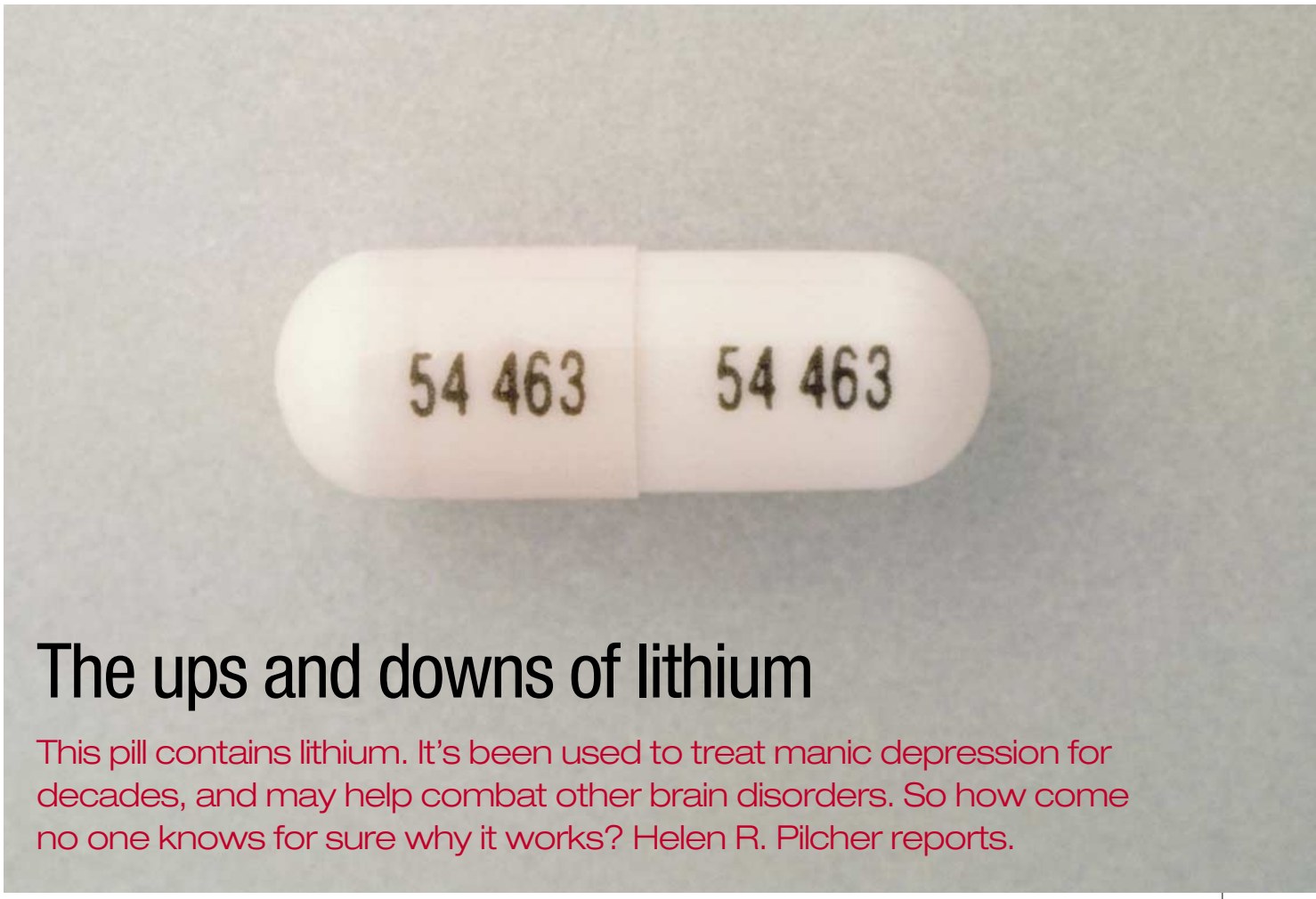


CUSTOM MEDICAL STOCK PHOTO/SPL

The ups and downs of lithium

This pill contains lithium. It's been used to treat manic depression for decades, and may help combat other brain disorders. So how come no one knows for sure why it works? Helen R. Pilcher reports.

