THE NORTHERN HOSPITAL

FLUVASTATIN

"Pensive Woman on a Sofa", (thought to be Maria Gunning), (Detail) *oil on canvas, 1749 Jean Etienne Liotard*

Psimithium also, that is, cerussa, is another production of the lead works. The most highly spoken of comes from Rhodes. It is made from very fine shavings of lead, placed over a vessel filled with the strongest vinegar; by which means the shavings become

dissolved. That which falls into the vinegar is first dried, and then pounded and sifted, after which it is again mixed with vinegar, and is then divided into tablets and dried in the sun, during summer. It is also made in another way; the lead is thrown into jars filled with vinegar, which are kept closed for ten days; a sort of mould that forms upon the surface is then scraped off, and the lead is again put into the vinegar, until the whole of the metal is consumed. The stuff scraped off is ground up and sifted and heated in shallow vessels and stirred with small rods till it turns red and assumes the appearance of sandarach. It is then washed with fresh water, until all the cloudy impurities have been removed, after which it is dried as before, and divided into tablets. Its properties are the same as those of the substances above mentioned, only it is the mildest of all the preparations of lead; in addition to which, it is also used by women to whiten their complexion, however, like scum of silver, it is a deadly poison…

Pliny the Elder, "The Natural Histories", Bk XXXIV, 175-76;
77-79 A.D

In 1751 there was no greater celebrity in all of London than eighteen year old Irish stunning beauty, Maria Gunning. In Dublin she had become famous, along with her two sisters as a stage actress, but really it was her head-turning irresistible beauty and haughty attitude that had all of London talking. Even the King wanted to meet her. When she was presented at court to King George II, she created such a sensation, that some of England's highest-born aristocrats, in total disregard of their status and dignity, were observed clamouring up onto chairs and tables in an effort to glimpse the astonishingly glamorous Ms. Gunning and her two equally glamorous sisters.

The Gunning sisters, and Maria in particular, had become the toast of every Coffee house in London. When word was spread that she had taken to daily strolls through Hyde Park, such immense crowds gathered that a military escort became necessary to protect her. To mid-Eighteenth century sensibilities, a particularly alluring feminine feature was fairness of complexion, and by all accounts this was Maria's strongest suit. But as the compliments came, she began to play to the public adulation by the heavy application of ever more powerful skin whiteners until she discovered the most powerful whitening cosmetic ever known to history, one that had been used by Queen Elizabeth I, and had in fact been known since antiquity. It imbued a tantalizing, almost glowing white shine to the skin, and it had became immensely popular amoung the "fashionable" women in London at the time. It need hardly be said that when Maria started to use it, it created an even greater public frenzy. Her shoemaker, began to charge sixpence for people just to see her shoes.

During one of Maria's jaunts in Hyde Park, she either by accident or perhaps by design, encountered the notorious courtesan Kitty Fisher. Kitty, a little piqued that Maria now upstaged her at court, enquired of Lady Coventry (as Maria was now known, since her marriage to the sixth Earl of Coventry), the name of the dressmaker who had made her dress. Maria turned up her nose, and merely answered that she hadn't a clue as she had been given it by her husband, and that she thought the question in any case, impertinent! Kitty, in a stifled rage, simply accepted the insult, because, as she later related, Maria was socially superior to her, since marrying Lord Coventry, but that she was now determined to marry a Lord herself in order that she could one day answer Maria back!

Sometime later, Lord Coventry discovered that his wife's cosmetics, which now also included a mercury based rouge, were extremely toxic and he begged her to stop using them. When Kitty refused, he chased her around the dining room table and forcibly wiped off her makeup with his table napkin. But still Maria refused to give up her cosmetics. Eventually her skin started to turn a dreadful bluish colour, which only made her apply ever heavier layers of her whitener to disguise her increasing disfigurement. She had trapped herself into a vicious circle from which she saw no escape. As time passed she became afflicted with an unrelenting and accursed constipation and gradually began to lose her mind. Devastated at the loss of her beauty she now refused to be seen in public, and hid herself away in a dark corner of her immense mansion, with only a small tea light to see by. In 1760, she died at the age of 27 years.

