

exchequer announced in last week's budget the introduction of tax credits to encourage UK based pharmaceutical research into diseases prevalent in developing countries. This measure, which stems in part from the work of the prime minister's task force on the pharmaceutical sector, is an important step. The chancellor also repeated his support for the creation of a new international fund for purchasing drugs and vaccines for the world's most vulnerable children and adults.

No commercial company can act as a charity without running the risk that it would soon have no more than good intentions to offer either its customers or its owners. But if policymakers can create purchasing funds, ensure that patented medicines supplied at low cost to poor populations do not "leak back" to rich world markets, and restrain medicine price negotiators in prosperous countries from demanding savings to match those offered to the poorest, progress could and should be made. Given appropriate incentives, the profit motivated pharmaceutical industry provides a

powerful force for improving both public health and private wealth throughout the global community.

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Obesity genes

Identifying single genes involved in polygenic inheritance is not easy

There is no doubt that obesity is strongly influenced by environmental factors. The prevalence of obesity increases so rapidly in many populations that the changes cannot be attributed to changes in genetic inheritance.¹ There are differences in prevalence between populations and between various groups within populations; these differences are closely associated with environmental factors, especially social and behavioural factors.¹ The degree of an individual's obesity can be modified by interventions that alter a person's energy intake or energy expenditure.¹ However, there is no doubt that obesity is also influenced by genetics. That obesity runs in families is an old observation,² and it has been repeatedly confirmed in multiple studies in populations from different parts of the world who have lived in different environments.² Studies of monozygotic and dizygotic twins have unambiguously shown that there is a much greater resemblance in the degree of obesity between genetically identical monozygotic twins; this indicates that the resemblance is related to their similar genes rather than their shared environment.² However, these studies may have overestimated the effect of genetics if monozygotic twins share exposure to more environmental effects than dizygotic twins do. A study of 311 pairs of twins who had been raised apart and 362 pairs who had been raised together corroborated the results of other twin studies and indicated that the shared childhood environment has little or no influence on obesity.³ Moreover, other studies that compared the degree of obesity of participants who had been adopted with the degree of obesity in their biological relatives and members of their adoptive family also confirmed the evidence of a genetic

influence on obesity and the absence of the effects of the environment in which they were raised.^{2, 4}

The pattern of inheritance of obesity strongly suggests that the effect is polygenic, with each variant of many different genes making a small difference in effect.^{5, 6} As a phenotype obesity is also heterogeneous, and there are at least two distinct but frequently overlapping subtypes: general obesity, which results in increased body fat mass, and abdominal obesity. These subtypes have different physiological, clinical, and prognostic implications.¹ The phenotypes seem to have some of the same genetic and environmental influences in common.⁷

Analyses of the distributions of the degree of obesity among family members suggest that a few genes have a discernible effect, but none that affect common obesity has yet been identified.^{5, 6} The strong environmental effects that have been observed lead to the belief that obesity is the result of an interaction between a genetic predisposition and environmental influences, although the specific evidence for these interactions is weak.¹

Since the identification of the leptin gene,⁸ many other single genes have also been investigated as candidates for causing obesity, and the entire genome has been scanned for loci associated with obesity.^{5, 6, 9} A few genes have been found to cause monogenic forms of obesity in humans.^{6, 9} This search for obesity genes, performed in conjunction with physiological and biochemical studies in animals and humans, has contributed to a rapid increase in the knowledge of the biological mechanism involved in obesity. However, there has been no convincing success in describing the polygenic background of common obesity.

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The paper by Rosmond et al in this issue of the *BMJ* (p 652) is a good example of this type of research.¹⁰ The researchers investigated whether a specific variant of the gene encoding for the glucocorticoid receptor might influence the degree of abdominal obesity, and they also investigated the hormonal, metabolic, and haemodynamic disturbances associated with this phenotype. The idea was that this particular genetic variant might lead to increased sensitivity to glucocorticoids, which might explain the similarity between the phenotype and Cushing's syndrome. The study found no such effects.

There are two sets of related problems in hunting for obesity genes: one is implicit in the research paradigm and one is related to the methodology. If the genetic influence on the various forms of common obesity is based on multiple, polymorphic single genes—each with a small effect—that interact with other genes and with exposure to specific environmental factors, then current research strategies seem destined to fail. When research focuses on the relation between single genes and obesity and fails to control for other genes and environmental exposures, neither of which have been clearly identified, then both experimental and observational studies have little chance of identifying the pertinent genes.

The other set of problems derives from the risk of false positive results and false negative results. These problems are inherent in the low frequency of genetic variants, in the study populations, in the sampling of these populations, and in the measuring of the various forms of obesity and their presumed pathogenic mechanisms.

An extreme example of these problems is found in the discrepant results of two studies: the paper by Rosmond et al¹⁰ and an earlier paper by Lin et al.¹¹ Both papers report on the same single gene polymorphism. Rosmond et al found no evidence that it is related to obesity but Lin et al found that the polymorphism was associated with an almost absolute risk of obesity.

It is not clear what would be the most effective way to proceed. The pressing need for progress is obvious in view of the continuing worldwide obesity epidemic and the complications of obesity, such as type 2 diabetes, hyperlipidaemia, hypertension, and eventual cardiovascular disease. One way forward might be to conduct controlled human experiments by manipulating environmental factors that are assumed to be pertinent, such as fat intake. Its effect on both gene expression and the function of gene products in people with different genetic variants may elucidate which genes contribute to common obesity.

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What is the optimal weight for cardiovascular health?

Debate about cut offs for obesity should not obscure need for population strategy

Although the health hazards of obesity have been clearly established, exactly where healthy weight ends and unhealthy weight begins is a matter of controversy.¹ Numerous studies have evaluated the association between weight and the metabolic abnormalities or diseases that occur in people whose weight is at the higher end of the scale, but comparatively few have examined these associations in people who fall into the lower or middle range of being overweight.

In the January issue of the *European Heart Journal*, Ashton and colleagues investigated the relation between body mass index (calculated as weight (kg)/(height (m)²) and several established risk factors for coronary heart disease using a cross-sectional survey of 14 077 apparently healthy women aged 30 to 64 years.² Ashton et al found that as the women's body

mass index (BMI) increased from <20 to >30, blood pressure also increased significantly, as did concentrations of total cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein B, fasting triglycerides, and fasting blood glucose. Concentrations of high density lipoprotein (HDL) cholesterol and apolipoprotein A I decreased. Using a modified version of the Framingham heart study's algorithm for predicting the risk of coronary heart disease, the investigators showed that the estimated 10 year risk of coronary heart disease also increased significantly in a dose-response fashion as BMI increased from <20 to >30.

Ashton et al's data are consistent with several previous studies of body mass index and metabolic risk factors for coronary heart disease in comparatively lean and apparently healthy adults in diverse populations,³⁻⁵ and thus have important implications. Firstly, they