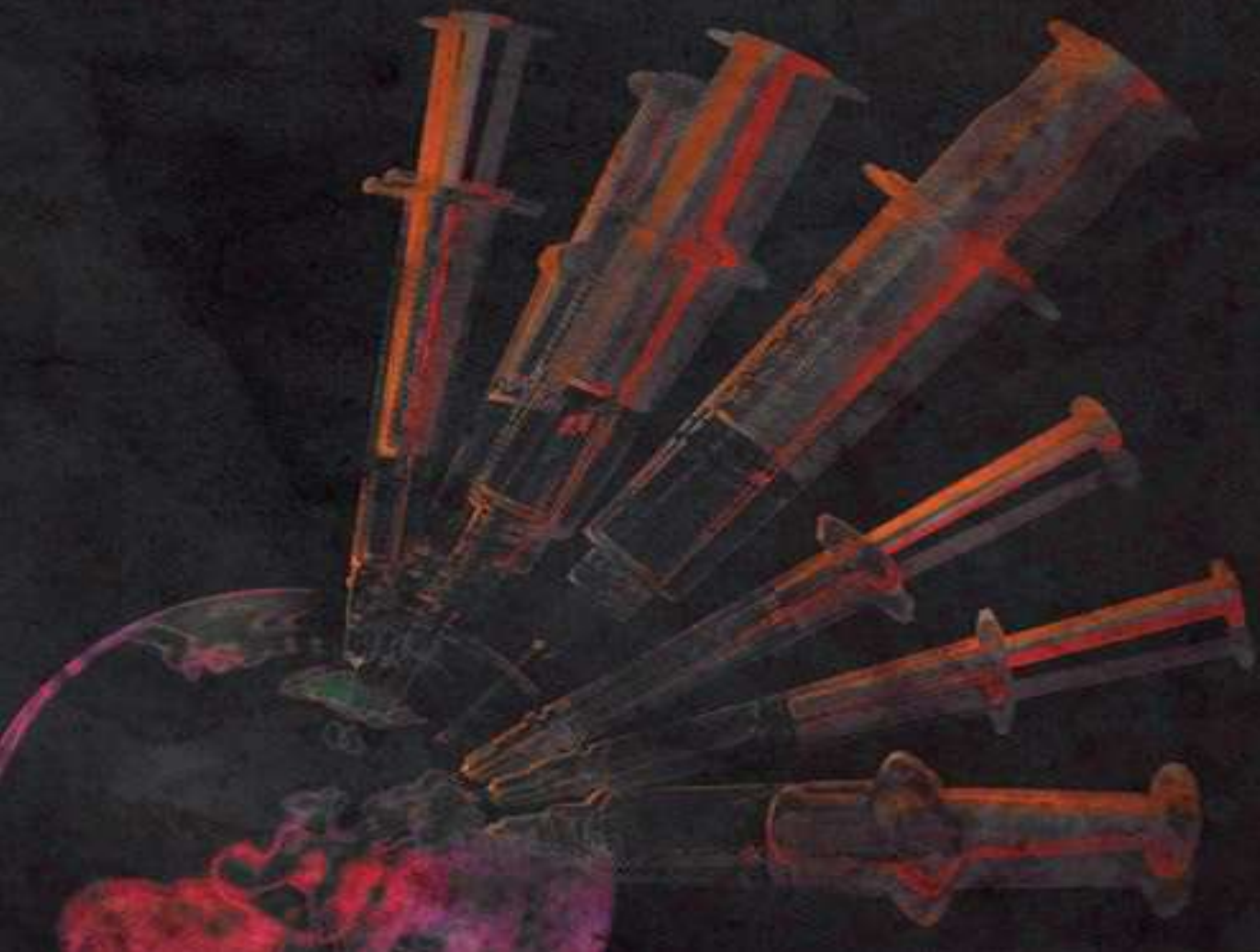
Deadly MEDICINES AND Organised CRIME

How big pharma has corrupted healthcare

PETER C GØTZSCHE

Forewords by
Richard Smith, former Editor-in-Chief, *BMJ*
Drummond Rennie, Deputy Editor, *JAMA*



Contents

Foreword by Richard Smith

There must be plenty of people who shudder when they hear that Peter Gøtzsche will be speaking at a meeting or see his name on the contents list of a journal. He is like the young boy who not only could see that the emperor had no clothes but also said so. Most of us either cannot see that the emperor is naked or will not announce it when we see his nakedness, which is why we badly need people like Peter. He is not a compromiser or a dissembler, and he has a taste for strong, blunt language and colourful metaphors. Some, perhaps many, people might be put off reading this book by Peter's insistence on comparing the pharmaceutical industry to the mob, but those who turn away from the book will miss an important opportunity to understand something important about the world – and to be shocked.

Peter ends his book with a story of how the Danish Society for Rheumatology asked him to speak on the theme *Collaboration with the drug industry. Is it THAT harmful?* The original title was *Collaboration with the drug industry. Is it harmful?* but the society thought that too strong. Peter started his talk by enumerating the 'crimes' of the meeting's sponsors. Roche had grown by selling heroin illegally. Abbot blocked Peter's access to drug regulators' unpublished trials that eventually showed that a slimming pill was dangerous. UCB too concealed trial data, while Pfizer had lied to the Food and Drug Administration and been fined $2.3 billion in the United States for promoting off label use of four drugs. Merck, the last sponsor, had, said Peter, caused the deaths of thousands of patients with its deceptive behaviour around a drug for arthritis. After this beginning to his talk he launched into his condemnation of the industry.

You can imagine being at the meeting, with the sponsors spluttering with rage and the organisers acutely embarrassed. Peter quotes a colleague as saying that he felt 'my direct approach might have pushed some people away who were undetermined.' But most of the audience were engaged and saw legitimacy in Peter's points.

The many people who have enthusiastically supported routine mammography to prevent breast cancer deaths might empathise with the sponsors – because Peter has been critical of them and published a book on his experiences around mammography. The important point for me is that Peter was one of few people criticising routine mammography when he began his investigations but – despite intense attacks on him – has been proved largely right.

He did not have any particular view on mammography when he was asked by the Danish authorities to look at the evidence, but he quickly concluded that much of the evidence was of poor quality. His general conclusion was that routine mammography might save some lives, although far fewer than enthusiasts said was the case, but at the cost of many false positives, women undergoing invasive and anxiety-creating procedures for no benefit, and of overdiagnosis of harmless cancers. The subsequent arguments around routine mammography have been bitter and hostile, but Peter's view might now be called the orthodox view. His book on the subject shows in a detailed way how scientists have distorted evidence in order to support their beliefs.

I have long recognised that science is carried out by human beings not objective robots and will therefore be prone to the many human failings, but I was shocked by the stories in Peter's book on mammography.

Much of this book is also shocking and in a similar way: it shows how science can be corrupted in order to advance particular arguments and how money, profits, jobs and reputations are the most potent corrupters.

Peter does acknowledge that some drugs have brought great benefits. He does so in one sentence: 'My book is not about the well-known benefits of drugs such as our great successes with treating infections, heart diseases, some cancers, and hormone deficiencies like type 1 diabetes.' Some readers may think this insufficient, but Peter is very clear that this is a book about the failures of the whole system of discovering, producing, marketing and regulating drugs. It is not a book about their benefits.

Many of those who read this book will ask if Peter has over-reached himself in suggesting that the activities of the drug industry amount to organised crime. The characteristics of organised crime, racketeering, is defined in US law as the act of engaging repeatedly in certain types of offence, including extortion, fraud, federal drug offenses, bribery, embezzlement, obstruction of justice, obstruction of law enforcement, tampering with witnesses and political corruption. Peter produces evidence, most of it detailed, to support his case that pharmaceutical companies are guilty of most of these offences.

And he is not the first to compare the industry with the Mafia or mob. He quotes a former vice-president of Pfizer, who has said:

> *It is scary how many similarities there are between this industry and the mob. The mob makes obscene amounts of money, as does this industry. The side effects of organized crime are killings and deaths, and the side effects are the same in this industry. The mob bribes politicians and others, and so does the drug industry …*

The industry has certainly fallen foul of the US Department of Justice many times in cases where companies have been fined billions. Peter describes the top 10 companies in detail, but there are many more. It's also true that they have offended repeatedly, calculating perhaps that there are large profits to be made by flouting the law and paying the fines. The fines can be thought of as 'the cost of doing business' like having to pay for heat, light and rent.

Many people are killed by the industry, many more than are killed by the mob. Indeed, hundreds of thousands are killed every year by prescription drugs. Many will see this as almost inevitable because the drugs are being used to treat diseases that themselves kill. But a counter-argument is that the benefits of drugs are exaggerated, often because of serious distortions of the evidence behind the drugs, a 'crime' that can be attributed confidently to the industry.

The great doctor William Osler famously said that it would be good for humankind and bad for the fishes if all the drugs were thrown into the sea. He was speaking before the therapeutic revolution in the middle of the 20th century that led to penicillin, other antibiotics, and many other effective drugs, but Peter comes close to agreeing with him and does speculate that we would be better off without most psychoactive drugs, where

the benefits are small, the harms considerable, and the level of prescribing massive.

Most of Peter's book is devoted to building up the case that the drug industry has systematically corrupted science to play up the benefits and play down the harms of their drugs. As an epidemiologist with very high numerical literacy and a passion for detail, so that he is a world leader in critiquing clinical studies, Peter is here on very solid ground. He joins many others, including former editors of the *New England Journal of Medicine*, in showing this corruption. He shows too how the industry has bought doctors, academics, journals, professional and patient organisations, university departments, journalists, regulators, and politicians. These are the methods of the mob.

The book doesn't let doctors and academics avoid blame. Indeed, it might be argued that drug companies are doing what is expected of them in maximising financial returns for shareholders, but doctors and academics are supposed to have a higher calling. Laws that are requiring companies to declare payments to doctors are showing that very high proportions of doctors are beholden to the drug industry and that many are being paid six figure sums for advising companies or giving talks on their behalf. It's hard to escape the conclusion that these 'key opinion leaders' are being bought. They are the 'hired guns' of the industry.

And, as with the mob, woe be to anybody who whistleblows or gives evidence against the industry. Peter tells several stories of whistleblowers being hounded, and John le Carré's novel describing drug company ruthlessness became a bestseller and a successful Hollywood film.

So it's not entirely fanciful to compare the drug industry to the mob, and the public, despite its enthusiasm for taking drugs, is sceptical about the drug industry. In a poll in Denmark the public ranked the drug industry second bottom of those in which they had confidence, and a US poll ranked the industry bottom with tobacco and oil companies. The doctor and author, Ben Goldacre, in his book *Bad Pharma* raises the interesting thought that doctors have come to see as 'normal' a relationship with the drug industry that the public will see as wholly unacceptable when they fully understand it. In Britain doctors might follow journalists, members of Parliament, and bankers into disgrace for failing to see how corrupt their ways have become. At the moment the public tends to trust doctors and distrust drug companies, but the trust could be rapidly lost.

Peter's book is not all about problems. He proposes solutions, some of which are more likely than others to happen. It seems most unlikely that drug companies will be nationalised, but it is likely that all the data used to license drugs will be made available. The independence of regulators should be enhanced. Some countries might be tempted to encourage more evaluation of drugs by public sector organisations, and enthusiasm is spreading for exposing the financial links between drug companies and doctors, professional and patient bodies, and journals. Certainly the management of conflicts of interest needs to be improved. Marketing may be further constrained, and resistance to direct consumer advertising is stiffening.

Critics of the drug industry have been increasing in number, respectability, and vehemence, and Peter has surpassed them all in comparing the industry with organised crime. I hope that nobody will be put off reading this book by the boldness of his

comparison, and perhaps the bluntness of the message will lead to valuable reform.

