

# “STATINS & SUNLIGHT”

by

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# “STATINS & SUNLIGHT”

## *PART – I*



***I HAVE GATHERED A POSY  
OF OTHER MEN'S FLOWERS;  
NOTHING BUT MY THREAD  
BINDS THEM TOGETHER.***

***-MONTAIGNE***

# STATINS

# SUNLIGHT



**SIMVA**

**PRAVA**

**LOVA**



**ATORVA**



**ROSUVA**



**S+FIBRATE (PPAR  $\alpha$  AGENT)**



**S+EZETIMIBE**



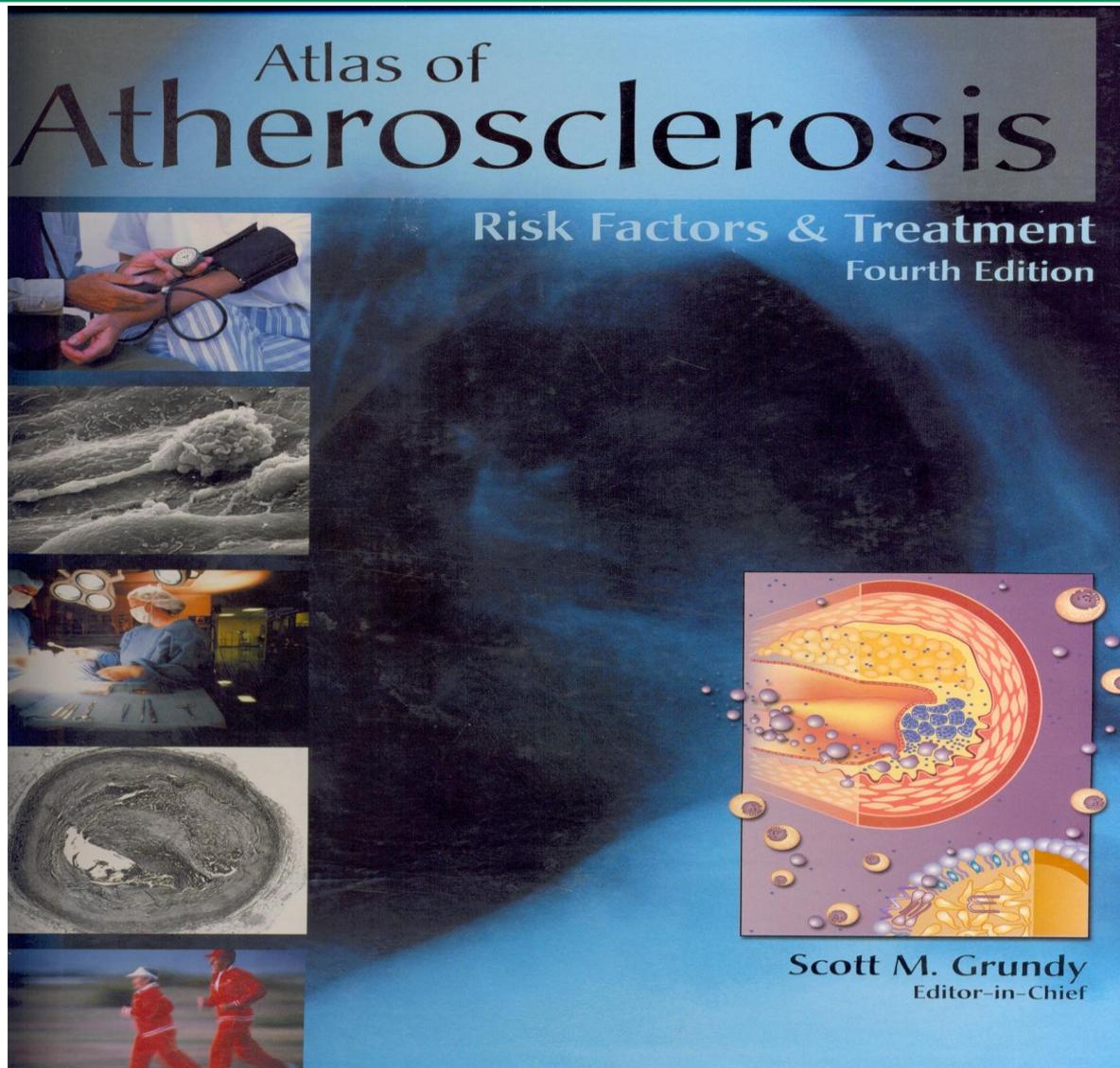
**S+cachannel  
blocker(AMLODEPINE)**



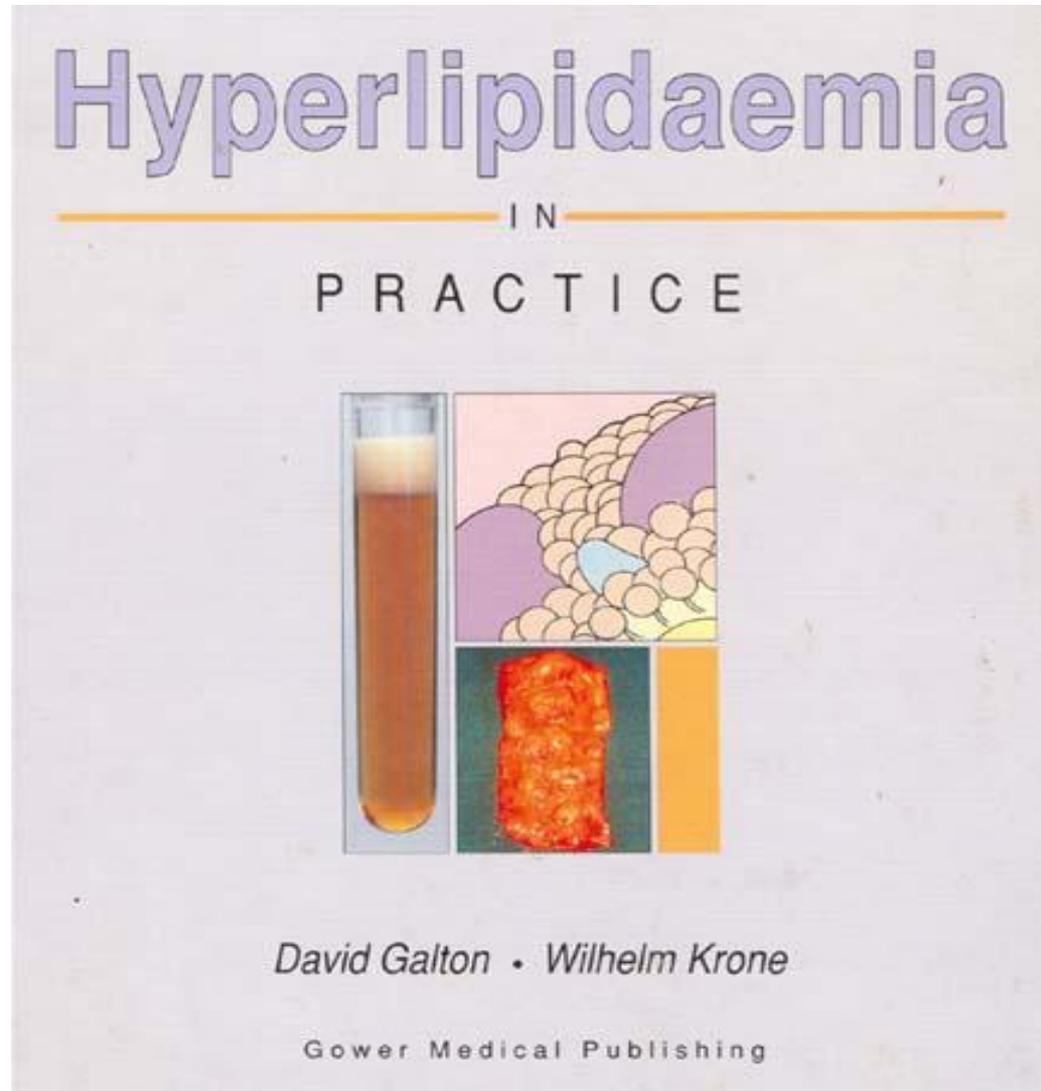
