From Dylan to Designer Drugs: what would Grannie think of her tablets now?

2006 WORNER RESEARCH LECTURE

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by

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Biography

Professor Kenn Raymond
Head of School, School of Pharmacy and Applied Science. Professor Raymond completed a degree in Pharmacy, a Masters in Pharmaceutical Technology and a PhD in Biopharmaceutics and Pharmacokinetics.

Professor Raymond was awarded the inaugural Pharmaceutical Society of Australia's award for 'Service to Education' and is an acknowledged leader in communication techniques, consulting for WHO in the ASEAN region in the 1990s.

His research interests include drug metabolism studies, teaching pharmaco-kinetics with computers and the education of patients by pharmacists. A report of the research by Professor Raymond and La Trobe Research Fellow, Dr Jiezhong Chen, into more effective treatment of the liver disease, cholestasis, was recently published in the prestigious British medical journal, *The Lancet*.

Professor Raymond's presentation will illustrate the ever-changing role of the pharmacist and the research areas that make the wide-ranging discipline of pharmacy research such an integral part of medical research generally. The talk will follow the debatable efficacy of the drugs of the 1950s and 60s, through the consolidation of basic pharmacological testing in the 70s culminating in the great advances in our understanding of molecular biology from the 1980s to the new millennium. He will examine the emergence of not only more complex drugs being used to treat our existing epidemics of diabetes and heart disease, but also new anti-viral and gene/genetic therapy. Professor Raymond will attempt to predict where drug research may be in 40 years time. The only thing that will not change is the commitment of the pharmacy profession to its social mandate of optimising therapy and practising high quality Pharmaceutical Care.

From Dylan to Designer Drugs: what would Grannie think of her tablets now?

by

Professor Kenn Raymond

It was the worst of times, it was the best of times, it was……

The 1950s

Was it really the worst of times? The best? As a young boy growing up in a Northern English town it was, looking back, at least happy! Poor too! As kids, unlike the children of today, we could play happily unsupervised in the street. There was no need for 'Neighbourhood Watch'. We drank water directly from the tap - no need for bottled water. Even worse – we rode our old fashioned bikes without using a 'stack hat'!! We were chastised by our parents and rebuked by the police and teachers. In turn we respected them. We played and got dirty – no sanitised play groups nor Occupational Health and Safety issues for us! Everyone's door in my street was open to all, no locked doors; we just wandered in if we had problems. So many differences then compared to now!

Sure, health was an issue then. We queued for ages to see the local doctor, in waiting rooms where we had chances of contracting even more germs from the snivelling masses. But at least we got to see the doctor the same day. The doctor was the father figure. After the consultation (free!) we were given bits of paper called prescriptions, hand written in Latin, that we took to another stalwart of the town, the pharmacist.

He, (and, in the main, pharmacists and doctors, in those days were males) was an intent person, mysteriously producing mixtures or pills that had, looking back, minimal therapeutic activities. Penicillin and the sulphonamides had been discovered, and antimicrobial resistance wasn't a big problem. The pharmacist told us how to take the mixture. And that was it. No discussion, in fact the pharmacist then was prohibited from giving information about the prescription to the patient. No additional information, no Consumer Medication Information Leaflets, no web information sheets. This was the age of 'Secundum artem' – let it be made. We took the mixture because we were told to! We complied because it was expected!

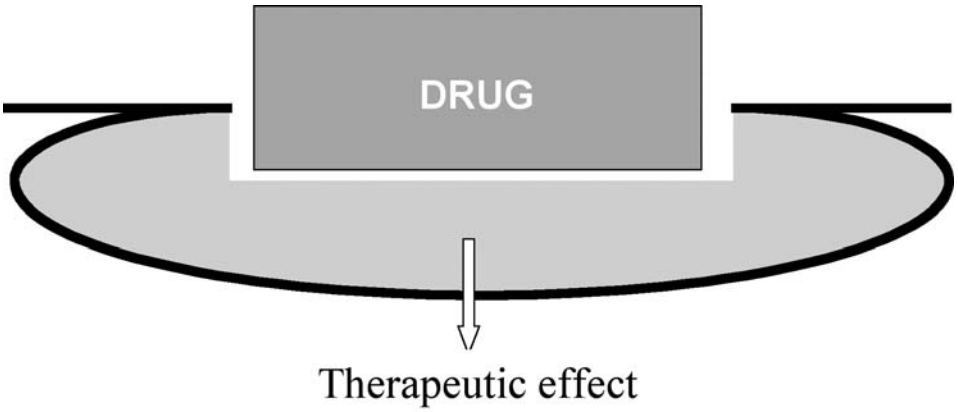
My dear old Grannie, Betsy Raymond, told me as a young child, of the scourges of ill health when she was young. Polio, smallpox[1], TB, and high child mortality were endemic, plus she listed the tens of young men who never returned to her small village after World War 1 and how her son, my father, was so lucky to be gassed at the battle of the Somme and came home early! How appendicitis and peptic ulcers, even tonsillitis, were very serious diseases and had high surgical risks.

In that era, the 1950s, drugs were not associated with the popular street connotation that they are today. So for the rest of this talk I will mainly refer to drugs as medicines: Drugs (the 'street drugs') being one of the problems of modern society. Hence, a definition of a drug, as Fleming and Florey would define penicillin, was that it was a chemical that altered the physiology of the body and helped cure disease. The 'drug' was, in the 50s, known to act at (one or more) receptors in the body, changing the function of the cells and exerting a therapeutic effect. Figure 1 shows, in the top panel, the preliminary ideas of those times, what was known about how drugs acted on receptors. Later discoveries in our knowledge of receptors are presented beneath this diagram of the 'old receptor', also in Figure 1. Note the changes!!

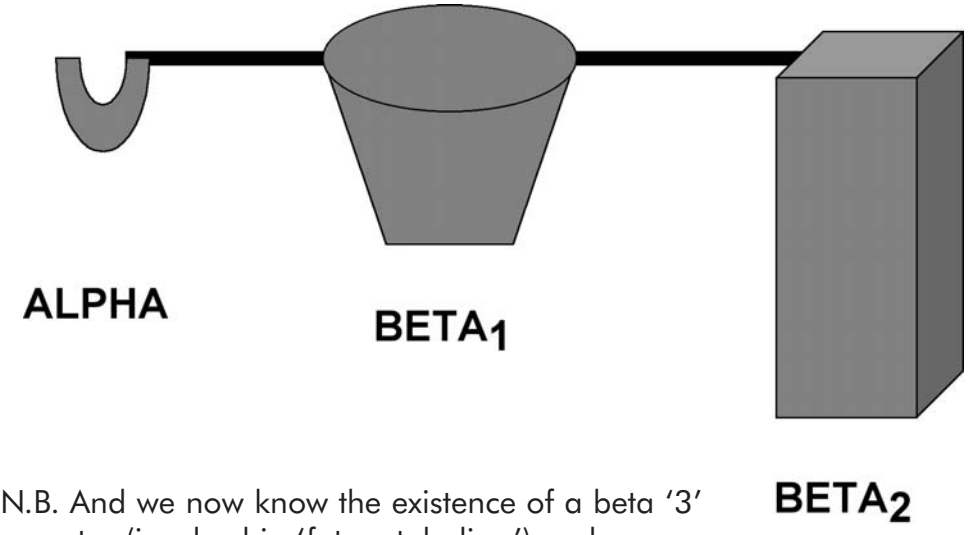
[1] Possibly smallpox was not endemic, maybe Grannie (or me) got that wrong. It was eradicated in 1979.

Figure 1 Ideas of receptors where drugs bind to the tissue receptors and exert a therapeutic response.

