3 Dubin L, Amelar RD. Surgery of male infertility. In: Behrman SJ, Kistner RW, Patton GW Jr, eds. Progress in Infertility. Boston/Toronto: Little, Brown and Company 1988: 689–712.
4 Nilsson S, Edvinsson A, Nilsson B. Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: fact or fiction? *Br J Urol* 1979; **51:** 591–96.
5 Madgar I, Weissenberg R, Karasik A, Goldwasser B, Lunenfeld B. Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertil Steril* 1995; **63:** 120–24.
6 Grasso M, Lania M, Castelli M, Galli L, Franzoso F, Rigatti P. Low-grade left varicocele in patients over 30 years old: the effect of spermatic vein ligation on fertility. *BJU Int* 2000; **85:** 305–07.
7 Unal D, Yeni E, Verit A, Karatas OF. Clomiphene citrate versus varicocelectomy in treatment of subclinical varicocele: a prospective randomized study. *Int J Urol* 2001; **8:** 227–30.
8 Royal College of Obstetricians and Gynaecologists. The management of infertility in secondary care: evidence-based clinical guideline no.3. London: RCOG Press, 1998.

Might the diabetic environment in utero lead to type 2 diabetes?

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> The day of my birth, my death began its walk.

That quotation from the French author and filmmaker, Jean Cocteau, reflects our unavoidable destiny. However, the speed and style of this walk may be determined well before birth, as Eugene Sobngwi and colleagues show in this issue of *The Lancet*, at least for type 2 diabetes.

Type 2 diabetes is a growing epidemic in developed countries, but the current burden may pale in comparison with the forecast estimated for developing countries during the next few decades. There are several factors conspiring to make diabetes and its precursors, glucose intolerance and insulin resistance, such a pervasive issue affecting both the present and future health of the world's population. The first relates to the global ageing of the population, exposing more people to the ravages of the disease; and the second involves the dramatic adverse changes in diet and exercise patterns.

Several models have been put forward to estimate the burden of type 2 diabetes in terms of population prevalence and economic cost.[1–3] Although the estimates vary, the dramatic increase in the prevalence of diabetes may cancel out many of the health benefits achieved during the past few decades from reducing other risk factors associated with cardiovascular disease, such as hypertension and hypercholesterolaemia. Prevention strategies have been advocated to reduce the staggering cost to public-health systems and the personal suffering associated with the disease.

Type 2 diabetes has a significant genetic component. However, unlike the dominant genetic defects responsible for rare monogenic diseases, current knowledge is consistent with the idea that the genetic factors that modulate type 2 diabetes in the general population are common polymorphisms at multiple genes. These polymorphisms have a modest effect at an individual level but, because of their high frequency, are associated with a high population attributable risk. These genes may not have a primary aetiological role in predisposition to disease, but rather act as response modifiers to exogenous and modifiable factors such as diet.

Several hypotheses have been proposed to explain the rise in diabetes cases and the differences in risk observed among different ethnic groups. One such hypothesis commonly cited, the so-called "thrifty genotype", proposes that gene variants which thrive during times of deprivation because of their adaptation to nutritional hardship may have adverse effects in times of plenty.[4] An alternative hypothesis, the "thrifty phenotype", focuses on the fetal origins of age-related diseases that result from a suboptimal intrauterine environment.[5] However, complex disorders such as diabetes may not be adequately explained with a single monolithic hypothesis. Therefore, integration of different points of view appears to be the key for understanding and preventing the disease. At present, the relative contribution of genes and environment and their specific contributions to each hypothesis remains a matter of debate.

Sobngwi and colleagues use a simple but ingenious approach to shed some light on this binomial complex of genes and early environment. The investigators attempted to define the role of intrauterine environment in the development of glucose intolerance. They examined the medical records of 352 adult patients with type 1 diabetes to identify offspring when only one of the parents had type 1 diabetes before the birth of the index subject. 15 offspring were classified as "cases" on the basis of having been born to a mother with type 1 diabetes (and exposed in utero to a diabetic environment). An additional 16 offspring, born to a father with type 1 diabetes, were the control group. Thus, these controls had similar chances of carrying the same susceptibility genes as the cases, but were exposed to a normal intrauterine environment.

