Clinical review

Recent advances

General medicine

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One review could not encompass all the noteworthy recent advances in general medicine, but research findings relevant to the treatment of HIV, congestive heart failure, prostatic hypertrophy, hypertension, hypercholesterolaemia, oestrogen replacement, osteoporosis, cancer screening, and symptoms of the common cold have generated particular interest.

Methods

For this review, I defined advances in general medicine as research that might change the management of chronic disease or the strategies to prevent disease. Given the breadth of the subject, I asked colleagues to nominate the three to five articles published in the previous 18 months that they believed had been most important to the practice of general medicine.

HIV infection

Advances in understanding of the pathogenesis and treatment of HIV related illness have resulted in new recommendations for antiretroviral treatment and disease monitoring. Plasma HIV RNA concentrations are now thought to be the most important predictor of outcome,¹⁻³ and reductions in the viral load are associated with a reduced risk of disease progression.⁴ Concerns that treatment with only one agent is associated with rapid selection of resistant virus variants have led to the current recommendation of a regimen incorporating three drugs—two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor. All patients with plasma HIV RNA concentrations > 5000 to 10 000 copies/ml should be given triple therapy, regardless of their CD4+ cell count. Triple therapy is also recommended for patients with symptomatic HIV disease or with CD4+ cell counts below $0.50 \times 10^9/l$.⁵ Unfortunately, these regimens are costly, complicated, and require great commitment on the part of both patients and health care providers. Lack of diligence in adhering to the complex drug regimen may result in emergence of drug resistant strains.

Prostatic hyperplasia

A comparison of two treatments for symptomatic benign prostatic hyperplasia may change practice. When the α -adrenergic blocker terazosin (10 mg daily) was compared to a 5- α -reductase inhibitor, finasteride

Recent advances

New recommendations for antiretroviral therapy and disease monitoring in HIV related illness have been drawn up

Blockade may be effective in selected patients with congestive heart failure but should not replace angiotensin converting enzyme inhibitors

Systolic and diastolic blood pressures were reduced by a diet rich in fruits, vegetables, and low fat dairy foods and low in saturated and total fats

Reducing low density lipoprotein cholesterol concentrations after myocardial infarction was effective even in patients whose cholesterol concentrations were average

Oestrogen replacement therapy prolongs life on average, and its protective effect in coronary artery disease is not lost when progestins are added

Vaginal smears after hysterectomy for benign disease have very low positive predictive value

(5 mg daily), and placebo in 1200 men, symptoms in the terazosin group promptly improved, and the improvement persisted at one year. The finasteride and placebo groups did not differ in the American Urological Association's symptom score or in peak urinary flow rates at baseline and one year.⁶

Congestive heart failure

Carvedilol, a β -adrenergic blocker, is one new treatment for congestive heart failure. In 415 selected patients, fewer in the treatment group died or were admitted to hospital ($P = 0.02$), but the two groups did not differ for mortality alone, exercise performance, or symptoms of congestive heart failure.⁷ The study of left ventricular dysfunction (SOLVD) showed that angiotensin converting enzyme inhibitors improve symptoms and reduce mortality in congestive heart failure,⁸ and now new data show that angiotensin converting enzyme inhibitors reduce long term mortality in patients with congestive heart failure who have an

acute myocardial infarction. In a study of 603 patients with confirmed myocardial infarction complicated by congestive heart failure, mortality was lower at three years in the group randomised to receive angiotensin converting enzyme inhibitors 2-9 days after infarction than in the placebo group (83 (28%) v 117 (39%) deaths, $P=0.002$).⁹ Given the expanding indications for angiotensin converting enzyme inhibitors, losartan, an angiotensin receptor blocker, may prove useful for patients with "captopril cough" or other side effects. A randomised trial comparing losartan to captopril in older patients with congestive heart failure (ejection fraction $\leq 40\%$) found that all cause mortality and hospital admissions were lower with losartan than with captopril, but there were relative few hard end points in comparison with large studies of angiotensin enzyme inhibitors.¹⁰ Until results of larger trials are available, new agents should not generally be used to treat congestive heart failure and should not be substituted for angiotensin converting enzyme inhibitors.