From about the 1950s:



From about the 1960s and 1970s:

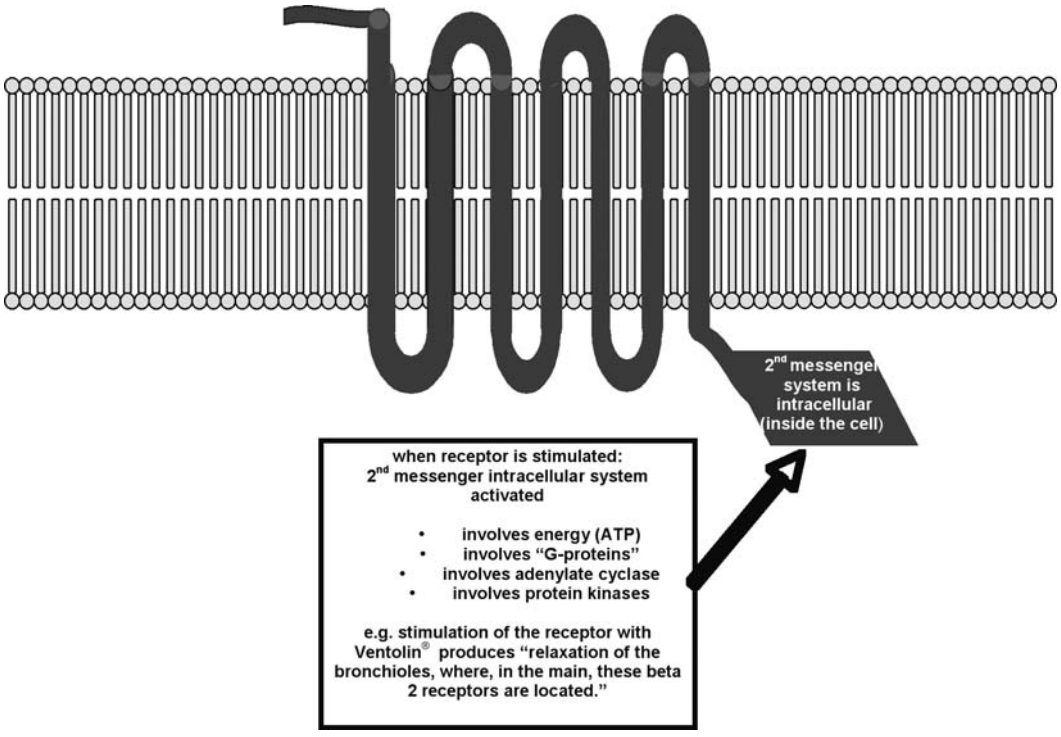


N.B. And we now know the existence of a beta '3' receptor (involved in 'fat metabolism') and we can subdivide up different receptors, e.g. we know about the alpha 1 and alpha 2 receptors. And subdivide these again e.g. alpha 1a-c.

Nowadays (the 2000s) (A typical beta receptor)

The receptor, 7 filaments, is located both within and outside of the cellular membrane. The amino acid characteristics of the membrane are well characterised. The receptors are dynamic; increasing or decreasing in number and/or sensitivity. Activation of the receptor by a drug binding with the outside cell membrane receptor portion results in conformational changes in the receptor(s) that activates secondary messengers, which, in turn, result in changed activity of the cell.

A good example of a drug stimulating the beta two receptor is salbutamol (Ventolin®). Stimulation of the receptor by the salbutamol causes changes in activity in the cell and opening up of the airways occurs (bronchodilation and this results in easier breathing for the asthmatic). However too much Ventolin® and the receptors down grade, in sensitivity and number and so the effectiveness of the Ventolin® becomes reduced. (Hence, for those asthmatics who need them, other medicines, such as inhaled corticosteroids (e.g budesonide, (Bricanyl Turbulaher®), fluticasone, (Flixotide®))and other preventive drugs, such as salmeterol and eformoterol (Serevent®, Seretide® and Foradile®, etc) are absolutely necessary). Needless to say, drugs that BLOCK the beta one receptors, which are situated mainly in the heart, e.g. beta blockers such as atenolol (Tenormin®) will decrease the cells activity (e.g. reduced heart rate with beta blockers so resulting in reduced blood pressure and less anginal pain).



But in the 1950s, what medicines were available? During the 1950s drugs such as cortisone, rauwolfia (for hypertension, and obtained from a plant), the anti-TB drug isoniazid and meprobamate (the first anti-anxiety drug/anti-depressant) were introduced. Chlorpromazine (with its large number of pharmacological actions, hence its brand name 'Largactil®') would be introduced later. For heart failure we used digoxin, originally discovered by Withering from the foxglove plant, *Digitalis purpurea*, in 1795, (and plants were still major sources of many drugs in the 1950s), and the tablets of digoxin would have a typical formula shown in table 1.

Table 1 'Typical' formula of a tablet. for example, say of digoxin tablets (Lanoxin®)

Drug (Digoxin)	0.125mg	(i.e. one eighth of a milligram!)
Calcium sulphate	100mg	
Sta-Rx starch	20mg	
Microcrystalline cellulose	20mg	
Dicalcium phosphate	12mg	
Sterotex	5mg	
Guar gum	15mg	
Ethyl cellulose	q.s.	
Colloidal silica aerogel	1.5mg	
Avicel PH101	30mg	
Solka-Floc BW 40	10mg	
Colour (FDC Yellow #6)	1.5mg	

AND (different) MANUFACTURERS ARE FREE TO CHOOSE WHICHEVER EXCIPIENTS THEY LIKE..... provided the final product complies with (the then) current standards.

q.s. = quantum sufficit.. 'enough'

Note that one part of digoxin has to be mixed absolutely uniformly with about another 1600 parts of the tablet[2]. During these times reasonable analytical techniques were used to check the purity of the drugs; what was not fully recognised was that these (100% pure) tablets might not work correctly.

[2] Try shuffling 30 packs of playing cards and getting the ace of spades right in the middle of the packs!

The 1960s

The therapeutic revolution was probably beginning. The idea of receptors for drug activity was expanded – classic work by eminent pharmacologists such as Gaddum and Dale showed that adrenaline acted on more than one receptor – the alpha and the beta receptors (middle part of Figure 1). This led to the development of a group of drugs called the beta blockers. Originally Eraldin®, Inderal®, and Trasicor® were marketed. As with many drugs, after marketing, a series of side effects became apparent that were maybe not fully recognised during clinical trials, and Eraldin® was withdrawn later in 1976. At this time we were beginning to recognise more completely, that drugs need to be dosed correctly to obtain levels of drugs in the blood stream that were within a defined therapeutic range; it being well recognised that some drugs were ineffective if not optimally administered. This led to a subject in pharmacy being taught called pharmacokinetics. A good example of how medicines could still be manufactured apparently correctly, and yet not exert their expected therapeutic effects, had been recognised eons earlier by the famous 'Father of tropical medicine' Frederick Manson.

As long ago as the1880s Manson wrote

> *"pills and potions of Quinine are not to be trusted since they are apt to pass into the bedpan unaltered"*
>
> *Manson's Treatise on Quinine 1882*

But why is this? What happens when we swallow a tablet?

Firstly, the majority of tablets are especially formulated so that on contact with fluids in the stomach and gastro-intestinal tract they break open (disintegrate). So, after swallowing the tablet it moves down the gullet (oesophagus) and enters the stomach. (That's why we really should wash some tablets down with lots of water so they don't lodge in and irritate the oesophagus, particularly the Fosamax® tablets, alendronate). In the stomach, which is 'churning about and mixing food quite nicely thank you', the tablet breaks into small granules that then have to dissolve, and it is only this dissolved drug that can pass across the membranes of the stomach and small intestine (gut) and get into the blood stream and so exert an effect, often by binding to a receptor.

