By the late 1970s, however, disappointment was universal. Departments of community medicine, social medicine, and public health were seen as the "departments of miscellaneous medicine," the soft underbelly of the medical school. They produced socially desirable talk but no hard data. That was in stark contrast to the pilot discipline, epidemiology, which had become widely successful as a method. Some of the talk about the lack of influence of clinical medicine on people's health proved plainly wrong.⁹ Chairs of social medicine, community medicine, and public health were turned into chairs of epidemiology with an aetiological, methodological, or clinical orientation. Again some older hands were uneasy that this methodological and clinical epidemiology had lost the real substance, the basic aim of serving the people, and had become sophistry.¹⁰⁻¹² Proponents of epidemiology retorted in two ways. Firstly, they directly attacked some of the fancier visions of public health oriented towards prevention—for example, they described the Lalonde report on the health of Canadians as epidemiology going wild and losing its medical and scientific basis. Secondly, they defended a division of tasks between scientists and political decision makers.¹³

Sooner than expected, we see a new movement arise from the latest ashes, calling itself the new public health.¹ Its phrasings have the flavour of the great tradition that seeks for the all embracing causes of disease in the fabric of our society. We read about "the interdependence of ecosystems and health systems" and about "reciprocal maintenance" (we should look after the things that look after us).¹ In a curious echo of last century's hygienic movement, the emergence of "new" infectious diseases like legionnaire's disease and AIDS is regarded as a failure of the curative model. More surprisingly, several proponents of the new public health want to divorce themselves from the erstwhile star discipline, epidemiology. To them epidemiologists have defected en masse to the arch enemy: the reductionist medical model. Thus in the minutes of a recent meeting we read that "Classical epidemiology and the medical model are institutionally powerfully entrenched."¹⁴ To remove the barriers to health the public needs to be empowered, and data on lay knowledge and beliefs should become equally valid as pseudo-objective numerical descriptions. This culminates in headlines like

"The problem with epidemiology" and "Understanding the whole."

To the sceptic, the "new" public health is a repetition of old style rhetoric, with the same stubborn tactics that will lead to a new academic downfall. As such, the young movement is highly controversial, especially in those departments of public health and community medicine that believe that good science should be the basis for public health action.

Still, one might wonder why these ideas keep arising. There will always be a legitimate branch of medicine that deals primarily with the health of groups in our society. (An essay on the roots of such a discipline, written in 1947 by the American historian and public health doctor George Rosen, is still worth reading, to whatever age of public health one belongs.¹⁵) In each new generation of doctors, however, this branch of medicine attracts not only analytical minds but also people who feel a strong personal vocation to improve health in society by attacking plain injustice. They are impatient with the distant attitude of science. Let their well meaning and ever re-emerging zeal be directed in good ways.

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Vascular disease: the next target for local molecular therapeutics

Reducing restenosis after angioplasty could be their first success

The resistance of atherosclerosis to conventional treatments reflects the complex pathogenesis of mature atheroma. The disease is diffuse, but the symptomatic lesions are often localised, and bypassing large stenosing plaques with vein grafts has been the mainstay of palliation. For the past 15 years, however, percutaneous transluminal coronary angioplasty has been used increasingly. In 1990 over 300 000 of these procedures were carried out in the United States¹ and about 8500 in Britain.² This number is still rising, but enthusiasm has been tempered by symptomatic restenosis in about one third of cases.³ Late recoil of the stretched vessel may contribute, but a rapid proliferation of vascular smooth muscle cells within the intima is the striking feature of restenosis, and this fibrocellular intimal hyperplasia has resisted all pharmacological interventions examined so far.³ Attention has turned to less conventional treatments, particu-

larly genetic manipulation of the arterial wall to alter its response to the injury induced by the balloon catheter. To distinguish this local approach from the use of gene therapy to correct inborn errors of metabolism we favour the term molecular therapeutics.

