THE NORTHERN HOSPITAL

ROSUVASTATIN

"Last Vision" marble, before 1903, Auguste Rodin, Musee Rodin, Paris, (author's photograph)

JULY 14, 1861. WASHINGTON, D.C.

Dear Sarah,

The indications are very strong that we shall move in a few days, perhaps tomorrow, and lest I should not be able to write to you again, I feel impelled to write a few lines that may fall under your eye when I'm no more.

I have no misgivings about or lack of confidence in the cause in which I am engaged, and my courage does not halt or falter. I know how American civilization now leans upon the triumph of the government, and how great a debt we owe to those who went before us through the blood and suffering of the revolution, and I am willing, perfectly willing, to lay down all joys in this life to help maintain this government and to pay that debt.

Sarah, my love for you is deathless. Its seems to bind me with mighty cables that nothing but omnipotence can break, and yet my love of country comes over me like a strong wind, and bears me irresistibly with all those chains to the battlefield. The memory of all the blissful moments I have enjoyed with you come crowding over me, and I feel most deeply grateful to God and you that I've enjoyed them for so long. And how hard it is for me to give them up and burn to ashes the hopes of future years, when God willing, we might still have lived and loved together, and see our boys grown up to honorable manhood around us.

If I do not return my dear Sarah, never forget how much I loved you, nor that when my last breath escapes me on the battlefield, it will whisper your name. forgive my many faults and the many pains I have caused you. How thoughtless, how foolish I have sometimes been. But, oh Sarah, if the dead can come back to this earth and flit unseen around those they love, I shall always be with you in the brightest day and the darkest night, always, always. And when the soft breeze fans your cheek, it shall be my breath, or the cool air at your throbbing temple, it shall be my spirit passing by. Sarah, do not mourn me dead. Think I am gone and wait for me, for we shall meet again….

Sullivan.

To stop the Union invasion, 22,000 Confederate troops had moved north from Richmond commanded by General Beauregard, who knew in advance the Federals were coming. Rose Greenhow, a prominent socialite in Washington and a Confederate spy, had alerted him. Now Beauregard made his headquarters in Wilmer McLean's farmhouse. The Confederates formed a meandering 8-mile line along one side of Bull Run Creek. They were less than 25 miles from Washington, and there they waited. Hundreds of Washingtonians in holiday mood rode out to Manassas, hoping to see a real battle. Some brought field glasses, picnic baskets and bottles of champagne!

"We saw carriages which contained civilians who'd driven out from Washington to witness the operations. A Connecticut boy said, "There's our senator", and some of our men recognized other members of congress. We thought it wasn't a bad idea to have the great men from Washington come out to see us thrash the Rebs".
(Private James Tinkham).

On the morning of the 21st, McDowell sent his men across Bull Run. They smashed into the left side of the Confederate line, driving the rebels from one position after another. The civilian onlookers waved hats and fluttered handkerchiefs. It was not yet noon, and all was going just as they wanted.

"On reaching a clearing separated from our left flank by a rail fence, we were saluted by a volley musketry which was fired so high that all the bullets went over our heads. My

first sensation was astonishment at the peculiar whir of the bullets, and that the regiment immediately laid down without waiting for orders".

"We fired a volley and saw the rebels running the boys were saying constantly in great glee, "We've whipped them. We'll hang Jeff Davis to a sour apple tree. They're running. the war's over".

An onlooker remembered that the advancing Union army looked like a bristling monster lifting himself by a slow, wavy motion up the laborious ascent. Union victory seemed so sure that on one part of the battlefield men stopped to gather souvenirs. But holding a hill at the center of the Southern line was a Virginia brigade led by general Thomas Jackson. While other Southern commands wavered, Jackson's held firm. One Confederate officer, trying to rally his own frightened men, shouted, "Look! There's Jackson with his Virginians, standing like a stone wall!" The name stuck.

He had the strange combination of religious fanaticism and a glory in battle. He loved battle. His eyes would light up. They called him "old blue light" because of the way his eyes would light up in battle. He was totally fearless, had no thought whatsoever of danger at any time when the battle was on, and he could define what he wanted to do. He said, "Once you get them running, you stay right on top of them, and that way a small force can defeat a large one every time". He knew perfectly well that a reputation for victory would roll and build.
(Shelby Foote, Civil War Historian)

It was the turning point. at 4:00, Beauregard ordered a counterattack. Jackson urged his men to yell like furies. The rebel yell first heard that day would echo from a thousand battlefields. Confederate reinforcements began to arrive. The first cane on horseback. More arrived by train, something new in war. The Northern army fell apart. The retreat soon became a rout, as Union guns became entangled with the carriages of fleeing spectators.

