

# Hypertension

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## INTRODUCTION

During my training in Neurology with Dr. Henry Barnett, we saw 500 patients each year with stroke; half of them were due to uncontrolled hypertension. That experience led me, after finishing my training in Neurology, to complete training in Internal Medicine and in Clinical Pharmacology. In 1977 we established the first Hypertension Clinic in the region, and since then have treated over 4,000 patients referred for difficult hypertension. (The clinic was later called the Atherosclerosis Prevention Clinic.) During that time the field has evolved tremendously, and feel I have learned a lot.

What is presented here is my approach to the management of hypertension. What follows is what I do and what I recommend.

### **Is hypertension still a big deal? I thought it was pretty much solved.**

**A.** Hypertension is still a very big unsolved problem. The Canadian Heart Health Surveys took blood pressure readings in 23,129 Canadians (Joffres et al., CMAJ 1992;146: 1997-2005). Hypertension was defined as a mean diastolic BP  $\geq 90$  mm Hg or a mean systolic BP  $\geq 140$  mm Hg. Of Canadians identified as hypertensive, 42% million were not aware of their condition. Their lack of awareness is especially striking in light of the fact that almost 3 in 4 of those surveyed had been screened for high blood pressure in the previous year.

Of hypertensive Canadians who had received treatment, approximately 60% had failed to achieve BP control. This “treatment gap” can be attributed to sub-optimal compliance in more than half of these cases, according to a separate review of factors associated with inadequate BP control.

Among the elderly the prevalence of hypertension is 60%; unfortunately of those with hypertension only about 68% are aware of it, and only 16% are controlled (Joffres MR, Ghadirian P, Fodor JG, et al. Am.J.Hypertens. 1997;10: 1097-1102). Reasons for these poor results are not entirely clear, but they may include poor compliance, the cost of medications, adverse effects of medications, and misdiagnosis of the underlying cause.

These findings highlight the need for increased vigilance among Canadian physicians in initiating and monitoring antihypertensive treatment, and for a more pro-active approach to patient education in order to raise awareness and improve compliance.

Hypertension indirectly contributes to risk of atherosclerotic events including myocardial infarction, but it is important to understand that the relationship between hypertension and atherosclerosis is indirect (probably through flow disturbances). High blood pressure *per se* directly causes small vessel disease in the brain and kidneys, and is the major cause of congestive heart failure.

The types of stroke that are caused by high blood pressure, and prevented by lowering of blood pressure, are hypertensive intracerebral hemorrhages due to rupture of arterioles, or lacunar infarctions due to blockage of arterioles and small resistance vessels, in the part of the brain that has been called by Hachinski the “Vascular Centrencephalon”. These small arteries perfuse the basal ganglia, internal capsule, brainstem and cerebellum. They are short straight arteries with few branches, so the brunt of the high systemic pressure is transmitted straight through to the arterioles; in contrast over the hemispheres the arteries are long with many branches, serving as a sort of step-down transformer, so the pressure in the resistance vessels is much lower. High pressure in the arterioles causes fibrinoid necrosis and hyaline degeneration, leading to lacunar infarction or intracerebral hemorrhage.

Treating high blood pressure prevents this type of stroke quite effectively. We were able to observe that effect in London, Ontario, because of the coincidence of a large Family Medicine study aiming to improve detection and treatment of hypertension, with the arrival at Victoria Hospital of the first CT scanner in the region. The CT scanner made it possible for the first time to accurately differentiate between strokes due to hypertensive small vessel disease, and strokes due to other causes. The study was a five-year study, which apparently had a remarkable effect on hypertension detection and treatment throughout the surrounding area: by 1984, the year after the study was completed, 94% of hypertensives were detected, 92% were on treatment, and 72% were controlled. The number of strokes declined from 500 per year to 250 during the five years the study was ongoing, and strokes due to hypertensive small vessel disease nearly disappeared: they went from half of stroke to less than 10%. Unfortunately, I have the impression that blood pressure control in our region has slipped since 1984. This will become a major problem with the aging of the population.

### Q. Why should I treat elderly patients with hypertension? Won't they feel worse?

A. The point of this is that what older patients fear is not death, it is disability. A nice quiet heart attack is a good way to go; being helpless, incontinent and unable to speak for the last few years of life is truly the *bête noir* of the elderly. The major cause of disability in the elderly is stroke; effective treatment of hypertension reduces stroke by half, so it is the best way to reduce the human and economic costs of what most threatens quality of life for older people. The table below shows the results of treatment of hypertension in the elderly.

