

# Great Discoveries in Psychiatry

Ronald Chase

*Cover image:* Dissection illustrating the brain's meninges.

In 1822, Antoine Bayle discovered inflamed arachnoid membranes (shown at left) in a certain type of mental patient. Drawn by Gerard de Lairesse for Govard Bidloo's *Anatomia humani corporis*, 1685.

[National Library of Medicine, USA]

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*Discovery consists of seeing  
what everybody has seen and  
thinking what nobody has  
thought*

Albert Szent-Gyorgyi

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# Introduction

This is a history of psychiatry told in stories of discovery. Historians generally agree that psychiatry began as a medical speciality in 1801, when Phillippe Pinel published his *Traité médico-philosophique sur l'aliénation mentale*. There were no psychiatrists at the time—only physicians—but Pinel was insightful about mental illnesses. He wrote his treatise shortly after becoming chief physician at the Salpêtrière hospital in Paris. Although officially responsible for all 7,000 female patients, Pinel worked almost exclusively in a ward of 200 mental patients. He was a compassionate caretaker who famously cut the chains that bound the most seriously ill. Beyond that, he experimented with physical and psychological treatments, defined the six most common types of mental illness, addressed causes and used statistical analysis. In short, Pinel was an intellectual, an innovator and a creative explorer in the strange world of psychiatric disorders. This book is about discoveries made by people like Phillippe Pinel.

The chapters follow a rough chronological order beginning around the year 1800 and continuing right through to the present. The subject matter varies from care and treatments to diagnostics, biomarkers and neuroscience. Some chapters recount a single discovery, whereas others summarize a series of connected discoveries. My definition of discovery includes not only scientific findings but also discoveries of an intellectual or intuitive nature. Science-based research offers our best hope for better treatments going forward, but good ideas help too.

The first chapter (Kindness) begins with a description of psychiatric care at Britain's oldest institution for mental patients, the Bethlem Hospital in London. At the turn of the nineteenth century, the buildings were in a state of collapse and patient care was generally dreadful. Progress was made when Samuel Tuke in York and Phillippe Pinel in Paris simultaneously discovered that kindness works better than harshness. The next two chapters are about early biomarkers of mental illness. A young physician performing autopsies at an asylum that held several Napoleon Bonapartes and the Marquis de Sade found inflamed cerebral membranes in a group of deceased patients who had claimed fabulous wealth and incredible fame.

Elsewhere, at a later time, a pair of psychiatrists found swollen ventricles in the brains of schizophrenia patients. Chapter 4 tells of how one woman's horror at seeing a dog drink water from a glass led Sigmund Freud to discover psychoanalysis.

Chapter 5 recounts how heredity came to be understood as a major risk factor for mental illness. The following chapter begins with the discovery of multiple mental illnesses in a Scottish family of 77 individuals and continues by tracing the early history of psychiatric genetics. With chapter 6 we move into the twentieth century with accounts of two child psychiatrists on two continents, both taking credit for the discovery of autism. The next four chapters (numbers 8–11) describe the discovery of new treatments: the dramatic introduction of electroconvulsive therapy, John Cade's single-handed discovery of lithium as a treatment for mania, and the chemical tinkering that produced the first effective treatments for schizophrenia and mania.

Modern neuroscientific findings in four key areas of research are described next. Chapters 12 and 13 focus on defects that constitute endophenotypes for one or another of the major mental illnesses, that is, biomarkers that lie intermediate between genes and symptoms. You will learn about the loss of gray matter in the brain, eye movement abnormalities and leaky nerve cell axons. Chapter 14 considers the role of memory in mental illness and discusses experiments in which harmful memories are either modified or removed. The final chapter is somewhat different in that it is about discoveries that bring into question traditional methods for diagnosing mental illnesses.

The reader will note a variety of story lines. Not every discovery arrives in a flash of lightning accompanied by a shout of joy. The discoveries of lithium therapy for mania and chlorpromazine for schizophrenia come closest to that romantic ideal, but the majority of discoveries featured here required years of effort. A few were made by individuals working alone (transcranial electrical stimulation, diffusion magnetic resonance imaging). The rest came from cooperative work by multiple investigators, often when in competition with other equally motivated teams. And finally, there is room in this book for discoveries (X-rays, insulin shock therapy) made through pure serendipity, defined as a chance event that carries unforeseen significance.

The Perspective sections at the end of each chapter go beyond the factual accounts to provide updates, additional interpretations and opinionated commentary. Each chapter also contains a short list of suggested readings.

# 1 Kindness

Kindness toward people with mental illness was not discovered at any particular moment, but rather around the year 1800. Even so, it happened almost simultaneously in London and Paris. To be clear, that was when *institutions* first acknowledged kindness, for there must have been at least some kind caretakers from the start. We assume that to be true even though we know very little about the care of mentally ill persons in earlier times.

Most people with mental disorders were kept at home, but others were outcast and occasionally brutalized. In the middle ages, some communities resorted to chaining troublesome individuals to posts. People were thought to be possessed by the devil if they acted strangely and had hallucinations. Church records from the fifteenth century tell of women claiming to have been transported over vast distances at night. Heinrich Kramer, a Catholic clergyman, explained the origin of the phenomenon, ‘The art of riding abroad may be merely illusory, since the devil has extraordinary power over the minds of those who have given themselves up to him, so that what they do in pure imagination, they believe they have actually and really done in the body.’<sup>1</sup> Acting on this line of thinking, women who admitted to ‘riding abroad’ were accused of witchcraft and, when found guilty, condemned to death. They were usually tied to a stake and burned.

As cities grew in size and density, concerns arose over public security, so places were set aside as refuges for persons considered suspicious or dangerous. Perhaps the first such institution was the Priory of Saint Mary of Bethlehem in London. Founded in 1247, it initially served all manner of misfits, be they sick, wounded, deranged or simply poor. Gradually, over centuries, it became increasingly specialized in caring for the insane. Even as witchcraft and their attendant punishments were sweeping across Europe, the small Priory in London offered safe housing for the insane. The name Bethlem gradually morphed into Bedlam, and while bedlam was a verbal corruption, not a true name of anything, it became associated with

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<sup>1</sup> Heinrich Kramer and James Sprenger, *Malleus Maleficarum (The Hammer of Witches)*. First published in 1486. Translation by Montague Summers, 1928. Quote in Part I, Question I.

madness, chaos and irrationality. Moved three times, the Priory first established in 1247 is today operating as the Bethlem Royal Hospital located in South London.

Let's take a look at the Bethlem hospital around the year 1800, at the time when kindness was just beginning to root in Britain. The hospital building, then located at Moorfields just north of London, was in such a state of physical dilapidation that wealthy citizens had begun collecting funds for a new building. Built on rubble, the walls were buckling, the roof was leaking and the whole place reeked of (mostly) human filth. A sense of what occurred at Bethlem and at similar asylums in England can be gleaned from historical documents such as the 'Report from Committee on Madness', submitted to the British House of Commons in 1815. The picture that emerges is one of unkindness bordering at times on outright brutality. However, we should not assume that the caretakers were inherently evil or sadistic. They were mostly uneducated, underprivileged men desperate for work. One can understand that they might have occasionally vent their frustrations, given that they had been placed in a situation where there were far too many patients, very few workers and no real prospects of recovery.

Consider also the lack of sanitation. On the very first page of the government report, George Higgins describes his experience upon visiting the York Lunatic Asylum, where Higgins himself was a governor. 'When the door was opened ... I found four cells of about eight feet square, in a very horrid and filthy situation; the straw appeared to be almost saturated with urine and excrement ... the walls were daubed with excrement; the air holes, of which there [was] one in each cell, were partly filled with it; in one cell there were two pewter chamber-pots loose.'<sup>2</sup> Another witness was George Wallet, the steward at Bethlem. He described the smells in the infirmary as 'very offensive'. Asked if the odor came from the sewers, he replied that it 'proceeded more from dirty patients.'<sup>3</sup>

All types of patients were thrown in together. Mild cases were mixed with severe cases, calm patients with excited patients, young with old. There are documented examples of epileptics, demented elders, intellectually handicapped and psychotic persons all occupying the same hospital unit. The mental patients were never formally diagnosed, but they would have been described as either melancholic or manic, these being the two grand categories of mental illness commonly acknowledged since ancient

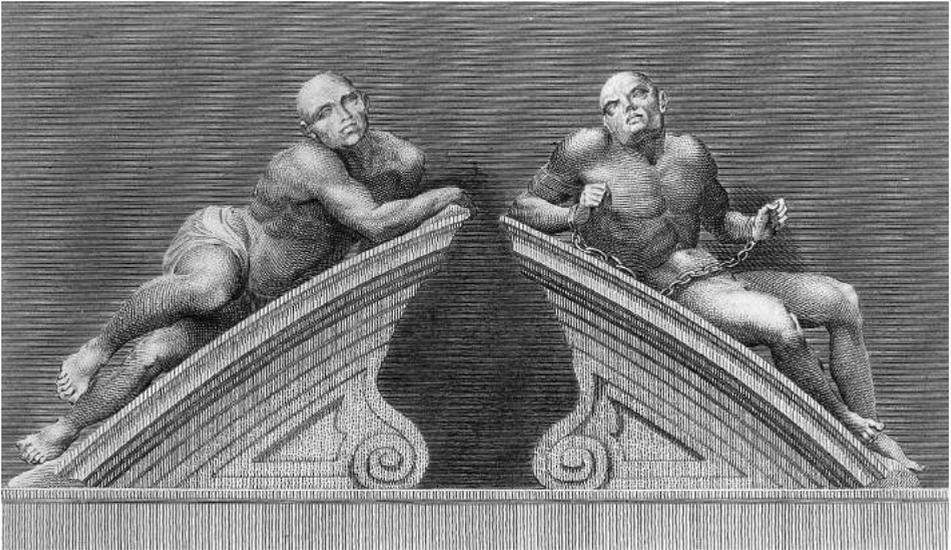
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<sup>2</sup> House of Commons, *First Report from the Select Committee on Madhouses* (1815), p. 1.

