The rat is on a carousel with clear plastic sides, rotating slowly in a small room. As it looks out through the plastic, it sees markings on the walls of the room from which it can determine its position. At a certain location it receives a foot shock—or, in experimenters’ jargon, a negative reinforcement. When that happens, the rat turns sharply around and walks tirelessly in the opposite direction, so it never reaches that same place in the room again. It will do this to the point of exhaustion.

Question: How do you get the rat to stop walking? Note that just turning off the shock will not suffice, because the rat will not allow itself to enter the danger zone. The rat needs an intervention that helps it forget its fear or that overrides its response with a competing signal of safety.

So much for the rat. Now think of someone who has been wounded in combat and suffers from the vague but real cluster of symptoms called post-traumatic stress disorder (PTSD). He, too, associates specific contexts or stimuli—open spaces, crowds, sudden loud noises—with something painful. He avoids those circumstances when he can. He is in the same bind as the rat on the turntable: unable to discover for himself that certain situations are now safe. How do we get him to stop running?

The rat on the carousel and the veteran on a crowded street are both prisoners of memory, of the extraordinary power of pain to forge an indelible impression on the brain: be it mammalian, reptile or even invertebrate. As some researchers labor to solve the mystery of memory loss in dementia, others are attacking the mirror-image problem of how to help patients escape the painful memories that dominate their daily life—and not just those with PTSD. An emerging new paradigm views such diverse conditions as phobias, obsessive-compulsive disorder, and even addiction and intractable pain as disorders of...
Some people never forget the time a spider fell into their glass of milk. Others cannot break the association of certain places or situations with getting high. Now researchers are finding that remembering is not just a process of passively storing impressions. It is a continuous, dynamic activity on the cellular level and an ongoing psychological process open to manipulation with drugs and cognitive therapy. This is wonderful news for combat veterans and victims of assaults and accidents. What it means for future generations of historians and personal-injury lawyers remains to be seen.

For the rat on the carousel, you can imagine different approaches to extinguishing its fear. You could let it walk to exhaustion and learn for itself that the shock has been turned off—a process psychologists call extinction. Or you could try tinkingering directly with the rat’s brain—specifically, the hippocampus, where place memories are formed and stored. Six years ago neuroscientist Todd Sacktor of S.U.N.Y. Downstate Medical Center in Brooklyn, building on work with his former colleague André Fenton, did just that. He injected a compound called ZIP into the hippocampus of a rat that had been trained on the carousel and, after two hours, tested it again and found the fear had been erased. Do that in a combat veteran disabled by PTSD, and you are on the way to a Nobel Prize or a billion-dollar drug bonanza.

To understand Sacktor’s experiment in forgetting involves some exploration into memory—and how the learning processes that underlie recollection can ultimately be undone. Neuroscientists who specialize in memory often start by considering long-term potentiation (LTP), the process by which two or more neurons that fire simultaneously, or in close sequence, develop a synchronous bond that makes them likely to fire together in the future. Basically, the neuron that encodes the experience of hearing a sudden loud bang can become associated with the neurons that cause you to look for cover and drop to the ground. The complex biochemistry of LTP involves the proliferation of glutamate receptors on the receiving, or postsynaptic, cell to amplify the electrochemical signal that crosses the tiny gap between one neuron and another. But, as Sacktor explains, these receptors are unstable; they are continually forming, disappearing and re-forming. A memory’s persistence implies the existence of an active biochemical process that keeps a fixed complement of receptors in place.

The agent involved in memory preservation was long assumed to be a protein because drugs that block protein synthesis systemically can prevent learning and memory formation in animals. Sacktor’s laboratory zeroed in on an obscure protein kinase—an enzyme that activates other proteins by attaching a phosphate group to them—known as PKMzeta. It is PKMzeta, Sacktor says, that is responsible for sustaining memories; without it, long-term potentiation fails, and the memory evaporates. PKMzeta has a specific antagonist, called ZIP, which was what Sacktor injected into the rat’s hippocampus to make it forget its aversion training on the carousel. Merely by blocking the continuing action of PKMzeta, ZIP acts on memory as if it were reformattting a hard disk.

For that very reason, ZIP is not likely to be tried on humans anytime soon as a drug for blotting out bad memories. If it could be chemically modified to prevent it from entering the brain, confining its activity solely to the spinal cord, it might one day turn up as a treatment to erase the hypersensitized reaction of the chronic pain sufferer to a poke or prod, a reaction that itself is a form of memory. For obliterating recall of traumatic events, the need is for a drug with the power of ZIP but enough specificity to target individual memories.