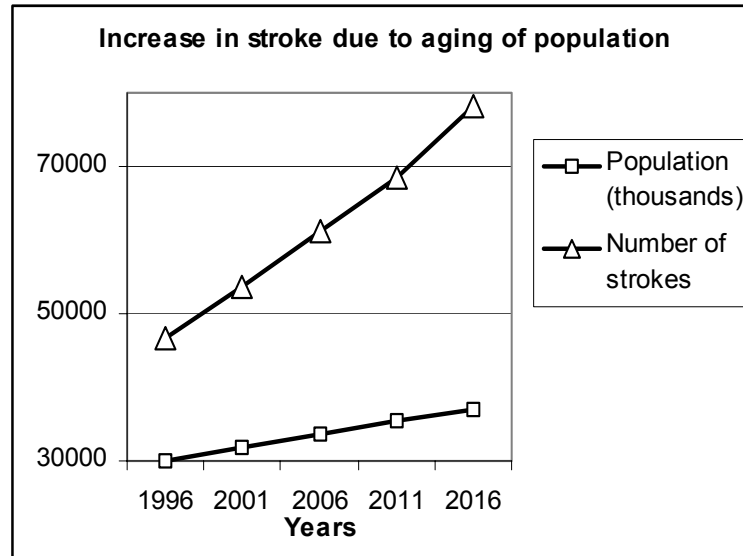
#### Results of treatment of hypertension in the elderly

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n	582	840	884	1627	4396	4736	2376	1632	4695
Age (years)	60-69	>60	60-79	70-84	65-74	60-80	60-69	60-79	>60
Mean entry BP (mmHg)	165/101	182/101	197/100	195/102	185/91	170/77	170/101	169/98	174/85
<b>Relative risk of event (treated versus controls)</b>									
Stroke	0.67	0.64	0.58*	0.53*	0.75*	0.67*	0.56*	0.43*	0.58*
Coronary artery disease	0.82	0.80	1.03	0.87	0.81	0.73*	0.85*	-	0.70
Congestive heart failure	-	0.78	0.68	0.49	-	0.45*	-	0.32	0.64
All cardiovascular disease events	0.69	0.71*	0.76*	0.60*	0.83*	0.68*	0.84*	0.38*	0.69*

(Reprinted from Spence JD, Hamet P. submission to the 1998 Canadian Hypertension Society Consensus Conference; considered in the 1999 Canadian Recommendations for the Management of Hypertension. Feldman RD, Campbell N, Laroche P, Bolli P, Burgess ED, Carruthers SG, Floras JS, Haynes RB, Leenen FHH, Leiter LA, Logan AG, Myers MG, Spence JD, Zarnke KB, for the Task Force for the Development of the 1999 Canadian Recommendations for the Management of Hypertension. CMAJ 1999; 161: (12 Suppl) S1-S17.)

The importance of stroke prevention has recently been highlighted by evidence that hypertension and stroke are strongly associated with dementia, which increases steeply with age. Systolic hypertension increases the risk of dementia (Starr et al., J Hum Hypertension 1997; 11: 777-781), and stroke markedly increases the risk of dementia: The Nun Study showed that even one or two small strokes increased the likelihood 20-fold, that Alzheimer's disease identified at autopsy was manifested during life as dementia. Furthermore, the European study on isolated systolic hypertension in the elderly (Syst-Eur) showed that treating ISH reduced Alzheimer's dementia by half (Forette et al., Lancet 1998; 352: 1347-51).

The biggest missed opportunity in hypertension is failure to treat isolated systolic hypertension in the elderly. The elderly are at the highest risk of stroke and myocardial infarction, and the slope of risk is much steeper: for a given increase in blood pressure the increase in risk is much greater in the elderly. With the aging of the population, it will be increasingly important to implement effective preventive measures. Figure 1 shows the impending disaster in vascular disease from projections developed by the Heart & Stroke Foundation of Ontario.



### **Aging of the population**

The Canadian population is aging rapidly. Because the risk of stroke goes up steeply with age, as does the risk of myocardial infarction, the aging of our population means that we are about to experience a major increase in stroke and MI. The Heart & Stroke Foundation of Ontario predicted in 1998 that stroke in Ontario can be expected to rise by 31% by the year 2006! It is therefore an urgent matter that effective preventive measures be implemented, and treatment of isolated systolic hypertension in the elderly is a key missed opportunity.

There is abundant evidence that treating isolated systolic hypertension in the elderly is beneficial. In the Systolic Hypertension in the Elderly Program, treatment reduced risk of myocardial infarction by about 40% and stroke by half (SHEP, JAMA 1991;265: 3255-64.). In that study the treatment was primarily thiazide diuretic, plus other drugs if the pressure wasn't controlled. That estimate of benefit is extremely conservative, since by the end of the study 40% of patients that were initially assigned to placebo had been started on active therapy because their blood pressure on placebo went too high. Had they been left on placebo they would have had more events, and active therapy would have been shown to be even more effective.

### **Why do the elderly seem harder to treat?**

Elderly patients are harder to treat for several reasons: they need smaller doses of medication; they are on many drugs and it is a challenge to keep the number of pills down, and some elderly patients seem to experience hypotensive symptoms at pressures that would usually be regarded as normal. As the elderly usually require diuretics to achieve blood pressure control, and because they are more sensitive to adverse effects of medication, it is even more important in this group to tailor therapy, as discussed below.