Maria Gunning, the most astonishing beauty of her day, died from a combination of mercury and lead poisoning. The skin whitener she was using was cerussite or white lead a carbonate mineral compound of lead. Mary Gunning was not the only woman to have died from white lead poisoning, it had been used as a skin whitener since antiquity, and up until as recently as the 1870s. White lead in addition to being an historical cosmetic was also a highly valued historical pigment used by Artists for centuries, in particular by the greatest Dutch masters of the Seventeenth century, Rembrandt van Rijn, Gerrit Dou, Jan Steen, Frans Hals and Johannes Vermeer. On many brilliant works of the Dutch Golden Age you can see the dazzling glow of white lead pigment, that almost makes one squint by the illusion of brilliant white light. It would not be until the mid Twentieth century that the extreme toxicity of white lead was fully appreciated. White lead was banned as a pigment in the US in 1977. Today Artists use a modern synthetic white pigment, made from titanium oxide. It is a good and permanent white pigment, though it doesn't quite have the same glowing retinal impact of the ancient but deadly white.

White lead was brilliant at its work, both as a cosmetic and as a pigment, but its deadly toxicity would see its eventual extinction and replacement with a far safer modern synthetic alternative in titanium oxide. And so it was with compactin. When discovered it was hailed as a brilliant new agent for the lowering of blood cholesterol levels, but with time its toxicity would see its extinction and replacement with far safer modern synthetic alternatives, such as fluvastatin.

FLUVASTATIN

Introduction

Fluvastatin (trade name in Australia, **"Lescol"**) 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.

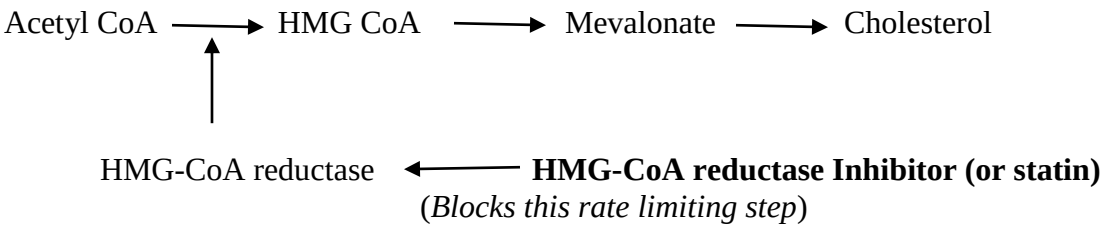
See also Appendix 1 below for a summary of the history of the statins

Chemistry

Fluvastatin is a synthetic HMG-CoA reductase inhibitor.

Fluvastatin sodium is a racemic mixture of the two enantiomers of which the 3R,5S form possesses more than 30 times the activity of the 3S,5R form.

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

Fluvastatin sodium as:

Tablets (extended release):

- 80 mg

The extended release preparation is 84.24 mg fluvastatin sodium which is equivalent to 80 mg fluvastatin free acid.

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:

- Fluvastatin is administered orally.

  It is absorbed rapidly and completely following oral administration of the immediate release formulation.

  Peak concentrations are reached in < 1 hour.

Distribution

- The parent drug is targeted to the liver and no active metabolites are present systemically.
- The apparent volume of distribution is estimated at 330 L
- Protein binding is around 98 %

- It is unknown if fluvastatin crosses the human placenta.

- It is unknown if fluvastatin is excreted into human breast milk.

Metabolism and excretion:

- Fluvastatin is metabolised in the liver, primarily via hydroxylation of the indole ring at the 5 and 6 positions. N-Dealkylation and β-oxidation of the side chains also occurs

  The major components circulating in the blood are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite.

  The hydroxy metabolites have some pharmacological activity, but do not circulate in the blood.

- Half-life is 2.3 ± 0.9 hours.

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. Avoid grapefruit juice

- May effect atorvastatin metabolism, and so increase the risk of toxicity.

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

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

Pregnancy

Fluvastatin is a category D class drug with respect to pregnancy.

