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"PROFIT IS MORE IMPORTANT THAN HEALTH: THE POWER AND INFLUENCE OF PHARMACEUTICAL COMPANIES IN MEDICINE"

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PROFESSOR JELINEK:

What I would like to discuss with you tonight is look at the pharmaceutical industry briefly to begin with to give you a sense of its size and profitability.

Then to look in a bit more detail in an evidence-based way at the quality of drug company sponsored research; the conflicts of interest that develop between the industry and the profession of medicine, supported by the views of a number of very prominent academics, particularly medical journal editors who have had quite a lot to do with the industry.

Then go into some detail about some of the techniques that the company use to increase their sales and again do that in an evidence-based way, looking at some particular examples of blockbuster drugs and using some of the legal actions that have been undertaken in different jurisdictions to uncover some of the practices that have gone on in the pharmaceutical industry.

Finally, looking a bit at regulation of the industry both here and in the United States and just raising the question of whether it's really adequate.

The industry: it's fair to say that these are enormous companies. Since the 1980s the pharmaceutical industry has been the most profitable industry in the world. When you look at Fortune 500 which rates the top 500 companies in the world by turnover and profit, the combined profits for the top ten drug companies when I last looked actually dwarfed the other 490 of the top 500 companies in the United States and, interestingly, the proportion of turnover that is kept as profit, much though we hear a lot about research and development, is

around four times what it is for the other companies in the stop 500. So, the industry is awash with money.

Where does the money go? Obviously, these companies do much of their work to ensure their shareholders get a reasonable return on their investment. Research and development in fact is a small proportion of where the money goes. Marketing is a very big proportion and this is something that probably should concern us. If we look just at the salaries of some of the individuals involved and I extracted this from a book I read some time ago, it's 2001 - but the CEO of one of the big drug companies got rather an amazing salary of around $75 million in 2001 and an equivalent amount in stock options which he in fact didn't exercise, according to the annual report, and kept them and rolled them over. Of course, a lot of the profits go - and I'll show you how this happens later on - towards educating doctors.

So what are the drug companies selling us? Well, it is commonly held and commonly felt that we are being delivered innovative new therapies, that there are research breakthroughs happening all the time which are delivering us pharmaceuticals which are making a big difference to our health. In fact the majority of new pharmaceuticals are not innovative new therapies, they are variations to existing drugs often with small chemical variations to side chains on molecules and so on to enable continuing patents to be held by those drug companies.

If we look at the period from 1998 to 2002 there were 415 new drugs approved by the FDA in the United States, only 58 of which were innovative drugs. The

remainder in fact were of roughly a similar efficacy to current drugs, mostly just had minor chemical modifications again to enable patents to be held. The reason that can happen is that the FDA has a loophole effectively in their regulations in that the drug companies only have to show that a new drug is effective, not that it's more effective or even as effective as current treatments. So, if they do a placebo control trial and show that it's more effective than placebo, on that basis the FDA will licence the drug's use.

Let's just look at a couple of examples of that because I think they're quite illustrative. Antidepressants I think are a really good place to start. In 1987 Prozac was approved for depression and as we know it rapidly became a blockbuster and blockbusters in the pharmaceutical industry are defined as drugs that earn over $1 billion per annum, that's the definition they use. Rapidly, Prozac replaced all other antidepressants on the market.

Those of us in medicine know that the tricyclics which were widely used rapidly fell out of favour and Prozac became the number one prescribed antidepressant. It soon became responsible for a quarter of all its drug company manufacturers' revenues. It was making about two and a half billion dollars US per annum for the drug company and that resulted in a flurry of selective serotonin re-uptake inhibitors of which Prozac is one example coming on to the market. Most of them are actually not particularly different than the original or any more effective but simply different.

When Prozac went out of patent in 2001 and was sold

as generic Floroxitine, which is the generic name of the drug, it rapidly fell in price to be one-fifth of the price it had been selling for but because marketing for the new drugs that were coming online was ramped up to compensate for that it was immediately taken over by other antidepressants as the most prescribed drugs and it's now no longer in the top ten drugs even though it was the world's number one best selling drug for a period.

But what about the effectiveness of the antidepressants anyway? The FDA in fact accepts the results of clinical trials from drug companies. They don't necessarily have to be published studies. They're simply studies that the drug company forwards to the FDA and they use them in their analysis.

Two psychologists looked at and accessed the 42 reviews that the FDA used for the six most widely used antidepressants over that twelve year period. Interestingly, these are drugs that many people stay on for many years but most of the 42 trials that they looked at lasted only six weeks. Of even more interest, the placebo that was used when you actually analysed all the trials together, the placebos were 80 per cent as effective as the drugs in alleviating depression, so there was a marked improvement in the symptoms of depression in the placebo group and an addition 20 per cent improvement in the antidepressant group.