The notion that elderly patients don't tolerate blood pressure medication is very likely based on extrapolation from a small proportion that have stiff arteries and therefore have a blood pressure reading that is falsely elevated; such patients are said to have "pseudohypertension", and commonly present with

the complaint that they feel lightheaded on any antihypertensive medication. This condition represents only 5% or so of the patients over age 65 in a hypertension clinic, but in my opinion their symptoms tend to be generalized to the elderly as a group.

In the Hypertension Optimal Treatment (HOT) Study, in which patients up to age 80 were enrolled and followed for an average of 4.7 years, quality of life actually improved with lower blood pressure targets.

A meta-analysis of participants over age 80 (874 actively treated and 796 controls) in randomized controlled trials of antihypertensive drugs did not reveal an age threshold beyond which hypertension should not be treated (Gueyffier et al., Lancet 1999; 353: 793-796).

**Q. I find it confusing to treat difficult cases of hypertension. Is there a way to simplify this?**

**A.** There certainly is. I find it tremendously helpful to tailor therapy according to the physiology of the patient. The basis of this approach is to measure a stimulated plasma renin (Spence JD. Am J Hypertension 2000; 13: 105-110).

In a patient whose blood pressure is not responding to medication, there are 3 main possibilities to be considered: non-compliance, consumption of exogenous substances that aggravate hypertension, and an underlying cause that requires specific therapy.

**Non-compliance:**

Compliance with antihypertensive therapy is difficult: as there are no symptoms from hypertension, medication can only make the patient feel worse. The problem has been aggravated in recent years by the tendency of pharmacists to give out more and more “information” about adverse effects of drugs. Unfortunately much of the information amounts to lists of all the symptoms known to mankind, with no attempt to make the link between the symptoms and causality. As a result most of the lists read the same: fatigue, dizziness, headache, impotence, diarrhea, constipation, etc. Wait a minute: diarrhea and constipation from the same drug – is this likely? Unfortunately, the patient looks through the list, marking the symptoms with a yellow highlighter, and brings it in as proof of causality. Much more useful information is available, but seldom provided to patients, from the large clinical trials done for registration of new drugs. Tables showing that most of the symptoms occur with equal frequency on placebo or active drug, but a few are more common on active drug, would be much more useful in trying to determine how likely it is that a given symptom is related to a given drug.

A particular problem is the patient who has experienced adverse effects in the past from one drug, and then becomes convinced that every subsequent symptom is caused by the subsequent drugs that are used. I call this the “poison pill” effect; it may explain the most interesting results of three studies reported recently.

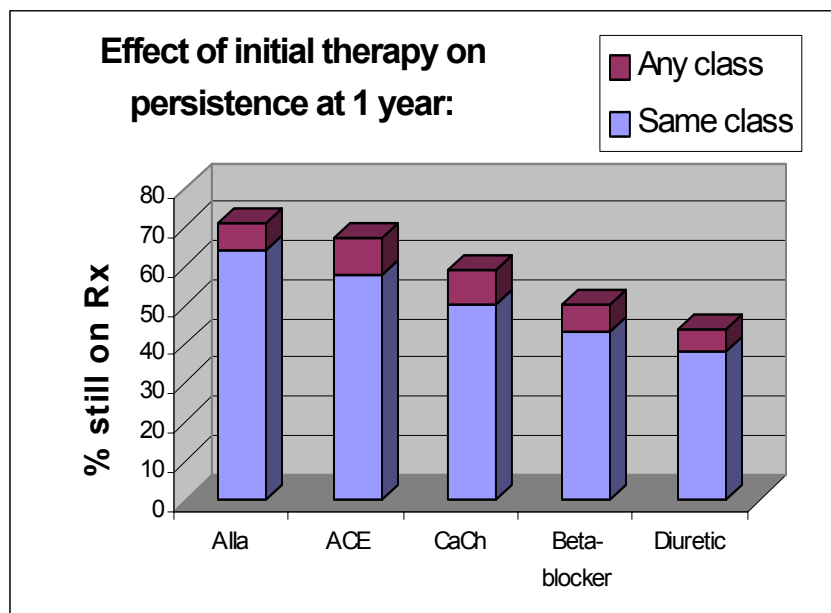
One approach to these most difficult patients with fixed ideation about unlikely causal relationships between symptoms and drugs is to do a blinded “n of 1” crossover trial. Although this involves some nuisance, it is worthwhile for patients at high risk that really need therapy, but have incriminated all the likely alternatives. Ask the pharmacist to make up two bottles of capsules, labeled “A” and “B”, and send you the code. One bottle contains capsules containing cornstarch, the other containing active drug. The patient alternates A and B, recording the date, the pill taken and symptoms; at the end of 14 crossovers the code is broken and analyzed to determine likelihood of causality. We have a form designed for this purpose, with a statistical table on it for looking up probabilities. Unfortunately, some patients are so fixed in their ideation that their response is essentially “my mind is made up; don’t confuse me with facts”; however this approach does work for about half such patients.