"We tried to tell them that there was no danger, called on them to stop, implored them to stand. We called them cowards. Put out our heavy revolvers and threatened to shoot, but all in vain"….

From the Confederate White House in Richmond, Jefferson Davis rejoiced.

"My fellow citizens, your little army, derided for its want of arms, derided for its lack of all the essential material of war, has met the grand army of the enemy, routed it at every point, and it now flies inglorious in retreat before our victorious columns. We have taught them a lesson in their invasion of the sacred soil of Virginia".
(Jefferson Davis)

"Today will be known as Black Monday. We are utterly and disgracefully routed, beaten, whipped by secessionists".
(George Templeton Strong).

London Times. "The inmates of the White House are in a state of utmost trepidation and Mr. Lincoln in despair. Why Beauregard does not attack Washington, I know not, nor can I well guess". It was remembered as the great skedaddle. For days, discouraged troops straggled back into Washington.

"I saw a steady stream of men, covered with mud, soaked through with rain, who were pouring irregularly up Pennsylvania avenue toward the capitol. A dense stream of vapor rose from the multitude. I asked a pale young man who looked exhausted to death whether the whole army had been defeated". "That's more than I know", he said. "I know I'm going home. I've had enough of fighting to last my lifetime".

The North was appalled at the 5,000 casualties. Both sides now knew it would be no 90 days war….

"Little did I conceive of the greatness of the defeat, the magnitude of the disaster which had entailed upon the United States. So short-lived has been the American union that men who saw it rise may yet live to see it fall".
(William Russell, London times).

David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.

Both North and South were shocked at the casualties sustained at the First Battle of Manassas as the Southerners referred to it, or First Bull Run as the Northerners referred to it. Nothing like it had been fought in the new world previously. And yet by the subsequent standards of the war casualties would be light. Some modern day estimates suggest that over 720,000 deaths (R. White) (as opposed to the traditional figure of 650,000) would be the eventual toll, to say nothing of the countless more terribly wounded and mentally destroyed. The American Civil War would result in more American deaths than in every other conflict, before or since it, including the two World Wars, Korea and Vietnam combined. The War would deeply affect every single American, a nation at that time of only 31 million people. It is incomprehensible to imagine human tragedy on such a per capita scale. Perhaps the only true sense of the human meaning of this Nineteenth century catastrophe can come from the surviving letters of people who lived it, like Union soldier private Sullivan Ballou. A week after Sullivan Ballou wrote to his wife, he was killed at the First Battle of Bull Run.

The imminent specter of death, can have a profoundly focusing effect of attitude towards one's own mortality. Previously taken for granted, life suddenly becomes a very precious thing. One can obviously see why soldiers on the eve of battle have this focus. Mercifully most of us will not have to face such an immediately confronting reflection. And yet the mortal reality may be no less real when confronting one's own death from causes other than war; the risk of death from cardiovascular causes as one ages for example. Myocardial infarction can kill just as surely as a musket shot, though the immediacy of the threat is of course is not quite the same thing as in war, and so this perhaps explains the puzzling phenomenon amoung some patients of "non-compliance" with their potentially life-saving medications such as the statins.

ROSUVASTATIN

Introduction

Rosuvastatin (trade name in Australia, **"Crestor",** amoung others) is a *synthetic* **HMG-CoA reductase inhibitor** that is used in the treatment of **hypercholesterolemia.**

The HMG-CoA reductase inhibitors are more commonly known as **statins.**

Standard nomenclature designates the suffix "**statin"** to all HMG-CoA reductase inhibitors.

Statins are the first line agent for the treatment of hypercholesterolaemia. They are the most effective oral LDL lowering agents and reduce the risk of cardiovascular events (i.e myocardial infarction and stroke) and mortality in high risk patients.

Myopathy and **rhabdomyolysis** are potentially serious *dose related* adverse effects.

