Insights from Broken Brains

A unique registry of patients with specific brain lesions, assembled by neurologists Antonio and Hanna Damasio, is helping shed light on how the human brain works

THE PATIENT KNOWN AS BOSWELL has a striking form of amnesia. In many respects his memory is normal, but he can neither form new memories nor recall anything about his personal life—including the fact that he is married and has children. Patient E. R. V. is very intelligent and was once a successful accountant, but since he had brain surgery he can't hold a job and seems incapable of making relatively straightforward judgments of right and wrong. Patient E. H. can read and write normally and can name objects presented to her, but she is completely incapable of recognizing people from their photographs—even people she knows intimately.

These three patients are all drawn from a remarkable registry of people with specific brain lesions that is being assembled by neurologist Antonio Damasio at the University of Iowa College of Medicine in Iowa City. Now numbering some 1500 individuals, the registry is the largest of its kind in the world. It represents a unique pool of subjects willing to participate in experiments designed to unravel the mysteries of the human brain.

While others are studying animals, using recordings from individual neurons and computational techniques to develop theories that explain brain function, Damasio is trying to infer how the human brain works by looking at it when it is broken. Even those skeptical of the value of such studies are impressed by what Damasio has accomplished, and his work is beginning to attract widespread recognition.

"People used to think you'll never really get the story from humans because you can't experiment on them," says neuroscientist Patricia Churchland from the University of California at San Diego. Most neuroscience researchers, according to Churchland, have considered neurologists' brain studies as mere descriptions, like those made famous by Oliver Sacks in his best-selling book *The Man Who Mistook His Wife for a Hat*: "an interesting story here, an interesting story there, but what do you make of it?" But Damasio, together with his wife Hanna who is his full-time collaborator, is changing that. "Tony and Hanna are really going about it in the right way by being very careful about the kind of subjects that will be acceptable for their studies," says Churchland. "They are not accepting patients with diffuse brain damage, but looking for certain special kinds of lesions."

"They do in-depth studies," says neuroscientist Terrence Sejnowski of the Salk Institute in La Jolla. "With an interesting patient they'll come back year after year after year. Most neuropsychologists don't have that luxury." Often after a neurology patient leaves the hospital, he is lost to follow-up. That isn't the case in Iowa. "Ninety-nine percent of people from the registry come in when called," says Damasio, who has been assembling the registry for the past decade.

L. W. Ward

Cause and effect. *The Damasios have studied the results of lesions in 1500 patients.*

There's nothing particularly new in trying to figure out how the brain works by studying patients with specific lesions. Physicians have been doing that for centuries. But lesion studies are "undergoing something of a renaissance," says Sejnowski. Part of the reason is that the lesion work has been transformed by modern methods. On the one hand, brain-imaging tools, such as magnetic resonance (MR) imaging and computer-assisted tomography, have made it possible to pinpoint the location of a brain lesion—something that used to have to wait until autopsy. On the other, there has been what Antonio Damasio calls "an incredible development of cognitive tools" for determining what psychological functions are impaired by the lesion.

Aside from these technical improvements, the Iowa registry is helping to overcome one of the biggest problems with using human brain lesion patients for systematic studies: researchers can't put the lesion where they want it—they have to take whatever disease or traumatic injury provides. But the registry—because of its size—dramatically increases the chance of finding a person with damage in just the area researchers want to study.

An early—and famous—example of the value of work with brain-damaged patients is the case of H. M., an amnesic patient studied by Brenda Milner at the Montreal Neurological Institute three decades ago. H. M. can remember events from his past, but has absolutely no ability to form new memories. He can have a normal conversation with someone he has never met before, but if that person leaves the room and returns a few moments later, H. M. has no recollection of ever having seen the person before.

H. M.'s lesion included nearly all of his hippocampus, a structure in the limbic system that has become the focus for understanding how memory works. Animal studies had indicated that the hippocampus plays a central role in memory. But researchers can only infer the status of animals' memory from their behavior, whereas with H. M., they could ask what he remembered; the answers made it clear that the hippocampus was the crucial structure. "If it hadn't been for H. M., and the history of human work with amnesia, we would still be arguing if the hippocampal lesions in rats had anything to do with memory or not," says psychobiologist Larry Squire of the University of California at San Diego.