Although the number of study participants was small, the data are enticing. Exposure to a diabetic environment in utero was associated with a high prevalence of impaired glucose tolerance in adulthood; about 33% in the cases versus none in controls. The underlying explanation for the glucose intolerance appeared to be a defective insulin-secretory response. Although in some participants, the in-utero environment seemed to be detrimental, in many of the cases there appeared to be no effect. These participants may have been carrying protective alleles or lower doses of predisposing genes. Alternatively, their mothers may have had better diabetic control during their pregnancy. A possible caveat may be that, in this study, maternal genes may have conferred increased susceptibility to deficient insulin secretory-response compared with the paternal genes. Of interest, two other studies recently demonstrated that the clinical onset of maturity-onset diabetes of the young, a monogenic type of diabetes, occurs at an earlier age if the mother had diabetes during pregnancy.[6,7] These data support the importance of the intrauterine environment, a period in which a human being is experiencing the most dramatic changes that will occur during his or her entire lifetime, as a determinant of adult health.

The message from Sobngwi's study is that prevention of diabetes may need to be started as early as possible, starting with improving the metabolic status of the mother before conception and during pregnancy. Such measures could contribute to reducing the epidemic of diabetes and its complications in the years to come. Our walk to death may then be slower and more gracious.

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1 Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of type 2 diabetes in the UK from 2000 to 2060. *Diabet Med* 2002; **19** (suppl 4)**:** 1–5.
2 Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med* 1997; **14** (suppl 5)**:** 1–85.

3 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025. *Diabet Care* 1998; **21:** 1414–31.
4 Neel JV, Weder AB, Julius S. Type II diabetes, essential hypertension, and obesity as "syndromes of impaired genetic homeostasis": the "thrifty genotype" hypothesis enters the 21st century. *Perspect Biol Med* 1998; **42:** 44–74.
5 Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 2001; **60:** 5–20.
6 Stride A, Shepherd M, Frayling TM, et al. Intrauterine hyperglycemia is associated with an earlier diagnosis of diabetes in HNF-1α gene mutation carriers. *Diabetes Care* 2002; **25:** 2287–91.
7 Klupa T, Warram JH, Antonellis A, et al. Determinants of the development of diabetes (maturity-onset diabetes of the young-3) in carriers of HNF-1α mutations: evidence for parent-of-origin effect. *Diabetes Care* 2002; **25:** 2292–301.

Alternative lengthening of telomeres: dangerous road less travelled

Most cancer cells prevent the ends of their chromosomes from shortening by expressing an enzyme, telomerase, that synthesises new telomeric DNA.[1] This prevention of shortening permits cancer cells to acquire an essentially unlimited proliferative capacity, by contrast with most normal somatic cells, which do not have a mechanism to maintain telomere length and consequently undergo a finite number of cell divisions. Telomerase inhibitors therefore hold considerable promise for cancer treatment, but the situation is complicated by the existence of one or more mechanisms to maintain telomere length, referred to as alternative lengthening of telomeres, that are telomerase-independent.[2–4] Not only will tumours with alternative lengthening be resistant to telomerase inhibitors, but there is also concern (not yet supported by experimental evidence) that treatment of telomerase-positive tumours with effective telomerase inhibitors will exert a potent selection pressure for the emergence of a population of tumour cells with alternative lengthening of telomeres. About 85% of all human cancers are telomerase-positive, and of the remainder some use alternative lengthening and some do not appear to have any mechanisms to maintain telomere length. Some tumours use both alternative lengthening of telomeres and telomerase to maintain telomere length.[2] Although alternative lengthening activity in tumours has not been studied extensively, it is now becoming clear that there are some types of tumours, including astrocytomas and osteosarcomas, where alternative lengthening of telomeres is common.