<sup>3</sup> *Ibid*, pp. 36, 37.

## 1 Kindness

Grecian times. Early in the seventeenth century, the Oxford cleric Robert Burton said of melancholic persons, 'I think I may truly conclude that they are not always sad and fearful, but usually so ... Some are afraid that heaven will fall on their heads; some afraid they are damned, or shall be.'<sup>4</sup> Thus, melancholia implied depression, but also delusions and anxiety. Mania meant extreme excitement and delusions. In common parlance toward the end of the eighteenth century, all patients, whether melancholic or manic, were simply 'mad'.



Sculpture depicting 'Melancholy' (left) and 'Raving Madness' (right), at Bethlem Hospital. Engraving by C. Warren, 1805 [Wellcome Library]

Patients who were highly excited, violent or dangerous posed a special problem because, at the Bethlem hospital, there were just 4 caretakers looking after 120 patients. Under the circumstances, caretakers routinely resorted to mechanical restraint by means of chains, wrist manacles, leg manacles and straitjackets. One outrageous use of these devices came to light in 1814 when Edward Wakefield, a real estate agent from the city of York, managed to inspect the Bethlem hospital at Moorfields. There he found a patient, aged 55, who had been held at the hospital for fourteen years. Wakefield described what he saw,

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<sup>4</sup> Robert Burton, *The Anatomy of Melancholy*. Quote from Edward Shorter, *A Historical Dictionary of Psychiatry*. New York: Oxford University Press (2005), p. 175.



Handout publicizing harsh treatment of James Norris [G. Arnald, artist]

A stout iron ring was riveted about his neck, from which a short chain passed to a ring made to slide upwards and downwards on an upright massive iron bar, more than six feet high, inserted into the wall. Round his body a strong iron bar about two inches wide was riveted; on each side of the bar was a circular projection, which being fashioned to and enclosing each of his arms, pinioned them close to his sides. This waist bar was secured by two similar iron bars which, passing over his shoulders, were riveted to the waist both before and behind. The iron ring about his neck was connected to the bars on his shoulders by a double link. From each of these bars another short chain passed to the ring on the upright iron bar.<sup>5</sup>

The patient's name was James Norris, an American who had been sent to Bethlem by the Office for Sick and Wounded Seamen. Various reports differ

<sup>5</sup> Jonathan Andrews et al. (1997), p. 424. See suggested readings.

with respect to the length of time that he was restrained in the described manner, but it was somewhere between nine and twelve years. Norris's case may have been exceptional in that no other patient was so heavily restrained for so long, but it shows the lengths to which the hospital would go in managing difficult patients.

Bethlem Hospital aimed to cure its patients, and many were discharged, but few if any were actually cured. Even the treatments were unkind. Probably the most common treatment was the cold water bath, used for centuries on the idea that it slowed the delivery of blood to the brain. Patients were immersed in cold water twice weekly from July to the onset of winter. In some cases, the water spilled down onto the patient from a spout placed a meter or so above the patient's head.

A second type of treatment was adapted from ancient practices going back at least as far as Hippocrates in the fourth century B.C. Hippocrates stated that madness is caused by poisonous substances circulating within the brain. In his time and later, physicians devised various methods for ridding the body of such substances. At Bethlem, the methods of choice were bloodletting, induced vomiting and diarrhea. The goal was chemical purification, but the experience itself was hellish. Thomas Monro, the sole physician at Bethlem, described the practice,

In the months of May, June, July, August and September, we generally administer medicines; we do not in the winter season, because the house is so excessively cold that it is not thought proper ... We apply generally bleeding, purging and vomit; those are the general remedies we apply ... all the patients who require bleeding are generally bled on a particular day, and they are purged on a particular day ... after they have been bled they take vomits once a week for a certain number of weeks, after that we purge the patients.<sup>6</sup>

If the House of Commons ordered a survey of British madhouses, its parliamentarians must have already known that all was not right in those institutions. Among the numerous witnesses who confirmed their suspicions was the aforementioned Edward Wakefield who reported on the iron-clad patient, James Norris. The committee minutes list Wakefield as a 'land agent', but he was also an active member of the Quaker community. He and a small group of friends were battling to reform Britain's prisons and mental asylums. After encountering patient James Norris at Bethlem, Wakefield hired

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<sup>6</sup> David Russell, *Scenes from Bedlam*. London: Harcourt Brace (1997), p. 64.

## 2 Cobwebs on the brain

We call them mental illnesses, but equally, they are brain illnesses because the brain generates the mind. *How* the brain generates the mind is a thorny, unsolved problem that is of no immediate concern to psychiatry. But what goes wrong in the brains of mental ill patients is crucial for designing physical treatments, whether they be pharmaceutical or electrical. Thus, the search for brain correlates, or biomarkers, of mental illness is a central theme in the history of psychiatry. The first significant finding was made by a young French doctor working in suburban Paris at an asylum not far from Philippe Pinel's hospital. His discovery followed a long line of speculation.

The ancients knew that inside the head there lies a bulky, wrinkled structure. They knew, too, that people behave oddly after suffering a blow to the head. Some cannot speak properly, others have trouble walking or remembering things. And, the ancients knew about epilepsy. In the time of Hippocrates, around 400 B.C., it was the 'sacred disease'. Most people thought that it had a supernatural, or divine, origin. One author—possibly Hippocrates himself—contested that opinion. In a work titled, 'On the Sacred Disease,' the author wrote,

Men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear, and know what are foul and what are fair, what are bad and what are good, what are sweet, and what unsavory.<sup>18</sup>

Hippocrates went even further in his account of the brain by specifically addressing not only the sacred disease, but other illnesses now said to be mental,

And by same organ [the brain] we become mad and delirious, and fears and terrors assail us, some by night, and some by

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<sup>18</sup> Translation by Francis Adams. <http://classics.mit.edu/Hippocrates/sacred.html>

day, and dreams and untimely wanderings, and cares that are not suitable, and ignorance of present circumstances, desuetude, and unskillfulness. All these things we endure from the brain, when it is not healthy ...

Hippocrates blamed excessive levels of certain biological substances—humors—as the causal agents. Each humor creates its own set of symptoms, and each acts through a different mechanism,

[T]he depravement of the brain arises from phlegm and bile, either of which you may recognize in this manner: Those who are mad from phlegm are quiet, and do not cry out nor make a noise; but those from bile are vociferous, malignant, and will not be quiet, but are always doing something improper. If the madness be constant, these are the causes thereof. But if terrors and fears assail, they are connected with derangement of the brain, and derangement is owing to its being heated ... He is grieved and troubled when the brain is unseasonably cooled and contracted beyond its wont. This it suffers from phlegm, and from the same affection the patient becomes oblivious.

Leaving aside such details as phlegm, bile and brain temperature, the overall intent of the argument has a modern flavor. It is specific in its identification of causes and plausible in its description of mechanisms. The only problem: no proof. It would be another two thousand years before writers proposed alternatives to the humoral model of insanity, and even then, the ideas were based on the claims of a physician, Galen, who lived 1500 years earlier. Galen believed that brain fibers (nerves) are filled with ‘animal spirits’, a kind of ethereal gas. Even as late as the seventeenth century, physicians held to the belief that muscle contractions and sensory experiences are triggered by messages carried by animal spirits. Thus, the French theologian and philosopher Nicholas Malebranche proposed that hallucinations, a common symptom of psychosis, are caused by exceptional agitation of animal spirits. In a similar vein, the English doctor Thomas Willis wrote that mental illness is the result of brain damage that follows from tiny internal explosions.

At the turn of the nineteenth century, when psychiatry was waking up to the advantages of kindness, knowledge of the brain had hardly progressed from the days of Malebranche and Willis, which is to say, doctors still knew very little. Although there were a few microscopes around, they were not

very powerful. The smallest biological objects brought to the human eye were the walls of certain plant cells, and no one had yet looked at a nerve cell. Few doctors accepted Aristotle's teaching that rational thought comes from the heart, but some clung to the fantasy of animal spirits.

Even if the majority of physicians assumed that the brain is somehow implicated in madness, they saw no signs of abnormality. The spirits were not visible. And besides, many prominent physicians, including Philippe Pinel, attributed brain-related mental disorders to diseases elsewhere in the body. Pinel told his students that mania originates in the stomach or the intestine, and spreads from there to the brain. For the most part, however, Pinel did not concern himself with biological mechanisms. For him, these mysteries were unhelpful in the practical business of diagnosis and treatment. He diagnosed patients entirely from observation of their symptoms, and his treatments—apart from baths—were psychological. If a woman was excited, delusionary and disoriented, she suffered from mania and was given a bath, preferably very cold. If, on the other hand, she was sullen and inactive, she was diagnosed as melancholic and given moral therapy.