Some of Damasio's work building on these earlier studies is controversial—particularly a general theory of brain function he has drawn from his studies. But he has made a series of important observations. Take the case of E. R. V., the once successful accountant, who was referred to the Damasios a few years ago. He arrived at the University of Iowa hospital after surgery to remove a tumor from a part of his cortex near the eye socket. A portion of the right parietal lobe was also removed. Following surgery he has been unable to hold a job, has been married and divorced twice, and has squandered his savings on questionable business ventures. Although highly intelligent—his IQ is around 140—E. R. V. seemed unable to avoid making self-destructive decisions about his life.

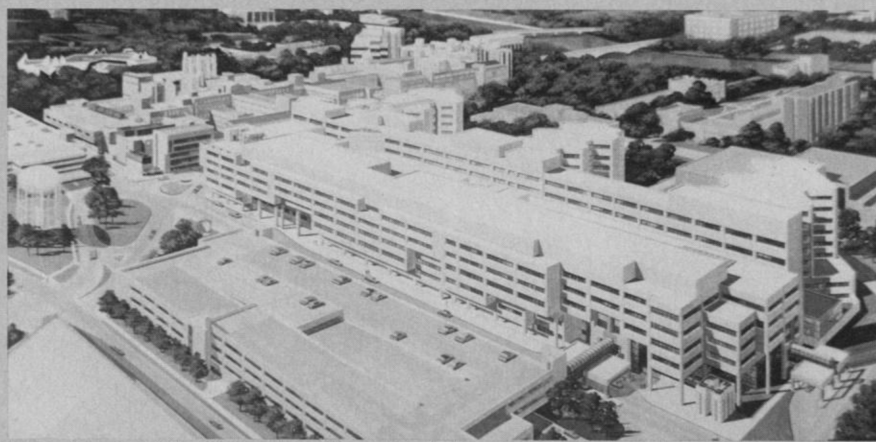
Damasio believes E. R. V.'s behavior can be explained by a theory of brain function that rests on a concept he calls "convergence zones." These are centers in the brain which, when activated, can stimulate a unique combination of other brain regions to produce some kind of internal representation. According to Damasio's notion, when you recognize an object such as another person's face, a convergence zone ties together visual information from the eyes with general knowledge about objects in the world and specific knowledge about known faces. This convergence of information makes recognition possible. Damasio believes similar convergence zones are activated when an individual makes social decisions. Just as a child learns that fire will hurt his hand if he touches it, more complex social learning takes place based on reward or punishment from a parent. And these rewards and punishments form a memory that "you feel in your gut," as Damasio puts it. Being scolded for talking to strangers would create a memory, retrieved later via a convergence zone, that would associate an unfamiliar situation with a negative visceral memory. Could it be that E. R. V. lost his associations to that gut memory?

To test the hypothesis, Damasio presented E. R. V. with a set of emotionally charged photos—a girl on fire following a napalm attack or a man with his hand severed and blood dripping from the wound—interspersed with bland photos of trees or random patterns with no particular significance. To measure this "gut" memory, Damasio looked at changes in skin conductance—the "sweaty palms" reaction used to detect changes in emotional state.

For normal subjects and patients with lesions in other brain areas, the photos elicited enormous changes in skin resistance: for E. R. V., there was no change at all. But E. R. V. had not lost his understanding that these were highly emotional pictures. When asked to describe them, he would say how terrible they were, and the skin response would switch on. Somehow, on first presentation, they did not have the same effect.

Damasio has now tested other patients with lesions similar to E. R. V., and found that they, too, fail to have a skin conductance change when viewing emotionally charged photos. Damasio says his discovery may explain why some convicted murderers seem unable to recognize that their behavior is wrong. "They clearly understand what killing is, and they know it will land them in jail. But they don't feel it in the flesh. They don't have a very adaptive, very basic system which is there for animals to protect themselves from getting into situations of danger, and that we humans have co-opted and used for this guidance."

Damasio's concept of convergence zones is not yet widely accepted, mainly because it is not clear exactly what anatomical structures might be implementing it in the brain. It is one of many attempts by researchers to solve what is called the binding problem: what ties the information from disparate



Broad base. *The University of Iowa hospital gets an unusually wide spectrum of patients.*

The Damasios' Research Web

Iowa City is not a particularly easy place to visit. Travelers from Berkeley or Boston or New York must go through an airline hub city, usually Chicago or St. Louis, to get there, and Midwest weather can unhinge the best laid plans. And yet more and more researchers are taking the time and trouble to make the trip to get a firsthand look at the operation Hanna and Antonio Damasio have mounted for studying brain lesion patients.