Richard Smith, MD
June 2013

Foreword by Drummond Rennie

Evidence-based outrage

There already exist hundreds of reports of scientific studies, and many books written, about the way pharmaceutical companies pervert the scientific process and, using their massive wealth, all too often work against the interests of the patients they claim to help. I myself have contributed to the piles. So what makes this book new and worth your attention?

The answer is simple: the unique scientific abilities, research, integrity, truthfulness, and courage of the author. Gøtzsche's experience is unequaled. He has worked in sales for drug companies either as a drug company representative pitching pills to doctors or as a product manager. He is a physician and a medical researcher and has built a high reputation as head of The Nordic Cochrane Centre. So when he speaks about bias, he bases his opinions on careful research over decades, published in peer-reviewed journals. He deeply understands the statistics of bias and the techniques of analyzing reports of clinical trials. He has been in the forefront of the development of systematic and rigorous review and meta-analysis of reports of clinical trials, to winnow out, using strict criteria, the true effectiveness of drugs and tests. He is often annoyingly persistent, but he is always driven by the evidence.

So I trust Gøtzsche to have his facts right. My trust is based on solid evidence, and on my own experience over several decades struggling with the results of pharmaceutical company influence upon my clinical researcher colleagues, and upon the public. In addition, I trust Gøtzsche because I know him to be correct when he writes about events of which I have independent knowledge.

My last reason for trusting Gøtzsche's account has to do with my own job as an editor at a very large medical clinical journal. Editors are the first to be able to examine the written report as it comes from a research institution. Editors or their reviewers detect problems of bias in the papers submitted to their journals, and it is to editors that complaints and allegations are directed.

I have written repeated, and often indignant, editorials revealing unethical behavior by commercially-supported researchers and their sponsors. At least three editors whom I also know well, Drs. Jerome Kassirer and Marcia Angell (*The New England Journal of Medicine*) and Richard Smith (*British Medical Journal*) have written books in which they have expressed dismay at the magnitude of the problem. Other editors such as Fiona Godlee of the *British Medical Journal* have written eloquently on the corrupting influence of money and the way it biases the treatment of patients and increases the costs.

I don't pretend to vouch for all Gøtzsche's facts – this is a foreword, not an audit – but the general picture he gives is only too familiar. While Gøtzsche may seem to talk in hyperbole, my own depressing experiences and that of medical editors and researchers I know personally tell me he's right.

In a lecture I gave to an audience of judges I noted that clinical researchers and the legal profession used the same word, 'trial', for two sorts of process, one legal and the

other scientific. Speaking for my own profession, I had to acknowledge that legal 'trials' were set up in a way that was generally fairer, and based on a sounder ethical footing than clinical trials. (Gøtzsche quotes this here.)

Gøtzsche has proposals and calls for revolution. To me nothing will help unless we disconnect completely the performance and assessment of trials from the funding of trials. We base our treatments on the results of clinical trials, so the results are a matter of life and death. Patients who allow themselves to be entered into trials expect their sacrifice to benefit humanity. What they do not expect is that their results will be held, and manipulated, as trade secrets. These results are a public good and they should be financed by the government using taxes paid by the industry, and available to all. As it is, we have the ironic situation in the US where the drug companies pay the agency, the FDA, to assess their projects. Is it any surprise that the agency has been captured by the industry it is supposed to regulate?

Revolution? Gøtzsche is right. We landed in our present mess because of innumerable mistakes in the past, and he describes many of these in his detailed inventory. They include failure of clinical scientists, their institutions and the editors of the journals publishing their science to understand how thoroughly they were being caught up by the marketers who paid them. I believe it will take a revolution to sweep away decades of self-dealing by industry.

I hope you will read this book and reach your own conclusions. Mine? If Gøtzsche is angry at the behavior of academia and industry, he has a right to be. What's needed is more of Gøtzsche's evidence-based outrage.

Drummond Rennie, MD
June 2013

1

Introduction

The big epidemics of infectious and parasitic diseases that previously took many lives are now under control in most countries. We have learned how to prevent and treat AIDS, cholera, malaria, measles, plague and tuberculosis, and we have eradicated smallpox. The death tolls of AIDS and malaria are still very high, but that's not because we don't know how to deal with them. It has more to do with income inequalities and the excessive costs of life-saving drugs for people in low-income countries.

Unfortunately, we now suffer from two man-made epidemics, tobacco and prescription drugs, both of which are hugely lethal. In the United States and Europe,

drugs are the third leading cause of death after heart disease and cancer.

I shall explain in this book why this is so and what we can do about it. If drug deaths had been an infectious disease, or a heart disease or a cancer caused by environmental pollution, there would have been countless patient advocacy groups raising money to combat it and far-ranging political initiatives. I have difficulty understanding that – since it is drugs, people do nothing.

The tobacco and the drug industries have much in common. The morally repugnant disregard for human lives is the norm. The tobacco companies are proud that they have increased sales in vulnerable low-income and middle-income countries, and without a trace of irony or shame, Imperial Tobacco's management team reported to investors in 2011 that the UK-based company won a Gold Award rating in a corporate responsibility index.[1] The tobacco companies see 'many opportunities … to develop our business', which the *Lancet* described as 'selling, addicting, and killing, surely the most cruel and corrupt business model human beings could have invented'.[1]

Tobacco executives know they are peddling death and so do drug company executives. It is no longer possible to hide the fact that tobacco is a major killer, but the drug industry has done surprisingly well in hiding that its drugs are also a major killer. I shall describe in this book how drug companies have deliberately hidden lethal harms of their drugs by fraudulent behaviour, both in research and marketing, and by firm denials when confronted with the facts. Just like the chief tobacco executives each testified at a US Congressional hearing in 1994 that nicotine wasn't addictive, although they had known for decades that this was a lie.[2] Philip Morris, the US tobacco giant, set up a research company that documented the dangers of sidestream smoke, but even though more than 800 scientific reports were produced none were published.[2]

Both industries use hired guns. When robust research has shown that a product is dangerous, numerous substandard studies are produced saying the opposite, which confuse the public because – as journalists will tell you – 'researchers disagree'. This doubt industry is very effective at distracting people into ignoring the harms; the industry buys time while people continue to die.

This is corruption. Corruption has many meanings and what I generally understand by it is how it is defined in my own dictionary, which is moral decay. Another meaning is bribery, which may mean a secret payment, usually in cash, for a service that would otherwise not be rendered, or at least not so quickly. However, as we shall see, corruption in healthcare has many faces, including payment for a seemingly noble activity, which might be nothing else than a pretence for handing over money to a substantial part of the medical profession.

The characters in Aldous Huxley's novel from 1932, *Brave New World*, can take Soma pills every day to give them control over their lives and keep troubling thoughts away. In the United States, TV commercials urge the public to do exactly the same. They depict unhappy characters that regain control and look happy as soon as they have taken a pill.[3] We have already superseded Huxley's wildest imaginations and drug use is still increasing. In Denmark, for example, we use so many drugs that every citizen, whether sick or healthy, can be in treatment with 1.4 adult daily doses of a drug every day, from cradle to grave. Although many drugs are life-saving, one might suspect that it is harmful to medicate our societies to such an extent, and I shall document that this is indeed the case.

The main reason we take so many drugs is that drug companies don't sell drugs, they sell lies about drugs. Blatant lies that – in all the cases I have studied – have continued after the statements were proven wrong. This is what makes drugs so different from anything else in life. If we wish to buy a car or a house, we may judge for ourselves whether it's a good or a bad buy, but if we are offered a drug, we have no such possibility. Virtually everything we know about drugs is what the companies have chosen to tell us and our doctors. Perhaps I should explain what I mean by a lie. A lie is a statement that isn't true, but a person who tells a lie is not necessarily a liar. Drug salespeople tell many lies, but they have often been deceived by their superiors in the company who deliberately withhold the truth from them (and are therefore liars, as I see it). In his nice little book *On Bullshit*, moral philosopher Harry Frankfurt says that one of the salient features of our culture is that there is so much bullshit, which he considers short of lying.

My book is not about the well-known benefits of drugs such as our great successes with treating infections, heart diseases, some cancers, and hormone deficiencies like type 1 diabetes. The book addresses a general system failure caused by widespread crime, corruption and impotent drug regulation in need of radical reforms. Some readers will find my book one-sided and polemic, but there is little point in describing what goes well in a system that is out of social control. If a criminologist undertakes a study of muggers, no one expects a 'balanced' account mentioning that many muggers are good family men.[4]

If you don't think the system is out of control, please email me and explain why drugs are the third leading cause of death in the part of the world that uses most drugs. If such a hugely lethal epidemic had been caused by a new bacterium or a virus, or even one-hundredth of it, we would have done everything we could to get it under control. The

tragedy is that we could easily get our drug epidemic under control, but our politicians who hold the power to make changes do virtually nothing. When they act, they usually make matters worse because they have been so heavily lobbied by the industry that they have come to believe all its luring myths, which I shall debunk in every chapter of the book.

The main problem with our healthcare system is that the financial incentives that drive it seriously impede the rational, economical and safe use of drugs. The drug industry prospers on this and exerts tight information control. The research literature on drugs is systematically distorted through trials with flawed designs and analyses, selective publication of trials and data, suppression of unwelcome results, and ghostwritten papers. Ghostwriters write manuscripts for hire without revealing their identity in the papers, which have influential doctors as 'authors', although they have contributed little or nothing to the manuscript. This scientific misconduct sells drugs.

Compared to other industries, the pharmaceutical industry is the biggest defrauder of the US federal government under the False Claims Act.[5] The general public seems to know what the drug industry stands for. In an opinion poll that asked 5000 Danes to rank 51 industries in terms of the confidence they had in them, the drug industry came second to the bottom, only superseded by automobile repair companies.[6] A US poll also ranked the drug industry at the bottom, together with tobacco and oil companies.[7] In another survey, 79% of US citizens said the drug industry was doing a good job in 1997, which fell to 21% in 2005,[8] an extraordinarily rapid decline in public trust.

On this background, it seems somewhat contradictory that patients have great confidence in the medicines their doctors prescribe for them. But I am sure the reason patients trust their medicine is that they extrapolate the trust they have in their doctors into the medicines they prescribe. The patients don't realise that, although their doctors may know a lot about diseases and human physiology and psychology, they know very, very little about drugs that hasn't been carefully concocted and dressed up by the drug industry. Furthermore, they don't know that their doctors may have self-serving motives for choosing certain drugs for them, or that many of the crimes committed by the drug industry wouldn't be possible if doctors didn't contribute to them.

It is difficult to change systems and it is not surprising that people who have to live with a faulty system try to make the most out of it, even though it often results in well-intentioned people doing bad things. However, many people at senior levels in the drug industry cannot be excused in this way, as they have deliberately told lies to doctors, patients, regulators and judges.

I dedicate this book to the many honest people working in the drug industry who are equally appalled as I am about the repetitive criminal actions of their superiors and their harmful consequences for the patients and our national economies. Some of these insiders have told me they would wish their top bosses were sent to jail, as the threat of this is the only thing that might deter them from continuing committing crimes.

References

2

Confessions from an insider

‘You should take two vitamin pills every day, a green and a red one,’ my mother said. I was only about eight years old but asked,
‘Why?’
‘Because they are good for you.’
‘How do you know?’
‘Because grandfather says so.’

End of argument. Grandfather had a lot of authority. He was a general practitioner and he was bright and therefore right. When I studied medicine, I once asked him whether he had spared some textbooks I could compare with my own to see how much progress there had been in 50 years. His reply stunned me. He had donated all his books to younger students shortly after he qualified. He felt he didn’t need them because he knew what they contained!

I had great respect for my grandfather and his superb memory, but I have scepticism in my genes. How could he be so sure the pills were good for me? In addition, the pills tasted and smelled bad despite being sugar-coated; opening the bottles felt like entering a pharmacy.

I dropped the pills and my mother undoubtedly found out why they lasted for so long but didn’t try to force me into eating them.

