscle pain during exercise which disappeared after a rest. Raised CK levels.	(Koenraads <i>et al.</i> , 2011)
P	14	Female	R50X and G205S.	Symptoms since the age of 5. Muscle tightness or "seizing up" if walking briskly for more than 300 metres or walking up a hill. CK levels were not tested.	(Miteff <i>et al.</i> , 2011)

Table 8.1 Clinical features of children with McArdle disease, information from published papers. (R50X homozygous means that in one person, both copies of the PYGM gene have the R50X mutation.)

8.2.3 McArdle's in adulthood/middle age

Most McArdle people experience McArdle's symptoms in childhood. Quinlivan *et al.* (2007; 2010) said that 84% of 45 McArdle people recalled symptoms before 10 years of age, although many were not diagnosed until adulthood. Only about half (51%) were diagnosed by the age of 30, with the remaining 49% being diagnosed when older than 30. Most of the classic symptoms of McArdle's are discussed in detail in other sections of this Handbook, including the typical symptoms listed below.

Typical symptoms and features of classic McArdle's in adulthood/middle age are:

- Muscle pain upon exercising
- Contractures
- Raised creatine kinase levels
- Second wind

8.2.4 McArdle's in older age

As discussed by Perez *et al.* (2008), historically, McArdle people were recommended to have a sedentary lifestyle to avoid the risk of exercise causing rhabdomyolysis. Elderly McArdle people are likely to have received this advice. They may have had a sedentary lifestyle since childhood or whenever they were diagnosed. In terms of lifestyle, Perez *et al.* say that it is well known that if children get into the habit of exercising when young, they are more likely to continue to exercise when older. Conversely, if McArdle people were advised not to exercise many years ago, they are likely to have continued this trend. It should be noted that the recommendations for McArdle people have now changed and a moderate level of exercise is now recommended (see section 4.2.2).

Perez *et al.* (2006) reported the case of a 78 year old male with McArdle disease who was able to do very little exercise when first tested, which he suggested was the result of a very sedentary lifestyle. At the time the paper was written, there had not been any studies performed to assess the amount of exercise which elderly people with McArdle's were able to do. The authors suggested that one reason why this study had not been conducted was because of the "risk of discomfort and rhabdomyolysis". They gave the 78 year old man 660ml of solution which contained 75g of sucrose. They gave him a 10 minute warm up period before testing his exercise capacity using a cycle ergometer test (see section 2.3.1.2). They also measured the amount of oxygen he breathed in (called the VO_2 peak). Based upon this single McArdle person, who had led a very sedentary lifestyle, the authors of study suggest that it is likely that elderly McArdle people have a decrease in their VO_2 peak. However, they also state that research on elderly people in general (mostly those who do not have McArdle's) suggests that elderly people are able to safely learn how to exercise and increase their ability to exercise. Although this report is interesting, it must be emphasised that a single case study is not considered a large enough sample size to base medical advice. This study would have been greatly improved if they had set a basic exercise programme for the patient, and then tested him again a year later to see if he was fitter and better able to exercise.

8.2.4.1 Muscle wasting and muscle weakness is a symptom of McArdle's which may develop or increase in older age

Case studies of several elderly McArdle people have been reported. Lucia *et al.* (2008) described an elderly McArdle person who was then 81 – this was the same person described when aged 78 by Perez *et al.* (2006). This person had lived a sedentary lifestyle since childhood. In older age, this person had quite severe exercise intolerance and had “proximal muscle atrophy” and “fixed weakness”. Pourmound *et al.* (1983) described a 76 year old McArdle man whose symptoms began at age 74 years with sudden onset of proximal muscle weakness and fatigability. Electromyography showed nerve activity and the muscle cells looked like there was inflammatory muscle disease. The diagnosis of McArdle disease was made by performing tests on a muscle biopsy, an abnormal ischemic lactate test, and absence of functional muscle glycogen phosphorylase.

The amount of muscle wasting and weakness seen in McArdle people appears to increase with age (Amato, 2003; Nadaj-Pakleza *et al.*, 2009). Quinlivan *et al.* (2010) reported that 24% of 45 McArdle people had muscle hypertrophy (increased muscle size), and 16% (all aged over 40 years old) had mild upper limb and trunk weakness. Nadaj-Paleza *et al.* (2009) found that 10% of 80 McArdle people, all aged over 40, had proximal fixed muscle weakness and that 37.5% of the McArdle people aged over 40 years old had muscle weakness.

There are many possible explanations for muscle weakness. It is not clear whether activity in younger life has an effect upon the development of muscle wasting and weakness. One possibility is that a sedentary/inactive lifestyle means that the muscles are not used, and become weak and waste away

An opposite possibility is that excessive exercise when younger could cause repeated damage, and that eventually the muscles become unable to repair themselves, leading to weakness and wastage. Voduc (2004) suggested that fixed muscle weakness could be caused by repeated muscle damage and loss of skeletal muscle fibres due to rhabdomyolysis.

Schotland *et al.* (1965) investigated muscle biopsies from two McArdle people, and suggested that glycogen accumulation may disrupt the structure of the muscle, and this could be one of the causes of permanent weakness that has been observed in the older people with McArdle disease.

Another possibility is that muscle weakness may be at least partially caused by damaged muscle being replaced as fat (De Kerviler *et al.*, 1996). Nadaj-Pakleza *et al.* (2009) carried out a scan which showed “fatty infiltration in the shoulder and pelvic girdle muscles”.

An alternative possibility is that a different gene (a phenotype modulator) may have an effect upon the strength of the muscle, and would explain why some (but not all) McArdle people develop weakness in older age. This gene may not have been identified. Phenotype modulators and other factors which affect the severity of McArdle's symptoms are discussed in section 9.

It should be remembered that muscle wastage and weakness with older age is not a specific symptom of McArdle's. Weakness and wastage in the muscles with age is common in the population unaffected by McArdle's.

8.2.5 Will I end up in a wheelchair?

The quick answer is no, most McArdle people do not need to use a wheelchair. “In McArdle disease, only a few patients were reported who were severely handicapped and complained of generalized pain with minimal exercise” (Rommel *et al.*, 2006).

McArdle people who use a wheelchair may have McArdle’s plus a second muscle disease (see section 9.6 on double trouble) or may not have McArdle’s (they may have been misdiagnosed and may actually have a different disease). They may also be people whose muscles have got very weak due to lack of exercise, and where exercise now results in severe muscle damage and weakness, so they are in a negative spiral of muscle weakness (anecdotal).

Some people who are unaffected by McArdle’s require the use of a wheelchair in old age or for other reasons. If a McArdle person requires the use of a wheelchair, it is likely to be for reasons unrelated to McArdle disease.

8.2.6 Does McArdle disease affect lifespan?

There is no published information on whether McArdle’s has any effect upon lifespan (how long you live). There are several published reports of elderly McArdle people, including a 76 year old McArdle man (Pourmand *et al.*, 1983), a 78 year old McArdle man (Perez *et al.*, 2006), and an 81 year old McArdle person (Lucia *et al.*, 2008a). The fact that there are many reports of elderly McArdle people suggests that McArdle’s does not have any effect upon lifespan.

Although in general McArdle disease does not appear to have any effect upon life expectancy, there are rare reports where people have died for reasons where McArdle disease may have been a factor. It has been reported that fatalities have occurred to McArdle people carrying out activities such as swimming or climbing, where muscle weakness has caused a fatal accident (source: http://www.specialisedservices.nhs.uk/library/23/Service_Specification___McArdles_Disease.pdf). There is also a press report of death where intensive exercise had led to acute kidney failure and cardiac failure (a heart attack) (source: http://www.leadertelegram.com/people/obituaries/article_3cf469d9-93a3-55ad-b0ad-5783477c2eb9.html). These reports highlight the importance of seeking medical attention if rhabdomyolysis (muscle damage) occurs, and of avoiding situations such as rock climbing or swimming where muscle weakness or fatigue could be dangerous.

9 Differences in severity of symptoms between people

The most obvious factor which might explain differences in the severity of symptoms is the amount of muscle glycogen phosphorylase which a person has. In general, the more functional muscle glycogen phosphorylase a person has, the better their ability to exercise. Unaffected people (who have normal levels of muscle glycogen phosphorylase) are able to exercise easily, carriers (who have approximately half the amount of muscle glycogen phosphorylase) are also able to exercise normally and do not have symptoms of McArdle disease. Very rarely, some McArdle people have a mutation which enables the enzyme to work a little. McArdle people with even a very low small amount of functional muscle glycogen phosphorylase were able to exercise more easily than typical McArdle people.

Almost all mutations in the *PYGM* gene result in a complete absence of functional muscle glycogen phosphorylase, so almost all McArdle people do not have any functional muscle glycogen phosphorylase. It would therefore be expected that all McArdle people would have similar symptoms. But this does not appear to be the case; some McArdle people report much more severe McArdle's symptoms than others.

Other proteins in the body, which are unrelated to muscle glycogen phosphorylase, may have an effect upon symptoms. For example, proteins which help the muscle cells take up glucose or produce energy more efficiently, could have an effect on the severity of McArdle's. How well these proteins work can vary from person to person. Interestingly, it has been found that some of these proteins have an effect on the severity of McArdle symptoms in women, but not in men.

McArdle symptoms can be more severe if the McArdle person has another muscle disease, or has a different disease which affects their ability to exercise or to get energy from food they eat. Carriers of McArdle disease do not usually have symptoms of McArdle disease, but in rare cases, a second disease which affects the muscles may result in the carrier having McArdle symptoms.

One study of McArdle women found that there were two different types of pain; pain caused by exercise, or constant chronic pain. Women who had pain caused by

exercise would cope by focussing on a completing a task; whereas for women with permanent pain, the pain had a greater impact on the daily life, work and social activity.

9.1 The amount of functional muscle glycogen phosphorylase is an important factor which determines the severity of symptoms

9.1.1 The amount of functional enzyme determines whether carriers of the *PYGM* mutation have symptoms of McArdle disease

McArdle carriers do not normally have symptoms of McArdle disease as they have some functional glycogen phosphorylase. Andersen *et al.* (2006) compared McArdle patients, carriers and unaffected people during exercise. Carriers had normal oxidative capacity and lactate responses which were identical to controls. They were therefore able to exercise normally and did not have symptoms of McArdle disease, an observation already reported by doctors treating McArdle people (Quinlivan and Vissing, 2007). (An exception where a carrier had McArdle's symptoms is discussed in section 9.7.) Carriers of the *PYGM* mutation have intermediate levels (approximately half the amount) of muscle glycogen phosphorylase enzyme activity compared to unaffected people. The amount of functional muscle glycogen phosphorylase in carriers has been reported as 25-45% (Bogusky *et al.*, 1986) and 30-45% (Manfredi *et al.*, 1993) that of unaffected people. It is likely that this amount of functional muscle glycogen phosphorylase is sufficient to enable carriers to exercise in a similar way to unaffected people.

9.1.2 Different mutations do not correlate to differences in severity of symptoms

The most obvious explanation for differences between McArdle people would be that different mutations in the *PYGM* gene could lead to differences in severity of symptoms. However, from a biochemical point of view, this idea does not work as most mutations result in a complete absence of functional muscle glycogen phosphorylase. (The exception is the small number of McArdle people who have a very low "residual" level of functional muscle glycogen phosphorylase. These are discussed further in section 9.1.4.) If differences in the mutation (the "genotype") had an effect upon the physical effect of those genes on the body (including severity of symptoms) (the "phenotype"), it could be described as a "genotype-phenotype" relationship. No clear genotype-phenotype relationship has been seen despite studies of large numbers of people with McArdle's (Martin *et al.*, 2001; DiMauro *et al.*, 2002; Deschauer *et al.*, 2007; Delmont *et al.*, 2008).

9.1.3 Rarely, some McArdle people have low levels of functional muscle glycogen phosphorylase

There have also been rare reports of McArdle people with functional muscle glycogen phosphorylase. One person had enzyme with 13% of normal activity, and three cases were 3% active compared to normal levels (Martinuzzi *et al.*, 1996). One person with 2% of functional muscle glycogen phosphorylase was described by Andersen *et al.* (2006). Delibas *et al.* (2008) and Delmont *et al.* (2008) each reported a McArdle person with just detectable functional muscle glycogen phosphorylase. Information about the mutations of these McArdle people with low levels of functional muscle glycogen phosphorylase would be very informative.

9.1.4 Even a very small amount of functional muscle glycogen phosphorylase improves the ability of McArdle people to exercise

Quinlivan and Vissing (2007) reported research by Haller that McArdle people with even a very low level of functional muscle glycogen phosphorylase (1-2.5%) had much higher "oxidative capacity" (were able to get more energy from food and able to exercise more easily). Vissing *et al.* (2009)

reported two McArdle people with unusually high exercise capacity. The two people had either R50X or G205S on one copy of the *PYGM* gene, and novel splice mutations in introns 3 [IVS3-26A>G (c.425-26A>G)] and 5 [IVS5-601G>A (c.856-601G>A)]. (For more information about different types of mutations see section 3.2.4.) It seems that these splice mutations allowed some functional muscle glycogen phosphorylase to be made in the muscles of these McArdle people, which allowed them to exercise more easily than typical McArdle people. These unusual McArdle people were able to reach a peak workload 2-fold higher than typical McArdle patients, and oxygen uptake was more normal. The authors claimed that this was the first published evidence of a relationship between the mutation and the ability of a McArdle person to exercise (called a genotype-phenotype relationship). This evidence suggests that even low levels of functional muscle glycogen phosphorylase can lead to an improved ability of the McArdle person to exercise.

9.2 Raised levels of cytokines may cause low-level inflammation in McArdle people

Cytokines are small proteins which are produced by almost all cells in the body. Cells use cytokines as a way to communicate either with neighbouring cells, or throughout the body (if the cytokines are carried in the blood). Chemokines are a sub-group of cytokines, and are also small proteins produced by cells. Some chemokines are used by cells to create an immune or inflammatory response. Cells can release chemokines during infection by bacteria or viruses, which attracts cells of the immune system to the location to fight the cause of the infection. (Information on cytokines and chemokines is summarised from Janeway, 2001).

Lucia *et al.* (2008b) studied the levels of many cytokines and chemokines in both McArdle people and in unaffected people before and after exercise. In McArdle people, Lucia *et al.* found raised levels of several cytokines; “tumor necrosis factor (TNF- α), interleukin (IL)-1ra, IL-10, IL-12 and IL-17”. They also found that McArdle people had a higher level of neutrophils. Neutrophils are cells which are part of the immune system. Neutrophils are some of the first cells which are attracted by the release of cytokines during infection. They also found that the amount of cytokine IL-6 (which the authors say has an anti-inflammatory effect), was increased in both McArdle people and unaffected people after exercise. The authors conclude that “Our results suggest that McArdle disease is associated with low-level systemic inflammation whereas appropriate exercise induces ... a significant increase in the anti-inflammatory *myokine* IL-6.” They suggest that this anti-inflammatory effect may explain why frequent moderate exercise has been shown to improve symptoms in McArdle people.

Several criticisms of the study conducted by Lucia *et al.* (2008b) may be made. These include the fact that they gave sucrose to the McArdle people but not to the unaffected control participants before exercise. This means that it is not possible to be sure that the differences in cytokine levels were due to McArdle’s rather than sucrose. For example, it may be that sucrose causes raised cytokine levels in people irrelevant of whether they have McArdle’s or not. Despite these criticisms, Lucia *et al.* found that the levels of many of the cytokines were higher in people with McArdle’s. This was a new discovery, and it would be ideal for it to be repeated and confirmed by other researchers.

The authors of this study suggested since exercise may cause muscle damage in McArdle people, the body might increase the amount of IL-6 in order to have an anti-inflammatory effect. I have an

alternative explanation (an unproven theory) why the amount of IL-6 may increase in McArdle people when exercising. There may be an association between the amount of glycogen in exercising muscle cells and IL-6 production. Exercise increases the amount of IL-6 in healthy athletes unaffected by McArdle's (Cannon *et al.*, 1999; Robson-Ansley *et al.*, 2007). IL-6 appears to be released into the blood by exercising muscles to stimulate the liver to break down stored glycogen and release energy via the bloodstream (Pedersen, 2001; Steensburg, 2001). Raised IL-6 levels in McArdle people reported by Lucia *et al.* may be due to the shortage of free glucose in the muscle cells. Pedersen (2001) described an increase in production of IL-6 by muscle cells due to lack of glycogen in unaffected people. However the same effect would occur in McArdle people as the glycogen can't be utilized and converted to glucose to provide energy. In McArdle people, IL-6 may be released by the muscle cells in an attempt to increase production of glucose by the liver.

Raised cytokine levels in McArdle people have several possible implications:

- 1) Many McArdle people are misdiagnosed with an inflammatory muscle disease such as polymyositis (which is often treated with steroids to reduce the inflammation) (section 2.5.1). If McArdle's is also an inflammatory muscle disease, it is easy to understand how this misdiagnosis could occur.
- 2) There appears to be a link between McArdle's and type II diabetes (characterised by insulin resistance). There is some evidence that the cytokine TNF- α (and possibly the cytokine IL-6) could lead to insulin resistance (see section 13.4.1.2).
- 3) Studies suggest that approximately a third of McArdle people experience anxiety or depression at some point in their lives (Rommel *et al.*, 2006; Quinlivan *et al.*, 2010). de Ridder *et al.* (2008) say that raised levels of some cytokines can produce feelings of fatigue, irritability, demoralisation, and may cause feelings of depression. It is possible that the feelings of depression experienced by McArdle people could be related to increased levels of some cytokines.

At present, none of these possible implications have been fully investigated or proven, so the implications are speculative.

9.3 Phenotype modulators (genes other than *PYGM*) may affect the severity of McArdle's symptoms

The combination of genes which a person has is known as a "genotype", the physical effect of those genes on the body (including severity of symptoms) is known as a "phenotype". A "phenotype modulator" is a second gene which affects the phenotype of the first gene. In a McArdle person, the first gene is the *PYGM* gene; being homozygous for mutations in the *PYGM* gene causes a person to have McArdle disease. It is possible that there are one or more secondary genes which have an effect upon how severe the McArdle's symptoms are. This second gene is not related to the *PYGM* gene. Depending what form of the second gene a McArdle person has, the severity of the symptoms could vary between McArdle people.

Phenotype modulators are a possible explanation for why different McArdle people can have different symptoms. Recent research has identified several genes which appear to be phenotype modulators. It is logical that proteins encoded by other genes, for example proteins which help the muscle cells take up glucose or produce energy more efficiently, could have an effect on the severity of McArdle's. Several researchers have looked at genes which may be phenotype modulators. Rubio *et al.* (2007), Rubio *et al.* (2008) and Martinuzzi *et al.* (2003) studied large numbers of McArdle people to try to find out which (if any) of these phenotype modulator genes could be having an effect upon the severity of McArdle's.

9.3.1 Angiotensin-converting enzyme

In skeletal muscle cells the angiotensin-converting enzyme (ACE) is involved in providing energy during exercise. The ACE enzyme is encoded by the *ACE* gene. There are two versions of the *ACE* gene, each of which have slightly different genetic sequences and produce a slightly different form of the ACE enzyme. The two versions are known as the "I" and the "D" form. Each person inherits two copies of the ACE gene, one from each parent. A person may inherit two copies of the D version of the ACE gene (DD), two copies of the I version of the ACE gene (II), or one copy of each version (DI).

In humans, the D version has the most ACE enzyme activity and the I version has the least activity. People unaffected by McArdle's who have the I version are thought to be able to take up more glucose from the bloodstream into muscle cells and seem to respond better to muscle training and aerobic conditioning. Scientists therefore suggested that McArdle people with the I version of the ACE enzyme might find it easier to exercise, and have fewer symptoms. Two studies have now found that McArdle people with two copies of the D version of the ACE enzyme have the most severe symptoms, McArdle people with one copy of the D version of the ACE enzyme have intermediate symptoms, and McArdle people with two copies of the I version of the ACE enzyme had less severe symptoms (Martinuzzi *et al.* 2003; Rubio *et al.* 2007).

These results led to a further study by Martinuzzi *et al.* in 2008 to test whether treatment with the ACE inhibitor Ramipril would improve McArdle's symptoms. A peptide (small protein) called "bradykinin" causes blood vessels to enlarge (dilate) and blood pressure to become lower. ACE enzyme is one of the enzymes which break down bradykinin. If an ACE inhibitor drug (such as Ramipril) is taken, less bradykinin will be destroyed, leading to an overall increase in bradykinin. This will have the effect of increasing the size of the blood vessels, which may allow more blood to be pumped to the muscles, bringing more glucose and fatty acids and oxygen to the muscle cells. When treated with Ramipril, a very small improvement in the ability to exercise was seen in McArdle people who had two copies of the D version of the ACE enzyme, but not people who had one copy of the D version and one copy of the I version of ACE.

9.3.2 Muscle adenosine monophosphate deaminase

In skeletal muscle cells, AMP deaminase is an enzyme which converts a molecule called adenosine monophosphate (AMP) to a molecule called inosine monophosphate (IMP) as part of a process called "purine catabolism" that produces energy within muscle cells. The AMP deaminase enzyme is encoded by the *AMPD1* gene. Adenosine monophosphate deaminase deficiency (AMDD) is caused by mutation in the *AMPD1* gene. Most cases of AMDD are caused by the premature termination codon mutation written as Q12X. In this mutation, a single mutation in the genetic code changes the

code from “c” to “t”; so that glycine amino acid is replaced by a premature termination codon. This results in the production of an abnormally short enzyme which cannot function. Mutations in *AMPD1* gene are very common, with MADD identified in approximately 2% of all muscle biopsy specimens tested by research labs (Gross, 1997). In many of these cases, people with the Q12X mutation are asymptomatic. Where people do have symptoms, the symptoms of MADD are muscle weakness, muscle pain and muscle cramps following exercise. MADD is usually inherited in an autosomal recessive way, where people only have symptoms of MADD if they have two copies of the *AMPD1* gene which both have mutations. People do not usually have symptoms of MADD if they are a carrier for the Q12X mutation. However, Rubio *et al.* (2008) wondered whether McArdle people might have more problems with exercise if they were carriers for the Q12X mutation rather than having two normal copies of the *AMPD1* gene (with no mutations in either copy of the *AMPD1* gene). They studied 44 Caucasian McArdle people (23 males, 21 females) who had two normal copies of the *AMPD1* gene or who were carriers for the Q12X mutation, and compared their ability to exercise using an ergometer test. No differences were seen in McArdle men, but in McArdle women, being a carrier for the Q12X mutation of the *AMPD1* gene was associated with reduced aerobic capacity.