Hypertension

While drugs have been the source of several interesting developments in treatment of various clinical conditions, a recent study found that a diet rich in fruits, vegetables, and low fat dairy foods, and with reduced saturated and total fat, reduced systolic and diastolic blood pressures respectively by 11.4 mm Hg and 5.5 mm Hg more than a control diet that was low in fruits, vegetables, and dairy products and had a fat content typical of the average American diet.¹¹ The authors suggest that the adoption of this diet should complement rather than supplant current recommendations—weight control, reduced sodium chloride intake, and reduced alcohol consumption. Since the reduction in blood pressure was similar to that observed in trials of single drug treatments, such a diet might be recommended as first line treatment for hypertension. In fact, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure advocates such a "stepped care" approach to treatment in its 1997 report.¹²

Alcohol intake and health

The relation between alcohol consumption and health has been a popular topic in the lay press. A review of case-control and cohort studies of alcohol consumption provides evidence that all types of alcoholic drinks are associated with lower risk for coronary heart disease.¹³ A study of alcohol intake and low density lipoprotein cholesterol in nearly 3000 men found a strong inverse association between alcohol intake and risk for coronary heart disease in subjects with low density lipoprotein cholesterol concentrations in the highest fifth. Compared with abstainers, men who drank 22 or more alcoholic beverages per week had a relative risk for coronary heart disease of 0.2 (95% confidence interval 0.1 to 0.8; $P<0.01$). In the lowest fifth (subjects with low density lipoprotein cholesterol ≤ 3.62 mmol/l), however, the inverse association between alcohol intake and coronary heart disease was not significant,¹⁴ implying that people with low concentrations of low density lipoprotein will not benefit from consuming alcohol.

First line treatment for hypertension?

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Cholesterol

A five year randomised trial of pravastatin treatment (40 mg/day) in patients whose cholesterol concentrations after myocardial infarction were average (less than 240 mg/dl (6.2 mmol/l)), showed that lowering low density lipoprotein concentrations reduced the incidence of a combined end point of fatal coronary events and non-fatal myocardial infarction. In addition, the need for revascularisation procedures was reduced in the treatment group. The fact that little or no effect occurred in patients with a baseline low density lipoprotein concentration <125 mg/dl (<3.2 mmol/l) is noteworthy.¹⁵ Taken with data from previous studies, it seems that most patients will benefit from aspirin, β blockade, and hydroxymethyl glutaryl coenzyme A reductase inhibition after a myocardial infarction.

Risk factors for atherosclerotic disease

Hypertension and hyperlipidaemia are well accepted risk factors for coronary heart disease, but new risk factors for atherosclerotic disease have been proposed. In survivors of myocardial infarction, titres of *Chlamydia pneumoniae* antibody were correlated with the likelihood of adverse cardiovascular outcomes.¹⁶ In another study, in which atherosclerosis was determined by direct immunofluorescence, *C pneumoniae* was present in 73% of patients with atherosclerosis who had atherectomy compared with 4% of those who did not have atherosclerosis.¹⁷

Plasma homocysteine values have been associated with overall mortality in patients with confirmed coronary heart disease,¹⁸ and risk of death from coronary heart disease during 15 years' follow up was associated with low serum folate concentrations.¹⁹ The effect is postulated to occur through the conversion of homocysteine to methionine, which requires folate.

Verifying risk factors

While many of the newly proposed risk factors for atherosclerosis are biologically plausible, atherogenesis is probably a product of several interacting determinants. The challenge of the next stage in research into risk factors for atherosclerosis will be to determine how these new risk factors interact with those identified in

the past and how to show that interventions, such as eradication of *C pneumoniae*²⁰ or folate supplements affect the incidence and outcome of coronary heart disease.

What contribution to the observed declines in the incidence of and mortality from coronary heart disease is made by various types of interventions that alter the accepted risk factors for atherosclerosis? A group of investigators sought to determine the proportional contributions of changes in various risk factors by using a computer simulation model of people in the United States between the ages of 35 and 84 years. They estimated that only a quarter of the fall in coronary heart disease mortality in 1980-90 was a result of primary prevention (decrease in incidence). Most could be explained by improvements in the management of patients with diagnosed heart disease through risk factor reduction (secondary prevention) and better treatment. Of various lifestyle changes, lipid profile improvements explained one third of the fall in mortality.²¹