The scale they use to measure that in these studies was a 62 point inventory of depression and the difference between the placebos and the antidepressants was two points on that 62 point scale. Interestingly, if you go

and look at the scale in some detail, six of those 62 points relate to sleep and the quality of sleep, the length of sleep. Really, to be more effective than placebo, all that these drugs had to do was improve people's sleep a little. So, if they'd been simply sedatives, which the majority of them are, people would have slept more soundly and that may well have accounted for the difference.

Actually, when you look at a difference of two points on a 62 point scale and judge whether that's clinically significant, the average person wouldn't be able to tell the difference with such a small difference on a 62 point scale. So, why then is so much of the population on these drugs? They have been very well marketed, extremely well marketed if they're generating these sorts of revenues.

Looking a bit further at antidepressants, a group looked at more recently at 74 studies that were registered with the FDA to licence antidepressants. 38 of the 74 had positive results and, interestingly, roughly half the studies had negative or questionable results, that is they didn't really show a difference between the antidepressants and the placebos. Of the ones that had positive results, essentially all of them were published. Of the ones that had negative results not all of them were published and quite a few, if they were published, were published in such a way that the spin that was put on the final paper in the journal indicated that they were more effective than they actually were when you looked at them in detail.

So, in the published literature 94 per cent of the

studies were positive because so many studies that were negative didn't get into the published literature but in the FDA literature only about half the studies were positive and when you actually - these authors did a meta-analysis of the published versus the FDA studies and they showed that in the published data there was a one-third greater effect size for the antidepressants than in the FDA data on which they'd been licensed. So, for the profession who read the journals, we get an inflated estimate of the benefit of those drugs which the FDA didn't have when they licensed the drugs. And, hence, when we come to prescribe them we prescribe them with a different core belief about their value than actually exists.

Looking at anti-hypertensives, which is another group of drugs used to control blood pressure - again, I'm concentrating on drugs here that are in widespread use in the population. For the drug companies these are always potential blockbuster drugs because you may well get patients on to these drugs quite young and they may stay on them for life, so potentially these are very lucrative drugs.

24 million Americans at the time of this study were taking anti-hypertensives and there had been a recent flurry of supposedly innovative new drugs that have come on to the market. Most of these studies were in fact run by the drug companies clearly who were trying to sell their drug but this group of investigators, the ALLHAT Collaborative Group did a major independent study, not drug-company funded, funded independently, comparing new anti-hypertensives, supposedly innovative ones against

the very old ones, the very cheap ones that had been on the market for years. It was a huge study: 42,000 patients, eight years long and they compared some of these new drugs against the old generic diuretic clorthalidone which had been used for 50-odd years and cost next to nothing.

The results: well, surprisingly, the old diuretic was just a good as the others at lowering blood pressure but it was better in a whole lot of ways as well. It was actually less likely to cause heart failure than one of the drugs, less likely to cause heart failure and stroke than another of the drugs and in fact they had to stop one of the arms of the trial early because of an excess of heart failure. They concluded this major independent study that the diuretics, the cheap old-fashioned drug was the best drug for hypertension.

Of course, that resulted in a flurry of editorials from the people within the profession who had run these trials on behalf of the drug companies disputing the findings and so the waters became so muddied that in fact people stayed on their drugs. You would imagine with that sort of data we'd get a sudden change in practice but that's not what happened.

This really leads on to the question of how reliable drug company sponsored research is; how much we can really believe the results that we see in the journals. A number of studies have looked at this (independent studies). Drug company research has been shown to be four times as likely to be favourable to a company's product than independently-funded research. Authors of company-sponsored research are five times as likely to

recommend a company's drug as independent authors and if you have industry connections you're far more likely to favour company drugs.

So, Norvasc, one of those blood pressure lowering drugs, 96 per cent of authors of papers that were favourable to the drug had financial ties to the company. When you looked at the papers that were unfavourable to the drug only about a third of those had financial ties to the company. There's clearly considerable conflict of interest in drug company sponsored research.

A really good Australian study was done fairly recently and reported in several different journals, different parts of the study. The authors looked at 823 medical specialists from a variety of specialties in Australia and the first thing they looked at was the influence of the industry on how research is conducted and how medical research is reported and they found, in fact, which comes as a great shock to someone in my position who has edited a medical journal for 15 years in emergency medicine where there is really negligible drug company influence because we don't put people on drugs for long periods, we just give them a dose of drugs when we see them, if we need to use drugs, and then they move on to someone else's care, so we're not targeted by the profession.

My journal had essentially no papers that were drug company sponsored. I don't recall ever having edited one in the time I was editor. This is very unusual for most major medical journals. And you'll see later, in the British medical journal, The Lancet where these trials are published frequently, they've got quite a bit of

experience with this and the editors have got quite strong opinions on how the industry influences research conduct.

Interestingly, one in eight of these specialists reported that the industry had written the first draft of the paper for them. That's actually not something I've ever done in my career and yet it's clearly widespread in medical practice in Australia. I must say, until I read this I felt it was probably more a problem in the United States and in Europe than in Australia. Nearly seven per cent reported that they had delayed publication of the results, five per cent non-publication of key negative findings and frank concealment of results which was dictated to them by the drug companies that had sponsored the research. So, overall eight and a half experienced at least one event that represented a breach of research integrity.