### Q. What about the cost of medication: isn't it better to use cheaper drugs?

A. Cheaper drugs are fine for many patients, but they won't work if the patients won't take them. The studies described below show that drugs with fewer adverse effects are associated with improved persistence with medication; noncompliance and switching account for 35% of the cost of drugs for hypertension.

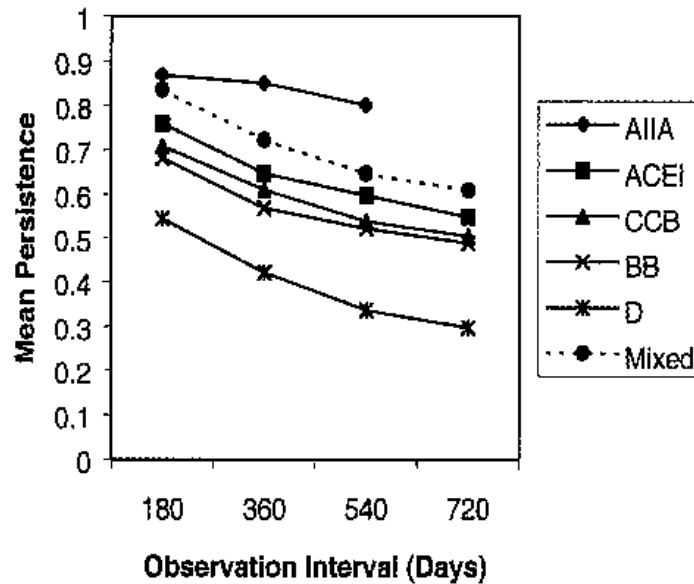
Caro et al. recently reported that the choice of initial therapy was important in persistence with therapy. Among Canadian patient started on ACE inhibitors persistence after 6 months was 89%, compared with 86% for calcium channel antagonists, 85% for  $\beta$ -blockers and 80% for diuretics (Caro et al., CMAJ 1999; 160: 41-6). After one year, persistence was down to 78% (Caro et al., CMAJ 1999; 160: 31-7).

In a US study of drug utilization from the records of over 1.3 million enrollees in health maintenance organizations, Bloom (Bloom BS. Clin Therap 1998; 20: 1-11) found that persistence after one year with the initial class of medication was substantially higher for drug classes with fewer adverse effects: 64% for angiotensin antagonists, 58% for ACE inhibitors, 50% for calcium channel antagonists, 43% for beta blockers and 38% for diuretics; persistence with any class of drugs was about 10% higher for each group.



This figure illustrates what I call the “poison pill effect”: once a patient has had an adverse effect from one drug, it is more likely that symptoms experienced by the patients will be attributed to the drugs they are taking. This explains why family doctors are so careful to avoid adverse effects of medications – they are managing not only their long-term relationship with the patient, but the patient’s life-long relationship with drugs.

Similar findings were observed in a Canadian study using the Saskatchewan drug data base (Marentette MA et al, Can J Cardiol 2002; 18: 649-656). As shown in the figure below from that paper, persistence was much better with drugs with few adverse effects, and the differences persisted over time.



Moore et al ( High Blood Press 1998;7:1-11.) showed in a study of 2686 patients in 283 community outpatient clinics that switching was significantly less in patients randomized to losartan ( $\pm$  thiazide) (9%) versus usual care (23%);  $p < .001$ ; adverse effects were significantly less with losartan/HCTZ than with usual care ( $p = 0.006$ ).

Thus, compliance/persistence is better, and switching less, with medications that have less adverse effects. These findings suggest that in addition to selecting patients on the basis of contraindications to  $\beta$ -blockers and diuretics as suggested in consensus recommendations, physicians may be appropriately choosing drugs with less adverse effects in the hope of achieving better persistence with therapy.

Such preference for drugs with less adverse effects may be cost-effective, given the high cost of untreated hypertension, and the costs of switching therapy. Hughes and McGuire estimated that the total cost of treating hypertension in the National Health Service in Britain was £76.5 million per annum, of which £26.9 million was attributed to the costs of discontinuation or switching of therapy (Hughes D, McGuire A. J Hum Hypertension 1998; 12: 533-7).

#### **Consumption of exogenous substances that aggravate hypertension:**

A number of things that hypertensive patients consume will aggravate their blood pressure, and may make them resistant to treatment. These include salt, licorice, alcohol, oral contraceptive pills, decongestants, nonsteroidal anti-inflammatory drugs (NSAIDs), and some herbal remedies containing licorice or ephedrine.

The Canadian Hypertension Society has recently updated its consensus guidelines on non-medical management of hypertension (Campbell et al., CMAJ 1999; 160: 1341-1343 and special supplement with that issue). These papers provide a full background on several of the issues that are touched on briefly here.

