$29 billion
Reasons to Lie about
Cholesterol

Making profit
by turning healthy people
into patients

Justin Smith

Matador
9 De Montfort Mews
Leicester LE1 7FW, UK
Tel: (+44) 116 255 9311 / 9312
Email: books@troubador.co.uk
Web: www.troubador.co.uk/matador

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ADDITIONAL RESOURCES

www.29billion.com

The above website has been created to accompany this book. It contains a range of resources and documents ready for downloading, including:

- Information on how to test blood glucose levels
- More information about customised nutrition and Metabolic Typing™
- Other resources for people who are concerned about cholesterol
- Web links to references used throughout the text

CHAPTER 9

How Did We Get Here?

If the cholesterol idea is wrong and is not based on scientific evidence, it is logical to question why so many people, including a large number of doctors, have been taken in by it. This question can be answered through an appreciation of the general environment that doctors now work in.

Many readers will be surprised to learn that there are a number of significant problems with medical journals and the way medical research is published. Few people, apart from medical researchers themselves, have the time or the inclination to investigate these problems. However, they certainly do exist, and they affect whether or not a drug is considered effective and safe.

It will not however be a surprise to most people that medicine is generally influenced far too much by drug companies. But there is significant evidence that this problem is getting out of control. Inappropriate connections between researchers/doctors and the pharmaceutical industry are hindering the scientific process and affect government policy.

Many doctors are extremely uncomfortable with the current situation, but their voices seldom reach the general public. The aim of this chapter is to highlight just a few of the problems faced by the medical community. This will help readers to appreciate how the cholesterol idea could have been so widely accepted in the absence of sufficient scientific evidence to support it.

The Business of Selling Drugs

Pharmaceutical companies are of course a business just like any other, and the people who work for them want to increase profitability. Shareholders also want to see a return on their investment. It is only natural that these companies want to sell more drugs and there is evidence that they have been very successful in doing this.

For example, in the UK, the Office for National Statistics publishes data concerning the number of prescriptions written in England between 1996 and 2006. During this ten year period there was an increase in the number of prescription items from 485 million to 752 million per year. The number of prescriptions per person in the population increased from 10 to 14.8. In fact the number of prescription items has increased significantly every year for the last ten years (1).

Some may argue that this is a good thing and an indication that new drugs are being made available to patients. In some cases this may be true; however, overall the trend may be more worrying.

Richard Smith worked for the *British Medical Journal (BMJ)* for 25 years and was Editor and Chief Executive of the BMJ Publishing Group from 1991 to 2004. During this time he became one of the most influential people within medicine. In his book titled *The Trouble with Medical Journals* (2), which is published by The Royal Society of Medicine, he analyses the problems and current trends in medical publishing. The book provides a fascinating and highly readable account of these issues. It is highly recommended to anyone (including those without a scientific background) who wishes to gain an insight into the world of medical research and how it influences our daily lives.

Richard Smith does not examine the subject of cholesterol, but he does explain how the pharmaceutical companies, although powerful and influential, are experiencing a "productivity crisis" (2). In order for these companies to grow and increase profits they need to develop innovative drugs that genuinely provide significant benefits for patients. Unfortunately the number of pharmacological breakthroughs in this respect have been much fewer than was hoped for (2).

It was hoped that new drugs would be discovered for the ever increasing degenerative diseases suffered by huge numbers of people in the developed world. However, these attempts have been unsuccessful. The number of new drugs approved in the United States by the Food and Drug Administration (FDA) in 2002 was significantly less than in previous years (2). Pharmaceutical companies have been forced to look at other ways to achieve business growth. This includes increasing marketing efforts to get more people to use their drugs, and creating new diseases: or converting more people into patients.

Some authors describe these activities as "disease mongering" (3, 4). They are concerned about the "invisible and unregulated attempts to change public perceptions about health and illness in order to widen markets for new drugs" (3).

Barbara Mintzes, in an article published in the *Public Library of Science* (*PLoS) Medicine* (4), describes the various forms that disease mongering by pharmaceutical companies can take. This includes:

- Promotion of anxiety about future ill-health in healthy people
- Exaggerating the number of people affected by the 'disease'

- Promotion of aggressive drug treatment for mild symptoms
- Introducing new conditions that are hard to distinguish from normal life, such as social anxiety disorder
- Promoting drugs as the first solution for problems previously not considered medical, such as: disruptive classroom behaviour or problematic sexual relationships

An advert was placed in a London newspaper in February 2008 designed to recruit people to take part in a drug trial. The trial is for a condition called *Hypoactive Sexual Desire Disorder (HSDD)*, otherwise known as: a low sex drive. Giving this problem a long technical name and publicising it creates a new disease or condition that requires new drugs to treat it. Traditionally, this kind of problem has been dealt with in other ways, without medication.