The same study reported that nearly half reported some involvement in industry-sponsored research in the year prior to the study. The doctors who were involved in industry-sponsored research were three and a half times more likely to have been offered industry-sponsored gifts, over $500 worth in value. They were five and a half times more likely than others to have been offered support for going to an international conference and nine times more likely if they were a paid consultant to industry, seven times more likely if they were a member of a drug company advisory board. So, the money is clearly very focused and very targeted to those specialists who are strongly affiliated with industry.

The inducements that were offered: we sometimes

don't pay enough attention to the offering of food and other things that appear innocuous, to have meetings sponsored by drug companies and have the food provided to many people seems innocuous. But the drug companies with their budgets, it doesn't seem feasible that they'd be doing that if they got no return on that investment.

Almost 100 per cent of those people had been offered food inducements or items for the office. Three-quarters had been invited to product launches, educational events, symposia, half had received offers of travel to conferences and personal gifts, journals, textbooks, and about two-thirds to three-quarters of those offers were accepted.

Looking at the US, the New England Journal published a paper last year showing that a similar sort of proportion of physicians there reported a relationship, again food and samples were very common. A third frankly received direct financial reimbursement; a bit over a quarter direct payments for lectures. The interesting thing to come out of this paper was that the marketing was very closely targeted to opinion leaders, so some specialties were particularly targeted and, as I was saying earlier, emergency medicine isn't one of those, we really don't have drug company representatives knocking at our door terribly often.

Cardiologists were particularly targeted and, again, because they are likely to put their patients on drugs that they stay on for a long time. Another specialty such as oncology where the drugs are very expensive and, more latterly, neurology which for a long time neurologists really dealt often with diseases that

weren't amenable to any therapy but increasingly, we're starting to see blockbuster drugs in neurology such as Betaferon and Copaxone and so on for multiple sclerosis. We're seeing neurologists targeted by the drug companies.

The Lancet reported this study that showed when they surveyed the Committee of Safety of Medicines in the UK which advises the regulatory agency on youth drug approvals in the United Kingdom about the financial conflicts of its committee members, they found that 23 of the 29 had conflicts of interest and some of them with an extraordinary number of companies, 20 companies even for some of the members of that committee.

Interestingly, the New England Journal of Medicine which for a long time had the most stringent policy as one of the big four medical journals in the world for restricting who could write editorials and declaring potential conflicts of interest. They in fact reversed that policy in 2002 because they simply couldn't find anyone to write their editorials because most people had a conflict of interest they had to declare and they wouldn't have been able to get people with sufficient academic clout to write the papers.

It is pretty established that these conflicts of interest exist but do they influence prescribing behaviour? We could say if they didn't then the drug companies wouldn't be doing it. But let's look at the evidence better and some of the papers that have looked at this have shown that doctors generally deny that there is any feeling that they've been influenced but when you actually survey people's prescribing behaviour after they've attended some of these pharmaceutical events

they're more likely to use the product even if there's no evidence being presented to back up the claims. It's often relatively non-rational prescribing, often off-label prescribing and I'll talk about that more in a moment.

A really good paper in the Medical Journal of Australia just recently tried to come up with some solutions for how we deal with this entrenched problem and they felt that, firstly, increased transparency was important. Just as we wouldn't go to a financial adviser and have any great confidence if they didn't declare the commissions they were receiving then, similarly, we should have transparency in knowing what our medical practitioners are receiving in the way of inducements from drug companies and preferably they suggested with strict independent auditing of what's being provided and to whom.

They suggested that journals should require opinion leaders to be free from conflicts of interest but, as we've seen, that's a very hard thing to police when most people do in fact have conflicts of interest. That opinion leaders as a generic thing throughout medicine be asked to provide expertise to drug companies pro bono so they don't ask for remuneration for it. That certainly would have a major effect on the issue that's going on.

That we have better medical student education so the students are aware of this. But, again, who do we get to teach them if the majority of people have conflicts of interest? And perhaps we really need to draw up some tight guidelines for academic centres and for opinion leaders so that there are in fact across the board bans

on any gifts, any food, any travel and perhaps these institutions should have an independent office of medical education to oversee funding for medical education, to ensure it doesn't come from these sources.

Some of the views of people who have edited the big medical journals are really interesting. When you look at the strength of what they're saying and the unequivocal nature of their comments, saying that "This industry uses its wealth and power to co-opt every institution that might stand in its way" - that's Marcia Angell who was former editor-in-chief of The New England Journal of Medicine. "Journals have devolved into information laundering operations for the pharmaceutical industry" - that's Richard Horton from The Lancet.

Marcia Angell again from New England Journal, she said "I became increasingly troubled that much published research is seriously flawed leaving doctors to believe in-drugs are generally more effective and safer than they actually are" and "In many drug intensive specialties it is impossible to find an expert who is not receiving payments from one or more drug companies".