So if the tablet doesn't dissolve, it doesn't get absorbed into the blood stream. Hence, possibly, non-optimised activity. This amount of drug getting into the blood stream is called bioavailability. Consequently the

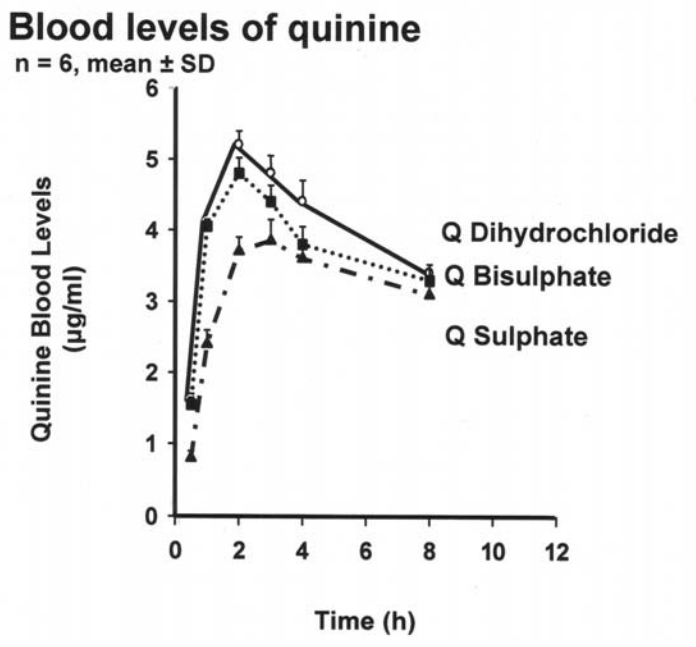
greater the solubility of the drug, often the better its levels in the blood stream and maybe the better its action.

Figure 2 shows some early research with different salts of quinine. The greater the solubility (Table 2) the higher the plasma levels. From this early research we could, in the '60s, safely say, with great respect to Mobil Oils (where 'all oils ain't oils'), that 'all tablets ain't tablets.'

Table 2 Different salts of quinine have different solubilities.
The hydrochloride salt has the highest, the sulphate the lowest. This affects how the drug dissolves and thus the resulting blood levels.

Salt	Solubility (water, 37°C)	Stoichimetric Equivalent
Dihydrochloride	1 in 0.5	105
Sulphate	1 in 810	103
Bisulphate	1 in 8	145
Base	1 in 2000	100

Figure 2: Blood levels of quinine following the different administration of specially prepared quinine tablets from three different salts. Note that as expected the highest blood levels and possibly the greatest efficacy results from the most soluble salt.

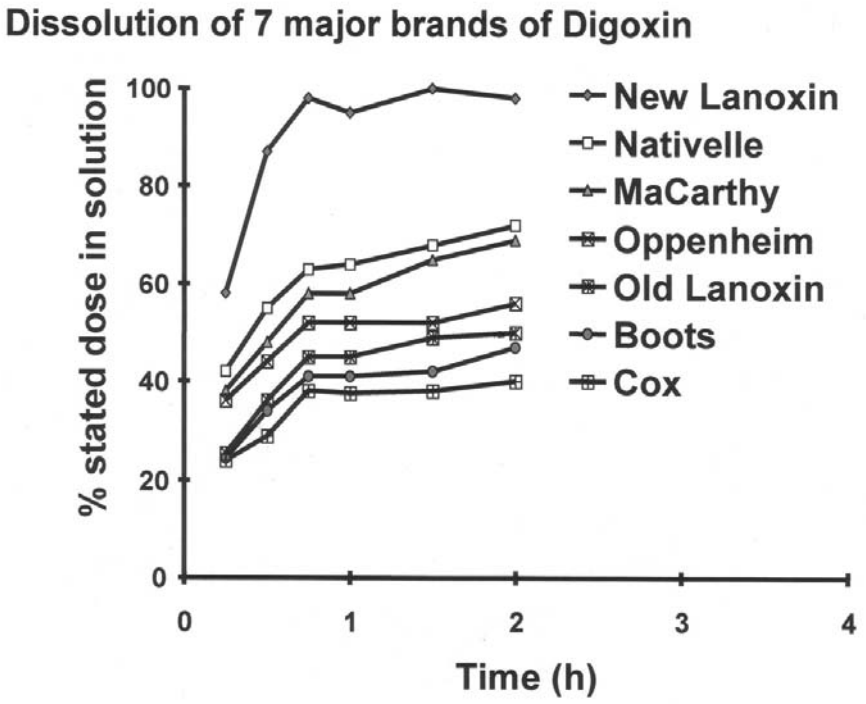


For quinine, this perhaps didn't matter too much? Cinchonism could occur with high blood levels of quinine yet it was probably unlikely to kill anyone. However, the heart drug digoxin is a different drug altogether!

The 1970s

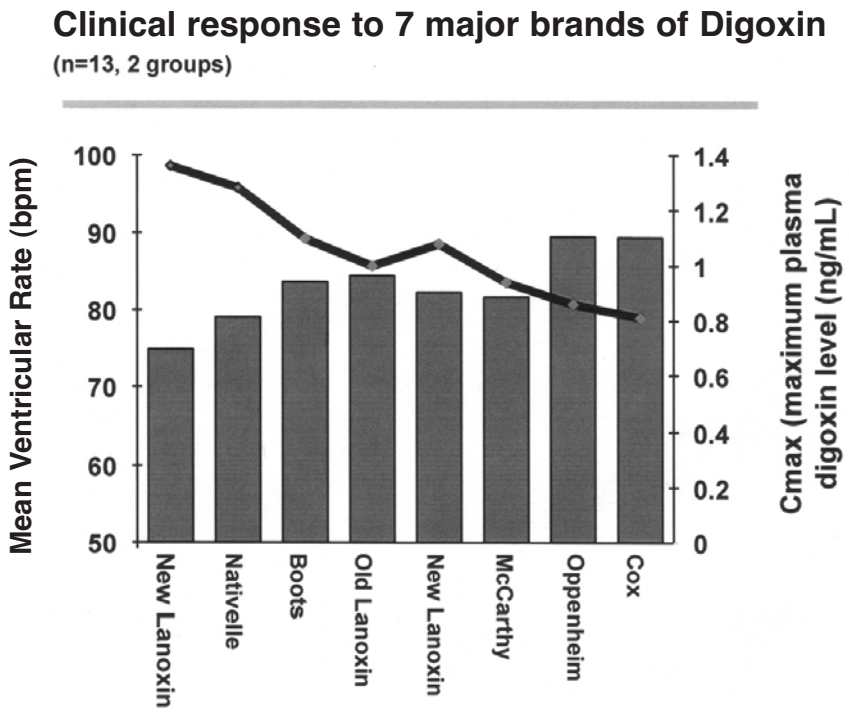
On Wednesday, August 2nd 1972 in the UK, the popularist newspaper the Daily Mirror splashed the headline (on the front page!) "Doctors Warned of Dangers in Heart Superdrug". What had seemingly happened was that a British pharmaceutical company (Wellcome) had changed the manufacturing process for their digoxin tablets. They had probably increased the milling (grinding) of the drug and changed the mixing process. As a result the bioavailability of the drug increased, since it now dissolved more quickly than previously. Although, as far as can be ascertained, no patients taking digoxin for abnormalities of heart rhythm and/or heart failure died, the problem was immense in that patients had to be re-stabilised on the dose of digoxin. Furthermore, different brands of digoxin, from different manufacturers, varied. As long as the tablet contained the correct amount of drug then the regulatory authorities at

Figure 3: Different dissolution profiles of digoxin tablets available in the UK in the 1970s. Note that the (then) New Lanoxin® dissolved far more quickly than the other tablets tested. The old formulation (Old Lanoxin®) was quite similar to other tablets but only dissolved about 50% that of the New Lanoxin®. Even within the other brands of "old" tablets there were marked differences in dissolution, the Nativelle brand dissolving 2xs that of the Cox brand.



that time, considered the drug to be 'OK'. But this was not the case. Different tablets did indeed have different effects. Figures 3 and 4 show some of the research that we carried out in conjunction with Guy's Hospital and the British Pharmacopoeia Commission. As a result of this we now have a 'Dissolution Standard' for several drugs, particularly those that have a small therapeutic range. For digoxin, 70% of the stated dose must be in solution under standardised testing procedures and this standardisation helps make sure all drugs now act the same! These dissolution standards, based on an American test, that we helped create in the UK were subsequently adopted by drug authorities worldwide, including Australia, and now we are satisfied that generic drugs marketed in Australia have equivalent bioavailability.