At first glance, the problem seems insoluble because there appears to be no biochemical distinction between good and bad memories that ZIP could exploit. A few research endeavors point toward ways around this issue. None are effective enough to completely blot out a specific unwanted memory, but they may still blunt some of the anguish associated with the painful recall of a disastrous event.

The hypothesized weak spot in the development of PTSD is consolidation, the process of moving significant memories from short- to long-term storage. The line between short and long term is difficult to quantify but simple to illustrate: you probably remember what you ate for dinner last night but not a year ago—unless it was your wedding reception or a meal that sent you to the emergency room. Long-term memories tend to be formed around emotionally significant or fearful events—or anything that releases the neurotransmitter norepinephrine, which promotes protein synthesis in the amygdala. As one famous experiment showed, even sticking a hand in a bucket of ice water will work.

By the same token, you ought to be able to interfere with long-term memory formation by lowering levels of norepinephrine. Several candidate drugs do just that, of which the best known is the beta blocker propranolol, widely used to treat hypertension and stage fright. (It is a fact of life for biomedical researchers that unless they work for a drug company with hundreds of millions of dollars to spend on human trials, they are more or less forced to experiment with drugs that are already approved for human use in another condition.) The window in which consolidation takes place is still being investigated, but it appears to be on the order of a few hours. In the early 2000s Roger Pitman, a neuroscientist at Harvard Medical School, got the idea of giving people propranolol right after a traumatic event—in his case, after an auto accident or an assault because he was working with civilians—to see whether blocking norepinephrine could in effect inoculate them against post-traumatic stress.

Note that Pitman’s intent was not to erase the memory of the trauma itself—
the episodic, autobiographical recall of the event—only the emotional valence associated with it. In theory, doing so runs the risk of compromising the psychological integrity of victims, a concern that would certainly arise if it were possible to alter the contents and not just the emotional tone of memories. Long after American society made peace with the idea of using drugs to alter consciousness and mood, memory, the sacred vessel of selfhood, remains off-limits to manipulation in the view of many. “I’ve had to debate the bio-ethicists every year on this,” says one of the pioneers of modern memory research, James McGaugh of the University of California, Irvine. “They make their living worrying about this—whether it’s a good idea to diminish traumatic memories, notwithstanding that people all the time tell [trauma victims], ‘There, there, you’ll get over it. That’s a good thing. Giving them a drug isn’t. Now why is that?’”

McGaugh himself, in a classic experiment with his UC, Irvine colleague Larry Cahill in the 1990s, showed that propranolol could affect, if not the accuracy, at least the specificity of episodic memories. These experiments were typically done with illustrated stories. McGaugh and Cahill presented subjects with either of two different variations on a story: one about a boy hit by a car and needing emergency surgery, the other about an emotionally neutral account of a visit to a hospital. The first group, as expected, remembered the story in much more detail. But when the experiment was done again, with subjects given propranolol the difference disappeared—the emotionally arousing story was remembered just as well as the neutral one.

One can envision prosecutors or personal-injury lawyers being made nervous by the prospect of anything that affects the recall of crime or accident victims. Even with factual memories unimpaired, a few tears on the witness stand can be worth more than their weight in gold when a jury is awarding damages. But it is also worth bearing in mind that the comparison is to a hypernormal state of recall induced by a rush of norepinephrine. All propranolol can do, though, is bring emotionally charged memories into line with recollections of neutral events. And from the victim’s point of view, that might be just what the doctor, if not the lawyer, ordered.

Pitman’s first report on using propranolol on trauma victims, published in 2002, showed some encouraging results, leading to exuberant predictions that before long patients arriving at an emergency room or a military field hospital would be evaluated for potential PTSD, just as they are x-rayed for broken bones, and treated accordingly. But a follow-up study published in 2011 failed to support the hypothesis. It also demonstrated just how hard this research is in the real world. Over a period of 44 months only 173 of 2,014 patients screened met the study criteria, the rest having been rejected for reasons of age, preexisting medical condition or insufficient trauma. Among other difficulties, federal law now forbids researchers from approaching patients directly; permission has to be obtained first by a clinical care-giver, typically an emergency medical specialist with more urgent things on his or her mind. “We just didn’t have much luck in getting to them” soon enough, Pitman says. “I wouldn’t do another propranolol study unless I could get them the drug much sooner, and I don’t see that happening. On the other hand, if people call me and say, ‘I’ve just been in an accident. Should I take propranolol?’ my answer is, ‘I can’t support it based on the data, but I still think it has potential.’” Drugs, though, may not be the only answer.

