1 Slamon D, Clark G, Wong S, et al. Human breast cancer: correlation of relapse and survival with amplification of the *HER2-2/neu* oncogene. *Science* 1987; **235:** 177–82.
2 Perou CM, Tibshirani R, Aas T, et al. Molecular portraits of human breast tumours. *Proc Natl Acad Sci USA* 2001; **98:** 10869–74.
3 Carlomagno C, Perrone F, Gallo C, et al. *c-erb B2* overexpression decreases the benefit of adjuvant tamoxifen in early-stage breast cancer without axillary lymph node metastases. *J Clin Oncol* 1996; **14:** 2702–08.
4 Berns E, Foekens J, van Staveren IL, et al. Oncogene amplification and prognosis in breast cancer: relationship with systemic treatment. *Gene* 1995; **159:** 11–18.
5 Seshadri R, Firgaira F, Horsfall D, et al. Clinical significance of HER-2/neu oncogene amplification in primary breast cancer: the South Australian Breast Cancer Study Group. *J Clin Oncol* 1993; **11:** 1936–42.
6 Zemzoum I, Kates RE, Ross JS, et al. Invasion factors uPA/PAI-1 and HER2 status provide independent and complementary information on patient outcome in node-negative breast cancer. *J Clin Oncol* 2003; **21:** 1022–28.
7 Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002; **20:** 719–26.
8 Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
9 Sieweke M, Bissell M. The tumor-promoting effect of wounding: a possible role for TGF-beta-induced stromal alterations. *Crit Rev Oncog* 1994; **5:** 297–311.
10 Martins-Green M, Boudreau N, Bissell M. Inflammation is responsible for the development of wound-induced tumors in chickens infected with Rous sarcoma virus. *Cancer Res* 1994; **54:** 4334–41.
11 Rowley D. What might a stromal response mean to prostate cancer progression? *Cancer Metastasis Rev* 1998–99; **17:** 411–19.
12 Hofer S, Shrayer D, Reichner J, et al. Wound-induced tumor progression: a probable role in recurrence after tumor resection. *Arch Surg* 1998; **133:** 383–89.
13 Burstein HJ, Harris LN, Gelman R, et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. *J Clin Oncol* 2003; **21:** 46–53.

Is there really an epidemic of type 2 diabetes?

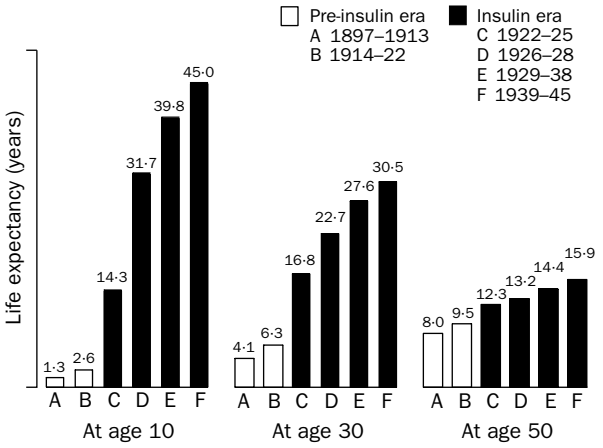
See page 537

Diseases are not immutable entities but dynamic social constructions that have biographies of their own.[1] Few diseases are more dynamic than diabetes. Type 2 diabetes, its most common form, is a heterogeneous condition that eludes aetiological classification and must still be defined in terms of its consequences—hyperglycaemia and late complications—and by the absence of features of type 1 diabetes. Risk is largely determined by the quartet of age, obesity, family history, and ethnicity. Type 2 diabetes targets the rich in poor countries and the poor in rich countries; it affects some 10% of those with a western lifestyle who survive into later life, rising to 30% or more depending on family history or ethnic background. Despite its high frequency, it is hard to quantify accurately, since known cases represent only the tip of an iceberg of hyperglycaemia within the population. Prevalence estimates will vary according to access to diagnostic facilities, the diagnostic cutoffs used at the time of the survey, the means of ascertainment, the nature and age-structure of the population under consideration, the ability to distinguish between type 1 and type 2 diabetes, and the longevity of those affected. Despite all these reasons for variation, recent estimates are consistent in showing a rising prevalence of obesity-related diabetes—"diabesity"—around the world. We are in the grip of a pandemic of type 2 diabetes. Or are we?