Figure 4: Effect of different brands of digoxin on the patients' heart rates. (Digoxin reduces heart rate). Note that New Lanoxin® decreased the heart rate the most. That is, these formulations were NOT therapeutically equivalent and depending on what brand was used different effects would be experienced by the patients. THIS IS NOT SO IN AUSTRALIA TODAY WHERE ALL GENERIC DRUGS ARE TESTED AND COMPLY FOR THIS 'BIOEQUIVALENCE'.
Note that the higher the dissolution, the greater the decrease in heart rate (Black line)



The 1980s/1990s

Pharmacokinetic research continued at a great pace in an effort to describe mathematically what happened to drugs in the body. Table 3 shows a very elegant study that my Masters student completed in conjunction with the PANCH hospital. Generally, if we carried out prospective (in the future) pharmacokinetic monitoring and worked out new doses in a pharmacokinetic manner, then asthma patients did better than standard medical care.

Table 3 Effect of pharmacokinetic monitoring on patients' responses in asthmatics.

Patient stay
- mean patient stay in pharmacokinetic group 6.3 days
- mean patient stay in 'control' group 8.7 days (p=0.029)

During IV infusions
- 37.8% patients in toxic range in control group
- 18.9% in pharmacokinetic monitored group (p=0.04)
- 71.1% of levels in therapeutic range in pharmacokinetic group
- only 44.4% in control group (p=0.018)

Outcomes
- tendency for more rapid improvement in pharmacokinetic group
- PEF normalised more quickly in pharmacokinetic group (NS)
- 2 patients died in control group (both with theophylline levels > 25ug/ml)
- no patients died in pharmacokinetic group
- no serious side effects noted in pharmacokinetic group

Pharmacology advanced in leaps and bounds. Advances in Biotechnology, particularly at a cellular (biochemical) level, meant we were at last beginning to understand how drugs worked inside the cell. With respect to the beta blockers, of which by then about another half a dozen were introduced into clinical medicine, we knew the receptors were not lumps of protein on a cell membrane but, were complexes of molecules of amino acids projecting both in and out of membranes; each linked to in-the-cell (intracellular) activities by a series of secondary messengers (bottom panel, Figure 1). Further discussion of such complexities are well beyond the scope of this lecture!

During this decade, new entities of drugs such as the statins (controllers of lipid metabolism, an example being simvastatin, e.g. Zocor®) were developed. Why did such a drug have such good effects and how was it invented?

The answer lies in the quite brilliant research (by Japanese researchers) carried out in conjunction with drug companies. By now it was well recognised that a risk factor for heart disease (angina/chest pain and heart attacks) was the level of the fats, notably cholesterol in the blood stream. So if the manufacture of the body's cholesterol could be reduced then perhaps we had a 'cure' for heart disease. Biochemical research showed that cholesterol was formed not only from dietary fats but also was made *de novo* in the body by a chemical reaction involving a series of about 11 steps; one of the early (rate controlling) steps being a major reaction involving a substance being produced called mevalonic acid under the control of an enzyme termed HMGCo-A[3] reductase that is, in turn, acting on a substrate called HMGCo-A. If we block this reductase enzyme then the whole cholesterol production line is reduced and blood cholesterol levels will fall (and so the arteries, particularly in the heart and brain, won't get clogged up). But what chemical can do this? Once the structures of the HMGCo-A substrate and the HMGCo-A enzyme, the reductase, were worked out, a molecule was found (strangely enough initially isolated from moulds and fungi, including a strain of penicillin), that was found to bind the reaction more than the substrate itself and so stopped the ensuring production of the cholesterol. And the chemical that did this? Simvastatin did; its chemical structure being somewhat similar to the mevalonic acid and the HMGCo-A substrate! That is, the statins block the enzyme because they were made to be similar to these two chemicals![4]

And this approach of finding chemicals that will bind to enzymes and stop the reactions in the body is now successfully pursued by many drug companies. For example, probably one of the best known involves the drug class called Angiotensin Converting Enzyme Inhibitors such as ramipril (Tritace®), lisinopril (Prinivil®), enalapril (Renitec®)[5]. In this case the medicines bind specifically to the enzyme ACE, inhibit it and so help bring down the blood pressure with hardly any interference in either other parts of the body or with the patient's Quality of Life. Very clever!

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[3] 3-hydroxy-3-methylglutaryl-Co-enzyme A for those who want to know!!

[4] But that's only (the major) part of quite a complex story. Statins have also other effects – see your friendly pharmacist for further details! Ask them about HDL and LDL, and apolipoproteins, plus reverse cholesterol transport!

[5] The oldest ACE inhibitor captopril (Capoten®) has probably been superseded by these newer drugs – they are more potent and seem to work better probably with fewer side effects. A good example of the pharmaceutical industry's ingenuity in pursuing great research.

And so on to designer drugs!! No I don't mean the back street chemists who make the 'speed', ecstasy (MDMA/ADAM), the 'China White', 'Tango' and 'Cash', and 'Goodfella', 'ice', 'angel dust', 'snow', MPPP, PEPAP, 'love and MDA' and so on. These drugs, as we will see, are also designer drugs but are outside the remit of this talk.

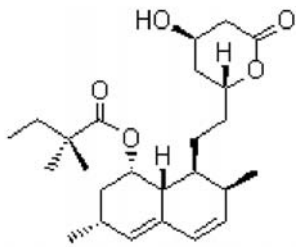
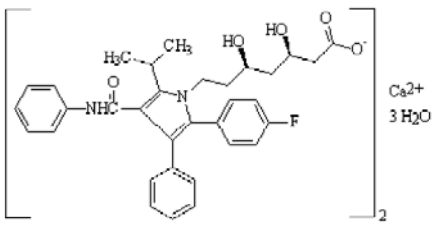
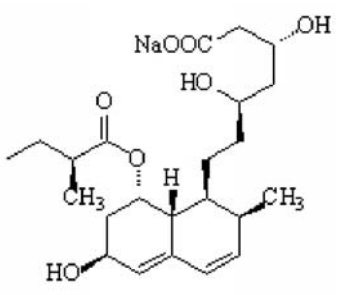
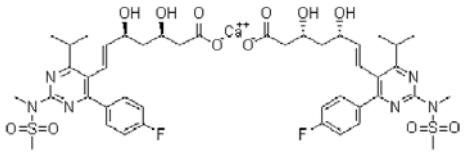
We can easy define 'designer drugs'… as being drugs produced by a minor modification in the chemical structure of an existing drug, resulting in a new substance with similar pharmacological effects. So soon after simvastatin was marketed several more statins came on the market. Medicines such as Pravachol® (pravastatin), Lipitor® (atorvastatin), Lescol® (fluvastatin) were introduced. Some fell by the wayside due to toxicity (cerivastatin), while other new drugs still await entry into the Australian market, e.g. rosuvastatin (but this is readily available overseas).

Why so many statins? Do any have real advantage over the others? How do they differ? Basically, and this is where the designer drug bit comes in – we know the major portion of the molecule that inhibits HMGCo-A reductase. Generally, as long as our statin molecule contains this entity, then the rest of the molecule can be modified to produce similar acting medicines with either more intense effects (i.e. 'stronger') or, hopefully, less side effects. This is shown on page 13.

And this type of chemical approach to the design of modern-day drugs is typical. Computers and informatics now play a vital role in the design of new drugs. In the old days the chemists had to think of a structure, work out how to chemically produce it and then actually make (synthesise) it, then test it. Nowadays, drug research is mainly done by 'combinatorial chemistry' and computer designed drug-screens – capable of 'analysing' many thousands, if not millions of medicines per year.

