drugs which in separate studies have been shown to improve endothelial vasomotor function experimentally.[8 9] None of these prevention studies prospectively measured endothelial function, so attributing the improved outcome to enhanced endothelial function is speculative.

Assuming that measurement of endothelial vasomotor function adds usefully to current methods of risk stratification, do we have a test that may be applied to the general population? At present we do not. Though widely used in research, flow mediated dilatation and venous plethysmography are not useful for population screening. Both require specialised equipment and skilled operators, and venous plethysmography requires insertion of an intra-arterial needle. A more widely applicable tool for assessing endothelial vasomotor function is needed, and methods such as pulse wave velocity analysis are currently under investigation.[14]

The drugs that improve endothelial vasomotor function are already available.[8–10] If further studies show clinical benefit after enhancing endothelial vasomotor function the race to find a clinically useful tool to measure it will begin. This will allow more accurate targeting and monitoring of therapy to reduce cardiovascular risk in the individual.

Sagar N Doshi *British Heart Foundation research fellow*
(DoshiSN@cardiff.ac.uk)

Malcolm J Lewis *professor of cardiovascular pharmacology*
Jonathan Goodfellow *senior lecturer in cardiology*

Wales Heart Research Institute, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN

SND is supported by a junior research fellowship from the British Heart Foundation.

1 Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med* 1990;323:27-36.
2 Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362:801-9.
3 Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986;315:1046-51.
4 Reddy KG, Nair RN, Sheehan HM, Hodgson JM. Evidence that selective endothelial dysfunction may occur in the absence of angiographic or ultrasound atherosclerosis in patients with risk factors for atherosclerosis. *J Am Coll Cardiol* 1994;23:833-43.
5 Goodfellow J, Bellamy MF, Gorman ST, Brownlee M, Ramsey MW, Lewis MJ, et al. Endothelial function is impaired in fit young adults of low birth weight. *Cardiovasc Res* 1998;40:600-6.
6 Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, et al. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol* 1995;26:1235-41.
7 Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88:2149-55.
8 Esper RJ, Machado R, Vilarino J, Cacharron JL, Ingino CA, Garcia Guinazu CA, et al. Endothelium-dependent responses in patients with hypercholesterolemic coronary artery disease under the effects of simvastatin and enalapril, either separately or combined. *Am Heart J* 2000;140:684-9.
9 Goodfellow J, Bellamy MF, Ramsey MW, Jones CJ, Lewis MJ. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. *J Am Coll Cardiol* 2000;35:265-70.
10 Title LM, Cummings PM, Giddens K, Genest JJ, Nassar BM. Effect of folic acid and antioxidant vitamins on endothelial dysfunction in patients with coronary artery disease. *J Am Coll Cardiol* 2000;36:758-65.
11 Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899-906.
12 Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000;101:948-54.
13 Shaper AG, Pocock SJ, Phillips AN, Walker M. Identifying men at high risk of heart attacks: strategy for use in general practice. *BMJ* 1986;293:474-9.
14 Naka KK, Doshi SN, Ashton M, Frenneaux MP, Jones CJH, Goodfellow J. Changes in pulse wave velocity in large arteries are nitric oxide-mediated. *Eur Heart J* 2000;21:357.

Bacteriotherapy: the time has come

Bacterial interference is an increasingly attractive approach to prevention and therapy

The worldwide emergence of bacterial resistance to antibacterial agents has produced a need for new methods of combating bacterial infections. This need is forced on us by the long time lag in developing new antibacterial agents. And even though new agents may be in the pipeline, they will not solve all current resistance problems. In addition, we also have to recognise that the use of antibacterial agents not only selects resistant bacteria but also disturbs normal human flora, which may itself further inhibit our defence against infection. Bacteriotherapy—using harmless bacteria to displace pathogenic organisms—is an alternative and promising way of combating infections.[1]

A recent paper in the *BMJ* by Roos et al showed how commensal α haemolytic streptococci were used to replace the normal nasopharyngeal flora in children with recurrent otitis media.[2] The results were astonishing. After treatment, recurrences of otitis media fell to half of those in the control group; at three months 42% of children given streptococci in nasal spray were healthy compared with 22% of the controls; and the need for new courses of antibacterial treatment decreased. This study is not the first of its kind from this group: Roos et al have also successfully used α haemolytic streptococci in preventing recurrent streptococcal tonsillitis.[3]

This approach to treatment is not new.[1] Bacterial interference was once widely studied, and attempts to influence colonisation of pathogenic bacteria with "harmless" bacteria were carried out some decades ago. In human health bacteriotherapy was probably forgotten because of the continuous development of new, more potent antibacterial agents and because of fears about possible side effects. Avirulent bacterial strains can, in principle, also cause infections. Though otherwise effective, *Staphylococcus* spp 502A caused minor skin lesions in a few individuals when it was introduced into the skin flora to interfere with a virulent strain of *S aureus*.[1] Nevertheless, bacteriotherapy has already long been used in animals—for example, to prevent salmonellosis in chickens.[4]

The results of Roos et al show also that antibiotic treatment itself increases the risk of recurrent otitis media, and we know that antibiotic treatment for any purpose increases the risk of urinary tract infections in young women.[5] Again, this increased risk is probably caused by the antibiotics disturbing the balance of normal genital and perianal flora.