Hormone replacement therapy

Reducing the risk for heart disease is certainly one reason for advising postmenopausal women to use oestrogen replacement therapy. An observational study documented that the protective effect of oestrogen for coronary disease is not lost when progestins are added. This protective effect was only present for the 0.625 mg dose of conjugated oestrogen and was no longer statistically significant three years after stopping treatment.²² The same group showed that hormone replacement therapy prolongs life on average, with less impressive prolongation for women who had been taking hormones for a decade or longer, for those who had not taken oestrogen for the previous five years, and for those with no cardiac risk factors.²³ A predictive model using data derived from published reports showed that hormone therapy should increase life expectancy for most women, including an increase of up to 41 months for women at the greatest risk for coronary heart disease and the lowest risk for breast cancer.²⁴ New, tissue specific oestrogens may provide the benefits of coronary disease and osteoporosis prevention without the risks for breast cancer.²⁵

Another observational study added additional items to the "benefit" side of the counselling equation for women considering oestrogen replacement therapy. A community based cohort of 1124 elderly women was followed longitudinally. Medication use was determined and blinded neurophysiological testing at baseline and follow up were performed to assess the presence of Alzheimer's disease. Altogether 5.8% of the cohort who had ever used oestrogen replacement therapy developed Alzheimer's disease compared to 16.3% of those who had never used it ($P < 0.001$). Importantly, the risk for Alzheimer's disease showed a dose-response effect. The risk fell as the duration of oestrogen replacement therapy increased.²⁶

Osteoporosis

More data regarding the use of alendronate in osteoporosis are available. In a randomised trial of postmenopausal women with low bone mass density

Questions that need answers

- Long term outcome of antiretroviral regimens in AIDS
- How postulated risk factors for atherosclerosis (such as *Chlamydia pneumoniae* infection or raised homocysteine concentrations) interact with identified risk factors
- Whether interventions such as eradication of *Chlamydia pneumoniae* or increased intake of antioxidants or folate supplementation affect the incidence and outcome of coronary heart disease
- Whether use of tissue specific oestrogens affects the risk of cancer, coronary heart disease, and tolerance of side effects
- Comparison of β blockers and angiotensin converting enzyme inhibitors for quality of life and mortality in coronary heart disease
- Long term outcome of the use of "lifestyle modification" to treat hypertension
- Mechanism for utility of zinc gluconate in treating cold symptoms, and its effectiveness in decreasing absenteeism, transmission of viruses, complications, and utilisation of health care

and at least one vertebral fracture at baseline, alendronate increased mean bone mass by up to 6.2% over placebo and reduced the number of new fractures. The groups did not differ in complications not related to fractures. These data are the first in women with established osteoporosis.²⁷

Smear testing and hysterectomy

For women who have previously undergone a hysterectomy for benign disease, there are now data that inform recommendations for cytological screening. A large study of inner city women in the southern United States showed that vaginal cytological screening after hysterectomy for benign disease had a very low positive predictive value. This result is not surprising, given the very low prevalence of cancer of the vagina.²⁸

Common cold

And finally, until a cure for the common cold is developed we must be satisfied with an advance in treating symptoms. In a randomised trial, zinc gluconate lozenges begun in the first 24 hours after cold symptoms developed reduced the median duration of symptoms (4.4 days in the zinc group compared with 7.6 days in the placebo group; $P < 0.001$). More patients in the intervention group noted an unpleasant taste or reported nausea, but the groups did not differ in relation to other side effects.²⁹

- 1 Mellors JW, Kinsley LA, Rinaldo CR Jr, Todd JA, Hoo BS, Kokka RP, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med* 1995;122:573-9.
- 2 Katzenstein DA, Hammer SM, Hughes MD, Gundacker H, Jackson JB, Fiscus S, et al for the AIDS Clinical Trials Group Study 175 Virology Study Team. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. *N Engl J Med* 1996;335:1091-8.
- 3 O'Brien TR, Blattner WA, Waters D, Eyster B, Hilgartner MW, Cohen AR, et al. Serum HIV-1 RNA levels and time to development of AIDS in the multicenter hemophilia cohort study. *JAMA* 1996;276:105-10.
- 4 O'Brien WA, Hartigan PM, Martin D, Esinhart J, Hill A, Benoit S, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS: Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med* 1996;334:426-31.