In addition to these advances in chemistry, we were now beginning to understand more of the diseases that we treated. For example, heart failure, a disease in which the heart cannot pump blood forward effectively to meet all the (metabolic) demands of the body, and which had a horrible prognosis, similar to some cancers, was now better understood. Previously we had thought that, if the heart was diseased, any attempt to 'block' the heart, say using beta blocking drugs, was detrimental. Not so. Now we realise that if we use low dose beta blockers such as carvedilol, (Dilatrend®), metoprolol controlled release (Toprol XL®), betaxolol[6] (Betacor®) or

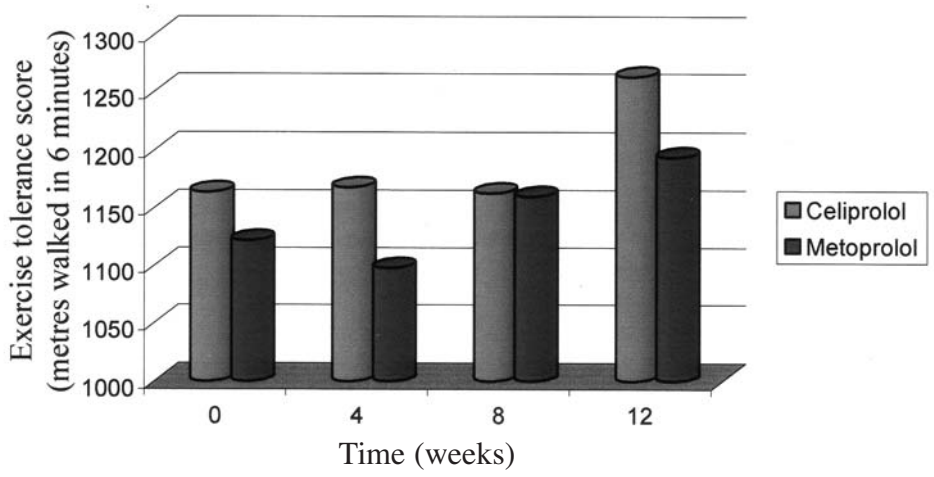
[6] Not available as yet in Australia

Statin	**Molecular Structure** the 'circle' indicates the major part of the molecular from which the activity is derived	**Advantages Claimed**
Simvastatin		The original one – the standard
Atorvastatin		One of the more potent ones. No real need to be taken at night
Pravastatin		No (minimal) interactions with say grapefruit juice. See later.
Rosuvastatin		One of the newest. Quite potent. Must limit dose in Chinese patients.

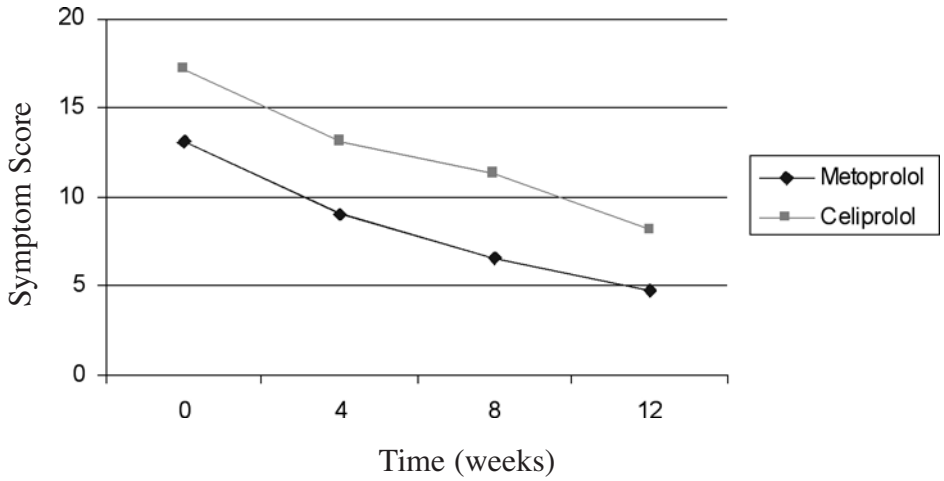
celiprolol[6] (Celectol®) then we can prolong life, even in severe heart failure patients, and increase substantially their Quality of Life (QoL). Some research conducted in Hong Kong shows some features of how metoprolol can be used, initially 'starting low and going slow,' in decreasing patients' symptoms of this debilitating disease. Figure 5 shows details – note the upper panel where symptoms were definitely improved after 12 weeks

Figure 5 Studies with beta blockers in heart failure.
The better the exercise tolerance score the less the symptoms of heart failure

(a) Increase in exercise tolerance for the 2 drugs celiprolol and metoprolol. Both drugs perform relatively similarly.

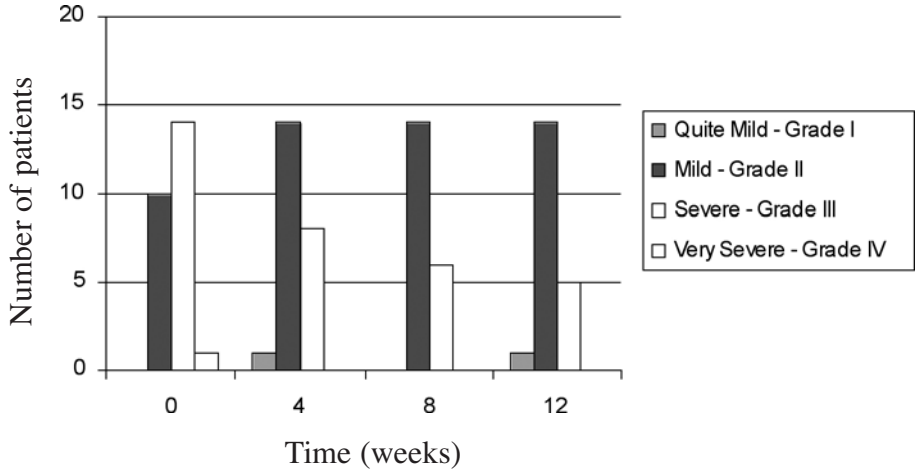


(b) Decreases in symptom scores after 12 weeks treatment with the 2 beta blockers. Note that a lower score equates to better control of the disease.

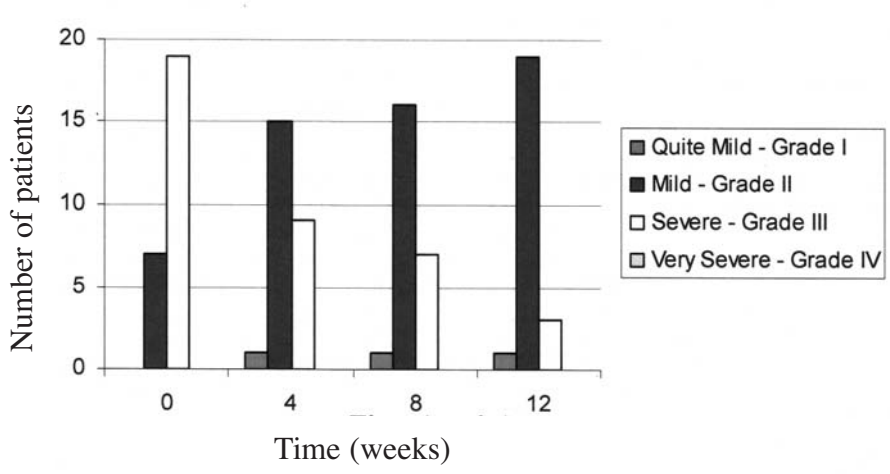


(c) Comparison of the 2 beta blockers over 12 weeks period. Changing status of the patient as treatment proceeds. Note that Grade IV is very severe symptoms (moribund), Grade I the least.

