

Magnetic resonance imaging scans of the human brain.

PSYCHIATRY

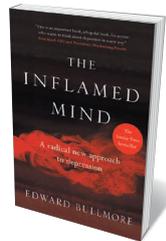
Depression revisited

Alison Abbott considers a persuasive case that inflammation is linked to the disorder.

Depression affects one in four people at some time in their lives. It is often difficult to treat, in part because its causes are still debated. Psychiatrist Edward Bullmore is an ardent proponent of a radical theory now gaining traction: that inflammation in the brain may underlie some instances. His succinct, broad-brush study, *The Inflamed Mind*, looks at the mounting evidence.

The book outlines a persuasive case for the link between brain inflammation and depression. Bullmore pleads with the medical profession to open its collective mind, and the pharmaceutical industry to open its research budget, to the idea. He provides a current perspective on how the science of psychiatry is slowly emerging from a decades-long torpor. He sees the start of a shift in the Cartesian view that disorders of the body 'belong' to physicians, whereas those of the more 'immaterial' mind 'belong' to psychiatrists. Accepting that some cases of depression result from infections and other inflammation-causing disorders of the body could lead to much-needed new treatments, he argues.

In 1989, during his clinical training at St Bartholomew's Hospital in London, Bullmore encountered a patient whom he



The Inflamed Mind: A Radical New Approach to Depression
EDWARD BULLMORE
Short (2018)

calls Mrs P, who had severe rheumatoid arthritis. She left an indelible impression. He examined her physically and probed her general state of mind. He reported to his senior physician, with a certain pride in his diagnostic skill, that Mrs P was both arthritic and depressed. Replied the experienced rheumatologist dismissively, given her painful, incurable physical condition, "You would be, wouldn't you?"

Mrs P is a recurring motif, as is the rhetorical question. Bullmore draws on more than two millennia of medical history — from ancient Greek physician Hippocrates to the work of neuroanatomist and 1906 Nobel laureate Santiago Ramón y Cajal — to illustrate his points. At times they seem like intellectual meanderings, but these passages also show how medical science often progresses by means of bold theories

that break away from received wisdom.

After his training, Bullmore specialized in psychiatry, and quickly experienced its limitations. He describes his growing awareness of how poorly science has served the field, using the development of selective serotonin reuptake inhibitors (SSRIs) as a prime example.

That long and winding road began with the antibiotic iproniazid. It was discovered through scientific logic: by screening chemicals for their ability to kill *Mycobacterium tuberculosis* in the test tube and in mice. Iproniazid transformed the treatment of tuberculosis in the 1950s. Patients clawed back from the jaws of death exhibited euphoria — well, you would, wouldn't you? — and the drug was soon launched as an antidepressant. Soon the theory emerged (based more on supposition than evidence, says Bullmore) that its psychiatric effects were the result of boosting the neurotransmitters adrenaline and noradrenaline. Drug developers began to focus on neurotransmission more broadly.

Prozac (fluoxetine), which boosts serotonin transmission, was launched in the mid-1980s, and many pharmaceutical

► companies quickly followed with their own SSRIs. It seemed to be the revolution psychiatrists had been waiting for. But it soon emerged that only a modest subset of patients benefited (estimates based on trials vary widely). That is unsurprising in retrospect, with the new appreciation that depression can have many causes. Bullmore holds that the emergence of SSRIs bypassed scientific logic. The serotonin theory, he writes, is as “unsatisfactory as the Freudian theory of unquantifiable libido or the Hippocratic theory of non-existent black bile”. He notes that, after SSRIs failed to live up to the hype, time once again stood still for psychiatry.

Bullmore recalls a teleconference in 2010, when he was working part-time with British pharmaceutical giant Glaxo-Smith Kline. During the call, the company announced it was pulling out of psychiatry research because no new ideas were emerging. In the following years, almost all of ‘big pharma’ abandoned mental health.

Then a window seemed to open — one that shed a different light on the plight of Mrs P. Some of the textbook certainty that Bullmore had learnt by rote at medical school started to look distinctly uncertain.

In particular, the blood-brain barrier turned out to be less impenetrable than assumed. A range of research showed that proteins in the body could reach the brain. These included inflammatory proteins called cytokines that were churned out in times of infection by immune cells called macrophages. Bullmore pulls together evidence that this echo of inflammation in the brain can be linked to depression. That, he argues, should inspire pharmaceutical companies to return to psychiatry.

It seems unfair that someone struck down by infection should have depression too. Is there a feasible evolutionary explanation? Bullmore hazards that depression would discourage ill individuals from socializing and spreading an infection that might otherwise wipe out a tribe.