The Damasios arrived in Iowa in 1975 after completing their graduate training in neurology at the University of Lisbon Medical School in their native Portugal. They have been frequent collaborators on research papers in the intervening years, but it is the eloquent, urbane Antonio who has drawn the spotlight to their work.

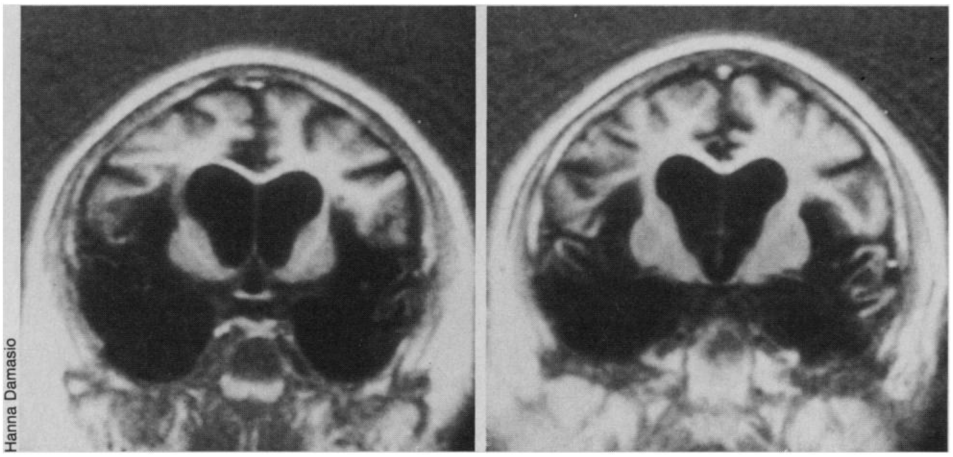
Damasio says working in Iowa has given him unique advantages in attracting interesting patients to study. Since the University of Iowa Hospital is the only tertiary care center in the state, it has a huge referral base, and no competition for patients. Damasio says he was offered a chair at Rockefeller University in 1985, but turned it down. "People in New York City only see a tiny fraction of what I see," he adds.

Neuroscientist David Hubel, the Nobel laureate from Harvard, says Damasio has an ideal arrangement for accruing patients for his studies. "He sits there like a spider in the center of the web," says Hubel and patients enter his lab.

Damasio has quite a nice "web" for himself. An entire wing of the newly constructed university hospital is home to the neurology unit. Inpatient and outpatient services are just across the hall from each other. The hospital has a pleasing architectural design, plenty of art on the walls, and comfortably appointed hospital rooms. The largest university-owned teaching hospital in the country, it is a far cry from the crowded, aging hospitals that serve many inner city medical schools.

Damasio has put himself on the fast track, making frequent appearances at international meetings and publishing lots of research papers. He has also begun to flirt with other opportunities by accepting an adjunct position at the Salk Institute in La Jolla, California. Some feel he may be trying to do too much, going a little too fast, and constructing grander theories than his data justify. But even his critics respect his intellect and acknowledge that his work is helping put brain lesion studies firmly on the research map. ■ J.P.

centers and pathways in the brain into a coherent picture? Neuroscientists at the Salk Institute—where Damasio has an adjunct appointment—are currently intrigued by work done by Charles M. Gray and Wolf Singer at the Max Planck Institute for Brain Research in Frankfurt showing that neurons in different brain areas fire in an oscillating pattern at the same frequency and in phase with each other. This phase-locked firing, they believe, may be the transient glue that binds together different neural centers. The idea has appeal because it does not require a separate anatomical entity to act as an "executive" for tying different brain areas together, but this theory is also highly speculative.