(i) - celiprolol

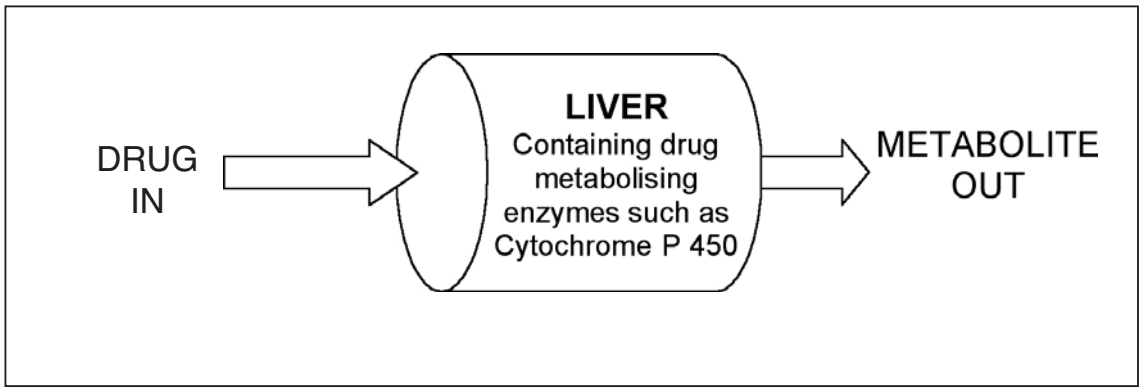


(ii) - metoprolol



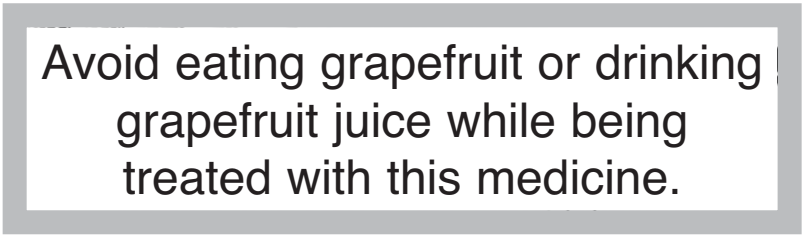
treatment. Thus, what we thought was 'correct' yesterday is not shown to be 'quite true today'. As Grannie would have said, "the more we know, the less we know really" – there is indeed always more to find out.

Equally during these years, research into how the body eliminated drugs was extending newer therapeutic horizons. Originally we had considered that the liver, one of the organs in the body that detoxifies drugs and foodstuffs, was a somewhat simple organ. Indeed pharmacokinetically in the 1970s it was described as a tube; the drug went into the tube (the liver), the drug was acted upon by enzymes (called cytochrome P 450 (CYP450) enzymes) and the metabolites came out of the tube.



What was debated was whether the drug was 'stirred in the tube' or not. A decade or more later this was proved to be an oversimplification. Firstly, the CYP450 enzyme was not a simple entity. It had many subsets and these were well quantified. These subsets, named 3A4, 2C9, 2D6, etc metabolise different drugs at different rates. (In total hundreds of thousands of substrates can be acted on by these enzymes in the body in over 60 types of reactions.) The products of these reactions/drug metabolism in the body is a change in the original medicine into generally a more inactive, less toxic, drug(s) in humans. Often these enzymes can be markedly influenced by other medicines; the enzymes can be made to either work harder (induced) or inhibited by other drugs. This is why certain medicines cannot be taken together – a good example being that we should not administer the antibiotic drug erythromycin with the statins. The erythromycin blocks the inactivation of the statin by the CYPs and, from a normal dose of the statin, toxicity such as joint pains, kidney failure and even destruction of muscle can ensue. On the other hand, the complementary alternative medicine St John's Wort will induce the liver enzymes, metabolise more simvastatin than usual and lead to ineffective treatment. Of interest is the fact that in the late 1980s a drug interaction with a foodstuff was reported (with quite a bit of sceptism). This concerned a drink such as grapefruit juice that would also induce enzymes and this was clinically significant! In the words of Karl Kruszelnicki "Why should this be so!?" The answer is

that grapefruit juice contains flavonoids (that give the juice its taste)[7] called naringenin, quercetin, naringin, bergamottin and kampterol. These are potent CYP3A4 inducers. That's why simvastatin (Zocor®) is labelled with a warning label.



On the other hand, another statin, pravastatin (Pravachol®) is NOT metabolised by these liver enzymes, not affected by enzyme inducers/ inhibitors and thus doesn't need such a warning label!

Yet the situation is far more complex than outlined above. In the late 1990s we knew that a more potent enzyme inducing medicine, rifampicin (Rifadin®, Rimycin® - an anti-TB drug), affected drug metabolism by changing the activity of enzymes such as CYP3A4. Indeed it was well known that rifampicin could induce its own metabolism. But since it, in turn, also might be metabolised by CYP3A4 (a minor route of metabolism, the drug is mainly hydrolysed in the body), then it will, of course, be altered by other medicines that affect 3A4! An excellent example, thankfully not too common clinically, is when an AIDS/HIV sufferer contracts TB. The anti AIDs/HIV medicines called protease inhibitors eg ritonavir (Norvir®, Kaletra®) will also decrease the metabolism of rifampicin but, in turn, ritonavir's metabolism will be induced by rifampicin! And St John's Wort is certainly not to be used concomitantly with these drugs!

What we found of great interest though was how did grapefruit juice exert its effect? In what we believed was a cutting edge, yet simple, experiment we dosed rabbits, which have similar CYP 3A4 to humans, with intra-venous (IV) rifampicin and measured its metabolism. The idea was that IV rifampicin would, if it acted on the liver, be extensively metabolised. It wasn't. So there must be another site where CYP 3A4 exists/resides. This has been found, by others, to be enzymes in the gastro-intestinal tract; the so called enteric-drug metabolising enzymes.

[7] Seville oranges also contain similar flavonoids – and have recently been reported to interfere with drug metabolism similar to grapefruit. Seville oranges per se aren't seemingly available in Australia.. the marmalade is though! BUT, it'd probably take kilograms of the marmalade to have any effect!

2000 and beyond?

One of the main thrusts in pharmacy research now is called pharmaco-genomics – how our genetic make up influences how drugs 'behave' in our body. Why, for example, does rifampicin induce its own metabolism? In conjunction with my colleague and friend, Dr Jason Chen, we have discovered, mainly from trying to understand the literature in this complex field, that, as mentioned previously, rifampicin's induction of hepatic drug metabolising enzymes is induced by CYP 3A4.

