turn oligomerise and translocate to the nucleus to alter gene transcription. BMPs 2, 4, 6, and 7 signal through their type II receptor, BMPR-II; there is evidence that they can bind to the type I receptors (ALK-3 and ALK-6) but maximum signalling seems to require cooperation between type I and type II receptors. Acting together with different type I receptors, BMPR-II can exhibit high-affinity binding for several BMPs and GDFs, whereas it has poor affinity for TGF-βs 1, 2, and 3.

How might the *BMPR2* mutations account for the disease? PPH is a disease of vascular remodelling par excellence, and BMPs 2 and 7 have been shown to inhibit vascular smooth-muscle-cell proliferation and to induce apoptosis in some cell types in culture.[5,6] The mutations would be expected to result in a truncated protein or to disrupt function by altering ligand binding or kinase activity. It is tempting to suggest that PPH arises out of an impairment of control of cellular proliferation. Clearly, this is an attractive hypothesis that can readily be tested in cell culture.

What about those patients with PPH who have not been shown to have a mutation in *BMPR2*? The investigators acknowledge that the techniques used to screen the *BMPR2* gene may miss large deletions or gene rearrangements and mutations in non-coding regions. This explanation may be more likely than the alternative possibility that the defect lies elsewhere, perhaps in a gene encoding another component of the BMP signalling pathway, because all the families suitable for linkage studies show linkage to the same locus.

However, since any genetic defect would be present from birth and potentially affect a wide range of tissues with similar expression patterns of BMPR-II to the lung, why would the disease be restricted to the pulmonary vasculature, and why would it manifest later in life in only a small proportion of individuals with the mutation? BMPR-II is essential for development since mice homozygous for a mutation in the kinase domain of BMPR-II die at day 9·5, before gastrulation.[7] By contrast, the heterozygous mice (comparable to the human PPH patients) are grossly normal, indicating that a 50% reduction in BMPR-II receptor function is not in itself sufficient to produce an obvious phenotype. The reason for the poor penetrance of the PPH phenotype may be that a second insult, perhaps in another component of the TGF-β signalling pathway, is required before the phenotype is expressed. An analogy could be hereditary haemorrhagic telangiectasia (HHT), in which causative mutations have been defined in two separate genes (*endoglin* and *ALK-1*) that encode different components of the TGF-β receptor complex.[8,9] In HHT, individuals inheriting the same disease gene display a wide variation in the severity and pattern of disease, and evidence is accumulating of genetic and environmental factors predisposing individuals and mouse models to particular patterns of disease. Perhaps herein lies the basis for the association of PPH with anorectic drugs, although how these agents affect BMP signalling, and why the phenotype should be restricted to the pulmonary vascular bed is not clear.

Attention will now focus on the biology of the BMP family and their receptors. Abnormal signalling through mutated BMPR-II needs to be confirmed, and how dysfunction of this system leads to pulmonary vascular rather than systemic vascular abnormalities needs to be explained. The extent to which sporadic cases of PPH arise from similar mutations will be explored and the role of TGF-β and BMPs in the remodelling of secondary pulmonary hypertension merits study. As is the case so often in medicine, elucidation of the genetic basis of a rare disorder has provided new insight into pathogenesis of disease and offered new prospects for therapy and intervention.

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1 http://www.who.int/ncd/cvd/pph.htm (accesssed on Sept 13, 2000).
2 Nichols WC, Koller DL, Slovis B, et al. Localisation of the gene for familial primary pulmonary hypertension to chromosome 2q31-32. *Nat Genet* 1997; **15:** 277–80.
3 Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet* 2000; **67:** 737–44.
4 The International PPH Consortium. Heterozygous germline mutations in BMPR2, encoding a TGF-β receptor, cause familial primary pulmonary hypertension. *Nat Genet* 2000; **26:** 81–84.
5 Kimura N, Matsuo R, Shibuya H, et al. BMP2-induced apoptosis is mediated by activation of the TAK1-p38 kinase pathway that is negatively regulated by Smad6. *J Biol Chem* 2000; **275:** 17647–52.
6 Soda H, Raymond E, Sharma S, et al. Antiproliferative effects of recombinant human bone morphogenetic protein-2 on human tumor colony-forming units. *Anticancer Drugs* 1998; **9:** 327–31.
7 Beppu H, Kawabata M, Hamamoto T, et al. BMP type II receptor is required for gastrulation and early development of mouse embryos. *Dev Biol* 2000; **221:** 249–58.
8 McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangectasia type 1. *Nat Genet* 1994; **8:** 345–51.
9 Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangectasia type 2. *Nat Genet* 1996; **13:** 189–95.
10 Pece Barbara N, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-β superfamily. *J Biol Chem* 1999; **274:** 584–94.