**S+ASPIRIN**



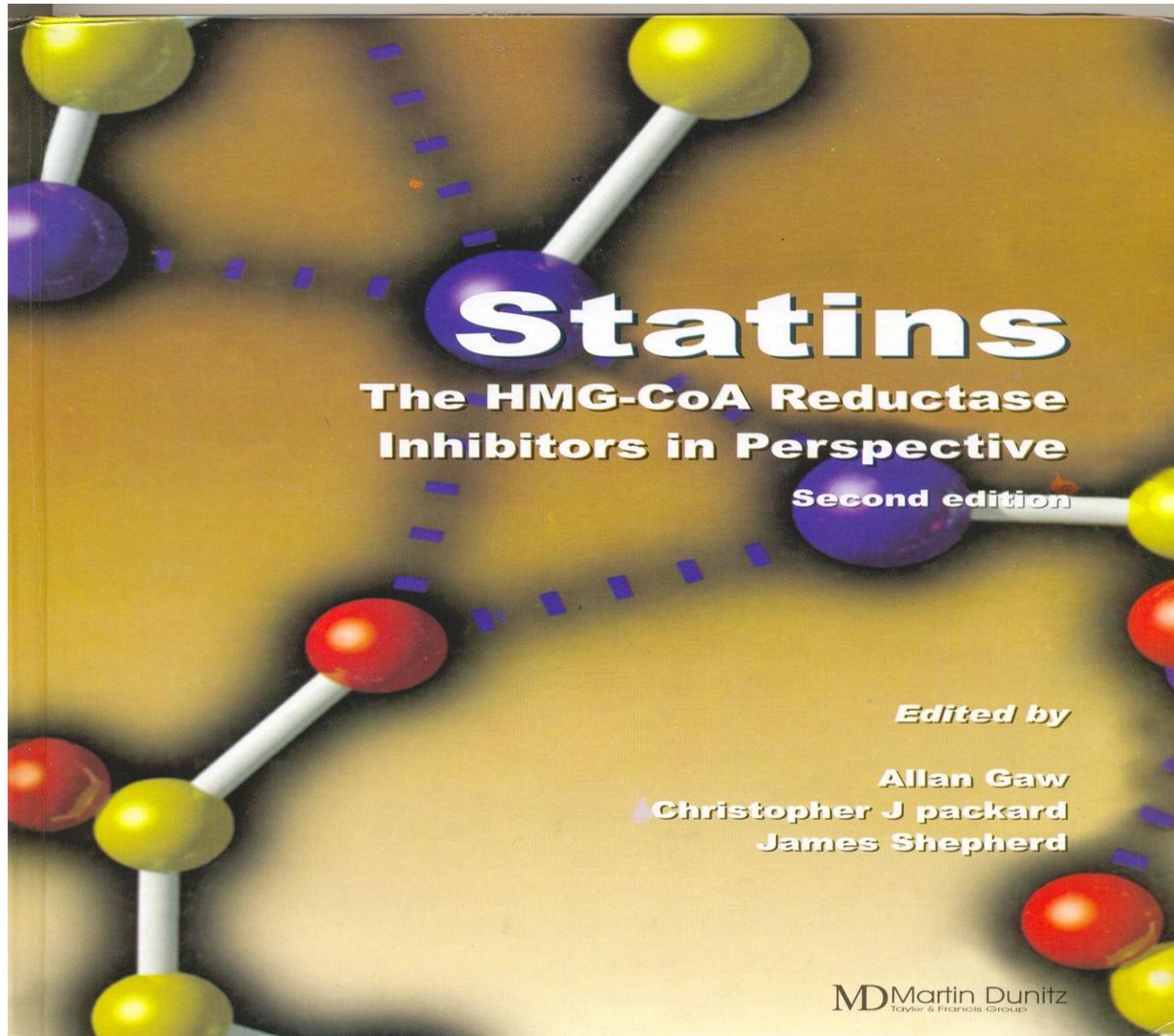
# ATLAS OF ATHEROSCLEROSIS



# HYPERLIPIDAEMIA



# The story of STATINS



**Reducing the risk of ASCVD by reducing / correcting Dyslipidaemia using pharmaceutical agents (Drugs) – The story of Statins and their development over the last 36 Years.**

# Preface to the First Edition

What targets, if any, should we strive for in cholesterol lowering? What is the significance of the non-lipid effects of the statins? Which statins should we use? Can we afford to use any?

This book tells the story of the statins, for the most part in the words of those who lived this story. The background, describing the lipid world before the statins, is told by the Framingham investigators. Akira Endo, working with his team in Japan, discovered the early statins and describes his breakthrough. The major clinical trials from Scandinavia, North America, Australia and New Zealand and, of course, Scotland are detailed by those who conducted them.

