

Seminar: NEW MODELS OF PRIMARY PREVENTION

CONTRIBUTION OF PHARMACEUTICAL PRODUCTS

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Professor Leeder has asked me to consider with you the contribution that pharmaceutical products are making, and could make to primary prevention of disease. (I am not associated with any pharmaceutical company).

This challenging topic was perhaps stimulated by Wald and Law's ingenious suggestion of a Polypill (1) that everyone 55 years and over could take to reduce (or delay) cardiovascular disease (CVD). It would have 6 ingredients: a statin, three blood pressure-lowering drugs each at half dosage (a thiazide, a β -blocker and an ACE inhibitor), fifthly 75 mg of aspirin (an anti-thrombotic dose, 1/4 the usual analgesic tablet) and 0.8 mg of folic acid, which lowers plasma homocysteine that appears from observational epidemiology to be a risk factor for CVD.

The Polypill suggestion caused much interest and discussion because Nick Wald is an outstanding professor of environmental and preventive medicine. It was he who planned and directed the British MRC international trial that gave the definitive proof that folic acid prevents neural tube defects (2).

Here then we could start with a pharmaceutical product, first synthesised at Lederle in 1948. Neural tube defects are today being routinely reduced with folic acid, either taken as a tablet periconceptually or put into some of the staple foods. This fortification is a mandatory addition to cereal foods in N. America, at present voluntary in ANZ, but mandatory folic acid in all our bread is this month proposed by our Food Standards authority.

Incidentally, folic acid is the only ingredient in the Polypill that we'd have a hope of getting in the food. This is because it's a vitamin, though neural tube defect is not a classic nutritional disease.

There were 94 letters about the Polypill article (and editorial) on the BMJ's website, with a wide range of reactions. One doctor wrote that old people are often on multiple medications, taking all or most of the components of the Polypill. These have been, slightly cynically called "Gerifix" and "Gerifix Forte" – and they seem to do some good overall. But most of the correspondents presented a number of reservations and concerns. Most were technical, some ethical.

The most obvious set of reservations is that, even if people take it, the effect of the components may not be additive and there may be more side effects (eg bleeding from aspirin) than Wald and Law estimated. Substantial clinical trial(s) are obviously essential, and not only in people at obvious high risk of CVD. The expected benefit of folic acid on CVD and dementia may be premature (on going trials indicate) (5,6). On the other hand the aspirin might prevent some colorectal cancers.

Other doctors wrote that doctors treat individuals and it is better, as at present for doctors, clinicians/physicians to prescribe and monitor drugs for prevention which are believed in type and dose to be suitable for the individual. This happens now to a varying extent. There are other pharmaceuticals being prescribed for prevention that are not in the Wald & Law Polypill, such as fish oil capsules, bisphosphonate, calcium and vitamin D to prevent osteoporosis, finasteride to reduce benign prostate hypertrophy, etc.

The Polypill concept was endorsed by Professor Lawrence Green – leading professor of health promotion - (3) at an international workshop on nutrition communication and family doctors in the Netherlands (that I edited). He is most enthusiastic. His article ends "Nothing else we have designed as an intervention could make such a large difference in so many lives". He thinks health promotion professionals, who are inclined to be anti-technology need to prepare for the arrival of combination of pharmacotherapies to prevent chronic diseases. "The Polypill is almost certainly coming soon in some developing countries, notably India..."

I agree with Lawrence Green that the time is passed when we can cheerfully ignore pharmaceuticals and devices to keep us healthy for longer. We rely on oral contraceptives and spectacles. My two main problems with the Polypill are that no combination of 6 drugs is

going to be right for everyone. We are in an era of genomics, including pharmacogenomics. People don't respond to drugs the same way, either in therapeutic benefit or adverse effects. Secondly, if much CVD is prevented we shall be more likely to have cancer or Alzheimer's in our last years – perhaps worse options.

Only last month Milton Weinstein (Health Policy, Harvard) with an epidemiologist and an expert on CVD in Africa (7) published (in the Lancet) Markov model analysis of aspirin, two anti-hypertensives and a statin (they'd thrown out folic acid and the most expensive anti-hypertensive). They estimate that this combination could be cost effective even in developing countries (in India pharmaceuticals are produced much more cheaply) for older people at high risk of CVD (found by screening).

But pharmaceuticals are not only useful for preventing CVD. This role is relatively recent. I'd like to have a quick look at the usefulness of individual pharmaceuticals in preventing the different major diseases.