9.3.3 Myostatin

Myostatin is a protein which helps to regulate and control skeletal muscle growth and may also affect muscle repair. Myostatin is also known as growth differentiation factor 8 and is encoded by the *GDF-8* gene. It may therefore have an effect upon the strength and ability of muscle to repair itself following damage. Normally, myostatin has a negative effect upon skeletal muscle growth. A mutation (like the K153R missense mutation) can stop myostatin being able to function. At present, the effect of the K153R mutation is not known, but one possibility is that having the mutation could enable an increased amount of muscle growth which could increase muscle strength. In women unaffected by McArdle's, those with the K153R mutation have lower muscle strength than those without the mutation. Gonzalez-Freire *et al.* (2009) found McArdle's women with the K153R mutation in the myostatin gene had worse McArdle's symptoms than McArdle's women who did not have the mutation.

9.3.4 α -actinin-3

α -actinin-3 is a protein which is the main component of skeletal muscle. It has a role in generating muscle contractions. α -actinin-3 is encoded by the *ACTN3* gene. The R577X mutation introduces a premature stop codon which results in an absence of α -actinin-3. In people unaffected by McArdle's, having the normal *ACTN3* gene may enable them to exercise for longer, and elite sportspeople often have two normal copies of the *ACTN3* gene, but studies are unclear, and having the R577X mutation does not appear to be a disadvantage for most of the population. Lucia *et al.* (2007a) found that McArdle's women with the R577X mutation were able to exercise better (when tested using a cycle ergometer) than those with a normal copy of the *ACTN3* gene, but the presence or absence of the mutation had no significant effect in McArdle's men. Rubio *et al.* (2007) also looked at whether mutations in *ACTN3* had any effect on severity of McArdle's symptoms. They did not find any effect, but did not separate the data for men and women.

9.3.5 Peroxisome proliferator-activated receptor γ coactivator 1 α

Peroxisome proliferator-activated receptor γ coactivator 1 α is a protein which is encoded by the *PPARGC1A* gene. Peroxisome proliferator-activated receptor γ coactivator 1 α is involved in regulating the expression/production of proteins involved in generating energy within the cell. As a missense mutation (G482S) had been shown to improve aerobic capacity in people unaffected by McArdle's, Rubio *et al.* (2007) looked at whether this gene might affect the severity of McArdle's symptoms. The results did not show that this gene had any effect on severity of McArdle's symptoms, but they did not separate the data for men and women.

9.4 There is a difference in the amount and type of pain felt by different McArdle people

Some McArdle people have constant and permanent chronic pain. Other McArdle people, only have exercise-induced pain, or occasionally experience muscle pain after exercise if some muscle damage has occurred. Rommel *et al.* (2006) studied 24 McArdle people. They asked many questions to determine whether McArdle people only had pain caused by exercise, or whether they had permanent pain. They found the majority of McArdle people who had permanent pain were women. 8 of the 24 McArdle people had permanent pain, and of these, 7 were women. There was only one man with permanent pain, so they used the women to compare those with permanent pain with those with exercise-induced pain. For the women with permanent pain, the pain had a greater impact on the daily life, work, and social activity. In contrast, where women principally had exercise-induced pain, their McArdle's symptoms had much less effect upon their daily life, work, and social activity. They found that those with permanent pain felt more fatigue, and tried harder to avoid pain. However, "differences regarding depression and pain-related help-hopelessness were not significant".

Differences in the type or level of pain felt were not related to which mutation was in the *PYGM* gene or which version of the *ACE* gene the McArdle people had (Rommel, 2006).

Rommel *et al.* (2006) found that women who had exercise-induced pain seemed to ignore the pain by endurance coping; making sure they finished projects they started, even if in pain, and not resting as often. They tried to ignore and play down any pain they experienced. On the other hand, women who had permanent pain seemed to feel that the pain was greater, and worry about it. They tried to avoid any activities which would cause pain. It is not obvious whether there was an original difference between the women who had exercise-induced pain or permanent pain, or whether the difference was due to differences in attitude and different methods of coping with pain. I inferred from the report that women who had exercise-induced pain found that it had less effect upon their lifestyle than those who had permanent pain. Women with permanent pain found that it had a greater effect upon their general activity, and caused sleep disturbance and fatigue. The authors suggest that regular moderate exercise may be a better way to cope with the symptoms of McArdle's than avoiding exercise. The authors do point out that this study was limited by the small number of participants (24 McArdle people), and a larger scale study would generate more useful information. The authors suggest that "Further studies should also address the question if these subgroups [people with permanent pain versus people with exercise-induced pain] respond differently to therapeutic strategies like glucose substitution, pain medication or regular moderate aerobic exercise".

9.5 Gender has an effect on phenotype modulators and the severity of McArdle's symptoms

Some studies suggest that McArdle women may experience more severe symptoms than McArdle men. "Among the middle-aged patients whom we studied, proximal muscle wasting, and weakness was more frequent in women than in men; in some cases, the severity was such that the patients had to use an electric toothbrush as they easily became fatigued when brushing their teeth manually. In addition, the few adult patients in whom respiratory muscles have been shown to be affected have all been women" (Lucia *et al.*, 2008a). As described above, Rommel *et al.* (2006) studied 24 McArdle people; 12 men and 12 women. They found that 8 of the 12 women had permanent pain, whereas only 1 of the 12 men had permanent pain.

As outlined above, researchers have found that in some cases the effects of phenotype modulators differ depending on gender. In McArdle's women (but not in men) a mutation in the myostatin gene led to an increase in the severity of symptoms (Gonzalez-Freire *et al.*, 2009). Lucia *et al.* (2007b) found that the R577X version of the *ACTN3* gene was associated with improved exercise capacity (using a cycle ergometer) in women with McArdle disease, compared to the R577R version of *ACTN3*, but had no significant effect in men. It is not clear why the effect of phenotype modulators could vary with gender, but they may provide a partial explanation for several studies which suggest that McArdle women may experience more severe symptoms than McArdle men.

9.6 McArdle symptoms may be more severe if combined with another disease

9.6.1 McArdle symptoms can be more severe if combined with another muscle disease, causing "double trouble"

Rarely, two muscle diseases may both occur in the same person causing "double trouble". Vladuitu *et al.* (2000) looked at nine McArdle people, and tested them for other muscle diseases (myopathies). Two of the McArdle people had a second muscle disease, one had a Q12X stop codon causing myoadenylate deaminase (AMPD) deficiency, and one had a S113L missense mutation causing carnitine palmitoyltransferase II (CPT II) deficiency. They suggested that the first muscle disease lowers the threshold for manifestation of the symptoms. Aguilera *et al.* (2001) reported a person with biochemical evidence of McArdle disease (heterozygous for R50X) and also with a mitochondrial DNA point mutation in the cytochrome c oxidase subunit I (*COI*) gene. Vockley *et al.* (2000) reported one person who was diagnosed with McArdle disease as they only had 0.04% functional muscle glycogen phosphorylase, and also was heterozygous for the S113L mutation in the *CPTII* gene. Lucia *et al.* (2007b) reported a 29 year old woman with McArdle disease and myasthenia gravis, for whom aerobic training significantly increased her exercise capacity.

The severity of symptoms will depend which two diseases the person has. There is a report of an infant girl born to consanguineous Moroccan parents, who died at 5 months of age. She had homozygous mutations in both the *PYGM* and the deoxyguanosine kinase (*dGK*) genes (Mancuso *et al.*, 2003) (see section 8.1.1). Pular *et al.* (2009) reported a man who started to have difficulty with exercise like walking upstairs from the age of 14. (He also had consanguineous parents.) His muscle weakness was much more severe than that usually seen in McArdle people, and he was subsequently diagnosed with both calpainopathy and McArdle disease. Calpainopathy is an

autosomal recessive limb girdle muscular dystrophy (LGMD2A) caused by mutations in the gene encoding calpain-3. Pular *et al.* (2009) said this “points to the need to search for other diseases in the presence of any unusual clinical manifestation.” (For example, further studies could be performed to see if a second disease is the explanation for a McArdle person with unusually severe symptoms.)

9.6.2 A second disease (which is not a muscle disease) may exacerbate the symptoms of McArdle disease

9.6.2.1 Bulimia and sickle cell anaemia can make McArdle symptoms worse

It has been reported that the eating disorder bulimia may exacerbate the symptoms of McArdle disease. Pillarisetti and Ahmed (2007) described a McArdle person who had both bulimia and sickle cell trait (by sickle cell trait the authors meant that the person was a carrier for sickle cell anaemia). The authors said that bulimia could cause electrolyte changes in the body like hypokalemia and hypophosphatemia which could make rhabdomyolysis more likely. The authors also say that both sickle cell trait and bulimia are known to make people (unaffected by McArdle's) more likely to have rhabdomyolysis.

9.6.2.2 Epileptic seizures can make McArdle symptoms worse

An example of a second disease making McArdle symptoms worse was presented by Ford *et al.* (1973) who describe a male McArdle person who also had epilepsy. Epileptic seizures caused the muscles to cramp up, spasm, and produced rhabdomyolysis. Salmon and Turner (1965) also reported a McArdle's boy aged 16 who was diagnosed with McArdle's after a grand mal epilepsy convulsion led to rhabdomyolysis.

9.7 A second disease may make carriers of McArdle disease more likely to have symptoms of McArdle disease

Carriers do not usually have symptoms of McArdle disease (Quinlivan and Vissing, 2007 and many other publications). If a person is a carrier for two similar diseases which affect energy metabolism, they may (uncharacteristically) have symptoms of one or both diseases. Vockley *et al.* (2000) described this as “synergistic heterozygosity”. They reported one person who was a carrier for McArdle disease (29% of normal amount of muscle glycogen phosphorylase), phosphorylase b kinase deficiency (a subdivision of GSD VI) (37% of normal) and CPT II deficiency (50% of normal; a carrier for Q12X mutation in *AMPD1*). This research suggests that a second disease may explain why symptoms are occasionally seen in carriers of McArdle disease.

Papadimitriou *et al.* (1990) described a man who developed McArdle's symptoms at the age of 30 years. His muscle weakness then increased as he got older. At the age of 40 he had myoglobinuria twice after heavy muscle exercise, but did not have cramps/contractures. When he performed a forearm ischaemic test, a rise in lactate was seen (which suggested a diagnosis of “It is not McArdle's”). However, he had increased creatine kinase levels (his CK level was 1040 IU, when the normal in this case would have been 20-93 IU). It was found that he was a carrier of McArdle disease, and had 25% functional glycogen phosphorylase. Possible explanations for why this man did develop symptoms of McArdle's could be because he had had a very physical lifestyle as a younger man (including time in the army). Alternatively, it may be that he had a second

(undiagnosed) muscle disease which led to muscle degeneration as he got older and triggered McArdle symptoms. The authors did not say if they had tried to rule out other similar diseases.

Recommend reading:

“Muscle pain in myophosphorylase deficiency (McArdle disease): The role of gender, genotype, and pain-related coping” by Oliver Romme, Rudolf A. Kley, Gabriele Dekomien, Jörg T. Epplen, Matthias Vorgerd and Monika Hasenbring

10 Mental and emotional aspects of McArdle disease

There is no published information on the psychological effect of McArdle's. McArdle's children may find that their parents and teachers don't believe that exercise can cause them to feel muscle pain. Adults may be told by family doctors that they are imagining the symptoms, are malingerers, or that symptoms are due to being overweight. Many McArdle people spend many years visiting family doctors and specialists before obtaining a correct diagnosis.

For many people, receiving a diagnosis of McArdle disease is positive because it proves that the symptoms are caused by a known disease, and enables them to begin to find out more about advice and treatments for McArdle disease. However, some people may feel depressed about having a condition which will affect them for life. There are many ways to deal with these emotions, including talking to friends, family members or the family doctor. The way in which McArdle people perceive their McArdle's symptoms can have an effect upon how difficult they find it to cope with symptoms on a day to day basis.

However, symptoms are not necessarily just emotional. One study suggested some McArdle people may suffer from symptoms similar to chronic fatigue. There is also a small amount of evidence that McArdle people may perform less well than people unaffected by McArdle's at some tests of how well the brain can perform. There is only a very limited amount of research into these factors and much more is needed.

Since McArdle people don't use a wheelchair or walking stick, they may occasionally have to deal with negative comments from members of the public who don't understand why they need to park in a disabled space or walk slowly. Even with friends and family, many McArdle's adults use coping mechanisms to allow themselves to rest without other people noticing. These techniques could include frequently pretending to tie up their shoelace, stopping to look in shop windows, or pretending to use a mobile phone.

Many McArdle people gain benefit from visiting a specialist who is knowledgeable about McArdle disease and can provide up to date information of the latest theories and treatments. McArdle people may find it helpful to meet each other at the annual AGSD-UK conferences. There are several online chat groups which allow

McArdle people to meet other people with McArdle's, which is especially valuable as the disease is rare. However, it is important to consult a McArdle specialist or your family doctor before following any recommendations or suggestions made on online chat groups.

10.1 Many McArdle people have symptoms which are like chronic fatigue syndrome

Almost half (40%; 18 of 45) of the McArdle people attending the UK McArdle Clinic reported chronic fatigue-like symptoms (Quinlivan *et al.*, 2010). Quinlivan *et al.* (2007) suggest that the fact that it often takes McArdle people many years to get a diagnosis could be a reason why many people have symptoms of chronic fatigue, depression, and anxiety. It is an understandable reaction to many years of wondering “What is wrong with me?” Chronic fatigue syndrome (CFS) causes long-term tiredness (fatigue) that affects everyday life. It does not go away with sleep or rest. CFS is also known as ME, which stands for myalgic encephalomyelitis. Myalgia means muscle pain, and encephalomyelitis means inflammation of the brain and spinal cord.

The causes of chronic fatigue-like symptoms in McArdle people may not be the same as in people unaffected by McArdle’s, and some treatments may therefore not be suitable. One treatment, called “pacing” is a way to even out how much activity a person does each day. This avoids having alternating good and bad days; a “good” day where the person feels good and does a lot of activity, but is then so tired that the next day is a “bad” day where they have to spend the whole day resting. Pacing is a technique to reduce the amount of activity done on a “good” day so that they are less tired the next day and therefore avoid having a “bad” day. It may be the case that for McArdle people who do have chronic fatigue-like symptoms, treatments such as pacing may help them cope with those symptoms better, and improve their overall quality of life. It is important to remember that the causes of chronic fatigue-like symptoms in McArdle people may not be the same as in people unaffected by McArdle’s, and that some treatments may therefore not be suitable. There is no published research that any treatments for chronic fatigue have been tried on McArdle people.

10.2 Lack of muscle glycogen phosphorylase may affect brain function of McArdle people

Edelstyn and Quinlivan (2007) described a pilot study of neuropsychological performance (brain function) in people with McArdle disease. Ten McArdle people were compared to ten unaffected people, and were found to perform significantly worse on tests of verbal fluency and verbal memory and less well than unaffected people in some other cognitive tests. This suggests that the lack of muscle glycogen phosphorylase may also be detrimental to brain function in McArdle people. There are several possible explanations for this.

In people unaffected by McArdle disease, the brain has been shown to contain muscle glycogen phosphorylase, brain glycogen phosphorylase and a dimer (pair) made of the brain and the muscle form. In unaffected human brain, muscle glycogen phosphorylase was found to provide 25% of the total amount of functional glycogen phosphorylase (Bresolin *et al.*, 1983). In McArdle people, muscle glycogen phosphorylase is absent in the brain, so this may reduce the total amount of glycogen phosphorylase in the brain. The brain consumes about 60% of the glucose used by the whole body when resting (Berg *et al.*, 2008). The lack of functional muscle glycogen phosphorylase may affect brain function in McArdle people directly by reducing the amount of glucose available to the brain.

80% of the vitamin B6 in the body is associated with muscle glycogen phosphorylase (Beynon *et al.*, 1995). Pyridoxal-5'-phosphate (PLP) is the metabolically active form of vitamin B6. Many reactions

in amino acid metabolism require the presence of PLP, such as decarboxylases which are required in the synthesis of neurotransmitters. An adequate PLP supply in brain tissue is therefore essential for normal brain function (Williams, 2003). If muscle glycogen phosphorylase is absent, this may decrease the amount of PLP available both in the brain and throughout the body (Beynon *et al.*, 1995).

It has been shown that muscle and brain glycogen phosphorylase can bind together (reviewed in Wright, 2009). If a small number of McArdle people have muscle glycogen phosphorylase which is present but not functional, this non-functional muscle glycogen phosphorylase could bind to brain glycogen phosphorylase, stopping it from functioning.

An excessive accumulation of glycogen in the brain may be detrimental. Edelstyn and Quinlivan (2007) mention a report of a McArdle person with abnormal deposition of glycogen detected by brain MRS. They also suggest that the abnormal rise in ammonia that occurs throughout the body in McArdle people during exercise may cause abnormal psychological function.

It should be noted that there has only been one study of psychological function to date (by Edelstyn and Quinlivan), and further studies are needed to confirm the results.

10.3 Psychological issues

There is no published information on the psychological effect of McArdle's. Anecdotally, McArdle people report childhood trauma, everyday embarrassment, depression, fear and in some cases possibly even hysteria or a hyper-awareness (hypochondria). These experiences are likely to be similar to those experienced by other people with rare diseases. Except where a reference is given, the information in this section is anecdotal.

10.3.1 Before diagnosis

10.3.1.1 Psychology of being an undiagnosed McArdle's

Most McArdle people were not diagnosed until adulthood, and therefore spent their childhood struggling to run and exercise, but unsure that there was a definite problem (such as McArdle's). Some McArdle's children found that their parents did not believe them when they said that exercise caused them pain. They may have suffered from teasing or bullying because they were unable to run around in play or during exercise and sports classes at school.

10.3.1.2 A rapid diagnosis in childhood is ideal

A person who gets a rapid diagnosis, ideally in childhood, is probably likely to have fewer psychological problems. An early diagnosis should allow the child to grow up following current recommendations (such as frequent moderate exercise) but avoiding intense exercise which is likely to lead to muscle damage. An early diagnosis would allow the parents to inform physical education/gym teachers to ensure that the McArdle's child is not pushed to exercise beyond their limits. An early diagnosis would allow the child to inform friends and family of their limitations, and hopefully feel unembarrassed about stopping and resting when necessary.

10.3.1.3 Psychology of being an undiagnosed McArdle's adult

A McArdle's adult who has not yet been correctly diagnosed may find that their family doctor doesn't believe that the symptoms are real, and dismisses them as a hypochondriac or malingeringer. A McArdle's adult may also find that family and friends also don't believe that the symptoms are real. They may find this very depressing and frustrating, as they know that there is something wrong, but it has not been correctly diagnosed. Family and friends may not be very sympathetic, since they have no proof that anything is wrong. An undiagnosed McArdle's adult may feel angry that family/friends/family doctor doesn't believe that they have a problem. Prior to being diagnosed, McArdle people may feel isolated because no-one else has similar symptoms.

10.3.2 Trying to get a diagnosis

10.3.2.1 It can take a long time for McArdle people to get a correct diagnosis

Many McArdle people spend many years seeking diagnosis before obtaining a correct diagnosis. They often have to see many different family doctors and specialists. Based upon a study of 45 McArdle patients visiting the UK McArdle Clinic, Quinlivan *et al.* (2010) reported that 84% had McArdle symptoms from the age of 10 years old or younger, but about half (49%) were not diagnosed until they were more than 30 years old. This suggests that it can take around 10-20 years for McArdle people to receive a correct diagnosis. Many McArdle people have been misdiagnosed, and some will have received treatments for this incorrect diagnosis. Some examples of these diseases are given in section 2.5.1.

10.3.2.2 Many family doctors may incorrectly imagine that a McArdle person is a hypochondriac, malingeringer or that symptoms are due to being overweight

McArdle's is a real condition, with a physical cause (the lack of muscle glycogen phosphorylase). Much is known about the cause of McArdle's, the way in which it affects the body, and current treatments (these are subjects covered in this Handbook). However, family doctors who have not heard of McArdle disease may dismiss a person with McArdle's as having hypochondria or being a malingeringer. Hypochondria is a mental disorder where people believe that they have a medical illness even though family doctors are unable to find anything wrong. In some cases the physical symptoms can be caused by the person thinking that they have the illness. People with hyperchondria may visit the family doctor frequently, and may have a high level of worry about their symptoms. People with hypochondria genuinely believe that they have an illness, even though family doctors are unable to find anything wrong. It is possible to understand how a family doctor can (incorrectly) imagine that a McArdle person who comes to see them frequently saying that something is wrong, but who is able to walk around and appears to be physically well could have hypochondria. A person who is a malingeringer knows that they do not have an illness, but pretends to have symptoms in order to avoid work or for financial reasons (e.g. to get disability benefit) or for another purpose (such as getting sympathy from family members).

Many family doctors have not heard of McArdle's, and don't recognise the symptoms. Many McArdle people are overweight (discussed in more details in section 4.2.3), and it is understandable that when a family doctor is presented with a patient who is overweight, struggles to exercise, and has muscle pains, then the family doctor may (incorrectly) imagine these symptoms are all caused by the person being overweight, and recommend more exercise.

10.3.3 After diagnosis

10.3.3.1 Receiving a diagnosis of McArdle's

Many people will feel relief at finally getting a diagnosis of McArdle's, especially if it has taken a long time to obtain that diagnosis. McArdle people may feel vindicated because a diagnosis will prove to family/friends/your family doctor that the problem is real not imagined. A diagnosis allows you to begin reading about McArdle's online and elsewhere and to find out more about treatments. It also allows you to make contact with other McArdle people via chat groups or e-mail groups who can provide support.