"He sleeps normally, eats normally," says Sarah. "He's a fairly typical kid." Her son is one of millions of patients with bipolar disorder (BPD) — manic depression — whose lives have been transformed by lithium. Children with the condition can see-saw between energetic highs and listless lows many times a day. Adults suffer similar swings, albeit at less frequent intervals.

During periods of mania, sufferers can experience euphoria and exercise poor judgement, perhaps going on spending sprees. Depressive episodes bring on fatigue, pessimism and anxiety. But lithium, administered as a salt, puts sufferers on an even keel, freeing some parents from the need to provide constant care for children with BPD. "One minute he'd be bouncing off the walls and giddy, the next minute he'd be crying," recalls Sarah. "Now, he has settled down within himself and can play with other children."

Despite being the most widely used treatment for BPD for over 30 years, lithium is an enigma: no one knows how it works. Even though it can transform lives, little funding is being channelled into clinical studies of the drug. Lithium cannot be patented, so drug companies are investigating more profitable alternatives. Many doctors are increasingly avoiding the treatment, fearing that it is difficult to prescribe. Lithium, it seems, is in need of some good PR.

Help may be at hand. Recent results have linked the drug to an enzyme involved in a range of cellular processes. The new studies could explain why lithium works, and provide hints about how it could treat other conditions, including Alzheimer's disease and schizophrenia. If these approaches bear fruit, lithium could become the 'aspirin of the brain' — just as aspirin is used to combat conditions from arthritis to heart attacks, lithium could treat a range of neurological disorders.

Wonder drug

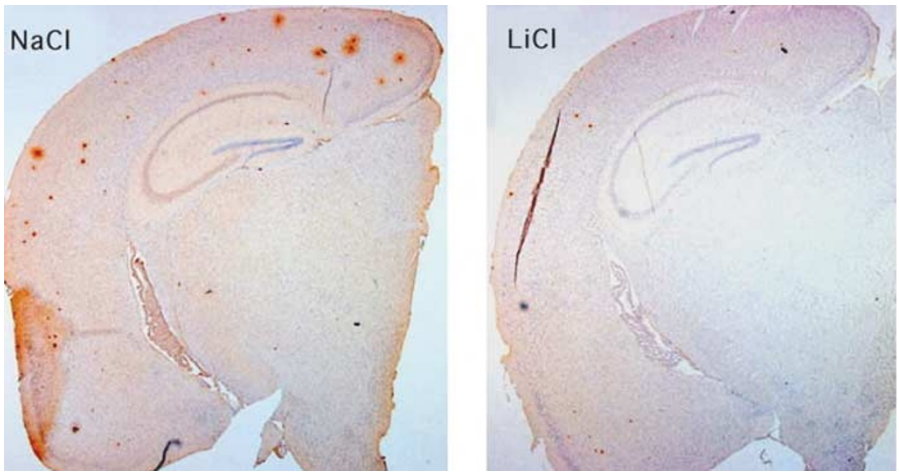
The drug's first advocate was John Cade, senior medical officer at the Victorian Department of Mental Hygiene in Melbourne, Australia. In 1949, Cade reported that lithium had a calming influence on guinea pigs, and that it lessened manic symptoms in humans[1]. Twenty-one years and many studies later, lithium was licensed in the United States for the treatment of BPD.

BPD is surprisingly common, affecting 1 person in 100. Without some form of therapy, up to 20% of sufferers will commit suicide[2]. Given these statistics, lithium has proved to be invaluable. It is not the perfect drug by any means: those who take it can experience short-term side effects such as weight gain and hand tremors, and long-term problems include an increased risk of kidney failure. But up to 80% of sufferers have a positive reaction to lithium[3], and the suicide rate is reduced by a factor of eight. "Lithium can keep people well for decades," says Richard Day, a psychiatrist at the University of Dundee, UK.

Our understanding of the causes of BPD is limited. Little is known about how the brains of sufferers differ overall from those of non-sufferers, although there is some evidence that people with the condition have smaller brain volume in certain areas[4] and that lithium treatment can help to correct this[5]. Knowledge about cellular abnormalities associated with BPD is similarly sketchy.