Boswell's brain. *Magnetic resonance images of the brain of a patient called Boswell. The dark regions at the bottom show damage to the left and right anterior temporal lobes.*

Whatever the explanation, the binding problem is evident in the patient whom Damasio calls Boswell, whose hippocampus and a portion of his temporal lobe called the entorhinal cortex were destroyed by herpes encephalitis. Like H. M., Boswell is unable to form new memories. But he has also lost the memory of his own biography. Remarkably, his memory for certain things remains completely intact. During an interview with *Science* in his office, Damasio picks up a book from his desk and describes a typical conversation he might have with Boswell: "If I ask him what is this, he'll look at this and say, 'that's a book, and it's a nice book and it has a nice glossy black cover, and it's well printed.' And he can pick up the book and say, 'it's a heavy book, probably quite expensive.' This is probably no more and no less than something we would say if we were asked to say something about this categorically." But when Damasio presents Boswell with a photograph of his wife, he can only say it is a picture of a woman in her fifties. "He doesn't know the uniqueness of that person, and he can't relate that person to his life." Damasio argues that Boswell has lost convergence zones that allow him to integrate his past experiences with the knowledge that he still possesses about objects.

Boswell is also remarkable for another reason: He is living proof that higher brain centers are not essential for consciousness. Says Churchland: "One might have thought that consciousness is a very high-level function that only mammals with an advanced neocortex would have. And yet as far as anyone can tell, Boswell is as conscious as you or I.""Most people thought the frontal lobes are where what you might call the central executive was," says Francis Crick, who in recent years has turned his attention to the brain. "If you knock that out, then people who held that theory would say you shouldn't be conscious. Well, Antonio showed that wasn't the case. We have to look for a more distributed thing [to explain consciousness]."

The notion of consciousness—and what it means to be conscious—is currently a hot area in neuroscience. There is a growing appreciation that the brain sometimes possesses knowledge that it can't consciously access. Damasio is probing this with his work on prosopagnosia—the inability to recognize familiar faces. Using the skin conductance test, Damasio has shown that some people with prosopagnosia will show a change in skin resistance when presented with a familiar face, even though they are not able consciously to identify the face. At some level, the face recognition system is still working.

As lesions are pinpointed more specifically, the existence—or absence—of convergence zones might become clear. That's where Hanna Damasio's work comes to the fore. She interprets data from MR scans to determine what structures are damaged in the Damasios' patients. Right now she can spot damage down to 1 millimeter. By tweaking existing machines and using newer machines with more powerful magnetic fields, the resolution will get even finer.

But Crick, who is now at the Salk Institute, points out that the usefulness of more detailed pictures of brain lesions may be limited by poor understanding of human neuroanatomy, a subject he says is "grossly neglected." "We know more about the visual system of the cat in neurophysiological and neuroanatomical terms than we know about man." Crick argues that improved anatomical understanding—specifically how regions of the human brain are interconnected—will help make sense of the lesion data by ruling out theories that are anatomically or physiologically impossible.

In addition to skepticism about his theory of convergence zones, Damasio's work has encountered some criticism at the methodological level. Squire at University of California, San Diego, emphasizes, for example, that to understand what deficits have occurred in brain-damaged patients, it is essential to ask the right questions. He is critical of neurologists like Damasio whom he feels don't do enough psychological testing to find out exactly what kinds of deficits they are dealing with. In an extended series of studies on recognition and recall, Squire's lab has shown that these two memory retrieval systems are equally damaged in most forms of amnesia. That wouldn't be obvious if a researcher failed to measure both.

Lucia Vaina, a psychobiologist with joint appointments at Harvard, Massachusetts Institute of Technology, and Boston University, agrees with Squire's criticisms. On one level, she and Damasio do similar work. They both study human brain lesion patients, but "we differ in a very essential way at the level of the questions about how the brain does things and the battery of tests," she says. Vaina uses a computational approach, sticking to basic mechanisms like motion perception rather than flying off into more theoretical speculations about higher brain function that are hard to test.

Nevertheless, the growing sophistication of the work with brain-damaged patients is shrinking the gap between human and animal brain research. Although the reductionist approach to studying the brain—recording from individual neurons—will probably not be possible for some time, if ever, in humans, new generations of MR images will bring even finer detail of brain structures, and new MR techniques should also give clues to metabolic functions within those structures. Positron emission tomography scanning has already started to show how cerebral blood flow changes in response to specific stimuli. In the meantime, the tools that do exist, and, in particular, the Iowa registry, are already helping develop a better picture of how the brain constructs our reality. ■ JOSEPH PALCA