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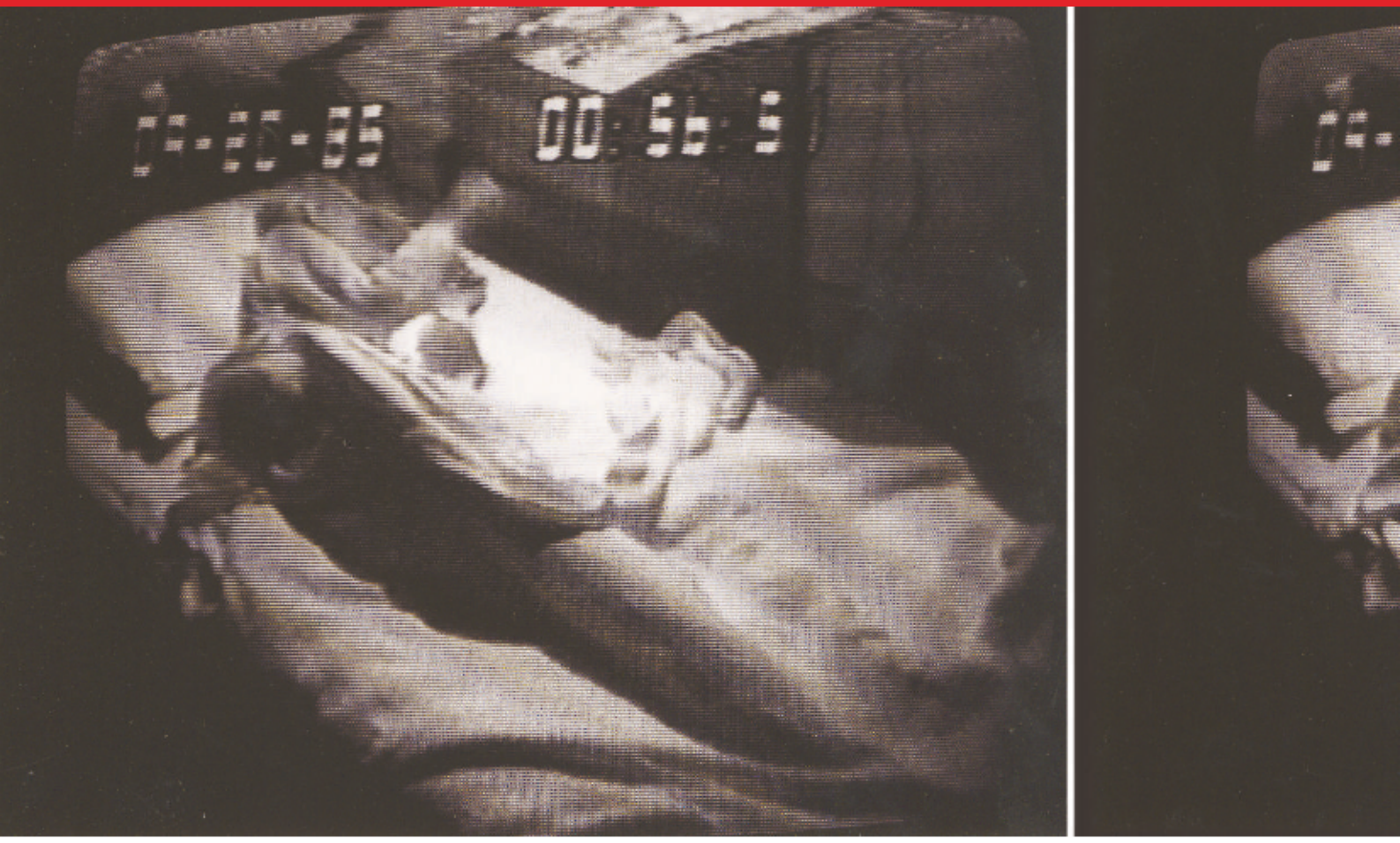


WHILE YOU WERE SLEEPING

The flailing limbs of someone acting out their dreams in bed may not seem the obvious place to seek a cure for Parkinson's disease. But, as Alison Abbott finds out, this sleep disorder is shedding fresh light on the development of neurodegenerative disorders.