Exercise prescription in cardiac disease

Although the importance of physical activity to health has long been recognised, the prescription of exercise for patients with cardiac disease was popularised only in the 1960s, specifically in relation to coronary artery disease (CAD).[1] Physical inactivity is an independent risk factor for CAD, posing a similar relative risk as hypertension, hyperlipidaemia, and smoking.[2] Exercise prescription in cardiac disease has been expanded, so it is prescribed not only for primary and secondary prevention of CAD but also in a range of other disorders, such as left-ventricular dysfunction and heart failure, and after various cardiac surgical procedures and interventions.

Exercise prescription is dependent on the specific disease state as well as the presence of other medical complaints, age, medications, and psychosocial factors. As with any prescription, the treatment is prescribed at a specific dose for a particular duration, and the response is monitored. Legal responsibility resides with the prescribing doctor, a feature that has raised concerns, particularly in general practice.[3] Despite good evidence of benefit, this treatment is commonly not offered. For example the American Heart Association (AHA) has recommended physical activities for patients with congenital heart disease[4] but recent evidence suggests advice even in specialist centres is suboptimum.[5]

Exercise prescribed consists of a combination of aerobic and, in most cases, progressive resistance training. Aerobic exercise should involve sustained rhythmic actions of large muscle groups, and the dose can be varied by intensity, duration, and frequency. Intensity can be defined by heart rate, heart-rate reserve, oxygen uptake, metabolic equivalents, or perceived

Effect of exercise

	Aerobic exercise	Resistance exercise
Body composition		
% fat	↓↓	↓
Lean body mass	↔	↑↑
Glucose metabolism		
Insulin response to glucose challenge	↓↓	↓↓
Basal insulin concentration	↓	↓
Insulin sensitivity	↑↑	↑↑
Serum lipids		
HDL cholesterol	↑↔	↑↔
LDL cholesterol	↓↔	↓↔
Resting heart rate	↓↓	↔
Stroke volume, resting and maximal	↑↑	↔
Blood pressure at rest		
Systolic	↓↔	↔
Diastolic	↓↔	↓↔
VO_{2max}	↑↑↑	↑↔
Submaximum and maximum endurance time	↑↑↑	↑↑
Basal metabolism	↑	↑↑

↑=values increase: ↓=values decrease: ↔=values unchanged
Single arrow=small effect; double arrows=medium effect; triple arrow=large effect
Adapted from Pollock and Vincent.[16]

exertion. Sessions should include a warm-up, a conditioning phase, and a cool-down. Warm-up and cool-down are especially important in cardiac disease and significantly reduce the chance of ischaemia, ventricular ectopy, and reduced left ventricular function.[6–8]

Exercise testing before the start of a training programme is recommended, to develop an individual specific prescription based on medical history, risk level, baseline functional capacity, and personal goals. Definitions of who are at high risk during exercise vary, but focus on those with a low ejection fraction, a poor haemodynamic response to exercise, an increase in ventricular arrhythmias with exercise, recent myocardial infarction complicated by serious arrhythmia, or silent ischaemia.

Significant improvements in physical fitness in patients with cardiac disease can occur at lower doses than those recommended for the general population, particularly in those who are in poor condition, with the threshold for benefit being considered to occur between 40 and 60% VO_{2max}.[9] The initial conditioning stage (4–6 weeks) enables familiarisation and reassurance and lasts 12–20 min, starting at the lower end of the target range (eg, 40–50% VO_{2max}). During the improvement stage the dose of exercise is gradually increased in terms of intensity (40–85% VO_{2max}), duration (20–30 min), and frequency (generally three to five times per week). In the maintenance stage, typically reached at 6 months, exercise continues to be done regularly at the level achieved.

Improvements in VO_{2max} start to plateau at three sessions weekly, with more than five sessions weekly conferring negligible further improvements,[10] whilst increasing the chance of musculoskeletal injury. Only modest gains in VO_{2max} are obtained with more intensive exercise.[11] Training regimens less frequent than twice a week do not produce a significant change in VO_{2max}, and loss of body weight/fat is minimal with less than thrice weekly sessions. Patients in poor condition may benefit from reducing the intensity and increasing the duration, and/or breaking up the sessions such that the total work done remains the same.[12]

Adaptations resulting from exercise in patients with cardiac disease are predominantly peripheral, in exercising muscle, rather than central. Functionally related exercise of both upper and lower limb muscle groups is therefore encouraged. Aerobic exercise with arm ergometers is generally prescribed at a slightly lower intensity than for leg exercise.