It all looked so simple back then, in the late 1950s. As vitamins are essential for our survival, it must be good to eat vitamin pills to ensure we get enough of what we need to thrive. But biology is rarely simple. Human beings have developed over millions of years into the current species, which is very well adapted to its environment. Thus, if we eat a varied diet, we can expect to get adequate amounts of vitamins and other micronutrients. If some of our ancestors had gotten too little of an essential vitamin, they would have had less chance of reproducing their genes than people who needed less of the vitamin or absorbed it better.

We also need essential minerals, e.g. zinc and copper, to make our enzymes work. But if we ingest too much, we get intoxicated. Thus, given what we know about the human body, we cannot assume that vitamin pills must be healthy. It is the earliest memory I have of a medical prophylactic intervention, and it took about 50 years before it became known whether vitamins are beneficial or harmful. A 2008 review of the placebo-controlled trials of antioxidants (beta-carotene, vitamin A and vitamin E) showed that

they increase overall mortality.[1]

Another childhood memory illustrates how harmful and deceitful the marketing of drugs is. Because of our generally bad weather in Denmark, my parents, who were teachers with long vacations, migrated south every summer. In the beginning only to Germany and Switzerland, but after some heavy bouts of bad weather with pouring rain even there, which isn't great fun when you live in a tent, northern Italy became the destination. My grandfather gave us Enterovioform (clioquinol) to be used if we got diarrhoea. This drug was launched in 1934 and had been very poorly studied.[2] What my grandfather didn't know and hadn't been told by the salesman from the Swiss company Ciba was that the drug only had a possible effect on diarrhoea caused by protozoans (amoebae and *Giardia*) and *Shigella* bacteria, and that even that effect could be disputed, as no randomised trials had compared the drug with placebo. Furthermore, it wasn't likely we would get exposed to such organisms in Italy. Traveller's diarrhoea is almost always caused by bacteria other than *Shigella* or by viruses.

Like so many other general practitioners, even nowadays, my grandfather appreciated visits by drug salespeople, but he had been the victim of shady marketing, which had caused the drug to be very commonly used.[3] Ciba started marketing clioquinol to fight amoebic dysentery,[2] but by the time the company entered the lucrative Japanese market in 1953, it was pushing clioquinol worldwide for all forms of dysentery. The drug is neurotoxic and caused a disaster in Japan where 10 000 people had developed subacute myelo-optic neuropathy (SMON) by 1970.[2] SMON victims suffered a tingling in the feet that eventually turned into total loss of sensation and then paralysis of the feet and legs. Others suffered from blindness and other serious eye disorders.

Ciba, which later became Ciba-Geigy and Novartis, knew about the harms but concealed them for many years.[4] When the catastrophe in Japan became known, the company released statements defending the drug, saying that clioquinol couldn't be the cause of SMON because it was essentially insoluble and couldn't be absorbed into the body.[2] However, attorneys preparing a lawsuit against the company found disturbing evidence that the drug could indeed be absorbed, which the company also knew. Already in 1944, clioquinol's inventors advised in light of animal studies that the administration of the drug be strictly controlled and that treatment should not exceed 2 weeks.

In 1965, a Swiss veterinarian published findings that dogs treated with clioquinol developed acute epileptic convulsions and died. Guess what Ciba's response was to this. Ciba inserted a warning in the drug's packaging in England that it should not be used in animals!

In 1966, two Swedish paediatricians studied a 3-year-old boy who had been treated with clioquinol and suffered severely impaired vision. They reported their findings in the medical literature and also informed Ciba that clioquinol was absorbed and could damage the optic nerve. These events, including the catastrophe in Japan, had no

visible effect on the company that continued its marketing efforts worldwide. In 1976, clioquinol was still widely available as an over-the-counter drug for the prophylaxis and treatment of travellers' diarrhoea despite the lack of evidence that it was effective.[3] Package inserts from 35 countries showed wide variation in dosage, duration of treatment, contraindications for use, side effects and warnings; a complete mess.

By 1981, Ciba-Geigy had paid out over $490 million to Japanese SMON victims, but the company didn't take the drug off the market until 1985, 15 years after the catastrophe struck. In contrast, the Japanese Ministry of Health banned the drug 1 month after it became known in 1970 that clioquinol was behind the SMON tragedy.

The story also illustrates an all-too-common gross failure of drug regulatory agencies, which should have taken action but did nothing.

A third of my childhood memories about the drugs my grandfather used is about corticosteroids. When the newly synthesised cortisone was first given to 14 patients with rheumatoid arthritis in 1948 at the Mayo Clinic in Rochester, Minnesota, the effect was miraculous.[5] The results were so striking that some people believed a cure for rheumatoid arthritis had been discovered. Corticosteroids are highly effective for many other diseases, including asthma and eczema, but the initial enthusiasm evaporated quickly when it was discovered that they have many serious adverse effects, too.

In the mid-1960s, my grandfather broke his hip and the fracture wouldn't heal. He spent 2 years in hospital, lying immobilised on his back with his leg in a huge plaster. It must have been some sort of a record for a hip fracture. I have difficulty remembering exactly what he told me, but the reason for his troubles was that he had abused corticosteroids for many years. It was something about the drug having so many good effects that he thought it worth taking even if you were healthy, to increase your strength and to be cheered up. As I shall explain in later chapters, it seems that the dream of a 'quick fix', whether by a legal or an illegal drug, that improves our natural physical performance, mood or intellectual capacity, never dies.

Back then, I found it very likely that my grandfather had been persuaded by a drug salesperson to take the corticosteroid, as salespeople rarely say much about the harms of their drugs while they routinely exaggerate their benefits and recommend the drugs also for non-approved indications. In terms of sales, nothing beats persuading those who are healthy to consume drugs they don't need.

All my childhood memories about drugs are negative. Drugs that were supposed to be beneficial harmed me. I suffered from motion sickness and my grandfather gave me a drug against this, undoubtedly an antihistamine, which made me so drowsy and uncomfortable that I decided after a few tries that it was worse than the disease and refused to have any more of it. Instead, I asked him to stop the car when I needed to vomit.

Young people are volatile and it can be hard to choose an occupation. When I was 15, I left school to become a radio mechanic because I had been a radio amateur for some

years and was fascinated by it. In the middle of the summer, I changed my mind and started in the gymnasium, now convinced I would become a graduate electrical engineer, but that didn't last long either. I switched my interest to biology, which was one of the most popular subjects in the late 1960s; the other was psychology. We knew there weren't many jobs in either discipline but didn't care about such a trivial issue. After all, we became students in 1968 when the traditions were turned upside down and the world laid at our feet. We bubbled with optimism and what was most important was to find a personal philosophy of life. After having read Sartre and Camus, I subscribed to the idea that one should not follow routines, traditions or other people's advice but should decide for oneself. I changed my mind again and now wanted to become a doctor.

As it happened, I ended up taking both educations. I spent many vacations with my grandparents, and one of these visits convinced me that I should not waste my life on being a doctor. My grandfather had invited me into his surgery during my final year at school. It was situated in a wealthy part of Copenhagen and I couldn't avoid noticing that many of the problems the patients presented with weren't really anything to bother about, but a reflection of boredom. Many women had very little to do, didn't have a job and had servants who helped them look after the house. So why not pay the gentle and handsome doctor a visit, like in the joke about the three women who met regularly in the waiting room. One day, one was missing, and one of the others asks the last one what happened. 'Oh,' she replied, 'she couldn't come as she is ill.'

The study of animals seemed more meaningful and I rushed through the education as if it were a sporting contest only to realise that I still didn't know what to do with my life. My chances of getting a job were small, as I had not done any research during my studies or had taken other initiatives that would make employers more interested in me than in 50 others.

What most people did in this situation was to become a school teacher. I tried, but it didn't work out. I had barely left school before I was back again, the only difference being that I was now on the other side of the teacher's desk. I wasn't much older than my pupils and felt I belonged more to this group than to my new tribe of teachers who, moreover, smoked to an unbelievable extent. Although I could learn to smoke a pipe, I wasn't mature for such a job and also had difficulty accepting that this was what I was going to do for the next 45 years. Like life being over before it had started.

Two things particularly annoyed me during the 6 months where I tried to learn how to teach, being supervised by another teacher. In biology, we didn't use textbooks much, although wonderful textbooks were available. We were now in the dark 1970s where our universities and academic life at large were heavily influenced by dogmas, particularly Marxism, and it was not healthy to raise too many questions that things could perhaps be done differently. My supervisor required of me that, instead of using textbooks, I should produce the educational material myself because it needed to be relevant for the time we were living in. Some have aptly called these years the history-free period. I found myself cutting newspaper articles about the oil industry and pollution and spent endless hours at the photocopying machine putting my 'breaking

news' compendia together. I don't wish to imply that such issues are not interesting or relevant, but my subject was biology, which goes back billions of years, so why this restless emphasis on something that happened yesterday?

The other problem was the prevailing fashion in pedagogy, which dictated that I needed to write down a detailed plan before each lecture outlining what learning goals I wanted to achieve, subgoals at that, how I would achieve them, etc., etc. After each lecture I was expected to analyse my performance and discuss with my supervisor whether I had achieved all these goals. Thinking through what you wish to achieve beforehand and evaluating it afterwards is very reasonable of course, but there was so much of it that it drained me, as I am not the bookkeeping type. I also lectured in chemistry, and particularly in that subject the rigid template felt like overkill. To teach people why and how chemical substances react is straightforward. Like in mathematics, there are some facts and principles people need to learn, and if they don't want to learn them, or cannot learn them, there isn't much the teacher can do. Imagine if a piano teacher was expected to construct similarly elaborate schemes before every music lesson she gave and evaluated herself afterwards. I am sure she would run away quickly.

The séances with my supervisors reminded me of the Danish lessons at the gymnasium where we were asked to interpret poems. I was quite bad at this type of guesswork and was irritated that the authors hadn't written more clearly what was on their mind if they wanted to communicate with us mortals. The lecturer was in a much better position, as he possessed a gold standard, which was a handbook written by a scholar who had interpreted the poems the teachers used. This is actually amusing. I have heard art critics interpret paintings, and when the artist was later asked whether they were right, he laughed and exclaimed that he didn't mean anything with his paintings, he just painted and had fun while doing it. Pablo Picasso painted in many different styles over the years and was once asked what he was searching for. Picasso replied: 'I don't search, I find.'

I did well according to my pupils but not according to my supervisors. I was told they could let me pass but with an evaluation that could make it difficult for me to get a job as a teacher. They preferred to fail me to give me a chance of thinking about whether I really wanted to be a teacher. This is the only time I have failed an exam, but I am immensely grateful that they made this wise decision. I had invested far too little effort in my new profession. My university years had been so easy that I hadn't dreamed about working in the evenings, in contrast to those teachers who were more successful than me. I had no idea that it was considered so difficult to teach. Later, I lectured at the university in the theory of science for more than 20 years.

After having applied for and not getting a few jobs as a chemist or biologist, my grandfather suggested I went into the drug industry. I sent three applications and was called for two interviews. My first experience was really weird. I could almost smell the vitamin pills of my childhood when I entered the office. The man who interviewed me had a dusty appearance and was partly bald-headed with long whiskers that would have made him a perfect character in a Western movie, selling snake oil or whiskey –

someone whose used car you wouldn't buy. He was also the type of salesman I associated with one who sold ladies' underwear or perfume. Even the name of the company was old-fashioned. It was pretty clear that we both felt uncomfortable in each other's presence.

The second company was modern and attractive. It was the Astra Group, with headquarters in Sweden. I got the job and spent 7 weeks in Södertälje and Lund on various courses, which mostly dealt with human physiology, diseases and drugs. There was also a course in 'Information technique', which I suggested to the course leader should more appropriately be called 'Sales technique'. He didn't comment on my suggestion, but the course was about manipulating doctors into promising to use the company's products rather than those of its competitors, and to use even more of the company's drugs, to new types of patients, and in increased doses. It was all about increasing the sales, which we learned through role plays where some of us played various types of doctors, ranging from the sour to the forthcoming ones, and others tried to penetrate the palisades and 'close the deal'.

