



SLEEP IT OFF

We've been told to eat less and move more to battle the growing obesity epidemic. But could getting more shut-eye also be a way to fight the fat? **Helen Pearson** investigates.

For nutrition researcher Arne Astrup, it was a tired, overweight young girl who got him thinking. Twelve years old and 20 kilograms overweight, she was bright and more active than the average kid. Genetics and lifestyle seemed to be on her side: her slim parents packed her a nutritious lunch for school and did everything to ensure she ate healthily at home. But she was also something of a night owl. She loved to read and watch television into the night and did not sleep for more than seven hours.

Astrup was aware of emerging research pointing to links between poor sleep patterns and appetite. After he discussed the possible connection with the family, the girl stayed in bed longer, for nine or ten hours. Within one month of starting to sleep longer, she started to lose weight and her cravings for junk food dropped.

Scenarios such as this one, Astrup says, heightened his interest in the research. "I think the sleep story is really fascinating," he says. "It seems to be something that might be quite fundamental." He is now planning studies on whether sleep-deprived people eat more from a buffet.

Astrup is one of many medical researchers who have been struck by the tale of two growing epidemics and how they are intimately intertwined. Sleeping and eating are two of our most elementary drives. But in Western soci-

ety both are veering out of control: we starve ourselves of sleep and gorge ourselves on food. Now many biologists are asking whether our cavalier attitude to sleep could be at least partly responsible for our expanding bodies.

The idea is not as far fetched as it sounds, because there are plausible (if sketchy) biological mechanisms that could explain it. Overlaps are emerging between the brain mechanisms that control sleep and those that control appetite — mechanisms that may, in our evolutionary past, have been essential to fend off starvation. Many groups are now trying to figure out exactly how these circuits interconnect. The US National Institutes of Health (NIH) plans to commit as much as \$2 million to such studies this year.

A diet of sleep

In one clinical trial at the NIH in Bethesda, Maryland, sleep is being doled out like a drug. The trial will test whether tired, obese people lose weight after increasing their sleep by just one and a half hours each night. "It's a possible way to control obesity that might even be pleasurable," says obesity researcher David Allison of the University of Alabama, Birmingham. "Most people would say 'Sleep a little more? Yes I'd love to.'"

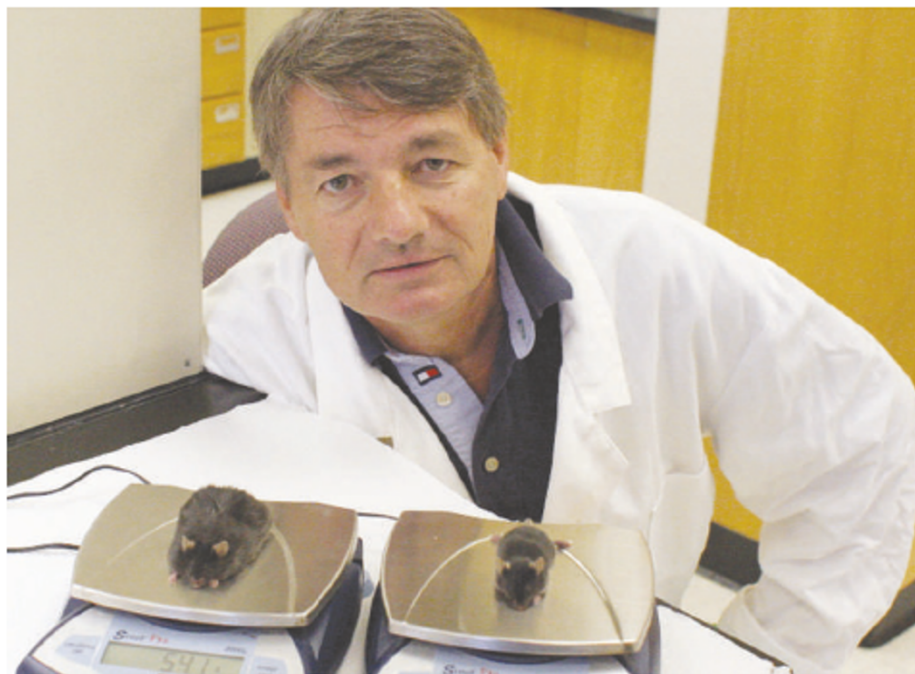
Some researchers question whether too much emphasis and money, in the obesity battle, has been placed on poor diet and lack of

exercise. They say that good sleep — an activity that we ideally spend around one-third of our lives doing — is an integral part of the package of good health. If so, then many people could be sabotaging their own attempts to lose weight simply by depriving themselves of sleep. "We need to add in a third strand," says circadian-biology researcher Fred Turek at Northwestern University in Evanston, Illinois.

