mice) fail to do so (M. Reitman, personal communication).

Leptin also improves insulin sensitivity in other settings. In normal animals, it reduces cellular lipid content, increases glucose uptake by muscle and increases insulin sensitivity[10]. In leptin-deficient *ob/ob* mice, an improvement in the efficacy of insulin is evident at doses that do not affect weight[11]. In each of these cases, the effects of leptin are evidently not just a consequence of its ability to reduce food intake[1,7].

How, then, does leptin clear lipid from non-adipose tissue? This is where Minokoshi *et al.*[2] come in. They first demonstrate that leptin increases fatty-acid consumption, by oxidation, in skeletal muscle. They also show that leptin activates an enzyme — AMP-activated protein kinase, or AMPK — in skeletal muscle. In cells, a delicate balance controls whether fatty acids are transported into mitochondria and metabolized or are stored in the cytoplasm as triglycerides (Fig. 1). This balance is mainly regulated by malonyl CoA, a fatty acid that is generated by the enzyme acetyl CoA carboxylase (ACC). Malonyl CoA inhibits transport of fatty acids into mitochondria, thereby preventing them from being metabolized[12]. AMPK phosphorylates ACC, inactivating it[13]. By activating AMPK in muscle, leptin inhibits malonyl CoA synthesis and shifts the balance towards fatty-acid oxidation and away from fat storage (Fig. 1). These effects are similar to those seen in mice in which the genes that encode ACC have been knocked out[14].

Leptin-mediated phosphorylation of AMPK seems to operate both directly through skeletal muscle and indirectly through the hypothalamus, although the mechanisms involved are not known. We now need to find out whether leptin's lipid-clearing effects on liver and other tissues work in the same way as those on skeletal muscle — interestingly, different forms of the ACC gene are present in skeletal muscle and liver[14].

All in all, the data suggest that we may now have an explanation for the association of obesity, insulin resistance and diabetes. The findings also suggest that leptin may be of benefit not only in obesity but in other settings as well. Some obese subjects are resistant to leptin and do not seem to respond to the genetically engineered form of the protein. However, some obese subjects do lose weight in response to leptin therapy, and the hormone could prove useful in a subset of obese patients, especially diabetic ones[15]. Leptin might also be effective in treating human lipodystrophy, a possibility that is now being tested (P. Gorden, personal communication). Lipodystrophy is rare as an inherited disorder, but some HIV-infected patients develop this condition. Indeed, it may be that, in both lean and obese leptin-sensitive individuals, leptin could reduce excess fat at sites such as the liver and heart, and in beta cells, and prevent the damage it causes.

Finally, there is an evolutionary angle to these results. Leptin's emergence in vertebrates may have helped to prevent excessive weight gain through lipid deposition in adipose tissue in times of surfeit. Excessive weight can easily be imagined to be disadvantageous if, for instance, it makes an animal less able to evade attack. But if lipid in other cells increases the risk of diabetes and other complications of obesity, and leptin acts to reduce this, then this hormone may also have evolved to limit accumulation of lipid in the wrong places[6]. ■

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**Behavioural science**

# The economics of impatience

Ernst Fehr

In experiments, animals often prefer smaller, immediate rewards over larger rewards that are deferred — thus failing to maximize their total gain. Many people exhibit similar behaviour.

The irresistible cravings of addicts provide an extreme example of short-term behaviour with adverse long-term consequences. The field of study known as experimental and behavioural economics indicates, however, that some of the principles that underpin addictive behaviour are quite common and can help us to understand human behaviour more generally.

At a meeting* held late last year, participants discussed how the tools and concepts of this field can be used to understand, predict and influence people's decisions in circumstances in which some of the rewards or costs of a choice accrue in the future. In trade jargon, these are known as 'intertemporal choices', and at some time or other we all have to make them. Examples are decisions about savings and the amount of credit-card debt we run up, and about eating habits and even marriage — all of these choices have positive or negative consequences that lie in the future.