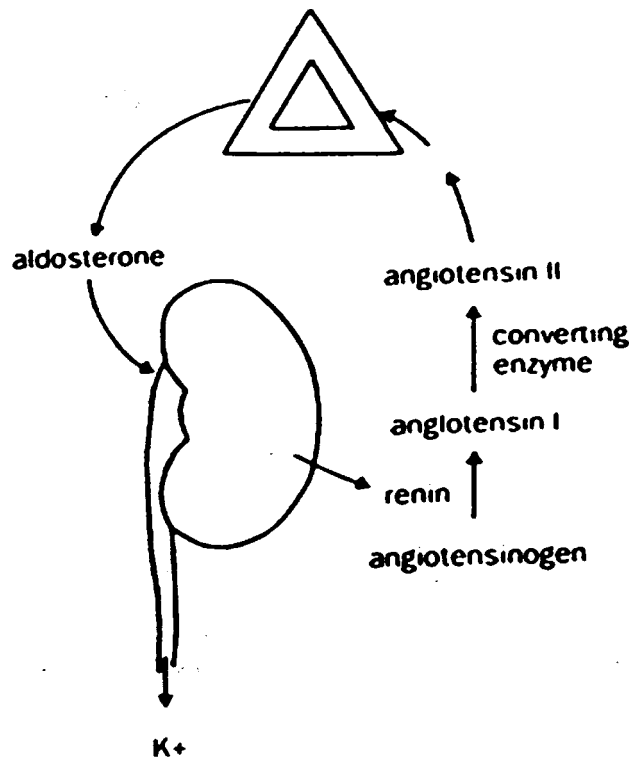
Although salt restriction has little effect on blood pressure in normotensive individuals, it is an important therapeutic maneuver in hypertensives, particularly in those with resistant hypertension. Salt restriction towards 2-3 grams daily can be achieved by eliminating added salt and avoiding salty foods such as pickles, potato chips and other salty snack foods. Alcohol intake should be reduced to 2 or less standard units per day. With respect to NSAIDs, alternatives include ASA up to about a gram per day, colchicine

and allopurinol for gout and gout prevention, and sulindac, which does not raise blood pressure (Wong et al, Lancet 1986; i:997-1001). Excess calorie consumption also aggravates hypertension in the long term; weight loss significantly reduces blood pressure and medication requirements.

### **An underlying cause that requires specific therapy:**

Diagnosis of the underlying cause, or at least knowing what is the pathophysiology that is driving the blood pressure in the individual case, is the key to control in difficult cases. I call this making the physiological diagnosis. The notion that most cases of hypertension belong to a monolithic entity called "essential hypertension", and are all the same and respond equally well to the same treatment is simply untrue. This notion, however, may underlie a large part of poor blood pressure control.

The renin-angiotensin system is the driver of hypertension in all but a few cases; perhaps the only exception is pheochromocytoma (even aortic coarctation operates in a sense as a proximal form of renovascular hypertension). The problem is to know which side of the circle is driving the pressure: an excess of adrenocortical hormones causing salt and water retention and loss of potassium, magnesium and other ions, or high levels of renin and angiotensin, with secondary hyperaldosteronism. Measuring plasma aldosterone alone does not help, since virtually all cases of difficult hypertension have hyperaldosteronism; in most cases it is secondary hyperaldosteronism, identifiable by a high level of



plasma renin.

Laragh et al recommended in 1972 that all hypertensives should be classified according to their renin status, and treated accordingly. (Laragh et al., Am J Med 1972; 52: 633-52.) They found that about a third of patients had high renin levels, a third had low levels, and a third were in between. In 1975, an important Canadian paper proposed that stimulated renin profiling be done to guide the diagnosis of secondary hypertension in resistant cases (Wallach L, Nyarai I, Dawson KG. Ann Int Med 1975;82:27-34). They pointed out that most North Americans eat so much salt that a random renin is useless; instead of a 24-hour urine sodium, as used by Laragh et al, they recommended stimulation with furosemide as a way to differentiate normals from patients with low non-stimulable renin levels due to adrenocortical hyperplasia. High renin levels are simply pushed higher by this maneuver. In practice, this test can be carried out by measuring plasma renin 30 minutes after intravenous furosemide, or 4 hours after an oral

dose of about 0.5mg/kg. It makes sense to measure plasma aldosterone at the same time, for calculation of the renin/aldo ratio.

This approach was used in over 4,000 patients at our Hypertension Clinic between 1977 and 1995, and was found to be extremely useful in the management of resistant hypertension (Spence JD. Am J Hypertension 1999, in press.) We saw only 50 patients with pheochromocytoma; the rest had their blood pressure driven by the renin-angiotensin system. (Licorice accounted for 5 cases; it produces low-renin hypertension because of a mineralocorticoid effect) There were 5 cases thought to have Conn's syndrome, but over 200 of primary adrenocortical hyperplasia ( i.e. about 10% of the resistant cases), so it is much more common than Conn's tumors as a cause of adrenocortical hypertension. Usually missed without stimulated renin testing, it can usually be managed medically (only 9% of patients require surgery), but can only be managed medically if the diagnosis is known. Such patients may require large doses of spironolactone or amiloride (men cannot take high doses of spironolactone because of mastalgia and gynecomastia), which would not be prescribed unless the diagnosis were recognized. Patients with low-renin hypertension due to excess mineralocorticoid require diuretics for treatment, but experience more adverse effects from thiazides because of depletion of potassium and magnesium; they need potassium/magnesium sparing diuretics such as amiloride for control.