This is Richard Smith from the BMJ. A fascinating character; I've always been a great fan of Richard Smith. 25 years editing the BMJ and really turned it into an enormously accessible journal for people, really concerned with humanitarian issues, global health issues, saying that "Medical journals are no more than an extension of the marketing arm of pharmaceutical companies". Gosh, that's a tremendously strong statement. And he had to confess that it took him almost a quarter of a century editing for the BMJ to wake up to

what was happening.

He made the point that, for instance, a lot of the journals will rely very heavily on the sales they get from reprints, so when an article is published, if the authors buy reprints to distribute to other colleagues that can be a substantial source of income. Now it's an even bigger source of income if a drug company wants to buy a hundred thousand reprints of an article of a drug company sponsored research that shows a new anti-diabetes drug works and that may run a bill up of half a million dollars or something, depending on how much the reprint costs.

If the journal feels that it shouldn't publish the paper, if there's some question about the paper's scientific value - "Should we publish it? Shouldn't we?" they have an editorial meeting and in the back of the journal editor's mind is the fact that that new publication assistant that we wanted and the new editorial assistant will be paid from this money, it's a powerful subconscious factor in the judgment about whether to publish that paper or not.

Richard Smith again: "How did we reach a point where so many doctors won't attend an educational meeting unless it's accompanied by free food and a bag of goodies? Something is wrong and medical journals are a part of what is wrong". I actually think he's got a really important point here, that this major breakthrough, the randomised control trial is being debased for marketing reasons. "The industry dominates healthcare and most doctors have been wined and dined by it". Now he didn't have a particular axe to grind; he

was a journal editor and wasn't in clinical practice but he certainly saw these things first hand.

So this is actually a list he published of how a list he put together of the things he'd seen over the years editing the journal of how drug companies got the results they wanted from clinical trials. The first is to trial your drug against a treatment that you know is going to be inferior so it shows up as better than it may otherwise have, so you pick the right thing to trial it against. You trial it against too low a dose of the competitive drug, there's a number of prime examples of that, or too high a dose if you want to show that it's less toxic. If you want to show a nil difference trial, that is an equivalence trial, your drug is equivalent to something else then you use numbers that are too low to show a difference, too small to show a statistically significant difference.

You select certain end points for publication that give favourable results or just from certain centres that have by chance produced favourable results or a favourite of some author's about sub-group analysis and you always get some sub-groups that show up with a positive finding if you do a big enough study on enough sub-groups. The other famous sort of statistical trick is to do relative risk rather than absolute risk reductions, so a difference between 50 per cent and 40 per cent is taken as not the ten per cent absolute difference but ten of 50, so 20 per cent relative risk reduction.

Another thing I found when I was reading through the literature was some of the techniques that drug companies use for increasing their sales: one is to use the drug

off label. Now when the FDA or the TGA approve a drug they licence it for a particular condition but a doctor can prescribe that drug once it's licensed for any condition, it doesn't have to be the particular condition for which it's licensed. If you can convince people in the profession that a drug is effective for a variety of conditions in which it hasn't really even been tested through educational meetings by enlisting the help of opinion leaders in that specialty then you might get quite a substantial increase in the use of that drug.

Another is actually to really invent new diseases for which the treatment is the drug, so social anxiety disorder now exists because SSRIs have been promoted heavily as a treatment for that and premenstrual dysphoric disorder which is the same fluroxitine that's in Prozac except it's not green any more, it's purple and it costs three times the price and it's now got the lovely name of Seraphine rather than Prozac and these are all genuine examples.

But more worrying is what happens to some of these big blockbuster drugs with this off-label use and in 1994, to use the example of Gabapentin which many of us in the profession prescribe, the FDA approved it in 1994 for epilepsy when other drugs had failed in combination with another, which is a very narrow therapeutic indication. In 1996 one of the people who worked for Parke Davis who was the drug company promoting it at the time sued the company alleging massive tampering with marketing to promote Neurontin for off-label use so that people were encouraged to use it for conditions other than this thirdline drug for epilepsy. So one of the few

ways we find out about these things is often by getting, when these companies are forced in a legal action like that, to table documents about what they've done in court and they're then freely available.

What transpired was that the company paid academics to put their names on research to show that the drug worked in other conditions besides epilepsy, so a whole range of things: essentially, sort of chronic discomfort if you like: insomnia, restless legs, tension headaches and so on and then had a series of educational meetings where they had doctors that they'd asked to speak about this who were paid quite well to lecture about these benefits and they tracked the prescribing of doctors after the meetings and this had to be shown in court and there was a 70 per cent increase in prescribing after the meetings.