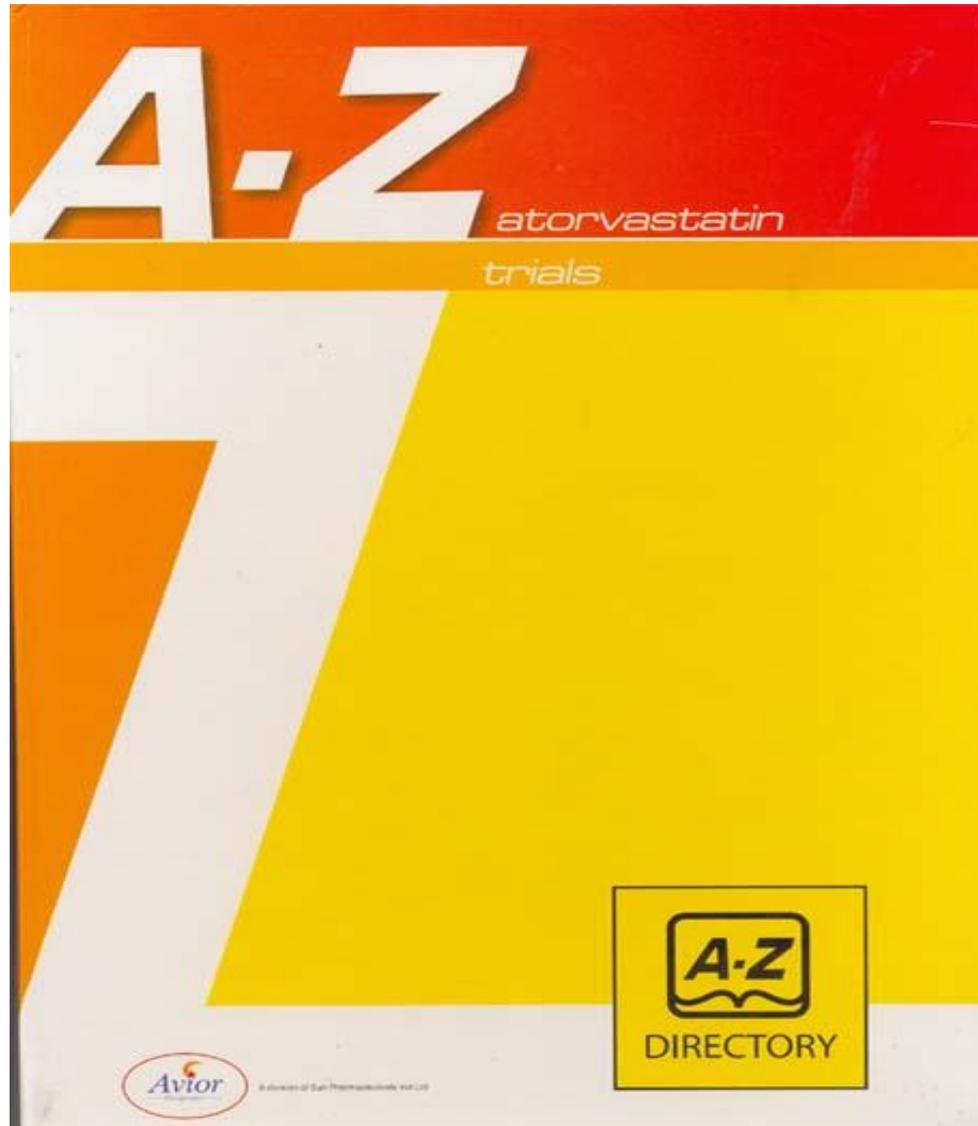
The concluding chapters detail the further statin trials, of which there are many and we take a look into the future of lipid-lowering therapy beyond statins.

## Preface to the Second Edition

Statins have become a global phenomenon in terms of both the market value of prescribed drugs and the spectrum of attributed clinical benefit. They are at the core of coronary prevention programmes, and are also under investigation for their impact on other diseases such as osteoporosis and rheumatoid disease. The evidence base underpinning their use in a wide range of patients has expanded year on year.

Yet further studies are planned to explore new aspects of statin Pharmacology, pleiotropic effects and the limits of clinical effectiveness.

# A-Z Atrovastatin



## TALK BACK: ARE STATINS READY FOR PRIME TIME?

In recent years, the status of a slew of drugs has switched from prescription to over-the-counter (OTC). For many consumers, this has meant less expensive, more convenient treatment for common health issues. Drug companies favor the switch too, as it usually extends the market for their brands.