INFECTIOUS DISEASES

In developed countries most of the serious infectious diseases have been primarily prevented by vaccines which are, of course, products of the pharmaceutical industry. Vaccinations have particularly reduced children's deaths and illnesses in older people. They also prevent us, when tourists, from serious illnesses in developing countries. It's perhaps surprising how long is the list of vaccines used in Australia – 15 or more. Paradoxically the earliest of them, vaccinia (cowpox) to prevent smallpox (Edward Jenner, around 1798) is no longer used, though older people here have been vaccinated.

Diphtheria	Haemophilus influenzae B
Pertussis	Fluvax
Tetanus	Pneumococcus
Poliomyelitis	Meningococcus
Measles	Hepatitis A
Mumps	Hepatitis B
Rubella	BCG (Tuberculosis)
Varicella/Zoster	Typhoid

Cholera

Yellow Fever

Q fever.

DENTAL CARIES

This is perhaps the oldest example of chemical primary prevention of chronic disease. Adding fluoride (1 ppm) to the drinking water supply started at one place in the USA in 1945. It started in Sydney 38 years ago, in 1968. Professor Noel Martin, who died in July, did more than anyone to bring this about. Two remarkable things about fluoridation are that it was not correcting a classic nutritional deficiency disease – though last year fluoride was classified an essential nutrient in Australia for the first time (8). And it has preserved our teeth and transformed the work of dentists, who had a vision to support a measure they might have thought would take work away from them. There are still vociferous critics of this “mass medication” and when they become too noisy we have a duty to state clearly that this is one of the great triumphs of public health. Today we have the battle of the bottles. The anti-fluoridationists are urging companies that sell bottled water not to add the fluoride we get in ordinary tap water.

Fluoride is also added to toothpaste, another pharmaceutical involved in prevention.

No only sugars but all fermentable carbohydrates provide substrate for the oral streptococci that produce dental caries. Nutritional prevention, reducing the time that fermentable carbohydrate is in the mouth, is not as effective as fluoridation.

HYPERTENSION

The three demonstrated nutritional ways of preventing high blood pressure (BP) as people get older are (i) salt intake below 6 g NaCl (100 mmol Na)/day (ii) avoidance of overweight/obesity (iii) alcohol intake under around 3 standard drinks (30 g ethanol)/day. I have myself reported (9) a remote hunter-gatherer community in Africa (the !Kung bushmen) in whom we found no hypertension; their urinary sodiums (reflecting intake) averaged 30 mmol/day. Australia was the first country in 1984 to have an official (NH&MRC) recommendation (10) that people should aim to take in not more than 100 mmol sodium (6 g salt) per day. But about 85% of the salt we eat is not discretionary. It's put in the food in the

factory before we buy it. Most is in carbohydrate-rich foods like bread. Industry has largely resisted calls to reduce this salt (which we don't need for food preservation now we have refrigerators) and if people are simply told 'eat less salt' they can't manage to do this with usual diets. With caring support and advice it can work, as Dr Trevor Beard has shown with his "Salt Skippers" (11). Meanwhile in the UK the Food Standards Authority has confirmed the scientific evidence and is leaning more heavily on the food industry than we were able to here.

The NH&MRC also has official advice no more than 2 alcoholic drinks/day in men and one in women for good health (12) and everyone knows by now that obesity carries health risks.

Many older Australians who are not obese and drink moderately have hypertension. They can't manage a low salt diet with our present Australian food supply. For them the offering of pharmaceutical products today is such that most people can run a more or less normal BP with little or no side effects and modest cost.

Five main groups of anti-hypertensives are widely used (there are others). Each has several different products to choose from or try. There are the thiazides (official names end in -'ide'), β -adrenoceptor blockers (names end in 'ol'), calcium channel blockers (names end in 'dipine'), ACE inhibitors (names end in -'pril') and angiotensin II receptor antagonists (names end in -'artan'). If necessary, by combining drugs from two groups the effect on BP can be increased without doubling risk of side effects. Prescription and taking of these in Australia is big. They aren't only used in secondary prevention (of strokes and heart disease) in people with definite hypertension. They are taken by people without symptoms who have been found at routine medical examination to have borderline hypertension – round 140/100.

In Australia, in the list of the top 100 PBS prescriptions for 2004-05 there were over 19 million prescriptions for anti-hypertensives at a government cost of \$385 million for subsidy. And this doesn't include inexpensive thiazides or several β -blockers.