Similarly, renovascular hypertension is easier to manage medically with drugs that block the renin-angiotensin system such as Angiotensin II antagonists (AIIa's) or Angiotensin Converting Enzyme inhibitors (ACEi's). They may require revascularization for control; among over 400 patients in our clinic with renovascular hypertension, some 200 had renal angioplasties, which were effective about 90% of the time; only 24 required bypass or endarterectomy of the renal origin, and 8 required nephrectomy (in the setting of renal artery occlusion with a non-functioning kidney that was still secreting high levels of renin). An important situation in which renovascular hypertension is often missed is heart failure; I think this happens because the pump is not capable of sustaining the very high pressures that otherwise might lead to diagnosis (MacDowall et al., Lancet 1998;352: 13-6)

A third group of patients have both a low renin and a low aldosterone, because of a renal tubular abnormality causing salt and water retention at the level of the renal tubule. Liddle's syndrome, and a recently described sodium channel mutation are examples of this problem.

	Adrenocortical hyperplasia or Conn's adenoma	Renal tubular abnormality: Liddle's, Na Channel T594M variant	Renal hypertension: eg renovascular, obstruction, cysts, tumor, etc
Renin	Low	Low	High
Aldosterone	High	Low	High
Treatment	Spironolactone (women) or Eplerenone once it's available (men or women); for now amiloride for men	Amiloride	Angiotensin receptor blockers or ACE inhibitors

**Q. How low should we go? What about combination therapy?**

**A.** The Hypertension Optimal Treatment (HOT) trial showed that lower is better, particularly for high-risk patients such as diabetics (Hansson L, Zanchetti A, Carruthers SG et al. Lancet 1998; 351: 1755-62). An optimal blood pressure target of 130/83 was suggested, meaning that a higher proportion of patients will now be classified as resistant. It also showed that only a minority (about 25%) of patients could achieve lower target pressures with monotherapy, meaning that to achieve the new lower target pressures, a higher proportion of patients will require combination therapy. It is to be hoped that the regulatory authorities will learn to drop their doctrinaire resistance to rational combination tablets, which offer a number of benefits: reducing the number of pills a patient has to take will not only reduce dispensing fees (which account for about 30% of the Ontario Drug Benefit budget) and improve compliance, but also has psychological benefits. Low doses of combinations of drugs are more effective with less adverse effects, and combinations that are chosen rationally can offset the adverse effects of one ingredient with others: for example beta-blockers will prevent the tachycardia from vasodilators; potassium/magnesium sparing diuretics will prevent potassium depletion from thiazide in patients with low renin hypertension, and drugs such as AIIa's will prevent secondary hyperaldosteronism and thus minimize potassium/magnesium depletion from thiazides in patients with high-renin hypertension. (ACE inhibitors may inhibit the renin-angiotensin system, but levels of angiotensin II escape via non-ACE pathways; it seems likely that the main action of ACE inhibitors may be through increases in bradykinin.)

**Q. Are family doctors abusing the system and wasting resources by prescribing newer drugs?**

There is a widespread belief that therapy based on consensus guidelines, beginning with diuretic or beta-blocker, is suitable for most hypertensive patients; this leads to the belief that widespread prescribing of newer more expensive drugs is inappropriate and wasteful of resources. In fact, when this issue was studied in a teaching family practice in London, Ontario, it was apparent that at most half, and perhaps as few as 43% of patients with hypertension, are suited to diuretic/beta-blocker therapy (Spence et al; submitted for publication). Only half the patients were free of diabetes, hyperlipidemia and heart failure, and only a 43% were free of those conditions as well as intermittent claudication, chronic obstructive pulmonary disease and gout. In that practice, 69% of patients on treatment were receiving beta-blockers and/or diuretics; of these 34.7% were also receiving other drugs for hypertension. Patient with complicated hypertension were less likely (41.9%) to be prescribed diuretic or  $\beta$ -blocker. These findings suggest that non-use of diuretic and/or  $\beta$ -blockers in Family Practice is less inappropriate than has been widely presumed.

Given the high costs of switching and non-compliance (35% of the cost of treating hypertension, in the British NHS study referred to above), it would seem that it is entirely appropriate for family doctors to prescribe drugs that are individualized (tailored) to the pathophysiology that is driving the blood pressure, and to the associated conditions influencing drug choice.

Restricting choice of therapy on formularies to conform to silo budgets is very likely counterproductive from the perspective of the third party payer: non-compliance and switching costs are high when choice is restricted, and costs rise in other silos. In the New Hampshire nursing home and the Quebec emergency room experiences, costs rose about 30% when choice of drugs for the elderly was restricted.