However, there is little evidence that statins have a measurable impact on primary outcomes such as cardiovascular mortality.

The other drugs switched from prescription to OTC status are indicated mainly for relatively minor, self-limiting conditions such as headache and seasonal allergies. None is for a chronic condition with no outward signs and symptoms.

Low-dose simvastatin (ZOCOR, MERCK) has been available OTC in Great Britain since summer 2004.

The Food and Drug Administration has been asked three times to approve an OTC statin, and three times the agency has said “no”.

What do you think? Should statins be switched to OTC status?

Send your comments to  
[docnews@diabetes.org](mailto:docnews@diabetes.org).

# RED ALERT

## Rosuvastatin: Risky in Indians

As Per data submitted to the U. S. Food and Drug Administration (USFDA). The pharmacokinetic behavior of rosuvastatin is ethnic-sensitive with blood levels reaching higher levels in Asian populations compared to Caucasians. This can lead to more severe side effects such as life-threatening rhabdomyolysis. Because of these findings, the innovator Company has been asked to generate more data on Asians.

Western drug regulators have made it obligatory that prescribers inform all patients that rosuvastatin can cause muscle injury which in severe cases “Can cause kidney damage and other organ failure that are potentially life-threatening.” Hence patients should “promptly report signs and symptoms of muscle pain and weakness, malaise, fever, dark urine, nausea or vomiting” to their doctors.

# PPAR $\alpha$ activation elevates blood pressure and does not correct glucocorticoid – induced insulin resistance in humans

PPAR $\alpha$  activation elevates blood pressure and does not correct Glucocorticoid – induced insulin resistance in humans.

**Savitha Subramanian**, <sup>1</sup> Michael A. DeRosa, <sup>1</sup> Carlos Bernal – Mizrahi, <sup>1</sup> Nicholas Laffely, <sup>1</sup> William T. Cade, <sup>1</sup> Kevin E. Yarasheski, <sup>1</sup> Philip E. Cryer, <sup>1</sup> and Clay F. Semenkovich <sup>1, 2</sup>

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INSULIN RESISTANCE, Frequently caused by obesity, is associated with vascular disease. The epidemic spread of obesity in industrialized countries has fueled an increase in metabolic abnormalities linked to insulin resistance and atherosclerosis. Glucose intolerance, dyslipidemia and hypertension are associated with impaired insulin signaling, and each is implicated in vascular disease. These conditions, along with central obesity, comprise the metabolic syndrome, which is associated with atherosclerosis and may affect nearly one – quarter of adults in United States (1).

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Pharmacological activation of peroxisome proliferator – activated receptor -  $\alpha$  (PPAR $\alpha$ ) has long been an attractive potential strategy of improving vascular disease in insulin resistance.

These affect have been attributed to increased metabolism of intracellular lipids, leading to less lipotoxic interface with insulin signaling. However, this drug also activates PPAR $\gamma$  (16), raising the possibility that some of the effects of WY – 14643 could be due to induction of PPAR $\gamma$  – dependent genes that enhance insulin sensitivity.

Am J Physiol Endocrinol Metab 291: E1365 – E1371, 2006  
First published July 25, 2006, doi: 10.1152/ajpendo.00230.2006

# PPAR $\alpha$ activation elevates blood pressure and does not correct glucocorticoid – induced insulin resistance in humans

Treatment with fenofibrate enhances insulin sensitivity in dyslipidemic patients with normal glucose metabolism (36) but has no effect on insulin responses in subject with metabolic syndrome (32).

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However, the present data suggest the PPAR $\alpha$  activation is unlikely to correct insulin resistance by glucocorticoids.

Our results also indicate that fenofibrate treatment alone elevates systolic blood pressure in healthy subjects. Mean determinations over 24 h using ambulatory monitoring showed that fenofibrate increased systolic pressure by 3 mmHg. Although this effect may seem small, the Prospective Studies Collaboration demonstrated a 7% increase in ischemic heart disease mortality and a 10% increase in stroke mortality with a 2 – mmHg elevation of systolic blood pressure (17).

In the Diabetes Atherosclerosis intervention study (DAIS) (3), fenofibrate was with a 2.5 mmHg increase in systolic pressure compared with a 0.5 mmHg increase for placebo. Experiments in mice suggest that PPAR $\alpha$  may affect blood pressure.