Other brain disorders might turn out to be prompted or promoted by inflammation. An exciting link with neurodegenerative diseases, including Alzheimer’s, is also being studied (see *Nature* 556, 426–428; 2018). But we need to learn from the rollercoaster history of brain research, and keep expectations in check. Beneath his bombastic enthusiasm, Bullmore acknowledges this, too. ■

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

“After SSRIs failed to live up to the hype, time stood still for psychiatry.”

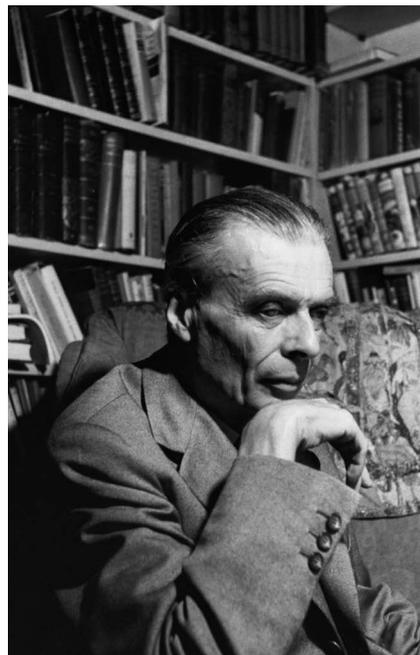
IN RETROSPECT

Ape and Essence

Richard Rhodes finds resonance with today’s uneasy nuclear age in Aldous Huxley’s satirical dystopia.

The atomic bombings of Hiroshima and Nagasaki in August 1945 shocked the world. More than 70 years on, these events have not been repeated — evidence that it was the United States’ temporary nuclear monopoly that made them possible. Yet few observers in the immediate postwar years foresaw the development of an uneasy nuclear truce, enforced by the certainty of mutual destruction. Fears of an arms race culminating in nuclear war were widespread. Such fears have now re-emerged, with North Korea’s burgeoning arsenal and the United States’ abrogation of its agreement with Iran.

J. Robert Oppenheimer, who directed the development of the first bombs, was among those who feared nuclear conflict, and worked for international control after the Second World War. Physicist Richard Feynman (whom I interviewed for my 1987 book *The Making of the Atomic Bomb*) recalled sitting in a bar in New York in 1946, watching the crowd passing outside and thinking: “You poor fools, you have no idea that in a few more years you’ll all be dead.” Aldous Huxley seems to have leapt to the same conclusion in his hybrid novel and film scenario *Ape and Essence*, published 70 years ago.



Aldous Huxley in the 1950s.

Ape and Essence

ALDOUS HUXLEY
Harper & Brothers
(1948)

The prolific novelist and essayist had been formulating his thoughts on the bomb since the end of the

war. In 1947, Huxley published the extended essay ‘Science, Liberty, and Peace’, a prelude to the novel. There, he wrote that the power-hungry and nationalistic “boy-gangster” in us all would easily prevail over the reasonable adult, exulting: “Press a few buttons and bang! the war to end war will be over, and I shall be the boss of the whole planet.” Huxley knew better. If more than one nation had such weaponry, he believed, the outcome of “the war to end war” would be world-scale destruction. And because that would be a kind of singularity, it seemed to him that almost anything might follow.

Ape and Essence is Huxley’s imagining of a post-nuclear world. The title is from William Shakespeare’s *Measure for Measure*: Isabella speaks of the proud man’s “glassy essence, like an angry ape”, which “plays such fantastic tricks before high heaven/As make the angels weep.” The angels have flown in Huxley’s novel, set in what remains of Los Angeles, California, in 2108 — a century after a third world war, which would have taken place around now, in Huxley’s fictional timeline.

In one of the book’s set pieces, intelligent baboons fight this twenty-first-century war, with scientific luminaries (Michael Faraday and two opposing Albert Einsteins) as leashed mascots. So much for scientists, Huxley insinuates — “good, well-meaning men, for the most part. But... they ceased to be human beings and became specialists.” Of the two opposing cultures described by scientist and novelist C. P. Snow in 1959, Huxley was clearly on the side of the humanities, as if locked in debate with his distinguished scientific kin — his biologist brother Julian, physiologist half-brother Andrew and zoologist grandfather Thomas Henry, known as Darwin’s bulldog.

Having introduced the baboons, Huxley kills them off: it’s a second false start to the novel’s stuttering story, a metafictional concoction as multilayered as an onion. The first storyline sees two screenwriters tracking down a legendary colleague, only to find him dead. The deceased’s abandoned screenplay (I suspect one of Huxley’s own unsold efforts, repackaged) is the book’s centrepiece. It is