10.3.3.2 Coping with a diagnosis of a chronic illness

Although many McArdle people will feel relief at having finally got a diagnosis, diagnosis of a chronic illness may also pose challenges. The information which follows is not specific to McArdle disease, but is general information about how to cope with a diagnosis of a chronic illness. de Ridder *et al.* (2008) define "chronic illnesses" as "disorders that persist for an extended period and affect a person's ability to function normally". Interestingly, de Ridder *et al.* say that it is estimated that half the population (50% of people) have a chronic physical condition which requires medical treatment. Examples of chronic illnesses include diabetes, which can be controlled with medication, or rheumatoid arthritis, which can cause physical disability and pain. Chronic illnesses can change the person's life in many ways; for example by limiting the amount of activity they can do.

Quinlivan *et al.* (2010) found that 31% (14 of 45) of McArdle people "had been treated at some time for anxiety and/or depression", and Rommel *et al.* (2006) reported that 29% (7 of 24) of McArdle people had experienced mild depression. de Ridder *et al.* (2008) note that people with "chronic illness typically have anxiety, depression, and other negative emotions". Emotional reactions to chronic illness can basically be divided into two groups; one is avoidance and suppression of emotions and the other is expression and acknowledgement of emotions. Despite the common belief that it is better to express emotions, the authors note that this is only the case in more expressive cultures such as North American and Western European cultures. The authors note that non-expression of emotions is better for people who live in less emotionally expressive cultures such as some Asian cultures. de Ridder *et al.* reviewed many studies and found that emotional expression led to improvements in the amount of physical activity people could do, mobility, and in the number of symptoms reported, and even produced positive changes in the body which could be measured by laboratory tests (suggesting it was a physical improvement, not just a change in the person's perception of the situation). It may be that discussing the emotions and feelings associated with being diagnosed with a chronic illness may help people to feel more comfortable with the diagnosis. People who do not discuss their feelings and "bottle them up" may feel more stressed. Stress is known to have negative effects upon health. Another benefit of discussing feelings and emotions may be that it leads to feelings of closeness with either the friend/relative or health professional who you talk to.

The challenge is how to learn to adapt life to work around McArdle's. de Ridder *et al.* note that many people with chronic diseases also have an increase of some cytokines (the cytokine IL-6 is discussed further in section 9.2). It has been shown that some cytokines can produce feelings of fatigue, irritability, demoralisation, and may cause feelings of depression. In this case, the cytokines are producing real changes in the feelings and emotions. Drugs which block the effect of these

cytokines have been tested in people with rheumatoid arthritis and have helped to improve the way those people felt. At present, it is not known if cytokines in McArdle people may have this effect, or whether drug treatments would help.

Humans have a natural response to illness which is to rest, as this “conserves energy and promotes healing” (de Ridder *et al.*, 2008). However, this response is not always of use to the person, and is in contrast to the moderate exercise now recommended for McArdle people (see section 4.2). Some people diagnosed with chronic illness find it hard to follow a new diet, exercise or other advice. This is most likely if people feel that a large amount of time and effort is needed to follow this advice and/or it may not produce much benefit. Some people may suffer from major depression, whereas other people may have guilt or anxiety about not following “the ideal diet” or “the ideal exercise programme”, or worry about the negative effects of the disease; such as worries about muscle wasting in older age. The authors also noted that having a positive mood can help people manage their condition better and improve wellbeing.

de Ridder *et al.* (2008) describe a person who has successfully adjusted to a chronic illness as having successfully adapted to the new situation; learning to work around the disability, staying emotionally balanced, and maintaining healthy relationships with friends and family. Not suffering from psychological disorders, not letting the disability have a negative effect on their life, and being able to do tasks, such as a job, which they want to do. A person who has successfully adjusted to a chronic illness will be able to feel satisfied and happy with their life.

10.3.3.3 Psychology of how other people perceive a McArdle’s adult

There are several issues which have been mentioned to me by McArdle’s adults. One problem is that you look completely “normal”. Since McArdle’s does not mean that you have to use a wheelchair or a walking stick, the general population may not realise that you struggle to walk long distances. Some McArdle people may feel embarrassed if they need to stop and rest during exercise, for example, during an exercise class, or while out for a walk with friends. Unless the class teacher or your friends knows about McArdle’s, it can be embarrassing to be the one person who needs to stop and rest. In particular, I would imagine that it is hardest being a young person or a young man, as these would be perceived by others as being fit and able to exercise easily. Some McArdle’s adults, who use disabled parking spaces, or lifts rather than stairs, have been accused of using them inappropriately by other people. McArdle people may also feel annoyed/depressed/frustrated that friends, family and work colleagues may have to help you out.

Many McArdle’s adults use coping mechanisms to allow themselves to rest without other people noticing. These techniques could include frequently pretending to tie up their shoelace, stopping to look in shop windows, or pretending to use a mobile phone.

10.3.4 Positive steps to dealing with these issues

Many McArdle people find that visiting a specialist (such as Dr Quinlivan at the UK McArdle clinic) can have a huge benefit. Unlike a family doctor, who may never have met a person with McArdle’s before, a specialist will have met many people with McArdle’s. The specialist will understand McArdle’s much better, and will know what is normal or unusual for people with McArdle’s. They are also likely to be involved in research and clinical trials and will keep up to date on the latest theories and treatments.

Many McArdle people gain huge benefit from being in contact with other people with McArdle's. E-mail chat groups (such as GSDnet) and web-based chat groups (such the McArdle Disease Facebook group) allow people with McArdle's to compare notes and share hints and tips. There can be differences in the advice given by McArdle's specialists, and this can be a way for McArdle people to tell each other about this advice. This is also a good way to find out if and when new treatment ideas are developed.

10.3.5 Websites and internet resources for people interested in McArdle disease

Several website and an e-mail chat group are listed below which offer the opportunity to chat online with other McArdle people (Table 10.1). However, it is important to remember that many of the people expressing views and opinions on these sites are not expert. It is also possible that some of them have a different disease and have been misdiagnosed with McArdle's or not received a proper diagnosis. It is therefore important to consult a McArdle specialist or your family doctor before following any recommendations or suggestions made on online chat groups.

Organisation	Type of organisation	Website address
AGSD-UK	Charity	http://www.agsd.org.uk/
AGSD (USA)	Charity	http://www.agsdus.org/
Facebook	Patient chat group	http://www.facebook.com/group.php?gid=2646925066
Muscular Dystrophy Campaign (MDC)	Charity	http://www.muscular-dystrophy.org/
Personal website	Web site and patient chat group	http://mcardlesdisease.org
NORD Rare disease community	Patient chat group (although this is not used much by McArdle people)	http://www.inspire.com/groups/rare-disease/discussion/glycogen-storage-disease-v-mcardles-disease/
GSDnet	E-mail chat group for people with glycogen storage diseases, including McArdle's	http://www.agsd.org.uk/Communications/GSDNet/tabid/1017/Default.aspx
Pubmed	Scientific resource. Search engine for medical and scientific publications. Can be searched using paper title, author and date.	http://www.ncbi.nlm.nih.gov/pubmed
Google scholar	Google resource. Search engine for medical and scientific publications. Can be searched using paper title, author and date.	http://scholar.google.co.uk/schhp?hl=en&tab=ws
Google books	Google resource. Search engine for published books. Can be searched using book title, author and date or topic. For some books a whole or partial online freeview is available.	http://books.google.co.uk/bkshp?hl=en&tab=sp

Table 10.1 Useful websites for McArdle people. No responsibility is taken for the accuracy of the information provided on these websites.

Online resources:

There is further information on chronic fatigue and ME on the following website. (It is important to remember that the causes of chronic fatigue-like symptoms in McArdle people may not be the same as in people unaffected by McArdle's, and that some treatments may therefore not be suitable.):

<http://www.nhs.uk/me/introduction.asp>

11 The effect of McArdle's on sexual activity, pregnancy and birth

Sexual activity usually involves movement and exercise. Very few publications mention this topic, but it has been reported that sexual activity can lead to muscle cramps for McArdle men and women. There is very little published advice, but one suggestion is to have a sugary drink prior to planned exercise (such as sexual activity). The most relevant expert for these issues would be a sexual therapist with an interest in helping people who have limited mobility.

McArdle's women anecdotally report a worsening of symptoms a week or two before menstruation (having a period). There have not been any studies to verify this suggestion or to provide any explanations for this.

There is no published information on whether McArdle disease has any effect upon fertility, but it seems likely that McArdle disease does not affect the fertility of men or women with McArdle's, so appropriate contraception should be used if pregnancy is not desired.

McArdle disease does not appear to increase the risk of complications for women during pregnancy or for giving birth. Most McArdle women are able to have a vaginal birth. A small number of McArdle women have caesarean delivery, but this is similar to the numbers of women unaffected by McArdle's who have caesarean delivery. Anecdotally, some McArdle's women say that they have fewer McArdle's symptoms when they are pregnant, but there is no published data to confirm this.

At present, no tests are available to screen an unborn or newborn child to diagnose whether they will have McArdle disease. A genetic counsellor can provide you with information about the chances of a child inheriting McArdle disease.

11.1 Sexual activity

Sexual activity usually involves exercise; this may be static (using your muscles to hold yourself in one position for a long time, like yoga), or repetitive movements for a long time, or fast movements. It is obvious that McArdle's is likely to have an effect upon the ability of McArdle people to do these activities. Unfortunately there is hardly any published information on the effect of McArdle disease on sexual activity and intimate relationships. Hockaday *et al.* (1964) reported the case of a 51 year old McArdle man who found that symptoms of muscle pain in the legs were worse if he had had "sexual intercourse the previous night". Quinlivan *et al.* (2010) said that McArdle men and McArdle women reported muscle cramps, with or without myoglobinuria, occurring as a consequence of sexual intercourse. The lack of published information is likely to be due to several reasons; because it can be hard to quantify, because McArdle people may be embarrassed to mention it to their family doctors, and because the doctors who diagnose and treat McArdle people tend to be neurologists and muscle specialists, and therefore do not have any expertise (and possibly no interest) in sexual issues. The most relevant expert for these issues would be a sexual therapist with an interest in helping people who have limited mobility.

In the absence of any published advice, here are some approaches I would suggest:

- Find and apply advice for people who have limited mobility (for example, advice for people who have arthritis), bearing in mind what you know about McArdle disease, and avoiding movements or positions which cause pain or are likely to lead to muscle damage or contracture.
- Use the latest advice regarding exercise. Warm up and get into a second wind if possible. The only published piece of advice relating to McArdle disease and sexual intercourse which I have been able to find is a suggestion to have a sugary drink just prior to sexual intercourse; "This [having a sucrose drink] might be a useful therapy prior to planned vigorous exercise, such as sexual intercourse" (Quinlivan and Vissing, 2007).
- Communication. Be willing to communicate what you want, what works, what doesn't work, what you enjoy or don't enjoy, being prepared to stop or change positions if your muscles begin to hurt.
- Consider using pillows or other accessories to reduce the need to use your muscles to hold you in a certain position.

11.2 The menstrual cycle and its effect upon exercise and perception of pain for McArdle's women

There is no published information on the effect of female hormones or the female menstrual cycle on McArdle's symptoms. It has anecdotally been reported by women with McArdle's that they experience a worsening of McArdle's symptoms a week or two before menstruation (having a period). Possible explanations for this anecdotal observation could include:

- The menstrual cycle could physically affect the ability of McArdle's women to exercise.

- The menstrual cycle could physically or mentally affect the perception of pain by McArdle's women.
- The menstrual cycle could mentally affect how distressing women find McArdle's symptoms.

There is no information available on these topics regarding women with McArdle's, but some research on similar topics on women unaffected by McArdle's is discussed below.

The menstrual cycle can be broken down into two parts; the time between the start of menstrual bleeding (the period) and ovulation (which is called the follicular phase), and the time between ovulation and the start of menstrual bleeding (called the luteal phase).

11.2.1 Does the menstrual cycle affect the ability of women unaffected by McArdle's to exercise

There have been many investigations into whether the menstrual cycle affects the ability of women to exercise. In particular, studies have focussed on the effect of menstrual cycle on the performance of female athletes. According to Janse de Jonge (2003), "current literature indicates that $VO_2\max$ is not affected by the menstrual cycle" (see 6.4.4.1 for further discussion of $VO_2\max$), which suggests that performance of female athletes is not affected by the menstrual cycle. However, the authors mention that some studies suggest that women unaffected by McArdle's may have "higher cardiovascular strain during moderate exercise in the mid-luteal phase". They noted that women athletes are able to exercise for a shorter time before becoming exhausted "during the mid-luteal phase, when body temperature is elevated." This may mean that McArdle's women may find exercise slightly harder during the mid-luteal phase, especially in hot conditions.

11.2.2 Studies on the perception of pain in women unaffected by McArdle's

Riley *et al.* (1999) reviewed 16 studies where women unaffected by McArdle's, who were healthy and had no conditions which caused pain, were tested to see whether their experience of pain varied at different times in their menstrual cycle. They found that the women experienced least pain from pressure stimulation, cold, heat, and ischemic muscle pain, during the follicular phase than at other points in the menstrual cycle. The authors of the review note that the research was not perfect as different stimuli were used to produce pain in different studies (stimuli included pressure, heat or cold). Other problems with the research are that only small numbers of women were studied, and the researchers may have struggled to define exactly which part of the menstrual cycle the women were in.

Pfleeger *et al.* (1997) carried out a study with 11 women unaffected by McArdle's, who performed an ischaemic forearm test. The women were asked to say when the pain from their forearm became too great for them to continue exercising. Their blood pressure and their pain levels from the forearm test were monitored at different times during the menstrual cycle, and it was found that the level of pain experienced and the blood pressure were both highest during the luteal phase. However, it should be noted that Hoeger Bement (2009) found the opposite results; that when women were asked to carry out a forearm test, their perception of pain was not affected by which stage of the menstrual cycle they were in. Clearly more research is required!

11.2.3 The emotional changes associated with the menstrual cycle may make McArdle's women consider their symptoms to be worse at certain points

It is possible that hormone changes during the menstrual cycle will affect how women perceive their symptoms. Women who are unaffected by McArdle's often report emotional changes during their menstrual cycle. The most dramatic of these occur just prior to the menstrual bleed/period, and are known as "premenstrual syndrome or tension (PMS/PMT)". It has been suggested that all women experience some PMS symptoms, which can vary from woman to woman. Since symptoms of PMS include a depressed mood, crying, and tearfulness, and anxiety, my theory is a woman with PMS may perceive her McArdle's symptoms as being worse than usual - although the difference may be in her frame of mind rather than the symptoms.

It has been reported that symptoms of chronic illnesses can be worse when women are experiencing PMS symptoms. Examples of physical illnesses which are known to become worse for a woman when she is premenstrual include migraine (Dzoljic *et al.*, 2002), epilepsy (Hussain *et al.*, 2007), asthma (Pereira Vega *et al.*, 2010), irritable bowel syndrome (Houghton *et al.*, 2002), rheumatoid arthritis and diabetes (Case and Reid, 1998). There does not seem to be any information published about whether symptoms of muscle diseases become worse during the menstrual cycle, which is probably because no research has been done into this topic.

11.3 Fertility and contraception

There is no published information on whether McArdle disease has any effect upon fertility, but it seems likely that McArdle disease does not affect the fertility of men or women with McArdle's, so appropriate contraception should be used if pregnancy is not desired. Unfortunately the promising sounding paper "Contraception and pregnancy in women affected by glycogen storage diseases" (Mairovitz *et al.*, 2002) is focussed on GSD I and the information is not relevant to McArdle's.

As discussed in section 14.2.2, it would be worthwhile discussing any medication or contraceptive method with your family doctor whilst also considering McArdle's. For example, you would want to discuss whether there could be any side effects, such as an increased risk of rhabdomyolysis, which might make some methods less suitable for a McArdle person.

11.3.1 Prenatal testing for McArdle's and infant screening

An absence of published reports suggests that prenatal testing is not currently available during pregnancy to determine whether an unborn baby will have McArdle disease. Theoretically it would be possible to obtain a DNA sample from cells obtained by chorionic villus sampling or amniocentesis. Milunky *et al.* (2010) say that although testing for the mutations which cause McArdle's is theoretically possible, "there are no reports in the literature that they have been done".

Prenatal testing may not be currently available partly due to the rarity of McArdle's. Also, the development of prenatal tests tends to be prioritized for diseases which are fatal or highly debilitating. As McArdle's symptoms are not as severe as many other muscle diseases (for example, Spinal muscular atrophy or Duchenne muscular dystrophy), it may be a lower priority. As McArdle's is recessive, unless one or both parents have McArdle's, there is often not a family history of McArdle's, and therefore no clue that prenatal testing should/could be considered.

Infant screening for McArdle's (e.g. by a heel prick or blood test from a newborn baby), is also not currently available. It is likely to be for similar reasons as those given above; because McArdle's is relatively rare, not as severe as some other diseases, and also because the advantage of having a diagnosis must be weighed against the cost of screening many newborns who would not have McArdle's.

Information about the chances of passing on McArdle's to your children should be discussed with a genetic counselor, but a scientific explanation of the inheritance of McArdle's is given in section 3.

11.4 Pregnancy and birth

McArdle disease does not appear to increase the risk of complications for McArdle women during pregnancy or for giving birth (Quinlivan *et al.*, 2010).

11.4.1 Some McArdle's women report having fewer McArdle's symptoms during pregnancy

Anecdotally, some McArdle's women say that they have fewer McArdle's symptoms when they are pregnant. There is no published data to confirm these anecdotal observations or to explain them. Possible explanations for these anecdotal observations include:

- Could a foetus (unborn baby) supply a McArdle's mother with the enzyme she is lacking?
- Do the pregnancy hormones increase the level of glucose in the bloodstream of the McArdle's mother, reducing symptoms?

Both these possibilities are discussed below.

11.4.1.1 *Could a foetus (unborn baby) supply a McArdle's mother with the enzyme she is lacking?*

The explanation for this theory is that in the foetus, the whole body is provided with energy by foetal glycogen phosphorylase (this has the alternative name of brain glycogen phosphorylase). The theory is that some of the foetal glycogen phosphorylase may be carried from the foetus in the bloodstream, and transferred across the placenta, into the mother's blood. It would then be carried to the mother's muscles, and be taken into the muscle cells. It could then function in the muscle cells to replace the missing muscle glycogen phosphorylase, so that the mother will no longer have symptoms of McArdle's.

I do not agree with this theory. It seems unlikely that the foetal glycogen phosphorylase could get out of the foetus into the blood and then into the skeletal muscles. If this was the case, it would be a form of enzyme replacement therapy. However, as described in section 16.3.2, enzyme replacement therapy is not a suitable treatment for McArdle's as the enzyme is taken up into the lysosome (the wrong location) not the cytoplasm (the location where glycogen phosphorylase is needed). In an McArdle adult who is not pregnant, the brain isoform does not leak out of the heart or smooth muscle (such as the smooth muscle of the digestive tract) and into skeletal muscle and "cure" McArdle's. This suggests that the foetal enzyme probably can't leak out of the foetus and into the skeletal muscle.

Walker (2006) carried out research into sheep and lambs with McArdle's or unaffected by McArdle's. The gestation of a lamb is approximately 150 days. Research by Walker suggests that foetal glycogen phosphorylase can be detected in a sheep foetus from the age of 40 days after conception (the earliest time period tested by Walker), and that foetal glycogen phosphorylase is the main isoform until 50 days after conception, when muscle glycogen phosphorylase begins to take over and become the main isoform in sheep muscles. It is likely that a similar situation occurs in humans.

11.4.1.2 Do the pregnancy hormones increase the level of glucose in the bloodstream of the McArdle's mother, reducing symptoms?

I suggest an alternative theory; that being pregnant raises the level of glucose in the blood (causing hyperglycemia), which would produce a similar effect to drinking a sugary drink, and would help pregnant McArdle's women exercise more easily with fewer McArdle's symptoms.

The foetus requires a high level of glucose for growth and development. During pregnancy, from about 6 weeks gestation, the placenta produces a hormone called human placental lactogen (HPL), also known as human chorionic somatomammotropin. HPL is released from the placenta into the mother's bloodstream. HPL has an anti-insulin effect, which results in an increased amount of both glucose and fatty acids in the bloodstream in order to supply enough nutrients and energy to the foetus. The amount of HPL secreted by the placenta increases as the foetus grows bigger. HPL can also increase the amount of fatty acids in the bloodstream. My unproven theory is that the increased levels of glucose and fatty acids in the blood would provide an improved energy source for the muscles, reducing McArdle's symptoms for a pregnant McArdle woman. HPL also has a small effect on increasing the production of tissues including muscle, in a similar but weaker way to growth hormone.

The increase in glucose during pregnancy in women unaffected by McArdle's is well known. If the levels of glucose in the blood are too high (possibly due to the effect of HPL), gestational diabetes may occur in pregnant women unaffected by McArdle's. Gestational diabetes can occur very early in pregnancy, and can last throughout pregnancy. Gestational diabetes usually stops following birth. If a phenomenon similar to gestational diabetes is occurring in pregnant McArdle's women, this could explain why they return to a normal level of symptoms following birth (which has been reported anecdotally by McArdle's women).

11.4.2 Method of giving birth; vaginal birth or caesarean delivery

McArdle's does not appear to have any effect upon the ability of McArdle's women to have a natural birth, and does not increase the need for a caesarean delivery. There are a limited number of reports about McArdle's women giving birth, but those which are available report both vaginal and caesarean births. Quinlivan *et al.* (2007; 2010) carried out a review of the McArdle women who had attended the UK McArdle Clinic. They described 14 McArdle's women, who had had 21 pregnancies between them; "all pregnancies were uncomplicated", although "one lady had mild myoglobinuria 24 hours after delivery". The authors found that 15% of these cases (about 3 of 25 pregnancies) had required intervention or caesarean, which was not dissimilar from the 15% national average in the UK. This is very limited data, but it suggests that having McArdle's does not make women more likely to require a caesarean.