Despite impressive beneficial effects of fibrates on dyslipidemia, these agents have yielded mixed results in trial with cardiovascular endpoints. Outcomes have ranged from decreased vascular events with an unexplained increase in mortality (21, 22) to no effect on the primary cardiovascular endpoint, with trends suggesting increased mortality (12, 29), to overall favorable outcomes (24). On the basis of results of the current study, it appears that fenofibrate does not reverse insulin resistance, a condition associated with several cardiovascular risk factor, and may elevate systolic blood pressure in healthy subjects.

# “STATINS & SUNLIGHT”

## *PART – II*

**David S Grimes – Lancet 2006;368:83–86 Blackburn Royal Infirmary, Lancashire BB68HE, UK**

There are many reasons why the dietary – heart – cholesterol hypothesis should be questioned and why statins might be acting in some other way to reduce the risk of coronary heart disease. Here, I propose that rather than being cholesterol – lowering drugs per se, Statins act as vitamin D analogues, and explain why. This proposition is based on published observation that the unexpected and unexplained clinical benefits produced by statins have also been shown to be properties of vitamin D. It seems likely that statins activate vitamin D receptors.

During the late 19th century, conventional wisdom held that masturbation was the cause of epilepsy, a more plausible explanation than the previous notion that epilepsy was the result of possession by the devil, and illness is generally the result of divine interface. Since bromide was thought to reduce sexual desire, it became the logical treatment. Although reasonably successful, bromide worked for reasons that are different from the theory on which it was based. Can the same be said of statins for heart disease?

The emergence of coronary heart disease (CHD) in the 20th century required an explanation.

Cholesterol was assumed to originate from diet, and the diet – cholesterol – heart hypothesis was established. The logical treatment was to reduce dietary and serum cholesterol concentrations.

## Are Statins analogues of Vitamin D?

Many inconsistencies in this hypothesis have emerged and been disregarded. London banking and transport study, <sup>1</sup> men with the highest dietary cholesterol intake had the lowest incidence of CHD. Finding of studies from Honolulu <sup>3</sup> and Paris <sup>4</sup> suggests a protective effect of high serum cholesterol concentrations, and the Leningrad paradox <sup>5</sup> indicates that those exposed famine subsequently have a high incidence of CHD, Europe populations that consume a large amount of dietary fat and cholesterol have a low incidence of CHD (the French paradox) <sup>6</sup> lowest incidence of CHD is seen in European nations with the lowest consumption of wine and the most socioeconomic deprivation (the Albanian paradox )<sup>7</sup>

Initial treatments to reduce serum cholesterol were not effective. When introduced, however, statins did greatly reduce serum cholesterol concentrations by interfering with its synthesis; the beneficial effects of statins in CHD have been assumed to be the result to cholesterol lowering, an assumption that I believe is a serious mistake.

Scandinavian Simvastatin Survival Study (4S) <sup>8</sup>. The results of the West of Scotland coronary prevention study (WOSCOPS) <sup>9</sup> also showed clinical benefits from statins (pravastatin).

In WOSCOPS, statins lowered serum cholesterol concentration of HDL cholesterol and lowered those of serum triglyceride indicating that inhibition of 3 – hydroxy – 3 methylglutaryl coenzyme A reductase was not the only metabolic action. The clinical experiment of cholesterol – lowering was thus intrinsically flawed and what must be understood is that 4s and WOSCOPS were trials of statins therapy and not trails of cholesterol – lowering.

# Are Statins analogues of Vitamin D?

## Unexpected benefits of statins

It is noteworthy that the participants treated with pravastatins in WOSCOPS had a reduced incidents of diabetes compared with control 11.

Statins also have an effect on bone, and women who take statins have a greater bone density than those who do not 16 10 – years follow up study of participants in 4S 17 indicates a significantly reduced risk of cancer, particularly colorectal, lung, and prostate cancer in those who received simvastatin.

In 1974, 19 a group of illustration diet – cholesterol – heart researchers studied the association between cholesterol and cancer. They noted that high serum cholesterol concentration conferred protection against colon cancer. The effect of statins mentioned above hence present a major paradox: how can a drug that lowers serum cholesterol concentrations reduced the risk of colon cancer when high serum cholesterol concentration are, in fact protective.