Hypertension is one of the major risk factors for coronary heart disease and the biggest risk factor for strokes. For this the main preventive measure is regular screening measurement of

blood pressure by doctors and if it is raised, the use of these five groups of drugs. Note that three of the components of the Polypill were anti-hypertensives.

RAISED SERUM CHOLESTEROL

About 50 large prospective cohort studies in several countries have shown consistently that high serum total and LDL-cholesterols are associated with increased risk of coronary heart disease events. Until about 10-15 years ago the best way to lower serum cholesterol was with a combination of dietary changes : reduced saturated and trans fat and dietary cholesterol, increased ω -6 polyunsaturated fat, increased soluble fibre, avoidance of unfiltered coffee, weight reduction if overweight. By strict adherence to such a diet people can reduce cholesterol by 25% (13).

The early cholesterol-lowering drugs were unimpressive. Clofibrate (Atromid) probably increased mortality and cholestyramine resin was bulky and unpleasant to take. The statins, which inhibit the first step of endogenous cholesterol biosynthesis have been a remarkable breakthrough. The good ones lower LDL cholesterol by around 20% (14); they are easy to take. Side effects on muscle are seldom a problem (14), except in professional athletes (15) (cerivastatin had to be withdrawn because of cases of fatal rhabdomyolysis). Statins also reduce strokes (16). Atorvastatin is one of the components of Wald's and Law's Polypill. They predict it would prevent 80% of heart attacks, but in the largest meta-analysis of statin trials the coronary mortality was reduced 19% (14) and any vascular event by 21%.

Brown and Goldstein (Nobel Laureates for their work on cholesterol receptors) recently point out (17) that the heart attack rates on statin treatment are somewhat disappointing compared with people who have had the same low cholesterol for more or less a lifetime. "The appropriate consideration may not only be how low, but also how long". Atherosclerosis is a chronic disease that begins in the late teenage years. By the time people go into a statin trial they usually have advanced atherosclerosis. This suggests to me the great preventive potential of a classic Mediterranean or Japanese type diet from the second decade of life. That is, unless people start taking statins when they leave school.

Generic simvastatin is now available over the counter in the UK (18) – a bad decision for public health.

In Australia, doctors are asked to only prescribe a statin for someone who has a serum total cholesterol above 5 mmol/L, repeated (because of within-individual variation) who has tried to follow a cholesterol-lowering diet. The cholesterol (and LDL) response should be monitored periodically and the person checked for side effects. The doctor should look for secondary high cholesterol (eg hypothyroidism) before prescribing and statins are contra-indicated in pregnancy.

There have been a very large number of statin prescriptions in Australia. In 2002 there were over 50 scripts per month (a month's supply) per 1000 (19). Statins cost the Pharmaceutical Benefit Scheme (PBS) more than any other type of medicine. By 2004-05 statins subsidy cost the PBS \$885 million for over 15 million prescriptions.

A group at Imperial College, London found prescriptions per 1000 of lipid regulating drugs (largely statins) rose 5 times from 1996 to 2002, in England but admission rates for myocardial infarction showed very little reduction (20). One would expect from the controlled trials that CHD events start to fall during the first year. Clearly advisers to the PBS will soon have to do a serious cost-benefit analysis.

It may well be that prescription of statins in Australia is not yet well targeted. Stocks et al, (19) noted that more prescriptions were for women and for people in higher socio-economic groups (who have lower CHD mortalities): an example, as they say of the inverse care law, that medical care varies inversely with need.

Increased serum LDL cholesterol is not the only risk factor for CHD. Smoking, hypertension, inactivity, diabetes and central obesity are all important. They are not reduced by taking statins. Omega-3 long chain polyunsaturated fatty acids (fatty fish or even capsules) have separate preventive actions, reducing the liability of the ischaemic myocardium to dangerous arrhythmia and possibly stabilizing atherosclerosis plaques. Omega-3s are more effective in lowering triglycerides than statins. Availability of statins does not mean that the other

evidence-based primary preventive measures like smoking can be relaxed. A cholesterol-lowering diet can improve the effect of statins and MIMS advises that it be continued along with the medicine.

OVRWEIGHT AND OBESITY

For these there are no good medicines like the anti-hypertensives and the statins. The pharmaceutical situation for obesity resembles that for blood pressure and serum cholesterol of the 1960s. Prescription of a medicine for someone with a Body Mass Index of say 27 kg/m^2 (ie overweight) could be thought of a primary prevention of obesity. The question is how often is this done and is it worthwhile? As George Bray (America's leading obesity researcher) put it "the history of drug treatment of obesity is indeed strewn with catastrophes" (21). They appear in older textbooks of medicine:

- Thyroid extract
- Dinitrophenol
- Amphetamines
- Structurally similar β -phenethylamines
- Digitalis
- Diuretics
- Aminorex
- Fenfluramine with phentermine.