History

Over a century ago the German pathologist **Virchow** observed that the artery walls of patients dying of occlusive vascular disease, such as myocardial infarction, were often thickened and irregular, and contained a yellowish fatty substance subsequently identified as **cholesterol.**

In the 1950s the **Framingham study** established the link between elevated cholesterol levels and atherosclerosis.

Later investigations established that the association with coronary heart disease mortality was attributable mainly to **low-density lipoprotein (LDL)** cholesterol, which typically comprises about 70% of total cholesterol, whereas **high-density lipoprotein (HDL)** cholesterol is *inversely* correlated with coronary heart disease mortality.

Before 1987, the lipid-lowering therapy was limited to dietary changes (reductions in saturated fats and cholesterol), the bile-acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments were limited by efficacy or tolerability, or both.

The first substance discovered that could inhibit the critical rate limiting enzyme in the synthesis of cholesterol, HMG-CoA reductase, was the **naturally occurring** chemical **compactin**. It was isolated from the mold *Penicillium citrinum* by the Japanese biochemist **Akira Endo** in the mid 1970s. He was awarded the **Japan Prize** in 2006 and the **Lasker Award** in 2008 for his work.

Clinical trials with **compactin** had been proceeding, but for reasons that have never been made public (but which were believed to include serious animal toxicity) the trials were stopped by Sankyo in September 1980.

Trials then began with **lovastatin,** another naturally occurring HMG-CoA reductase inhibitor, closely structurally related to compactin. Lovastatin produced significant reductions in LDL cholesterol with *minimal* adverse reactions. Lovastatin became the first approved inhibitor of HMG-CoA reductase. It was introduced into clinical practice in 1987 and revolutionized the treatment of hypercholesterolemia. It achieved peak annual sales of more than US $1 billion.

Following the introduction of lovastatin the semisynthetic statins were developed. Simvastatin was introduced in 1988 and Pravastatin followed in 1991.

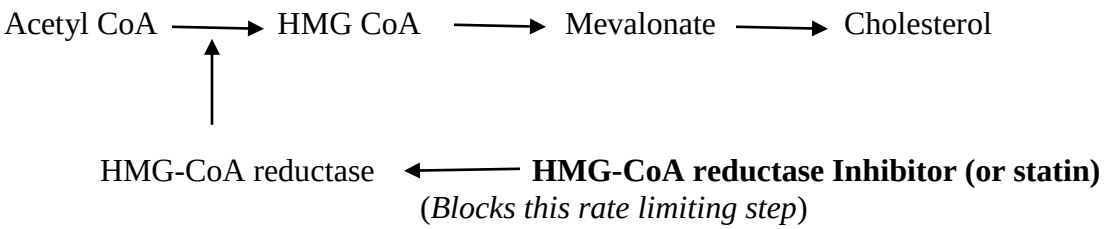
Finally fully synthetic statins were developed and introduced into clinical practice, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998 (later withdrawn due to a high incidence of fatal rhabdomyolysis), and **rosuvastatin** in 2003.

See also Appendix 1 below for a summary of the history of the statins

Chemistry

Rosuvastatin is a synthetic HMG-CoA reductase inhibitor.

Physiology



The **rate limiting** enzyme in the cholesterol biosynthetic pathway, HMG-CoA reductase

See also Appendix 2 below for a more detailed biochemical pathway of cholesterol synthesis in the body

See also Appendix 3 below for a summary of lipid metabolism

Classification

Statins include:

1. Natural agents:
    - Compactin (not used clinically)
    - Lovastatin (not available in Australia)
2. Semi-synthetic agents:

- Simvastatin (a semisynthetic derivative of lovastatin) (trade name Zocor)
- Pravastatin (derived from the natural product compactin) (trade name Pravachol)

3. Fully synthetic agents:
   - Atorvastatin (trade name Lipitor)
   - Fluvastatin (trade name Lescol)
   - **Rosuvastatin** (trade name Crestor)

Preparations

Rosuvastatin as:

Tablets:

- 5 mg, 10 mg, 20 mg, 40 mg.

Fixed combination with ezetimibe:

- Rosuvastatin 5 mg + ezetimibe 10 mg
- Rosuvastatin 10 mg + ezetimibe 10 mg
- Rosuvastatin 20 mg + ezetimibe 10 mg
- Rosuvastatin 40 mg + ezetimibe 10 mg

Mechanism of Action

The statins competitively inhibit **HMG-CoA reductase** which is the rate limiting enzyme controlling cholesterol synthesis.