Interest in the brain picked up in the second decade of the nineteenth century. However, the research that drew the most public attention involved a false claim. It was said that the barely perceptible bumps on the skull are due to local swellings in the underlying brain, and every bump—depending on its location—indicates a particular personality trait. A bump here meant that you have deep religious beliefs, a bump there meant that you love money. It could imply a heightened sense of smell or a tendency for violence. From this fantasy grew the pseudo-science of phrenology. By the time they finished, the phrenologists had mapped out nearly forty bumps representing an equal number of personality traits. It became big business for physicians, psychiatrists and outright fraudsters, all seeking to cash in on brain 'science'.

A few men with brighter minds and better technical skills challenged the phrenologists' claims. One was an Italian named Luigi Rolando whose anatomical investigations showed that the phrenologists' bumps are simply places of intersecting sulci,<sup>19</sup> and the size and position of the sulci does not differ between brains. In France, a French doctor named Jean Pierre Flourens conducted experiments to answer the question whether different

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<sup>19</sup> A sulcus is a normally occurring groove in the cerebral cortex. Collectively, sulci have the effect of expanding the surface area of the brain, thus allowing for additional neuronal circuits.

### 3 Swollen ventricles

Antoine Bayle's discovery of inflamed arachnoid membranes opened the door to biological explanations of mental illness, but only slightly because the arachnoid membranes are not actually *in* the brain. Psychiatrists were understandably more interested in what was happening in the brain itself, where the mind resides. Following upon Alois Alzheimer and Franz Nissl's report of brain abnormalities in progressive paralysis of the insane, the search was on for abnormalities in other mental disorders. Attention turned to *dementia praecox*—now called schizophrenia—the most prevalent and most striking of the psychotic disorders. Schizophrenia is a multi-faceted disorder featuring hallucinations (usually auditory), delusions (more often of the paranoid variety than of the grandiose variety), disorganized thought, loss of motivation and social withdrawal.

Emil Kraepelin, the German psychiatrist who first identified *dementia praecox*, was initially sceptical about brain science. Only in the final edition of his textbook, completed near the end of his life in 1919, did Kraepelin devote eleven pages to a description of 'morbid anatomy'.<sup>24</sup> Much of Kraepelin's anatomical summary is based on the work of Alois Alzheimer, who had published his first paper on *dementia praecox* while working in Frankfurt. Recognizing his talents, Kraepelin persuaded Alzheimer to move to Heidelberg, where Kraepelin had established a small research group. Later, they both moved to a newly built psychiatric hospital in Munich. It was in Munich that Alzheimer found 'severe and widespread disease' in the cerebral cortex of patients with *dementia praecox*. What mostly caught his attention were changes in the small nerve cells occupying the superficial layers. 'The nuclei are very much swollen, the nuclear membrane greatly wrinkled, the body of the cell considerably shrunk with a tendency to disintegration.' There were also accumulations of fat, 'amoeboid hyperplasia' of glia cells, a thinning of nerve fibers, and a 'diffuse loss of cortical cells.' Franz Nissl, also a member of Kraepelin's research team, reported similar changes.

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<sup>24</sup> Emil Kraepelin, *Dementia Praecox and Paraphrenia*, trans. Mary Barclay. Edinburgh: E.& S. Livingstone (1919).

### 3 Swollen ventricles

Like any good scientist with data in hand, Kraepelin offered a detailed interpretation of these anatomical findings. He focused on damage to the small nerve cells of cortical layers 2 and 3 (there are six layers in total). He assumed that these neurons transform sensory information into abstract concepts. Any loss of these cells, therefore, would necessarily destroy the ‘permanent foundations of the psychic life’, and lead to the characteristic disruption of ‘inner harmony’ seen in *dementia praecox*. Although there may be some broad truth in Kraepelin’s interpretation, subsequent research poured cold water on its specific claims.

Because Kraepelin was Europe’s most esteemed psychiatrist, his assertions encouraged further studies of neural pathology. Sadly however, very little of that research stood the test of time. By the late 1950s most of Alzheimer’s work and that of his contemporaries it had been discredited, and schizophrenia become the ‘graveyard of neuropathologists.’ Reviewing the history of the field in 1968, one author wrote,

Brain tissue changes have been described in schizophrenia, but controls have been inadequate and findings have been inconclusive or conflicting ... All the reported microscopic abnormalities (in the brains of schizophrenia) have been challenged as non-specific ... attributed to misjudgment of the limits of normal variation, misinterpretation of artifacts, or the uncritical attribution of special significance to casual, coincidental findings.’<sup>25</sup>

One big problem with early neuroanatomical studies was their use of post-mortem specimens. As previously noted, the brain immediately degrades once it is deprived of oxygen. Although invisible to the naked eye, cellular changes are inevitable. To avoid mistaking the resulting damage for pathology caused by disease, the schizophrenia brains should have been compared with ‘normal’ brains, but that was not done. Hence, the frequent ‘misinterpretation of artifacts’ mentioned above. Not until the afternoon of November 8, 1895 did anyone think of examining an intact, living brain.

We are indebted to Wilhelm Röntgen, a professor of physics at the University of Würzburg in Germany, for enabling us to look inside our bodies. He did so only after overcoming significant obstacles. The original source of his problems was an incident in high school where he allegedly circulated a caricature of one of his teachers. Whether true or not, Röntgen was expelled

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<sup>25</sup> Peter C. Rosenbaum, ‘Metabolic, physiological, anatomic, and genetic studies in the schizophrenias: A review and analysis.’ *The Journal of Nervous and Mental Disease* 146:103–126 (1968), p. 111.

from school and denied a diploma. At the time, he was living in Holland, but after the incident he was blocked from attending any university in that country. Fortunately, he was able to continue his education in Zurich, and after establishing his own laboratory at Würzburg, he began experimenting with vacuum tubes.

European physicists were fascinated with vacuum tubes, which were simply glass tubes that had been vacuumed under high pressure to remove air. The tubes were usually fitted with a pair of metal electrodes. If an electrical current was passed from one electrode to the other—thus through the vacuum—the glass near the positive electrode, the anode, turned a greenish color. Physicists attributed the phenomenon to the emission of an invisible something from the negative, or cathode, electrode. They named those things ‘cathode rays’, and they were eventually found to be electrons traveling from the cathode to the anode.

On the historic day, Röntgen was working with one of these tubes when he noticed a piece of paper lying about one meter away. This particular paper had been coated with a fluorescent paint that made it sensitive to light. To prevent the paper from being affected by cathode rays, he covered the tube with black cardboard prior to the experiment. Nevertheless, as soon as he switched on the electrical current, he noticed a faint green glow on the sensitive paper. The room was pitch black and Röntgen saw no light leaking through the cardboard, yet something—again that word—had travelled from the vacuum to the fluorescent paper. When later asked by a journalist what went through his mind at that moment, he replied, ‘I did not think. I investigated ... I assumed the effect must have come from the tube ... I tried it successfully at greater and greater distances, even at two meters. It seemed a new kind of invisible light ... clearly something new, something unrecorded [up until then].’<sup>26</sup> Not knowing what they were, he called them X-rays. Unlike cathode rays, which consist of charged electrons, X-rays are massless, pure electromagnetic radiation. They differ from visible light, radio waves and microwaves only in wavelength. The wavelengths of X-rays are shorter than those of any light that can be detected by the human eye.

Röntgen went on to tell the journalist that ‘having discovered the existence of a new kind of rays, I of course began to investigate what they would do.’ He set up a fluorescent screen and placed his hand between it and the radiating tube. Turning to the screen, he saw each of his finger

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<sup>26</sup> H.J.W. Dam, ‘The new marvel in photography.’ *McClure’s Magazine*, VI (5), 1896, p. 413.

## 4 The dog that drank from a glass

Late in the nineteenth century, a young woman from a prominent Viennese family walked into her doctor's office concerned about a persistent cough, loss of appetite and crossed eyes. The physician, Dr. Josef Breuer, was a highly respected general practitioner. Earlier in his career, he had researched how nerves control the amount of air that we take into our lungs. The patient was Bertha Pappenheim, twenty-one years old at the time of her first consultation with Dr. Breuer. According to Breuer, 'She was markedly intelligent, with an astonishingly quick grasp of things and a penetrating intuition.' Although 'bubbling over with intellectual vitality,' Bertha evidently 'led an extremely monotonous existence in her puritanically-minded family.' To compensate, one might suppose, 'she embellished her life ... by indulging in systematic day-dreaming.'<sup>36</sup>

Bertha Pappenheim's father had a serious medical condition, and it was after she became his primary caretaker that Bertha's own symptoms worsened. The more she attended to his numerous needs, the more tired she grew, and the more concerning became her physical disabilities. Whereas she had previously been 'energetic, tenacious and persistent,' she was now beset with frequent headaches (on the left side) and partial paralysis in her arms and legs. She also felt as though the walls of her room were tumbling down all around her. Despite his wide experience, Breuer did not know how to treat this patient. All he could think of doing was give her choral hydrate, a sedative drug that comes with a strong, nauseating odor.

Five months after Bertha Pappenheim first began seeing Breuer, her beloved father died. This led to a further deterioration in her health. The problems with her vision worsened in a troublesome manner. Presented with a bundle of flowers, she saw only one. She didn't recognize friends and associates because their faces looked waxed. There were also striking changes in her speech and in her understanding of the languages spoken to her. Prior to her illness, she conversed comfortably in German, English,

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<sup>36</sup> Josef Breuer and Sigmund Freud, *Studies on Hysteria*, translated by James Strachey and included in the *Standard Edition of the Complete Psychological Works of Sigmund Freud*. London: Hogarth Press (1895, 1955). Quotations pertaining to Bertha Pappenheim are from this source.