Category D drugs are those 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 fetoplacental 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 following exposure to other statins, but not with fluvastatin. However, the absolute risk of teratogenicity of statins appears to be small.

Women who are pregnant or planning pregnancy should discontinue fluvastatin 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 outcomes. 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

Reports describing the use fluvastatin during breastfeeding have not been located.

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 for fluvastatin is:

- **80 mg orally 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

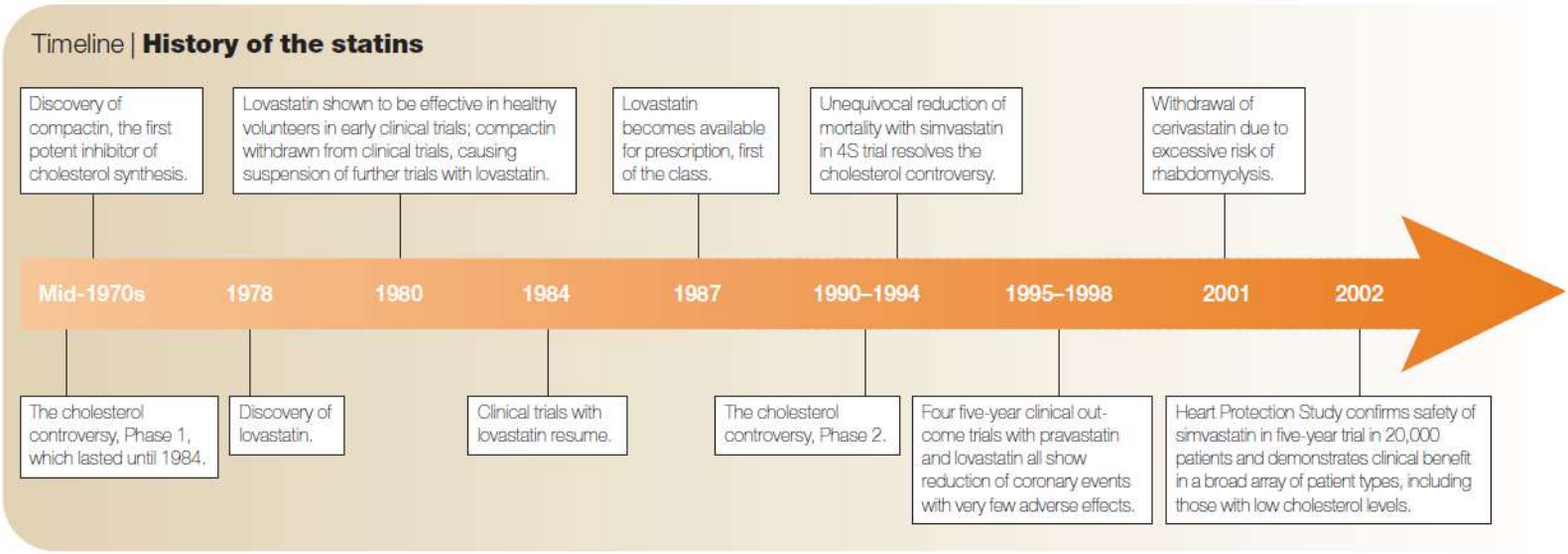
2. Using a lower dose (as these adverse effects are dose-related)

