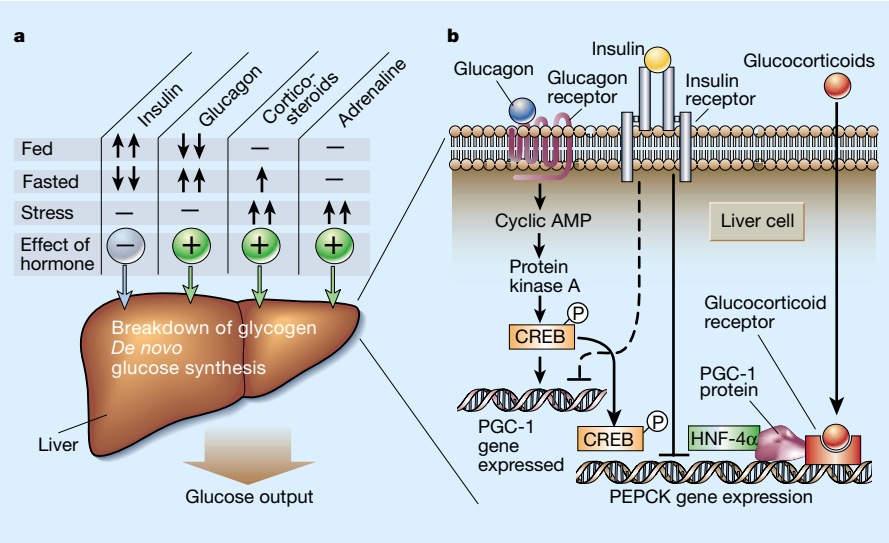

Figure 1 **Glucose production in the liver.** a, **Hormones that regulate the liver's glucose output, and their fluctuation (short arrows) in different circumstances.** b, **Molecular details of the processes shown in** a. **Yoon *et al.*[2] and Herzig *et al.*[3] find that the protein PGC-1 is a key regulator of gluconeogenesis (glucose synthesis). It works with transcription factors, including hepatic nuclear factor-4α (HNF-4α) and glucocorticoid receptors, to activate the expression of gluconeogenic genes, such as that encoding phosphoenolpyruvate carboxykinase (PEPCK). Left, glucagon activates the cyclic-AMP signalling pathway, which increases glucose production through a mechanism that involves the expression of PGC-1. Centre, insulin counteracts gluconeogenesis by blocking the expression of genes such as the PEPCK gene, perhaps by inhibiting PGC-1 expression(dashed line). Right, glucocorticoids enter cells and bind to receptors, which, with PGC-1, activate the expression of gluconeogenic genes.**

regulator of glucose output from the liver, with hormones like glucagon, adrenaline and glucocorticoids having a secondary role, particularly under stress. For example, after the pancreas is removed — depriving the liver of both insulin and glucagon — the liver responds by massively increasing glucose production because of the lack of insulin, not by shutting off glucose production because of a glucagon shortage[10].

So it is intriguing that interfering with liver cAMP-mediated pathways alone can lead to such low levels of blood glucose in intact organisms[3]: one might expect that a reduction in insulin secretion, occurring in response to small decreases in blood glucose, would compensate. In the mouse models studied by Herzig *et al.*, insulin levels do indeed drop a little, but not enough to compensate for the loss of cAMP signalling. This should make us think more deeply about which signals, other than glucagon and adrenaline, might be important in maintaining 'physiological' cAMP signalling in the liver. Another unanswered question is the extent to which alterations in PGC-1 expression can explain the suppressive effects of insulin on glucose production.

The new observations may also have relevance to human disease. Diabetes mellitus, particularly when poorly controlled, is characterized by increased gluconeogenesis in the liver[11]. One of the main treatments for the most common form of diabetes is metformin, which works mainly by reducing glucose production by the liver[12]. But this drug is not without side effects, and its mechanism of action is unknown. A better knowledge of the molecules that control gluconeogenesis might allow the design of more focused drugs.

Finally, perhaps the most important aspect of these papers[2,3] is their illustration of how a range of hormonal signals can regulate a metabolic process by altering the levels of a coactivator protein. Coactivators interact indirectly with many genes through many transcription factors, making this an economical way of orchestrating a complex transcriptional response. It seems unlikely that PGC-1 is an isolated example of this strategy. ■

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Daedalus

Extremes of rubbish

Burial or incineration? This dilemma applies not only to your mortal remains, but to all the rubbish you discard throughout life. Incineration promises (but seldom delivers) an immediate output of useful thermal power. Landfill, curiously, also offers energy, but more slowly. Most rubbish dumps slowly evolve methane, from bacterial fermentation of their biochemical content (food residues, paper, disposable nappies and so on). The gas is a major nuisance — it makes old landfill sites hazardous to build on, for example —but there are schemes to exploit it as a fuel.

As a fermenter, says Daedalus, a landfill dump is absurdly big, runs absurdly slowly, and degrades only a tiny fraction of its contents. The organisms that inhabit it are simply not up to the job. To be economic, it should be much smaller, with a much faster throughput. Daedalus recalls the 'extremophile' bacteria found in hot springs, volcanic black smokers and similar thermal and chemical extremes. They perform the most amazing chemistry, and at speeds accelerated by the high temperature. So DREADCO biochemists are now playing with promising extremophiles — swapping their genes around, exposing them to radiation, selecting the survivors of really brutal conditions, and so on — seeking the ideal cultural mix for DREADCO's Extreme Rubbish Fermenter, or ERF. It will challenge the accepted limits of the conditions under which life can survive.

Daedalus cannot guess what those limits will be. He hopes that ERF will operate at 100 °C at least; with luck it will even go superheated. The harsher the conditions, the more types of rubbish will become fermentable. Not only will plastics and other synthetics soften, dissolve and decompose, becoming food for the voracious extremophiles, but even metals may begin to succumb. Only glass and ceramics (of which ERF itself will be made) will remain aloof.

ERF will resemble an intense, high-pressure, giant variant of the garden compost-bin. Rubbish will be rammed into the top, fuel gas will be extracted from peripheral pipes, and the sterile residue, a sort of rusty grit, will emerge at the bottom. It will be self-heating. Its ferocious internal conditions will impose intense evolutionary pressure on the extremophiles inside. They should steadily evolve further, perhaps imitating the way that life itself developed in the hot and chemically aggressive environment of the young Earth. David Jones