Pharmacodynamics

The statins as a group produce:

1. Reduced concentrations of total cholesterol
2. Profound reductions of apolipoprotein-B-containing lipoproteins, especially LDL cholesterol.
3. Moderate reductions of plasma triglycerides:

- Statins do decrease triglycerides, although less than fibrates, fish oil or nicotinic acid.

4. Minor increases in HDL cholesterol.

All inhibitors of HMG-CoA reductase produce a *qualitatively* similar effect on the lipid profile.

The mean reduction in LDL cholesterol attainable with the maximal recommended dose of different statins ranges from 35 to 55%. [5]

High levels of LDL contribute to the development of atherosclerotic cardiovascular disease.

Reducing LDL is associated with reductions in cardiovascular events and mortality; the greater the reduction, the greater the benefit.

A 1 mmol/L reduction in LDL, by using a statin, reduces the rate of fatal and non fatal cardiovascular events by about 20 - 25%.

Raised triglyceride concentrations are a risk factor for coronary heart disease, however, there is no conclusive evidence that reducing them with drugs improves cardiovascular outcomes.

Severe hypertriglyceridaemia (>10 mmol/L) increases the risk of **acute pancreatitis**, and so may be used for this indication, seek specialist advice.

Low levels of HDL appear to be associated with *higher* cardiovascular risk, however there is **no** current evidence that using drugs to raise levels is beneficial.

People at the highest absolute risk of cardiovascular events (e.g. those with pre-existing ischaemic heart disease) will derive the greatest benefit from lipid lowering drugs.

Target drug treatment to those at **greatest risk**, rather than considering lipid levels *alone.*

Pharmacokinetics

Absorption:

- Rosuvastatin is administered orally.
- Absorption increases linearly over the normal dose range.
- Absolute bioavailability is around 20%.

Distribution

Volume of distribution of rosuvastatin at steady state is approximately 134 L.

- Protein binding is around 90%
- It is unknown if rosuvastatin crosses the human placenta.
- Rosuvastatin is excreted into human breast milk.

Metabolism and excretion:

- Rosuvastatin undergoes limited metabolism (around 10%), mainly to an N-desmethyl metabolite.
- 90% is eliminated as unchanged drug in the urine.

Indications

Current indications for the statins as a group include:

1. Hypercholesterolaemia
2. High risk of coronary heart disease, with or without hypercholesterolaemia

Contra-indications/precautions

These include:

1. Severe intercurrent illness such as infection, trauma, metabolic disorder:

    - Increases risk of myopathy, rhabdomyolysis and renal failure; consider withholding statins during significant illness.

      In the case of **surgery** treatment should be *continued* during the perioperative period, especially if there are symptoms of an ACS.

      Avoid stopping statins if there are symptoms of an ACS because stopping is associated with an increased rate of cardiac events (especially in the first week after stopping).

2. Renal impairment:

    - Impairment increases the risk of myopathy and rhabdomyolysis.

3. Hepatic impairment:

    - Statins do not appear to worsen liver disease, however, chronic liver disease itself can increase the concentration of atorvastatin, which may therefore increase the risk of adverse effects; seek specialist advice.

4 Elderly:

- The elderly (especially > 80 years) are at greater risk of myopathy.

5. Rosuvastatin 40 mg is contraindicated in patients with predisposing factors for myopathy/ rhabdomyolysis.

   Such factors include:

   - Hypothyroidism.
   - Personal or family history of hereditary muscular disorders.
   - Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
   - Alcohol abuse
   - Situations where an increase in rosuvastatin plasma levels may occur

6. Pregnancy - breast feeding - contraindicated (see below).

   - Avoid in women planning to conceive or who are using inadequate contraception.

Pregnancy

Rosuvastatin is a category D drug with respect to pregnancy.

Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Cholesterol is essential for embryonic development and feto-placental growth.

The inhibition of HMG-CoA reductase by statins may have a negative impact on the development of the placenta and interfere with fetal development.

Abnormal pregnancy outcomes, including central nervous system (CNS) malformations, limb deficiencies and cleft palates have been reported.

However, the absolute risk of teratogenicity of statins appears to be small.