Josef Breuer and Bertha Pappenheim [Gamma-Rapho via Getty Images/API]

French and Italian. Now, she spoke only English. When people used German words—those of her native tongue—she behaved as though she did not understand. And whereas she had earlier eaten very little, she now stopped eating altogether. Breuer, who visited Bertha Pappenheim almost daily, had to personally place food in her mouth. He was gravely concerned and uncertain how to proceed.

Breuer thought it might be a brain problem, ‘a tubercle in the left *fossa Sylvii* with a slowly expanding chronic meningitis.’ On the other hand, the nervous character of her coughing and the hallucinations suggested a psychological cause. Breuer, in his written account of the case describes two very different states of mind. At times, she would seem relatively normal, although anxious and somewhat depressed (melancholic). At other times, she rapidly switched to an alternative state characterized by hallucinations and ‘naughty’ behaviors. Her hallucinations featured dead heads, skeletons and black snakes in her hair. As for the naughty behavior, it consisted of throwing cushions, tearing buttons from her bedclothes and the like. What happened next was not just a breakthrough in the case, it was a revolution in the treatment of mental illness.

Bertha had gotten herself into a daily rhythm. Afternoons, she’d become drowsy and enter into a kind of hypnotic state, which she described as being ‘in the clouds.’ While up there, she would sometimes give voice to

the hallucinations that had haunted her during the day. Afterwards—back on earth—she'd be calm and cheerful. Evidently, by recalling details of the hallucinations and making them vivid in her mind, she got them to disappear—at least temporarily. In telling others about this experience, she would speak of her 'talking cure' or 'chimney sweeping'. Once Dr. Breuer realized what was happening, he encouraged Bertha to tell him about her hallucinations, or simply talk to him about what was troubling her. On some occasions, he used hypnosis to loosen her memory and lessen her anxiety. These tactics apparently worked, because the bad memories vanished. Breuer spoke of it as 'catharsis', from a Greek word meaning purification or cleansing. Aristotle used the word to describe what happens to theatre goers while watching an exceptionally dramatic performance.

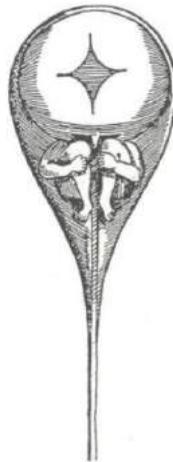
One particular episode of chimney sweeping proved especially significant, more so even for future generations of psychiatrists than for either Josef Breuer or Bertha Pappenheim. It occurred during a summer of extreme heat. Although suffering badly from thirst, Bertha, for no obvious reason, found it impossible to drink. As soon as her lips touched the glass of water, she pushed it away. This behavior continued for about six weeks, during which time she satisfied her thirst by eating fruits. Then one day, during hypnosis,

she grumbled about her English lady-companion whom she did not care for, and went on to describe, with every sign of disgust, how she had once gone into that lady's room and how her little dog—horrid creature!—had drunk [water] out of a glass. The patient said nothing, as she wanted to be polite. After giving further energetic expression to the anger she had held back, she asked for something to drink, drank a large quantity of water without any difficulty and woke from her hypnosis with the glass at her lips; and thereupon the disturbance vanished, never to return.

Sigmund Freud's creative mind would later turn this minor incident into a major theory and a popular therapeutic method. We will come to that, but first, the conclusion of Bertha Pappenheim's story. Sometime after the dog hallucination, Bertha Pappenheim was sent to a private clinic on Lake Constance in Switzerland, a tranquil spot on the northern flank of the Alp mountains. While there, she acquired a severe facial pain and became reliant on heavy doses of chloral hydrate and morphine. She also experienced multiple relapses of a psychological kind, including recurrent mental 'absences'

## 5 Twins have their day

Members of a family tend to look alike: the son looks like his father, the sister looks like her brother. Likewise, mental illness runs in families: the grandmother had bipolar disorder, the grandson has bipolar disorder. We call it heredity. As early as the fourth century B.C., the wise Hippocrates pondered how it could happen. ‘The seed,’ he wrote, ‘comes from all parts of the body, healthy seed from healthy parts, diseased seed from diseased parts.’<sup>40</sup> When all the various seeds unite in the embryo, they create a complete body that resembles the parents. Since the offspring may be born of ‘diseased seed from diseased parts,’ diseases carried by one or both parents are passed on to the children. Hippocrates’s ideas influenced the so-called preformationists of the late seventeenth century. Their explanation was simpler, yet all the more fantastic, for they believed that the entire form of the unborn adult is already present in the sperm or egg.



Preformation, a human homunculus inside a sperm [Nicolaas Hartsoeker, 1695]

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<sup>40</sup> Hippocrates, *Airs Waters Places*, part 14.

While the similarity of physical features across generations was plainly visible to all ancients, it may not have been obvious that family similarities also extend to behaviors. Since there were no written histories of family life, patterns of behavior could have gone unnoticed. Even psychological traits are heritable, but these too could have been missed, because mental life is complex and infinitely variable. And, while it is true that most mental illnesses are at least partially inherited, none is so strongly tied to genetics that the same illness invariably appears in every generation. These considerations complicated and delayed the realization that heredity plays a strong role in the genesis of mental illness.



Political cartoon mocking a minister with a large nose [Honoré Daumier, 1833]

Asylums started recording information about patients in the eighteenth century, but the earliest surviving documents show only admissions, deaths and discharges. Over time, the data became more fulsome and included case histories. Doctors took what patient information they had to categorize cases according to probable cause. The conclusions they drew from these data were discussed by William Black in his book published in 1789.<sup>41</sup>

<sup>41</sup> William Black, *Comparative View of the Mortality of the Human Species at All Ages; and of the Diseases and Casualties by Which They are Destroyed or Annoyed*. London: C. Dilly (1788), pp. 249–250.

With regard to certain of these proposals, Black wrote, ‘Most of the proximate causes assigned in authors [sic] for madness, are mere hypotheses; and of no active use to the community or to medicine.’ He refused to believe one author who had written that insanity at Bethlem—in one particular year—was caused entirely by financial losses ‘in the South-Sea scheme.’ Determined to prove this man wrong, Black ‘took the trouble’ to investigate for himself records kept at the same hospital. In a sample that contained ‘nearly one third of the whole patients during fifteen years,’ Black found the leading cause to be ‘misfortunes, troubles, disappointments and grief (206 cases), followed by family and hereditary (115 cases), fever (110 cases) and religion and methodism (90 cases). As for revolutions of the seasons and effects of the moon, these had ‘no conspicuous effects.’

Other analyses, conducted elsewhere, further implicated family and heredity as the leading causes of insanity. A report from the York Retreat in England stated that parental illnesses caused insanity in 70 patients, while indirect ancestors were responsible in 143 cases. Overall, heredity—either direct or indirect—was the presumed cause of illness in 51 percent of cases at York. Doctors and asylum directors throughout Europe and North America welcomed such reports, because they were feeling pressure from the rising tide of patients. Coming to grips with the cause of mental illness was seen as an essential first step in dealing with the problem.

Asylum populations further exploded in the second half of the nineteenth century. Reports spoke of astonishingly high rates of insanity. In Scotland, one study found that one of every 390 citizens was insane. Topping that, a Norwegian investigator named Ludvig Dahl compiled census data from dozens of individual parishes, counting a total of 5,071 insane persons (including ‘idiots’), or one in every 293 citizens. These startling statistics drove people to look deeper into the phenomenon of heredity, it being the likely cause. Dahl, for example, created what was probably the first pedigree chart, or family tree. His chart showed relationships among five generations of a single family, complete with the mental status of every individual. Fourteen of the 27 family members in recent generations were identified as insane (including ‘idiots’).

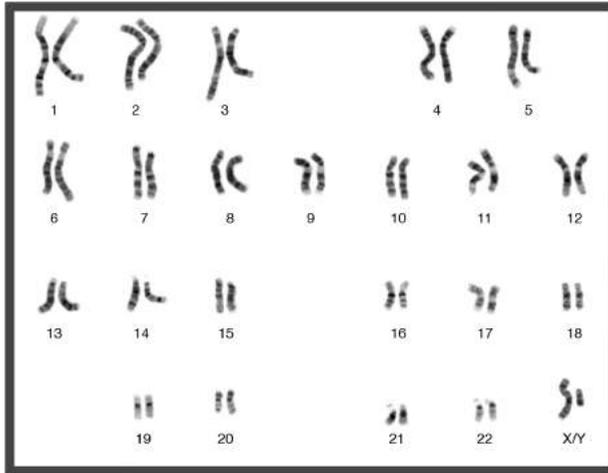
When heredity became a hot topic among European intellectuals, it was inevitable that two of England’s most prominent scientists would get involved. Charles Darwin, of course, knew all about heredity because it was central to his theory of evolution. But it was also, for him, a personal issue because he and his wife had the same grandfather, Josiah Wedgwood, the

## 6 A disruption at 1q42.1

Confirming a role for heredity in mental illness was a great starter, but harder tasks lay ahead. Many scientifically minded psychiatrists thought that the mechanism of hereditary transmission would be quickly ascertained after Georg Mendel discovered dominant and recessive genes, but Ernst Rüdin proved them wrong. Later, just when DNA was about to be discovered—on the early morning of November 1, 1952 to be exact—a big bang was heard on a small Pacific island.