Fenfluramine and dexfenfluramine, which had been moderately effective were withdrawn from the market in 1997 because of cases of pulmonary hypertension and cardiac valvular abnormalities that had not been anticipated.

The only drugs now approved for treatment of obesity are orlistat (Xenical) which inhibits pancreatic lipase, and sibutramine (Reductil) which works in a quite different way, by inhibiting the re-uptake of noradrenaline and serotonin. Each of these costs the consumer \$115/month. There is no PBS subsidy.

Orlistat has to be taken with each meal; it produces gastro-intestinal symptoms and steatorrhoea unless patients limit their fat intake. Sibutramine has a list of contra-indications

to its use and a number of side effects (including hypertension, tachycardia, constipation and insomnia) (22). Both these drugs are only suitable for people who are obese, who have a BMI over 30 kg/m². If we take obesity (BMI >30) as a disease (23) then the drugs available at present to assist dietary weight reduction are not appropriate for primary prevention.

New Drugs may of course be developed and there is intense research activity to understand the physiology of human appetite and energy regulation. More complexity is discovered every year. Any pharmaceutical to prevent weight gain will, I imagine, have to work by suppressing appetite but no other brain function. Something as efficient and safe as statins may be a long way in the future. So for now and for the foreseeable future, primary prevention of obesity means helping people to eat a little less and exercise a little more – and some people have to change more than others.

Partial success of the campaign against smoking could give us hope, though reduction of smoking is likely one reason for the increase of overweight because smoking reduces appetite and may also increase the metabolic rate a little. Here was a pharmacological contributor to prevention of obesity that we can't have any more.

No drug is available to prevent type I diabetes. A trial of large doses of nicotinamide proved disappointing. Overweight and obesity are major risk factors for type II diabetes. The most effective preventive measures for pre-diabetics are serious weight loss and physical exercise shown in two randomised controlled trials in Finland and the USA. Metformin was only half as effective. An editorial in the June 2006 Diabetes Care (24) argues that health insurance systems should be reorganised to pay for Diabetes Prevention Programs involving intensive behaviour change.

OSTEOPOROSIS

For primary prevention: exercise, adequate dietary calcium and adequate vitamin D for its absorption are all important. Enough calcium can be obtained from the diet and, if not, from calcium tablets. These have been generally recommended for about 25 years, originally from the work of Chris Nordin (25), now in Adelaide. It's possible that adequate vitamin K (eg from green vegetables) is also beneficial. A new development is realisation that we can't take

vitamin D for granted in Australia, in spite of all our sun. A large number of old people are indoors all the time and get hardly any sun exposure. Our diet doesn't provide the requirement (7) of vitamin D if there's no sun. These people have been found to have low or "deficient" plasma 25-hydroxyvitamin D and compensatory increase of parathormone. Even people who aren't housebound or institutionalised are avoiding the sun to prevent skin cancer, with big hats and sunscreen lotions. We have in press (26) a paper that argues we need more foods, fortified with vitamin D, starting with milk (as in North America) and all institutionalised and housebound people (like the submariners) should regularly be taking one or other pharmaceutical form of vitamin D – for primary prevention of osteoporosis. Another pharmaceutical group, the bisphosphonates (eg, alendronate. 'Fosamax') are also used in primary prevention of osteoporotic fractures. [Overweight, however, may be protective.]

This leaves CANCER, DEPRESSION, ARTHRITIS and DEMENTIA.

I think the only reliable pharmaceutical for primary prevention of one type of CANCER is the papillomavirus vaccine Gardasil (developed in Australia) for prevention of cancer of the uterine cervix. The present cost is US\$360 for the necessary three, spaced injections.

Lastly, I hear talk about benefit from earlier treatments of DEPRESSION. But I can't imagine this would be safe for everyone. It would have to be for those who, on screening have psychiatric or genetic evidence of risk. There is no general pharmaceutical for primary prevention here.

For OSTEOARTHRITIS eg, of the knee some (small) trials with glucosamine or chondroitin sulphate have reported improvement in symptoms.

For DEMENTIA new potential medicines are being developed that may reduce β -amyloid formation.