A lot of money can be made from healthy people who believe they are sick (3), since disease mongering exploits our deepest fears of suffering and death (5). Substantial and lucrative professional careers have been built on the pursuit of new diseases or risk factors for disease (5). The pharmaceutical companies are exploiting opportunities in this area for business growth by making more people aware of certain 'conditions'.

In some cases more emphasis appears to be placed on risk factors than on the disease itself. High cholesterol has become synonymous with heart disease to the extent that the management of cholesterol levels has become more of a concern than the prevention of heart disease.

A number of studies have been completed that focus solely on cholesterol levels. One study looked at how many people in

England have low HDL levels (so called 'good' cholesterol) and how many people are taking cholesterol lowering drugs (6). Another study looked at HDL levels in various European countries (7). According to the supporters of the cholesterol idea, low HDL levels contribute to the risk for developing heart disease. Therefore, investigations such as these may seem valid, but they create an impression that having the suggested 'risk factor' is the same as having the disease.

The authors use the data obtained to conclude that more people need to take cholesterol lowering drugs, or additional drugs should be used that specifically target HDLs. This conclusion is reached without regard to the many factors that contribute to heart disease.

By just looking at one of the suggested risk factors we lose sight of the main objective: which is to actually save lives. In the previous chapter we discussed a clinical trial for a drug used specifically to increase HDL levels. Readers will recall that this trial was terminated because of an increase in deaths and heart attacks in people who took this drug along with a statin. This is what can happen when focus is placed solely on risk factors, especially in a condition such as heart disease that has numerous complex mechanisms associated with it.

Drug companies have been restructuring their organisations: shifting more of their resources into marketing and 'education' so that they can take full advantage of the opportunities. In American research-based drug companies, the number of people employed in research and development has fallen 2% since 1995, but marketing staff have increased by 59%. Twice as many people are now employed in marketing than in research and development (2). It has been estimated that around US$10,000 a year is spent

on marketing to each doctor in the United States and that around US$2.5 billion was spent in 2000 on marketing to consumers (2).

The pharmaceutical industry spends millions of dollars supporting the 'education' of doctors. It has been estimated that 99% of doctors use information provided by pharmaceutical companies in their clinical practice (5). If the prescribing of drugs and profits for drug companies were not affected by this support, it would not be offered (5).

Doctors and Drug Companies

Pharmaceutical companies should be allowed to sell their products to doctors. This is a necessary part of the overall process involved in medicine. However, connections between doctors and drug companies can in many ways become inappropriate and have an unnatural influence on prescription habits. This is particularly true when doctors who hold influential positions determining treatment protocols are supported by the pharmaceutical companies. Readers will recall from chapter 8 that the panel of expects responsible for deciding who should be prescribed statins, was mostly made up of doctors who were supported by statin manufacturers. Eight out of nine of the experts had connections with the companies that make the drugs. No surprise then that the threshold for statin use was lowered: making millions more people eligible to use the drugs and massively increasing the size of the market for them.

According to a survey completed in America, 94% of doctors have some kind of link with the pharmaceutical industry (8). The frequency of different types of connections is listed below:

- Receiving food and drinks in the workplace – 83%
- Receiving drug samples from a sales representative – 78%
- Reimbursement for costs associated with professional meetings – 35%

Other payments are received for consulting, serving as a speaker, serving on an advisory board, and enrolling patients on clinical trials (8, 9).

Some doctors are of the opinion that these ties with industry do not influence the prescribing of drugs. However, there are certain social obligations associated with gifts and human beings often feel the need to reciprocate in some way when they receive one – even if the gift was something that they didn't want. Likewise, if a doctor has received excellent hospitality from a pharmaceutical company during a seminar or conference, they are less likely to be openly critical of the company's drugs. Doctors are of course only human like the rest of us.

Interestingly, a survey conducted on medical students found that 86% thought it was improper for a politician to receive a gift, but only 46% thought it was improper for themselves to receive a gift of a similar value from a pharmaceutical company (10).