Only a few American weapon experts were there to watch the first detonation of a hydrogen bomb (H-bomb, fusion bomb, thermonuclear bomb). Dubbed ‘Mike’, the bomb was almost 500 times more powerful than the bomb that devastated the Japanese city of Nagasaki a few years earlier. Not to be outdone by Mike, the Soviet Union quickly conducted its own thermonuclear weapon test, and on March 1, 1954, the United States completely destroyed a pristine Pacific atoll named Bikini. These explosions not only wreaked havoc on the ground, they also sent vast amounts of radioactive dust into the air. The radioactive fallout from the Bikini blast alone contaminated an area of 7,000 square miles. Because radiation of the type present in that dust damages cellular DNA, it didn’t take long for doctors to realize the risk to human health, especially if there was to be more testing, let alone thermonuclear warfare.

As a precaution, the Medical Research Council of the United Kingdom established a research group in Scotland. They named it the Clinical Effects of Radiation Unit and charged it with analyzing the blood of newborn babies. The unit faithfully carried out its job, not stopping until it had obtained 10,000 samples. In addition to biochemical testing, the researchers put blood cells under a microscope to examine chromosomes, the small, wiggly packages of DNA present in all human cells. It is not possible to identify gene mutations with this method, but it is relatively easy to see chromosomal abnormalities. Humans have 24 different chromosomes (including the two sex chromosomes, X and Y). Each one can be uniquely identified by its characteristic size and shape. After staining, it is also pos-



Human chromosomes [National Human Genome Research Institute, USA]

sible to see light and dark areas, called bands, that are also distinctive for each chromosome.

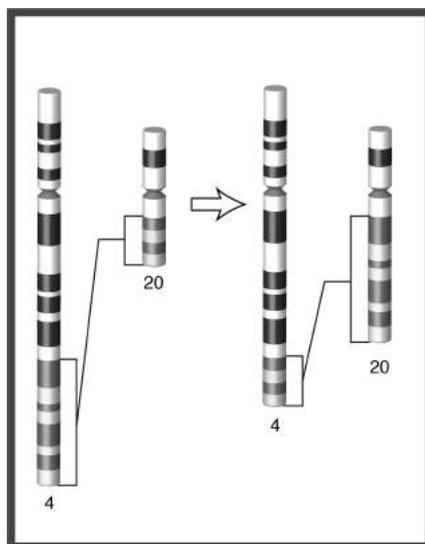
A related project took blood samples from boys detained at institutions for juvenile delinquents; the Brits called them borstals. One of these samples came under scrutiny after it was found to contain a chromosomal abnormality. The sample in question was provided by a ‘physically normal’ 18-year old who had been diagnosed with ‘adolescent conduct disorder’. Tests on members of the boy’s family revealed similar chromosomal abnormalities in the father, the paternal grandfather and other individuals scattered across four generations. This was the beginning of a tortuous path that eventually led to the identification of gene mutations contributing to mental illness.<sup>55</sup>

We pause here to understand in more detail the nature of the abnormalities seen in the Scottish family. As mentioned, chromosomes have light and dark bands. They are so distinctive and so consistent that any deviation from the normal pattern can be immediately recognized by a trained observer. In cells of the borstal boy, experts saw a band on chromosome 1 that is ordinarily found on chromosome 11, and another band on chromosome 11 that had evidently moved from chromosome 1. Events such as these, where two chunks of DNA trade places across two chromosomes, are called balanced translocations. If the translocation occurs in a sperm cell or an ovum, it will be present in every cell of the newborn child, and it

<sup>55</sup> Patricia A. Jacobs et al., ‘Studies on a family with three cytogenetic markers.’ *Annals of Human Genetics* 33:325–336 (1970).

## 6 A disruption at 1q42.1

will be passed on through successive generations, but not in every individual. Chromosomal translocations are fairly common, appearing about once in every 500 newborns. Usually they cause no harm, and indeed, it was said at the time that everyone in the Scottish family was healthy. Except, of course, for the 18-year-old, who was a juvenile delinquent.



Schematic illustration of translocation, here involving chromosomes 4 and 20 [Human Genome Research Institute, USA]

Twenty years after the initial report, scientists in Edinburgh began to suspect that, actually, all was not well within the family. Their concerns surfaced after learning of a paper read at a meeting of the American Society of Human Genetics. Scientists at the meeting reported on an American family in which five members had a chromosomal translocation, and all five were ill with ‘an affective disorder’. The report rang a bell with the Edinburgh investigators, causing them to question the now decades-old assessment of mental health in the Scottish family. They decided to track down as many family members as they could, update all the medical histories and re-examine all the chromosomes. For the medical histories, they scrutinized relevant hospital records, notes taken by family doctors and pharmaceutical prescriptions. They conducted in-person interviews with family members and their caregivers. And, when warranted in a particular case, a psychiatrist made a specific diagnosis. All of this was done by one group of researchers, while a second group re-examined the chromosomes.

## 7 A new disorder twice discovered

While it may be true that histories are written by winners, it is equally true that no writer knows the whole story, and some first-person witnesses know more than they wish to divulge. To get the true story, the full story, one must read several versions. Such is the case with the discovery of autism, about which there are competing claims. Initially, at least in North America, it was assumed that autism was discovered in 1943 by the American psychiatrist Leo Kanner who described ‘early infant autism’. German historians, however, told the story of a young Austrian doctor named Hans Asperger who had already spoken of ‘autistic psychopathy’ as early as 1938. In the midst of the controversy, a bombshell landed, forcing a re-examination of claims and an affirmation of ethical priorities.

Kanner was born in Austria, lived with his family in Berlin, then resettled in the United States, where he established a child psychiatric clinic at Johns Hopkins University in Baltimore. A photograph of Kanner appears to validate contemporary descriptions of him as warm and sympathetic. He spoke English with a heavy Germanic accent that matched the American stereotype of a psychiatrist, even though that stereotype was based on the voice of Sigmund Freud, and Kanner himself was not a psychoanalyst. Kanner’s textbook on child psychiatry was the first ever published in English (1935), a language that he mastered doing *New York Times* crossword puzzles.

One day Kanner received a long letter from a man living in Forest, Mississippi (population 3,000). It came from Oliver Tripplet, father of five-year old Donald Tripplet who had been living at an institution during the previous two years. The institution was neither a mental hospital nor any other type of hospital, but rather a place advertised as providing protection against infection by tuberculous. Donald’s parents thought it a convenient location for Donald’s safekeeping, but his mother, Mary, may also have been acting on her belief that her son was ‘hopelessly insane’.<sup>66</sup> Oliver’s characterization was more concrete, and heavily detailed in his letter. He wrote that the

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<sup>66</sup> Quotations pertaining to Donald Tripplet are from John Donvan and Caren Zucker, ‘Autism’s first child.’ *The Atlantic*, October 2010.



Leo Kanner [National Library of Medicine, USA]

boy had withdrawn ‘into his shell’ with the intention of ‘living within himself.’ He seemed ‘perfectly oblivious to everything about him,’ and acted as though his parents were simply part of the landscape. Donald had ‘a mania for spinning blocks and pans and other round objects.’ He was fascinated by numbers, pictures of United States presidents and letters of the alphabet. Other things—such as milk, swings and tricycles—he intensely disliked. He talked very little, but endlessly repeated the words ‘business’, ‘chrysanthemum’ and ‘trumpet vine’. Any change of routine or interruption of his mental state triggered a temper tantrum.

Oliver also mentioned several of Donald’s unusual mental skills. By the age of two, for example, he was able to recite by heart the 23rd Psalm and had memorized 25 questions and answers from the Presbyterian catechism. In Oliver’s opinion, Donald seemed to be ‘always thinking and thinking.’ He was ‘happiest when left alone.’

Oliver’s letter so intrigued Dr. Kanner that he invited the entire family to come see him at his Baltimore office. Once in the room, Donald went straight to the wooden blocks ‘without paying the least attention to the persons present.’ Kanner further recalled that Donald remained completely indifferent to him throughout the visit, regarding him as though he were simply ‘the desk, the bookshelf, or the filing cabinet.’

Kanner’s curiosity about Donald led him to retain Donald at his clinic for two weeks. After Donald returned home, Mary kept Kanner informed of her son’s behavior by supplying him with further details of Donald’s strange behaviors. Four years passed. Kanner remained baffled, the Trip-

plets remained frustrated. At one point, Kanner confessed to Mary, ‘Nobody realizes more than I do myself that at no time have you or your husband been given a clear-cut and unequivocal ... diagnostic term.’ The reason, he explained, was that he was seeing, ‘for the first time a condition which has not hitherto been described by psychiatric or any other literature.’ Finally, in a letter to Donald and Mary dated September 1942, Kanner wrote ‘I have now accumulated a series of eight other cases which are very much like Don’s.’ Moreover, he had a diagnosis—a new condition that he was calling ‘autistic disturbance of affective contact’ (affective refers to moods and feelings). He later renamed the condition ‘early infantile autism’.

In the following year, an article published in *The Nervous Child*, introduced the journal’s professional readers to the new diagnostic category.<sup>67</sup> Kanner began, ‘There have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits ... a detailed consideration of its fascinating peculiarities.’ Although Kanner’s definition of autism drew from his personal observations of eleven children, five pages were devoted to a discussion of Donald Triplet. Kanner emphasized Donald’s preoccupation with objects, his strong desire for maintaining consistent routines, and his limited language. Even more striking, however, was the paucity of the child’s social interactions, especially those calling for emotional expression. It is significant that Kanner pointedly distinguished autism from mental retardation and schizophrenia, two conditions with which he was well acquainted. He noted that contrary to schizophrenia, no child had hallucinations, and contrary to mental retardation, several of his autistic children had exceptional memories or cognitive skills.