Take the subject sitting in an office at the Emory University School of Medicine. In his mind, he is years back in time and thousands of miles away, at the wheel of a Humvee in Iraq. The script playing out on the virtual-reality goggles he wears is drawn from his memory and is being fed back to him in real time by a therapist at a keyboard. Following his account, she plants an imaginary sniper on an overpass, detonates a land mine on the road and sends shadowy figures running down an alleyway. The chair shakes with each explosion. Now the subject is breathing hard, looking urgently to the left and right, wrenching an imaginary steering wheel. He breaks out in sweat and throws an arm up to protect his face.

As soon as Russian psycholo-gist Ivan Pavlov discovered the mechanisms of classical conditioning, it was natural to ask about the opposing phenomenon of extinction: If you rang the bell and did not feed the dog, how long would it be before he stopped salivating? Not very long, it turned out, leading to a question that is still worth asking: Why does PTSD not self-extinguish in the same way? The world, after all, is full of sudden loud noises that do not signify a mortar attack, and yet some people never seem to unlearn the responses they learned in Afghanistan or, for that matter, Vietnam. One way to think about this is that in PTSD, anxiety and distress become, in effect, their own negative reinforcement; reliving the original trauma with each succeeding reminder is
Learning to Forget

Once formed, recollections of trauma may seem indelible. But researchers now believe they are more like files on a hard drive that can be altered, overwritten or even erased. Ridding the brain of toxic memories induced by traumatic life events requires tweaking individual neurons, each of which connects to thousands of others.

Neuroscientists are now studying biochemical and behavioral measures to assist in forgetting. This line of research starts with the basics of how memories form. A memory arises when a series of neurons fire together in a similar way—a process called consolidation. First one neuron fires in response to a sound, a visual perception or another input, which triggers another to switch on and, later still, other nearby cells. Then, when any neuron is stimulated again, even weakly, other neurons in the network also fire—a physical embodiment of what happens when you recall getting bitten by a neighbor’s dog.

A memory is weakened, and they begin to fire in near synchrony, establishing a distinctive firing pattern—a memory connection. With repeated firing, links between neurons are strengthened, and they begin to fire in near synchrony, establishing a distinctive firing pattern—a memory. Then, when any neuron is stimulated again, even weakly, other neurons in the network also fire—a physical embodiment of what happens when you recall getting bitten by a neighbor’s dog.

Initial state

First stimulus

Primes neighboring neuron

Activated

With repeated firing, links between neurons are strengthened, and they begin to fire in near synchrony, establishing a distinctive firing pattern—a memory. Then, when any neuron is stimulated again, even weakly, other neurons in the network also fire—a physical embodiment of what happens when you recall getting bitten by a neighbor’s dog.

MEMORY BLOTTER

Erasing Memories

Erase: Blotting out a memory occurs by unlinking interconnected neurons. This involves inactivation of a protein called PKMζ, which acts as a kind of preservative chemical—ensuring that the connections among brain cells in the network remain intact. A compound known as ZIP serves as a finish remover that unhooks these neural links and abolishes the memory along with it. Researchers have yet to devise a means of targeting specific memories. Simply ingesting a drug like ZIP would cause all recollections to disappear.

Dampen: Instead of wiping the slate clean, other researchers have investigated ways to weaken the connections among neurons in parts of the brain that record or recollect a fearful event. They have tried to do this by administering a drug, such as the beta blocker propranolol, either before an anticipated fright or else during the recall of an incident afterward to allow the drug to dull the painful memory.

Replace: A memory makeover is yet another option. It turns out that when a memory is recalled later, it can be manipulated—through behavioral intervention and perhaps one day with a drug—so that a past incident is brought to mind in a safe setting and then “reconsolidated” in a different emotional light.

Illustration by Emily Cooper
which is activated when neurons fire simultaneously. It depolarizes the cell membrane on the downstream neuron, admitting calcium and setting in motion the sequence of reactions leading to long-term potentiation, memory and learning.

From the ease with which fear memories are acquired, Davis concludes that a single frightening event must unleash a flood of them in the amygdala. You do not need chemical help to remember an encounter with a lion, about which the adage “once bitten, twice shy” is profoundly appropriate. Extinction, in contrast, seems to have evolved as a slow, almost reluctant process. Survival is enhanced by remembering danger, not by forgetting it. As Davis says, though, if you have a patient with a germ phobia, and the cure is to make him touch a toilet seat, the dropout rate is pretty high. If the typical course requires eight sessions, and you can do it in two by adding d-cycloserine, that is obviously a pretty high. If the typical course requires eight sessions, and you can do it in two by adding d-cycloserine, that is obviously a big improvement. Clinical trials are now under way to assess how using d-cycloserine can help speed extinction in PTSD. Yet, again, overwriting bad memories may not require popping a pill.