The uterus/womb is made of smooth muscle. Smooth muscle has a different isoform of glycogen phosphorylase and is therefore not affected in McArdle's. For this reason, McArdle's women should not have a problem having a vaginal birth. During vaginal birth, your family doctors may choose to give you sucrose by an intravenous drip to provide an energy source to the muscles. Cochrane and Alderman (1973) reported a case of a 21 year old McArdle woman. She had a normal pregnancy. She had a relatively normal vaginal delivery. The second stage (pushing stage) was quite slow as she had been given an epidural anaesthetic (which is known to slow down delivery in women unaffected by McArdle's). Labour began spontaneously, but was quite slow (not unusual in a first birth). She received dextrose (a form of simple sugar) and oxytocin (chemical which stimulates contractions of the uterus) intravenously. The baby was healthy. Both mother and child made "normal progress" after delivery. The authors reported that contractions of the uterus were normal, further suggesting that it is smooth muscle with another isoform of glycogen phosphorylase.

During pregnancy, in case a planned or emergency caesarean is required, you should remind your family doctor that McArdle people are at increased risk of malignant hyperthermia (see section 12.3). Anecdotally some McArdle's women have reported that their arms were tired after giving birth, so that they found it harder to hold the baby immediately afterwards.

Online resources:

There is further information on premenstrual syndrome on the NHS website:

<http://www.nhs.uk/Conditions/Premenstrual-syndrome/Pages/Introduction.aspx>

12 Medicines, activities and other things which may be a greater risk for McArdle people

Some drugs are known to have a potential side effect of rhabdomyolysis (breakdown of muscle cells) in people unaffected by McArdle's, and these drugs may be more likely to cause rhabdomyolysis in McArdle people. For example, statins are a lipid-lowering drug which is known to have a high risk of rhabdomyolysis in McArdle people. It is best to avoid taking drugs which could cause rhabdomyolysis, but if your family doctor feels that it is essential to prescribe the drug, they may arrange to regularly monitor you to check for rhabdomyolysis. Rhabdomyolysis can be detected by checking the levels of creatine kinase (CK) in the blood – ideally by measuring your CK levels before taking the drug, and then checking CK levels whilst being treated by the drug. If the CK level becomes raised, it could suggest that muscle damage is occurring.

McArdle people should beware of using painkillers for muscle pain. Muscle pain has a protective effect to warn you not to exercise a damaged muscle. Painkillers could mask this warning so that you continue to exercise, resulting in further damage to the muscle. The phrase “No pain, no gain” does not apply to McArdle people!

During surgery, McArdle people are at increased risk of a complication similar to malignant hyperthermia, caused by certain anaesthetics. It is important to make sure that the surgeon and anaesthetist are aware of this risk so that they can monitor you closely during surgery. McArdle people are also at risk of a rare condition called “compartment syndrome”. This can be caused if a tourniquet or cuff is used, which can lead to a build-up of fluid in the muscle, with potential to cause muscle damage.

Shivering from the cold, and getting angry or scared could cause a McArdle person to tense their muscles which could lead to muscle pain and damage. Swimming is a potentially dangerous activity for McArdle people because if the muscles run out of energy, you may not be able to tread water or swim to safety.

12.1 Medicines

There are some drugs which have an increased risk of causing rhabdomyolysis as a side effect in people unaffected by McArdle's, and are summarised in table Table 12.1. These drugs are more likely to cause rhabdomyolysis in McArdle people. Some of these drugs have been reported to cause rhabdomyolysis in McArdle people, and this is discussed in more detail below. Rhabdomyolysis is discussed further in section 5.

If your family doctor suggests that you take one of the drugs listed in Table 12.1, I would recommend that you discuss with them whether McArdle's puts you at increased risk of rhabdomyolysis during the treatment. Your family doctor may still decide to prescribe the drug, but may regularly monitor you. See section 14.2 for more information on helping your family doctor to treat you.

12.1.1 Lipid-lowering drugs such as statins may exacerbate rhabdomyolysis in McArdle people

Some people unaffected by McArdle's had side effects including rhabdomyolysis when treated with lipid-lowering drugs such as statins (Vladutiu *et al.*, 2006). When these people were tested and compared to people receiving the therapy with no symptoms of muscle damage and also to people who had not been treated with statins, it was found that 10% of the 110 people with side effects were heterozygous or homozygous for mutations causing carnitine palmitoyltransferase II (CPT II) deficiency (which affects fatty acid metabolism), McArdle disease or myoadenylate deaminase deficiency (MADD) (involved in energy metabolism in muscle cells). The effect of the statins upon energy metabolism combined with a genetic disease affecting mitochondrial or fatty acid metabolism seemed to exacerbate muscle damage and rhabdomyolysis.

12.1.2 When combined with a statin, some drugs produce a much higher risk of rhabdomyolysis

Combination of a statin with a fibrate or with nicotinic acid carries an increased risk of side-effects such as rhabdomyolysis in people unaffected by McArdle's. Also, any drug which increases the concentration of a statin in the blood is likely to increase the risk of rhabdomyolysis (BNF, 2009).

12.1.2.1 Fibrates

Fibrates include bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil. They act by decreasing the amount of triglycerides in the blood. However, a combination of a fibrate with a statin increases the risk of rhabdomyolysis in people unaffected by McArdle's. The British National Formulary (edition 58) states that gemfibrozil and statins should **not** be used at the same time.

12.1.2.2 Nicotinic acid

Nicotinic acid can be used to lower cholesterol and triglyceride concentrations by reducing the amounts of these compounds made by the body. In people unaffected by McArdle's, muscle pain and rhabdomyolysis have been reported as rare side effects.

Type of drug	Examples of the type of drug
Lipid regulating (used to reduce levels of cholesterol or triglycerides in the blood)	Ezetimibe, Nicotinic Acid, Fibrates, Rosuvastatin, Bezafibrate, Gemfibrozil, Statins
Used to treat Parkinson's disease	Entacapone, Tolcapone, Levodopa
Antiviral drugs (used to treat HIV infection)	Lamivudine, Tenofovir Disoproxil, Raltegravir, Protease Inhibitors, Didanosine
Antiepileptics (used to treat epilepsy)	Zonisamide, Pregabalin
Illegal stimulants	Ecstasy (Also known as Methylenedioxymethamphetamine, Mdma)
Antipsychotic drugs (used to treat psychoses and other mental health problems)	Aripiprazole, Olanzapine
Used to treat some kinds of cancer	Dasatinib
Antibacterial drugs (used to treat infections caused by bacteria)	Levofloxacin, Daptomycin, Ofloxacin, Co-Trimoxazole
General anaesthetics (also see section 12.3)	Suxamethonium Chloride, Propofol
Antidepressant drugs (used to treat depression)	Venlafaxine
Used to treat rheumatic diseases and gout	Adalimumab
Used for pain relief	Morphine Salts

Table 12.1 Drugs which have a side effect of rhabdomyolysis in people unaffected by McArdle's (information summarised from BNF, 2009).

12.1.3 Other drugs to reduce cholesterol may exacerbate rhabdomyolysis in McArdle people

Perez-Calvo (2005) reported a case of a McArdle man who was treated with ezetimibe. Ezetimibe is a drug which inhibits absorption of cholesterol in the intestine. The person was treated for many months. The person had no ill effects for 20 weeks, and then began to suffer from fatigue, myoglobinuria, and weakness. His CK levels also rose. The family doctors treating him decided to discontinue the treatment and the CK values went down to normal after 4 weeks. It must be noted that this is a single case study, and that this person also had several other medical problems including type 2 diabetes mellitus, which could have affected the outcome.

Ezetimibe is used to treat primary hypercholesterolaemia (high cholesterol levels). Ezetimibe may be marketed alone as a drug called Ezetrol or Zetia. Simvastatin is a kind of statin. Ezetimibe combined with simvastatin (Zocor) is marketed as Inegy (BNF, 2009) or Vytorin.

12.2 Pain relieving mediation

Anecdotal advice is that drugs for muscle pain should not be used routinely. The principle reason for this is because if muscle damage is causing the pain, then the pain will warn the person not to exercise, which could cause further muscle damage. In this way, the pain has a positive effect to protect the muscles from being damaged further. Pain relieving medication would remove this pain, and could lead to the muscle being used and damaged further.

Some forms of pain relief may also have an increased risk of rhabdomyolysis (see Table 12.1).

It is important to note that the adage “No pain, no gain” does not apply to McArdle people!

12.3 McArdle people are at increased risks of particular complications during surgery

12.3.1 Lack of muscle glycogen phosphorylase may put McArdle people at increased risk of malignant hyperthermia-like symptoms caused by anaesthetics

Malignant hyperthermia is a life-threatening condition which is triggered by certain anaesthetics, one example of which is muscle relaxant suxamethonium chloride. These drugs can cause a major increase in skeletal muscle oxidative metabolism whereby the muscle cells run out of oxygen and develop an excess of carbon dioxide. The increase in metabolism can cause an abnormal rise in body temperature, which is why the condition is described as hyperthermia. Medical treatment to stop the temperature rise is essential as in the worst case scenario it would be possible for the body temperature to continue to rise until it leads to death (Price Evans, 1993).

Malignant hyperthermia is an autosomal dominantly inherited disorder associated with central core disease. Central core disease is caused by a mutation in the *RYR1* gene which encodes ryanodine receptor 1, a channel for calcium ions in skeletal muscle, required for muscle contractions (the role of calcium in muscle contractions is discussed further in section 4.3). Central core disease causes a lack of functional muscle glycogen phosphorylase within the core of the muscle cell (Isaacs *et al.*, 1975; Dubowitz *et al.*, 2007), although it is found in other regions of the muscle cell. This may suggest that McArdle people (who also don't have functional muscle glycogen phosphorylase) could

be at risk of malignant hyperthermia caused by anaesthetics. Cases of McArdle people being positive for malignant hyperthermia have been reported; Isaacs *et al.* (1989) reported one person, and Aquaron *et al.* (2007) described two families, one with three affected siblings and one with two affected siblings. One current test for susceptibility to malignant hyperthermia is an *in vitro* contracture test (a muscle biopsy is bathed in a solution containing caffeine or halothane to see whether contracture occurs), which is positive for many McArdle disease people (Bollig *et al.*, 2005). If a person is susceptible, malignant hyperthermia usually occurs within one hour of being given a general anaesthetic (Rosenberg *et al.*, 2007). Dantrolene sodium can be used to prevent/treat malignant hyperthermia. (Dantrolene sodium is discussed further in section 7.1.5.)

IMPORTANT: Before having a general anaesthetic, you should inform your surgeon/anaesthetist that McArdle people are at an increased risk of malignant hyperthermia. (Ideally you would inform them in advance of the surgery, and then remind them on the day of surgery.) This will allow the medical staff to decide carefully which anaesthetic to use, and to ensure they monitor you carefully. They may also decide to have dantrolene sodium available in case malignant hyperthermia does occur. If a caesarean delivery is required for a pregnant McArdle woman, the surgeon should be aware of the risk of malignant hyperthermia. Bollig *et al.* (2005) also recommend to surgeons that “measures for preventing muscle ischaemia and rhabdomyolysis should be kept in mind, as well as the potential for these patients [with McArdle disease] to develop postoperative fatigue, myoglobinuria and renal failure”.

12.3.2 McArdle people may be at risk of a rare condition called “Compartment syndrome” caused by use of a tourniquet or cuff

Compartment syndrome is also known as “compartment pressure syndrome”. This is a rare complication caused by use of a tourniquet or cuff. The compartment is a small area between the layers of the muscle. Usually, a very small amount of fluid is present in this space, and is used for contraction and relaxation of the muscle. There is no room for any additional fluid. Compartment syndrome is a build up of fluid in the compartment. Symptoms of compartment syndrome include severe muscle pain, muscle weakness, and very tense skin over the muscle. It can reduce the ability of blood to pass through the muscle (so that no pulse can be felt), and the worst case scenario is paralysis.

There is a report of compartment syndrome in a person with Hers disease. Niepel *et al.* (2004) reported a person with Her’s disease who was given an ischaemic forearm test. “Later that afternoon”, he had “continuing pain in his forearm and inability to extend his fingers”, followed by reduced sensation in his hand. Compartment syndrome was diagnosed, and an emergency operation was performed. Unfortunately “his recovery was incomplete “and he was left with some loss of sensation. Although this case occurred in a person with Her’s disease, there is also a single reported case of compartment syndrome in a McArdle person who performed the ischaemic forearm test (Lindner *et al.*, 2001). Anecdotally, McArdle people have reported getting compartment syndrome following on from a fixed contracture. A possible explanation is that the muscle contracture causes pressure on the muscle cells, which causes damage and leads to compartment syndrome.

General recommendations (for people unaffected by McArdle’s) are that a patient’s own and family history (information about previous cases of compartment syndrome) should be obtained.

Tourniquet time should be limited to less than 90 minutes, and that the tourniquet should be released before encasing a muscle in a solid cast (such as that used on a broken arm).

IMPORTANT: Before having a surgery, you should inform your surgeon/anaesthetist that McArdle people are at an increased risk of compartment syndrome. Ideally the surgeon would avoid use of a tourniquet or cuff, although this would have to be balanced against the risk of not using it (for example if a person might bleed to death). If a tourniquet is still needed, the surgeon should be informed about the possible risk of muscle damage with subsequent myoglobinuria (Bollig *et al.*, 2005). Medical advice should be sought urgently if, after carrying out an ischaemic forearm exercise test, a loss of sensation is felt in the fingers, continued pain is present, and an inability to extend (move) the fingers.

12.4 Some situations may make McArdle's symptoms worse

12.4.1 Cold temperature

Rommel *et al.* (2006) found that some McArdle people had increased pain caused by environmental factors such as a cold temperature.

12.4.2 Getting angry

Rommel *et al.* (2006) found that some McArdle people had increased pain caused by factors such as a psychological distress. Becoming very angry can cause a McArdle person to tense up their muscles. I have heard an anecdotal case where a McArdle person became very angry so that their muscles all tensed up, resulting in contractures and rhabdomyolysis. It is possible that being very scared could produce a similar effect.

12.4.3 Swimming

Swimming is an activity which is potentially dangerous for McArdle people. This is because if the muscles run out of energy whilst a McArdle person is swimming, they will not be able to tread water or swim to safety. This could result in the McArdle person drowning. For this reason, McArdle people should never swim in water in which they cannot stand up. There is a published report of a 6 year old McArdle's child who almost drowned whilst swimming (prior to being diagnosed with McArdle's) (Roubertie *et al.*, 1998).

12.4.4 Treatment by anyone who moves the body e.g. physiotherapy, osteopathy, chiropractor, massage

If you require treatment by a person who moves the body; treatment for muscle pain, massage, or bone related issues, it is very important to ensure that the person understands McArdle's.

Anecdotally, some McArdle people report that treatment by a physiotherapist can cause muscle pain and potentially muscle damage.

13 McArdle disease may increase the chances of having some diseases and conditions

McArdle people may be more likely to have some gout. McArdle people may also be more likely to have symptoms similar to insulin resistance (type 2 diabetes). These symptoms may be caused by the accumulation of glycogen in the muscle cells of McArdle people and may not be exactly the same as type 2 diabetes.

McArdle's does not appear to cause heart problems or liver problems, although compounds from damaged muscle cells may cause incorrect results in some tests for liver disease.

13.1 McArdle's may increase the risk of gout

Gout is a painful swelling of the joints which is caused by build up of uric acid crystals. It can be caused by high concentrations of uric acid crystals in the blood. Uric acid can be produced during the breakdown of purines in food during digestion. It is also possible that the level of uric acid in the blood may increase following exercise, although whether this is the case, and what the mechanism could be is still unclear (McCrudden, 2008).

There is some evidence that having McArdle's may increase the risk of having gout. 11% (5 out of 45) of the McArdle people attending the UK McArdle Clinic had received treatment for gout (Quinlivan *et al.*, 2010), compared to approximately 3% of the general population. Puig *et al.* (1992) reported the case of a person with McArdle disease who also had gout. They carried out investigations to measure the amount of purine in the blood and urine after the McArdle person had vigorously exercised, but did not see an increase in the level of uric acid in the blood or urine. They therefore concluded that "in this patient, the association of McArdle disease with gout is coincidental".

Jinnai *et al.* (1993) reported the case of a 28 year old McArdle man who had continuous hyperuricemia (raised levels of uric acid in the blood). They found that when the McArdle man carried out aerobic exercise using a bicycle ergometer, it led to an increase in uric acid. Exercise seemed to make the muscles speed up the rate of purine degradation, which increased the levels of uric acid. In this case report, the authors claimed that there was a relationship between exercise and increased uric acid in the bloodstream. They described the condition as "myogenic hyperuricemia" ("myogenic" means it is caused by muscle contractions, and hyperuricemia" means an increased level of uric acid in the blood). Mineo *et al.* (1995) said that myogenic hyperuricemia is seen in glycolytic defects (McArdle's is a glycolytic defect). They say that myogenic hyperuricemia is caused by excessive degradation of muscle purine nucleotides, presumably as an energy source, as the cells are not able to make energy in the usual way (the usual way would be glycogenolysis). Mineo *et al.* (1987) carried out a study where they examined the amounts of purine in the bloodstream after exercise. They found that for a person with McArdle's (and also two people with GSD III and one person with GSD VII), exercising led to accelerated breakdown of purines in the muscle cells. This resulted in increased levels of breakdown products (ammonia, inosine and hypoxanthine) in the blood. The authors noted that these breakdown products can be used by the body to produce uric acid, leading to hyperuricemia.

13.2 Brain functioning

There is some evidence that McArdle people may struggle more with some aspects of psychological functioning than people unaffected by McArdle's. This is discussed in more detail in section 10.2.

13.3 Respiratory problems

Respiratory problems appear to be unusual in McArdle people, but there have been some cases reported. Lucia *et al.* (2008a) reported some McArdle people who had respiratory problems, but they were all women. (Differences in the severity of symptoms between men and women are discussed further in section 9.5.) Paradas *et al.* (2005) report a McArdle woman with shortness of breath (also known as dyspnea). This same woman had been previously reported in the paper

“McArdle disease presenting as unexplained dyspnea in a young woman.” by Voduc *et al.* (2004). Harris *et al.* (1985) also reported an elderly McArdle woman with shortness of breath.

There are a few reports of a rare infant form of McArdle's which was fatal due to respiratory failure, but there were only 3 cases published, and I strongly suspect that they all had a second disease/problem which caused the respiratory failure. (This rare infant form is discussed further in section 8.2.1.)

13.4 McArdle's may cause symptoms of insulin resistance (similar to type 2 diabetes)

Insulin plays a key role in controlling the amount of glucose in the blood and in enabling muscle cells to absorb glucose from the bloodstream, which can then be used to provide energy (see section 6.2). Diabetes is the inability to control the level of glucose (sugar) in the blood. There are two forms of diabetes; type 1 and type 2. Information about these forms of diabetes (in people unaffected by McArdle's), is provided in Table 13.1.

McArdle people have very high levels of glycogen stored in their muscle cells. There are several published reports that high levels of stored glycogen reduce the ability of insulin to stimulate the cells to take glucose from the bloodstream into the muscle cells. This is known as “insulin resistance”, and is similar to type 2 diabetes (also known as non-insulin dependent diabetes mellitus). There has not been much research into insulin resistance in McArdle people, but it is an important topic. Personally, I wonder if future research will show that almost all McArdle people have some insulin resistance caused by the high amount of glycogen stored in their muscle cells, so I have included the following information. Many more studies will be needed to show if this is the case.

Yamauchi *et al.* (1996) reported a 64 year old McArdle woman who had type 2 diabetes (NIDDM). “Thus, we suggested that high plasma glucose and insulin due to NIDDM may induce blood-borne glucose uptake with exercise.”

Maeda *et al.* (2002) reported a case of a 29 year old McArdle woman who also had insulin resistance. “Pre-administration of glucagon had no effect on serum lactate and pyruvate levels after ischemic forearm exercise test while serum glucose elevated. The glucose clamp test confirmed insulin resistance.” Maeda *et al.* noted that that there was no reduction in the number of insulin receptors. Her weight was 78.4kg and BMI was 32.0, so the authors suggested that “Her obesity might be a causative factor of insulin resistance.” I wonder if instead it may have been excess glycogen storage (due to McArdle's) which had caused insulin resistance.

Dorin *et al.* (1996) reported a McArdle person with type 2 diabetes (NIDDM). They hypothesised that insulin resistance would reduce the ability of the muscles to take up glucose during exercise and suggested that adding insulin (intravenously) would improve this. They found that when they artificially added insulin, it increased the amount of glucose able to get to the muscles, and increased the amount of work that the McArdle person was able to do.

Type of diabetes	Also known as	Age when this type of diabetes first begins	Can be associated with	Is insulin required as a treatment	Insulin receptors on cells	Symptoms	Out of all the people with diabetes, how common is this form
Type 1	Type 1 diabetes, Insulin dependent diabetes mellitus (IDDM), Ketosis-prone diabetes, Brittle diabetes, Diabetes mellitus type 1	Less than 20 years of age, although occasionally older than 40 years of age	Viral infection	Yes	Normal	Quite severe	Rare (5-10% of people with diabetes)
Type 2	Type 2 diabetes, Non insulin dependent diabetes mellitus (NIDDM), Adult-onset diabetes, Ketosis-resistant diabetes, Stable diabetes, Diabetes mellitus type 2	Older than 40 years of age	Obesity (being very overweight)	No	Low or normal	Quite moderate	Very common (90-95% of people with diabetes)

Table 13.1 Information about diabetes in people unaffected by McArdle's (information from McArdle *et al.*, 2006).

Nielsen *et al.* (2002a) compared 6 McArdle people with 6 unaffected people. They gave each person a glucose drink, and investigated whether the body could use insulin to stimulate the muscle cells to take up the glucose. They found that the McArdle people had much less insulin-stimulated uptake of glucose than the unaffected people

Mineo *et al.* (1984) gave McArdle people glucagon prior to exercise. This relieved “patients with McArdle disease from muscular symptoms during exercise and enhanced exercise performance”. It is likely that glucagon acted upon the liver, causing a release of glucose into the bloodstream. This would have acted in a similar way to having a sugary/glucose drink immediately prior to exercise, which is known to help McArdle people exercise more easily (section 7.1.6.3). The authors note that a similar improvement in the ability to exercise was seen after giving glucose, or glucose plus insulin (the insulin would probably have helped the muscle cells to take up the glucose). Interestingly, the authors did not see an improvement in the ability to exercise when McArdle people were given insulin alone, without glucose.