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Bacteriotherapy has also been used for other indications. Faeces or a mixture of faecal bacterial strains have been used to treat recurrent *Clostridium difficile* infection.[6] Although the efficacy of this treatment method still remains undecided because no randomised trials have been performed, *Saccharomyces bourlardii* yeast was used for the same indication in a randomised trial, with good results.[7] Milk containing *Lactobacillus* GG, given to children in day care centres, seems to reduce the rate and severity of respiratory infections.[8] Lactobacilli have been used in various clinical conditions—for example, for prophylaxis of antibiotic induced diarrhoea (decreasing the diarrhoea rate to one third compared with placebo) but also in promoting recovery from acute diarrhoea in children.[9] Moreover, non-pathogenic *Escherichia coli* have successfully been used to treat ulcerative colitis.[10]

Why are strategies such as bacteriotherapy arousing more interest in our attempts to combat antibacterial resistance? Although restrictions on use of antibacterial drugs in hospitals are effective in reducing bacterial resistance, the increasing number of immunocompromised patients in hospitals nevertheless tends to increase their use. And although we have shown that the reduction of antibiotics used in the community can reduce bacterial resistance,[11] this is a long row to hoe. Also, it may be that bacterial resistance is still too remote a problem for most physicians, patients, decision makers, and the medical industry to cause any concerted action in reducing antibacterial consumption. We do not even know the total consumption of antibacterial agents among humans in the European Union.[12]

In addition to bacteriotherapy, other strategies to reduce infection and bacterial resistance include improved hygiene measures, especially in hospitals but also in day care centres, and new bacterial vaccines.[12] In the future, treatment opportunities may include antibody treatment and bacteriophage therapy.

In the meantime bacteriotherapy seems to be a promising candidate for the future treatment and prevention of respiratory tract and gastrointestinal infections. Several questions remain open, however, such as safety. The α haemolytic streptococci chosen by Roos et al were selected for their superior ability to inhibit the growth of respiratory tract pathogens. Even if bacteriotherapy is safe for individual patients, the possibility remains that large quantities of active bacteria used clinically might change the human flora at population level.

Indeed, we still know very little about the complex system of human flora. There is an immediate need for basic research, and new molecular techniques should help.[13] This research is needed not only to develop bacteriotherapy and other medical treatments but also to better understand the role of human flora—for example, in food processing. Certainly the human microbiome will present plenty of challenges to eager explorers over the next few years.

Pentti Huovinen *chief physician*

Antimicrobial Research Laboratory, National Public Health Institute, 20520 Turku, Finland

1 Sanders WE, Sanders C. Modification of normal flora by antibiotics: effects on individuals and the environment. In: Root RK, Sande MA, eds. *New dimensions in antimicrobial therapy: contemporary issues in infectious diseases*. New York: Churchill Livingstone, 1984:217-41.
2 Roos K, Grahn Håkansson E, Holm S. Effect of recolonisation with "interfering" α streptococci on recurrences of acute and secretory otitis media in children; randomised placebo controlled trial. *BMJ* 2001;322:210-2.
3 Roos K, Holm SE, Grahn-Håkansson E, Lagergren L. Recolonization with selected alfa-streptococci for prophylaxis of recurrent streptococcal pharyngotonsillitis—a randomised placebo-controlled multicentre study. *Scand J Infect Dis* 1996;28:459-62.
4 Nurmi E, Rantala M. New aspects of Salmonella infection in broiler production. *Nature* 1973;241:210-1.
5 Smith HS, Hughes JP, Hooton TM, Roberts P, Scholes D, Stergachis A, et al. Antecedent antimicrobial use increases the risk of uncomplicated cystitis in young women. *Clin Infect Dis* 1997;25:63-8.
6 Tvede M, Rask-Madsen J. Bacteriotherapy for chronic relapsing Clostridium difficile diarrhoea in six patients. *Lancet* 1989;i:1156-60.
7 McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA, et al. A randomised placebo-controlled trial of Saccharimyces boulardii in combination with standard antibiotics for Clostridium difficile disease. *JAMA* 1994;271:1913-8.
8 Hatakka K, Savilahti E, Pönkä A, Meurman JH, Poussa T, Näse L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001;322:1327-9.
9 Arvola T, Laiho K, Torkkeli S, Mykkänen H, Salminen S, Maunula L, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomised study. *Pediatrics* 1999;104:e64.
10 Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon A. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999;354:635-9.
11 Seppälä H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effects of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med* 1997;337:441-6.
12 Huovinen P, Cars O. Control of antimicrobial resistance: time for action. *BMJ* 1998;317:613.
13 Hooper L, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationship in the intestine. *Science* 2001;291:881-4.

Phytoestrogen therapy for menopausal symptoms?

There's no good evidence that it's any better than placebo

Popular media would have us believe that plant constituents with a phenolic structure similar to oestrogen, known as phyto (plant) oestrogens, provide a natural alternative to the use of postmenopausal hormone replacement therapy. Are the popular media right?

Phytoestrogens, found in a wide variety of edible plants, may display both oestrogenic and antioestrogenic effects. Epidemiological studies, primarily comparing Asian and Western populations, have been interpreted to indicate that consumption of a diet rich in phytoestrogens ameliorates oestrogen deficiency symptoms in postmenopausal women—and may protect against breast cancer, bone loss, and cardiovascular disease. Consequently there is a global movement towards increased consumption of foods rich in phytoestrogens, and tablet formulations of concentrated isoflavone extracts are being heavily promoted. However, more recent intervention studies question the validity of the proposed benefits of phytoestrogen

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