If animals have to choose repeatedly between a smaller reward arriving soon (SRS) and a larger reward arriving later (LRL), the SRS is often preferred even though the repeated choice of the LRL would maximize the overall gain[1–3]. One experiment[2], for instance, involved hungry pigeons, with an initial trial phase lasting 30 seconds and an outcome phase of 10 seconds. Irrespective of the pigeons' choices, each trial of the experiment lasted 40 seconds. In each trial, the pigeons could press one of two keys 2 seconds before the end of the initial phase. One key led to 2 seconds of access to a grain hopper right at the start of the outcome phase; the other key led to 4 seconds of grain-hopper access after 4 seconds of the outcome phase. Almost all pigeons preferred the immediate, but more limited, access to the grain. They thus strongly 'discounted' the LRL in favour of the SRS — in other words, they subjectively devalued the LRL relative to the SRS.

The pattern of discounting also gives rise to preference reversals, because animals are very 'impatient' in the short term and relatively 'patient' in the long run[1–3]. If, for example, the choice between the two keys had to be made after 2 seconds of the initial phase, leaving a 28-second wait until the beginning of the outcome phase, the pigeons preferred the LRL in more than 80% of cases. So if both the SRS and the LRL were shifted into the future, the animals changed their preferences in favour of the LRL, despite the fact that the absolute time difference between the two options remained unchanged. Their behaviour was thus not consistent over time.

One explanation for this is that, throughout evolutionary history, future rewards have been uncertain. An animal foraging for food may be interrupted or, in the case of reproductive opportunities, die before it

*Nobel Symposium on Experimental and Behavioural Economics, Saltsjöbaden, Sweden, 4–6 December 2001.

BELLY/ULYSSES AND THE SIRENS/ BRIDGEMAN

Figure 1 **Ulysses resists the Sirens' call by being bound to the mast of his ship, the ears of his crew having been blocked with beeswax. Saving for the long term presents a similar, but less exciting, dilemma.**

is successful. For humans, the promise of future rewards may be broken. And if the risk faced by a person varies over time, he or she applies various discounts to future events[4,5] and so behaves inconsistently.

But to what extent do people exhibit similar behaviour to that of hungry pigeons? At the conference, evidence was presented that, for many people, the discount rate for short-term events is likewise much higher than for events that have outcomes further in the future (G. Loewenstein, Carnegie Mellon Univ.). For example, when a small reward is due tomorrow, and a larger reward is due one year hence, many people prefer the small reward. But when the small reward is due in one year and one day, and the larger reward in two years, they tend to prefer the larger reward. For events that are far enough in the future, people are prepared to be patient, and so behave inconsistently depending on the time frame. This conclusion constitutes a challenge for economists who, for decades, have assumed that individuals discount future rewards at a constant rate.

This evidence provides an explanation, going beyond a general tendency to discount future events, for why there is conflict between long-term human intentions and our short-term actions. For instance, if their craving is sated, addicts almost universally prefer not to consume substances that are detrimental to their long-term health. In the craving state, however, they cannot resist the temptation of their favoured substance.

Likewise, when planning for the long term, most people in developed countries intend to save enough for their retirement, eat healthy foods, exercise regularly, watch less television and quit smoking. But such plans require gratification to be delayed, and most of the time most people put off doing anything about their long-term aims even when they know they should act on them[6]. For example, in a 1997 poll in the United States (where social security is much less generous than in Europe), over 75% of those questioned reported that they should be saving more for their retirement. And looking only at respondents who believed they were at an age at which they "should be seriously saving already", the survey found that more than 50% reported being "behind" in their savings and only 6% reported being "ahead".