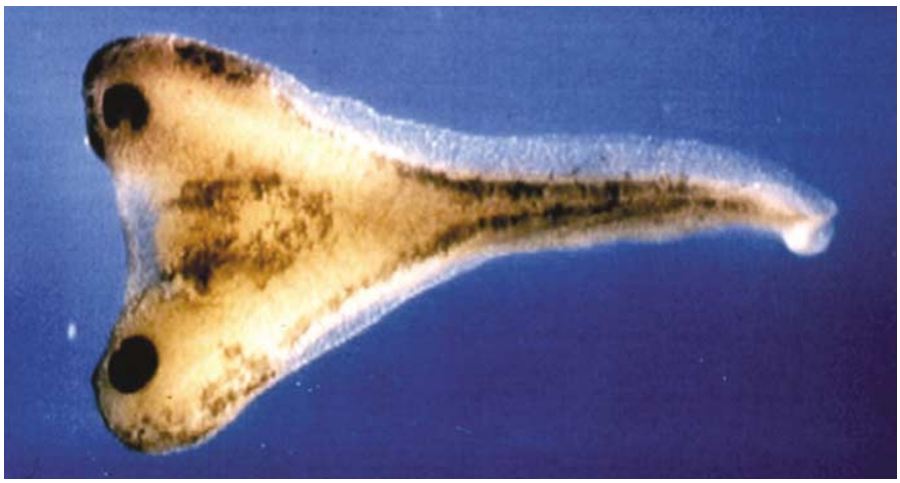
Given this lack of information, ideas about lithium's action tend be speculative. One possibility, born in the early 1980s, centred on lithium's effect on a sugar called inositol. This sugar is involved in a signalling pathway that regulates the ability of neurons to exchange signals; lowering inositol levels damps down these signals.

C. WILSON & V. LEE



Build-up of protein thought to cause Alzheimer's (orange spots) is cut in brains treated with lithium.

P. KLEIN



Two faced: treatment of frog embryos with lithium can result in two-headed tadpoles, similar to this. Lithium may target an enzyme involved in many cellular processes.

Lithium inhibits inositol production[6], so some researchers reasoned that BPD might be linked to excessive signalling by overactive neurons, and that lithium worked by calming these cells.

Mood change

Patients with BPD who take lithium do indeed have lowered inositol levels, but the link with the drug's therapeutic effects is not clear. In 1999, Husseini Manji, a lithium researcher at the National Institute of Mental Health (NIMH) in Bethesda, Maryland, found that lithium causes brain inositol levels to drop. Together with Gregory Moore, a physicist at the Wayne State University School of Medicine in Detroit, Manji found that after a week of lithium treatment, inositol levels in particular parts of the brain fell by 30% in patients with BPD — but their mood did not change for another two to three weeks[7]. "This makes it very difficult to ascribe a therapeutic relevance," says Manji.

In the 1990s, a two-headed tadpole and a developmentally challenged slime mould heralded the arrival of an alternative theory. Researchers knew that the number of spores produced by the slime mould *Dictyostelium* is cut when lithium is applied[8] — a reduction that is also seen when the activity of glycogen synthase kinase-3 (GSK-3), an enzyme that helps control several cellular processes, is disrupted[9]. Lithium also prompted frog embryos to turn into two-headed tadpoles[10], and it was believed that this abnormality might be due to disruption in GSK-3 activity.

In 1996, Peter Klein, a developmental biologist at the University of Pennsylvania in Philadelphia, proposed that the effects of lithium on frog embryos and *Dictyostelium* might be due to some kind of effect on GSK-3. "I had an epiphany," he says. He showed that lithium inhibits GSK-3 (ref. 11), and subsequent work has shored up his initial findings. Researchers now know that lithium binds to GSK-3 and causes the activity of the enzyme to drop. Phosphate molecules then attach to GSK-3, deactivating the enzyme further[12]. In turn, this affects the expression of the various genes influenced by GSK-3 levels.