Individualised, mild to moderate progressive resistance training has been the subject of recent position paper from the AHA[13] and is an important component of the conditioning programme, even in high-risk patients. It may reduce the rate-pressure product and myocardial oxygen consumption, control risk factors, and increase treadmill and cycle endurance time to fatigue, although it has little effect on the VO_{2max} (panel).

Adverse effects with exercise are infrequent, but acute infarction and ventricular fibrillation are most likely in those with ischaemia, severe ventricular damage, or both. Transient arrhythmias and angina are more common than is hypotension.

Evidence of benefit with therapeutic exercise has been described mostly with CAD and include reduction in blood pressure, body weight, improved lipid profiles, and improved psychological well being. In congestive failure there is increased functional capacity, aerobic capacity, and anaerobic threshold, reduced minute ventilation at submaximum exercise, and increased peak blood flow to exercising limb. Cardiac output and ejection fraction remain unchanged.[14]

Exercise is now being prescribed after cardiac transplantation, valve replacement, and patients with implanted devices. The risk of accelerated graft atherosclerosis in cardiac transplant patients necessitates aggressive risk-factor modification, including exercise training, which confers significant benefit. Exercise prescription after valve replacement increases aerobic capacity and work capacity and reduces the rate-pressure product and its rise.[15] Patients with variable-rate pacemakers and implantable defibrillators may also benefit from exercise prescription.

There is a need for more research into the effects of exercise in cardiac disease. Studies have focused predominantly on white men, and the effects of factors such as sex, psychology, socio-economic status, ethnicity, and other cultural factors warrant evaluation. For long-term benefit, regimens must be maintained and, for practical purposes, unsupervised. Identification of the key components that confer benefit, promote compliance, and keep adverse events to a minimum will enable the development of more specific regimens.

In most places there are well-developed hospital-centred post-myocardial infarction rehabilitation services. However, for other cardiac diseases such arrangements are generally fragmented and ad hoc. Training and the wider provision of specialist facilities, both hospital and community based, may help encourage the prescription of appropriate exercise for patients with cardiac disease.

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1 Bethell HJN. Exercise in cardiac rehabilitation. In: MacAuley D, ed. Benefits and hazards of exercise. London: BMJ Books, 1999: 339–60.
2 The pooling project research group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG

abnormalities to incidence of major coronary events: final report of the pooling project. *J Chronic Dis* 1978; **31:** 201–306.
3 Burrows S Exercise prescription: do we prescribe or do we just recommend? *Br J Sports Med* 1999; **33:** 287–88.
4 Fletcher GF, Froelicher VF, Hartley LH, Haskell-WL, Pollock ML. Exercise standards: a statement for health professionals from the American Heart Association. *Circulation* 1990; **82:** 2286–322.
5 Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: a long way to go. *Heart* 2000; **83:** 685.
6 Foster C, Anholm JD, Hellman CK, Carpenter JK, Pollock ML, Schmidt DH. Left ventricular function during sudden strenuous exercise. *Circulation* 1981; **63:** 592–96.
7 Barnard RJ, Gardner GW, Diaco NV, MacAlpin RN, Kattus AA. Cardiovascular response to sudden strenuous exercise: heart rate, blood pressure and ECG. *J Applied Physiol* 1973; **34:** 833–37.
8 Barnard RJ, MacAlpin R, Kattus AA, Buckberg GD. Ischaemic response to sudden strenuous exercise in healthy men. *Circulation* 1973; **48:** 936–42.
9 Franklin BA, Gordon S, Timmis GC. Amount of exercise necessary for the patient with coronary artery disease. *Am J Cardiol* 1992; **69:** 1426–32.
10 Pollock ML, Miller HS, Linnerud AC, Cooper KH. Frequency of training as a determinant for improvement in cardiovascular function and body composition of middle-aged men. *Arch Phys Med Rehabil* 1975; **56:** 141–45.
11 Oberman A, Fletcher GF, Lee J, et al. Efficacy of high-intensity exercise training on left ventricular ejection fraction in men with coronary artery disease (the Training Level Comparison Study). *Am J Cardiol* 1995; **76:** 643–47.
12 Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*; **273:** 402–07.
13 Pollock ML, Franklin BA, Balady GJ, et al. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription. An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* 2000; **101:** 828–33.
14 Sullivan MJ, Higginbotham MB, Cobb FR. Exercise trainingin patients with severe left ventricular dysfunction; hemodynamic and metabolic effects. Circulation 1988; 78: 506–15.
15 Sire-S. Physical training and occupational rehabilitation after aortic valve replacement. *Eur Heart J* 1987; **8:** 1215–20.
16 Pollock ML, Vincent KR. Resistance training for health. The US President's Council on Physical Fitness and Sports Research Digest. December 1996, series 2, no 8.