There is no suggestion that McArdle’s may be associated with type 1 diabetes (IDDM). Davies *et al.* (1977) reported a McArdle person who had type 1 diabetes. At present this appears to be the only published report of a McArdle person with type 1 diabetes. In the absence of any evidence to suggest a link, it is likely that a report of a person having both McArdle’s and type 1 diabetes is likely to be a coincidence.

13.4.1 A discussion of whether insulin resistance could be caused by McArdle disease

It is not clear to me whether the insulin resistance observed in some McArdle people is exactly the same as type 2 diabetes (NIDDM) observed in people unaffected by McArdle’s. It is possible that there are important differences between the insulin resistance seen in people with McArdle’s and those unaffected by McArdle’s. In McArdle people, the cause of insulin resistance may be different to the cause in people unaffected by McArdle’s. Nielsen *et al.* (2002a) suggested that the high level of glycogen storage in the muscle cells of McArdle people might cause insulin resistance. This is not the cause of insulin resistance in people unaffected by McArdle’s. My personal unproven theory is that most McArdle people have some level of insulin resistance caused by glycogen storage in their muscle cells.

13.4.1.1 A high level of glycogen in the muscle cells of McArdle people may lead to insulin resistance

Usually, insulin can stimulate muscle cells to take glucose from the bloodstream into the muscle cells. This functions as a way of keeping the amount of glucose in the bloodstream constant. It also helps to increase the amount of glucose in the muscle cells. Derave *et al.* (2000) found that a very high amount of glycogen in muscle cells led to the GLUT-4 proteins not responding to insulin (this is called “insulin resistance”). Nielsen *et al.* (2002a) compared McArdle people with unaffected people. They gave each person a glucose drink, and investigated whether the body could use insulin to stimulate the muscle cells to take up the glucose. They found that the McArdle people had much less insulin-stimulated use of glucose than the unaffected people. The authors concluded that the high level of glycogen in the skeletal muscle cells caused McArdle people to be insulin resistant in terms of glucose uptake, and stated that “insulin action is decreased by high muscle glycogen content in skeletal muscle”. In addition, the ability of insulin to decrease and increase the use of fat and carbohydrate to produce energy was also reduced in people with McArdle disease.

13.4.1.2 High levels of some cytokines, such as TNF- α and IL-6, in the bloodstream of McArdle people, could lead to insulin resistance

There is some evidence that McArdle people have raised levels of two cytokines (small proteins) called TNF- α and IL-6 (Lucia *et al.*, 2008b). (These are both discussed further in section 9.2.) It has been found that people with type 2 diabetes (unaffected by McArdle's) have high levels of TNF- α . TNF- α is known to decrease the ability of insulin to stimulate muscle cells to take up glucose in rats by inhibiting the action of GLUT-4 and inhibit insulin receptor activity. A possible explanation for the insulin resistance seen in McArdle people could be that the high levels of TNF- α (and possibly IL-6) may reduce the ability of insulin to stimulate uptake of glucose from the bloodstream by GLUT-4. TNF- α (and possibly IL-6) could therefore lead to insulin resistance. (This is an unproven theory.)

13.4.2 Anecdotal reports of a feeling of low blood sugar could be explained by insulin resistance preventing muscle cells taking up glucose, despite test results showing high blood glucose levels

Several McArdle people have reported on online chat groups that they experience a feeling of low blood sugar levels. If these people have insulin resistance, a feeling of low blood sugar could occur because the insulin isn't able to act, and the cells aren't able to take up glucose, even though there are high glucose levels in the blood. If this was the case, blood test results would show high blood sugar levels, but the McArdle person would feel that they had low blood sugar. Although studies have shown that some McArdle people have insulin resistance, these studies did not ask McArdle people whether they felt that their blood sugar levels were low. If this were the case, I wonder whether insulin resistance could lead to weight gain in McArdle people. If McArdle people have a feeling of low blood sugar, this would make the person want to eat a high sugar or high carbohydrate food. If the muscle cells are unable to take in glucose, the muscle will not be able to use the glucose to provide energy for movement. Instead, this excess glucose would be stored as glycogen or as fat. This is an unproven theory.

Weight gain should be avoided by McArdle people (see section 4.2.3).

13.4.3 Exercise can be used to prevent and treat insulin resistance in people unaffected by McArdle's

People unaffected by McArdle's are less likely to develop type 2 diabetes if they have a physically active lifestyle. In people unaffected by McArdle's, "an increase in abdominal fat accumulation and loss of muscle mass are highly associated with the development of insulin resistance" (Ivy, 1997). Exercise burns this fat, can prevent muscle wastage, and stimulate muscle development.

Hawley (2008) found that in studies of people unaffected by McArdle's, who have type 2 diabetes, even a single bout of exercise can increase the amount of glucose taken up into the muscle cells. In this case, the glucose is taken up in a different way, which is stimulated by exercise. However, the authors say that this effect will only last for approximately 48 hours. "In contrast, repeated physical activity (i.e. exercise training) results in a persistent increase in insulin action in skeletal muscle of obese and insulin-resistant individuals". In addition, they found that regular training seemed to increase the ability of the muscles to use fat for energy.

Exercise has been reported as beneficial for McArdle people (see section 4.2.2), but at present no research has been carried out to see whether exercise could be used to treat McArdle people with insulin resistance.

13.4.3.1 Research suggests that a sugary drink before exercise can be effective even in McArdle people with insulin resistance but should only be used under medical supervision

Although sugary drinks are not recommended for people with diabetes (see important note below), they have been experimentally tested on two McArdle people who also had insulin resistance (NIDDM). These tests were performed under close medical supervision. Vissing and Haller (2003) tested a McArdle person with NIDDM. They found that a sucrose drink was equally effective in this person as in McArdle people who did not have NIDDM. Similar experimental results had been previously found by Yamuchi *et al.* (1996) who found that a McArdle person with NIDDM was able to take up and use glucose from the blood during exercise. Yamuchi *et al.* struggled to explain this observation, but Vissing and Haller, suggested that glucose uptake in these McArdle people with NIDDM may have been induced by muscle contractions, not by insulin sensitivity.

IMPORTANT: People with diabetes are not recommended to have sugar or sugary drinks. McArdle people with diabetes should obtain medical advice before using sugar or sugary drinks.

13.5 There is no evidence that McArdle's may increase the risk of heart problems

The heart muscle in unaffected people has a 50:50 mixture of brain glycogen phosphorylase and muscle glycogen phosphorylase (Miranda *et al.*, 1979; Bresolin *et al.*, 1983). Although McArdle people do not have muscle glycogen phosphorylase, brain glycogen phosphorylase is present. The presence of brain glycogen phosphorylase in the heart appears to be sufficient for it to function normally, and heart problems are not generally reported in McArdle people.

In McArdle people, an increased (very rapid) heart rate is seen during intense exercise (before the second wind). This response to exercise is discussed further in section 6.4.4. The increased heart rate during exercise is only seen for a short period and when the muscle pain causes the McArdle person to stop and rest the heart rate becomes lower.

I have heard a suggestion that as McArdle people are not able to maintain a high heart rate during exercise (which is normally recommended for people unaffected by McArdle's); this may lead to an increased risk of heart disease or increased cholesterol. Perez *et al.* (2006) reported a case of a 78 year old McArdle man who had had coronary heart disease. However, this single case report is not sufficient evidence to support this theory.

Nicholls *et al.* (1996) reported a case of a 66 year old McArdle man with angina. Angina is pain in the heart which is caused by narrowing of the arteries of the heart. This narrowing can reduce blood flow. This narrowing can be caused by several factors, one of which is cholesterol. Anti-cholesterol drugs called statins may therefore be prescribed, but these should be avoided if possible by McArdle people (see section 12.1.1).

13.6 McArdle's is not reported to cause liver disease, but can have an effect on the results of blood tests for liver disease

There is no published data that McArdle's can cause liver disease. Liver disease can be shown by an increase in the levels of proteins called Alanine Transaminase (ALT; formerly called SPGT)) and Aspartate Transaminase (AST; formerly called SGOT), which can be detected by a blood test. However, skeletal muscle cells also contain AST and ALT. If muscle damage has occurred, raised AST and ALT levels may be seen. Tuzun *et al.* (2002) reported a case of a McArdle person who had raised levels of transaminases in the blood. Measuring creatine kinase levels in the blood could indicate if muscle damage has occurred. (Note: Raised AST and ALT levels can be caused by taking drugs, viral hepatitis or excessive alcoholic consumption, so if you are treated by a family doctor unfamiliar with McArdle's, you may have to explain that McArdle's could also cause this result.)

14 McArdle's specialists and family doctors

Because McArdle disease is rare, many McArdle people find it difficult to get accurate and reliable advice on all aspects of McArdle disease, including diet, exercise and lifestyle. They may find it very helpful to have a consultation with a medical professional who has specialised knowledge of McArdle disease. The primary benefit of visiting a McArdle specialist is that they are familiar with the disease, and hopefully have met a large number of McArdle people giving them an overview of common differences in McArdle symptoms between men and women and common changes with age. They also may have noticed other secondary problems or complications (for example, gout). McArdle specialists may be able to confirm the diagnosis of McArdle's, offer advice on how to reach second wind, and update you on current treatments. They should also be able to discuss with you how to deal with problems caused by McArdle disease such as myoglobinuria and contractures. McArdle specialists often have a strong interest in other similar muscle diseases or glycogen storage diseases, and this can have an additional benefit in that they may be aware of new advice or information which could also be applied to McArdle disease.

Most of the time, McArdle people will consult their family doctor for medical advice (including advice on problems or complaints which are unrelated to McArdle disease). Anecdotally, many McArdle people report that their family doctor does not know very much about McArdle's. As well as being aware that McArdle disease may make you slightly more likely to have some other diseases/conditions, such as gout and symptoms similar to insulin resistance, it is also important to remind your family doctor that not all problems and symptoms will be due to McArdle disease.

Keeping your own record of medical investigations and treatments (test results, CK values, medications, etc.) can be helpful to allow you to monitor your progress over time and for reference if you change family doctor or McArdle specialist.

14.1 McArdle specialists

There are several medical professionals who have a strong interest and specialise in McArdle disease. Some of them are listed below. The McArdle clinic in London is the only McArdle's clinic in the UK. McArdle people in the UK must be referred to the McArdle clinic by their family doctor. Further information about the clinic and obtaining a referral is available from the AGSD-UK website. It is sometimes possible for McArdle people in Ireland to also visit this clinic. In the USA, the Muscular Dystrophy Association (MDA) is able to put people in contact with specialists who are located nearby. Many of the McArdle's specialists carry out research into McArdle's and run clinical trials as well as seeing patients in a clinic. There are some differences in opinion between McArdle's specialists, such as what is the ideal diet for McArdle people (see section 6.6), and so the advice you receive may not be exactly the same from each specialist.

14.1.1 Benefits of visiting a McArdle specialist

Visiting a McArdle's specialist can be of great benefit to McArdle people. Unlike your family doctor, McArdle's specialists have a much more thorough understanding of McArdle's. McArdle's specialists may be able to:

- Confirm the diagnosis of McArdle's is correct.
- Teach you how to reach second wind.
- Provide you with information about the usual symptoms and variations of McArdle disease.
- Guide you with physiotherapy and advice on diet.
- Tell you about current treatments and recent research.
- Provide genetic counselling as appropriate.
- Recruit you for clinical trials into treatments for McArdle's.
- Provide you with a letter/note/instruction sheet with information about McArdle's to take into hospital and show the doctors and nurses if you require emergency treatment (for example for severe muscle damage).
- Devise a personal treatment plan for if you suffer an episode of myoglobinuria. Myoglobinuria is the most obvious sign of muscle damage which can be assessed by eye without any medical tests. You should discuss whether a low level of myoglobinuria could be treated at home (for example by drinking plenty of fluids), or whether you should go to a hospital each time. (Anecdotally, this seems to vary from person to person, but any decision to treat myoglobinuria at home should be made in consultation with a medical specialist.)
- Discuss how to treat contractures; whether they will prescribe a strong painkiller (anecdotally McArdle people say that normal painkillers often are not strong enough to treat the pain of a contracture). If strong painkillers are prescribed, they should provide clear instructions about when and how to take the drug (e.g. how many pills, how often), and

whether it is safe to take with any other drugs you take. Also whether it would affect your ability to drive or operate machinery.

14.1.1.1 The UK McArdle clinic

The McArdle's clinic at London is one of the few McArdle's clinics in the world. It was previously located at the RJA Orthopaedic Hospital in Oswestry, Shropshire, and in 2010 it was relocated to the National Hospital for Neurology and Neurosurgery, London, WC1N 3BG. I attended the clinic (while it was located in Oswestry) several times between the years of 2005 and 2008 as an observer where I was able to sit in on consultations between patients and Dr Quinlivan and other members of the team. The clinic offers McArdle people an opportunity to meet specialists from several disciplines. Dr Ros Quinlivan is one of the leading McArdle's specialists. She primarily sees patients, but is also involved in clinical trials and in collaborations with other people carrying out research into McArdle's around the world. Other members of the multi-disciplinary clinic include a physiotherapist who specialises in neuromuscular conditions, a dietician, and an exercise physiologist (who can measure the ability to exercise and help people learn to reach second wind). Dr Quinlivan also runs clinics for other muscle diseases, so her team are experienced at dealing with people with muscle diseases and any associated problems.

14.1.2 Paying to see a McArdle's specialist

In the UK, referral to the McArdle clinic is made under the National Health Service (NHS). The patient does not have to pay for the consultation, although it may be necessary to pay for any prescriptions required.

In many other countries, patients must either pay for their consultation or have a health insurance policy which will cover the cost. Anecdotally, patients report that some McArdle's specialists do not accept health insurance payments for consultations. It would be sensible to enquire about how to pay for the consultation and whether health insurance payments are accepted prior to arranging an appointment.

14.2 Your family doctor- how to help them treat you, what information to give them, what to remind them

14.2.1 Your family doctor may not know very much about McArdle's

Many McArdle people anecdotally report that their family doctor does not know very much about McArdle's. I would suggest that you ask your family doctor to obtain and read the medical paper "McArdle disease: what do neurologists need to know?" by Alejandro Lucia, Gisela Nogales-Gadea, Margarita Pérez, Miguel A Martín, Antoni L Andreu and Joaquín Arenas. This is a very useful and informative (and relatively short) paper, which summarizes most of the key information about McArdle's.

14.2.2 Important things to remind your family doctor

- You should check with your family doctor that any prescribed medicine does not have the side effect of rhabdomyolysis (see section 5). If it does have this side effect, you must decide together with your family doctor how to monitor for or reduce the risk of

rhabdomyolysis. One approach would be frequent measuring of creatine kinase levels in the blood to check for muscle damage.

- That a raised CK level, even at rest, is usual for McArdle people (see section 5.3.2.1).
- That muscle damage could lead to an increase in the AST and ALT levels, and so high levels of these proteins in the blood is less likely to indicate liver damage (see section 13.6).

McArdle disease may make you slightly more likely to have certain other diseases/conditions, such as insulin resistance (see section 13.4) or gout (see section 13.1).

14.2.2.1 It's not all about McArdle disease

It is also important to remember that not all problems or symptoms will be due to McArdle disease. If a person has McArdle's, their family doctor may assume that any other symptom or disease is due to McArdle's. However, unless there is a well known relationship between McArdle's and the second problem/disease, then it is important that the second problem is investigated thoroughly and treated appropriately. (You may have to remind your family doctor that other symptoms or problems could be completely unrelated to McArdle's.)

14.3 Become your own personal expert on McArdle's

If you have an on-going medical condition (such as McArdle disease), it can be very helpful to keep your own record of medical investigations and treatments you have. This can be particularly useful if you see different specialists over time. Or if you move house or country, you may need this information to tell your new family doctor.

You may also find it helpful to write relevant ideas in your notebook for future reference, for example if you hear something relating to McArdle's in the media or on a chat group.

Information to make a note of could include:

- Tests that were performed and the results, for example if you regularly have your CK levels measured in blood tests, over time you will find out what level is "normal" for you. (If the CK level is higher than usual, it might be helpful to note what activity you were doing before the test was done.)
- Medicines you are prescribed. Once you have finished a course of medicine, you could stick the medicine box or information leaflet into your notebook. Useful information to note could include: manufacturer, the active ingredient(s) (or all ingredients), the trade name of the product, the date you started taking and finished taking the medicine. If you have positive effects (it cured the problem), or negative effects (like side effects).
- Similar notes could be made if you decide to try supplements or herbal medicines or to alter your diet or exercise regime (although you should consult your FAMILY DOCTOR prior to any of these).
- Everyday differences. For example, if you go for a walk on the beach, and have severe contractures later that day, this could be noted in the notebook. Or if you find that your symptoms are better in summer or winter.

- Keeping notes like these can help you to see how the disease is progressing, for example whether it gets worse as you get older or remains constant. It can be useful to have a record of different treatments you have tried, and to see which had beneficial or negative effects.

Online resources:

There is further information about the UK McArdle clinic on the AGSD-UK website:

<http://www.agsd.org.uk/tabid/1143/default.aspx>

Contact details for McArdle specialists in the USA are available via the Muscular Dystrophy website:

<http://www.muscular-dystrophy.org>

15 Models of McArdle's can be used to test treatments

Animals with McArdle disease or cells in the laboratory which mimic the disease are known as “models”. Models provide a useful way to test potential treatments. This is safer than giving the treatments humans, in case the treatments cause negative side effects. For many other muscle diseases, it is possible to use muscle cells obtained from a muscle biopsy from a person with the disease. These muscle cells can be grown in a laboratory and used to test the effects of potential treatments. Unfortunately, this technique does not work very well for McArdle disease. Once muscle cells are removed from the body they stop trying to produce muscle glycogen phosphorylase. Muscle cells from people unaffected by McArdle disease produce muscle glycogen phosphorylase at high levels in the human body but produce very low levels once they are removed from the body. This means that muscle cells from McArdle people can't easily be used in a laboratory to test a treatment, because even if a successful treatment was found which enabled the mutant muscle glycogen phosphorylase to become functional, the muscle glycogen phosphorylase would not be produced! A secondary problem is that cells grown in the laboratory begin to produce the brain and liver glycogen phosphorylase, which are so similar that it is hard to detect whether a treatment has caused an increase in the amount of the muscle glycogen phosphorylase. Animal models of McArdle disease are therefore particularly valuable.

McArdle disease has been found to occur naturally in sheep and also in cattle. As in humans, sheep and cattle also inherit McArdle's as an autosomal recessive disease. Animals also have a reduced amount of muscle glycogen phosphorylase and an accumulation of glycogen in the muscle cells. In a similar way to humans, sheep with McArdle's sheep also struggle to exercise. These animals have the potential to be used for scientists to learn more about McArdle's, and also to test possible treatments. It is very useful to be able to test the effect of treatments within the body; for example to test whether an oral treatment will be carried around the body in the bloodstream and taken to the muscles.

15.1 Models can be used to test potential treatments

Many researchers are interested in developing treatments for McArdle's. It is often not sensible to test treatments directly on humans, in case they may produce bad side effects or not even work. During the development of a treatment, initial trials are usually performed on cells which have been made to mimic the disease. If positive results are seen, the treatment is then tested upon animals with the disease, usually mice, but occasionally birds or other animals. If positive results are seen (and no or few bad side effects), the treatment may then be tested upon humans. Cells which have been made to mimic the disease, and animals with the disease, are usually known as "models". Animal models of McArdle disease could provide valuable information about the disease and offer a valuable opportunity to test out possibly forms of treatment. There are two existing whole animal models of McArdle disease, which are Charolais cattle (Angelos *et al.*, 1995) and Merino sheep (Tan *et al.*, 1997). Both of these animal models have occurred naturally. These animals have the potential to be used to test possible treatments which, if successful, could then be used to treat humans with McArdle's.

15.1.1 Sheep with McArdle disease

In Australia, a sheep model of McArdle disease has been identified (Tan *et al.*, 1997). The mutation is a bit complicated as it is G to A mutation in the introns 19 3' splice site, which leads to a new splice site 8 base pairs into exon 20. This causes a frame shift, scrambling of 18 amino acids and then a premature truncation of the enzyme removing 31 amino acids from the C terminal of the protein. (Basically the amino acid sequence gets mixed up at the end and is shorter than usual.) In the sheep, the amount of *Pygm* mRNA is reduced and is only about 20% the level of mRNA of normal unaffected sheep (carrier sheep produced almost as much mRNA as normal sheep) (Walker, 2006). McArdle sheep do not have any functional muscle glycogen phosphorylase (Tan *et al.*, 1997; Walker, 2006). Not even non-functional muscle glycogen phosphorylase protein can be detected from McArdle's sheep (Walker, 2006). It has also been found that the McArdle's sheep have exercise intolerance (are unable to run). Carrier sheep do not appear to demonstrate McArdle symptoms of difficulty with exercise or myoglobinuria (Walker, 2006). A muscle biopsy showed the absence of functional muscle glycogen phosphorylase, and increased glycogen storage (Tan *et al.*, 1997). Walker (2006) found that carrier sheep have approximately 45% of normal levels of glycogen phosphorylase and Tan *et al.* (1997) found carrier sheep had 24-62% of normal levels of glycogen phosphorylase.

15.1.2 Cows with McArdle disease

In 1995, six Charolais cows were described with rhabdomyolysis. Muscle biopsies were used to show increased muscle glycogen concentrations and an absence of functional muscle glycogen phosphorylase. McArdle cows have a reduced amount of muscle glycogen phosphorylase compared to unaffected cows, and an increased amount of glycogen in the skeletal muscle cells (Angelos *et al.*, 1995; Tsujino *et al.*, 1996). Each cow had a common ancestor from both parents, suggesting autosomal recessive inheritance (Angelos *et al.*, 1995). Tsujino *et al.* (1996) identified the mutation as R490W. This mutation results in detectable *Pygm* mRNA, but a reduced amount of muscle glycogen phosphorylase.