When I learned about drug usage, my first thought was: 'Gosh, it's amazing that there are so many drugs around and that they are used so much, for all kinds of ailments. Can it really be true that they are so effective that it justifies such massive use?'

I toured my district as a drug salesman, officially called a drug representative, and visited general practitioners, specialists and hospital doctors. I didn't like it. I had a full academic education with high marks behind me but felt inferior when I talked to doctors who sometimes treated me badly, which I fully understand. It must have been a nuisance to spend time with salespeople and I often wondered why they didn't say no. There were so many companies that it was common for a general practitioner to have more than one visit a week.

The academic challenges were very small and I realised that my university education would wither pretty quickly if I didn't move on to another job. The job also threatened my self-esteem and identity as a person. To be an effective salesman, you need to behave like a chameleon, adapting your own personality to the person in front of you. The risk of playing so many roles and pretending to agree with doctors you disagree with is that you lose yourself. I had read some of Søren Kierkegaard's works and knew that losing yourself was the worst mistake you could make. If you deceive not only the doctors but also yourself, it becomes too painful to look in the mirror and accept what you see. It is easier to be living a lie and it moved me deeply when I saw Arthur Miller's 1949 play, *Death of a Salesman*, years later at a theatre in London. I knew exactly what this was about.

The doctors listened to my sales pitches without asking uncomfortable questions, but on a couple of occasions they told me I was wrong. Astra had developed a new type of penicillin, azidocillin, which it had given a catchy name, Globacillin, as if it were effective against everything. In one of our campaigns, we tried to sell the drug for acute sinusitis. We informed the doctors about a study that showed that the drug penetrated into the mucosa in the difficult-to-reach sinuses where the bacteria were located and indicated that this was an advantage over usual penicillin. An ear, nose and throat

surgeon told me that it wasn't possible to take biopsies and measure the concentration of an antibiotic in the mucosa, as one would inadvertently include capillaries in the sample where the concentration was higher. It was very humiliating for me to be told by a specialist that my company had cheated me. Academics are trained to think for themselves, but I lacked the skills to do so in a medical context.

Another argument for using the new, more expensive drug was that its effect on a particular bacterium, *Haemophilus influenzae*, was 5–10 times better than penicillin. This claim resulted from laboratory experiments in a Petri dish. The right questions to ask would have been:

1. Were these studies performed by the company and have the results been replicated by independent researchers?
2. What is the effect of treating acute sinusitis with penicillin or azidocillin, compared with placebo? And if there is an effect, is it then large enough to justify routine treatment of sinusitis with antibiotics, considering the adverse effects of the drugs?
3. Most important, has azidocillin been compared with penicillin in randomised trials of acute sinusitis, and was the effect any better?

Such questions would have made it clear that there was no rational basis for using azidocillin. We nevertheless succeeded to sell the drug with our doubtful arguments to some doctors for some time, but it is no longer on the market.

After only 8 months as a salesman, I left the roads and became a product manager with responsibility for written materials and for our 3-yearly sales campaigns, in collaboration with the sales manager. It doesn't make me proud to recollect what we were doing. We sold a drug against asthma, terbutaline (Bricanyl), and in one of the campaigns we tried to convince the doctors that the patients needed not only constant treatment with pills but also with a spray. Again, we didn't give the doctors the relevant information, which would have been the results of randomised trials of the combination treatment versus treatment with either spray or pills.

Asthma deaths were caused by asthma inhalers

Today, regular treatment with inhalers containing drugs like terbutaline is not recommended; in fact, such treatments have been proscribed in most guidelines because of safety concerns. Epidemiologist Neil Pearce from New Zealand has written a most disturbing account of the powers of the drug industry and its paid allies among doctors in relation to asthma.[6] When the inhalers came on the market in the 1960s, asthma death rates went up in the same way the sales did, and after the regulators had warned about overuse, they both went down again. Pearce wanted to study one of the drugs in detail, isoprenaline from Riker, and received data from the company that expected his research would show that the theory about the drugs causing the deaths was wrong. However, he confirmed the theory and when he sent his manuscript to the company

(which one should *never* do), they told him he would be sued. His university promised to make its lawyers available in case of litigation and he published the paper, but now became fiercely attacked by asthma specialists.

Doctors tend to become very angry if you tell them they have harmed their patients, even when they have done that in good faith. I have written a whole book about my experiences after I demonstrated in 1999 the harmful consequences of mammography screening, which converts many healthy women to cancer patients unnecessarily.[7]

This was in 1972. But, although Pearce's findings were supported at the time, asthma experts told him 16 years later when he entered asthma research again that the theory had been proven wrong. No one was able to tell him how or what the explanation then was for the increase and fall in asthma deaths in the 1960s. The misconception seemed to have been created and fuelled by the doubt industry, i.e. drug companies commissioning substandard research to their hired consultants among the asthma specialists. 'Doubt is our product' a tobacco executive once said,[8] and this smokescreen always seems to work. Create a lot of paid noise and confuse people into disbelieving the original, rigorous study and believing the noise instead.

In 1976, a new epidemic of asthma deaths began in New Zealand. When Pearce's colleagues suggested it might be caused by overtreatment, they were met by extremely hostile reactions from the official Asthma Task Force that believed the problem was undertreatment. This is a standard industry position, and indeed the major funder of asthma research in New Zealand was Boehringer Ingelheim, the maker of fenoterol (Berotec).

When Pearce *et al.* found out that the new epidemic mirrored the sales curve for fenoterol, all hell broke loose. They met resistance from all quarters and demands that others should carefully scrutinise their data, not only people with amicable relations to the company; the company itself also requested the data. A lawyer prudently advised them to ignore all legal threats and not show the paper to the company before it was accepted for publication.

Pressures mounted, also from the Medical Research Council, although it hadn't funded the study, and the university. They didn't understand, or chose to ignore, that they had no right whatsoever to interfere with the research. The only way out was therefore to go to the top, the Department of Health, where the researchers learned, however, that Boehringer Ingelheim had been there first.

All sorts of false rumours were spread, including false allegations that there was no protocol for the study, although this protocol had been seen by the Asthma Foundation and the Medical Research Council that refused to fund the study. Boehringer Ingelheim succeeded in postponing – and almost preventing – publication in the *Lancet*, which got cold feet after having accepted the paper because of the immense pressure. *Lancet* received several lengthy faxes every day from the company and had to ask them to stop.

Boehringer Ingelheim had invested a lot in the physicians and it paid off. Their sympathy was on the company's side, being concerned that its New Zealand branch might close down; they were not thinking of their patients. The Department of Health

also sided with the company and broke the confidentiality by giving the company a copy of the manuscript it had requested from the researchers.

It was as bad as it could be. The researchers' first study was unfunded and so was the next one, and Dunedin Hospital refused to allow them access to its records. The Department of Health would not give the researchers any assurance that it would not also show the manuscript from the second study to the company, and when it didn't get it in the first place from the researchers, it requested it from their university under the Freedom of Information Act. Boehringer gave the researchers' data to its paid friends so that they could come up with other results even before the original data appeared in print.

This was an outrageous transgression of the ethical ground rules for science, but despite its dirty methods, Boehringer lost the battle. The market share for fenoterol dropped from 30% to less than 3% in just 3 years and asthma deaths plummeted simultaneously, vindicating the research by Pearce *et al.*

Shady marketing and research

At one time, we visited chest physicians and showed them a film of small white particles that had been placed in the mucus in the windpipe. The movement of these particles towards the mouth was recorded with and without giving the patients terbutaline, and the story was that the cilia moved the particles faster when patients were treated. The idea was to convince the doctors that they should not only use the drug for asthma, but also for smoker's lungs (chronic bronchitis). These patients cough a lot, which is why a quicker transport of irritants out of the lungs was speculated to be beneficial. But yet again, a simple question would have revealed that the emperor had no clothes. There were no randomised trials that had shown that terbutaline was effective in patients with chronic bronchitis. Even today, terbutaline is only approved for asthma and other bronchospasm, not for chronic bronchitis.

It is illegal to market a drug for non-approved indications, so-called off-label use. As we shall see in the next chapter, illegal marketing is very common, and it is also routine that the companies circumvent the law. It is not illegal to discuss research results with doctors, and we could therefore show the film without breaking the law as long as we did not suggest to the doctors to use the drug for chronic bronchitis. If they had asked, we could say that we weren't allowed to recommend the drug for this indication but that the results were interesting, and that the doctors were free to use drugs for whatever purpose they found reasonable. Absurdly, such indirect recommendations are not illegal. In my opinion, they should be. There is no good reason to present preliminary research results to practising clinicians; it is only reasonable to discuss them with academic researchers with the purpose of embarking on a definitive clinical trial hoping the new indication will be approved by the drug regulators.

We also balanced on the edge of the law with another indication, but before I come to this, I need to explain what The Cochrane Collaboration is. It is a non-profit organisation that was started in 1993 by Iain Chalmers in Oxford, United Kingdom. It

built on a common frustration among researchers and others that most medical research is of poor quality and biased, and a realisation that we needed rigorous systematic reviews of the randomised trials that could tell us more clearly what the benefits and harms of our interventions are. Once established, The Cochrane Collaboration grew quickly and currently engages about 30 000 people. The reviews are published electronically in The Cochrane Library, and there are more than 5000 such reviews, which are regularly updated. Half of the world's population have free access to the full reviews through national subscriptions usually financed by governments; the other half have access to the abstracts.

Coughing is very common and there is a huge market for over-the-counter cough medicines. A Cochrane systematic review of the randomised trials shows that none of them are effective,[9] which means that the huge market is also a huge waste of money. Drugs like terbutaline don't appear to work either,[10] but someone in Astra coined the idea that we should suggest to doctors that terbutaline had an effect on cough, with reference to the study illustrated in the mucosa film.

I didn't believe this. Why should a drug used for dilating the airways in patients with asthma work for cough that was not caused by bronchospasm? Whatever the legal technicalities, I regard this as off-label promotion, and there were no witnesses that could testify to which degree the doctors were directly encouraged to try the drug for cough, as most encounters were on a one-to-one basis where only the doctor and the salesperson were present.

We also did something good. We produced an illustrated guidance for patients with asthma in eight steps about how to use the spray, which also showed how one could estimate the remaining number of doses by immersing the container in water and see whether it floated or went to the bottom.

During my 2 years with Astra, from 1975 to 1977, we launched a new product, zinc lozenges, which was approved for treatment of venous and ischaemic leg ulcers and a very rare zinc deficiency disease, acrodermatitis enteropathica, which affected the uptake of zinc. I still have the 20-page brochure I wrote for the launch, which was based on a similar brochure in Swedish.

It is revealing to compare the brochure with the Cochrane review on zinc for leg ulcers.[11] The first study in the brochure is also the biggest and it was published in a prestigious journal, the *Lancet*, which is very attractive for marketing purposes. The results were impressive.[12] According to the brochure, the ulcers in the 52 patients treated with zinc were healed after 32 days whereas it took 77 days for the 52 placebo-treated patients. However, the trial was unreliable. The brochure stated that because the results for the first 16 patients clearly showed which group was treated with zinc, it was not possible to continue the study in a double-blind fashion. The study was excluded from the Cochrane review because it wasn't randomised, which we usually expect blinded studies to be.

The brochure reported positive effects from the randomised trials, but the Cochrane authors interpreted the same trials differently. They included six small trials of mediocre

quality and found no evidence of a beneficial effect of zinc. Like Globacillin, zinc disappeared from the market.