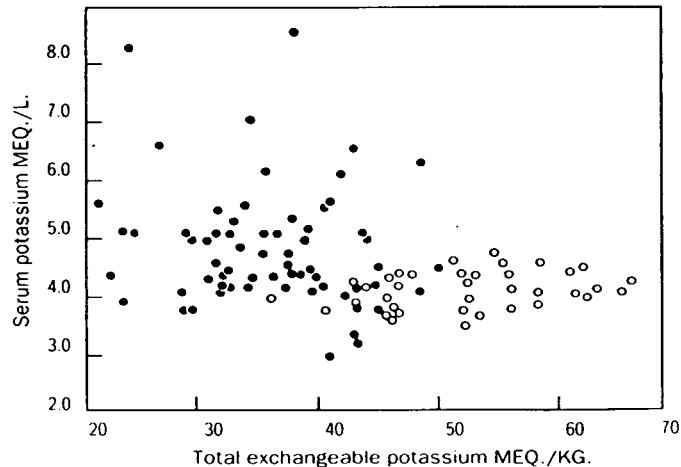
**Q. What are some of the key issues about antihypertensive drugs?****What about adverse metabolic effects of diuretics?**

Diuretics are particularly important in the elderly, as well as in patients with low renin hypertension. The thiazides are the diuretics of choice for hypertension, despite the adverse effects. Problems include aggravation of gout, insulin resistance, glucose intolerance, dyslipidemia, and depletion of potassium. In

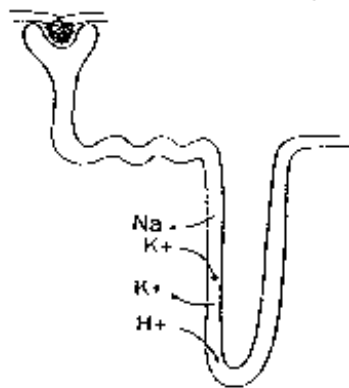
fact, as Wester and Dyckner showed, it isn't just potassium depletion: patients on diuretics develop depletion of potassium, magnesium, zinc, selenium and even rubidium (sounds suspiciously like serum rhubarb!) (Dyckner T, Wester PO. *Acta Med Scand* 1987;222:231-236). They also showed that administering potassium supplements is ineffective unless magnesium is co-administered (Dyckner T, Wester PO. *Am Heart J* 1979; 97: 12-18); this means that potassium supplements for the most part only increase the cost of the nation's toilet water.

### To avoid potassium/magnesium depletion:

It is important to understand that measuring serum potassium does not sort out the problem. The serum potassium is usually normal, through a wide range of whole body potassium levels (Figure below from Brater and Morelli, *Clin Pharm Ther* 1974).



Depletion of potassium, magnesium, and the other ions, is due to an aldosterone-driven exchange in the kidney tubule. Every sodium ion coming down the tubule has a chance of being reabsorbed; when it is, a potassium ion is excreted to maintain electrical balance in the membrane; once potassium depletion develops, hydrogen ions are excreted in exchange for reabsorbed potassium ions (Figure below).



Potassium depletion can be inferred from aciduria in the face of systemic alkalosis (Brater C, Morelli H, *Clin Pharmacol Ther* 1977; 22: 21-33), but the more practical test is to ask the patient about symptoms. Aching, cramps, fatigue, impotence, impairment of glucose tolerance all suggest whole body potassium depletion.

In order to reverse the problem of potassium depletion there are three key maneuvers: reduce the dose of hydrochlorothiazide to 12.5 mg, reduce the salt intake towards 2-3 grams/day, and measure the stimulated plasma renin to determine whether the problem is primary or secondary hyperaldosteronism. If the renin is low, block primary hyperaldosteronism with K<sup>+</sup>/Mg<sup>++</sup> sparing diuretics; if the renin is high, block Secondary hyperaldosteronism with AIIa's (or ACEi).

**Calcium channel antagonists**

Several years ago a retrospective analysis of data from a large HMO showed that patients on calcium channel antagonists had a higher cardiovascular mortality. Ignored was the fact that a significantly higher proportion of those patients had coronary artery disease, smoking and diabetes as risk factors. This was a molehill turned mountain, and evidence is now accumulating that calcium channel antagonists reduce events as well as reducing blood pressure. The new Canadian Hypertension Society consensus guidelines will recommend that they be considered useful drugs, particularly for the elderly. There are several points to be made about the practical use of these drugs. They are very expensive, and in my opinion have different uses depending on the class.

Dihydropyridines are more effective for blood pressure lowering. They are potent vasodilators with little cardiac depression; they cause headaches, flushing and edema which is not due to fluid retention, but redistribution of fluid, and they are better tolerated in longer acting forms. Short-acting nifedipine in liquid pulvules should never be used in adults, and in particular the popular “sublingual” use of this drug in hypertensive emergencies is to be deplored because it is uncontrollable and can cause stroke or myocardial ischemia when the pressure crashes (Grossman et al., JAMA. 1996;276:1328-31). The drug is not absorbed from the buccal mucosa; it is swallowed and then absorbed (van Harten et al., Lancet 1987;2:1363-1365).