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

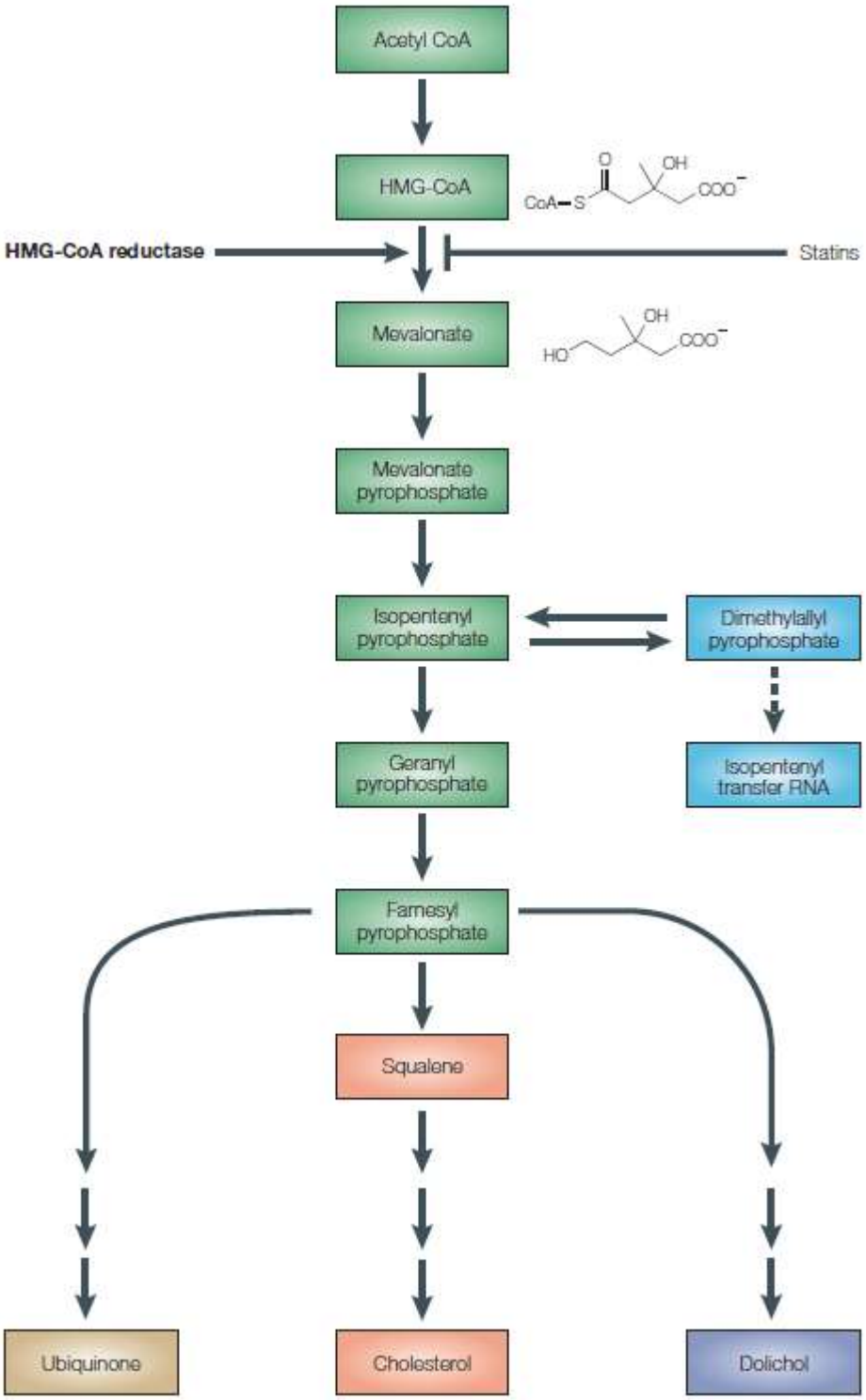
If the problem recurs on rechallenge, stop statins permanently

Appendix 1

History of the Statins:

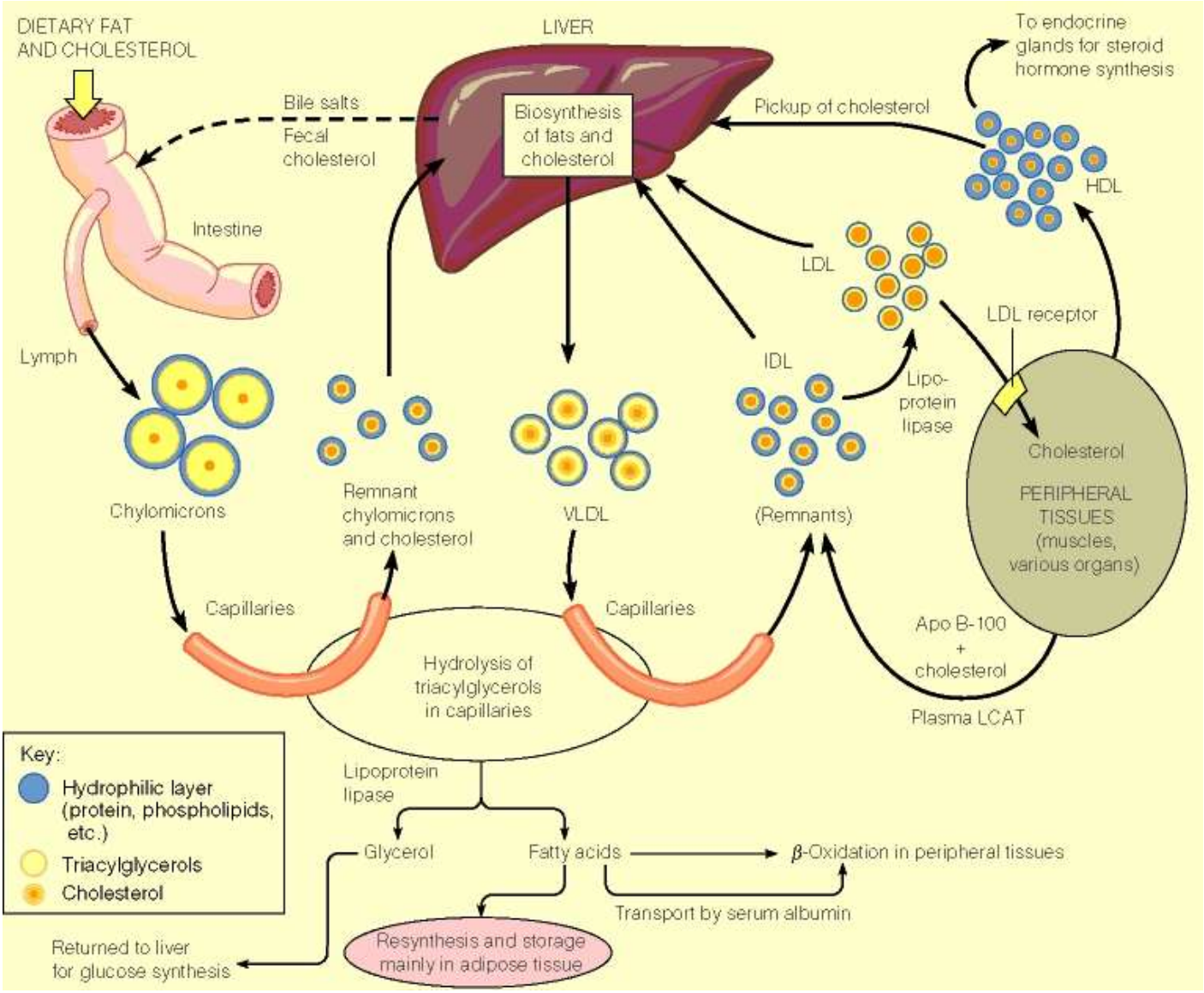


Appendix 2



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.*

Appendix 1

Titanium (Time-Life, "Matter", 1963)

Although the ninth most abundant element in the Earth's crust, Titanium, named for the Titans of ancient Greek mythology, was not recognized as an element until relatively recently in 1791 by the clergyman and amateur geologist, William Gregor.

Physical Properties:

Elemental symbol	**Ti**
Atomic number	22
Atomic weight	47.867
Melting point	1668 °C
Boiling point	3287 °C
Classification	Metal
Physical Appearance	Lustrous grey - white

The Darnley Portrait of Queen Elizabeth I, oil on canvas, late Sixteenth century, Artist Unknown. Elizabeth was famous for her fair complexion, a visage she maintained by the use of a host of expensive cosmetics, amoung them, white lead.

Astronomer by Candlelight, (Detail), oil on canvas, c.1658, Gerrit Dou.

The brilliant white glow of the Astronomer's candlelight in this masterpiece by the Seventeenth century Dutch Artist, Gerrit Dou, was achieved by the pigment, white lead.

References

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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.

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