The divergence between intention and action creates a demand for commitment: people prefer to be bound to their long-term plans in the same way that Ulysses had himself tied to the mast of his ship to prevent himself and his vessel being lured onto the rocks by the Sirens' song (Fig. 1). The positive value of commitment may be one reason why, in many developed countries, the state forces people to save for retirement through automatic deduction of contributions from their wages. It may also account for why many households hold a large part of their wealth in illiquid forms such as housing or educational qualifications.

It has proved difficult to devise convincing mathematical models of sub-optimal short-term behaviour. One reason for this is that models in which short- and long-term discount rates differ quickly become analytically intractable. Another is that the evidence about the causes of inconsistent and short-sighted behaviour is ambiguous. It could also be that humans simply aren't good at handling choices that involve many different future consequences with different probabilities[7–9].

At the conference, however, a new model of the way in which people consume goods and services was presented (D. Laibson, Harvard Univ.). This approach is based on the idea that the divergence of short- and long-term discount rates produces a conflict within the individual, and that the individual is perfectly aware of this. The model is surprisingly successful in predicting certain aspects of economic behaviour, and is much more accurate than a competing model based on constant discount rates. Among other things, the conflict-awareness model correctly predicts the large drop in consumption that typically occurs when people retire, as well as the high rates of credit-card borrowing despite the high interest rates on this kind of debt.

Another group of researchers described how people's saving behaviour can be changed using the insights on time discounting (R. Thaler, Univ. Chicago; S. Benartzi, Univ. California, Los Angeles). People who are impatient in the short term are reluctant to save more for retirement out of their current income because this requires a delay of gratification. But because they are patient in the long term, they are willing to commit themselves to saving more out of future salary increases.

Thaler and Benartzi persuaded a US company to offer its employees the opportunity to commit themselves to saving more out of future salary increases. Most of the several hundred employees were unwilling to save more out of their current incomes. But most were prepared to save more in the future, and over only 28 months the average savings rate rose from 3.5% to 11.8% of income. So the results of basic research on time discounting can be used to help people to implement their long-term plans.

There is, however, more to experimental and behavioural economics than these examples indicate. In recent years, we have gained deeper insights into the patterns of human reciprocity and altruism, into decision-making under conditions of uncertainty and risk, and into the regularities of human


**100 YEARS AGO**

**Mr. G. Archdall Reid contributes to the current number of the *Monthly Review* an instructive and clearly written account of "the rationale of vaccination"… After passing in review the theories which have previously been held to explain acquired immunity, Mr. Reid shows that it is due to an habituation to the toxins of that disease. This result is brought about by the digestion in the blood of the toxins, so that there are present in the animal's blood toxins in all stages of attenuation, from those newly produced by the microbes, and extremely virulent, to those produced in the beginning of the disease and now in a state of great enfeeblement. Up that graduated scale the cells of the animal react till complete immunity is attained. The serum treatment artificially supplies digestive substances and, what is even more important, a scale of attenuated toxins. Applying these principles to the case of small-pox, the necessity for periodical vaccination is established. It is pointed out that, since small-pox is an air-borne disease, isolation, by itself, has no greater power of controlling small-pox than the historic old lady with a broom had of sweeping back the Atlantic.**

**From *Nature* 16 January 1902.**

**50 YEARS AGO**

***Patterns of Marriage.* It is possible to give only a few of the results of this research. One point that soon became obvious was that like tended to marry like — the intelligent man, the intelligent woman; the neurotic, the neurotic. Sexual attraction played only a minor part in drawing two people together. Among the psychiatrically sound couples 45 per cent claimed to be happily married, 36 per cent considered their marriage satisfactory, 10 per cent unsatisfactory and 9 per cent admitted to being positively unhappy. In the neurotic group happiness or satisfaction in marriage was less frequent. It is clear also from the answers given that children ranked highest in bringing about marital happiness and that other factors, in diminishing order of importance, were as follows: "clerical rating of personality, economic status, intelligence, orgasm adequacy of the female, pre-marital chastity, good looks, stature, rating of personality by test, similarities between husband and wife and test responses". Frequency of intercourse and youth bore no relationship at all to marital happiness.**

**From *Nature* 19 January 1952.**

learning when people with partly conflicting interests interact with each other. For researchers in this field, these are exciting times, not least because we are witnessing a partial reunification of psychology and economics. ■

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AIDS vaccines

# One step forwards, one step back

Jeffrey D. Lifson and Malcolm A. Martin

New AIDS-virus vaccines induce cellular responses that can contain, but not prevent, infection. Mutations can allow the virus to escape this immune control, emphasizing the challenges in developing an effective vaccine.