People often wonder what happens to autistic children when they become adults. The question bubbled up in the minds of two journalists who realized that Donald Triplet was still alive in 2010.<sup>68</sup> Tracking him down in his hometown of Forest, Mississippi, they found Donald—seventy-seven years old—playing golf. He had worked in a bank and traveled extensively by car. He still had unusual traits such as assigning a unique number to every person he met, but overall he was leading a fairly normal life.

While Leo Kanner was discovering autism in America, Hans Asperger was doing the same in Austria at the University of Vienna. Asperger was

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<sup>67</sup> Leo Kanner, ‘Autistic disturbances of affective contact.’ *The Nervous Child* 2:217–250 (1943). Although Kanner’s article became a classic of the psychiatric literature, the journal itself folded a few years later.

<sup>68</sup> J. Donovan and C. Zucker (2010).

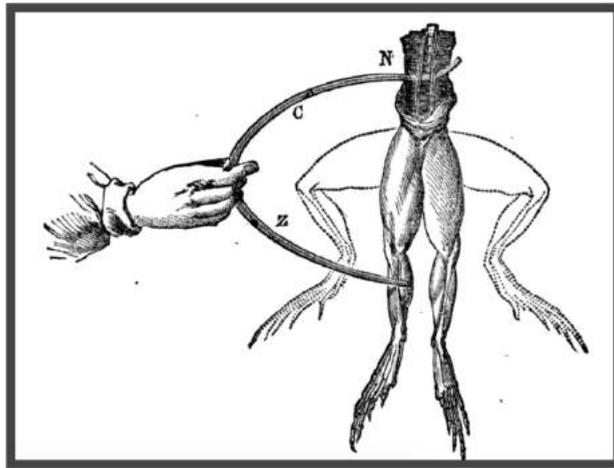
## 8 How shocking it was

Strange though it may be, all our weightless mental experiences come from a three-pound, electro-chemical machine. This bizarre relationship between the physical and the mental allows for two fundamentally different treatment options in psychiatry. Psychotherapy (talk therapy) directly addresses the mental aspect without bothering with the physical brain. It works reasonably well for many minor illnesses, but not at all for conditions such as schizophrenia, bipolar disorder, major depression, and obsessive-compulsive disorder. For serious mental illness, psychiatry relies on treatments that target the electro-chemical machine. In this chapter, we look at discovered procedures for altering—in a beneficial way—the electrical side of brain activity.

Long before people thought about medical treatments for mental illness, they thought about what, exactly, the brain is made of and how it works. The fact that it works with electrical phenomena like voltages and currents escaped notice until late in the eighteenth century. Prior to that time, both popular opinion and scholarly authors held to Galen's view—dating from the second century—that nervous function relies on animal spirits bubbling within nerve fibers.

Against this background of imagined spirits, a celebrated discovery changed everything around the year 1780. Luigi Galvani, an Italian physician and biological researcher, was dissecting a frog. Galvani dissected many frogs, and exactly what transpired in the course of that particular dissection is lost in the fog of history, but two speculations survive. Either Galvani's wife touched an exposed nerve with a metal instrument, or Galvani himself was attaching a hook to the frog's leg. Whatever the action, it caused the leg to twitch. Galvani understood the significance of what he witnessed: the nerves—and the muscles—work by electricity! He proceeded to conduct experiments looking for the source of electricity within the animal, while his contemporary, Alessandro Volta, contended that the electrical current came from *outside* the frog. Volta invented the battery and lent his name to the standard measure of electromotive force, so it is fair to assume that he knew something about electricity.

One thing Volta knew was that when two dissimilar metals touch, they create an electrical charge, essentially a battery. He also understood that when you connect the two poles of a battery, you complete an electrical circuit that allows current to be drawn from the battery. Therefore, he surmised that Galvani created a kind of battery by attaching a hook made of one type of metal to a railing made of another type of metal. Alternatively, his wife used a probe composed of two dissimilar metals. The illustration combines both scenarios. It shows a hand holding an arc made of zinc (z) and copper (c), with the frog's body completing the circuit. Volta was right about the source of the current, but Galvani gets credit for discovering the electrical basis of nervous function.



Luigi Galvani stimulates the frog's leg using a type of electrical battery

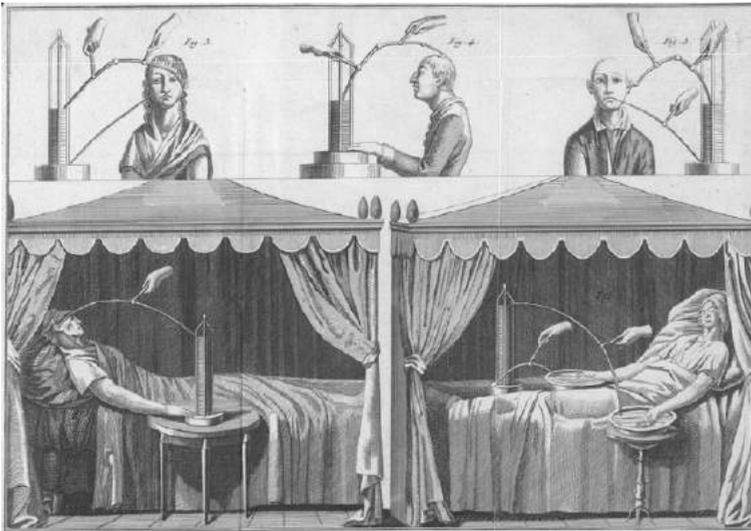
Galvani's discovery eventually led to treatments for mental illness based on electrical stimulation. But electrotherapy began long before Galvani. Even as early as 46 A.D., a Roman physician named Scribonius Largus was using it to relieve the pain of headaches and gout. He didn't have a battery, but he had a fish. Plato and Aristotle had earlier commented upon the electrical discharges produced by Torpedo fish (a type of ray), but evidently no one before Scribonius had exploited the discharges for medical purposes. He describes how he helped one patient,

For any type of gout, a live black Torpedo should, when the pain begins, be placed under the feet. The patient must stand on a moist shore washed by the sea and he should stay like this

until his whole foot and leg up to the knee is numb. This takes away present pain and prevents pain from coming on if it has not already arisen. In this way, Anteros, a freedman of Tiberius was cured.<sup>80</sup>

Shocks from electric fish continued to be used for centuries, most commonly for numbing pain during birthings and surgeries. As late as 1777, just before Galvani's breakthrough research, an announcement in a London sheet advertised 'Torpedo eel' shocks for just two shillings sixpence.

The current produced by the Torpedo is of the 'direct' type, meaning that it flows constantly in the same direction, as opposed to the 'alternating' type used in most homes. Direct currents are also known as Galvanic currents, and it was Galvani's nephew, Giovanni Aldini, who conducted probably the first test of Galvanic currents in the treatment of a mental condition. Aldini was a professor of physics and very much involved in the Galvani-Volta debate. Although he protested Volta's interpretation of his uncle's experiments, he did not hesitate to use Volta's batteries in his own experimentation. He started by giving demonstrations with fresh human corpses. Performing before astonished audiences across Europe, he elicited muscle twitches from otherwise inert bodies.



Giovanni Aldini's arrangements for treating depression and other illnesses

<sup>80</sup> P. Kellaway, 'The part played by electric fish in the early history of bioelectricity and electrotherapy.' *Bulletin of the History of Medicine* 20:112-137 (1946).

## 9 Lithium: the first drug that worked

The discovery of effective drugs for mental illness ranks among the great successes of modern medicine. The first such drug, lithium, was found to be effective against mania in 1949. Soon after, in 1951, came chlorpromazine for schizophrenia and imipramine for depression. The so-called ‘golden era’ of psychopharmacology closed in 1955 with the discovery of benzodiazepine for anxiety.

Popular accounts often depict the treatment of mental patients in bygone days as either barbaric or absent, but that is not entirely fair. There were treatments, and not all were harsh. A few were actually kindly, as we saw in chapter 1. Some treatments reduced symptoms—usually by putting the patient to sleep—but none had lasting effects. Mostly, it was the agitated, disruptive patients who got treated. Hippocrates had recommended giving the powdered roots of hellebore plants, and even as late as the early nineteenth century, hellebore was still being used in some hospitals. It is a nasty substance that burns in the mouth and makes you vomit. When alcoholic drinks became widely available in the mid-nineteenth century, they quickly replaced hellebore. In Munich, for example, patients were allowed up to three and one-half liters of beer per day, even more if authorized by the patient’s family. Highly agitated patients were given morphine or potassium bromide, the latter a cheap and effective drug but dangerous if taken too often. Most popular among physicians, however, was the synthetic compound, chloral hydrate. Although it has a strong calming effect, it is addictive, toxic and expensive. Asylum doctors also used two compounds obtained from plants belonging to the nightshade family, principally hyoscyamine and hyoscine, both of which were cheap to purchase. None of the drugs mentioned here were antipsychotic or anti-depressive. They were indiscriminate with regard to specific mental disorders, effective only because they put the patients to sleep.