15.1.3 Mouse and rat models of McArdle disease

Although various research groups are reported to be working on a genetically modified mouse model of McArdle disease (Lucia *et al.*, 2008a), none have yet been published. Various physical mechanisms have been used to create a model of McArdle disease, which have contributed to understanding about glycogen phosphorylase but were not used to test therapies for McArdle disease. These have included injection of sodium iodoacetate in adult male rats (Brumback, 1980). This led to muscle cramps during exercise, rhabdomyolysis, elevated creatine kinase levels and damaged muscle fibres after exercise. Gorin *et al.* (1996) stopped some of the leg muscles of rats being able to contract by injecting them with botulinum toxin A (which is also used for cosmetic Botox). This prevented the nerve transmitting signal to the muscles to stimulate contraction for 10-12 days, which then slowly recovered. Baker *et al.* (2006) used an inhibitor to inactivate muscle glycogen phosphorylase which created a model of McArdle disease, although this was not their purpose.

15.1.4 Muscle cell culture from unaffected people and McArdle people

Cultured muscle cells from McArdle people would be a useful model for McArdle disease. These would be obtained by a muscle biopsy from McArdle people, and then grown in a research laboratory. When cells are grown in a laboratory this is known as “cell culture”. These muscle cells could be used to test potential treatments. Muscles cells have successfully been used to create models of many other human diseases, but unfortunately it seems that it is not possible to use muscle cells as a model for McArdle’s. The problem is that during normal muscle development, muscle glycogen phosphorylase is not usually produced by the muscle cells until a late stage in muscle development, when the muscles become mature. Before that, immature muscles produce a different isoform; brain glycogen phosphorylase, which is also known as foetal glycogen phosphorylase. (This is also produced by immature muscle cells (new cells) as they regrow after muscle damage, see section 6.5.4.)

The research into whether muscle cells will produce muscle glycogen phosphorylase in culture is confusing and contradictory. Sato *et al.* (1977) observed that cultured muscle cells from both unaffected people and McArdle people did not produce muscle glycogen phosphorylase. In contrast there have been two reports of muscle glycogen phosphorylase “re-appearing” in cultured McArdle muscle cells (Meienhofer *et al.*, 1977; and Martinuzzi *et al.*, 1993) despite a lack of muscle glycogen phosphorylase in a muscle biopsy from the same McArdle people. It is difficult to interpret these results in the absence of knowing which mutations were present, as some mutations may allow the enzyme to be made and even have some activity.

If muscle cells are grown with nerve cells in culture, is called “innervation”. Growing nerve cells in the same container as the muscle cells can help the muscle cells become mature. (Muscle cells grown in culture without nerve cells are called “aneural” culture.) Several studies by Andrea Martinuzzi showed that only very low levels of muscle glycogen phosphorylase mRNA and enzyme are produced by normal control differentiated muscle cells in culture unless the cells are innervated with either chick or rat nerve explant (Martinuzzi *et al.*, 1986; Martinuzzi *et al.*, 1988; Martinuzzi *et al.*, 1993).

Some early studies were limited by lack of knowledge of the different phosphorylase isoforms, lack of specific antibodies (which can be used to detect and differentiate between different isoforms),

and absence of knowledge of the specific mutations in each McArdle person. It seems likely that some of these cases may be due to mis-interpretation of the brain or liver form as the muscle form of glycogen phosphorylase. DiMauro *et al.* (1978) reported the brain isoform to be the principle isoform in cultured muscle cells from McArdle people. Martinuzzi *et al.* (1986; 1993) found that about 40% of functional glycogen phosphorylase in innervated cultures and about 60% in aneural cultures was the brain and possibly liver isoform, and Gorin *et al.* (1989) found that primary rat skeletal explants expressed “non-muscle phosphorylase isoforms” in vitro. A recent study by Nogales-Gadea *et al.* (2010) reported that cultured muscle cells from McArdle’s people and from people unaffected by McArdle’s produced the brain and liver isoforms of glycogen phosphorylase. In addition, cultured muscle cells from people unaffected by McArdle’s also produced a small amount of muscle glycogen phosphorylase.

The problems with using cultured muscle cells as a model of McArdle’s are therefore:

Only a low level of muscle glycogen phosphorylase is produced in cultures of muscle cells from unaffected people.

The brain and liver isoforms are also produced by muscle cells in culture. The isoforms are so similar that this makes it much harder to see whether there is a complete absence of muscle glycogen phosphorylase in cells from McArdle people, and also harder to see if a treatment has caused an increase in the amount of the muscle glycogen phosphorylase.

Unless a special (and complex) procedure called “immortalisation” is performed, muscle cells can only be grown for a certain period of time before the cells will stop growing. This limits the amount of time in which experiments can be performed on the cells, and would mean repeated muscle biopsies to obtain fresh muscle cells to culture.

15.1.5 Creation of cell models of McArdle’s

My Ph.D. project was to create other types of cell models of McArdle’s (Wright, 2009). These cell models were produced to overcome/avoid the problems of using muscle cells. At present this research is unpublished, but a fuller description of the research will be included in this section at a later date.

15.2 Animal and cell models can be used to test potential therapies for McArdle disease

As discussed in the next section (section 16), the sheep model of McArdle disease has been used to test several different potential treatments for McArdle disease. The sheep model has the advantage of being a whole animal, which offers the opportunity to explore and try to overcome difficulties of getting the treatment to move around the body to the muscles. However, the sheep are more expensive to maintain than cells in culture. The cow model of McArdle disease has not been used to test any treatment, probably because cows are large and it would be expensive to maintain them and to use them to test potential therapies. Cell culture models have also been used to test potential therapies, and these are discussed below.

16 Potential therapies for McArdle disease

Currently the best treatment available for McArdle disease is regular moderate exercise. There are many other possible therapies which have been suggested. Some of these have been tested in humans, or in animal or cell models of McArdle's, but only exercise is currently in use as a treatment for McArdle people.

Gene therapy would involve trying to correct the DNA sequence of the *PYGM* gene within each muscle cell or to provide an additional "correct" copy of the gene to each muscle cell. Gene therapy is currently considered too dangerous for use in people except those with a life-threatening disease.

Other treatment could include drugs which manipulate the machinery of the cell so that it ignores premature stop codons, and produces full length enzyme. Both Ataluren (a novel drug, previously called PTC124), and one family of antibiotics (aminoglycosides) have been shown to have this effect in some models of muscle disease which are similar to McArdle disease. They require the mRNA to be present, and are therefore less likely to work on certain mutations (such as the very common R50X mutation) where the mRNA has been destroyed by nonsense-mediated decay.

Enzyme replacement therapy (where the enzyme is given by injection into the bloodstream) is unlikely to be successful for McArdle disease because it does not go into the part of the muscle cell where it is needed. However, an alternative approach is to use drugs (for example, valproate) to stimulate the body to produce brain glycogen phosphorylase. This version of the enzyme works in almost the same way as muscle glycogen phosphorylase, and is produced in the muscle cells before birth, but stops being produced in the muscle cells around the time of birth. Initial trials of valproate in sheep with McArdle disease appear to have promising results, although further studies are needed.

16.1 Therapies to correct or replace the *PYGM* genomic sequence

McArdle disease is caused by mutations in the *PYGM* gene. There are several therapies which could be used to correct or replace these mutations.

16.1.1 Gene therapy to provide a normal copy of the *PYGM* gene

Gene therapy could be used to provide McArdle people with an additional copy of the *PYGM* gene which does not have any mutations. If this gene worked well, it could change the symptoms of the McArdle person to be similar to a carrier. Carriers do not usually have symptoms of McArdle's. Methods to put this additional copy of *PYGM* gene into the cells could include a kind of electric shock (Yoshida *et al.*, 2004), using a modified virus called an "adenovirus" to put the additional copy of the gene into the body, or to remove muscle cells from a McArdle person, add the gene in a laboratory using an adenovirus, and then put these muscle cells back into the McArdle person's body (Neuwelste, 1995). Adenoviruses are an attractive option because they are very efficient at putting genes into cells, can easily be produced at a high concentration, and have already undergone much research (Parker *et al.*, 2008).

However, at present the risks of gene therapy make it an unacceptable treatment. Possible risks of gene therapy include:

- An immune reaction to the new protein (in this case muscle glycogen phosphorylase).
- An immune reaction to the adenovirus.
- The new gene may be put into the genome of the cell at a location which interferes with cell growth or cell survival. (This could even have the effect of causing cancer.)
- There is also a worry that even though the adenovirus has been modified to make it safe, it could use some of the virus DNA sequence which is naturally found in the human genome and together form a more dangerous virus.

The immune system is the body's natural defence system against organisms like parasites and worms, bacteria, and viruses such as adenovirus, which may try to invade the body. Although the adenovirus used for gene therapy has been inactivated so that it cannot harm the body, the body may still recognise it as a virus and cause an immune reaction to try to destroy the virus. An immune reaction is also more likely to occur if the body is exposed to a new and unfamiliar protein. As most McArdle people do not have any muscle glycogen phosphorylase, if gene therapy treatment leads to the protein being produced, the body may not recognise the enzyme and may assume that it is a foreign organism. This could lead to an immune reaction against the enzyme. This is discussed further in section 16.3.2.

At present gene therapy is only being tried on people with a life-threatening disease. X-linked SCID (SCID-X1) is an inherited disease which causes children to not have any immune system to protect them from everyday colds, bacteria, and viruses. Children with SCID-X1 are sometimes called "bubble boy/bubble girl". Schwarzwaelder *et al.* (2007) carried out a trial where ten children with SCID-X1 were treated with a kind of modified virus called gammaretrovirus-mediated to provide them with a normal copy of a gene to treat the disease. The treatment improved their immune system without any serious adverse events for at least 5 years after treatment. However, more than 9 months after treatment, some of the cells from the treated children were examined. It was found that in some cases the retrovirus had inserted itself into the genome of the cells in areas which

contained important genes. The insertion of the retrovirus may have disrupted genes which were necessary for cell survival and growth.

Gene therapy for McArdle disease by providing an additional (normal) copy of the *PYGM* gene involves the new copy being inserted into a random location of the genome in the cell. However, it is most likely to be inserted into a region of the genome which the cell is using at the time (Berns and Linden, 1995). Some genes help to prevent cancer (these are called tumour-suppressor genes) and if the new copy of *PYGM* was inserted into this gene and stopped it working, it could increase the risk of cancer (Temin, 1998). It is also possible that the *PYGM* gene could integrate into a different important gene and inactivate it (Nienhuis *et al.*, 2006). It is impossible to predict the outcome if an essential gene was inactivated. The risks make gene therapy a currently unacceptable treatment for McArdle disease.

Gene transfer has been tried on some cell based models of McArdle disease. Baque *et al.* (1994) used an adenovirus vector to introduce mouse muscle glycogen phosphorylase into mouse muscle cells which had been grown in culture for a very long time (this type of cells was called C2C12 cell line). The amount of muscle glycogen phosphorylase mRNA and the amount of functional muscle glycogen phosphorylase increased in the cells for up to 20 days. An adenovirus containing full length human muscle phosphorylase has been put into muscle cells cultured from McArdle human and sheep muscle. The authors claimed that this led to production of muscle glycogen phosphorylase, suggesting this procedure could be tried in muscles of McArdle people (Pari *et al.*, 1999). However, I think that the results are questionable as the antibody was “reactive against all isoforms” and would also have detected the liver and brain isoforms of glycogen phosphorylase which would normally be expressed by the muscle cells in culture (see section 15.1.4).

16.1.2 Targeted correction of mutation within the *PYGM* gene

Rather than adding a whole new copy of the *PYGM* gene (as described in section 16.1.1), it may also be possible to specifically correct the mutation in the gene. This is called “*in vivo* gene correction”. “*In vivo* gene correction would be an alternative approach to replacement gene therapy” (Thorpe *et al.*, 2002), and because it would correct the *PYGM* gene, it would provide a long term “cure”. The major benefit of correcting a defective copy of a gene in-situ in the genome is that once it has been repaired, the cell could control how much of the enzyme to make in the normal way. It would be a permanent cure because the corrected gene will be passed on during cell growth and division.

Methods to specifically correct the mutation are complicated, but basically involve putting a short stretch of DNA into the cell which contains the correct sequence. The cell then uses this as a template to correct the gene within the genome by a process known as “homologous recombination”. Sometimes a bit of protein (called a carrier peptide) can be added to the end of this DNA to stimulate the cell to use it to repair the gene (Svasti *et al.*, 2009). An alternative technique uses specific enzymes which cut up the DNA. This stimulates the cell to repair and correct the gene. Some proteins called “zinc finger nucleases” can be used to direct correction and homologous replacement of a region of a gene (Paques and Duchateau, 2007).

Problems with current gene correction strategies include the difficulty in carrying this out in all the cells of a whole animal as the process doesn’t work very well (it was found to correct DNA in less than 0.1% of the cells in a mouse model of Duchenne muscular dystrophy (Kapsa *et al.*, 2001)). It

may be necessary to put the short stretches of DNA in to the cells many times (Kapsa *et al.*, 2001). There is also a risk that the short stretches of DNA could interfere with other genes, possibly stopping them working, and the long term risks are currently unknown.

Gene correction has been used successfully in several animal models of disease; correction of a zebrafish model of Menkes disease using antisense oligonucleotides (Madsen *et al.*, 2008), correction of a mouse model of Pompe Disease (GSD II) by modified single-stranded oligonucleotides (Lu *et al.*, 2003) and correction of the mdx mouse model of Duchenne muscular dystrophy using single-stranded short-fragment homologous replacement (Kapsa *et al.*, 2001).

16.1.2.1 An *in vivo* trial of gene therapy in the sheep model of McArdle disease

Gene replacement using an adenovirus has been tested in the sheep model of McArdle disease (McC Howell, 2006). Two different types of adenovirus which had a copy of human *PYGM* gene were injected into skeletal muscle of McArdle's sheep. The injection caused some muscle damage, which also led to expression of the brain and liver isoforms by regenerating "immature" muscle cells. Muscle cells which had been injected with the adenovirus did produce functional muscle glycogen phosphorylase. Although this appeared to be very successful, the production of muscle glycogen phosphorylase was limited to the region of the injection, and did not spread to other regions of the muscle. As suggested by the authors a method of getting the adenovirus into all regions of the body would be required.

16.2 Therapies to read-through mutations in the mRNA transcript to produce full-length muscle glycogen phosphorylase

16.2.1 Read-through of premature stop codons by aminoglycoside drugs

More than 1800 inherited human genetic disorders (up to 70% of individual cases) can be caused by premature stop codons (Kellermayer, 2006; Welch *et al.*, 2007), usually resulting in lack of protein. Premature stop codons can also produce shortened (truncated) proteins which can cause disruption in the cell and sometimes cause a disease (Frischmeyer and Dietz, 1999).

Aminoglycosides are a group of antibiotics already used in humans. Aminoglycoside antibiotics can bind to different parts of the ribosome and interfere with the production of protein. At a low level this can be used therapeutically to allow the ribosome to ignore and read-through premature stop codons, resulting in production of full-length protein. However, at a higher concentration, this may interfere with protein production leading to cell death. Wolstencroft *et al.* (2005) tested six aminoglycosides: geneticin, gentamicin, lividomycin, streptomycin, tobramycin and amikacin in a cell model of Spinal Muscular Atrophy. Spinal Muscular Atrophy is a disease caused by the lack of several SMN proteins. They found that two of the aminoglycosides caused read-through of premature stop codons which increased levels of the SMN protein. Kimura *et al.* (2005) treated muscle cells which were a cell model of Duchenne muscular dystrophy with gentamicin, which caused read-through of a premature stop codon mutation in the dystrophin gene.

A premature stop codon (the codon is TGA) causes the R50X amino acid mutation in about 80% of UK McArdle patients (DiMauro *et al.*, 2002). It is possible that aminoglycosides could be used to read-through the premature stop codon and produce full-length functional muscle glycogen phosphorylase. Schroers *et al.* (2006) tested whether gentamicin could be used as a treatment to

enable read-through of R50X and R270X premature stop codons in the *PYGM* gene in McArdle patients. They treated four patients with gentamicin sulphate at 8mg/kg/day intravenously for 10 minutes each day for 10 days. No increase in amounts of functional phosphorylase was seen with gentamicin in the experiments in McArdle people. Possible explanations for this lack of success could be: A) the wrong amount of gentamicin was used. Further studies using various different amounts of gentamicin could be performed to find out which concentration is best. B) The treatment needs to be continued for longer. It is not known how quickly the muscle cells would begin to respond to gentamicin. It may be that a longer period of treatment would be needed. Further studies could include giving McArdle people the treatment for longer periods of time. C) Perhaps the biggest challenge in treating patients with the R50X mutation is caused by an absence of mRNA for the treatment to work on. Read-through therapies such as aminoglycoside drugs and also PTC124/Ataluren require *PYGM* mRNA to be present. (See section 3.1 for an explanation of mRNA). However, it is known that *PYGM* mRNA which has the R50X mutation is destroyed by a process called nonsense-mediated decay. (Nonsense-mediated decay is explained further in section 3.2.1.1.) If the mRNA is destroyed, then there is nothing available for the aminoglycoside treatment to act upon. Only some mutations (only premature stop codons) are destroyed by nonsense-mediated decay, and more may be identified in the future. At the moment, it is known that the R50X mutation is destroyed by nonsense-mediated decay, but it is not known whether the R270X mutation is affected by nonsense-mediated decay too. If both *PYGM* mRNA with either R50X or R270X mutations are destroyed by nonsense-mediated decay, then that could explain why the gentamicin treatment did not work in the McArdle people tested.

Schroers *et al.* (2006) also took muscle cells from one person and tested them with different concentrations of gentamicin (zero, 400 or 1000ug/ml) for 5 days. No increase in amounts of functional phosphorylase was seen with gentamicin in either the experiments in people or in cells. However, this experiment was flawed because they didn't get muscle cells from a person who was unaffected by McArdle's and show that muscle glycogen phosphorylase was produced in culture. It is therefore not possible to determine whether the lack of results was because a) muscle glycogen phosphorylase is not produced by cells in culture even when the cells are from unaffected people, or b) gentamicin treatment did not produce an increase in muscle glycogen phosphorylase. (The problems with trying to use muscle cells as a model of McArdle's are discussed in section 15.1.4).

One worry would be whether an aminoglycoside would read-through the stop codons which are naturally found at the end of a gene. These natural stop codons play an important role in telling the ribosome that it has reached the end of making a protein. The good news is that aminoglycosides seem to work better on premature stop codons and have less effect on natural stop codons. Aminoglycosides are unlikely to read-through the natural stop codon of the gene because there are often multiple stop codons. A new drug called Ataluren (formerly called PTC124) has been shown not to read-through multiple stop codons (Welch *et al.*, 2007).

16.2.1.1 The future of read-through drugs: Ataluren (also called PTC124)

Before Ataluren was developed, gentamicin had been the most promising aminoglycoside drug, and read-through experiments had been done in the *mdx* mouse model of Duchenne muscular dystrophy and in the mouse model of cystic fibrosis. However, gentamicin was not highly effective, and had damaging side effects because it was toxic and damaging to the kidney and ear. An additional problem was that gentamicin had to be injected into the areas of the body needing treatment. In

contrast, Ataluren could be taken orally (by mouth) (Du *et al.*, 2008). Ataluren is not an aminoglycoside, but works in a similar manner. “PTC124 [Ataluren] is a novel, non-antibiotic drug which promotes read-through of mutant stop codons in mRNA” (Bönnemann *et al.*, 2007). Ataluren has only mild to moderate adverse side effects, which do not increase with increased dosage.

There are three different stop codons (TAA, TAG and TGA) which can occur in a gene. Any of them can be premature stop codons. Some aminoglycosides are better at reading-through one stop codon than another. Ataluren was shown to be able to read-through all three premature stop codons in a cell model. TGA was the stop codon which was most efficiently read-through by Ataluren (Welch *et al.*, 2007). Ataluren has been tested on muscle cells from humans with Duchenne muscular dystrophy and on muscle cells from the *mdx* mouse model of Duchenne muscular dystrophy. In these muscle cells, Ataluren was able to read-through a premature stop codon so that dystrophin was produced. Ataluren also helped to improve muscle function after 2-8 weeks of treatment when given to the *mdx* mice (Welch *et al.*, 2007). Ataluren was found to read-through the G542X premature stop codon mutation in a mouse model of cystic fibrosis. This resulted in production of the CFTR protein. Mutations in the CFTR protein can reduce the chloride currents in humans and mice with cystic fibrosis. When mice with cystic fibrosis were treated with Ataluren, their chloride currents were increased to 24-29% that of normal mice (Du *et al.*, 2008).

Ataluren is still in development but could be a promising potential treatment for McArdle disease; however, premature stop codons (such as R50X) often induce nonsense mediated decay, which causes rapid destruction of *PYGM* mRNA. A read-through drug would need to protect mRNA from nonsense mediated decay to allow it to remain present for long enough for the ribosome to read-through the stop codon and produce full length protein. There have been no published data to suggest that Ataluren may stabilize mRNA or protect it from nonsense mediated.

16.2.2 Therapeutic exon skipping

As discussed in section 17.4, splicing occurs to mRNA whereby the coding regions (exons) are spliced (joined) together, and the non-coding regions (introns) are discarded. Exon skipping can be done by adding a short stretch of DNA (called an oligonucleotide). This can be used to help the cell to ignore an exon which contains a mutation, and remove it during splicing. One form of therapy for diseases caused by a single premature stop codon mutation or a single missense mutation is to skip (avoid) the exon which contains the mutation. This form of therapy is not suitable for some other forms of genetic disease such as increased triplet repeats – like Huntington’s Disease.

Structural proteins act as building blocks to provide structure to the cell. Exon skipping appears to be successful in genetic diseases caused by mutations in structural proteins. Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin protein which lead to a loss of protein in the muscle cells. Dystrophin is a long protein with many exons. The aim of exon skipping is to skip past the exon with the mutation so that an almost full length, functional protein can be produced. The protein that is produced as the results of this exon skipping is sufficient to function and to reduce the severity of the disease.

Enzymes are proteins which change something from one thing to another. Exon skipping does not seem to be a successful way to treat genetic diseases caused by a mutation in an enzyme. Many enzymes (including muscle glycogen phosphorylase) must form specific shapes to be functional.