**Beta-blockers**

One of the most glaring care gaps nowadays is the high proportion of patients being discharged on calcium channel antagonists rather than beta-blockers. This happens despite good evidence that beta-blockers substantially reduce mortality following MI, and consensus recommendations recommending their routine use in that circumstance unless contraindicated. I suspect that in part this situation exists because beta-blockers have a somewhat undeserved reputation for adverse effects.

About 20 years ago doctors knew a lot more about beta blockers, because the alternatives we now have available did not exist. We had to be pretty good at figuring out how to avoid adverse effects, and we had to understand that not all beta blockers are the same.

For the most part, the adverse effects of beta blockers are due to blockade of the beta-2 receptor: asthma, reduced muscle blood flow, impaired glucose tolerance, and aggravation of dyslipidemia are all due to beta-2 blockade. These symptoms can be avoided by using relatively cardioselective beta blockers (metoprolol and atenolol), or beta-blockers that block beta-1 receptors but stimulate beta-2 receptors. The latter property is called partial agonist effect, or Intrinsic Sympathomimetic activity (ISI); drugs with ISI include pindolol (the most potent), oxprenolol and acebutolol.

Fatigue is much more complex than it might seem. It is important to differentiate physical fatigability (“doc, my muscles turn to lead when I climb stairs) from subjective tiredness (“doc, I have to take a nap when I get home from work”). Subjective tiredness is mainly due to brain penetration; propranolol, with a CNS:plasma ratio of about 28:1 is the worst for this problem. Physical fatigability is usually due to a fixed low heart rate due to excessive beta-1 blockade, but may also be due to reduced muscle blood flow and muscle metabolism due to beta-2 blockade; pindolol is likely the best answer for that one. Unfortunately pindolol and oxprenolol penetrate brain about 50:1 over plasma, so they can cause vivid dreams, anxiety, tremor and cramps; for those patients acebutolol is a reasonable alternative.

**ACE inhibitors**

These drugs are also not created equal. The most expensive ACE inhibitor (for doses with equivalent effects) is captopril, which also uniquely has the problems associated with the mercaptan group, producing penicillamine-like adverse effects: a morbiliform rash and loss of taste.

All ACE inhibitors can cause hyperkalemia, particularly when used with  $K^+/Mg^{++}$  sparing diuretics, and all can cause acute renal failure in patients with bilateral severe renal artery stenosis. The modest impairment of renal function that occurs more commonly should usually be accepted as the price of long-term maintenance of function, in patients at risk of renal failure such as diabetics.

### **Angiotensin II antagonists**

This class of drugs was foretold by Franz Gross 20 years ago in an honorary lecture at the International Hypertension Society; he guessed that they would be the “ideal” antihypertensive drugs.

They are remarkably free of adverse effects; virtually all studies show less adverse effects with these drugs than with placebo. (Patients with well-controlled blood pressure have a higher quality of life, as shown in the HOT study.)

### **Q. Are there important differences among AIIa's?**

The drugs all selectively block the AT1 receptors, that mediate all the adverse effects of angiotensin II; these include vasoconstriction, activation of secondary hyperaldosteronism, and proliferative changes that contribute to atherosclerosis and cardiac hypertrophy. They raise blood levels of angiotensin II, which paradoxically may have beneficial effects by stimulating the AT2 receptor, with putative beneficial antiproliferative effects. This is an active area of research that cannot yet be said to have clinical meaning.

Other theoretical differences between AIIa's can also be said, in my opinion, to have no clinical meaning: competitive vs insurmountable antagonism, affinity for receptors, prodrug vs metabolite, and pharmacokinetic differences. All these differences determine dosing regimens, but in equivalent doses the drugs appear to be equally effective. A recent meta-analysis of all published studies with the common AIIa's on which a substantial body of published literature exists supports the conclusion that all these drugs reduce blood pressure to about the same extent (Conlin PR, Spence JD, Williams B, Ribeiro AB, Saito I, Benedict C, Bunt AMG. Angiotensin II antagonists for hypertension: are there differences in efficacy? *Am J Hypertension* 2000; 13: 418-426.).

### **SUMMARY**

Hypertension is very common and poorly controlled; it is thus a major missed opportunity or “care gap”, and this is particularly true with respect to isolated systolic hypertension in the elderly. In addition to reducing myocardial infarction, renal failure and congestive heart failure, controlling blood pressure reduces stroke by half, and reduces Alzheimer's dementia by half. In difficult cases it is very helpful to use a stimulated plasma renin to determine what pathophysiology is driving the blood pressure; this guides both diagnostic testing and therapy. This maneuver also helps with management of potassium/magnesium depletion from diuretics, by defining whether the problem is due to primary or secondary hyperaldosteronism. Non-compliance and switching of medication accounts for 35% of the cost of treating hypertension; these problems can be minimized by drugs with fewer adverse effects, such as the antagonists of angiotensin II.