SUBJECTS FACE A COMPUTER SCREEN and trail wires from electrode pads on their wrists and fingers. One set will deliver a shock; the other will record skin conductance, a standard measure of fear. The subjects are in three groups, all of which undergo identical conditioning to expect a shock in association with a blue square shown on the screen. The next day the groups all undergo extinction training, viewing the figure repeatedly without receiving a shock, until they no longer show a reaction to it. Two of the groups, however, get something extra first: a single “reminder” trial, either 10 minutes or six hours before the extinction session. In practice, the reminder trial is identical to a single extinction trial: the subject sees the figure and does not receive a shock. Yet it functions very differently in the brain. The kind of conditioned fear induced by a shock often reappears spontaneously after extinction, and a day later, in two of the three groups, it did. But in the group that received the reminder trial 10 minutes before extinction, there was virtually no spontaneous recovery; extinction somehow was much more effective with them. Amazingly, the difference persisted even one full year later.

How can this be? The answer, according to Elizabeth Phelps, at whose New York University lab the study was done, goes back to consolidation theory—the idea that it requires several hours for memories, together with their emotional valence, to be fixed in long-term storage. The implication is that there is a window during which they can be manipulated, which is what Pitman and his collaborators tried to do, unsuccessfully, in the emergency room at Massachusetts General Hospital. A now famous paper from 2000 by Karim Nader, now at McGill University but at the time a fellow in the N.Y.U. lab of memory researcher Joseph E. LeDoux, revived an earlier, out-of-favor hypothesis: that old memories can be changed when they are recalled to consciousness. In this view, the proper metaphor for memory is not a scrapbook or a diary but a hard drive containing files that can be modified each time they are called up. Memories are “labile” for a period after they are recalled—the function of the reminder trial in Phelps’s experiment—and then undergo reconsolidation after several hours.

Debate persists about the evolutionary value of this feature, although the most convincing explanation is that it allows for the updating of memories with new information. Being bitten by a lion and being bitten by, say, a mongoose are very different experiences; once the shock of being attacked subsides and the wound heals, there is survival value in being able to think back and distinguish between them. When Nader, LeDoux and Glenn E. Schafe, now at Yale University, showed in 2000 that the same drugs that block consolidation of new memories in rats could erase existing ones during the reconsolidation window, the race was on to find ways to harness the effect in humans.

Unfortunately, the drugs used in rats, which block protein synthesis systemically, are toxic. Hence, researchers have turned to drugs that block propranolol and mytarapone; the latter inhibits cortisol, another stress hormone that is associated with the formation of emotionally charged memories. (Do not try this at home, but alcohol and morphine might work, too.) The results so far have been inconclusive, reflecting the difficulty of isolating one psychological parameter in conscious, self-aware organisms whose preexisting memories and personalities are considerably more varied than those of most lab rats.

Merel Kindt, a researcher at the University of Amsterdam, reported a few years ago that giving propranolol during reconsolidation reduced fear (as measured by the strength of the electrical potential in the muscles controlling eye blinks) in subjects who had been conditioned to fear a picture of a spider. Pitman thinks “the jury is still out” on propranolol—which is why there was so much excitement in 2010, when Phelps and her colleagues, including lead experimenter Daniela Schiller, published their reconsolidation study. Their work did not rely on drugs for its effect.

The findings, they wrote, “suggest a non-invasive technique that can be used safely and flexibly in humans to prevent the return of fear.” Moreover, “this effect is specific to the targeted fear memory, and not others, and persists for at least a year.” The response was so positive, in fact, that Phelps feels the need to caution that the work is “still in its infancy. There are hundreds of papers on rats since 2000 and a handful in humans. Ever since the first animal studies, people have been talking as if we cured PTSD. And for a decade, we hadn’t been able to show anything in people—in healthy undergraduates, in the lab, alone with patients in the real world. Now we’ve done that, but it took seven years. I made people afraid of a blue square on a screen, and I got them to sweat a little less.”

Will propranolol be the answer? Or will it be some as yet undiscovered compound that, in Sacktor’s dreams, combines the potency of ZIP with the specificity of reconsolidation blocking? LeDoux thinks memory research is “on the cusp of bearing fruit” in the form of treatments for such crippling disorders as PTSD. Others are less certain. But if we weigh the pain this condition has caused so many people, it is hard to dispute Rothbaum’s view: “The primary prevention for PTSD,” she says, “is not to have any more wars.”