trial. The National Cancer Institute has launched the national lung screening trial, a controlled study of 50 000 people that randomises participants to chest screening by computed tomography or *x* ray and uses mortality as an end point. It is the right way to address this issue, but it could take a decade to produce an answer.

How should patients, especially those who smoke, be advised in the meantime? After providing counselling for nicotine dependence doctors could suggest that patients enrol in the national lung screening trial or similar trials. If patients simply want to get scanned, doctors should take the time to discuss the pros and cons. Doctors without financial conflicts of interest are best positioned to give balanced informed consent. As patients' fiduciary, doctors should tell patients in explicit terms that such screening has no proved benefit and that serious risks could outweigh benefits (if there are any). Patients should understand that the stakes are high.

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1 Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, et al. Lung cancer screening with CT: Mayo clinic experience. *Radiology* 2003;226:756-61.
2 Yang M, Hasegawa S, Jiang P, Wang X, Tan Y, Chishima T. Widespread skeletal metastatic potential of human lung cancer revealed by green fluorescent protein expression. *Cancer Res* 1998;58:4217-21.
3 Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med* 1995;333:1757-63.
4 Rak JW, St Croix BD, Kerbel RS. Consequences of angiogenesis for tumor progression, metastasis and cancer therapy. *Anticancer Drugs* 1995;6:3-18.
5 Liotta LA, Kleinerman J, Saidel GM. Quantitative relationships of intravascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. *Cancer Res* 1974;34:997-1004.
6 Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998;351:1242-5.
7 Bernard A. Resection of pulmonary nodules using video-assisted thoracic surgery. The Thorax Group. *Ann Thorac Surg* 1996:61;202-4.
8 Mack MJ, Hazelrigg SR, Landreneau RJ, Acuff TE. Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. *Ann Thorac Surg* 1993;56:825-30.
9 Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992;101:1332-7.
10 Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 2003;289: 313-22.

Failures of the therapeutic chain as a cause of drug ineffectiveness

Promotion, misinformation, and economics work better than needs

Failure of drug treatment may be due to wrong diagnosis, selection of an inappropriate drug or dosage, use of an adulterated or fake drug, the patient's non-adherence, a drug's poor bioavailability or lack of efficacy, medication error, or occurrence of an adverse reaction. The potential causes of therapeutic failure depend on a complex interplay of social and medical factors. Failures can occur at every step of the therapeutic chain, which is the process describing the life of medicines in a community. This process includes development, regulation (including registration), marketing, distribution, prescription, dispensing, and use of the drug.[1]

The following are only some examples of failures in drug treatment. In 2001 the top five best selling medicines globally were atorvastatin, omeprazole, simvastatin, lansoprazole, and amlodipine, although available evidence indicates that only two of these drugs are first choice in their class. In recent years, various non-essential non-innovative drugs had to be withdrawn from the market because of serious adverse effects after a few years of growth in sales. One of these drugs, troglitazone, was associated with a risk of liver failure, which had been played down by the manufacturing company.[2] More recently, serious flaws in the published pivotal trial that served as the basis for the global promotion of celecoxib were made public,[3] and alosetron was reapproved by FDA amid accusations that the FDA had become a servant of the drug industry.[4]

Prescription patterns are far from optimal. Although evidence supports thiazide diuretics as the treatment of first choice of hypertension, angiotensin converting enzyme inhibitors and calcium channel blockers are the most consumed antihypertensive drugs. Although in multiple sclerosis azathioprine is backed by better evidence of long term efficacy and (perhaps because) it is 125 times cheaper than interferon beta, interferon beta is the preferred treatment in many specialised centres.[5] In the United States adverse drug effects rank fourth to sixth in the list of causes of death.[6] Ineffective drugs, such as cinnarizine or bovine gangliosides, have been identified in clinical trials and voluntary reporting systems as causes of serious adverse effects.[7 8]

How are these and many other failures possible? Firstly, the methods and objectives of medical research are driven mainly by industrial priorities and the fulfilment of regulatory requirements, rather than by a conceptual framework that aims to answer questions that arise in medical practice. Clinical trials are designed to evaluate drugs rather than patients or diseases.

Secondly, the term efficacy is merely a higher probability of clinical improvement, compared with placebo, in selected end points that may have varying clinical relevance. The implication is that in practice therapeutic failure is, and should be, common. In addition, efficacy does not necessarily translate into effectiveness in usual practice.[9]

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Thirdly, drug regulatory agencies grant market authorisations for new drugs on the basis of a set of standards, which have been suggested by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, whose secretariat is provided by the International Federation of Pharmaceutical Manufacturers Associations. The international conference has established detailed standards for drug development, but it has not shown much interest in developing standards for the review of obsolete drugs, the provision of information to prescribers and consumers, the use of international non-proprietary names of medicines, transparency about pricing, international norms to control promotion and advertising, transparency in drug safety monitoring, or access to information.