In 1977, I was offered a job at Astra-Syntex, a new joint-venture company between Astra and the California-based Syntex. My task was to establish a medical department and to be responsible for clinical trials and registration applications for new drugs and indications. I was very happy to leave marketing but also had concerns about the research the industry did and wanted to leave. I chose the most arduous way out and started to study medicine in 1978 while I continued to work for the company. I qualified 6 years later and left the company to work at different hospitals in Copenhagen.

Astra-Syntex's survival hinged on just one drug, naproxen (Naprosyn), a nonsteroidal anti-inflammatory drug (NSAID) used for arthritis. I performed several trials with the drug and discovered along the way that I wasn't immune to company influence. There were many NSAIDs on the market, but somehow you get so used to the idea that *your* drug *might* be better than the others that you end thinking it *is* better, just as if it had been your child. One of the reasons why marketing of medicines is so effective is that the salespeople believe they are selling a very good drug.

A clear indication of my naïvety was that I asked the European headquarters in London why we didn't perform a trial comparing naproxen with a simple analgesic such as paracetamol, for example in sports injuries. The medical director kindly explained that they were not interested in such a trial but never said why, although I asked on more than one occasion. The reason was of course that such a trial might show that a much cheaper analgesic was equally effective, and on top of that we already knew that paracetamol was much safer than naproxen. In order to lure people into preferring naproxen for paracetamol, it was therefore necessary to give the doctors the impression – without having any data to support it – that naproxen was more effective.

The trick was done using theoretical arguments. This is a very powerful marketing tool, although the arguments rarely hold water. In textbooks of pharmacology, naproxen is described as having anti-inflammatory properties and the hyped argument goes somewhat like this: When you have a sports injury, there is tissue injury and inflammation with oedema, and it is important to dampen the inflammation to speed up the recovery.

It is very easy to lure doctors into doing wrong things by making them listen to the songs of the sirens while paying many of them, both for singing and for listening (*see* Chapter 8). As I shall explain in detail later, NSAIDs are dangerous drugs and many thousands of people are killed every year because of bleeding stomach ulcers and heart attacks, to mention just the two worst harms. But marketing is all that is needed. A couple of years ago, Danish TV focused on the liberal use of NSAIDs in professional football clubs for all sorts of pain. The prescription status of the drugs wasn't a hindrance, as the sports doctors provided large supplies of the drugs, letting the footballers take as many as they wanted without even asking. There was a scandal, but as is usual with scandals, it quickly died out and I suppose it is now business as usual.

Around 1980, I was approached by a rheumatologist who looked after the Danish

national football team. He wanted to find out whether naproxen was better than aspirin for sports injuries. Aspirin is also an NSAID – the oldest one in existence and very cheap – but it is often used in low doses where it is assumed to have no anti-inflammatory effects, only an analgesic effect. We did the trial, using low-dose aspirin despite the concerns of my superiors in London, and just as they had predicted, there were no significant differences between the two drugs. However, the results were analysed by our statistics department in Sweden, which went on a 'fishing expedition' that eventually found something that could lessen the company's pains that naproxen wasn't any better than aspirin. The abstract of the published paper says:[13]

'Fresh injuries were over-represented in the acetylsalicylic acid group ($p < 0.01$), and when all patients were analyzed together [i.e. from both treatment arms], a significantly better treatment result was obtained the shorter the interval between injury and start of treatment. This might have influenced the results from this study.'

Oh boy. I have contributed to this as an author. In principle, there is nothing wrong with reservations in an abstract, but imagine if naproxen had been significantly better than aspirin and there had been more fresh injuries in the naproxen group. Would this reservation about the good news for the company then have made it into the abstract? Hardly, and I doubt there would have been anything about this in the main text of the article either.

We first submitted our paper to *British Journal of Sports Medicine*. The editor was keenly aware of the commercial priorities in the industry; he said he was surprised that we posted our study from Syntex, as our work contradicted the claims the company had made about naproxen being more effective than paracetamol and aspirin. We were startled that an editor so frankly sided with a company's commercial interests and his next remark made us laugh. He noted that 18 patients received aspirin during the first 3 days of injury compared to only 2 on naproxen. He then suggested that a more fair comparison could be made if we were to treat another group of patients, at least 16 in number, with naproxen during the first 3 days following the injury. If we were willing to do this, he would reconsider our paper seriously. My goodness! How did he imagine we could include another 16 patients on only one of the drugs in a randomised double-blind trial? It cannot be done. We effectively buried the trial – although it wasn't our intention – by publishing it in a fairly unknown journal that stopped coming out 5 years later.[13]

I always wondered how it was possible to say that NSAIDs have anti-inflammatory effects, or whether it was only a marketing ploy. If a drug has an analgesic effect, it will lead to faster mobilisation, which would be expected to decrease the oedema. How could one then postulate that there was also a separate anti-inflammatory effect? NSAIDs had some effect in rats that had been treated in such a way that their paws were swollen and tender, but what did that prove? I often raised this issue with rheumatologists, but I never received a satisfactory answer.

However, one day I was contacted by a group of orthopaedic surgeons who wanted to study the effect of naproxen in ankle distorsions. I grabbed the opportunity to study also

the effect on the oedema, which we measured by immersing the foot in water and comparing its volume with that of the other foot. It was a highly interesting study. We randomised 173 patients twice: to crutches or no crutches (mobilisation), and to naproxen or placebo. This so-called factorial design is much underused despite its elegance, which is that it can provide answers to two questions without needing more patients than if only one question was asked. The results surprised us.[14] The patients recovered faster when they were mobilised, which also decreased the oedema, whereas naproxen had no effect on the oedema. Our marketing-oriented bosses in Sweden interfered again with our research, and there were no numerical data on either of these outcomes in our published paper. However, I have kept the more comprehensive internal study report and the effect of mobilisation was dramatic. At the first follow-up visit after 2–4 days, 30 of 68 patients had recovered, compared to only 10 of 63 patients in the group using crutches, and the difference in volume between the two feet was only 28 mL when the patients were mobilised, compared to 71 mL when crutches were used.

It was a beautiful study that had implications for practice. Years later, after a serious ankle distorsion, I stumbled along in great pain during a trip to London to attend the *British Medical Journal*'s (*BMJ*) advisory board meeting and I moved with immense difficulty. One of the other members of the board asked me why I didn't use crutches and I replied that I had shown in a trial that patients recover faster if they don't. Our trial inspired him to do a systematic review of bed rest for all diseases and he identified 39 trials (5777 patients) with 15 different conditions.[15] He found that it is harmful to immobilise people in a bed; not a single outcome improved significantly whereas several outcomes worsened.

We submitted our trial to *Acta Orthopaedica*, a humble Nordic journal, but its editors didn't understand how important it was and rejected it. We had also tried the *BMJ* and my co-authors now just wanted to get the trial out. I couldn't convince them that it was too important to publish in Danish, but that's what happened after we had translated the paper. Years later, I was approached by a researcher working on a systematic review of treatment of soft tissue injuries, and he told me that our study was not only the largest but also the best, so he asked me to translate our Danish paper into English!

In 1990, I defended my doctoral thesis, *Bias in Double-Blind Trials*,[16] which consisted of six papers. I had analysed 244 reports of trials in depth that had compared one NSAID with another. It was the first time a whole therapeutic area had been so thoroughly investigated and I uncovered an overwhelming amount of bias favouring the sponsoring company's drug over the control drug. The trial reports were generally so unreliable that they should be seen not as scientific publications but as advertisements for the drugs.

I had also assembled trials that compared an NSAID with placebo, which I used to study whether there is any anti-inflammatory effect with NSAIDs. In some trials, the researchers had used jeweller rings to measure if the drugs had an effect on swollen finger joints in patients with rheumatoid arthritis. They hadn't.[17] I therefore believe the

idea of an anti-inflammatory effect of NSAIDs is a hoax, like so many other myths about drugs that the drug companies have invented and marketed.

It is highly unfortunate that the drug companies define for us how we should think about drugs, as their manipulations are so massive. For example, it is common to talk about second-generation or even third-generation drugs, e.g. second-generation antipsychotics. This gives you the impression that they are better than old drugs, which is rarely what independent, publicly funded researchers find when they compare them in large randomised trials.

Like Astra, Astra-Syntex also engaged in unethical marketing. The standard dose of naproxen was 500 mg daily, but the salespeople were asked to persuade the doctors to use 1000 mg, equipped with dose-response studies that had been written up by the company. I reviewed such studies as part of my thesis,[18] and they were terribly flawed. In the naproxen studies, the patients received placebo and two or three different doses of naproxen in a crossover design where all patients tried each treatment in random order. The doses varied between 250 mg and 1500 mg daily. Many of the outcomes were not reported and with a British understatement I called the statistical methods 'rather unusual'.[18]

None of the papers presented any graphs that could tell the readers what was gained by using a higher dose. Instead, a significant linear relationship between dose and response was claimed, which gives the readers the clear message that by doubling the dose, they double the effect. This comes close to fraud. I presented nine dose-response curves in my review of NSAIDs and an example is shown in Figure 2.1. There is nothing to be gained by using higher doses. The difference between 250 mg and 1500 mg naproxen is six times in terms of money but only 1.0 cm on a 10 cm pain scale, and the least difference in pain patients can perceive is about 1.3 cm.[19] The difference of 1.0 cm therefore makes no difference for the patients. The smallest clinically relevant effect, i.e. an effect that might make it worthwhile to take a drug or increase the dose, is larger than what the patients can barely perceive. In contrast, the harms actually *do* increase in a linear fashion so that twice the dose means twice the amount of harms.[20] As some harms are serious, e.g. bleeding ulcers and death, these drugs should be used at the lowest possible dose.

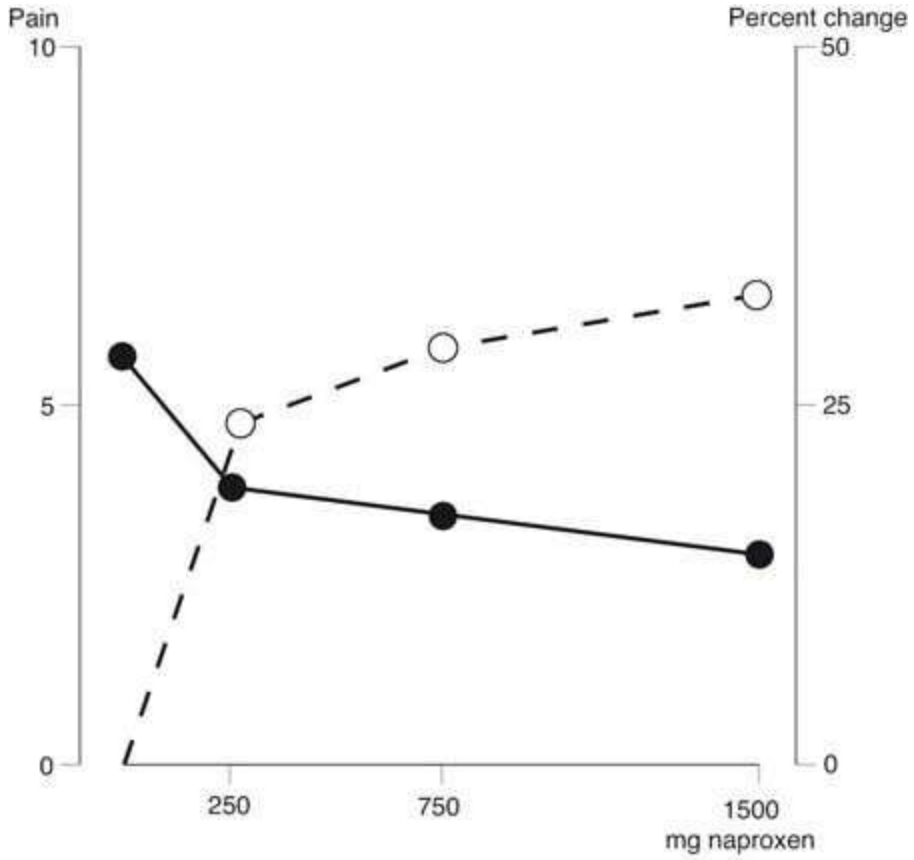


Figure 2.1 Dose-response curve for naproxen. The effect on pain is shown with black dots (10 is the highest pain possible) and the mean percentage improvement for all the reported outcomes is shown with open circles

Such manipulations with the science have the intended effect, to increase sales. Few doctors are able to read research reports critically and they might have forgotten what they learned in clinical pharmacology. The dose-response curves for drugs virtually always have the shape of a hyperbola and standard doses are quite high, corresponding to the uppermost part of the curve where the effect levels off and approaches a ceiling (*see* Figure 2.1).