Many couples suffer in silence, for fear that the police may be called. But those who make it to the sleep clinic have some bizarre tales to tell. Sleep neurologist Brad Boeve recalls one couple who described a particularly horrendous night-time event. While they slept in their bed, the husband suddenly grabbed his wife's head, shook it around roughly, then slammed it down hard and threw up his arms.

Far from being intentional, this distressing episode was the result of a disorder that sees sleeping people physically act out their dreams. In this instance, when the husband woke up he revealed that he had been playing rugby in his dream, had scored a try and then raised his arms in victory.

The case is just one of many that Boeve has investigated at the Mayo Clinic in Rochester, Minnesota. Beyond the obvious immediate trauma, Boeve believes that the sleep problem could hint at something more sinister. A large proportion of those affected by it go on to develop Parkinson's disease or a closely related neurodegenerative condition.

"I get weekly e-mails from people who have had these episodes and are afraid," says Boeve. The idea that the sleeping problem, known as REM sleep behaviour disorder, or RBD, and Parkinson's could be linked poses difficult ethical questions for doctors. But it could also overturn current theories on how Parkinson's disease works and how it could be treated.

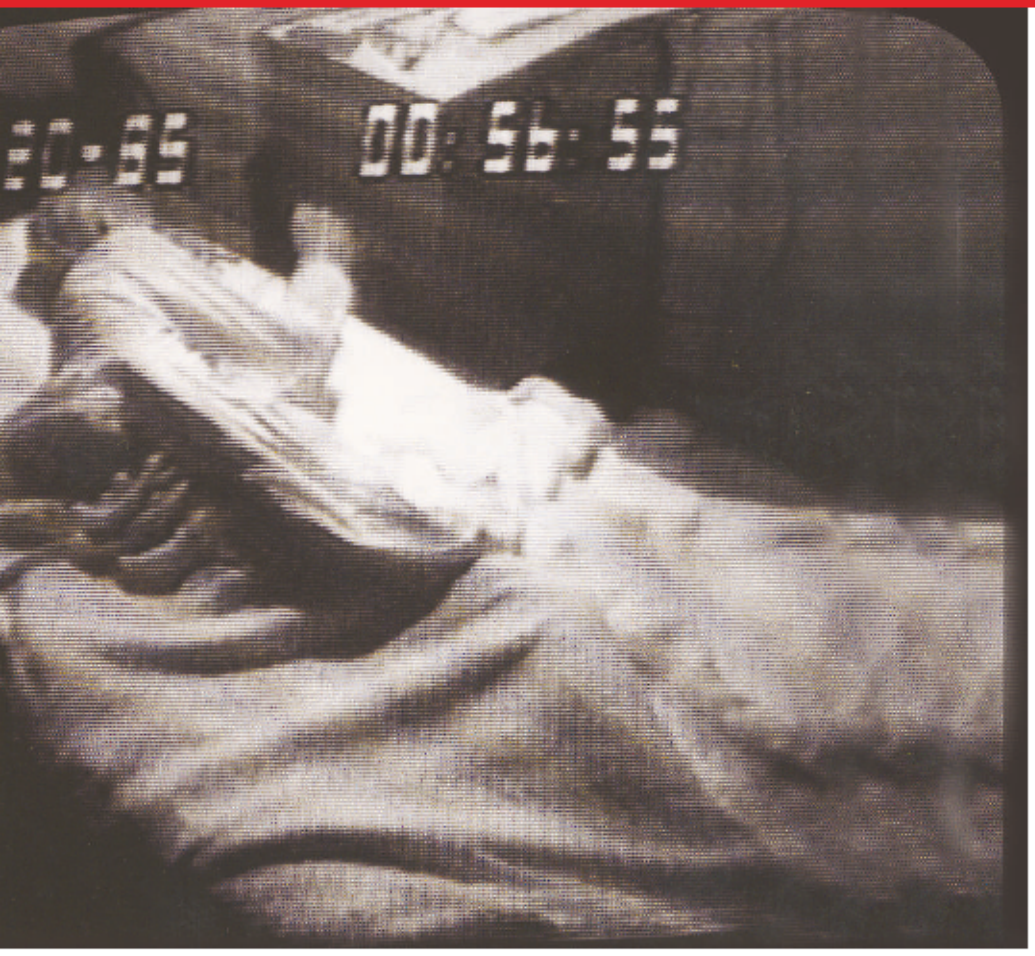
There are many sleep disorders, from insomnia to sleep-walking (see page 1253), but few are more bizarre and disturbing than RBD in its chronic form. About a quarter of a healthy night's sleep is occupied by rapid eye movement (REM) sleep, snatched in ever lengthening stretches as the night progresses. REM sleep is the time of dreaming, and voluntary muscles — apart from those of the eyes, which flicker continuously — become temporarily paralysed. Described as REM atonia, this paralysis stops us from physically acting out our dreams.