Some positive outcomes have been found as a result of these links with drug companies, such as doctors being better able to identify the treatment for complicated illnesses (10). However, most studies have found negative outcomes, such as:

- Doctors not being able to identify wrong claims about medication
- Doctors requesting new, more expensive drugs that have no demonstrated benefit over existing ones

- Increased prescription rates
- Irrational prescribing behaviour (10)

Prescription rates and practices are probably compounded by short consultation times with doctors. A study published in the *British Medical Journal* in 2002, compared average consultation times in six European countries. The average consultation time with doctors in the UK was 9.4 minutes. However the authors of the study highlighted the fact that in reality, average consultation times may be lower, since the doctors in their study had lower workloads than the average for the country as a whole. The consultations in the study were also videotaped: which may have influenced the consultation time. Interestingly, in Belgium and Switzerland, where patients pay the doctor directly at the end of their consultation, the average consultation time was 15 minutes and 15.6 minutes respectively (11).

Bias in Publishing Results

Clinical drug trials are increasingly sponsored by the pharmaceutical industry. Various studies have found that when a pharmaceutical company sponsors research into a drug, the results are considerably more likely to show the drug in a favourable light. Systematic bias occurs when the drugs being tested are made by the company funding the research (12).

In addition, drug trials that show favourable results are more likely to be published (13), and pharmaceutical companies have attempted to prevent studies that show unfavourable results (for their products) from being published (12).

An example of this can be found in the *ENHANCE* trial. This was

a two year trial to test the effects of using a drug called *ezetimibe* in conjunction with a statin to achieve greater reductions in cholesterol. The people who took part in the trial were split into two groups: one group was given ezetimibe and the statin, and the other group were given just the statin. LDL levels (so called 'bad' cholesterol) were reduced to a considerably lower level in the group who were given both ezetimibe and the statin (14). According to the cholesterol idea, these greater reductions in LDL levels should result in greater reductions in heart disease compared with the people who just took the statin. The greater reductions in LDLs should also reduce the build up of plaque within arteries. However, the researchers found the opposite to be true. Rather than providing any benefit, the addition of ezetimibe actually lead to a slight increase in the amount of plaque found in the main arteries that supply blood and oxygen to the brain (15).

The results of the ENHANCE trial raises questions about the idea that cholesterol levels are related to the build up of plaque in arteries. But this issue is over-shadowed by the fact that the drug companies attempted to hide these results from the public for as long as possible.

The ENHANCE trial ended in April 2006, but the companies that make the drug being tested; Merck and Schering-Plough, did not report the results until January 2008. Even then, the results were only released after pressure from Congress in America (14), and after articles started to appear in the news media questioning the delay (14, 16).

The companies blamed the complexity of the data for the delay. A spokesman for Schering said the delay was unrelated to the negative findings and that the results were not known until two weeks before they were released. However, deadlines were

repeatedly missed for reporting the results and in the meantime, millions of people continued to take the drug unaware of the negative results of the trial (14). Global sales of the drug in question were US$5 billion in 2007 (17). In England alone, more than two million prescriptions were written in the two years prior to the release of the results, costing the National Health Service £74 million (17).

All of this is bad enough, but there were also problems with the registration of the ENHANCE trial. An official register of clinical trials is used to stop researchers changing the objective of the trial that is being conducted. Since these changes could be done in order to cover-up unfavourable results. The ENHANCE trial was not registered until 18 months after the trial had ended and the objective of the trial has been reported to have been altered in the register (18).

Subsequent studies have been completed on ezetimibe showing that the use of this drug in conjunction with a statin increases the risk for cancer (19). Investigators dismissed this as a chance finding (20), but significant questions remain (21). Patients are being expected to continue to take this drug on faith, potentially exposing themselves to serious side effects. The drug is used under the trade names *Zetia, Vytorin*, *Ezetrol*, and *Inegy*.

The ENHANCE trial is just one example of problems that can arise when focus is placed on suggested risk factors rather than on the disease itself. In order for drugs to be approved by the FDA in America, it is not necessary to show benefits in terms of a reduction in heart disease risk – merely demonstrating that the drug lowers 'bad' cholesterol (LDLs) is enough to get it approved (22). This is a dangerous and risky approach for patients, and it distracts research away from finding the true causes of a disease.

In the ENHANCE trial the suggested risk factor (in this case cholesterol) was significantly reduced, but this resulted in absolutely no benefit for patients. Even if the trial was designed to investigate a valid hypothesis, the results should have been released immediately. As stated by Ben Goldacre, writing in the *Guardian* newspaper "the data belongs to patients – and to the people whose bodies are used" (18).