But how does this relate to BDP? Some evidence comes from lithium's ability to protect and regenerate cells. Patients with BPD have up to 40% less grey matter — tissue that is mainly composed of cell bodies — than normal in brain regions associated with mood[4]. Lithium may help counteract this cell loss: a month's treatment boosts the volume of total grey matter by an average of 3% (ref. 5). The drug may do this by prompting the production of new neurons, a process that some researchers believe involves GSK-3 . De-Maw Chuang, a neurobiologist in the Mood and Anxiety Disorders Program at the NIMH, has shown that lithium stimulates neural stem cells in culture, causing them to multiply faster[13].

Such results do more than suggest a connection between lithium, BDP and GSK-3 — they also suggest ways in which the drug could treat other neurological disorders. Chuang, for example, has looked at whether lithium could be used to tackle Huntington's disease, a condition involving neuron loss in the striatum, a region associated with the control of movement. As part of a group of National Institutes of Health researchers, he tracked the effects of lithium on stem cells from a rat model that simulates Huntington's disease.

Neuronal stem cells line the edges of ventricles, cavities containing a fluid that protects the brain. Chuang's team, which has not yet published its results, found that lithium prompts these cells to leave the ventricles and migrate to the striatum. "You see many dividing cells near the site of injury," he says. After lithium treatment, cell death is cut by 80%. "It's too early to say if the same thing is happening in the human brain," Chuang says, "but it is a possibility."

Lithium also helps rats to regain balance and mobility after suffering strokes, in which loss of blood supply to the brain causes areas of neurons to die. Lithium treatment decreased the size of the dead areas by up to 40% (ref. 14). This recovery may, in part, be the result of stem cells dividing to produce replacement cells, speculates Chuang.

Shattered illusions

There is, however, an alternative explanation for lithium's ability to increase brain volume in patients with BPD — and it also has implications for the treatment of other diseases. In 2000, Manji showed that the brains of patients with BPD contained fewer shrunken and withered neurons when they were treated with lithium. He also showed that lithium boosts levels of *N*-acetyl aspartate[5], a marker for healthy cells in grey matter. This suggests that the drug could be protecting cells in patients with BPD, instead of, or as well as, prompting the growth of new neurons.

Such protective properties suggest that lithium could be used to treat psychotic disorders such as schizophrenia. This

condition, which is characterized by hallucinations and delusions, has been linked in some patients to cell loss. Abnormal levels of some neurotransmitters, the chemicals used to send signals between neurons, are thought to be involved. High concentrations of one neurotransmitter — glutamate — can kill cells.

In cell culture, lithium can protect cells against glutamate-induced death[15], although it's unclear how it does this, and whether GSK-3 is involved. Researchers are investigating several leads, including the possibility that lithium turns on genes that help to protect cells against glutamate or prompts cells to release nourishing growth factors.

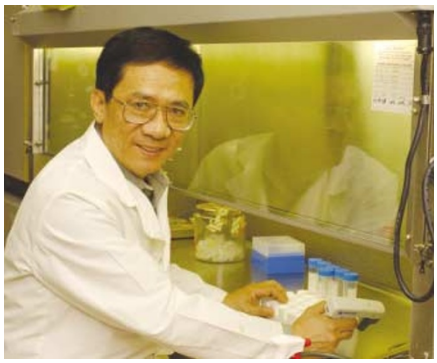
Whatever the mechanism, the new studies are enough for scientists to want to test lithium in humans with psychosis. "Given early on, a low dose of lithium may delay or even prevent the onset of psychotic disorders, including schizophrenia," says Gregor Berger, a psychiatrist at the University of Melbourne's Personal Assessment and Crisis Evaluation Clinic. He is testing a group of 30 young adults deemed to be at risk from developing psychosis — they have a family history of schizophrenia or a record of brief psychotic disturbances. Without treatment, about a third would be expected to develop psychosis[16]. One year on, his unpublished study shows that all of the subjects given daily doses of lithium are free from symptoms.

Untangling the knot

Lithium might also ward off Alzheimer's disease, a form of dementia. This disease has two hallmarks in the brain: protein plaques and tangles of protein fibres. Tangles are thought to be caused by the addition of phosphate molecules to a protein called tau, a process that involves GSK-3 (ref. 17). This might explain why, in cultured cells at least, lithium can prevent tau phosphorylation[18].