Neurontin, a thirdline epilepsy drug became a blockbuster worth over a billion dollars per annum in income for the drug company. $2.7 billion in fact in 2003. When they looked at that in detail, 80 per cent of the sales were for these off-label conditions, essentially of chronic discomfort. In May 2004 at the end of this action, Visor who is now the drug company marketing it pleaded guilty to illegal marketing and a damages bill of $430 million was imposed. But, really, in comparison to an annual intake of $2.7 billion it wasn't a lot and we have to really ask what about all the people who are still on the drug and what about all the doctors who keep prescribing it who may well be unaware of what happened in that court case.

I somehow got myself on the mailing list of this new

industry. I opened my email one day and I got an advertisement for this conference: "The Sixth Annual Off-Label Usage Conference to minimise the legal risk associated with off-label marketing" at the Hilton in Philadelphia, I was tempted to go. The conference highlights - I mean just looking down the list, it's all about how to deal with the FDA to get these drugs used off-line without being caught and this is widely advertised and it gets a very large attendance. I don't know how I got on their mailing list.

If we look at the top ten Australian drugs in 2006/7, the last lot that have been released, if you take the top drugs by defined daily dose, so how many out of 1,000 population take the standard dose every day, Atorvastatin and Simvastatin, the two cholesterol-lowering drugs, are at the very top. Some ace inhibitors, which are blood pressure drugs essentially, below that; Aspirin makes it on to the list; Omeprazole, an indigestion drug next; a fluid drug Furisimide and another indigestion drug coming in tenth.

I will just put the cost to the Australian Government on the side there for ones that have made it to the top ten in cost. If you compare that to the world top ten drugs, again we've got a similar list and I've shown you the indications down the side but the sales of these things are actually staggering. To think that so much of the population is on cholesterol-lowering drugs that we're generating $13.6 billion dollars. That is the amount that the Oxford Leadership Academy has indicated would enable all the children in the world who were starving to be able to eat every day. It's an

extraordinary amount of money. And when you look at the indications down the side, most of them are actually lifestyle disorders that we've got in western society that are manageable through actually approaching health in a different way than through pharmaceuticals.

Another example of a great off-label drug. This was AstraZeneca's shark fin project and when Omeprazole, which is the indigestion drug, was nearing the end of its patent in 2001 after earning enormous amounts of money over the time they'd been licensed, they realised that like a shark fin the sales which were going up would suddenly come straight back down once it became a generic drug and the price dropped. So, they developed a think tank to deal with it - this has all come about through - we're aware of this through transcripts of legal proceedings - and they decided that they should market one of the two isomers of Omeprazole.

Now Omeprazole was actually composed of trans stereoisomer of the same drug so they were mirror images of each other which just were together in the same package as Omeprazole. They took one of them out and marketed it separately as a new drug which technically speaking I guess it was. But then they compared 40mg, so double the dose of this drug which was part of the whole drug against the old drug to make it look better and the trials of course showed it was better and then they filed for a patent for Nexium, they got their patent and spent half a billion dollars on marketing and direct to the consumer marketing and for those of us in the profession I think we all sort of spotted that window when we suddenly moved from Omeprazole to Nexium, when everyone

started prescribing it and it became a blockbuster. But even though it's essentially the same drug or half of the old drug it sells for $4.09 per tablet in the US versus 67 cents for the old drug.

In Delaware in February 2005 a class action was proceeded with in the US District Court alleging false and misleading and deceptive advertising. The suit was dismissed. The judgment was that the ads complied with FDA approved labelling and really that was all that the FDA could be concerned about in terms of the marketing whether or not it complied with labelling requirements. So there was an appeal to the third US Circuit Court of Appeals in 200p7.

The appeal again was dismissed and the judgment was that the FDA has exclusive authority to regulate drug advertising but one dissenting judge said "Such implied conflict pre-emption of state law is unwarranted since the FDA has no power to require pre-approval of ads and lacks the resources to police ads". So, in the end the pharmaceutical industry had a monumental win. They were unable as a result of those judgments to continue marketing this drug which is very much more expensive than the old drug but almost certainly no more effective.

Just quickly looking at inventing diagnoses for which your drug might be the treatment. I just pulled a few diagnoses out the DSN4 Psychiatric Manual, I thought you'd be interested: disruptive behaviour disorder; mathematics disorder (I have that from time to time); partner relational problem (which most of us have experienced at one time or another) and I certainly have an academic problem every now and then. My age-related

cognitive decline, I'm sure will soon have some therapy for it and I won't proceed beyond that one.

But when you looked at the DSN4 connections of the people who actually wrote the manual and you looked at the diagnostic sections of it, in that psychiatric and mood disorder section 100 per cent of those people who had written that section have direct connections to pharmaceutical companies and overall in the manual about half of them do and these are research-funding consultancies, speaking payments and so on. The authors of this particular paper, looking at it, concluded that the connection was especially strong in those areas where drug therapies are the first line of treatment, as you might expect.