As someone accustomed to persevering on a long-term project in which repeated periods of hard work lead to modest progress, only to be followed by setbacks, Sisyphus would be well suited to a career in AIDS-vaccine research. Papers on pages 331 and 335 of this issue[1,2] illustrate the point. In the first paper, Shiver and colleagues[1] describe how they immunized groups of rhesus macaques against a protein from a monkey AIDS virus, the simian immunodeficiency virus (SIV), effectively stimulating antiviral cellular immune responses. The immunizations did not prevent, but did help to control, subsequent infection with a related virus. But Barouch and colleagues[2] show that AIDS viruses can mutate to evade such vaccine-induced, virus-controlling cellular immunity, calling into question a vaccination strategy based solely on such responses.

The aim of most vaccines that offer protection against viruses is to stimulate antibody molecules that can neutralize the virus or otherwise help clear the infection, and cellular immune responses, particularly by cytotoxic T lymphocytes (CTLs) that bear the surface marker CD8 and can kill virus-infected cells. But for the human AIDS virus HIV-1 it has proved difficult to generate vaccines capable of inducing antibody responses that neutralize the broad range of virus strains found in patients. CTL responses may be able to cope with a wider range of virus strains, and appear to help control HIV-1 in infected people, so much current attention in AIDS-vaccine research is focused on vaccines that stimulate CTL responses.

Pursuing this approach, Shiver *et al.*[1] systematically compared vaccination strategies using DNA molecules or engineered non-SIV viruses (a vaccinia virus or an adenovirus known as Ad5) to express a single SIV protein, Gag. After immunizing macaques with these potential vaccines, the authors detected strong and sustained responses by T cells that express CD8, most notably in animals immunized with the Ad5 vaccine — either alone or after 'priming' immunization with DNA.

To assess the efficacy of the vaccines, the authors[1] then challenged the macaques with a highly pathogenic chimaeric simian–human immunodeficiency virus (SHIV), SHIV 89.6P (ref. 3). This virus contains a gene encoding the viral glycoproteins from the HIV-1 outer 'envelope', as well as several SIV genes, including a Gag-encoding gene matching that used in the vaccines. Like HIV-1 and SIV, SHIV 89.6P infects and kills 'helper' T lymphocytes bearing the cell-surface marker CD4 (ref. 3).

Shiver *et al.* found that their vaccination strategies did not prevent infection with SHIV 89.6P, but did modulate its course, most strikingly in animals immunized with the vaccine based on Ad5. Early on, peak levels of virus in the macaques' blood were only slightly lower than in controls. But by 70 days after challenge, vaccinated animals showed markedly lower levels of virus and preservation of CD4-expressing T lymphocytes. This 'partial protection' is similar to that obtained with other vaccine approaches[4,5] against challenge with SHIV 89.6P. Used clinically, a vaccine that controlled HIV infection might result in a longer period of infection without symptoms, and a decreased risk of transmission.

However, Barouch *et al.*'s work[2] provides a cautionary counterpoint to these encouraging results, and raises questions about the strategy of controlling infection by using vaccines that stimulate CTLs alone. These authors describe the course of infection in a rhesus macaque that was at first partially protected from SHIV 89.6P by a DNA-based immunization approach[5]. This vaccinated animal showed high peak levels of virus after challenge, but viral levels eventually