Women who are pregnant or planning pregnancy should discontinue rosuvastatin for the duration of the pregnancy. Inadvertent exposure to statins during early pregnancy does not appear to increase the risk of congenital malformations or adverse pregnancy outcome.

However, fetal ultrasound is recommended before decisions are made regarding further pregnancy management.

Consider an alternative, such as dietary modifications, to reduce cholesterol where possible.

Breast feeding

A single case report has described rosuvastatin excretion into breast milk.

There are concerns that the use of statins in breastfeeding may disrupt cholesterol biosynthesis and interfere with infant development.

Therefore, treatment is recommended to be with-held where possible and consider an alternative, such as dietary modifications, to reduce cholesterol.

Adverse Effects

These include:

1. GIT upset:
    - Usually only mild and transient.
2. Myalgia
3. Allergic reactions (rare)
4. Dermatological hypersensitivity reactions (rare)

5 Liver impairment:

- Elevated liver aminotransferases occur in a small percentage pf patients, around 0.5 - 2%.

  This effect it dose dependent, generally responds to a reduction in dosage.

6. Diabetes mellitus:

- Statins are associated with a *slightly* increased risk for new onset diabetes which appears highest in those who are *already more likely* to develop diabetes.

  A meta-analysis reported that, on average, treating 255 patients with statins for 4 years resulted in 1 additional case of diabetes (while possibly preventing > 5 major coronary events). [2]

7. Myopathy / rhabdomyolysis:

The risk of myopathy (with or without CK elevation) and rhabdomyolysis is related to:

- Dose:
  - ♥ The risk of statin induced myopathy increases with increasing plasma concentration.

    Most statins are metabolised by CYP (i.e cytochrome P450) and their metabolism and risk of adverse effects may be affected by treatment with other drugs.

    There are fewer interactions with fluvastatin, pravastatin and rosuvastatin than with atorvastatin or simvastatin.
- Severe concurrent illness, such as:
  - ♥ Infection, trauma, metabolic disorders, (but *excluding* ACS and surgery)

    Severe intercurrent illness increases the risk of myopathy, rhabdomyolysis and renal failure; consider withholding statin during significant illness.
- Certain drug interactions:
  - ♥ Sodium fusidate
- Elderly:
  - ♥ The risk of myopathy is higher in the elderly, especially if frail, age > 80 years or with multiple comorbidities; use cautiously and start at low dosage.

Effects on ocular muscles may cause visual disturbances (e.g. diplopia or blurred vision).

There have been rare reports of an **autoimmune necrotising myopathy,** generally with CK concentration >10 times the upper limit of normal and with anti-HMG-CoA reductase autoantibodies, which does not resolve solely on stopping the statin.

Dosing

Before starting drug treatment, obtain a plasma lipid profile:

- Total cholesterol (TC)
- HDL/ LDL
- Triglycerides

Identify secondary causes of dyslipidaemia, e.g. diabetes, hypothyroidism, and treat these as required.

Reduce other modifiable cardiovascular risk factors

Markedly raised cholesterol levels (e.g. TC **> 7.5 mmol/L**) and family history of premature coronary heart disease may indicate familial hypercholesterolaemia; seek specialist advice

Usual adult dosing is:

Hypercholesterolaemia:

- Oral, initially 5 or 10 mg once daily. Usual range, 5 - 20 mg once daily. Maximum 40 mg once daily (specialist supervision).
- High cardiovascular risk (men > 50 years, women > 60 years), oral 20 mg once daily.
- Treatment with cyclosporin, maximum 5 mg once daily.
- Treatment with gemfibrozil or lopinavir with ritonavir, maximum 10 mg once daily.

Renal impairment:

- CrCl < 30 mL/minute, oral, initially 5 mg once daily; maximum 10 mg once daily.

Severe hepatic impairment:

- Oral, initially 5 mg once daily; maximum 10 mg once daily.

Monitoring:

Monitor aminotransferase and CK at baseline, repeat during treatment if indicated clinically.

Stop the statin if: [2]

1. Aminotransferase concentrations are persistently elevated to >3 times ULN

2. CK concentration is >10 times ULN

3. There is persistent unexplained muscle pain (even if CK is normal)

If raised CK concentrations persist after stopping the statin, consider other causes for myopathy (such as asymptomatic hypothyroidism or neuromuscular diseases), some of which may be **unmasked by statin treatment.**

Treatment may be resumed after at least 4 weeks if myopathy/myositis was mild and CK concentration, if raised, has returned to normal.