How is the industry regulated? Well, Medicines Australia has grown from the Drug and Perfumery Manufacturers' Association, it has passed through several permutations to become Medicines Australia as it currently is since 2002. But, interestingly, when you look at the mission statement of that group their mission is the continued sustainable growth of the innovative and research-based prescription medicines industry. So they are very clearly in the corner of the pharmaceutical industry and they are the ones that apply the code of conduct to the pharmaceutical companies in Australia but only if you are a member, so you can't be sanctioned unless you're a member of Medicines Australia.

If we look at the complaints they received in 2006/7, there were 41. The majority, interestingly, were by other pharmaceutical companies who thought they were marketing a bit shonkily and really wanted to get them

back into line: four were by the TGA, very few by individuals or by doctors and none at all by the general public. Out of those 41, 29 cases found at least one breach and the total fines were $695,000, so not a lot.

If you look at one of those specific components - this is actually the one that got the biggest fine, a complaint by Biogen and Sanofi about Shearing alleging eight breaches of code of conduct at an MS conference regarding promotion of Betaferon which is now a blockbuster drug for MS. It was unanimously upheld. They'd been promoting direct to the public for an off-label indication, so secondary progressive MS, the information wasn't balanced and it raised the expectations beyond what is deliverable in terms of treatment outcome. But the fine, $150,000, that was the highest of any of the 41 and the drug has currently taken in about US$5 billion along with one of the other disease modifying medications in MS.

Another example, Sigma Pharmaceuticals who make the Herron and Chemist's Own brands sponsored a luxury Mediterranean cruise for 300 doctors and pharmacists in October 2007 from Piraeus in Greece, an eleven-day cruise. They denied there were any educational activities on board. Interestingly, they also run a rewards scheme for pharmacists who earn points for a variety of different bits of merchandise and they provide financing to pharmacists to buy or upgrade their shop. Because they weren't a member, Medicines Australia couldn't investigate that or sanction them at all.

The TGA: I just briefly want to, before concluding, just look at the regulation of the industry in Australia.

The TGA is part of the Department of Health and Ageing and their mission is to ensure therapeutic goods available in Australia are of an acceptable standard with the aim of ensuring that the Australian community has access within a reasonable time to therapeutic advances.

Again, I must say looking at that dispassionately, there seems to be a bias towards ensuring that the drugs can be got out there, not so much about the consumer, although they say their framework is based on a risk management approach designed to ensure public health and safety but at the same time freeing industry from unnecessary regulatory burden. That's a short synopsis of their history.

The NH&MRC actually had a lot to do with this, along with the AMA. The Medical Journal of Australia actually was a key player in the formation of the TGA, too, in 1963 and then the Therapeutic Goods Act in 1966, until we ended up with the TGA fairly recently, actually, and now we have a system of therapeutic goods regulation that's internationally harmonised.

The TGA controls the supply of therapeutic goods through auditing an assessment of the quality of manufacturing, pre- and post-market assessment but, interestingly, they look at medicines with higher risks, so prescription medicines for quality safety and efficacy but not lower risks, over the counter medicines, for efficacy. They look at quality and safety but not efficacy, so they can't ask a company to withdraw, for instance, vitamin E. We've got really good meta-analyses on vitamin E now showing that there's a four per cent increase in mortality for people who take vitamin E

tablets. I have a placebo. Very strong evidence. We've got evidence of vitamin A supplements, that there's a 16 per cent increase in mortality in randomised controlled trials against a placebo in quarter of a million patients, big studies, yet the TGA can do nothing about this because it's not part of their charter, so it's not just pharmaceutical agents that are a problem.

The approval of drugs for funding by the public purse in the UK, Australia and New Zealand, the three bodies that do it in the UK: the National Institute for Health and Clinical Excellence, in Australia the Pharmaceutical Benefits Advisory Committee and in New Zealand the Pharmaceutical Management Agency or PHARMAC. And NICE, the group in the UK, do a list of the most and least cost-effective drugs available.

Their list of the ten least cost-effective drugs were actually all approved for public funding in the UK, most of them in Australia and about half of them in New Zealand and these bodies made exceptions, after heavy lobbying by the industry, for drugs for some dread diseases. So, Betaferon is actually - the one that we talked about before that got the biggest fine from Medicines Australia - judged the least effective medication that we have, the least cost-effective medication. So, for each quality adjusted life year extra that a patient gets it costs about 70,000 pounds of public money yet licensed in Australia and the UK.

To conclude, I hope I've given you a broad picture of what the pharmaceutical industry is; the size of it; the profitability of that industry and the fact that its profits are enormous in comparison with other companies

and that really a very large proportion of the moneys that go through the pharmaceutical companies are spent on marketing rather than research and development.

A number of companies have been prosecuted for and admitted illegal marketing and some of the blockbuster drugs that have been marketed in that way have actually caused enormous damage. So, I haven't even spoken about Vioxx tonight but I think most people here would be aware of the tens of thousands of excess deaths in the United States from heart attack and stroke due to Vioxx.