Apart from drugs, the standard nineteenth century treatment was baths, sometimes hot, sometimes cold. Philippe Pinel, in Paris, is said to have preferred ‘surprise’ baths, whereas Emil Kraepelin, in Heidelberg, believed in long baths. One of Kraepelin’s female patients was kept in a bath for

three consecutive days. Forced bed stays were ordered for mildly agitated patients, usually in conjunction with sedation. More troublesome were the agitated patients. If they could not be quieted with sedatives, they were physically constrained by straight-jackets, hand cuffs and leg cuffs. They might also be locked into jail-like rooms.

Whereas sedatives, water baths and the like were somewhat useful, what psychiatrists really needed was drugs tailored to specific conditions. Their hopes were raised by advances made in general medicine, where doctors were finding cures for diseases by targeting the germs that cause the disease. One such advancement was announced in 1882 during a meeting of the German Physiological Society in Berlin. It was a small gathering of top-notch scientists including the physician Robert Koch who had brought with him a collection of microscope slides. On each of his slides, Koch had smeared a bit of lung tissue taken from an animal that had died of tuberculosis. As each man took his turn at the microscope (there were no women), none was surprised to see grey tubercles, because they were recognized as signatures of the disease. What did come as a surprise, were the worm-like profiles of the bacterium, *Mycobacterium tuberculosis*, made visible by Koch's new staining technique. Right there, with their own eyes, they were looking at the cause of tuberculosis. Following upon the discovery, Paul Ehrlich, Koch's student and collaborator, reasoned that a specific cause called for a specific cure, a 'magic bullet' to kill the pathogen. He and Koch tried but failed with a drug for tuberculosis, but he later succeeded with a drug for syphilis, the first synthetic medication against an infectious disease.

In psychiatry, the search for a magic bullet, or a cure of any kind, was compounded by the ill-defined nature of the target. At the beginning of the nineteenth century, none of the major disorders—mania, melancholia, dementia and idiocy—was seen as an actual illness equivalent to tuberculous and syphilis. That perception gradually changed, however, as psychiatry became accepted as a legitimate medical speciality. It happened in the final decades of the nineteenth century, and mostly in Germany. Emil Kraepelin was one of the leading voices in the campaign to modernise psychiatry. He believed that mental illnesses are very much like physical illnesses. Each one, he said, can be accurately diagnosed by reference to specific signs and symptoms, each has its own biological cause, and each can be cured—in principle—by using the proper physical agent. But belief was one thing, proof something else. With no psychiatric pharmacology yet in sight, Kraepelin tried other cures. As one example, he injected patients with extracts

of testes on the theory that schizophrenia is caused by a toxin affecting the sexual organs. When none of the patients improved, he terminated the experiment.

Sigmund Freud bought none of this. Since he didn't go for the disease concept in psychiatry, he had no use for biological explanations or chemical cures (despite his background in biological research). He and Kraepelin agreed to disagree about these things, but psychiatrists elsewhere tended to take sides. John Cade, Director of the Bundoora Repatriation Mental Hospital in the state of Victoria, Australia, was an exception. He chose the middle ground between Kraepelin's disease concept and Freud's psychology. He followed Kraepelin in matters relating to severe illnesses—mostly schizophrenia and depression—and followed Freud in respect to neurosis. Cade had little tolerance for Freud's speculations, defining psychoanalysis as 'the art of describing the commonplace in terms of the incomprehensible, and commenting that 'Freudian psychology [had] cast a blight upon the minds of men that will last perhaps another fifty years.'<sup>97</sup> Cade's views are important because they led him to treat mania with lithium, which turned out to be the first psychiatric drug that actually worked.

What makes the story of lithium in psychiatry remarkable is first, the simple nature of the substance, and second, the fascinating character of its discoverer, John Cade.<sup>98</sup> Different from the large and chemically complex molecules that are the staples of modern medicine, lithium isn't even a drug according to our popular understanding of the word. It is, after all, a chemical element, fundamentally like 117 other elements in the periodic table. A light-weight alkali metal with three protons in its nucleus (atomic number 3), lithium sits immediately above sodium (atomic number 11) in the periodic table. Lithium is abundant in the seas, in spring waters and in rocks. Fittingly, in light of John Cade's nationality, Australia contains some of the largest deposits anywhere. It is widely used in the manufacture of glasses, as an ingredient in greases and as a component of household batteries. Despite being the best remedy for one of the most severe mental disorders, it has never been marketed by any pharmaceutical company. The reason? It is literally 'dirt cheap'.

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<sup>97</sup> John F. J. Cade, 'Research in psychiatry.' *The Medical Journal of Australia*, vol II (7):213–219 (1951), p. 215.

<sup>98</sup> Cade's story is delightfully told in a one-hour film produced by Film Australia. The work artfully combines documentary images, interviews and staged reenactments. For details, see the listing at the end of this chapter.

## 10 Chlorpromazine: the first antipsychotic drug

Doctors first learned about the new treatment for schizophrenia in 1952, three years after John Cade announced his lithium treatment for mania. Although both discoveries unfolded in an unusual manner, the circumstances were quite different. While Cade worked pretty much alone, far away from the centers of pharmacological research, the researchers who discovered chlorpromazine worked for a large biochemical company. Cade was looking for a toxic substance in manic patients, the chemists at Rhône-Poulenc company were seeking a better anaesthetic. In the end, Cade discovered a novel use for the element lithium, while the French chemists created an artificial molecule 50 times heavier than lithium.

Rhône-Poulenc wanted to develop a drug that could counter the actions of histamine, a natural compound present in the human body. Histamine has numerous beneficial functions, but it is also implicated in certain unpleasant and even dangerous reactions, including allergy, inflammation, sleeplessness and stress. In the 1940s, many pharmaceutical companies were trying to develop antihistamine drugs. Rhône-Poulenc was in the game with a drug called promethazine which they hoped to sell as a sedative and sleep inducer.

Meanwhile, Henri Laborit, a surgeon in the French navy, was thinking about how to combat his patients' physiological stress. Initially stationed in Tunisia, he was re-assigned to a military hospital in Paris, and it was there that he became friendly with Pierre Huguenard, a fellow surgeon with similar concerns. Both men ordinarily anaesthetized their patients with a gaseous chemical delivered through a facial mask. But one day Huguenard needed to operate on a woman's nose, and the mask did not fit. So, instead of the gas anesthetic, Huguenard used a cocktail containing a mix of Rhône-Poulenc's drug, promethazine, and pethidine, an opioid with the trade name Demerol. Afterwards, Huguenard told Laborit that the patient was not only relaxed but indifferent to what was being done to her. Laborit tried the same cocktail on several of his own patients, and he too noted the unusual psychological effect. Recognizing that it was promethazine, not the opioid,

that had produced the indifference, he asked people at Rhône-Poulenc if they could create an antihistamine that was like promethazine but even more potent. Laborit wanted something that would render the patients oblivious to the surgeon's knife. Did he know that a few taxi drivers, dulled by antihistamines, had been driving through Parisian stop lights with barely a pause?

The chemist charged with improving upon promethazine found the trick he needed in his specialist's bag. After selecting a number of antihistamines already at hand, he added a single chlorine atom to each one. Confident that chlorine would increase the potencies of at least some of these compounds, he handed them all to Simone Courvoisier for testing. Courvoisier was head of the pharmacology group at Rhône-Poulenc. Ordinarily, she tested drugs using biochemical and physiological methods, but how to test for 'indifference'? For that, she designed a novel type of assay. First, she assembled an experimental environment that consisted of nothing but an elevated platform and an attached rope that hung beneath. On top of the platform, she placed some smelly food which she knew her hungry lab rats would want to eat. The rats had to climb the rope to reach the food. Unmedicated (control) rats quickly ascended the rope to access the reward, but the majority of rats that had been injected with a chlorinated antihistamine were slow to climb. Compound RP4560 stood out among the others, for rats injected with that compound lazied around at the base seemingly uninterested in eating. When later renamed, compound RP4560 became chlorpromazine.

Laborit found that chlorpromazine worked really well. He had wanted an agent that would stabilize multiple body systems, and chlorpromazine seemed to do just that. Not only did it produce the desired calming effect, it dampened down the sympathetic nervous system, steadied the heart and prevented vomiting. He convinced Rhône-Poulenc to sell it under the name Largactil, meaning 'large in action'. After Laborit published a short report on the drug, other surgeons began using it. Those doing open-heart surgeries found chlorpromazine especially useful because, as part of the procedure, they had to temporarily halt blood circulation. With the heart stopped, they cooled the body to reduce its metabolism and hence its need for oxygenated blood. However, the procedure often triggered a compensatory warming response that negated the desired effect. By inhibiting the body's temperature control system, chlorpromazine allowed the surgeons to maintain the body in a chilled state.

Laborit mentioned chlorpromazine's psychological effects to his psychiatrist colleagues, and a few of them decided to try it on their own patients.



Simone Courvoisier [Science History Institute]

Jacques L., a highly agitated 24-year-old got the first of twenty injections on January 19, 1952. While his condition improved, it was not clear how much of the improvement was due to chlorpromazine, because he was also given barbiturates and electroconvulsive shocks. Nevertheless, Jacques L's psychiatrists were sufficiently impressed to report the trial at the next meeting of the Société Médico-Psychologique.