The report by Henrik Stovring and colleagues from Denmark in this issue of *The Lancet* comes as a useful antidote to oversimplification. Analysis of prescription and mortality data for the island of Fyn for 1992–99 shows an increasing prevalence of diabetes, but suggests that the increase was driven by improved longevity rather than by a rise in the number of new cases. A fairy tale from the birthplace of Hans Christian Andersen? The answer is tough but interesting.

To begin with, the pharmacoepidemiological approach taken by these Danish investigators has clear limitations—eg, the risk of counting cases twice and the omission of people with diet-treated diabetes. Nor does this approach distinguish between types of diabetes. Nonetheless, within these limits, such analysis gives a useful indication of disease prevalence in relation to mortality. So how should we interpret this report? The number of people affected by a disease is determined by the balance between the rate at which they are diagnosed and (with an irreversible disease) the rate at which they die. An imbalance between the two does not necessarily mean that the disease is affecting a greater number of people. Earlier use of oral hypoglycaemic agents in diet-treated patients will also give a spurious impression of rising incidence, as will earlier diagnosis, bearing in mind that 50% of cases of late-onset diabetes are picked up on routine examination, and that the interval between onset of hyperglycaemia and diagnosis may be as long as 10 years.[2]

Diagnosis is a fairly soft endpoint, but death is unequivocal. A lesson learned by anyone who maintains a register of people with type 2 diabetes is that the death rate is high, and a UK study from the same period as the Danish study found that 25% of all patients with diabetes identified in January, 1994, had died by December, 1999.[3] High mortality might be expected for an age-related condition which accelerates arterial disease, and a diagnosis of diabetes in middle age has been estimated to result in the loss of between 5 and 10 years of life.[4] Does the falling death rate in the Danish study imply that the outlook is getting better? Not necessarily, since it could also be explained by earlier diagnosis or treatment. There are, however, some grounds for optimism. Treating blood glucose has had a dramatic effect on the survival of young people with diabetes, although the effect in older age groups has been much less impressive (figure). A review in 1987 commented that it was quite uncertain whether conventional therapy for type 2 diabetes had improved prognosis.[4] One of the achievements of the UK Prospective Diabetes Study was to show that more intensive control of blood glucose did improve survival,[6] although it also showed that blood-pressure control is of at least equal importance. The



Life expectancy of people with diabetes before and after introduction of insulin

Experience of George F Baker Clinic, Boston, MA, USA, 1897–1945 (redrawn from reference 5).

implication is that an aggressive combined assault on all risk factors for arterial disease is needed. It is reasonable to anticipate—but not as yet confirmed—that this approach will improve the overall survival of people with type 2 diabetes.

Given that the link between increasing obesity and type 2 diabetes is securely established, the stable rate of diagnosis in the Danish report might simply indicate that their population did not become more obese over the study period, although this information is not provided. Alternatively, it has been suggested that Europeans living in their ancestral countries might be uniquely resistant to diabetes compared with other populations.[7] However, the report provides a useful opportunity to review the rhetoric about the "diabesity" pandemic. Each disease has not only its own biography but also its own politics, backed by its patients' lobby and powered by the ambitions of those who have made it their career. It suits disease lobbies to argue that research funding should reflect public fear of a disease or its economic impact, rather than the likelihood of real scientific advance. The "diabesity" pandemic is a useful message for the diabetes community to broadcast, not least when funding is at stake, but this report reminds us that the rising prevalance of type 2 diabetes is complex and deserves more detailed examination. Make no mistake, obesity and diabetes are indeed on the increase, a problem big and deadly enough to need no supporting rhetoric, but not all increases are sinister. Let us take some comfort from the hint that, in some populations at least, the prevalence of type 2 diabetes may have risen mainly because people are being picked up and treated earlier or are living longer.