Prevention of pneumococcal disease by vaccination: does serotype replacement matter?

Recent clinical trials of conjugate pneumococcal vaccines suggest they will be highly effective at preventing invasive disease caused by isolates of the vaccine serotypes.[1,2] However, the long-term efficacy of vaccines that target only a proportion of the isolates of a bacterial species that cause disease, and the possible impact of the selective pressures exerted on a bacterial population by such vaccines, need to be considered.[3,4] For the pneumococcal conjugate vaccines, which target only 7–11 of more than 90 serotypes, the major concerns are whether non-vaccine serotypes will replace vaccine serotypes in the nasopharynx, and the possible consequences, if any, of the increased carriage and transmission of non-vaccine serotypes within the community.

Unlike polysaccharide vaccines, pneumococcal conjugate vaccines affect the prevalence of nasopharyngeal carriage.[5,6] An early study of Gambian infants immunised with a five-valent pneumococcal conjugate vaccine, and then re-immunised with a 23-valent pneumococcal polysaccharide vaccine at the age of 2 years,[7] showed a reduction in the prevalence of nasopharyngeal carriage of pneumococci of the vaccine serotypes. However, replacement with pneumococci of non-vaccine serotypes occurred, so the overall prevalence of pneumococcal carriage in vaccinated children was little changed. A second study of Gambian children 1–4 months after completion of a primary course of vaccination with a nine-valent conjugate vaccine at the ages of 2, 3, and 4 months showed a similar trend,[8] but the effect was smaller than in the initial study, perhaps because these children had lower antibody concentrations. Although a study from Israel did not find evidence for replacement,[9] subsequent studies in South Africa and in Israel did so.[10,11] In the second Israeli study, which was undertaken in children attending day-care centres, pneumococci of non-vaccine serotypes were found infrequently in very young children and remained uncommon in non-vaccinated children. However, in vaccinated children, the proportion of pneumococci isolated from the nasopharynx of non-vaccine serotypes, relative to those of vaccine serotypes, increased gradually with age and, by the age of 3 years, pneumococci of non-vaccine serotypes predominated.[11]

The results of these carriage studies suggest that replacement of vaccine serotypes by non-vaccine serotype in the nasopharynx will occur after mass implementation of the conjugate pneumococcal vaccine. Whether this replacement will increase the incidence of invasive disease caused by pneumococci of the latter types is difficult to predict. Pneumococci of non-vaccine serotypes may, as commonly assumed, be inherently poor at causing pneumonia and invasive disease, and the increased carriage and transmission of these isolates would have no consequences for these forms of pneumococcal disease. Alternatively, pneumococci of some non-vaccine serotypes may have high attack rates, but currently cause little pneumonia or invasive disease because they compete poorly with vaccine serotypes for colonisation of the nasopharynx. If they were given a competitive advantage at colonisation because of vaccination, they might become an important cause of pneumonia and invasive disease. The most likely long-term outcome is somewhere between these extremes—pneumonia and invasive disease caused by non-vaccine serotypes will probably increase after vaccination but the overall prevalence of these pneumococcal diseases will remain substantially below pre-vaccination levels.

Serotype replacement may be of more concern for the control of acute otitis media than of invasive disease. It is not known whether there are particular strains (as opposed to serotypes) of pneumococci that preferentially cause otitis media or whether almost any pneumococcus that colonises the middle ear can cause this infection. If the latter is the case, the conjugate vaccines are unlikely to have any sustained effect on the prevalence of otitis media, since serotype replacement following vaccination would simply lead to otitis media being increasingly caused by pneumococci of non-vaccine serotypes. There is some support for this view from the conjugate vaccine trial in Finland, where the incidence of otitis media caused by pneumococci of non-vaccine serotypes increased by 37% in vaccinated children.[12]

High-level penicillin resistance is found almost exclusively among isolates of the vaccine serotypes, presumably because selective pressures for resistance are strongest on isolates carried in the nasopharynx of children, which are predominantly of these serotypes. Thus, introduction of the conjugate vaccines should lead to a reduction in the prevalence of carriage and disease caused by penicillin-resistant isolates. However, if serotype replacement results in a new set of childhood