- 5 Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, et al. Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society-USA panel. *JAMA* 1997;277:1962-9.
- 6 Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, et al. Efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996;335:533-9.
- 7 Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997;349:375-80.
- 8 SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
- 9 Hall AS, Murray GD, Ball SG, on behalf of the AIREX Study Investigators. Follow-up study of patients randomly allocated to ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) study. *Lancet* 1997;349:1493-7.
- 10 Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52.
- 11 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336:1117-24.
- 12 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413-6.
- 13 Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *BMJ* 1996;312:731-6.
- 14 Hein HO, Suadicani P, Gynzelberg F. Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year follow-up in the Copenhagen male study. *BMJ* 1996;312:736-41.
- 15 Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
- 16 Gupta S, Leatham EW, Carrington D, Mendall MA, Kaski JC, Camm J, et al. Elevated Chlamydia pneumoniae antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. *Circulation* 1997;96:404-7.
- 17 Muhlestein JB, Hammond EH, Carlquist JF, Radicke E, Thomson MJ, Karagounis LA, et al. Increased incidence of Chlamydia species within the coronary arteries of patients with asymptomatic atherosclerotic versus other forms of cardiovascular disease. *J Am Coll Cardiol* 1996;27:1555-61.
- 18 Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997;337:230-6.
- 19 Morrison HI, Schaubel D, Desmeules M, Wigle DT. Serum folate and risk of fatal coronary heart disease. *JAMA* 1996;275:1893-6.
- 20 Gurfinkel E, Daroca A, Beck E, Mautner B. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS pilot study. *Lancet* 1997;350:404-7.
- 21 Hunink MGH, Goldman L, Tosteson ANA, Mittleman MA, Goldman PA, Williams LW, et al. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. *JAMA* 1997;277:535-42.
- 22 Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WD, Rosner B, et al. Postmenopausal estrogen and progestin use and risk of cardiovascular disease. *N Engl J Med* 1996;335:453-61.
- 23 Grodstein F, Stampfer MJ, Colditz GA, Willett WD, Manson JE, Joffe M, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;336:1769-75.
- 24 Col NF, Eckman MH, Karas RH, Pauker SG, Goldberg RJ, Ross EM, et al. Patient specific decisions about hormone replacement therapy in post-menopausal women. *JAMA* 1997;277:1140-7.
- 25 Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337:1641-7.
- 26 Tang M, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348:429-32.
- 27 Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. for the Fracture Intervention Trial Research Group. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535-41.
- 28 Pearce KF, Haefner HK, Sarwar SF, Nolan TE. Cytopathological findings on vaginal Papanicolaou smears after hysterectomy for benign gynecologic disease. *N Engl J Med* 1996;335:1559-62.
- 29 Mossad SB, Mackinn ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold. A randomised, double-blind, placebo-controlled study. *Ann Intern Med* 1996;125:81-8.

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Lesson of the week

Late onset interstitial nephritis associated with mesalazine treatment

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Mesalazine is widely prescribed for the treatment of inflammatory bowel disease. It is a single molecule of 5-aminosalicylic acid (5-ASA), and is structurally similar to phenacetin and aspirin. Occasionally, treatment with mesalazine may lead to a severe indolent interstitial nephritis causing appreciable morbidity. Unless detected and treated early this may progress to end stage renal failure despite withdrawal of the drug.¹ It is obvious from the increasing number of reports of nephritis and renal failure occurring after treatment with mesalazine that the premise that "there is no need for routine monitoring of renal function"² needs to be reviewed; the need for a review has been suggested by a number of recent reports.¹⁻³⁻⁹ We report two cases of late onset interstitial nephritis induced by mesalazine (Asacol); the first presented after at least 5 years of continuous treatment with the drug and the second after 1 year.

Case reports

Case 1

A 38 year old laboratory technician began taking mesalazine for ulcerative colitis. After 2 years of

continuous treatment he remained well with normal renal function (serum creatinine concentration 76 µmol/l; normal range 71-133 µmol/l) and negative results on urinalysis. He had an exacerbation of his colitis during the third and fourth years of treatment. On each occasion he responded to a combination of oral prednisolone treatment and an increase in the dose of mesalazine to 1.2 g twice a day. Each time, steroid treatment lasted for 3 months and began with 40 mg a day of prednisolone which was rapidly tapered down to a maintenance dose of 10 mg a day. Repeat serum creatinine concentration measured after 3 years of mesalazine treatment was 79 µmol/l. Thereafter the dose of mesalazine fluctuated between 800 mg and 1.2 g twice a day depending on the severity of his colitis.

After 5 years of treatment he noticed that his urine was frothy. He carried out his own urinalysis; protein was + + +. Mesalazine treatment was discontinued, low dose prednisolone and azathioprine treatment were introduced to control his colitis, and he was referred to the nephrology clinic. At this stage his

Patients taking mesalazine should have renal function monitored regularly to avoid nephrotoxicity

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