RBD sufferers lose this atonia. Instead, they flail their limbs and carry out coordinated movements — like the head-grabbing — following the course of their dreams. These dreams are always vivid and frequently involve fighting or being chased. Experts believe that the subjects of the dreams are, in turn, influenced by the mobilized limbs whose movements get woven into the stories.

Strong link

Episodes of RBD may occur only once a year, or as often as four or five times a night. So far, there seems to be no link between the frequency of the episodes and the likelihood of developing a neurodegenerative disease — or how soon such a disorder might appear. Of the 26 RBD patients studied by neurologists Carlos Schenck and Mark Mahowald at the University of Minnesota in Minneapolis, 18 have developed Parkinson's disease or closely related conditions[1].

The degenerative diseases that have been linked to RBD have a common underlying feature. A protein in the brain called α-synuclein becomes misfolded and clumps together to form aggregates. Collectively, these diseases are called synucleinopathies, although it remains unclear exactly what role the



α-synuclein protein plays in the conditions.

RBD patients develop diseases involving misfolded α-synuclein disturbingly often. Schenck, for example, notes that about 70% of his RBD patients go on to develop a synucleinopathy. In his patients, it took an average of 13 years from the onset of RBD until the patient began to show symptoms of synucleinopathy — although the range was between 3 and 29 years.

Other centres report similar experiences. In unpublished work, Boeve, for example, has studied more than 250 RBD patients, many of whom had Parkinson's disease or another synucleinopathy when they arrived at his sleep clinic. About half of those who showed up with just RBD developed a synucleinopathy an average of eight years later. Tell-tale α-synuclein aggregates called Lewy bodies were found in the brains of 26 of the 27 patients who died during the study.

By the mid-1990s, it was clear that there was probably a connection between RBD and synucleinopathies[2]. But researchers had no idea what might lie behind the link — anatomically it just didn't add up. A muscle's readiness to contract, or its tone, during REM sleep seems to be controlled by the brain stem, a complex structure that shuttles information between the body and higher areas of the brain. This was demonstrated in the 1960s by sleep researcher Michel Jouvet at the University of Lyon, France. He damaged the pons, part of the brain stem, in cats and found that the animals no longer slept peacefully but would, for example, stalk imaginary prey during REM sleep[3].

But according to scientific dogma, Parkinson's disease results from the death of nerve cells in the substantia nigra, a different region that sits above the brain stem in an area called the midbrain. These nerve cells release a chemical called dopamine, which transmits signals to other parts of the brain and so helps to control movement. The link between Parkinson's and the loss of these cells in the substantia nigra is reasonably well established. Treating Parkinson's patients with dopamine, for example, can dramatically improve their movement control, at least for a while. And autopsies of people with the disease have shown that they had lost at least 80% of their dopamine-producing cells in the substantia nigra.

> "I have a feeling that in Parkinson's disease we may have trouble seeing the forest for the tree." — William Langston

So how can this be reconciled with the apparent correlation between RBD and Parkinson's disease? The small community of scientists researching this field are now wondering whether the dogma needs a rethink. They suspect that RBD is the first sign of a degenerative process that begins in or near the brain stem and then creeps up the brain to other areas. According to this idea, first put forward by Boeve[4], RBD results from damage to a brain area affected early in the course of a more extensive condition. This disease really cripples only when it hits, and strips, the substantia nigra.