It is clear that fresh ideas about obesity are needed. Two-thirds of Americans, and some 1 billion people worldwide, are overweight or clinically obese. The clinical definition of overweight is having a body mass index of 25 kg m^{-2} or more, but health risks can creep up at lower levels. The World Health Organization's 2002 World Health Report, for example, attributed about 58% of diabetes, 21% of ischaemic heart disease and 8–42% of certain cancers to a body mass index above 21 kg m^{-2} .

Researchers have pinned most of the blame for obesity on genetic make-up, too many calories and too little activity. But genes cannot, for now, be changed and efforts to get people to switch their diets and exercise habits seem to have had little effect so far.

Alongside the rising levels of obesity has been a parallel decline in the number of hours people spend sleeping — the first hint that sleep patterns could be connected to obesity. Americans' daily sleep has dropped from between



Fred Turek has found disturbed sleep patterns in mice, caused by a faulty body clock, are linked to obesity.

eight and nine hours in 1960 to less than seven hours today. A similar trend is thought to have occurred in most industrialized nations. Most people blame televisions, computers, all-hour supermarkets and the attitude held in some countries that sleep is a superfluous pastime that could more usefully be filled by school, work or play.

Burning the midnight oil

The anecdotal correlation between poor sleep and obesity has been borne out by epidemiological studies. At least a dozen reports, from different parts of the globe, in both children and adults, have consistently found that people who sleep less are more likely to have a weight problem.

In one well-publicized study¹, James Gangwisch at Columbia University in New York and his colleagues matched up the self-reported sleep habits and body mass index of more than 9,500 people from across the United States, gathered between 1982 and 1992. They found that those between the ages of 32 and 49 who slept for five hours each night were 60% more likely to be obese than those who slept for seven or more. This was true after they controlled for other obvious factors connected with obesity, such as education, age, physical activity and smoking. And a study tracking British children as they grow up showed that poor sleep in three-year-olds is an important factor in predicting obesity at the age of seven, alongside well-established risk factors such as having overweight parents or watching television for long periods².

Of course, a host of mundane explanations could account for the observation that poor sleepers tend to be overweight. One possibility is that obese people tend to sleep badly because they are obese and unhealthy. Another possibility is that people who are awake for longer simply have more time on their hands to eat. A third is that tired, irritable people lack the motivation to eat healthily or go to the gym — as Gangwisch puts it, “they might say screw this, I’ll eat a bag of chips”. For now, researchers cannot rule out some of these explanations and it is likely that they play at least a part in the connection.

But the ties between sleep and obesity are thought to run deeper than this because of another line of evidence from studies in humans and animals. This shows a biological mechanism by which sleep can promote appetite. “Some of the biggest names in the field, who people trust, are saying there is a link,” says neuroscientist Cliff Saper of Harvard Medical School in Boston, Massachusetts, who is starting his own studies into the association.

One of those big names is Eve Van Cauter at the University of Chicago in Illinois, whose laboratory has produced a series of studies showing how sleep deprivation leaves its mark on metabolism and hormones. In one study³, 12 young men were allowed to sleep for only four hours a night on two consecutive nights. The researchers tested levels of hormones including

leptin, which is released by fat cells and signals satiety, and ghrelin, which is produced by the stomach and signals hunger. They compared these hormone levels with those recorded after two nights of nine hours’ sleep.

Out of synch

After two sleep-deprived nights, the men’s blood levels of leptin had dropped by an average of 18% and their ghrelin levels had soared by 28%. At the same time, the bleary-eyed men said that they felt more hungry, particularly for carbohydrate-rich foods such as cakes, biscuits, crisps and bread, compared with proteins, fruit and vegetables.