The restenotic lesion after angioplasty can be viewed as part of general healing and repair. Giving potent treatments systemically to modify this is likely to have systemic side effects, which local administration could circumvent. In preliminary studies, administration has been to the outside of vessels visualised directly, with vehicles such as pluronic gels being used to hold the agent of therapeutic potential in the vicinity for at least some hours.⁴ Although this is unlikely to be clinically useful, application from the luminal side is already possible through modified conventional catheters. The molecular therapeutic approach to restenosis requires

two further considerations. Firstly, specific therapeutic targets have to be identified, and, secondly, ways of genetically manipulating the specific targets have to be devised.

The involvement of many growth factors in the formation of fibrocellular intimal hyperplasia makes it difficult to identify which steps in the process are pivotal and will individually make good targets for gene therapy. Several DNA binding proteins that regulate transcription have been considered. Periadventitial and abluminal administration of antisense oligonucleotides (oligonucleotides that are complementary to the mRNA transcribed from specific genes and that bind to the mRNA, inhibiting its translation and promoting its metabolism) has been shown to be effective in rat models of vascular injury.⁴⁻⁶ Such oligonucleotides could be clinically useful if their stability and administration can be optimised. Chemically modifying the oligonucleotides and packaging them into liposomes with viral coat proteins, which may improve their uptake into cells, are two means of addressing these problems.⁶

Investigating transfection

Alternatively, transfected genes could be used to influence the subsequent response of the injured vessel wall. Model systems have been used to test this by transfecting marker genes into cultured vascular cells and then transplanting the modified cells into the artery or on to a vascular graft before implantation.⁷⁻⁹ Direct transfection of genes into arterial cells is also possible. There are two main methods: either using modified viruses to carry the new genes into the cells or giving genetically engineered DNA in a fatty emulsion, which facilitates uptake into cells (lipofection). Low efficiency of transfection has been a substantial problem with both methods of transferring genes: as few as 1 in 1000 cells may incorporate and express the transfected reporter gene. For therapeutic effects such transfection would have to induce the local production of substances with potent paracrine effects.

Pathological effects of transfection of genes on the arterial wall have now been reported. Nabel *et al* recently described the effects of introducing the genes for platelet derived growth factor B or acidic fibroblast growth factor into the pig iliac artery.^{10,11} Although the efficiency of transfection was low (with only 0.1-1% of cells in the arterial segment containing transfected DNA), the intimal area was considerably thickened. Both growth factors have been implicated in atherogenesis and the vascular response to injury, but this is the first demonstration that their local expression, even without endothelial damage could directly influence intimal thickness.

Expression of acidic fibroblast growth factor also induces neovascularisation. Interestingly, the observable effect of the transfection of either agent was confined to the intimal layer even though the distribution of the plasmid DNA and histochemical demonstration of gene expression suggested that transfection was transmural (E Nabel, atherosclerosis and restenosis University of Washington symposium, Seattle, September 1993). The studies implicate these growth factors further in the pathogenesis of fibrocellular intimal hyperplasia

and possibly provide a model against which therapeutic agents may be tested.

Other vectors are also available, and recent reports suggest that adenoviruses may overcome many of the problems previously encountered with retroviruses. Adenoviral vectors accept relatively large recombinant genes (up to 7.5 kilobases) and can be propagated in mammalian cell culture, and transfection does not require that the cells are replicating. Marker genes have been transfected into normal sheep and injured rat vessels with this vector, and high levels of transfection and expression (up to 75%) occur.¹²⁻¹⁴

These adenoviruses may have additional advantages over other transfection vectors. An effect that is limited to a few critical days or weeks after angioplasty would be beneficial in this situation, and fortunately the adenovirus vectors, unlike retroviruses, generally do not show stable integration into the genome (reducing also the risk of insertional mutagenesis). Many adenoviruses are used in vaccines and have been extensively examined in clinical trials; their safety is being evaluated further in the United States as part of programmes assessing gene therapy, particularly therapy targeting cystic fibrosis.

Restenosis after angioplasty is now a common clinical problem and has important financial implications. Reducing the restenosis rate to 25% would result in an estimated saving of \$500m (£333m) in the United States.¹⁵ These factors drive the studies that could make local vascular molecular therapeutics a clinical option in the next few years.

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