However plausible it seems, this idea leaves many questions unanswered. Why, for example, do only two-thirds of Parkinson's patients seem to suffer from RBD — shouldn't they all? But there is also some compelling support for the concept, particularly from the work of Heiko Braak, a neuroanatomist at the University of Frankfurt in Germany.

Braak performed detailed anatomical investigations of 41 autopsy brains from people who had Parkinson's disease. He also looked at 69 brains from people who had no clinical record of neurodegenerative disease but whose autopsies revealed that parts of their brains contained Lewy bodies[5].

Body of evidence

Braak showed that the emergence of Lewy bodies seemed to follow a defined and fairly predictable path, which he graded into six distinct steps (see graphic, overleaf). In the least affected brains, the Lewy bodies are confined to distinct areas of the lower brain stem. In stages 3 and 4, damage extends into the upper brain stem. And in stages 5 and 6, the damage reaches the substantia nigra and, ultimately, the cortex, impinging on areas involved in emotional and intellectual activities[5]. The Lewy bodies seem to multiply and spread through the brain, never appearing at higher levels unless they are also present lower in the brain stem. "By the time you see the distressing motor symptoms of Parkinson's, the damage is well advanced," says Braak.

But because the early stages of this condition don't seem to have any obvious symptoms, it is very difficult for clinicians to correlate Braak's stages with signs of disease. So it is impossible categorically to conclude that the progression of the Lewy bodies has anything to do with Parkinson's. "It is only a hypothesis, although a plausible one" Braak says. "We'll have to see if any symptoms are eventually associated with early stages."

His idea certainly resonates with clinician-researcher William Langston, who heads the Parkinson's Institute in Sunnyvale, California. Langston is keenly aware that his patients report all manner of weird symptoms that at the moment are not classified as part of classical Parkinson's. "There is a ringing association on the clinical side," he says. "I have a feeling that in Parkinson's disease we may have trouble seeing the forest for the tree — the tree being the devastating motor effects."

What would it mean if the early stages identified by Braak were indeed relevant to the disease? And what if the march of the Lewy bodies could be tracked in the living brain, for example through unexpected clinical manifestations such as RBD? "Then we could

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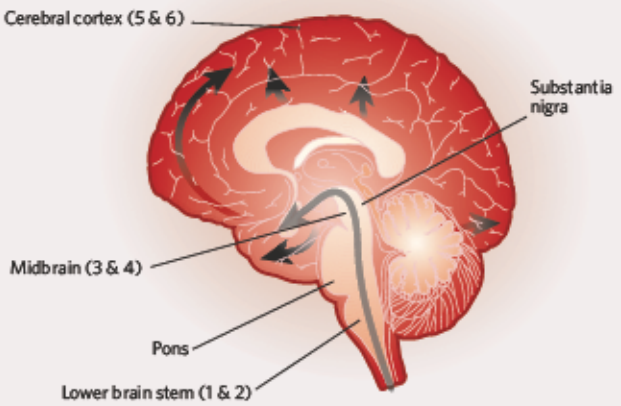
IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

The loss of motor control in patients with Parkinson's disease may be the late-stage symptoms of a long-term degenerative condition.

A FRESH VIEW OF PARKINSON'S DISEASE



Parkinson's disease results from the loss of neurons in part of the brain called the substantia nigra. Researchers now suggest that its symptoms are a late sign of a more extensive disease that begins in the brain stem and spreads throughout the brain in six stages.

give people advance warning that they were at very high risk for Parkinson's," says Ilonka Eisensehr, a neurologist now in private practice whose research at the University of Munich has added to the body of evidence linking RBD with synucleinopathies.

Eisensehr found that some patients who came to her sleep clinic for reasons unrelated to RBD had some muscle tone during REM sleep. In other words, they no longer had complete sleep paralysis, although they had not yet begun acting out their dreams. She carried out brain imaging studies on a group of these 'subclinical' RBD patients, comparing them with RBD patients, those with Parkinson's disease and healthy controls. She measured levels of proteins called dopamine transporters in the upper brain stem. These proteins are found only on dopamine-producing neurons, giving Eisensehr a way of monitoring the fate of these cells in patients.