Mutations at almost any place in the amino acid chain of muscle glycogen phosphorylase prevent correct formation or functioning of muscle glycogen phosphorylase. For example, skipping the first exon of *PYGM*, which contains the R50X mutation, would seem a likely target to treat McArdle disease, but it contains Serine 15, an essential binding site for the enzyme. It therefore seems that exon skipping would not be a suitable therapy for McArdle's.

Fernandez-Cadenza *et al.* (2003) reported a McArdle person who had the Y573X premature stop codon and the K608K silent mutation. Some of the mRNA with the K608K mutation had skipped (did not contain) exon 15 of *PYGM*. This mRNA could be a natural example of exon-skipping. However, no functional muscle glycogen phosphorylase was detected in this McArdle person. This natural experiment suggests that exon skipping wouldn't work for McArdle people.

16.3 Therapies to replace absent muscle glycogen phosphorylase within skeletal muscle cells

16.3.1 Upregulation of an alternative isoform (such as brain/foetal glycogen phosphorylase)

It may be possible to alleviate symptoms of McArdle disease by upregulating the production of the brain or liver isoform of glycogen phosphorylase in the skeletal muscle cells. Within mature skeletal muscle cells, the expression of many genes, including foetal genes, is prevented. The DNA containing these genes is tightly wound around proteins called histones (the DNA is like cotton wrapped around cotton reels). While the DNA is tightly wound around the histones, the cell cannot use the genes to make proteins. Valproate/valproic acid is an enzyme which can help the DNA to become unwound and detached from the histones. Once the DNA is unwound, the cell can use the genes to make proteins. In adult human skeletal muscle, foetal/brain glycogen phosphorylase is not produced. Theoretically, treatment with valproate could cause the DNA to be unwound so that the cell can use the brain glycogen phosphorylase DNA to make brain glycogen phosphorylase. Brain glycogen phosphorylase could then replace muscle glycogen phosphorylase in the muscles of McArdle people. Valproate is commonly used as an anti-epilepsy drug which stabilises electrical activity in the brain, and is already approved for use in humans. Valproate is now being trialled therapeutically for several muscle diseases such as spinal muscular atrophy (SMA) (Tsai *et al.*, 2008), DMD (Gurpur *et al.*, 2009), and amyotrophic lateral sclerosis (ALS) (Rouaux *et al.*, 2007).

16.3.1.1 Trials of valproate and notexin in the sheep model of McArdle disease

A trial was carried out whereby valproate or saline was injected into the muscles of McArdle sheep by Howell *et al.* (Saline is salt solution in water. It is used as a placebo as it is not known to have any effect). Nine days after the injection there were 2861 muscle fibres which were expressing phosphorylase in the muscle which had been injected with valproate. There were 283 muscle fibres expressing phosphorylase in the muscle injected with saline. Since this could have been due to physical injury from the needle, an oral trial was carried out. McArdle's lambs were given a drink of valproate similar to the way in which humans take valproate. Preliminary results indicated that phosphorylase was present in some of the fibres (Howell, 2008). This treatment has a lot of promise as a therapy for McArdle's, but further experiments will be needed to determine whether valproate also activates other proteins, which could have a negative effect.

Notexin, a toxin from the tiger snake, damages muscle fibres, leading to regeneration. Regenerating fibres express the foetal/brain isoform of glycogen phosphorylase, but once they are mature, they stop expression of the foetal isoform, and switch to expression of the muscle isoform. Trials were carried out by injecting notexin into muscles of the McArdle's sheep. Brain and liver isoforms of glycogen phosphorylase were expressed (McC Howell, 2008) due to damage from either the notexin or physical damage from the injection. The expression of the brain and liver isoforms of glycogen phosphorylase improved the strength and fatigueability of the muscle fibres in the treated McArdle sheep, although not totally. This is not a very practical form of treatment for McArdle people, as it would involve the use of a toxin which damages muscles and would involve frequent injections throughout skeletal muscles.

16.3.2 Enzyme replacement therapy

More than 3,500 people across the world have received enzyme replacement therapy, and have subsequently had a better quality of life (Weinreb *et al.*, 2005). At present enzyme replacement therapy (ERT) is available for three lysosomal diseases: Type 1 Gaucher Disease (GD1), Fabry Disease, Hunter syndrome (MPS II), and also Maroteaus-Lamy syndrome (MPS VI). It is also available for Glycogen Storage Disease II (Pompe disease). An account of the development of ERT is given in the film "Extraordinary Measures" produced by CBS Film Company and first shown in 2010. This film is about the development of enzyme replacement therapy (ERT) as a treatment for Pompe disease.

Diseases caused by the lack of an enzyme in the lysosome can be corrected by ERT. The replacement enzyme is manufactured by a drug company. One method is to put the gene for that enzyme into special cells in a laboratory which then use the gene to produce lots of enzyme. The enzyme is then purified, and infused into the patient. The enzyme is taken around the body in the bloodstream, and then taken into muscle cells. When muscle cells take up proteins from the bloodstream, they usually put them into the lysosome. The lysosome is like the recycling centre of the cell.

Diseases caused by the lack of an enzyme in the lysosome can be treated because the cells take up the enzyme from the bloodstream and transport it into the lysosome. The lysosome is the desired location for the enzyme, so it treats the disease. Myozyme (manufactured by Genzyme) is a form of ERT which is given as an intravenous injection. Myozyme provides human acid α -glucosidase, which is lacking in GSD II /Pompe disease. This was the first example of ERT to skeletal muscle. This therapy has aided cardiac muscle and extended the life of infant patients, but has been less effective in skeletal muscle than hoped. It was successful in decreasing the amount of glycogen stored in the skeletal muscle (Schoser *et al.*, 2008). Gaucher disease is an autosomal recessive lysosomal storage disease caused by a deficiency in β -glucocerebrosidase enzyme. Recombinant human replacement enzyme Cerezyme (made by Genzyme) is given intravenously and reduces the symptoms (Weinreb, 2008). Laronidase enzyme replacement therapy has been used for MPS I since 2003, and recombinant arylsulfatase B (Naglazyme, made by Biomarin (Bailey, 2008)) used for MPS VI since 2005. Irdursifase (Elaprase made by ShireHGT (Bailey, 2008)) is now available for treatment for MPS II (Heese, 2008). These are all rare inherited metabolic disorders caused by lack of an enzyme. Without treatment, cell damage occurs, leading to physical and mental impairment. The number of diseases which can be treated with intravenous ERT is continually expanding; however, it is still generally restricted to defects based in the lysosome. An exception is oral ERT which is used to

replace enzymes which are needed in the pancreas in cystic fibrosis patients (Walkowiak *et al.*, 2005).

Negative reactions such as anaphylactic shock, tachycardia, hypertension, chest and throat tightness, nausea, vomiting, rashes and headaches can occur during intravenous administration, which is initially conducted in a medical setting. In some Pompe patients, their bodies viewed ERT as foreign and produced antibodies against the enzyme. This was particularly likely if the Pompe patients did not have any enzyme (not even non-functional enzyme) before they received ERT. These antibodies made further ERT unsuccessful (Schoser *et al.*, 2008). A limitation of ERT is that at present it can't cross the blood-brain barrier (Brady and Schiffmann, 2004).

Since the symptoms of McArdle disease are caused by the lack of the enzyme muscle glycogen phosphorylase, one obvious form of treatment would be ERT. At the moment ERT is only used to treat lysosomal storage diseases. There is no published data of any enzyme therapy being tried in people with McArdle's or non-lysosomal defects (apart from oral treatment). This may be because McArdle disease is less suitable for enzyme therapy. Muscle glycogen phosphorylase is needed in the sarcoplasm/cytoplasm of the muscle cells, which is the wrong location for enzyme therapy. In ERT, the enzyme is infused into the bloodstream. It is then taken up by the cells. Anything which the cells take up is usually put into the lysosome, where they are broken down into smaller parts for reuse. ERT works for lysosomal storage diseases because the enzyme is taken into the lysosome - exactly the place it is needed. This would not work for McArdle disease as the enzyme is needed in a different place; the cytoplasm/sarcoplasm. (Please note: the enzyme needed in Pompe disease is different to the one needed in McArdle disease.) At the moment, no-one has found a way to make the cell take up the enzyme and put it into the cytoplasm. If muscle glycogen phosphorylase was given as ERT, it would probably be taken into the lysosome and destroyed. ERT is unlikely to be a suitable therapy for McArdle's unless a method of packaging the enzyme is developed which tells the cell to put it into the cytoplasm and not the lysosome. I am not aware of any scientists working on ERT as a treatment for McArdle disease at the moment, probably for the reasons I've just outlined.

16.3.3 Enzyme chaperone therapy

It is likely that many of the missense mutations in muscle glycogen phosphorylase may prevent the enzyme from forming the correct structure. Muscle glycogen phosphorylase with a missense mutation may have the wrong shape. The cell may recognise that the structure is wrong and destroy the enzyme. Some chemicals (called "pharmacological chaperones" or "active site inhibitors") may be able to bind to muscle glycogen phosphorylase which contains a mutation. This would probably be a chemical that was similar in shape to glucose or glycogen. These chaperones may be able to help muscle glycogen phosphorylase form the correct shape. This may have several benefits. It may prevent the quality control system of the cell from recognising or destroying the enzyme. It may also help muscle glycogen phosphorylase begin to work properly. Enzyme chaperone therapy could only be used as a treatment for a person who had a missense mutation in the *PYGM* gene. It would not work for a person who had a premature stop codon. Enzyme chaperone therapy has not been tested as a treatment for McArdle's, so at the moment it is only a theoretical treatment for McArdle disease. However, enzyme chaperone therapy has been tested for some other glycogen storage diseases.

At the moment, the only commercially available pharmacological chaperone therapy available is for patients with GD1/Gaucher disease, and is available as an oral treatment (Alfonso *et al.*, 2005; Weinreb *et al.*, 2005; Pastores *et al.*, 2009). The treatment available for Gaucher disease is called “N-butyl- deoxynojirimycin” (NB-DNJ; Miglustat made by Actelion), and is a chemical that is very similar in shape to glucose (a glucose analogue). A similar chemical called “deoxynojirimycin” (DNJ) may be a treatment for Pompe disease. DNJ (or some chemicals made from it) have been found to increase the amount and activity of acid alpha-glucosidase (GAA) in Pompe disease, but this result varied depending upon the exact missense mutation (Schoser *et al.*, 2008). DNJ is similar in shape to glucose, so the GAA enzyme bound to it. DNJ allowed the GAA enzyme to be made properly and to be functional. Increasing amounts of DNJ allowed an increased amount of enzyme to be made when it contained a missense mutation, but not when it contained a nonsense mutation (Okumiya *et al.*, 2007). However, DNJ is not yet in used as a standard treatment for Pompe disease.

16.4 A discussion of research into therapies for McArdle’s

There are many ways in which therapies could help to reduce symptoms of McArdle’s. All of these are covered in this Handbook, and are summarised in Table 16.1. I have included therapies which at present are only theoretical, and have not yet been tested as potential treatments for McArdle’s. Some of these therapies have only been tested for a few different diseases at present, and are relatively new. For example, enzyme chaperone therapy was first suggested in 1999. Ten years is a relatively short period of time for a therapy to be explored by scientists and to become a treatment used for patients.

Future research may reveal other phenotype modulators, which have not yet been discovered. It may be possible to use drugs that work with these genes (in a similar way to the use of ACE inhibitors), to improve symptoms of McArdle’s.

Type of therapy (Section of this Handbook)	Purpose of the therapy	Current recommendations from recent research	Comments	How quickly is this treatment likely to be available?
Frequent moderate aerobic exercise (Section 4.2)	Helps to improve the ability of the heart to pump blood around the body, to get more oxygen per breath, and for the muscles to use energy more efficiently.	This is highly recommended.	This is one of the best forms of treatment for McArdle's at present.	Available now.
Sugary drink before exercise (Section 6.4.5)	Quickly provide muscles with energy before exercise.	Can be used 5 minutes before exercise, can make it easier to exercise.	Having a sugary drink can lead to weight gain. It may reduce the ability to get into second wind.	Available now.
Diet (Section 6.6)	How to get the maximum amount of energy from food you eat, and ensure enough protein is eaten for muscle growth.	A diet high in carbohydrate and moderate in protein.	There is still some debate about what the ideal diet is for McArdle people.	Available now.
Supplements (Section 7)	Various	Low dose creatine supplements may help. No other supplements shown to help.	High dose creatine can increase muscle pain.	Available now.
ACE inhibitor drugs e.g. ramipril (Sections 7.1.7 and 9.3.1)	May increase the amount of glucose taken from the bloodstream into the muscles to give muscles energy.	No recommendations at present.	It would only be a treatment for McArdle people who have the DD isoform of the ACE gene. McArdle people would have to be genetically tested to see if this treatment was suitable for them.	Not available, as not enough evidence to justify its use. If more research was carried out, it could be available relatively quickly as it is already approved for use in humans.

Type of therapy (Section of this Handbook)	Purpose of the therapy	Current recommendations from recent research	Comments	How quickly is this treatment likely to be available?
Giving insulin as treatment for insulin resistance (Section 13.4)	May increase the amount of glucose taken from the bloodstream into the muscles to give muscles energy.	No recommendations at present.	Not enough research has been done. It is not known whether the insulin resistance seen in McArdle people is similar or different to type 2 diabetes.	Not available, as not enough evidence to justify its use. If more research was carried out, it could be available relatively quickly as it is already approved for use in humans.
Gene replacement therapy or gene correction (section 16.1)	Add a correct copy of the PYGM gene or correct the mutation	No recommendations at present.	At present, this is just a theoretical treatment. There are too many risks for this to be considered as a treatment. If these risks could be overcome, it could provide a permanent cure for McArdle's.	Not available. Not likely to be available for a long time.
Read-through of premature stop codons with aminoglycoside drugs (Section 16.2.1)	Read-through premature stop codon to produce full length enzyme.	No recommendations at present.	A single study of one aminoglycoside drug (gentamicin) found that it was not successful as a treatment for McArdle's. Aminoglycoside drugs such as gentamicin are known to have side effects including causing damage to the kidney and the ear. It isn't known if the full-length enzyme would be functional. Would not work if nonsense-mediated decay destroys PYGM mRNA which has the R50X mutation. Would not work on mutations which are a frameshift followed by a stop codon.	Not available, as not enough evidence to justify its use. If more research was carried out, it could be available relatively quickly as it is already approved for use in humans.

Type of therapy (Section of this Handbook)	Purpose of the therapy	Current recommendations from recent research	Comments	How quickly is this treatment likely to be available?
Read-through of premature stop codons with PTC124/Ataluren, or drugs which work in the same way (Section 16.2.1)	Read-through premature stop codon to produce full length enzyme.	No recommendations at present.	Hasn't been tried for McArdle's. It isn't known if the full-length enzyme would be functional. Would not work if nonsense-mediated decay destroys <i>PYGM</i> mRNA which has the R50X mutation. Would not work on mutations which are a frameshift followed by a stop codon.	Not available as still in development. Clinical trials are underway to treat similar muscle diseases. If successful and approved for human use, it may be available for clinical trials for McArdle's. These clinical trials would have to show that treatment would be successful before it would become available as a treatment for McArdle's.
Exon skipping (Section 16.2.2)	Skip (avoid) an exon which contains a mutation, producing a version of the enzyme which isn't quite full-length.	No recommendations at present.	At present, this is just a theoretical treatment. Highly unlikely to work as a treatment for McArdle's. No research has been done into it.	Not likely to become available.
Valproate/valproic acid, or other drugs which work in the same way (Section 16.3.1)	Upregulation of an alternative isoform of glycogen phosphorylase, which would be functional	No recommendations at present.	Valproate is already licensed for use in humans (to treat epilepsy). Some success has been seen in treating McArdle's sheep. It is not known if it would upregulate other genes, which you don't want turned on.	Not available, as not enough evidence to justify its use. If more research was carried out, it could be available relatively quickly as it already approved for use in humans.

Type of therapy (Section of this Handbook)	Purpose of the therapy	Current recommendations from recent research	Comments	How quickly is this treatment likely to be available?
Notexin (section 16.3.1.1)	Causes muscle damage. Regenerating muscle temporarily produces the brain and/or liver isoform of glycogen phosphorylase.	No recommendations at present.	Not a practical treatment as it would require inducing muscle damage.	Not likely to become available.
Enzyme replacement therapy (section 16.3.2)	An injection of functional enzyme into the bloodstream which would go to the muscle cells.	No recommendations at present.	At present, enzyme replacement therapy only works for lysosomal storage diseases. The current method would not work for McArdle's. If a method is found in future to label the enzyme so that it is taken in the cytoplasm of the muscle cells, then it could be a potential treatment. It has not yet been tried as a treatment for McArdle's.	Not likely to become available, as the current method would not work for McArdle's.
Enzyme chaperone therapy (section 16.3.3)	Provide a small molecule, similar to glucose, which helps muscle glycogen phosphorylase that contains a mutation fold into the correct shape, and hopefully become functional.	No recommendations at present.	Has not been tried as a treatment for McArdle's. It is not known if a chaperone would help muscle glycogen phosphorylase fold correctly, or if it would become functional.	Not available, as not enough evidence to justify its use. It may take a long time to produce enough scientific evidence to justify clinical trials.

Table 16.1 A summary of current, future and potential treatments for McArdle's (including those which are not suitable for McArdle's). Information in this table is based upon the information given (with references) throughout this Handbook, and my personal opinion.

17 Details about this Handbook and the information in it

Research papers are used as a way for scientists and medical doctors to communicate with each other the results of clinical trials, scientific research, or if they notice something unusual or unique in a patient. Clinical trials are the only way to reliably determine whether a potential treatment for McArdle's disease really works. Clinical trials can involve testing drugs, but can also include testing different exercise regimes or diets (such as a sugary drink before exercise) to find out whether the treatment has any positive (or negative) effect upon the participants. It is important that clinical trials are carefully planned and performed, ideally so that the participants do not know if they are receiving an active drug or an (inactive) placebo. Researchers usually publish the results of the clinical trial as a scientific paper. The results should be published whether the treatment has a positive effect, negative effect or no effect. This provides a method of communicating the results to other scientists and medical professionals, who can use this information to decide whether or not to give their McArdle patients the treatments described.

This handbook is written using information which Kathryn Birch obtained mostly from reading scientific and medical research papers, as well as some text books. Where possible, for each statement, the author's name and date of the published paper or book is given. The name and date can be used to look up the full information about each paper from the References list at the end of the Handbook. Many research papers can now be bought online from the publisher, and downloaded onto your computer, so that the original publication can be read.

17.1 The purpose of this Handbook

The purpose of this Handbook is to clearly explain medical and scientific research so that it can be understood by McArdle people and people interested in McArdle disease. The information provided is as up-to-date and accurate as possible, but reflects current theories and opinions. Future research may improve the understanding of McArdle's and change these theories.

Information in this Handbook is not intended as medical advice, it is not intended to replace medical advice, and is not intended to be a guide to treatments for McArdle's. The author (Kathryn Birch) has no medical training, and is not qualified to offer medical advice.

17.2 About the author

Kathryn Birch (nee Wright) is a scientist and has not had any medical training. She studied Biology, English Literature, Mathematics and Music GCE "A" Levels at secondary school, before reading for an undergraduate degree in Natural Sciences at Cambridge University, UK, specialising in Genetics in her final year. She worked for three years as a Research Assistant in a laboratory in Berkshire, learning experimental techniques. She then moved to a research lab at the RJ&AH Orthopaedic Hospital in Oswestry, UK, where she carried out a Ph.D. project creating cell models of McArdle disease, through Keele University, UK. Kathryn Birch had the idea of writing this Handbook during her Ph.D., when she became aware that a lot of the medical and scientific research into McArdle disease was inaccessible to people with McArdle's because it was either written in complex scientific language or too expensive to obtain.

17.3 How to understand references given in this Handbook

A reference is the original paper or book which I have used to find out information. Where possible, each sentence or paragraph is referenced. References given in this Handbook enable the reader to identify and read the same paper or book which I read before I wrote that sentence or paragraph. This allows the reader to get more information than I provided, or to check if I reported the information accurately. (If you think I have made a mistake, please visit the AGSD-UK web site at: www.agsd.org.uk and use the "Contact Us" page, choosing "McArdle Disease Handbook".)

References are given as either:

Birch *et al.* (2009) said grass is green. Or Grass is green (Birch *et al.*, 2009).

In these examples, Birch is the name of the lead author who wrote the paper or book, and the date is the date when the paper or book was published. The title of the paper or book can be found in the References list (section 19) at the end of the Handbook. References are listed alphabetically, in order of the surname of the first author. So, for example, Birch *et al.* (2009) would be near the start of the list of references. You will be able to look up the whole name of the paper or book, which could look like;

Birch KE and Birch EK (2009) Studies of Grass. *Journal of plants* **2**: 133-134.

You can then use these details to obtain the paper from Journal of Plants, pages 133-134. This paper is located in volume number 2. (This reference has been invented, to serve as an example.)

If no reference is given, and it includes phrases like “I think...”, or “my theory”, this indicates that it is my theory, which has not been scientifically proven.

17.4 A note about the names of the muscle glycogen phosphorylase gene, mRNA and enzyme

There are standard ways to write the names of the muscle glycogen phosphorylase gene, mRNA, and protein, which are useful to know if you are reading scientific papers. These are summarised in Table 17.1. Although only humans are discussed in this section, animal models of McArdle disease are discussed further in section 15.

For clarity, in this Handbook “muscle glycogen phosphorylase” has been used rather than “PYGM”.

	Humans	Animals
Name of the gene	<i>PYGM</i> (capitals, italic)	<i>Pygm</i> (mixed case, italic)
Names of the mRNA	<i>PYGM</i> (capitals, italic)	<i>Pygm</i> (mixed case, italic)
Name of the enzyme	PYGM (capitals, non italic)	PYGM (capitals, non italic)

Table 17.1 Standard ways to write the gene, mRNA and enzyme name for muscle glycogen phosphorylase (correct in 2011).

17.5 How to read medical/scientific papers critically

Rather than simply accepting everything that is stated, scientific papers (and other documents such as this Handbook) should be read critically as the data in them and the interpretation of the results could be affected by many things, some of which are outlined below.