The marketing of naproxen is an unequivocal example that drug companies put profits before patients and don't care that their actions increase deaths. The worst company was not Astra-Syntex, however, it was Pfizer. There was general agreement in other companies that Pfizer's marketing was particularly aggressive and ruthless.[21] Pfizer's NSAID, piroxicam (Feldene), was also touted at a very high dose.[18] Piroxicam has a long half-life and we therefore felt it was inappropriate to use it in the elderly, as their impaired elimination mechanisms lead to accumulation of the drug and increased toxicity.

Pfizer's marketing was very successful and completely untruthful, stating that piroxicam was more effective than aspirin and had a lower rate of gastrointestinal side effects than many other NSAIDs.[22] The truth was the opposite: piroxicam had more fatal reactions and more fatal gastrointestinal side effects than other drugs. Nonetheless, the US and UK drug regulators protected Pfizer all along instead of protecting the patients, and Pfizer tried to dissuade the editors of the *BMJ* to publish a paper that concluded

about the high incidence of severe ulcer disease with piroxicam.[23] Pfizer even denied indisputable facts, e.g. that greater concentrations of an NSAID in the blood increase the risk of harms, and the company tried to get away with a ludicrous statement that the gastrointestinal toxicity to a large part was due to a local effect on the stomach rather than a systemic effect. Even if it had been correct, the harms inflicted on the patients would be the same. It is telling in relation to whether good or bad manners pay off that Pfizer became the largest drug company in the world.

Another company, Eli Lilly, also continued its aggressive marketing of its NSAID, benoxaprofen (Opren or Oraflex), undisturbed by the terrible harms they knew their drug caused.[22] The company touted that, based on laboratory experiments, the drug was different from other NSAIDs in having an effect on the disease process, but this wasn't true. Lilly presented a series of 39 patients that experienced a worsening of their joint damage, but the company concluded exactly the opposite.

Lilly ignored or trivialised the harms and failed to inform the authorities of liver failure and deaths, which a subsequent court case described as 'standard practice in the industry'.[24,25] Lilly published a paper in the *BMJ* that claimed that no cases of jaundice or deaths had been reported, but this wasn't true.[22] Furthermore, benoxaprofen causes other horrible harms, e.g. photosensitivity in 10% of patients and loosening of the nails from the nailbed in 10%, but it was approved despite this and despite insufficient animal toxicology studies, in violation of the Food and Drug Administration's (FDA's) own rules. When independent researchers found that benoxaprofen accumulated in the elderly, Lilly tried to prevent the study from being published and, as always, the UK drug regulator's action was grossly inadequate and allowed Lilly to trivialise the problem. These omissions proved fatal for some elderly patients, and the drug was withdrawn after only 2 years on the market.

I doubt any drug regulator can convince the patients that it was a good idea to approve a drug that harms at least one in five patients pretty badly when there were many less harmful NSAIDs on the market.

The FDA violated its own rules for several other NSAIDs, which, for example, had shown troubling carcinogenicity in animals and should therefore not have been approved, or drugs for which the animal studies were either insufficient or fraudulent, as many of the rats had never existed. The FDA even downplayed highly statistically significant findings in two rodent species and called them marginal or benign although they were malignant.[22]

The NSAID area is a horror story filled with extravagant claims, bending of the rules, regulatory inaction, and complacency with what the industry wants even though statements from industry scientists were often logically inconsistent or plainly wrong.[22] Several drugs that were so kindly treated by the FDA were later withdrawn from the market because of their toxicity despite claims to the contrary, e.g. 'Excellent gastrointestinal tolerance' (benoxaprofen), 'superior tolerance' (indoprofen), 'proven gastrointestinal safety' (rofecoxib), 'hurts the pain not the patient' (ketorolac) and 'least

possible side effect profile' (tolmetin).[24] Sheer nonsense, as a least possible side-effect profile can only occur if you don't take a drug at all. Other withdrawn drugs are, for example, zomepirac, suprofen and valdecoxib.[22,26]

The NSAID story illustrates that drug regulators are consistently willing to award the benefit of scientific doubt to manufacturers rather than patients and also that the regulators became even more permissive during the 1980s.[22] As I shall show in later chapters, and illustrate with newer NSAIDs and other drugs, this decline in drug safety has continued.

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3

Organised crime, the business model of big pharma

Drug companies never talk about the benefits and harms of their drugs but about their efficacy and safety. Words create what they describe and the preferred semantics is seductive. It makes you think it can only be good for you to take drugs, as they are both efficacious and safe. Another reason why patients and doctors generally trust their drugs as being both efficacious and safe is that they think they have been carefully tested by the drug industry and carefully scrutinised by the drug regulatory agencies using high standards before they are allowed onto the market.

It's the other way round. In contrast to food and water, which are not only pretty harmless but something we need to survive, drugs are generally neither efficacious nor safe. Paracelsus stated 500 years ago that all drugs are poisons and that the right dose differentiates a poison from a remedy. Drugs always cause harm. If they didn't, they would be inert and therefore unable to give any benefit. For all drugs, it is therefore essential to find a dose that causes more good than harm in most patients. Even when we succeed with this, most patients will still not achieve any benefit from the drugs they take (*see* Chapter 4).

Although it is rather obvious that drugs can kill you, this is often forgotten, both by patients and doctors. People trust their medicines to such a degree that the Canadian physician Sir William Osler (1849–1919) wrote that 'the desire to take medicine is perhaps the greatest feature which distinguishes man from animals'.[1] A particularly amusing example is botulinum toxin, which is a neurotoxin produced by the bacterium *Clostridium botulinum*. It is one of the strongest poisons in nature, and a dose of only 50 ng killed half of the monkeys in a toxicity study (which means that 1 g can kill 10 million monkeys). I wonder who needed this information so badly that it was worth killing our animal relatives to get it. And yet, what is this amazing killer drug used for? For treating wrinkles between the eyebrows! This comes with age, but you shouldn't be too old and have too much tremor when you inject the toxin, as it can be absorbed from the mucous membranes in the eye and kill you. The package insert warns that deaths have occurred. Is it really worth running a risk of dying, however small it might be, just because you have wrinkles? Other questions that pop up are: Can the drug be used for suicide or murder? Why was it ever approved?

The fact that drugs are dangerous and should be used with caution means that the ethical standards for those who do research on drugs and market them should be very high. I have talked to many people in the drug industry to find out what the companies think of themselves, and the replies have ranged from very positive ones from people who were proud of the clinical trials they carried out to very negative ones. What is perhaps more interesting is to see which impression the drug companies want to give of themselves to the public and to compare this with what they actually do. The

Pharmaceutical Research and Manufacturers of America (PhRMA) claims its members are 'committed to following the highest ethical standards as well as all legal requirements'.[2] Its *Code on Interactions with Healthcare Professionals* states that:[3]

> Ethical relationships with healthcare professionals are critical to our mission of helping patients … An important part of achieving this mission is ensuring that healthcare professionals have the latest, most accurate information available regarding prescription medicines.

Here is another quotation. Under the heading, FOCUS ENGAGEMENT HONESTY, came this text: 'Our goal is to be the world's most successful, respected and socially responsible consumer ware producer.'[4] As you'll see shortly, the drug industry's actions have very little to do with honesty, respect and social responsibility. How could they then write this about themselves? Well, they didn't. They could have, but the quotation comes from a newspaper advertisement for Philip Morris that shows a portrait of a smiling young woman who won't continue to look so good if she smokes.

I tell you this to illustrate that not even the most deadly industry on the planet can resist the temptation of spreading bullshit while they increase the total consumption of tobacco because their marketing is directly targeted towards teenagers in the developing countries who have not yet started smoking. This marketing more than compensates for the decline in smoking in developed countries. How can it be socially responsible to deliberately kill millions of people every year who didn't need the product in the first place? People who have tried to smoke a cigarette know what I'm talking about. Aged 15, I only succeeded in smoking half a cigarette before I became so intoxicated that I vomited and left school to go directly to bed, as white as my sheets. My mother wondered what terrible disease had hit me so hard and told me later that she'd found half a cigarette in my shirt pocket.

The disconnect between the drug industry's proclamations of 'highest ethical standards', 'following … all legal requirements' and 'most accurate information available regarding prescription medicines' and the reality of big pharma's conduct is also vast. The top executives' views of themselves – or rather the impression they try to convey about their activities – are not even shared by their own employees. An internal 2001 survey of Pfizer employees, which is not available to the public, showed that about 30% didn't agree with the statement, 'Senior management demonstrates honest, ethical behavior.'[5]

In 2012, Pfizer agreed to pay $60 million to settle a US federal investigation into bribery overseas. Pfizer wasn't only accused of bribing doctors, but also hospital administrators and drug regulators in several countries in Europe and Asia.[6] The investigators said Pfizer units sought to hide the bribery by listing the payments in accounting records as legitimate expenses, such as training, freight and entertainment. According to court papers, the company wired monthly payments for what it described as 'consultancy services' to a doctor in Croatia who helped decide what drugs the government would register for sale and reimbursement. Pfizer didn't admit or deny the allegations, which is routine practice when drug companies settle accusations of fraud.

Hoffman-La Roche, the biggest drug pusher

The 10 largest drug companies[7] are all signatories to the US PhRMA code, apart from Hoffman-La Roche, Switzerland,[3] which was the largest corporate fraudster worldwide in the 1990s according to a 1999 listing of all industries, including banks and oil.[8] High-level Roche executives led a cartel that, according to the US Justice Department's antitrust division, was the most pervasive and harmful criminal antitrust conspiracy ever uncovered.[9] Top executives at some of the world's biggest drug companies, largely from Europe and Asia, met secretly in hotel suites and at conferences. Working together in a coalition they brazenly called 'Vitamins Inc.', they carved up world markets and carefully orchestrated price increases, in the process defrauding some of the world's biggest food companies. Roche alone had revenues of $3.3 billion in the United States while the conspiracy was running, and during that time, the conspirators gradually and artfully raised the prices of raw vitamins, so as not to attract notice; they also rigged the bidding process.[9]

The Justice Department charged Kuno Sommer, former Director of Worldwide Marketing, Hoffmann-La Roche Vitamins and Fine Chemicals Division, with participating in the vitamin cartel and for lying to Department investigators in 1997 in an attempt to cover up the conspiracy.[10] Sommer pleaded guilty and got a 4-month prison term. After the conspiracy collapsed, those involved agreed to pay nearly $1 billion to settle federal antitrust charges, and virtually every big vitamin maker in the world was on the brink of agreeing to pay an additional $1 billion. Roche agreed to pay $500 million, equivalent to about 1 year's revenue from its vitamin business in the United States, and two executives were sentenced to prison terms of a few months. In Europe, the European Commission fined some of the world's biggest drug companies, including Roche, a record £523 million in 2001.[11] It is surprising that the cartel could exist for so long, as a Roche insider blew the whistle already in 1973, which the European Commission acted on (*see* Chapter 19).