She saw a clear pattern: the greatest loss of dopamine transporters was in patients with Parkinson's disease, although RBD patients also showed fairly low levels. In the subclinical RBD patients, the transporter level was better but was still lower than than in the healthy controls, and the loss correlated directly with how much muscle tone they had during REM sleep[6]. "Loss of REM atonia could indeed be a measurable, very early indicator for Parkinson's disease," Eisensehr says.

Karin Stiasny-Kolster at the University of Marburg in Germany has taken this further by showing that nearly all of her 30 patients with clinical or subclinical RBD had a badly disturbed sense of smell, a very common complaint among Parkinson's patients[7]. These observations fit well with Braak's hypothesis that Parkinson's progresses up through the brain in distinct stages, says Stiasny-Kolster. Smell signals enter the brain directly in the olfactory bulb, one of the areas, along with the brain stem, that Braak categorizes as stage 1.

Despite this evidence, some sleep neurologists have yet to be convinced. One of them is Alex Iranzo at the University of Barcelona in Spain. He says that over the past nine years, 40% of his RBD patients have developed a neurological disease, but in many cases that disorder was not a synucleinopathy. "RBD is certainly an anatomical disease, but I'm not sure there is a simple molecular explanation for it," Iranzo says.

Clearly the phenomenon requires a lot more research to unravel exactly what is going wrong in the brains of those who suffer from RBD. But whatever the outcome, the statistics are stark: these patients have a highly increased risk of developing Parkinson's disease, or another irreversible degenerative disorder. At the moment there are no drugs to protect neurons against the disease, raising the ethical dilemma of whether or not patients should be warned when they are diagnosed with RBD.

Policy of truth

Like Eisensehr, Schenck thinks they should be. "Then they will stay in touch with clinics and may eventually be able to be recruited into studies testing potential neuroprotective agents," Schenck says. Many drug companies are trying to develop such drugs, and enrolling people at high risk of developing Parkinson's, but who have no symptoms, into clinical trials could help bring products to the market faster. Recruiting those who already have Parkinson's disease is not ideal as they have already lost a high proportion of their dopamine-producing cells, leaving few neurons to protect. "Most trials have failed because we are not getting in early enough," says Langston.

Jacques Montplaisir, a neurologist at the University of Montreal in Canada, prefers not to bring the issue up with his patients unless one of them specifically asks. He is concerned about needlessly alarming the subgroup of RBD patients who are not suffering from a neurodegenerative disease. Montplaisir tests his RBD patients' sense of smell as well as their ability to discriminate colours, which is also frequently lost in Parkinson's disease, hoping that this will help to identify those who are at high risk. Only at such a point, or when a neuroprotective agent is available, would it be ethically justified to inform patients, he says.

"The best approach is to make clinicians aware of the possible correlation between RBD and Parkinson's, so they will be alert to danger signals such as RBD, and also disturbances to the sense of smell," says Kieran Breen, director of research at the Parkinson's Disease Society in London. "Clinicians could then monitor the patients closely." But Breen adds that patients should be told they have Parkinson's only when the first motor symptoms start. "It would not be fair on the patient otherwise," he says, "given the uncertainty of the link and the long time-lag that can sometimes occur between onset of RBD and onset of Parkinson's."

Neurologists currently prescribe clonazepam, a drug used to treat epilepsy, to RBD patients to suppress their dream enactment. But no prescription can help patients live with the fear that a diagnosis of RBD brings. In the future, those with early warning signs may turn out to be the lucky ones if effective neuroprotective agents are developed.

"We are facing a revolution in Parkinson's disease," says Langston. "We've been fixated on movement disorder linked to cell death in the substantia nigra, but we may now have to think more broadly." He believes that early warning signs such as RBD may turn out to be exactly what is needed to understand this terrible disease and learn how to stop it in its tracks. ■

Alison Abbott is *Nature*'s senior European correspondent.

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