Consider:

1. Whether a precipitant (e.g. trauma, surgery) or a drug interaction contributed to this adverse effect

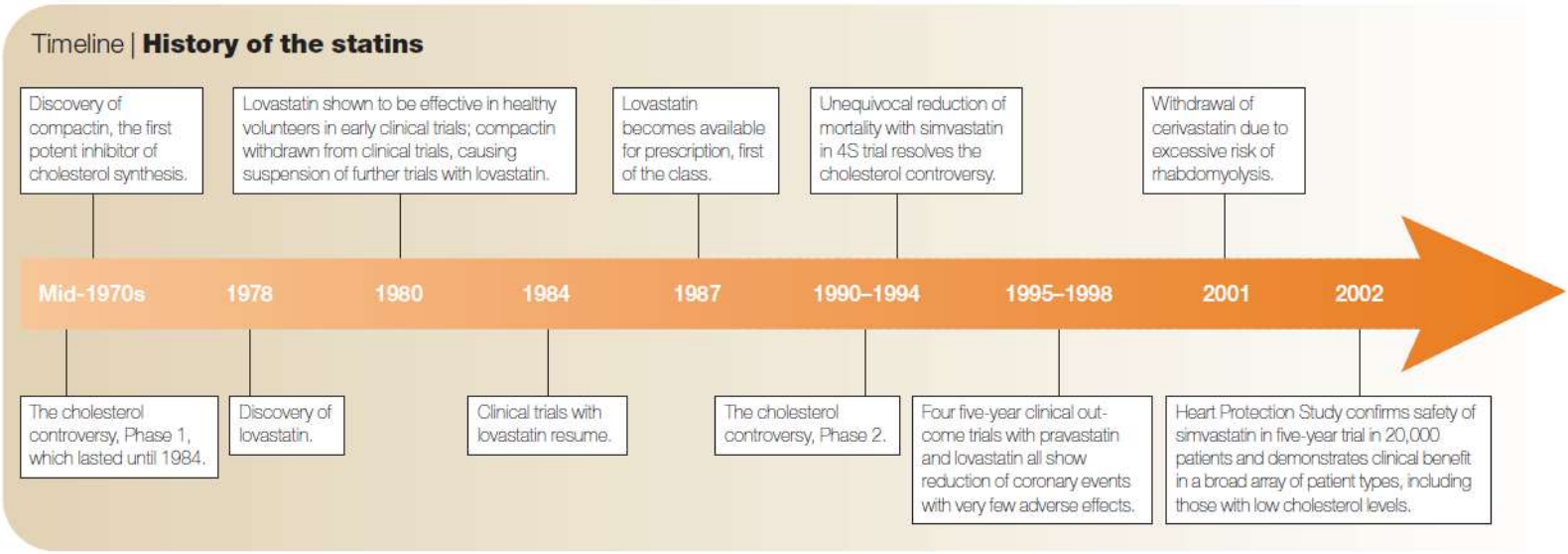
2. Using a lower dose (as these adverse effects are dose-related)