These findings in people have been mirrored by studies in tired mice. Mimicking human sleep deprivation in mice and rats is normally difficult because the methods used to keep the animals awake, such as plunging them in water, are also stressful or require extra physical activity from the animal. So although sleep-deprived rats tend to eat far more, they still lose weight.

But studies on mice whose body clock is faulty underline the link between sleep patterns and obesity. Turek studied mice genetically engineered to lack a working version of a protein called Clock, which is active in a brain region called the suprachiasmatic nucleus that orchestrates the body’s 24-hour rhythm. This region forms part of the brain called the hypothalamus, which controls many of our unconscious body functions including sleep and appetite.

Mice without Clock lose their normal patterns of sleep, feeding and activity — and, as Turek and his colleagues found⁴, after several weeks, they grow obese and develop the hallmarks of metabolic syndrome in a few months. This has an array of symptoms including high blood sugar and cholesterol, and low insulin that, in humans, tend to be precursors to diabetes and heart disease.

Together, Van Cauter and Turek’s experiments suggest that poor sleep can rapidly wreck the body’s normal systems for regulating appetite and predispose people and animals to obesity. What is not clear is the precise cellular and molecular chain of events that links one to the other — and it is these details that the NIH’s \$2-million injection is designed to reveal. “What we’re missing is the piece of evidence that would make it definitive,” Allison says.

Researchers do know that there are overlaps between the systems that regulate sleep and those that control appetite in the brain. Much

“Increasing sleep is a possible way to control obesity that might even be pleasurable.”

— David Allison

attention has focused on a huddle of cells in the hypothalamus and the two proteins they produce. These proteins are known as either orexins or hypocretins — two groups simultaneously discovered and named them in 1998. At that time, researchers found that an injection of orexins into the brains of rats stimulated feeding, indicating that the proteins were involved in controlling appetite.

Later on, other teams found that the system is defective during narcolepsy, a condition in which people fall swiftly and deeply asleep at inappropriate times. Intriguingly, narcoleptics are also often overweight. Researchers now think that orexin neurons promote wakefulness, feeding and exploration in animals.