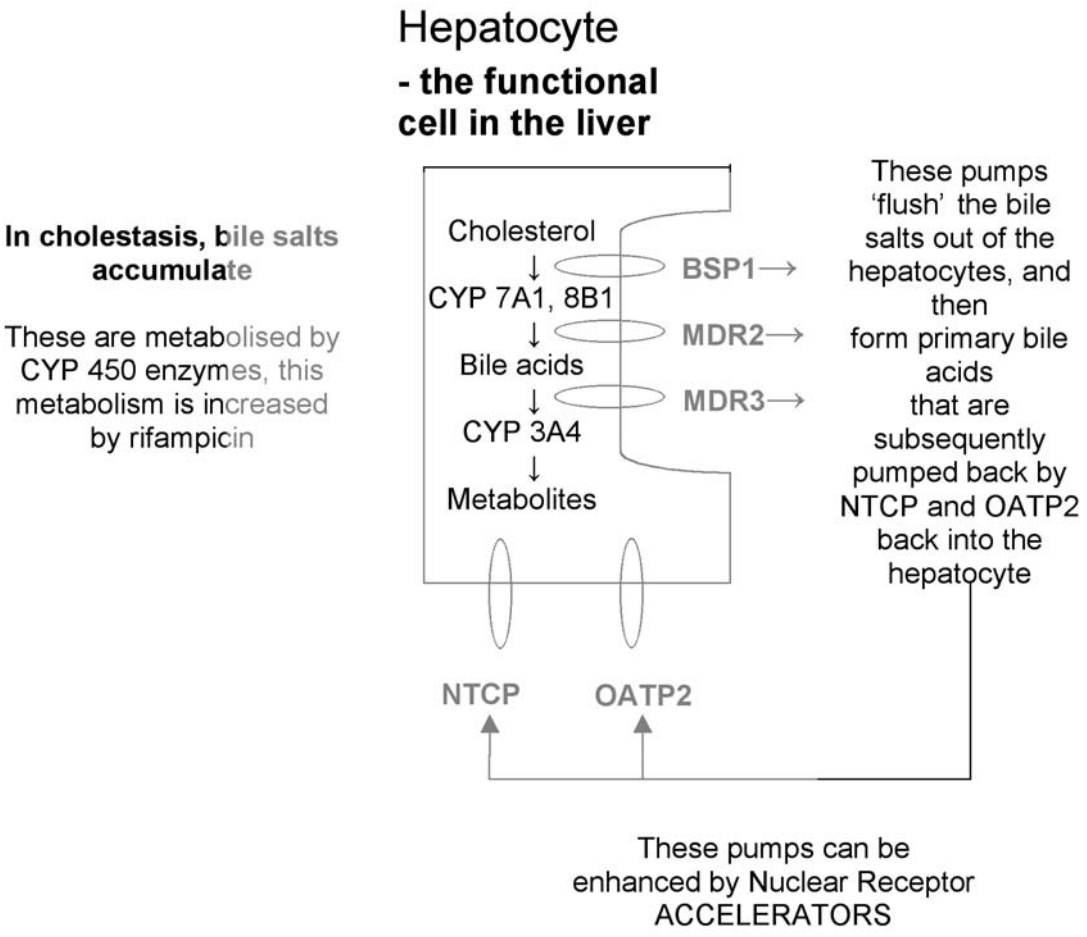
However, modern biotechnology now has shown that the activities of the majority of liver enzymes are controlled genetically. Particularly we know the existence of receptors (called nuclear receptors, NR) on cells (in the case of the liver, these cells are termed the hepatocytes), that control not only how active the drug metabolising enzymes are but we know now that the NR control drug-efflux pumps such as p-glycoprotein and multi-drug resistance protein (MDR1), organic anion transporter (OAT), sodium taurocholate protein (NTCP), multi-drug associated resistance protein (MRP 3 and 4), bile salt excretory protein (BSEP), all of which pump the drug out of the cells. Some of these pumps are very specific for the liver. The nuclear receptors in turn are controlled by at least two other receptors, The Farnesol-X (FXR) and pregnane-X receptors (PXR) we think are at least involved, and these control our genes. When rifampicin enters the hepato-cyte we believe that it binds with at least PXR, possibly CAR, and this complex enters the nucleus of the cell where it forms another complex with RXR (a retinoic acid receptor). This then uses the genes to make more protein that can be assembled into the transporter pumps and so increase the exit of drug from the cell through p-glycoprotein, OAT, BSEP, NTC, MRP, MDR, as well as inducing the enzymes responsible for normal metabolic activities in the liver[8]. Figure 6 shows a simplified diagram of what might be happening.

So what is the value of all this knowledge? How can this knowledge and understanding of drugs assist patients? To me, the answer is that it must be applied to assist humans and to treat disease. Equally since rifampicin affects the liver, can it assist in curing some liver diseases? Amongst the myriad of liver diseases, cholestasis (blockage of bile in the liver) is quite a difficult medical problem to solve. Although cholestasis has many causes it often produces high morbidity (and occasional deaths) in patients; they

[8] If you have understood this far, please give yourself a bonus!!

Figure 6 A diagrammatic representation of the functional liver cell, the hepatocytes.
Note the idea of many 'receptors' on the cell surface – compare with Figure 1 (the 'receptor of the 1950s').

Most, if not all, of these surface proteins on cells are genetically controlled. In the diagram below the receptors are, in turn, controlled by nuclear receptors, CAR, PXR.



Because the roles of the pregnane X and farnesol X receptors are complementary, their inducers might have synergistic effects. Indeed, the pregnane X-receptor agonist rifampicin used with the farnesol X-receptor inducer ursodeoxycholic acid has been shown to have complementary effects in a clinical trial in 30 patients with gallstones. However, 6ECDCA and GW4064 are more potent farnesol X-receptor inducers. Thus the combination of rifampicin and 6ECDCA or GW4064 might reduce or even normalise bile-acid concentration, leading to curable cholestasis.

generally present with lethargy, severe itching (pruritis, which can be described by affected patients as "maddening at times"), maybe jaundice, insomnia, derangement of fat metabolism and high lipid levels, failure to thrive in infants, and, if associated with pregnancy, an increase in still-births. Modern-day therapy is not brilliant. Itching often can only be partially relieved and the drugs we use are not too effective. Ursodeoxycholic acid (Ursofalk®) (aka 'Urso') can lower bile salts but often causes diarrhoea. Cholestyramine (Questran Lite®) will bind bile salts in the gut but may also interfere with normal fat absorption and has the propensity to inhibit the absorption of other drugs. Urso is an interesting drug, as we know it acts at the liver receptors (previously mentioned) to increase the excretion of bile salts out of the liver (and so decrease the build up of bile salts in the liver during cholestasis!). Its action here is somewhat weak. If we combine it with rifampicin then its activity is increased. Why? As mentioned earlier rifampicin induces its metabolism (and that of many other drugs), leading to lower levels of drugs. This it does by stimulating the receptor(s) in the liver. We know that the bile salts causing cholestasis are also metabolised by CYP 3A4. So if we increase the metabolism of the bile salts, their concentration in the liver will be decreased. Thus two synergistic approaches to the treatment of cholestasis are possible (Figure 6) and we were honoured to have a paper accepted in the prestigious medical journal *The Lancet* that reported on our ideas. Based on our theory, the best lines of attack are:

1. to decrease the pool of bile salts by increasing their metabolism (and rifampicin does this) and;
2. pump more bile salts out of the liver cells so their concentration in the hepatocytes falls. Urso, and stronger enhancers of the pumps described above can achieve this.

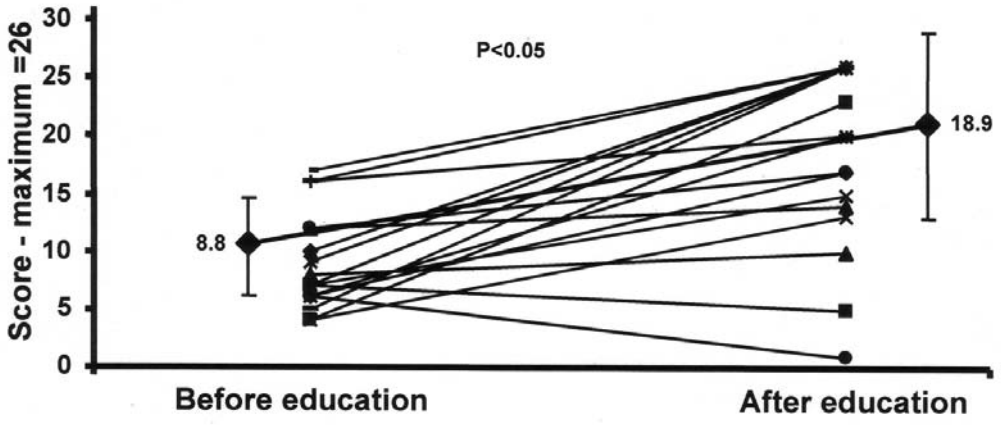
Thus the nuclear receptor inducer rifampicin in combination with the pregnane receptor inducer urso (or stronger drugs such as a new experimental compound, GW4064, or 6ECDCA (6-· ethylchenodeoxycholic acid)) could indeed be much better therapy than we have today. That is, a thorough understanding of how medicines act at the molecular level is nowadays needed to optimise therapy.

But would these advances have helped my old Grannie? Could I have talked to her, say in my pharmacy, of farnesol, OAT[9] and cytochrome P450? No way!!

[9] The only OAT(S) Grannie may have known were *Scotts* (or *Quaker's*) *Porridge Oats*!