Contribution of Pharmaceutical Products to PRIMARY Prevention

	Per Cent
FOETAL MALFORMATION	20
INFECTIONS	70
TEETH	60
HYPERTENSION	65
CHOLESTEROL	40
CARDIOVASCULAR DISEASE*	55
OBESITY	5
DIABETES	10?
OSTEOPOROSIS	15
CANCER	2
DEPRESSION	?
ARTHRITIS	?

*Two preceding lines plus fish oil, aspirin, anti-arrhythmics.

REFERENCES

1. Wald NJ and Law MR (2003) A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326 : 1419-1423.
2. Medical Research Council Vitamin Study Research Group (1991) Prevention of neural tube defects: results of the Medical Research Council vitamin study. *Lancet*, 338 : 131-137.
3. Green LW (2005) Prospects and possible pitfalls of a preventive Polypill : confessions of a health promotion convert. *European Journal of Clinical Nutrition*, 59, Suppl 1 : S4-S9.
4. <http://bmj.bmjournals.com.ezproxy.library.usyd.edu.au/cgi/eletter> Rapid responses to NJ Wald & MR Law (see ref 1).
5. Comment (2005) Folate supplementation and cardiovascular disease. *Lancet*, 366 : 1679-1681.
6. Mooijaart SP Gussekloo J, Frölich M et al (2005) Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age : the Leiden 85-plus study. *Am J Clin Nutr*, 82 : 866-871.

7. Gaziano M, Opie LH & Weinstein M (2006) Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *Lancet*, 366 : 679-686.
8. Australian Government Department of Health & Ageing/National Health & Medical Research Council AND Ministry of Health, New Zealand (2006) Nutrient Reference Values for Australia & New Zealand, including Recommended Dietary Intakes. Fluoride is on pp 175-180. NHMRC Publications, Canberra.
9. Truswell AS, Kennelly BM, Hansen JDL & Lee RB (1972) Blood pressures of !Kung Bushmen in northern Botswana. *Amer Heart J*, 84 : 5-12.
10. National Health & Medical Research Council (1984) Report of the working party on Sodium in the Australian diet. Australian Government Publishing Service, Canberra.
11. Beard TC (2004) Salt Matters. A consumer guide. Lothian Books, South Melbourne.
12. Truswell AS (2003) Limit your alcohol intake if you choose to drink. In Food for Health. Dietary Guidelines for Australian Adults. A guide to healthy eating. pp 151-169. Commonwealth Department of Health and Ageing/NHMRC, Canberra.
13. Lewis B, Katan M, Merx I, Miller NE, Hammett F, Kay RM, Nobels A & Swan AV (1981) Towards an improved lipid-lowering diet : additive effects of changes in nutrient intakes. *Lancet*, 2 : 1310-1313.
14. Cholesterol Treatment Trialists (CTT) Collaboration (2005) Efficacy and safety of cholesterol-lowering treatment : prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*, 355 : 1267-1278.
15. Sinzinger H & O'Grady J (2004) Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. *Brit J Clin Pharmacol*, 57 : 525-528.
16. Sever PS, Dahlof B, Poulter NR and 11 others for the ASCOT Investigators (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*, 361 : 1149-1158.

17. Brown MS & Goldstein JL (2006) Lowering LDL- not only low, but how long? *Science*, 311 : 1721-1723.
18. Editorial (2004) OTC statins : a bad decision for public health. *Lancet*, 363 : 1659.
19. Stocks NP, Ryan P, McElroy H & Allan J (2004) Statin prescribing in Australia: socioeconomic and sex differences. A cross-sectional study. *Med J Australia*, 180 : 229-231.
20. Dr Foster's case notes (2004) Prescribing of lipid regulating drugs and admissions for myocardial infarction in England. *BMJ*, 329 : 645.
21. Bray GA (1998) Drug treatment of obesity : don't throw the baby out with the bath water. *Am J Clin Nutr*, 67 : 1-4.
22. British National Formulary (March 2003) British Medical Association and Royal Pharmaceutical Society of Great Britain.
23. Kolata G. (1985) Obesity declared a disease. *Science*, 227 : 1019-1020.
24. Teutsch S (2006) Preventing diabetes: the time is now. *Diabetes Care*, 29 : 1447-1448.
25. Nordin BEC, Morris HA, Need AG & Horwitz M (1996) Dietary calcium and osteoporosis. In Pietinen P, Nishida C & Khaltav N (eds) *Health Issues for the 21st Century. Nutrition & Quality of Life*. WHO, Geneva.
26. Shrapnel W & Truswell AS (2006) Vitamin D deficiency in Australia & New Zealand : what are the dietary options. *Nutrition & Dietetics* (in press).