A drug can act as a poison by blocking normal metabolic process, but to produce a beneficial effect (other than antibacterial) we should assume that it is switching on or enhancing a normal metabolic process. I therefore suggest that statins mimic many of the actions of vitamin D and can be considered analogues of vitamin D.

# Are Statins analogues of Vitamin D?

## Sunlight and Vitamin D

### Heart disease

In Europe, there is a higher rate of mortality from CHD in the northern than in the southern countries, with the lowest rates noted along the Mediterranean coast. 20 This pattern suggests that susceptibility to CHD is affected by duration of exposure to sunlight. This notion is supported by findings from the USA 21,22 that the higher the altitude of residence, and hence the sunlight intensity the lower the risk of heart disease.

### Multiple Sclerosis

Multiple sclerosis also show a latitude gradient in Europe, with the world's highest incidence reported in Scotland. 26 The risk of developing the disease is reduced by a third by regular supplementation with vitamin D 27.

### Cancer

The risk of breast cancer and colon cancer is high in northwest Europe and much lower in the Mediterranean countries 28. And in the UK, people die more readily from cancer in the north than in the south of the country. After being diagnosed, 34% of men with cancer and resident in Oxfordshire survive for 5 years compared with 26% of those who live in the northwest and Yorkshire.

## Are Statins analogues of Vitamin D?

### Diabetes

The international distribution of diabetes in children is very similar to that of CHD with incident increasing with distance from the equator 36 again suggesting a protective effect of sunlight and vitamin D. Furthermore, children of women who do, compare with those who do not, take cod liver oil during pregnancy have a reduced incidence of type 1 diabetes 37 the findings of a retrospective study, 38 undertaken in Finland and involving 10821 children born in 1966, indicate that the incidence of diabetes in adulthood is almost ten times higher in those who do not, compare with those who do, take vitamin D supplements in childhood. The benefits of vitamin D supplementation during infancy has been further strengthened by the findings of large study undertaken in Norway

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# Are Statins analogues of Vitamin D?

## Rheumatoid Arthritis

Kroger and colleagues 40 noted that 16% of 143 women with rheumatoid arthritis, compared with the general population, had very low concentration of serum calcidiol.

## Testing of my hypothesis

In view of the above, there is a striking similarity between the benefits of vitamin D and the benefits of statin therapy. I believe that the unexpected and unexplained beneficial effects of statin therapy might be mediated by activation of vitamin D receptors by this group of drugs. This hypothesis is, in theory, easy to test.

A prospective study should be undertaken in cancer treatment and prevention, with a factorial design, So that patients receive statins, Vitamin D, a combination of statins and vitamin D, or placebo.

Intervention studies should also be undertaken to look at the relapse rates of established illnesses, including CHD multiple sclerosis, and rheumatoid arthritis, comparing statins and vitamin D.

The difficulty in doing these studies is that we know only the minimum dose of vitamin D necessary to prevent and heal rickets: We do not know the dose necessary to increase to a maximum the other affects, Especially those that enhance immune competence. The same applies to statins that effects on serum cholesterol concentrations is easy to measure, but we do not know what to measure as a biochemical surrogate for the other effects, again probably those enhancing immune competence.

## Are Statins analogues of Vitamin D?

Colonic mucosa and colonic cancer cells contain vitamin D receptor, 42 strengthening my suggestion that vitamin D is biologically active in these tissues. Furthermore, vitamin D has an inhibitory effect on colonic carcinoma cell lines. 43 Do statins have a similar effect?

Statins should be looked at objectively and the diet – cholesterol hypothesis on which the treatment was based disregarded. Statins have been described as wonder drugs because of their unexpected benefits; my hypothesis gives an opportunity for new thinking. The explanation of statins as analogues of vitamin D, if correct, would be reassuring to the millions of people who take them every day. Finally, sunlight and vitamin D might at last be recognised for their widespread health benefits.

### Conflict of interest statement

I declare that I have no conflict of interest.