Between the two world wars, Roche supplied morphine to the underworld. Other drug companies in the United Kingdom, Germany, Japan, Switzerland and the United States also participated in the trade with opium, morphine and heroin.[12,13,14] The CEO of Roche in the United States, Elmer Bobst, had great difficulty persuading his superiors in Basel that they should stop their unethical business practice.[13] Roche continued to ship narcotics to the United States behind Bobst's back, but he came across a cryptic telegram while visiting the headquarters, which left no doubt that it came from US criminals. It spoke about a shipment of sodium bicarbonate, which is used for baking cakes!

Roche agreed to stop the trade when Bobst reported that the US government had threatened to exclude Roche from doing business in the United States if the company didn't stop. However, Roche took up the habit again, and again without telling Bobst. In his book,[13] Bobst mentions that the man who was responsible for this wasn't at heart an immoral man, but utterly amoral in business. Bobst couldn't understand how it was

possible to have two ethical standards, one for private life and one for business. He also describes how Roche avoided Swiss taxes by setting up a company in the tax refuge, Lichtenstein.

Pushing drugs that people don't need is a highly lucrative business, particularly when the drugs affect brain functions. Roche pushed Valium (diazepam) to become the top-selling drug in the world, although many indications for its use were highly doubtful and the wholesale price was 25 times the price of gold.[12] In the early 1970s, Roche was fined by antitrust officials in Europe for engaging in anticompetitive behaviour in the sale of Valium and another best-selling tranquilliser, Librium (chlordiazepoxide).[9]

It took 27 years after the first report about dependence had been published before the drug regulators fully acknowledged that tranquillisers are strongly addictive,[15] just like heroin and other narcotics. I believe that the fact that some drugs affecting the brain are legal and others are illegal is irrelevant from an ethical perspective, if we try to understand what the drug industry is doing to the population. Another reason why the distinction is irrelevant is that the drug industry doesn't really bother whether their actions are legal or not, as illustrated by the pervasive use of illegal, off-label marketing. Furthermore, what is legal isn't static, but can change with country, fashion and prevailing beliefs. For example, narcotics haven't always been illegal, and although it's illegal to sell hash in most countries, it's legal to smoke hash in the Netherlands. It is sold in so-called coffee shops, and this funny name once fooled me. Breakfasts at hotels are exceedingly expensive compared to how little most of us eat in the morning, so I went into a coffee shop one morning in Amsterdam. The owner was very amused when I asked for coffee, which he didn't have. Shortly afterwards, three lovely girls from the Middle East entered the shop and told me that Black Lebanon was the best and that they were going to smoke just that.

As another example of legal inconsistency for substances affecting the brain, it is illegal to produce your own brandy but legal to buy it in a shop.

Whatever the legal status of brain active substances, drugs are being pushed in both cases. After having examined the drug industry in great detail, John Braithwaite published his observations in the book *Corporate Crime in the Pharmaceutical Industry*. In it he said:[12]

> *People who foster dependence on illicit drugs such as heroin are regarded as among the most unscrupulous pariahs of modern civilisation. In contrast, pushers of licit drugs tend to be viewed as altruistically motivated purveyors of a social good.*

Hall of Shame for big pharma

The *BMJ* comes out weekly and most issues describe one or more scandals related to the drug industry in its News section or elsewhere. The *New York Times* also publishes many stories about drug industry misconduct, and most of the documentation I have collected over the years comes from these two highly respected sources. In recent years, numerous articles and books have described serious cases of research misconduct and marketing

fraud committed by big pharma,[2,5,6,16,17,18,19,20,21,22] but although the facts are overwhelming, the standard response from the drug industry when a company has been caught is that there are a few bad apples in any enterprise.

The interesting question is whether we are seeing a lone bad apple now and then, which might be excusable, or whether pretty much the whole basket is rotten, i.e. whether most companies routinely break the law.

To find out, I did 10 Google searches in 2012 combining the names of the 10 largest drug companies[7] with 'fraud'. There were between 0.5 and 27 million hits for each company. I selected the most prominent case described in the 10 hits on the first Google page and supplied the information with additional sources.

The 10 cases were all recent (2007–2012) and were all related to the United States.[23,24] The most common criminal offences were illegal marketing recommending drugs for off-label uses, misrepresentation of research results, hiding data on harms, and Medicaid and Medicare fraud. I describe the cases in descending order according to the size of the company.

1 Pfizer agreed to pay $2.3 billion in 2009

This was the largest healthcare fraud settlement in the history of the US Department of Justice at the time.[25] A subsidiary of the firm pleaded guilty to misbranding drugs 'with the intent to defraud or mislead', and the firm was found to have illegally promoted four drugs: Bextra (valdecoxib, an anti-arthritis drug, withdrawn from the market in 2005), Geodon (ziprasidone, an antipsychotic drug), Zyvox (linezolid, an antibiotic) and Lyrica (pregabalin, an epilepsy drug).

An amount of $1 billion was levied to resolve the allegations that Pfizer paid bribes and offered lavish hospitality to healthcare providers to encourage them to prescribe the four drugs, and six whistle-blowers would receive $102 million. Pfizer entered a Corporate Integrity Agreement with the US Department of Health and Human Services, which means that good behaviour is required for the next 5 years. Pfizer had previously entered into three such agreements,[26] and when Pfizer promised the federal prosecutors not to market drugs illegally again in 2004, Pfizer was busily doing exactly this while they signed the agreement.[27]

Pfizer's antibiotic, Zyvox, cost eight times as much as vancomycin, which even Pfizer admitted in its own fact book is a better drug, but Pfizer lied to the doctors, telling them Zyvox was best. Even after the FDA had told Pfizer to stop its unsubstantiated claims because they posed serious safety concerns, as vancomycin is used for life-threatening conditions, Pfizer continued to tell hospitals and doctors that Zyvox would save more lives than vancomycin.[27]

2 Novartis agreed to pay $423 million in 2010

The payment concerned criminal and civil liability arising from the illegal marketing of Trileptal (oxcarbazepine, an epilepsy drug approved for the treatment of partial

seizures, but not for any psychiatric, pain or other uses).[28] The company unlawfully marketed Trileptal and five other drugs, causing false claims to be submitted to government healthcare programmes. The agreement resolved allegations that the company paid kickbacks to healthcare professionals to induce them to prescribe Trileptal and five other drugs, Diovan (valsartan, for hypertension), Zelnorm (tegaserod, a drug for irritable bowel syndrome and constipation, which was removed from the market by the FDA in 2007 because of cardiovascular toxicity), Sandostatin (octreotide, a drug that mimics a natural hormone), Exforge (amlodipine + valsartan, for hypertension) and Tekturna (aliskiren, for hypertension).

The whistle-blowers, all former employees of Novartis, would receive payments of more than $25 million, and Novartis signed a Corporate Integrity Agreement.

3 Sanofi-Aventis to pay more than $95 million to settle fraud charge in 2009

According to the settlement, Aventis had overcharged US and local health agencies for medications destined for indigent patients.[29,30] The Justice Department said they would ensure that programmes for the most vulnerable parts of the population did not pay any more for drugs than they should under the law. Aventis acknowledged that it misreported drug prices for patients in the Medicaid Drug Rebate programme for poor patients. The firm deliberately misquoted the prices, underpaying rebates to Medicaid and overcharging some public health agencies for the medications. The fraud occurred between 1995 and 2000 and concerned steroid-based nasal sprays containing triamcinolone.

4 GlaxoSmithKline to pay $3 billion in 2011

This is the largest healthcare fraud settlement in US history.[31,32,33] GlaxoSmithKline pleaded guilty to having marketed a number of drugs illegally for off-label use, including Wellbutrin (bupropion, an antidepressant), Paxil (paroxetine, an antidepressant), Advair (fluticasone + salmeterol, an asthma drug), Avandia (rosiglitazone, a diabetes drug) and Lamictal (lamotrigine, an epilepsy drug).

The Justice Department charged a former vice president and top lawyer for Glaxo a year earlier with making false statements and obstructing a federal investigation into illegal marketing of Wellbutrin for weight loss.[34] The indictment accused the vice president of lying to the FDA, denying that doctors speaking at company events had promoted Wellbutrin for uses not approved by the agency, and of withholding incriminating documents.

The company paid kickbacks to doctors, failed to include certain safety data about rosiglitazone in reports to the FDA, and its sponsored programmes suggested cardiovascular *benefits* from Avandia despite warnings on the FDA-approved label regarding cardiovascular *risks*. Avandia was withdrawn in Europe in 2010 because it increases cardiovascular deaths.

Allegations of Medicaid fraud by misreported prices were also covered by the agreement. The whistle-blowers were four employees of GlaxoSmithKline, including a

former senior marketing development manager and a regional vice president. The company entered into a Corporate Integrity Agreement.

5 AstraZeneca to pay $520 million in 2010 to settle fraud case

The charges were that AstraZeneca illegally marketed one of its best-selling drugs, the antipsychotic drug Seroquel (quetiapine), to children, the elderly, veterans and inmates for uses not approved by the FDA, including aggression, Alzheimer's, anger management, anxiety, attention-deficit hyperactivity disorder (ADHD), dementia, depression, mood disorder, post-traumatic stress disorder and sleeplessness.[35] Further, the company targeted its illegal marketing towards doctors who do not typically treat psychotic patients and paid kickbacks to some of them. Other doctors were sent to lavish resorts to encourage them to market and prescribe the drug for unapproved uses. The whistle-blower would get more than $45 million.

The fine was small, as the drug sold for $4.9 billion in 2009.[36] AstraZeneca denied wrongdoing although its misdeeds were obvious. The US Attorney General said about them:[35]

> 'These were not victimless crimes – illegal acts by pharmaceutical companies and false claims against Medicare and Medicaid can put the public health at risk, corrupt medical decisions by healthcare providers, and take billions of dollars directly out of taxpayers' pockets.'

6 Roche convinces governments to stockpile Tamiflu

Roche has committed what to me looks like the biggest theft in history,[37,38,39,40,41,42,43,44,45,46,47] but no one has yet dragged the company to court. In preparation for the mild 2009 influenza epidemic, the European and US governments spent billions of Euros and dollars on the purchase of Tamiflu (oseltamivir).

Roche has omitted publishing most of their clinical trial data and has refused to share them with independent Cochrane researchers. Based on unpublished trials, Roche has claimed that Tamiflu reduces hospital admissions by 61%, secondary complications by 67%, and lower respiratory tract infections requiring antibiotics by 55%.[38] Curiously, the company convinced the European Medicines Agency (EMA) to approve the drug for prevention of influenza complications, and the agency's summary of product characteristics stated that lower respiratory tract complications were reduced from 12.7% to 8.6% ($P = 0.001$).[38]

In contrast, the FDA sent Roche a warning letter that the company should stop claiming that Tamiflu reduces the severity and incidence of secondary infections, and it required Roche to print a disclaimer on the labels: 'Tamiflu has not been proven to have a positive impact on the potential consequences (such as hospitalizations, mortality, or economic impact) of seasonal, avian, or pandemic influenza.'[37,47]

When the FDA first reviewed a similar drug, zanamivir (Relenza) from GlaxoSmithKline, the advisory committee recommended by a vote of 13 to 4 that the drug should not be approved.[39] In analysis after analysis, zanamivir was no better than

placebo when the patients were taking other drugs such as paracetamol.[39] Within days after this decision, Glaxo sent a fiery letter to the FDA stating that the decision was 'completely at odds with the will of Congress that drug development and approval proceed swiftly and surely'.[40] This threat made the FDA's leadership overrule the committee and criticise its reviewer, biostatistician Michael Elashoff, for giving negative testimony. Elashoff was originally assigned also the oseltamivir application, but this was taken away from him[39] and he left the agency after its demonstration of how an ineffective drug gets approved. When zanamivir was approved, the FDA also had to approve oseltamivir later the same year.[41]

There is no convincing evidence that Tamiflu prevents influenza complications or reduces the spread of influenza to other people. However, Roche used ghostwriters, and one of the ghosts said: 'The Tamiflu accounts had a list of key messages that you had to get in. It was run by the marketing department and you were answerable to them.'[38] At best, Tamiflu reduces the duration of influenza by 21 hours,[42] which can likely be obtained with far cheaper drugs like aspirin and paracetamol.[44] Furthermore, Tamiflu has important harms, but they were concealed to such an extent that the Cochrane researchers could not report on them in their Cochrane review. Even so, the Cochrane researchers found that cases of hallucination and weird accidents have been fairly commonly reported in Roche's post-marketing surveillance of Tamiflu,[41] in accordance with case series from Japan and experiments in rats that exhibited many of the same symptoms. A journal article signed by a group of Roche authors claimed that rats and mice given a very high dose of Tamiflu showed no ill effect, but according to documents submitted to the Japanese Ministry of Health, Labor, and Welfare by Chugai, the Japanese Roche subsidiary, the exact same dose of Tamiflu killed more than half of the animals![41]

If Roche's unpublished data had really shown what the company purports they have, Roche would hardly have hesitated to share them with Cochrane researchers or to publish them. Stunningly, however, Roche has stated that the additional studies 'provided little new information and would therefore be unlikely to be accepted for publication by most reputable journals'.[38] These claims are ridiculous. I cannot abstain at this point from quoting Drummond Rennie, editor of *JAMA*, who, in his announcement for the first peer review congress, stated:[43]

> *'There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egoistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print.'*

After much media attention, Roche promised in 2009 to make the full study reports of the unpublished trials available on its website, but this hasn't happened.