Delaying the results of a trial, or never publishing the results, is one way that publication bias is introduced. Another way is publishing studies more than once. Researchers often perform what is termed a *systematic review* of all studies that have been completed on a drug in order to gain an overall view on the effectiveness of treatment. If positive results are published more than once and negative results not published at all, the conclusions of a systematic review will be affected substantially. The end result may be that patients are given toxic and expensive treatments that do not benefit them (2).

A paper published in the *New England Journal of Medicine* investigated the extent of publication bias in antidepressant drug trials. It was found that 31% of the trials had not been published and that almost all of the unpublished trials showed negative results associated with the drug being tested. According to the published studies 94% of trials found favourable results for the drug, but when the unpublished trials are included only 51% of the trials had a favourable result (23).

In February 2008, Professor Irving Kirsch and colleagues conducted a detailed analysis of all the clinical trial data submitted to the FDA on antidepressant drugs (24). They analysed all of the data: both published and unpublished. The conclusion they reached was that antidepressant drugs were no more effective

than a *placebo*. This caused an outcry, since the drugs are used by 40 million people worldwide (25). It may be true that some people have benefited from taking antidepressant drugs but the benefits appear to be due to the *placebo effect*. This example shows just how the effectiveness of drugs can be exaggerated if data about them is not published. This publication bias can help pharmaceutical companies to make more profit.

News Media

Most people do not see their doctor regularly, and as we have seen, consultation times are often short in duration. Therefore the media represents the most significant source of health information for the general public.

Television, radio and newspaper medical reporters have a difficult job. They must be accurate, authoritative, and compassionate. They also need to understand the terminology, physiology, epidemiology, study design, and statistical analysis to keep health news in context for the viewer/listener/reader (26).

The way information about drugs is presented through the media has a huge impact on the share price of pharmaceutical companies. In February 2008, Jean-Pierre Garnier, chief executive of the drugs giant GlaxoSmithKline (GSK), gave a presentation in London in which he discussed the reasons for the disappointing financial results for the company during the previous year. The financial results were poor because of reports about the company's diabetes drug *Avandia* being linked with heart problems. Garnier partly blamed the media for the drop in sales that resulted from this (27).

The negative reports about Avandia came after a study published

in the *New England Journal of Medicine* found that the drug was associated with an increased risk for having a heart attack (28). The author of the study was Dr Steven Nissen, a cardiologist at the respected Cleveland Clinic. The study was particularly important because heart disease is the most serious complication associated with diabetes. As a result of this published paper and the media reports communicating it to the general public, more than US$10 billion was wiped off the value of GSK during afternoon trading in the United States (29).

At the time, GSK strongly disagreed with the study published by Dr Nissen and said that the conclusions reached were based on incomplete evidence (30). However, Dr Nissen was also part of the scientific team that completed an analysis of the available data on the drug *Vioxx*. This analysis found that Vioxx increased heart attack and stroke risks. A patient trial was subsequently completed that came to the same conclusion. This forced Vioxx to be withdrawn (31).

The debate about the increased risk of suffering a heart attack while taking Avandia has continued. This is another example where people are being expected to carry on taking a drug on faith. One study, supported by GSK, stated that the data was insufficient (32). However, the same study did find evidence of a significant increase in the risk of *heart failure* with Avandia (32). GSK announced that it would make chances to the labeling of the drug in Europe to inform people about this risk (33).

A large clinical trial started in 2001 (the *ACCORD* trial) that included a range of diabetes drugs, including Avandia (34). This trial was designed to evaluate the use of drugs to intensively lower blood glucose levels compared with the use of drugs to moderately lower blood glucose. The trial was due to be

completed in 2009, however, the use of drugs to intensively lower blood glucose was stopped 17 months early because of an increased number of deaths in this group.

Since the ACCORD trial included a range of drugs, it is not possible to determine which drugs caused the increased deaths. GSK have pointed out that there is no direct link between Avandia and the increased deaths found during the trial (35). However, Avandia was used more extensively in the group that experienced more deaths.

Avandia may or may not increase the risk of having a heart attack and/or increase the risk of death, but this case provides an example of the media just doing its job – informing patients of the potential risks associated with a widely used drug. Media reports such as this may not be good for share holders' profits but they are absolutely vital to patients. Even a small increase in risk in a fragile population of patients with diabetes is of considerable concern (36).