Market authorisations tend to be granted on the basis of superiority over placebo or non-inferiority with respect to alternative treatments rather than on the basis of relative efficacy and cost benefit.[10] While the ratio of therapeutic benefit to risk of drugs depends on the circumstances surrounding their use, agencies regulating drugs increasingly tend to assess quality, efficacy, and safety as if these were independent of the way and the context in which drugs are prescribed, dispensed, and used. The result is that drug and industry oriented clinical research and regulation are leading to drug and industry driven therapeutic practice.

Fourthly, pharmaceutical companies have an increasing direct or indirect influence on the mechanisms of drug selection and purchasing in healthcare systems. In the United States, most health maintenance organisations subcontract with pharmaceutical benefits managers who negotiate prices of prescriptions with pharmacies, institute mandatory generic substitution programmes, and develop purchase agreements with manufacturers. Several of the largest pharmaceutical benefits management organisations have been purchased by pharmaceutical companies, which in 1994 controlled 113 million people enrolled with health maintenance organisations..[11] In the European Union drugs are generally reimbursed according to their market value rather than their therapeutic value, and the result is that new drugs, which are more expensive than old established ones (and therefore generate more profits), are most heavily promoted.

Fifthly, the marketing budgets of the pharmaceutical industry are larger than the research and development costs. The industry increasingly controls scientific societies and continuing medical education, and this has become a new marketing strategy. It is a failure that healthcare systems, where decisions are based on knowledge, do not consider continuing education as a strategic priority and that the field has been left primarily to the technology industry.

Sixthly, the trade related intellectual property rights agreement of the World Trade Organization, which grants patents for 20 years, has an important negative effect on the equitable access of populations to drugs. In addition, it makes companies concentrate their promotional efforts on the newest and most expensive drugs while they are protected by a patent. Lack of access to essential drugs is certainly a failure.

Finally, the opportunity for therapeutic failure is especially high in less developed countries, where the standards of regulation, quality control, training of health professionals, financial access, and drug and therapeutic information are low if they exist at all.

Much can be done at all stages of the therapeutic chain. Medicine is deeply and increasingly embedded with market values and industrial culture. Research skills have to be built up inside the health system, which is the natural laboratory of clinical pharmacology. The new information technologies may be of great help to set up networks of health professionals, which should monitor what is relevant, feasible, necessary, and effective in therapeutics.[12] Large changes of prescription patterns cannot be achieved by passive transfer of information, and so a need exists to build up a critical mass of professionals practising in the healthcare system and involved in research that should produce knowledge rather than mere information.

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1 World Health Organization Expert Committee. WHO model list of essential medicines—12th list. Geneva: WHO, April 2002. who.int/medicines/organization/par/edl/edl2002core.pdf (accessed 18 Jul2002).
2 Gottlieb S. Company played down drug's risks, report says. *BMJ* 2001;322:696.
3 Jüni P, Rutjes AWS, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? Adequate analysis of the CLASS trial indicates that this may not be the case. *BMJ* 2002;324:1287-8.
4 Moynihan R. Alosetron: a case study in regulatory capture, or a victory for patients' rights? *BMJ* 2002;325:592-5.
5 Rudge P. Are clinical trials of therapeutic agents for MS long enough? Lancet 1999;353:1033-4.
6 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA* 1998;279:1200-05.
7 Laporte JR, Capellà D. Useless drugs are not placebos. *Lancet* 1987;1:1324.
8 Figueras A, Morales-Olivas FJ, Capellà D, Palop V, Laporte J-R. Bovine gangliosides and acute motor polyneuropathy. *BMJ* 1992;305:1330-1.
9 Stolley PD, Laporte J-R. The public health, the University, and pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology*. Chichester: Wiley, 2000:75-89.
10 Ferner RE. Newly licensed drugs. *BMJ* 1996;313:1157-58.
11 Schulman KA, Rubenstein E, Abernethy DR, Seils DM, Sulmasy DP. The effect of pharmaceutical benefits managers: is it being evaluated? *Ann Intern Med* 1996;124:906-13.
12 Tognoni G, Bonati M. Second-generation clinical pharmacology. *Lancet* 1986;1028-29.