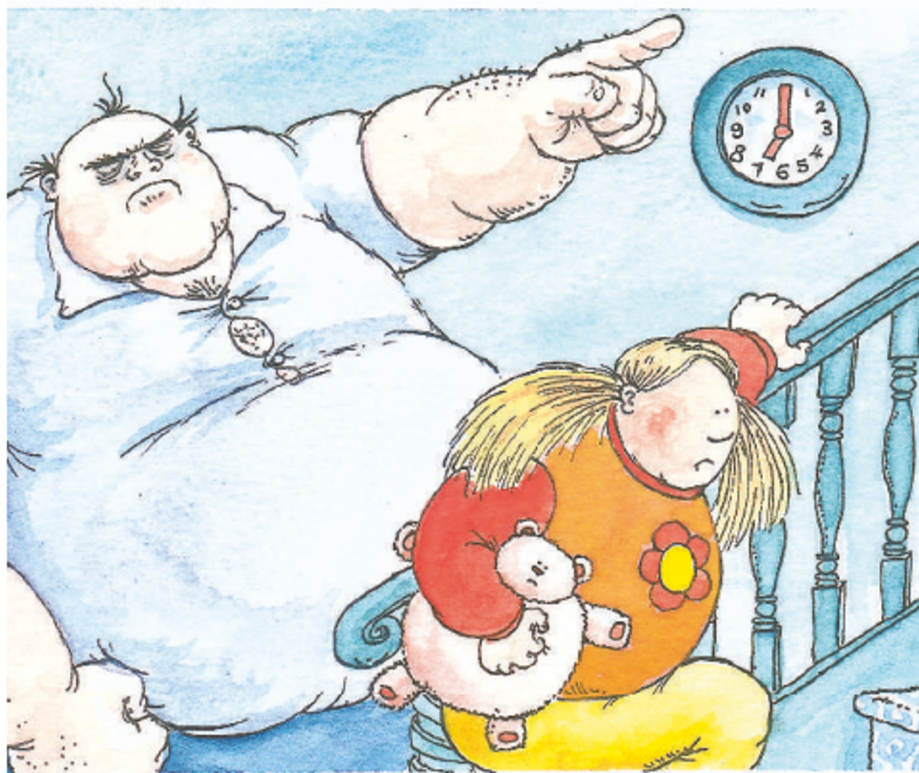
Curbing the epidemic

It is not clear how orexins are involved in the sleep-deprivation and obesity story. One idea is that lack of sleep interferes with normal circadian activity in the hypothalamus and boosts the activity of orexin neurons. This may directly affect energy expenditure and feeding, and could also alter the production of leptin, ghrelin and perhaps other appetite-control hormones. But this is just one of several possible mechanisms. "It's a concert of disharmony," Van Cauter explains. "Sleep affects our entire physiology and sleep deprivation will have adverse effects at all different levels."

In evolutionary terms, it is vital to hook up appetite and wakefulness. A mouse must eat to stay alive and be awake to forage — so it needs a mechanism that can recognize when fuel supplies are low and wake it up to find food. It is possible that humans have a similar control system that, when our ancestors were battling starvation, sent them searching for essential food. But now, anything that keeps us awake more than usual somehow taps into this circuit, sending us scavenging in the refrigerator for extra calories that we no longer burn off.

A study by Tamas Horvath and Xiao-Bing Gao at Yale University⁵ found that orexin neurons have a low threshold for activation. Overnight food deprivation boosts the formation of new synapses that excite them — which presumably encourages foraging and eating. Horvath suggests that these neurons are too easily stimulated, for example by stress or stray thoughts about work. Eating "is an unfortunate by-product of arousal," he says.

A pressing question for public health is whether the link with sleep patterns can be exploited to help battle obesity. Giovanni Cizza at the National Institute of Diabetes and Digestive



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and Kidney Diseases in Bethesda, Maryland, hopes to tackle this issue in a clinical trial funded by his institution. Cizza is recruiting 150 tired, obese people who sleep for six hours per night or less. Some of them will be taught to increase their sleep to seven-and-a-half hours (and offered a small fee as encouragement). The team will test whether, over a year, the extra sleep has an effect on weight, body fat, and leptin and ghrelin levels. If sleep can help shed even a fraction of excess weight, it could have a big impact on the health of the population, Cizza says.

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Following this logic, sleeping drugs could double as diet pills. Van Cauter says that she has been approached by one pharmaceutical company to discuss this possibility. Sanofi-Aventis, the Paris-based manufacturers of the widely used sleeping pill Ambien say that they do not have any planned trials. And drugs may not mimic the beneficial effect of a normal night's sleep if they do not fully recapitulate the pattern of sleep phases.

The US Department of Defense has funded a four-year, \$2-million study to examine whether the anti-fatigue drug called modafinil, which is taken by pilots to keep them awake, could be contributing to a rise in obesity in airforce veterans. Modafinil, also prescribed for narcolepsy and certain sleep disorders, is thought to exert some of its rousing effects on the orexin system.

Many experts doubt that more sleep, be it natural or drug-induced, will be the simple answer to weight loss. Once a person is over-

weight, then poor sleep and uncontrolled appetite could become part of a vicious cycle: obesity might make it hard to sleep, and poor sleep might make weight harder to shed. "It's not like we can get everyone to sleep eight or nine hours a night and we'll solve America's obesity problem," Turek says.

Instead, researchers are keen to identify those with 'high-risk' sleeping patterns in order to prevent problems before they arise. Van Cauter is interested in finding the seemingly lucky people who survive on a few hours of sleep without appearing to suffer. (One of the many mysteries of sleep is why some people naturally sleep nine hours and others only four.) Even though this group think they can manage fine on so little sleep, they may unwittingly be vulnerable to the long-term health effects of sleep deprivation. So an early warning sign, such as altered leptin, might alert doctors that the body is actually suffering more than its owner knows.

It may, say some, be most useful to identify children who are not sleeping enough and encourage parents to change their children's sleep habits before they become ingrained. "If it's true that by sleeping half an hour extra a night our kids could be less obese it could have a huge public-health impact," Saper says.

Helen Pearson is a reporter for Nature based in New York.

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