However, journalists can unwittingly become 'mouthpieces' for those with vested interests (26). Pharmaceutical companies can use the media to portray exaggerated benefits associated with their drugs. This is what happened in the case of the follow up of the *West of Scotland Coronary Prevention Study (WOSCOPS)* which appeared as a major success for statins in the media. A closer look at this study shows that some of the conclusions reached were misleading. This example is discussed in more detail in chapter 13.

Medical Journals: Powerful, but Also Problematic

The examples described above show how influential medical journals are. Most people think of medical journals as dull and obscure, however the content of them influences the lives of us

all. Not only do they affect what doctors do with individual patients and the actions taken by public health authorities on whole populations, but they also influence how we think about birth, death, pain and sickness (2). However, there are a number of serious problems with medical journals.

Pharmaceutical companies generate influence through medical journals in a number of ways. One obvious way is through advertising. Advertising in journals can increase the prescribing of drugs (2). A large number of doctors receive journals such as the *British Medical Journal*, the *New England Journal of Medicine*, and the *Journal of the American Medical Association*, for free because of the financial support the journals get from pharmaceutical company advertising. Publishers of medical journals are always worried that these companies will cut back on advertising and they argue that advertising produces a better financial return for the pharmaceutical industry than employing more company representatives (2).

Authorship is also a serious problem with medical journals. Surprisingly the list of authors that appear at the top of a medical paper may not reflect true authorship. It has been stated that there are four types of lie: lies, damned lies, statistics, and the authorship lists of scientific papers (37). Scientific communities call this problem *ghost authorship*. Ghost authors are people who have contributed to a research study or been involved in writing the paper, but their name does not appear on the list of authors.

There are a number of implications associated with ghost authorship. One of the main concerns is that the ghost author is employed by a pharmaceutical company – this creates a conflict of interest that is not declared and may mean that the paper is not looked at in its true light. One study found that 75% of trials had

ghost authors (38). In this case the ghost authors were statisticians who were employed by the pharmaceutical companies supporting the trials. Clinical trials are often complex and generate large datasets; the statistical report is a fundamental part of the research and has a crucial influence on what is written in the publication (38). Not declaring the statistician deceives the reader about the role of the supporting company.

Potential problems also exist with the *peer review* process. Richard Smith, in his book, explains these problems in detail: "Peer review is at the heart of all science – It is the method by which grants are allocated, papers published, academics promoted and Nobel prizes won. Yet it is hard to define … and its defects are easier to identify than its attributes" (2).

Peer review could loosely be described as getting a third party to verify or make a decision about whether to publish a paper. Ideally the third party should not be connected with the research, have no competing interests, but still be in a position to technically appraise the methodology and findings. Richard Smith explains that peer review sometimes seems to be a simple case of someone saying "the paper looks all right to me" (2) and examples of a comprehensive, detailed review of a paper are difficult to find. These issues directly impact the quality of what gets published and what does not get published - influencing the conclusions that are reached about a wide range of medical conditions and treatment protocols.

Doctors Are Paid More If They Lower Your Cholesterol

In April 2004, the National Health Service (NHS) in the UK introduced the *Quality and Outcomes Framework (QOF)*. This is a kind of performance related pay and is applied to every general

practitioner medical practice. QOF contains 146 quality indicators which doctors have to report on. The better the practice does in terms of these indicators, the more money it will get from the NHS.

Around half of the potential revenue from QOF is associated with indicators of clinical quality (39). Specific indicators have been identified for a range of common conditions. For example, a list of indicators has been identified for diabetes. These include body mass index (BMI) and blood glucose levels. The more diabetic patients that have a BMI and blood glucose level below a specified value, the more money the doctor will get from the NHS.

One of the problems with QOF is that many of the indicators are based on risk factors for disease and targets are set without regard to how they are achieved. There are performance measures, or targets, set for cholesterol.

If a patient has heart disease, diabetes or if they have had a stroke, doctors are expected to lower their cholesterol so that it is below 5mmol/l (millimoles per litre). If, say, 40% of a doctors diabetic patients have a cholesterol level below 5mmol/l, the doctor will be paid less than if 50% of diabetic patients have a cholesterol level below 5mmol/l. In summary, there is a strong financial incentive for doctors to lower the cholesterol levels of certain patients. Since the majority of people in the UK happen to naturally have a cholesterol level above 5mmol/l, the doctor has little choice but to put more people onto statins.

An article published in the *New England Journal of Medicine* describes the problems associated with performance measures being based on risk factors for disease (40). This paper cites a number of examples where the focus on the risk factor has actually caused more harm and increased the number of deaths.

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