There is clearly a widespread conflict of interest related to the pharmaceutical industry and that conflict of interest results in over-prescribing many medicines that are really of dubious benefit. So, I think we now have a major problem in the medical profession in that conflict of interest is leading us to neglect genuine health and genuine health which is achievable for most people in lifestyle change - eating well, exercise and so on - in favour of pharmaceuticals.

The fact that there's actually a paucity of funding now for investigating these mainstream issues related to health because so much of the funding in health research is drug company in origin. I think it's important for doctors in general wherever they are to consider whether they should really accept anything at all from drug companies, whether it's food or sponsorship of a meeting or something more substantial, research money, and for a lot of us that's a very important career decision. You may be faced with a prospect of researching something that's very dear to your heart but it comes with ties because it comes from the pharmaceutical industry.

Finally, I just raise the question that do our current regulatory bodies have adequate control of this industry given their charter and given their mission? Thank you very much for your attention tonight. I've put a list there of five books that you might want to consider reading. The one that I found the most interesting is "The Truth about the Drug Companies" by Marcia Angell who was the editor of the New England Journal. But Jerome Kassirer has also been editor of the New England Journal and these people generally have a very good working knowledge of the industry. Thank you very much.

QUESTIONS:

I go to the US every year and I was really amazed to note how much advertising there is on the TV stations with respect to drug products. It seems to me just from talking to people I know in the US that it's not a lifestyle change, "If you've got diabetes take a drug, there's a drug out there" and this is very heavily promoted by TV advertisements. Okay, do you know that this is so?

PROFESSOR JELENIK: There is a debate going on in Australia about whether direct to consumer advertising should be allowed. In the States it is and so you can directly market to consumers. Currently, it's not allowed in Australia in its most direct form but you've probably all seen ads of a couple dancing and they get whisked away on a sort of starry moonbeam and then at the bottom it says "If you want a good weekend then visit the website below" and the website will be the drug company website but it

will be called weekendforfun.com or something and when you get there it's directed to consumer marketing but they can't do it directly on the TV. So, we're just at the tip of the iceberg in Australia and if it becomes allowable then we'll see the same thing as the US.

QUESTION: There is much advertising particularly on pay TV which almost everybody watches. Another comment is in the '60s I worked for G.D. Searle as a medical writer and we got these little imperfect research packages from various doctors that we were supposed to put into papers with a positive spin. I didn't work too long for G.D. Searle but this was about the time of the birth control medicines were coming out and so forth and we all know how that developed. The question I have here is if a researcher finds negative results in such cases, what happens?

PROFESSOR JELENIK: In such cases where?

QUESTION: Well, especially on funding by a drug company, let's say, to research a certain product and the results he finds are not positive to the drug company's product.

PROFESSOR JELENIK: I think we've seen from the research that Kerridge and others did in Australia that the drug companies will frequently suppress those findings, so keep them on file but not publish them and that is now a relatively common event. It's interesting that some of the bigger journals are starting to tackle that issue and I know I submitted a paper to The Lancet a couple of weeks ago and I haven't done that recently and I looked at the list of check boxes that you have to go through and it asks specifically "Was anyone other than a member of the authorship group an author of this paper?" and

quite a few other questions that very directly address whether or not there was a ghost writer or a ghost author, which I think is - yes - until I'd been to a conference some years ago on medical editing, I didn't realise that ghost writers actually did such a big amount of the writing for pharmaceutical companies simply because I edited a journal that never saw that. But the big ones like The Lancet and the BMJ I think are seeing papers like that come through all the time.

MR BURNSIDE: Julian Burnside. Thank you very much for a really marvellous paper. During the "cash for comment" enquiry in 1999 the only people in Australia who thought that they had not been influenced by the millions they received from secret sponsorship were Alan Jones and John Laws. I don't think anyone else in Australia believed them when they said that. That being our understanding of the gravitational influence of money, why is it that opinion leaders who are recognised to receive moneys from pharmaceutical companies are still opinion leaders? Why do people listen to their opinions?

PROFESSOR JELENIK: I think there's probably a number of reasons. One probably is that it's relatively opaque, that whole conflict. I think if it was more transparent who was receiving from whom then it would be less likely to happen. I know a number of conferences now ask that before you speak you deliver your conflict of interest statement and I've had friends who have been at a couple of these conferences in the States and about 15 minutes into the talk they still haven't gotten to the end of their conflict of interest statement and they kind of lose interest in the talk a little bit.

But I think there's probably more to it than that in that people who - apart from the fact that the sheer issue of numbers that so many of us have these conflicts of interest that it's hard to find people who don't, I think for those of us who have worked very hard to get in the position where you are, an opinion leader in your specialty, and someone approaches you to deliver a talk, many of us convince ourselves that we can deliver it in a really objective independent way and the evidence suggests that that's not true. And it's a difficult thing to accept personally for many people in that position, I think, that they actually are being influenced when they believe they aren't.