Another curiosity is that Roche sent one of the Cochrane researchers a draft agreement, which stipulated that if signed, he could not even mention that such an

agreement existed![38] Apparently, Roche intended not only to keep its data concealed but also the fact that it silenced people who asked for the data. The Cochrane researcher asked for clarification the next day but never received a reply.

The Council of Europe has criticised national governments, the World Health Organization (WHO) and the EU agencies for being guilty of actions that led to a waste of large sums of money.[45] Many people have wondered why the WHO selected people to write guidance about influenza drugs who were paid by the companies marketing the drugs, and who didn't disclose this in their guidance reports, and why there was so much secrecy around it that it wasn't even possible for outsiders to get information on who were on the WHO committee.[39]

WHO has been an ideal partner for Roche's excesses and Roche has boasted that it works as 'a responsible partner with governments to assist in their pandemic planning'.[39] Roche's actions belie this statement, and in 2012 I suggested that the European governments should sue Roche to get the billions of Euros back they had spent on needlessly stockpiling Tamiflu, which might also have the effect that the hidden trial results came out in the open.[46] Furthermore, I suggested we should boycott Roche's products until they publish the missing Tamiflu data.

7 Johnson & Johnson fined more than $1.1 billion in 2012

A jury found that the company and its subsidiary Janssen had downplayed and hidden risks associated with its antipsychotic drug Risperdal (risperidone).[48] The judge found nearly 240 000 violations under Arkansas' Medicaid-fraud law. Jurors returned a quick verdict in favour of the state, which had argued that Janssen lied about the potentially life-threatening side effects of Risperdal which, like other antipsychotic drugs, include death, strokes, seizures, weight gain and diabetes. The FDA had ordered Janssen to issue a letter to doctors correcting an earlier letter saying the drug didn't increase the risk of developing diabetes. Janssen continued to maintain after the verdict that it didn't break the law. Previous verdicts against the company a few months earlier included a $327 million civil penalty in South Carolina and a $158 million settlement in Texas.

The worst of all this was that the crimes hit hard also on children.[49] More than a quarter of Risperdal's use was in children and adolescents, including non-approved indications, and a panel of federal drug experts concluded that the drug was used far too much. A world-renowned child psychiatrist, Joseph Biederman from Harvard, pushed the drug heavily to children and also extorted the company. Internal emails released for use in court cases revealed that Biederman was furious after Johnson & Johnson rejected a request he had made to receive a $280 000 research grant. A company spokesperson wrote: 'I have never seen someone so angry … Since that time, our business became non-existant [sic] within his area of control.'

The fraud case could become even bigger. In April 2012, the US government stated in a motion in a potential multibillion-dollar healthcare fraud case against Johnson & Johnson that Alex Gorsky, Vice President of Marketing, who was set to become Johnson

& Johnson's next chief executive officer, was actively involved and had firsthand knowledge of the alleged fraud.[50] The allegations were that Johnson & Johnson paid kickbacks to induce Omnicare, the nation's largest nursing home pharmacy, to purchase and recommend Risperdal and other of the company's drugs. The company didn't inform Omnicare or members of Janssen's sales staff that the FDA had warned the company that marketing Risperdal as safe and effective in the elderly would be false and misleading because the drug had not been adequately studied in that population, or that the FDA had rejected the company's attempt to get approval to market Risperdal for treatment of psychotic and behavioural disturbances in dementia (by far the most prevalent use of Risperdal in Omnicare-served nursing facilities) because of inadequate safety data. Despite the weight of federal and state investigations of the Risperdal allegations, Johnson & Johnson's board of directors rewarded Gorsky by selecting him to be the next CEO. It's like in the mob: the greater the crime, the greater the advancement.

8 Merck to pay $670 million over Medicaid fraud in 2007

Merck had failed to pay the appropriate rebates to Medicaid and other government healthcare programmes, and had also paid kickbacks to doctors and hospitals to induce them to prescribe various drugs.[51] The allegations were brought in two separate lawsuits filed by whistle-blowers, and one of them would receive $68 million. From 1997 to 2001, Merck's sales force used approximately 15 different programmes to induce doctors to prescribe its drugs. These programmes primarily consisted of excess payments to doctors disguised as fees for 'training', 'consultation' or 'market research'. The government alleged that these fees were illegal kickbacks intended to induce the purchase of Merck drugs. Merck agreed to a Corporate Integrity Agreement.

9 Eli Lilly to pay more than $1.4 billion for illegal marketing in 2009

Eli Lilly entered into a settlement with the Department of Justice concerning a wide-ranging, off-label marketing scheme for its top-selling antipsychotic drug, Zyprexa (olanzapine), with worldwide sales of nearly $40 billion between 1996 and 2009.[52] In the settlement, Eli Lilly would pay $800 million in civil penalties and pleaded guilty to criminal charges, paying an additional $600 million fine. The allegations were raised by six whistle-blowers from Lilly who would share in approximately 18% of the federal and qualifying states' recoveries. All whistle-blowers were fired or forced to resign by the company. According to the complaint, one sales representative had contacted the company hotline regarding unethical sales practices but received no response.

Lilly successfully marketed Zyprexa for numerous off-label uses including Alzheimer's, depression and dementia, particularly in children and the elderly, although the harms of the drug are substantial, inducing heart failure, pneumonia, considerable weight gain and diabetes. Lilly salespeople were posed as persons in the audience who were interested in Zyprexa's expanded use and asked 'planted questions' during off-label lectures and audio conferences for physicians. Another tactic was that, while knowing

the substantial risk for weight gain posed by Zyprexa, the company minimised the connection between Zyprexa and weight gain in a widely disseminated videotape called *The Myth of Diabetes* that used 'scientific studies of questionable integrity as well as the haphazard reporting of adverse events'. The settlement agreement included a Corporate Integrity Agreement.

10 Abbott to pay $1.5 billion for Medicaid fraud in 2012

Abbott settled allegations of Medicaid fraud for the company's illegal marketing of the epilepsy drug Depakote (valproate); $84 million would be paid to the whistle-blowers.[53,54] Abbott would pay $800 million in civil damages and penalties to compensate Medicaid, Medicare and various federal healthcare programmes for harm suffered as a result of its conduct. Abbott also pleaded guilty to a violation of the Food, Drug, and Cosmetic Act and agreed to pay a criminal fine and forfeiture of $700 million.

The states alleged that Abbott promoted the sale and use of Depakote for uses that were not approved by the FDA as safe and effective; that Abbott Laboratories made false and misleading statements about the safety, efficacy, dosing and cost-effectiveness of Depakote for some unapproved uses; improperly marketed the product in nursing homes for demented patients while the company had halted a trial in such patients that showed increased adverse effects; and paid kickbacks to induce doctors and others to prescribe or promote the drug. Abbott entered into a Corporate Integrity Agreement.

The crimes are repetitive

My survey showed that corporate crime is common and that the crimes are ruthlessly carried out, with blatant disregard for the deaths and other serious harms they cause. You'll see in the rest of this book that corporate crime kills people[12] and it also involves huge thefts of taxpayers' money.

It was easy to find additional crimes committed by the same top 10 companies,[24] crimes committed outside the United States and crimes committed by other companies. I used 'fraud' in my searches, but I could also have used 'criminal', 'illegal', 'FBI', 'kickback', 'misconduct', 'settlement', 'bribery', 'guilty' and 'felony', which would have uncovered many additional, recent crimes. I shall describe here some other crimes and will give more examples later.

In 2007, the FDA slammed Sanofi-Aventis over its failure to act on known instances of fraud during a pivotal trial of its antibiotic Ketek (telithromycin).[55] The FDA had required this trial after its first review of the drug, and the company enrolled over 24 000 patients in just 5 months by recruiting more than 1800 physicians, many of whom were new to clinical trials.[56]

Sanofi-Aventis continued to deny the accusations, although, according to company records and testimony by a former employee, the company was aware of fraudulent data but didn't take any action. One of the physician investigators was convicted of

fraud over the enrolment of patients and faking consent forms and was sentenced to 57 months in prison. The convict had enrolled over 400 patients, at a payment of $400 per patient, and no patients had withdrawn from the study or were lost to follow-up, which is clearly too good to be true.

After having inspected nine other sites enrolling many patients, the FDA referred three of them for criminal investigations.[56] However, although the FDA knew about the misconduct, it didn't mention any problems with the data at its advisory committee meeting, with the excuse that they were legally barred from this because there was a criminal investigation.[56] This is not a valid excuse, as they could have decided not to present any data from this trial or postponed the meeting till the issues had been resolved.

Unaware of the problems, the committee voted 11 to 1 to recommend approval. The FDA furthermore accepted foreign post-marketing reports as evidence of safety, although such uncontrolled data are unreliable and although the criminal investigators recommended the FDA to examine whether Sanofi-Aventis had been involved in systematic fraud. The FDA didn't follow the advice and it exerted internal pressures on its scientists to alter their conclusions in favour of the drug, which, as we shall see later, seems to be standard practice at the FDA.

Sanofi-Aventis boasted that the launch of Ketek was the most successful launch of any antibiotic in history. However, already 7 months after the launch, the first death in liver failure was reported, and more cases followed. The FDA held an emergency meeting among 'senior managers' – which do not include the safety officers – and announced that the drug was safe, with reference to the study the FDA knew was fraudulent![56] One month later, one of the reviewers for Ketek alerted FDA senior management to the irregularities, but no substantive actions were taken, and some months later, when 23 cases of severe liver injury and four deaths had been reported, the FDA's Commissioner Andrew von Eschenbach prohibited the scientists to discuss Ketek outside the agency. The FDA didn't relabel Ketek to indicate its hepatotoxicity until 16 months after the first case became public. The agency's defence to all this is an embarrassing read, very similar to when the drug industry tries to defend the indefensible.[57]

Amazingly, Ketek is still available in the United States, but carries a black box warning, and it's no longer approved for mild respiratory illnesses such as sinusitis. The official FDA information about Ketek is such that I don't understand that any doctor would dare use the drug, but the likely explanation is that doctors don't read 26-page accounts of individual drugs and don't know the history behind Ketek.[58]

AstraZeneca paid $355 million in 2003 after pleading guilty to charges that it encouraged physicians to illegally request Medicare reimbursements for its drug against prostate cancer, Zoladex (goserelin), and bribed doctors to buy it.[35]

Johnson & Johnson was to pay more than $75 million to UK and US authorities in 2009 to settle corruption charges spanning three European countries and Iraq.[59] The