The drug might also tackle the plaques seen in Alzheimer's disease. These insoluble deposits of the protein amyloid build up around neurons, impairing the cells' ability to communicate. When GSK-3 is added to cultured cells, the levels of amyloid protein go up. In mice that have been genetically engineered so that they are prone to plaques, lithium inhibits GSK-3, stops the protein from building up[19] and cuts the number of plaques. Human trials have not yet been conducted, but Klein suggests that, given early on, lithium might reduce the rate of tangle and plaque formation, or prevent them altogether, ultimately putting the brakes on dementia.

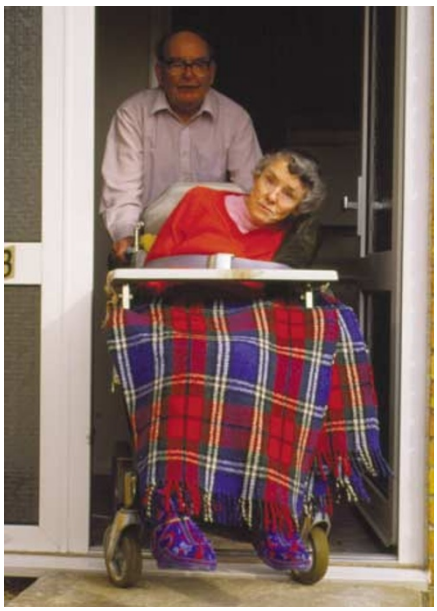
So, are drug companies rushing to set up trials for the treatment of Alzheimer's disease and other conditions? Unfortunately not. The original patent on the use of lithium as a drug has long since expired. It cannot be repatented, and so lithium lacks the potential for profit. "Drug companies prefer to plough their resources into more profitable alternatives," says Berger. This makes his research, which involves human subjects, something of a rarity. Berger's research is currently funded by the Stanley Medical Research Institute, a Bethesda-based non-profit organization that supports research on schizophrenia and BPD.



Brain power: De-Maw Chuang is probing links between lithium and neural stem cells.

Drug companies and doctors are also deterred by lithium's side effects. In younger people, these can be managed. Whether or not elderly people could tolerate the drug is a separate issue. With age, the problems can worsen, cautions Day. "A fine tremor could become a coarse tremor," he says. Nausea could become vomiting, and, in extreme cases, drowsiness might slip into coma.

Pharmaceutical companies are focusing instead on developing lithium-like drugs that have less extreme side effects. GSK-3 occurs in two forms, known as α and β, but only GSK-3α is required for amyloid production. Klein speculates that molecules that selectively inhibit the α version might rid the brain of plaques while minimizing adverse reactions. Most major pharmaceutical companies are currently developing GSK-3 inhibitors, but are tight-lipped about the details.



C. CAFFREY/SPL

Lithium could help prevent the cell loss that impairs the movement of Huntington's sufferers.

If such research produces a better alternative to lithium, no one will complain. But in the meantime, lithium's reputation is being tarnished. The drug has a narrow therapeutic window — too little is ineffective, too much is toxic — so finding the right dose can take time. Even then, patients need regular psychiatric assessments and blood tests. Such problems mean lithium is losing popularity as a treatment for BPD, just when its activity is beginning to be understood. "Most doctors don't know how to use it and are needlessly afraid of lithium," says Martha Hellander, executive director of the Child & Adolescent Bipolar Foundation, Wilmette, Illinois. "Lithium has a tainted reputation," agrees Manji.

This, say advocates of the drug, is restricting its use. Hellander would like to see it studied in children with BPD. Currently, although the condition can be diagnosed before puberty, no medications are approved for the treatment of children under 12 years old with BPD in the United States.

And lithium could still find a use in Alzheimer's disease, despite its side effects. Lower doses would cut the side effects, yet could still be beneficial, says Berger, who is using low doses in his study. But unless lithium gets some better press, and its action becomes better understood, such potential benefits could go unexploited. "Hardly anyone speaks up for lithium," says Hellander. "It's like the orphan child of treatment." ■

Helen R. Pilcher works in *Nature*'s news syndication team.

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