MR COURT: John Court, physician. Two questions: First of all, do you think that medical students in medical schools are adequately educated along the lines of what you've been talking tonight which might then perhaps influence their long-term consideration of drugs? And the second question is what do poor innocent doctors out there - how do they get their information if they're not allowed to get it through these nice dinners they might get, all the handouts and the other information and visits from drug company representatives, particularly when you've given some doubt about many of the written information that they get?

PROFESSOR JELENIK: John, I think medical students would love to be more educated about this. Whenever I am involved with medical students I'm always amazed at how open they are to different viewpoints and things that often they seem to lose as go on in their training. The difficulty again is a numbers issue. We don't have a lot of people

who aren't conflicted to teach medical students.

But there's quite a few bodies now growing up within the medical student fraternity in Australia that have set up websites that other students can join, so there's a thing called healthy scepticism.org and nofreelunch.org and the students are actually starting to do it for themselves because they're finding that they're not getting great teaching in this from their senior colleagues.

The issue, I guess, for doctors out there, particularly in general practice, I think in hospital medicine there's often such an interaction academically in meetings and so on that it's relatively easy to keep up and particularly in teaching hospitals and if you're involved in teaching trainees. But in general practice, I think, and solo private - well not "solo" necessarily but private practice in a number of specialties where you're less exposed to that then it is I think a serious issue where you get your information from Maybe it's something that needs to actually be regulated from government even that we start looking at other agencies that provide or oversee medical education or perhaps via divisions of general practice through the Department of Health and Ageing, set up some sort of system there where we can provide education that isn't tainted by drug company background but it's not by any means an easy problem.

MR MARSHALL: Robert Marshall. As a surgeon I must congratulate you very much for lifting the lid on the behaviour of my medical colleagues. I wonder whether everybody here would perhaps come to the conclusion that

they should believe surgeons rather than physicians. But I would add a note of warning, just be careful about the ones who want to operate too quickly. The question I have for you though is this: I wonder whether you're aiming at the wrong target. I've been in practice now for nearly 60 years and the thing that has most impressed me in the last 30 has been the appalling situation which has arisen in the medical profession when in 1970 I think it was, the very first time that Labor got into power after a long time, they changed all the rules and people started advertising. If everyone in this room has not studied the Yellow Pages to see how doctors advertise, I invite them to do so when they get home this evening and if you haven't done it you will be absolutely appalled. In that environment of course the drug companies will do exactly what you have so brilliantly described but surely, isn't it governments who have to do something to stop doctors advertising and to stop this bastardry that goes on?

PROFESSOR JELENIK: I think you're right, Robert, and I think it's the regulatory environment that is the thing that needs looking at if we're to get rid of some of these issues.

DR BALL: Richard Ball, psychiatrist. I, too, have been in the game a long time, graduated in 1951 and was one of the few people interested in psychiatry before I graduated. Osler, when he wrote his famous textbook in the late 1800s said "They should throw away the pharmacopea because there are only three things that worked", I think it was opiates, foxglove and aspirin. On the other hand, I wouldn't like to go back to what I remember of medicine

50 years ago. I think there is a danger of throwing baby and bathwater out. Medicine has changed enormously and we do have a lot of very effective drugs. I agree entirely with most of what has been said. I certainly would agree that modern antidepressants are really not much better than the old ones we had, they might be a bit cleaner, and I think it's hard enough to treat people who are sick, it's bloody difficult to treat people who are well and this is one of the problems that we're faced with. I think one of the things that Osler did do, of course, and it's clear looking at his life, he was very aware of the power of the placebo and subsequently Shapiro from Columbia wrote a very good paper on the power of the placebo and we've known this as doctors for thousands of years. We were giving stuff to patients that really didn't do anything specific but it helped make them better and I think it's a good thing the pharmaceutical industry hasn't got on to that otherwise we'd be in worse trouble. Thank you.

PROFESSOR JELENIK: They are very pertinent comments. I don't want to give the impression that I'm anti medication or advances in pharmacological interventions because we're clearly living in a very different age than our forefathers were in terms of what we can provide to people with serious illness and we just need to look at things like childhood leukaemia and some of the dread diseases that really were associated with almost 100 per cent mortality that we can now expect 80 or 90 per cent survival from, to know that some of those interventions, some of those medications are enormously valuable.

But it's easy to be seduced by those shiny examples

into a broad brush approach to the whole of the pharmaceutical industry and believe the spin that these are all going to help our health. A recent meta-analysis in the British Medical Journal of Type 2 diabetes, people with pre-diabetes who have got impaired glucose tolerance and are going to get diabetes showed that if you took the standard medication, Metformin or one of the other medications, then about 50 per cent of people went on to get diabetes, so it prevented about 50 per cent going on to get diabetes. But if you lost weight, exercised, ate a good diet then 70 per cent of people were prevented from going on to get diabetes and yet we've embraced Metformin.

But very few people who are diagnoses with pre-diabetes or early Type 2 diabetes really make any substantial change to their lifestyle and maybe we need to take the best of the pharmaceutical industry but also have a really close look at what we've not been doing for people's genuine health.

End.