Two studies in cancer models have suggested that tumours that use alternative lengthening of telomeres may not be fully malignant. When SV40-immortalised human cells that were positive for alternative lengthening were transduced with a mutant *RAS* oncogene, they were unable to form subcutaneous tumours in immunocompromised animals unless telomerase activity was induced by exogenous telomerase catalytic subunit (TERT).[5] Consistent with other data suggesting that telomerase contributes more to the malignant phenotype than maintenance of telomere length alone,[6] a mutant TERT that is unable to lengthen telomeres but presumably retains other functions was also able to render the cells tumorigenic. In addition, the TERT-transduced cells had a significantly increased growth rate under adverse cell-culture conditions.[5] In another study,[7] the *Ink4a/Arf* tumour-suppressor gene locus was disrupted by gene targeting in telomerase-null mouse cells, and the cells were further transformed with *MYC* and mutant *RAS* oncogenes. These cells were able to form tumours that were positive for alternative lengthening of telomeres when injected subcutaneously into immunocompromised mice, but were unable to metastasise unless telomerase activity was reconstituted. These data have been interpreted as indicating that it is very unlikely that alternative lengthening of telomeres will provide a robust resistance mechanism against antitelomerase cancer therapy.[8]

For at least one type of human tumour, alternative lengthening of telomeres may indeed be associated with less aggressive tumour behaviour. 19 (25%) of 77 patients with high-grade brain tumours (glioblastomas multiforme) had tumours that were positive for alternative lengthening of telomeres and four of these were also telomerase-positive.[9] The median survival of the patients with telomerase-negative, but positive for alternative lengthening, tumours was 672 days compared with 236 days for the telomerase-positive, but negative for alternative lengthening, tumours (p=0·0002), and 174 days for the four tumours with both mechanisms to maintain telomere length (p=0·018). Despite longer survival of the patients, almost all of the glioblastomas that were positive for alternative lengthening were nonetheless fatal.

In another tumour type, however, alternative lengthening of telomeres is not associated with a more favourable clinical outcome. In a study of patients with osteosarcomas treated at the Memorial Sloan-Kettering Cancer Center, New York, Gary Ulaner and colleagues[10] recently found telomerase in 31 (44%) and alternative lengthening of telomeres in 47 (66%) of 71 osteosarcoma samples. 19 of the tumours (27%) had both telomerase and alternative lengthening, and 12 (17%) had no mechanism to maintain telomere length. The absence of any such mechanism was more strongly associated (p<0·05) with improved survival than stage or response to chemotherapy. Some metastatic tumours had alternative lengthening as their sole mechanism to maintain telomere length, demonstrating that telomerase is not essential for metastasis. The telomerase-negative, but positive for alternative lengthening, tumours seemed to equal the telomerase-positive tumours in clinical aggressiveness.

The reasons for the differences between the behaviour of the human cancers and the model systems need to be clarified, and may include differences in cell type and the limitations of xenotransplantation for assaying tumorigenicity. What is clear is that the model systems have given a false sense of security. Alternative lengthening of telomeres may be the road less travelled,[8] but it is a dangerous one.

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1 Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. *Eur J Cancer* 1997; **33:** 787–91.
2 Bryan TM, Englezou A, Dalla-Pozza L, Dunham MA, Reddel RR. Evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor-derived cell lines. *Nat Med* 1997; **3:** 1271–74.
3 Dunham MA, Neumann AA, Fasching CL, Reddel RR. Telomere maintenance by recombination in human cells. *Nat Genet* 2000; **26:** 447–50.
4 Henson JD, Neumann AA, Yeager TR, Reddel RR. Alternative lengthening of telomeres in mammalian cells. *Oncogene* 2002; **21:** 598–610.
5 Stewart SA, Hahn WC, O'Connor BF, et al. Telomerase contributes to tumorigenesis by a telomere length-independent mechanism. *Proc Natl Acad Sci USA* 2002; **99:** 12606–11.
6 Blasco MA. Telomerase beyond telomeres. *Nat Rev Cancer* 2002; **2:** 627–33.
7 Chang S, Khoo CM, Naylor ML, Maser RS, DePinho RA. Telomere-based crisis: functional differences between telomerase activation and ALT in tumor progression. *Genes Dev* 2003; **17:** 88–100.
8 Greenwood E. The road less travelled. *Nat Rev Cancer* 2003; **3:** 84.