17.5.1.1 What is the date (year) when the paper was published?

New research and understanding can mean that the advice in old research papers is now inappropriate or incorrect. For example, in the past, McArdle people were recommended not to exercise, but current advice is that frequent moderate exercise is best for McArdle people.

Some older research papers can be hard to understand and interpret as only limited information was known at the time. For example, in the past, some researchers did not realise that there are different isoforms of glycogen phosphorylase, so they do not specify in their research paper which isoform of glycogen phosphorylase they studied, which can make it hard to understand.

17.5.1.2 Who are the authors?

Authors may be biased. Not all McArdle’s specialists share the same point of view. They may emphasise their point of view strongly in a paper, even if there is very little scientific evidence to support this view. If you find more than two papers, which have no authors in common, but both give the same conclusion, then it is likely that it is a genuine result.

17.5.1.3 How good is the clinical trial?

Not all clinical trials are equal. The best clinical trials are double blind clinical trials (where neither the participant nor the researcher knows whether the participant is receiving the treatment or a placebo). Single case studies are of limited use, whereas multi-person trials reduce the effect of any

non-compliance, external factors, etc. It is important to have good controls. The placebo effect should be avoided. (See section 17.6.1 for further information on clinical trials).

17.5.1.4 Was the result “statistically significant”?

A statistically significant result suggests that a treatment probably does cause an effect and that the changes observed are unlikely to have occurred by chance (see section 17.6.6). However, different statistical tests can give different results, and some scientists (incorrectly) try lots of different tests until they find one which gives the result they want, which is poor scientific technique.

17.5.1.5 Errors can occur

Despite several levels of proof reading before a paper is published, errors can still occur. For example, I believe that the mutation which Hadjigeorgiou *et al.* (2002) describe as a R207X mutation at c.808 in exon 6 is actually the R270X mutation, but the authors refer to it throughout the paper incorrectly as R207X.

17.5.1.6 The same person may be mentioned in more than one study

As McArdle’s is very rare, the same person may be mentioned in more than one paper, especially if they have an unusual complication. It can require quite a bit of detective work to figure out if this is the case. But it is important because if one individual has particularly unusual symptoms, they may be reported on more than one paper. If you didn’t realise this (or your family doctor didn’t realise), you may think that the symptom is much more common than it really is. For example, there is a case of a woman with McArdle’s who has respiratory problems because the muscles involved in breathing didn’t work as well as they should. But she is mentioned in two papers; “McArdle disease presenting as unexplained dyspnea in a young woman” by Voduc *et al.* (2004), and “Variable presentation of the clinical phenotype of McArdle disease in a kindred harbouring a novel compound genotype in the muscle glycogen phosphorylase gene” by Paradas (2005). The clue is usually (although not in this case) if the two papers have one or more author in common. If these two papers are taken together, it suggests that McArdle disease might cause respiratory problems, but in fact both are describing the same person.

17.5.1.7 The numbers of the mutations have changed

When reading papers about McArdle’s, it is important to remember that the mutation formerly known as “R49X” is now known as “R50X”. The reason is as follows. In the *PYGM* gene, the DNA code and the mRNA have the first amino acid of muscle glycogen phosphorylase as methionine (single letter code “M”). (This is shown in section 3.1.1.) When a protein is made, the methionine is used as the first amino acid of the amino acid sequence. However, in the process of making the enzyme, the first methionine is chopped off and removed. When the first scientific studies were performed on muscle glycogen phosphorylase, scientists studied the enzyme, and found that it had 841 amino acids. At this time the mutation was known as “R49X”. However, at a much later date, scientists studied the *PYGM* gene, and discovered that there was genetic code for the first methionine, even though it was chopped off in the process of making the enzyme. Muscle glycogen phosphorylase is now considered to have 842 amino acids and the “R49X” mutation has been renamed as “R50X”.

When reading papers, it can be confusing trying to understand whether the mutation being described is an old one or is newly discovered. I would suggest looking out for whether the old numbering scheme of “R49X” and “G204S” or new numbering scheme of “R50X” and “G205S” are being used.

17.6 An introduction to clinical trials

Clinical trials are an essential method of testing whether a potential treatment for McArdle’s (or any other disease) really works. Clinical trials are conducted by researchers; either scientists or doctors, or the two working together. Clinical trials are based upon a hypothesis that a particular treatment may help to alleviate symptoms of a disease. For example; a theory that taking drug X may enable McArdle people to exercise for longer. Clinical trials are designed to test whether this theory is correct. The best clinical trials have the components described below: they include a placebo, are randomised, are double blind, and are statistically significant.

Although clinical trials often involve testing new or existing drugs, they do not need to involve drugs. Non-drug clinical trials carried out on McArdle people have included prescribing regular exercise and testing a sugary drink.

Clinical trials must have ways of measuring whether the treatment has produced any benefit. The best ways are to measure something which the participant has little or no control over. Examples would include using ^{31}P MRS to measure changes within the cells, measuring heart rate, or VO_2 max (6.4.4.1). It is less accurate to ask participants how they feel – for example whether they feel that they have much less muscle pain. It can be very hard for participants to give useful and accurate answers, and hard for the researchers to use this answer to determine if a treatment is working. For example, if the participant has just had an argument with their partner, they may feel more negative about muscle pain than on a different day – but this would be unrelated to a treatment.

The researchers carrying out a clinical trial will want to publish the results once the trial is completed. The results should be published whether or not the treatment has a positive effect, negative effect or no effect. Positive results may lead doctors to start prescribing the treatment/drug for their McArdle’s patients. Negative results may warn doctors to avoid prescribing the treatment/drug for their McArdle’s patients. Often, clinical trials are first done on small group of participants, and if a positive effect is seen, they will be repeated on a larger number of participants. It is ideal to wait until a positive result has been seen in a large scale clinical trial before considering it as a conventional treatment for that disease. In a rare disease like McArdle’s, there may not be enough people with McArdle’s for large scale trials to be possible.

Most countries now have very strict guidelines for researchers wishing to carry out clinical trials. The trials have to be approved by a committee, often at the hospital where the trial would be carried out. The committee will consider whether the potential side effects and risks of the treatment are worthwhile compared to the potential benefit of the treatment. The researchers also have to prepare information sheets written in plain (non-technical) language, to ensure that the participants fully understand all the risks and tests involved. For example, that the participants are willing to give a blood sample or undertake a muscle biopsy if that is required. When participants fully understand the risks and tests involved, and then agree to take part, this is known as “informed consent”. In the UK, and some other countries, researchers are not allowed to pay participants to take part in clinical

trials, although they are allowed to pay a certain amount for travel and other costs incurred by the participant in getting to the location where the trial is taking place.

Most trials involve comparison; for example, a group of McArdle people may be compared to a group of people unaffected by McArdle's. (A person who is "unaffected by McArdle's" is often described as a "control" in scientific papers.) Or, a group of McArdle people may be given a treatment, and compared to a group of McArdle people who were not given the treatment.

17.6.1 The placebo effect

During a clinical trial, the "control" group are the group of people who do not receive the treatment, and in many cases these people receive the placebo. A clinical trial must be carefully planned in order to determine whether a treatment is having a real effect or a "placebo effect". The placebo effect is a well-known phenomenon whereby some people feel that their symptoms improve even if they are given a pill with no active medicine – for example a pill made of sugar or flour. The placebo effect was demonstrated in a clinical trial of dantrolene sodium carried out by Poels *et al.* (1990); some improvement was felt by one McArdle person on treatment and three McArdle people taking the placebo. There are various explanations for the placebo effect. Taking a placebo pill may change the way in which the person perceives their symptoms. Sometimes being part of a clinical trial may make a person feel more important. Having a family doctor/specialist discussing McArdle's, acknowledging symptoms and providing support and encouragement may lead to a more positive view of the symptoms. (This is why cognitive behaviour therapy (CBT) is sometimes used. CBT can help people come to terms with symptoms and limitations of their condition even if no treatment or cure is available.) Some participants, either deliberately or unknowingly, will give the researcher the answer they think they want to hear.

To determine whether a drug treatment is having a real or placebo effect, it is important that the people being tested are given either the real drug or a placebo which looks/smells/tastes like the real drug. The participants should not be able to tell the difference between the placebo and the real drug. If the participant doesn't know if they are receiving the placebo or real drug, this is known as a "blind" trial. In the best studies, the researcher also does not know which participants are receiving the real drug or the placebo, and does not find out until the very end of the experiment. If the participant doesn't know if they are receiving the placebo or real drug AND the researcher doesn't know which participants are receiving each treatment, it is known as a "double blind" trial (because both the participant and researcher are blinded to the treatment). If the participant and researcher don't know whether the participant is receiving the treatment or placebo, this is also known as "allocation concealment".

An "open label" trial is when the participant know which drug they are receiving, or know if they are receiving the placebo. This is not such a good trial as participants may be biased by whether or not they are receiving the treatment. Sometimes it is impossible to blind the participant, and the trial has to be open label. One example would be a trial of diet; where it would be very difficult to prevent the participant seeing whether they are receiving a high fat or high carbohydrate meal.

17.6.2 Randomised trials

A really good trial will be designed so that the researcher cannot unwittingly bias the outcome. One way in which this could occur would be if the researcher divides the participants into two groups; for

example so that one set can receive the placebo and the other set receive the real drug. If the researcher picks which people should be in each group, the researcher may not divide the people evenly; one example would be to put all the women in one group and the men in the other – in this case it wouldn't be possible to say if the results were an effect of the real drug or an effect due to differences in gender. Another example would be to put all the fit people in one group and all the unfit people in the other group. These are extreme examples to illustrate the problems of allowing the researcher to choose who goes into which group. A much better method is to allocate each person a number, and to use a computer (or even draw numbers out of a hat) to randomly allocate each person into a group. This removes the possibility of the researcher choosing who goes into which group.

17.6.3 Cross-over trial

A cross-over trial occurs when the participants are divided into two groups; let us call them group A and group B. For the first period of time (several days to several years, depending on the study), group A will receive the placebo and group B will receive the real drug. The researchers will then perform tests to see if the treatments have had any effect, for example on the ability of the participants to exercise. There may then be a “wash-out” period, when no drug/placebo is given. This is to allow the amount of real drug in the body to reduce and be removed by the body. In a cross-over trial, group A will now receive the real drug, and group B will receive the placebo. Further tests will then be performed. A cross-over trial is particularly important when there are only a small number of participants (often the case in trials with McArdle people). If one person was much more fit than the others, this might disproportionately affect the results if no cross-over was performed. For example, if a very fit person was put into the group taking the real drug, and the real drug actually had no effect, the ability of the very fit person to exercise could lead the researchers to think that the drug had helped that person exercise. A cross-over trial allows the researchers to compare results obtained with the real drug and placebo each in the same person.

17.6.4 Single case study

A single case study is when just one participant is studied. Published papers are used by family doctors and scientists as a way of communicating. Single case studies are sometimes reported if a new phenomenon occurs; for example, if it is found that a person with McArdle's had a particularly bad reaction to a drug or treatment. Specialists who read the study will be aware that McArdle's may lead to sensitivity to that drug or treatment, and will be aware to look out for it in the McArdle person they deal with. The disadvantage of single case studies is that it is very hard to determine if a treatment will work in other McArdle people. A single case study cannot determine what other factors may affect whether a treatment may work.

Here is an example of a result from a large scale study which could not have been obtained from a single case study: The *ACE* gene is unrelated to the *PYGM* gene which encodes muscle glycogen phosphorylase (see section 9.3.1 for more information on the *ACE* gene). McArdle people (and other people in the population) may have either the DD, DI or II genotype. It has been found that the drug treatment ramipril only helps people who have the DD genotype for the *ACE* gene (Martinuzzi *et al.*, 2007). It was only possible to find out this result because many McArdle people took part in the drug trial. If only one person had taken part in a single case study, it could have had

very different results. For example, if the one participant had the II genotype, the drug treatment would not have had any effect, and would probably not have been tried again.

A further problem with a single case study (or a study with very few participants) is the lack of statistical significance.

17.6.5 A home trial is an alternative to a clinical trial

The alternative to a clinical trial would be a trial performed at home. Many McArdle people on internet chat groups say that they have carried out home trials. Home trials are not planned or carried out by a researcher. They will not have been assessed by a committee to decide if they have any health risks or negative effects. People carrying out a home trial on themselves are likely to know whether they are taking the treatment/drug or not, which does not exclude the placebo effect. If a home trial suggests that a treatment does work, it is not sufficient evidence to prescribe the treatment to others. It would be sensible to discuss any treatment/drug with your family doctor before carrying out a home trial.

17.6.6 Statistical significance

Clinical trials are usually carried out to determine whether a treatment or drug has a positive (or negative) effect upon participants. However, it is always possible that any changes observed could have occurred by chance, and be unrelated to the treatment. Mathematicians have devised several statistical calculations which can be used to determine the likelihood of a change occurring by chance. These calculations take into account the number of participants, and how great the observed changes are. The result of the calculation can be looked up in a special table to determine if the result is “statistically significant”. (These calculations are nowadays performed using a computer.)

A statistically significant result suggests that a treatment probably does cause an effect and that the changes observed are unlikely to have occurred by chance. A result may be classed as “not statistically significant” if there were not enough participants, or if very little difference was seen between the treatment and non-treatment (or drug and placebo). Single case studies and trials with a small number of participants are less likely to generate statistically significant results. It is possible that if the trial were repeated with more participants, it would generate results that were statistically significant.

An example of a statement in a paper is given below. Lucia *et al.* (2008b) performed some tests to look at the amount of cytokines in the blood of patients (McArdle people) compared to controls (people unaffected by McArdle’s). The authors say “...circulating levels of several cytokines were **significantly higher ($P \leq 0.05$)** in patients than in controls”. The important parts of this sentence are in bold. This can be translated as:

They measured the amount of cytokines in patients and controls, and compared them using a statistical test. “Significantly” means that the statistical test result showed that the levels were statistically different – they appear to be “real” differences and are unlikely to occur by chance. “Higher” obviously tells you that there were more cytokines than in controls. “ $P \leq 0.05$ ” is another part of the result of the statistical test. A result that is $P \leq 0.01$, $P \leq 0.05$ or $P \leq 0.001$, tells you that the statistical test showed that the differences unlikely to occur by chance.

18 Glossary

Most words are defined at the point when they are used in the Handbook. Only scientific or medical words which are used repeatedly in the Handbook are defined below.

Adipose tissue	Special cells in the body which store energy in the form of fatty acids.
Amino acids	The building blocks of proteins.
Amino acid sequence	The order of the amino acids in a protein.
Autosome	A chromosome which does not determine gender.
Carrier	In this Handbook, “carrier” is used to describe a person who has one copy of the <i>PYGM</i> gene without any mutations, and one faulty copy of the <i>PYGM</i> gene which does have a mutation. Carriers usually have approximately half the normal level of functional muscle glycogen phosphorylase. Carriers do not usually have symptoms of McArdle disease. In research papers, carriers of McArdle disease are often described as “heterozygotes”.
Cell culture	Cells obtained from a person or animal (for example, cells obtained by a muscle biopsy from a McArdle person) then grown in a research laboratory.
Chemokines	A sub-group of cytokines, which are small proteins produced by cells.
Chromosome	A structure within the cell which is basically a string of genes.
Codons	The mRNA is translated in triplets with each triplet being used to identify one amino acid. These triplets are known as codons.
Contractures	Severe muscle cramps.
Cytokines	Small proteins which are produced by almost all cells in the body. Cytokines are used by the cells as a method to communicate.
Double blind trial	A trial where neither the participant nor the researcher know which participants are receiving each treatment.
Double trouble	When two unrelated muscle diseases occur in the same person.
Electrolytes	Several compounds including potassium, sodium and calcium. The body must maintain the correct amounts of these compounds in order to function properly.
Endoplasmic reticulum (ER)	A compartment within the cell involved in producing proteins (basically the protein-making-factory).
Enzyme	A type of protein which has a special function of changing or breaking down one compound to another. Muscle glycogen phosphorylase is an enzyme which breaks down glycogen into glucose-1-phosphate.
Exons	The coding regions of genes which are used to make messenger RNA (mRNA). The exons encode the sequence for making proteins.
Fatty acid oxidation	A mechanism where fatty acids are broken down to release compounds which can be used to produce energy. This provides the energy for the “second wind” in McArdle disease.
Frameshift mutations	These are mutations which occur if nucleotides are added to or removed (deleted) from the gene. This leads to the production of a protein which doesn’t have the right sequence of amino acids, and is not able to function in the normal way.

Genotype	The combination of versions of each gene that a person has.
Genotype-phenotype relationship	The relationship between which versions of each gene a person has and the physical effect of those genes on the body (including severity of symptoms).
Glycogen storage disease (GSD)	A disease caused by a mutation which prevents the functioning of an enzyme normally required for the breakdown of glycogen into glucose. Glycogen storage diseases result in intolerance to exercise, and in general (excluding GSD 0), result in storage of increased amounts of glycogen in the affected tissues or organs.
Glycogenolysis	A process to convert glycogen into glucose. This is the process which does not work in McArdle disease.
Glycolysis	The breakdown of glucose to produce ATP.
Homozygote	The scientific/medical term for someone who has two copies of the gene which are the same; either two normal copies of the gene or two faulty copies of the gene.
Hyper-CK-emia	Extremely high creatine kinase levels, sometimes seen in McArdle people following muscle damage.
Hyperglycaemia	Excessive level of glucose in the blood.
Hyperkalemia	Excessive level of potassium in the blood.
Hypertrophy	Excessive development and bulking of the muscles.
Hypocalcemia	Abnormally low levels of calcium in the blood.
Informed consent	When participants agree to take part in a clinical trial having fully understood the risks and tests involved.
Innervation	Culture of muscle cells in the same container as nerve cells.
Introns	Non-coding regions of genes which are not used to make messenger RNA.
Ketogenesis	The use of fatty acids as the main energy source to produce energy.
Malignant hyperthermia	An inherited predisposition whereby some anaesthetic drugs produce an adverse reaction which includes an extreme rise in body temperature. McArdle people may be more likely to have this reaction.
McArdle person	In this Handbook, "McArdle person" is used to mean a person who has received a definitive diagnosis of McArdle disease (who has no functional muscle glycogen phosphorylase enzyme in their skeletal muscle cells).
Models of a disease	Cells which have been made to mimic disease, or animals that have a similar disease, which can be used for research such as testing possible treatments.
Messenger RNA (mRNA)	A temporary copy of the DNA sequence of the gene. mRNA is made in the nucleus and then transported to the ER where it is used to produce a protein.
Muscle glycogen phosphorylase	One of a group of enzymes which break down glycogen into glucose.
Myoglobinuria	The presence of myoglobin in the urine. Myoglobin is a protein which is released from damaged muscle.
Nonsense-mediated decay	A process which identifies and destroys mRNA which contains premature termination codons.
Nucleotides	Chemical compounds which act as building blocks to make up DNA. There are four nucleotides in DNA, which are cytosine (C), thymine (T), guanine (G) and adenine (A).
Pharmacological chaperones	Particular chemicals which could bind to non-functional enzymes to help them form the correct shape and become functional.
Phenotype	The physical effect of genes on the body (including on the severity of symptoms).

Placebo effect	A phenomenon where some people feel that their symptoms improve even if they are given a treatment with no active medicine – for example a pill made of sugar or flour.
Premature stop codons	A mutation which has incorrectly introduced a stop codon too early in the DNA sequence. It is also called a “nonsense codon”, “nonsense mutation” or “premature termination codon”.
Protein sequence	The order of the amino acids in a protein.
Proteinuria	An excess of protein in the urine. When mentioned in relation to McArdle disease, proteinuria is generally used to describe myoglobin in the urine, and is therefore used to mean the same as myoglobinuria. In other circumstances (for example in people unaffected by McArdle’s), proteinuria can also be used to describe the presence of other proteins.
Pyridoxal 5'-phosphate (PLP)	A co-factor (special compound) which is usually found bound to glycogen phosphorylase. The vitamin B6 complex is a source of PLP.
Rhabdomyolysis	Breakdown of muscle cells.
Ribosomes	A component of the protein-making-factory (ER) which decodes the mRNA and joins amino acids together into a long chain to produce a protein.
Second wind	Initially exercise depletes the free glucose in the muscle cells of McArdle people. After a period of slower paced exercise or short rests, other sources of energy become available to the muscle cells, allowing McArdle people to continue to exercise.
Sequencing	A process of using special techniques and machinery to determine a genetic/DNA sequence.
Sex chromosomes	The X and Y chromosomes. The number of these chromosomes which a person has will determine their gender.
Splice sites	The locations in the mRNA where exons are joined together after removal of the introns.
Statistically significant	Where an experimental result (for example the effect of a drug or treatment) is unlikely to have occurred by chance.
The citric acid cycle	Part of the mechanism to produce energy from food.
Unaffected by McArdle’s	In this Handbook “unaffected by McArdle’s” is used to describe a “normal” person who has no mutations in either copy of the <i>PYGM</i> gene. People unaffected by McArdle’s have two normal copies of the <i>PYGM</i> gene.

Online resources:

There is an on-line medical dictionary at: <http://www.merriam-webster.com/medlineplus/>

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The McArdle Disease Handbook

A guide to the scientific and medical research into McArdle Disease, explained in plain English.

This handbook explains, in layman's terms, the cause, method of inheritance, history, and current and future treatments of McArdle disease (also known as Glycogen Storage Disease Type V).

The handbook puts into plain English the published information about McArdle Disease which is normally written in technical language as it is aimed at medical or scientific professionals. Some sections are necessarily still rather technical, but in general the handbook should be understandable to those without any medical or scientific training. It is fully referenced to the source publications.

Each chapter has an introduction which summarises the coming pages as simply as possible. Then more detail is given in the chapter text, using slightly more technical language.

The AGSD-UK is grateful to the Vodafone Foundation's "World of Difference" programme, which allowed the winner to prepare this handbook.



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Kathryn Birch, Ph.D. is a scientist who has worked on McArdle Disease for four years. She completed a Ph.D. creating cell models of McArdle disease. During her studies she read most of the papers published on McArdle disease, building an up-to-date knowledge of the historical and current scientific and medical research on the condition. She has attended McArdle Clinics and AGSD-UK Annual Conferences, during which she has met dozens of people with McArdle disease and learned from their experiences.



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