# “STATINS & SUNLIGHT”

## *PART – III*

# **MALIGNANT MEDICAL MYTHS.**

## **Prof. B. M. Hegde, MD, FRCP, FRCPE, FRCPG, FRCPI, FACC, FAMS.**

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- ❖ Visiting Prof. Indian Institute of Advanced Studies, Shimla,
- ❖ Retd. Vice Chancellor, Manipal University,

# MALIGNANT MEDICAL MYTHS.

**“Doing what’s right isn’t the problem. It’s a knowing what’s right.”**

**Lyndon B. Johnson.**

Every area of human endeavour will, per force, have some myths. However, the myths in the field of modern medicine are not only plenty but they could be very dangerous to the common man as they might even send him / her to meet the maker in heaven prematurely. While many of the drugs in use help human beings, they are also an important cause of premature death due to adverse reactions. Around 305,000 people die every year in the US alone due to ADR Medical Myths, therefore, are very malignant. How do these myths get perpetuated? There are vested interests in keeping up many of these myths as the myths make very good business sense. Medical profession seems to have conveniently forgotten the Hippocratic aphorism written 24 centuries ago: “Primum Non Nocere”- first do no harm!

## **Fat theory of Atherosclerosis:**

This is the next malignant medical myth. Despite the unequivocal result of the first Diet-Heart study (1954-59) in Framingham which spent more than \$110 million dollars of the US tax payers’ money showing that diet has very little to do with heart disease and the painstaking work of William Stehabens showing that the whole fat theory is a myth, the medical world, goaded and aided by the industry, went for the kill with powerful drugs to lower apparently healthy people’s cholesterol with some success in that marginally more people died in the drug treated group compared to the placebo. All these drugs from the most nauseating cholestyramine to all powerful statins, at the end of the day, did not bring down total deaths.

## MALIGNANT MEDICAL MYTHS.

Another \$415 million federal study involved nearly 49,000 women aged 50-79 that were followed for eight years. In the end, those assigned to a low-fat diet had the same rates of breast cancer, colon cancer, heart attacks and strokes as those who ate whatever they pleased, researchers are reporting now. “These studies are revolutionary,” said Dr. Jules Hirsch, Physician in chief emeritus at Rockefeller University in New York City, who has spent a lifetime studying the effects of diets on weight and health. “They should put a stop to this era of thinking that we have all the information we need to change the whole national diet and make everybody healthy.”

The whole cholesterol saga and the dangers of statins are summed up in the following words of Duane Graveline, a Physician and a former NASA astronaut, who had very serious near fatal side effects from statins, in his own words: “Surprisingly, we are discovering that our 40-year war on cholesterol through the use of drugs and the now infamous low fat / low cholesterol diet seems to have been grossly misdirected. We have become a nation of fattened sheep, prone to type 2 diabetes and with unchanged proneness to arteriosclerosis. Despite the mounting evidence for cholesterol’s irrelevance and our growing awareness of inflammation as the basis of atherosclerosis, our public still remains desperately focused on cholesterol. Statins have never been more aggressively marketed. (In the book Lipitor, Thief of memory). In fact, administering exogenous cholesterol has helped in many infections, especially in tuberculosis, which is threatening to be a global epidemic even in the west, thanks to AIDS!

# Conclusion

There is Urgent need for a paradigm shift in the thinking of the medical profession, shunning extraneous considerations and influences, and focusing on HUMAN HEALTH with futuristic objectivity and use chemical (DRUG) interventions Judiciously in disease and not be savaged into the temptation of using them like WOMD (Weapons of Mass destruction), falling a prey to the DOOMSDAY PREDICTORS (Ever increasing number theorist masquerading as epidemiologists linear increase of diseases like Diabetes, CAD,etc.)

Because the milieu of the human body functions in a Non-Linear manner, both in health (Physiologically) and in disease (Pathophysiologically).

In the Ultimate analysis we in the practice of medicine should at all times be aware of Humanism V12.Values, Rights, and may I dare to add medical morality, (however flexible that term may be!) in the treatment of our patients who trust us with their body and mind!!



**"The low-minded are happier than men who know goodness,  
for they are never troubled by the pangs of conscience."**

**Thirukkural – Kural 1072.**



**Mahakavi Kalidasa**

"पुराणमित्येव न सादु सर्वं,  
नचापि काव्यं न वमित्यवदयं,  
संतः परीक्ष्य अन्यतरत् बजन्ते,  
मूढः परप्रत्ययनेय बुद्धिः"

*Do not accept anything as good  
Just because it is old  
Do not reject anything as useless  
Just because it is new  
The wise weigh the substance and  
decide for themselves  
It is the unwise who are led by  
the opinion of others*

*Source: Poet Kalidasa's 'MALAVIKAGNIMITRA'*

***Thank You***

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