Edwin A M Gale

Diabetes and Metabolism, Medical School Unit, Southmead Hospital, Bristol BS10 5NB, UK
(e-mail: Edwin.Gale@bristol.ac.uk)

1 Hudson RP. Disease and its control. The shaping of modern thought. Greenwood Press, London, 1983.
2 Harris MI. Classification, diagnostic criteria, and screening for diabetes. Diabetes in America, Second Edition, NIH Publication No 95–1468, 1995.
3 Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM. Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population-based study. *BMJ* 2001; **322:** 1389–93.
4 Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1987; **30:** 123–131.
5 Dublin LI. The facts of life from birth to death. New York: MacMillan, 1951.
6 Stratton IM, Adler AI, Neil HAW, et al, on behalf of the UK Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321:** 405–412
7 Diamond J. The double puzzle of diabetes. *Nature* 2003; **423:** 599–602.

Prevention of venous thromboembolism after major orthopaedic surgery: is fondaparinux an advance?

Osteoarthritis of the hip or knee, and hip fractures, are major causes of disability in older people. Orthopaedic surgery for these conditions is a major component of healthcare, relieving pain and restoring mobility and quality of life. Complications of surgery include infection, bleeding, and venous thromboembolism. Routine venography (usually 5–14 days after surgery) in research studies of such patients not receiving specific antithrombotic prophylaxis shows that about half develop deep-vein thrombosis. The thrombosis is usually adjacent to the hip fracture, or the prosthetic joint, possibly reflecting local alterations in venous blood flow, endothelial disturbance, and activation of platelets and coagulation. Most such thrombi are asymptomatic; but without specific prophylaxis symptomatic deep-vein thrombosis occurs in about 2% of patients after hip surgery and in about 9% of patients after knee surgery. Without specific thromboprophylaxis, symptomatic pulmonary embolism occurs in about 2% of patients after elective hip or knee surgery and in about 6% of patients after hip-fracture surgery.[1] Routine antithrombotic prophylaxis is therefore usually given with mechanical methods, aspirin, unfractionated heparin, low-molecular-weight heparin, or coumarin derivatives. Mechanical and pharmacological methods are often combined.[1]

What is the place of the new synthetic pentasaccharide, fondaparinux, in the prophylaxis of venous thromboembolism after major orthopaedic surgery? This anticoagulant was compared with the low-molecular-weight heparin, enoxaparin, in four randomised controlled trials of major orthopaedic surgery (elective hip or knee replacement, or hip-fracture surgery).[2–5] These trials were rapidly followed by three meta-analyses of those same four studies.[6–8] The latest of these[8] concluded that "fondaparinux . . . showed a major benefit over enoxaparin, achieving an overall risk reduction of venous thromboembolism greater than 50% without increasing the risk of clinically relevant bleeding". The manufacturer's promotional literature in the UK[9] states that "due to a favourable risk benefit profile compared to enoxaparin, fondaparinux sodium has the potential to contribute to the improvement of basic NHS Trust Performance Indicators such as death . . . and discharge rates". Such aims should be critically examined, especially since it has been pointed out that in these four trials the sponsor (manufacturer) had majority membership of the committee which designed and supervised the trial; and collected and analysed the data.[10]

First, the primary efficacy outcome of the studies was "venous thromboembolism up to day 11". This endpoint was unusual, in that it combined a common but surrogate endpoint of no direct clinical relevance (asymptomatic deep-vein thrombosis, detected by routine venography 5–11 days after surgery) with a less common, but clinically relevant endpoint of symptomatic deep-vein thrombosis or pulmonary embolus. It is inappropriate to combine surrogate and clinical endpoints in a primary combined-efficacy outcome. Clinical and surrogate endpoints should have been analysed separately, and the risk-benefit analysis should be based on clinical endpoints only—ie, clinical haemorrhage versus clinical venous thromboembolism.