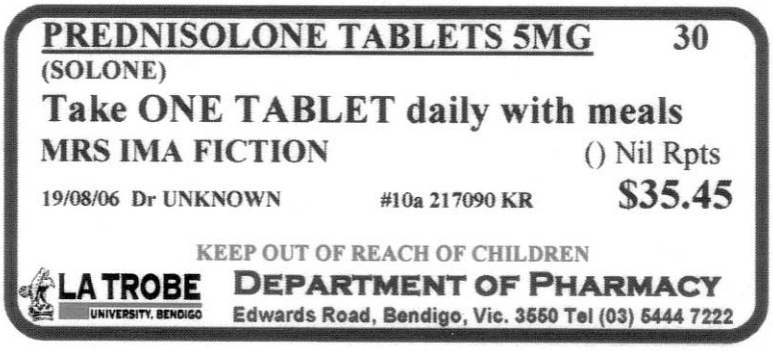
Within our innovative Bachelor of Pharmacy programme some of our very talented and most gifted students carry out additional honours studies in the 4th year of their studies. Our pharmacy practice research has focused on seeing if our patients in Bendigo know much about their drugs, and indeed if they really understand the label on a dispensed medicine. Let's look at diabetes. When asked about the knowledge of a medicine used to treat maturity onset diabetes (Type II, NIDDM), metformin (Diabex®, Diaformin®) we found that initially patients had very little knowledge about their medication, but after education by the pharmacy student this improved tremendously (Figure 7). We are now trying to see if this increase in knowledge and understanding of the drug translates into better control of this ever-increasing disease and a reduction in the problems that result from uncontrolled diabetes.

Figure 7 Influence of education by a pharmacy student on Type II (NIDDM) diabetics taking metformin.
Initial score (out of 26) was about 9, after education this rose to 19. Initially, before education the results were disappointing – patients knew little about this important medication. Research now under way will show if this increased knowledge leads to improved therapeutic outcomes and control of the patients' diabetes.



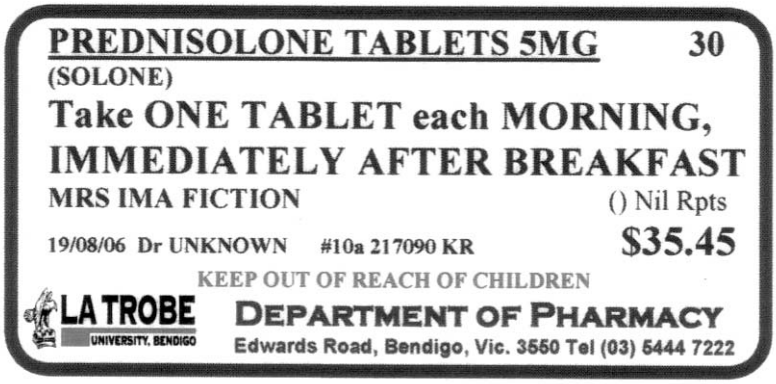
Each line represents an individual patient. Most patients increased their knowledge after education, two did not!

With respect to patients reading the labels on dispensed medicines, we were astonished to learn that the label below (surely words that are simple to understand by any health care professional!!)



can easily be misunderstood by the patient and THREE tablets taken daily, ONE WITH EACH MEAL! (With maybe disastrous consequences if the medicine is somewhat toxic and only to be taken once a day!)

Surely a much better label would be:



And is this the best label, the most readable? We have just commenced a new project in which we will try and improve these 'good English' labels, particularly in designing newer 'cautionary and advisory' labels – those multicoloured ones that pharmacists place on your box of dispensed medicines!

Hence, even all the good, state of the art, cutting edge research alluded to above needs to be put into the context of not only what the patient needs to know but also what the patient wants to know. Even fantastically new, expensive, life saving drugs still need good old fashioned patient counselling!

Conclusions

It is now almost 40 years since Grannie passed away, and the likes of her generation we will not, regrettably, see again. What would she make of all these advances? I believe that Grannie would indeed go "wow" in wonderment at the drugs and medical practices today. (Please note the deliberate use of the 'W' words!).

So, in 2006 et seq, are we better off than in the 1950s? My baby boomer generation has beget the 'X' generation. Another new generation of their kids is now entering this University – I call them the 'W' generation. They want the latest and best, they want it now and can't or won't wait! Their medical needs and expectations will be much higher than mine[10]. In my lifetime I have witnessed great advances in medicine and pharmacy. Generation 'W' will, in their lifetime, also experience great leaps; human embryo cloning will, in my opinion, occur, monoclonal antibody treatment will be 'normal', gene therapy and stem-cell therapy will cure diseases that we presently can't, transplantation of organs will be 'easy', antibiotics will have outlived their usefulness since antibiotic drug resistance will be rife (maybe our only major hope there will be genetically modified bacteriophages?). However, longevity will increase!

What is sure, in my mind, is that the need for information for the optimum use of medicines will continue unabated. Information that only well trained, personable, caring pharmacists and health care professionals can provide. Since nothing is so sure as change[11], the future generations of pharmacists will witness a wonderful world of technologically brilliant advances. Their challenge will be to deliver old fashion care, much as the caring pharmacists did in the 1950s. Care, coupled with a thorough understanding of the science of medicine, plus an ability to communicate this to the patient will, in the future, be the keywords for success.

Based on my experiences of the 'super' students here in the Pharmacy programme at La Trobe University, I believe generation 'W' has this ability. If they do indeed deliver what they promise, if they can show they care, then we can indeed safely say that the future "will be the best of times"!

[10] Whether the PBS can afford it is another question!
[11] And death, and income taxes!

The author thanks, with deepest gratitude, the following:

Wifey, the bears and pud-cat, and our kids

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Plus all the wonderful undergraduate and postgraduate students in pharmacy, my friends, pharmacists, medical practitioners, and academics I have had the pleasure to have known and worked with.

Pharmacy has indeed been good to me.

The Worner Research Lecture

The Worner Research Lectures form a series of public lectures at the Bendigo campus of La Trobe University. The aim of the series is to publicise research carried out at the Bendigo campus.

The University is proud to be associated with the Worner brothers, Howard, Neil and Hill, who were students at Bendigo School of Mines, a forerunner of La Trobe University, Bendigo. The three brothers were raised on a farm in the Mallee. In the early 1930s, they studied at Bendigo School of Mines: Howard for a Diploma of Industrial Chemistry, Neil for a Diploma of Civil Engineering, and Hill for a Diploma of Industrial Chemistry. All three brothers later won prestigious scholarships to Melbourne University.

Howard Worner's distinguished career in academia and industry led him to an honorary professorship at the University of Wollongong and position of Director of the Microwave Applications Institute. He was a recipient of a Centenary Medal issued by the Federal Government and was also the first non-American to win the Benjamin F. Fairless Award, the most prestigious award given out by the international steel industry. In 1994, La Trobe University conferred on him the degree of Doctor of Science (honoris causa).

Neil Worner went on to a career in civil engineering, including the job of Chief Civil Engineer with the Snowy Mountains Hydro-Electric Authority. His career continued in senior and advisory capacities in Australia and overseas on projects such as the design and construction of major dams. Neil is currently a resident of Bendigo.

Hill Worner's career included several years on the Executive of the CSIRO, and twenty-two years as Professor of Metallurgy and three as Dean of Engineering at The University of Melbourne, later being awarded the position Professor Emeritus in Engineering on his retirement. Sadly Hill passed away in 2002.

The Worner Research Lecture Series

Lecturers in the series so far have been the following:

1995	R. J. Seviour, *Micro-organisms: the Good, the Bad and the Ugly*
1996	T. M. Mills, *Join the Dots and See the World*
1997	Howard K. Worner and R. Findlay Johnston, *Bendigo Gold: Past Present and Future*
1998	John Humphreys, *Rural Health and the Health of Rural Communities*
1999	Vaughan Prain, *Learning in School through New Technologies*
2000	Bruce Johnson, *Soils: Our Interface with the Environment*
2001	Jill Francis, *I Would be Good, I Should be Good, but gee, oh gee oh gee: The development of a psychological theory*
2002	Ruth Endacott, *Developing Clinical Wisdom: a Challenge for Academia and Health*
2003	Roger Sworder, *Is the Poetry of Homer Philosophical?*
2004	Rhett H. Walker, *On the Value of a University - A Journey of Discovery*
2005	Hal Swerissen, *Health and Ageing in 2025: the 'boomers' go grey*