3. Using an alternative statin (although there are few data comparing risk between agents)

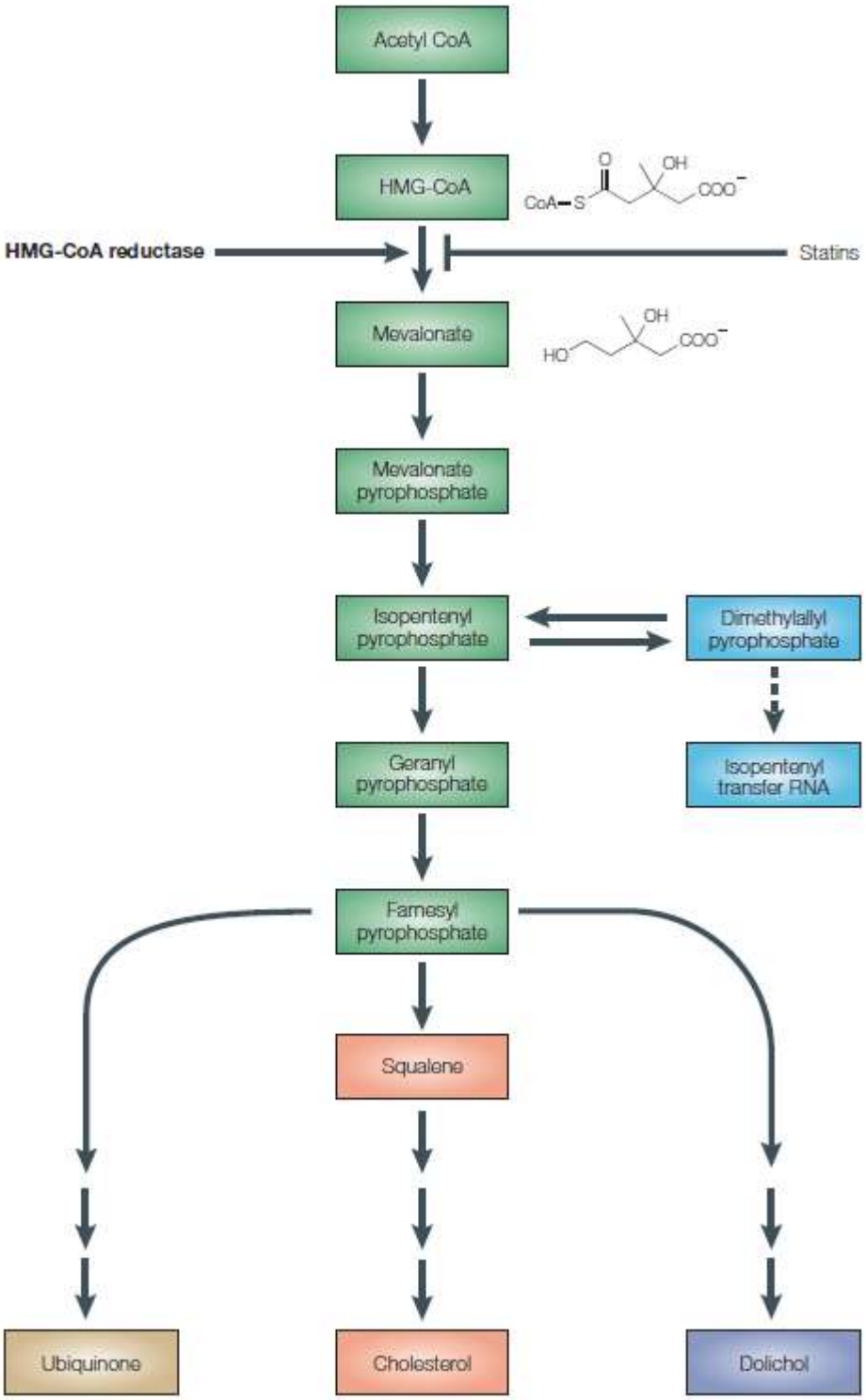
If the problem recurs on rechallenge, stop statins permanently

Appendix 1

History of the Statins:

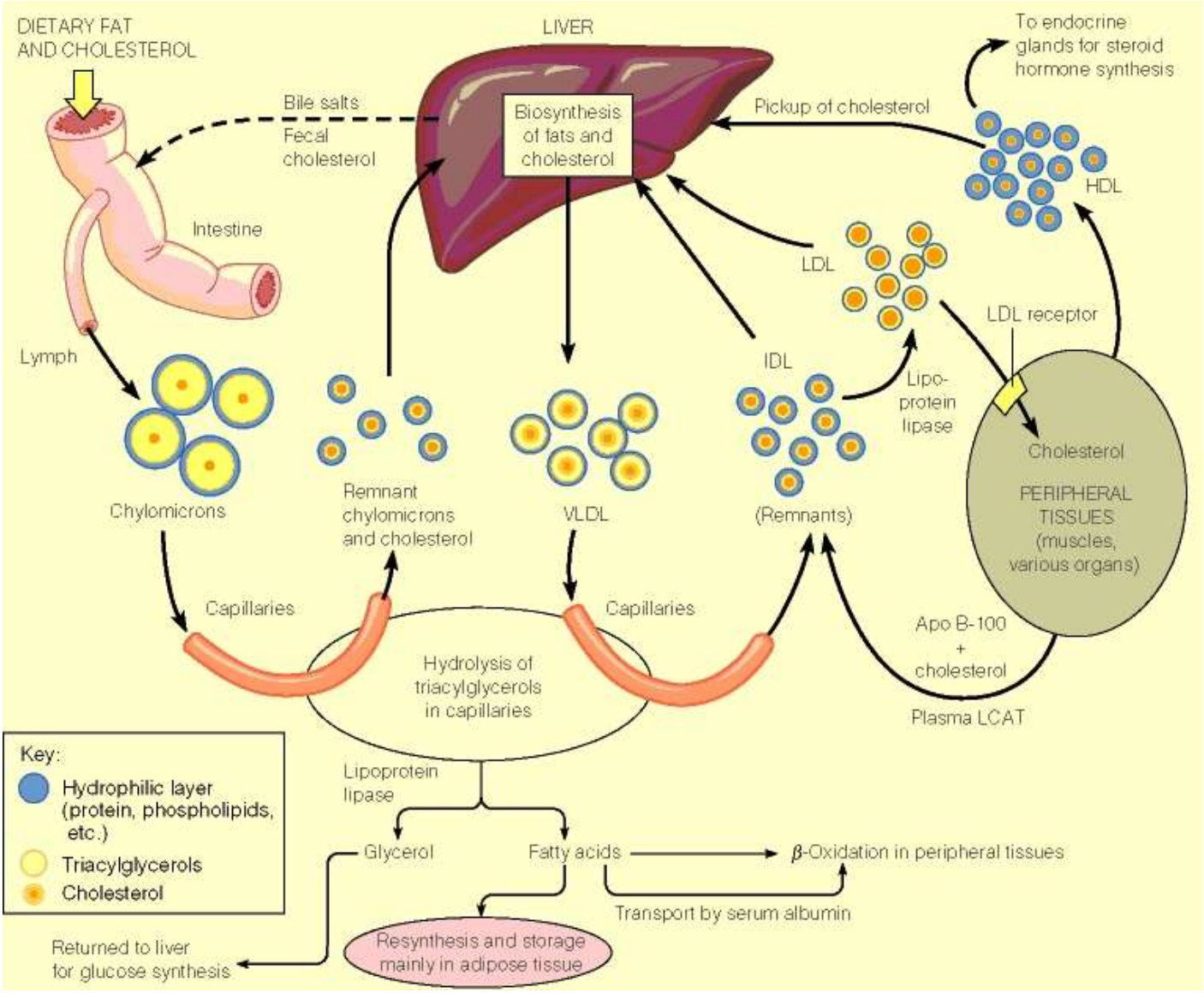


Appendix 2



The cholesterol biosynthesis pathway. Cholesterol biosynthesis is a complex process involving more than 30 enzymes. A simplified version is shown here, which highlights the step inhibited by statins, and shows the chemical structures of the starting material (HMG-CoA) and product (mevalonate) of this step.

Appendix 3 *Summary of lipid metabolism:*



Note that LDL transports cholesterol to the peripheral tissues. HDL takes it from the tissues, back to the liver. (Diagram: Dr. James Thompson; http://www.apsubiology.org/)

LDL transports lipids, particularly cholesterol, and neutral fats (triglycerides), from the liver to most somatic tissue cells for their various metabolic needs.

HDL transports lipids, particularly cholesterol, and neutral fats (triglycerides), back to the liver for ***catabolism and elimination****.*

Coronary heart disease mortality is attributable mainly to ***low-density lipoprotein (LDL)*** *cholesterol, which typically comprises about 70% of total cholesterol, whereas* ***high-density lipoprotein (HDL)*** *cholesterol is inversely correlated with coronary heart disease mortality.*

Rare contemporary photograph of a civilian house destroyed during the First Battle Of Bull Run (Library of Congress)

The house belonged to Judith Henry, who at 85 years of age, was too terrified and too frail to flee the battle that engulfed her. Her house was completely destroyed and she was killed. Judith Henry was thus one of the first of countless civilian casualties during the American Civil War.

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2. Rosuvastatin in Australian Medicines Handbook Website, Accessed May 2017.

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5. Jonathan A. Tobert, "Lovastatin and Beyond: The History of the HMG-CoA Reductase Inhibitors. Nature Reviews: Drug Discovery vol. 2 July 2003. P. 517-526.

Dr J. Hayes
5 April 2018