The better efficacy of the fondaparinux regimen over the enoxaparin regimen in the latest meta-analysis for the commoner surrogate endpoint (asymptomatic deep-vein thrombosis) masked the opposite finding for the less common, clinically relevant endpoint (symptomatic deep-vein thrombosis or pulmonary embolism)—ie, that the point estimate was 47% higher in the fondaparinux group.[11] The reports did not provide confidence intervals in analyses of the major clinical outcomes, but for events by day 11 we calculate the odds ratio as 1·47 (95% CI 0·76–2·84). Hence the possibility cannot be excluded that fondaparinux increased the risk of symptomatic venous thromboembolism by 184% compared with enoxaparin.

Second, the reports of the trials[2–5] and meta-analyses[6–8] minimised not only the possible increased risk of clinically significant venous thromboembolism, but also the increased risk of major bleeding in the fondaparinux

Type 2 diabetes is a form of diabetes mellitus caused by insulin resistance that leads to high blood sugar. In this detailed overview, learn how to spot diabetes signs, build a diabetic diet, manage insulin and medication, and help prevent complications.Â Type 2 diabetes, a form of diabetes mellitus, is likely one of the better-known chronic diseases in the world â€” and it makes sense that this would be the case. Data from the Centers for Disease Control and Prevention (CDC) suggests in the United States alone, 30.3 million people, or 9.4 percent of the U.S. population, have diabetes, and the majority of these people have type 2. Type 2 diabetes is a lifelong condition that causes a person's blood sugar level to become too high. It mainly occurs in people aged over 40.Â Eye checks usually include taking photographs of the back of your eye (retinal photography) to see whether there are any problems. This needs to be done at a specialist eye screening clinic. The guidance recommends that: You should be referred to a specialist local eye screening service as soon as you are diagnosed with type 2 diabetes. If your eyesight suddenly deteriorates significantly without any obvious explanation, you should be referred to a specialist eye doctor (an ophthalmologist). How urgently you are referred will depend on your symptoms and personal circumstances. Diabetes and pre-diabetes have reached epidemic proportions. In order to reduce your own risk, it is important to learn more about the disease. What is type 2 diabetes and how can the epidemic be slowed down? What Is Type 2 Diabetes?Â The obesity epidemic actually parallels increase in the incident of type 2 diabetes. Risk factors for developing diabetes include:[1]. A diet high in processed food and sugar.Â This is the stage that we really need to focus on making lifestyle changes in order to reduce the progression to type 2 diabetes. It is important to understand that pre-diabetes is not a benign condition. Once youâ€™ve reached this stage, you may have already begun to suffer from what we call microvascular complications. (Prevalence of type 2 diabetes mellitus and glucose intolerance in the Setif area (Algeria)). Diabetes Metab 2001; 27: 164â€“171.PubMedGoogle Scholar. 23.Â Colagiuri S, Borch-Johnsen K, Glumer C, Vistisen D. There really is an epidemic of type 2 diabetes. Diabetologia 2005; 48: 1459â€“1463.PubMedCrossRefGoogle Scholar. 55. Green A, Stovring H, Andersen M, Beck-Nielsen H. The epidemic of type 2 diabetes is a statistical artefact. Diabetologia 2005; 48: 1456â€“1458.PubMedCrossRefGoogle Scholar. 56. Gale EA. Is there really an epidemic of type 2 diabetes? Lancet 2003; 362: 503â€“504.PubMedCrossRefGoogle Scholar. 57. Wareham NJ, Forouhi NG. Is there really an epidemic of diabetes?