Less than one month later, structured trials with chlorpromazine began at the Sainte-Anne mental hospital in Paris. Dr. Pierre Deniker was responsible for about one hundred male patients housed in a special, locked ward. It happened that Deniker's bother-in-law was an anesthetist, and it was through him that Deniker heard about chlorpromazine. According to a Canadian psychiatrist who knew him, Deniker was 'a real Parisian intellectual'.<sup>111</sup> Deniker's boss, Dr. Jean Delay, was also an intellectual, but aloof and patronizing. Deniker asked for permission to try chlorpromazine and Delay consented. A colleague later recalled the individuals selected for Deniker's drug trial, describing them as 'maniacal patients ... who for weeks would shriek and injure other patients; who had to be put in a straitjacket and even tied to the bed with straps.'<sup>112</sup> One patient in the drug trial was

<sup>111</sup> Interview with Heinz Lehmann in David Healy, *The Psychopharmacologists*. London, CRC Press (2001), p. 168.

<sup>112</sup> Jean Thuillier, *Ten Years That Changed the Face of Mental Illness*. London, CRC Press (1999), p. 111.

## 11 The first antidepressants

Nearly everyone gets depressed from time to time, but whether you *have* depression depends on the definition. Just as the meaning of melancholia has changed considerably from the time when it was virtually synonymous with madness, so too has depression taken on a new meaning in recent times. By the early eighteenth century, depression had come to imply intense sadness and self-loathing often accompanied by despair and thoughts of suicide. People with symptoms like that are seriously ill. They often require hospitalization and are prone to becoming psychotic. The antidepressive drugs discovered in the 1950s—those featured in this chapter—were intended for people with this type of depression. Back then, negative mood states of a less serious nature were largely ignored. When Prozac and other drugs of its type arrived, they helped men in boring jobs, lonely housewives and bankrupted investors, but not those on the verge of suicide. To clarify the distinction between these patient groups, psychiatrists coined the term ‘major depressive disorder’ to cover severe conditions, leaving less serious conditions with the tag ‘minor depression’, or simply ‘depression’. Whereas it is assumed that major depression has a biological basis, the cause or causes of minor depression are less certain. To summarize, although many people experience occasional, minor depression, relatively few people become seriously ill with major depressive disorder.

Lithium and chlorpromazine changed the psychiatric landscape by proving that chemicals can dramatically improve the lives of mental patients. With mania and schizophrenia now manageable by means of medication, dulling sedation and electroconvulsive shock fell to the wayside. Doctors eagerly awaited additional drugs for treating other conditions, and pharmaceutical companies stood ready to cooperate. It was a natural pairing that brought forth lasting alliances between businesses and psychiatrists. Company chemists generated a seemingly endless number of compounds of unknown value, and the psychiatrists tested them for efficacy. Many of these compounds were initially intended as treatments for medical conditions such as tuberculosis and inflammation but were given to the psychiatrists just in case. It is only a slight exaggeration to suggest that the

pharmaceutical companies first created drugs, then searched for matching diseases. It was mostly a matter of trial and error.

There are currently more than 70 drugs for depression licensed for sale worldwide (according to Wikipedia). Two of these, imipramine (Tofranil) and fluoxetine (Prozac), will be discussed here, along with iproniazid (Marsilid), which was important in the early stages of drug development, but was later withdrawn over concerns of its toxicity. Laboratory research played a significant role in the discovery of the antidepressants, and once they were proven effective, efforts were made to understand their mechanisms of action. Ultimately, scientists proposed a specific hypothesis that explains the biological basis of depression. However, as we will see, questions have been raised about whether, in fact, the hypothesis is true.

The story begins at the end of World War II, when Germany grounded its fleet of Messerschmitt fighter planes. These planes, as well as the German rockets, were fueled by hydrazine, a colorless, highly inflammable liquid. With hostilities ended, vast stores of hydrazine sat unused and unwanted by anyone but the Swiss pharmaceutical company Hoffmann-La Roche, which bought large quantities at cheap prices. The Swiss were thinking tuberculosis, not mental illness. They already had two closely related drugs in hand, both synthesized from hydrazine and both performing well in clinical trials. Although intended primarily for tuberculosis, Hoffmann-La Roche conducted smaller trials with the same drugs to explore possible applications in psychiatry. However, few of the patients in these trials were depressed. Most had schizophrenia, and the drugs didn't help them.

Word got around that some of the patients being treated for tuberculosis got decidedly happy, even mildly euphoric, after receiving one of the two candidate drugs but not the other. They were talking about a compound called iproniazid, and the reports of its effect on mood prompted Dr. Nathan Kline, at the Rockland State Hospital in New York, to conduct trials with psychiatric patients. Kline was an active researcher and a vocal backer of new ideas—usually those of his own making. Jumping at the opportunity to try iproniazid, he set up trials both at the hospital and in his private practice. He surprised colleagues by reporting at a medical conference in 1957 that 47 percent of his chronically depressed patients had improved after five weeks on iproniazid, and 70 percent showed a 'measurable response' after treatment for five months. Kline characterized iproniazid as a 'psychic energizer' and urged Hoffmann-La Roche to conduct further research with the goal of marketing iproniazid as an antidepressant. He was disappointed to learn that Hoffmann-La Roche was in no hurry to proceed. 'Here indeed

## 11 *The first antidepressants*

was a fairly unique situation!’ wrote Kline. ‘A group of clinical investigators [was] trying to convince a pharmaceutical house that they had a valuable product rather than the other way around.’<sup>125</sup>



Nathan Kline [Nathan S. Kline Institute for Psychiatric Research]

In the end, of course, Hoffman-Roche did come around to Kline’s way of thinking. They renamed iproniazid as Marsilid, sold it as an antidepressant and chalked up about 400,000 prescriptions in the first year. Many patients who would otherwise have needed electroconvulsive shock therapy were kept stable on Marsilid. The drug was also helping individuals with less severe depressions, those of the ‘ordinary’ variety. The historian Edward Shorter dug up evidence suggestive of the latter usage in the fact that ‘a horse named Marsilid won in the ninth at Belmont racetrack outside of New York city on September 4, 1959.’ Shorter explains, ‘It is tempting to think

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<sup>125</sup> Nathan Kline, ‘Monoamine oxidase inhibitors: An unfinished picaresque tale.’ In Ayd, F. J., Jr. and Blackwell, B., eds., *Discoveries in Biological Psychiatry*. J. B. Lippincott: Philadelphia (1970), p. 200.

## 12 Endophenotypes

In this chapter we jump into modern findings about brain mechanisms underlying mental illness. As noted at the conclusion of the previous chapter, the brain is incredibly complex at all levels of organization, from enzymes to tiny structures like synapses to long distance neural networks. Consequently, the number of structural problems and physiological malfunctions *possibly* responsible for mental illness is huge, all the more so because there are different types of mental illness. Research in this area is highly productive—at least numerically—with several hundred studies on the subject of neural mechanisms published every week in the scientific literature. Our challenge lies in selecting the meaningful studies from the irrelevant studies, the great discoveries from the simply mundane.

Already in this book, we have considered damaged arachnoid membranes (Chapter 2) and swollen ventricles (Chapter 3), both of which are biomarkers of mental illness. Although each is indicative of illness, neither contributes to scientific explanation or clinical application because neither participates in the work of the brain. Only neurons can generate fears, compulsions, hallucinations, paranoia, et cetera. Other biomarkers, even those in the brain, can be ignored if they are *caused by the illness*. For example, biomarkers that result from medication, lifestyle changes and the like are useless for most purposes. What we want are brain abnormalities that *cause the illness*, or more exactly, cause the symptoms of the illness. Ideally, we need symptom-causing abnormalities that link directly to genetics, because we know—from heritability analyses—that every one of the major mental illnesses is, to a large extent, heritable. The biomarkers that satisfy these criteria are called endophenotypes. We will consider two endophenotypes in this chapter, two more in the next chapter.

Before endophenotypes entered the stage, the action was all about biomarkers, and mostly in relation to schizophrenia. Arguably the most devastating of all mental illnesses, schizophrenia accounts for the majority of hospitalizations and is highly costly for society. German anatomists first reported microscopic biomarkers for schizophrenia at the close of the nineteenth century, principally in misshaped neurons but also in glia cells.

However, those claims were ultimately rejected due to lack of confirmation, leaving one author to write, in 1972, 'It is widely stated that in schizophrenia there is no visible pathology, nor do we really know whether there is irreparable damage in schizophrenics.'<sup>138</sup>

Forsaking anatomy ('visible pathology'), researchers turned to biochemistry in their search for biomarkers. But here again they came up with false leads, among which high levels of non-metabolized neurotransmitters (norepinephrine and epinephrine) and high levels of bufotenine (a metabolite of indolylalkylamines); vitamin deficiencies and abnormal amounts of a copper-containing enzyme (ceruloplasmin) in blood. But it was urinary 'pink spots' that drew the most attention.

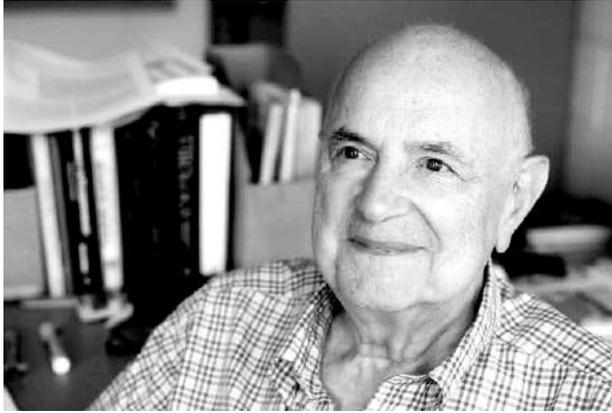
Pink spots were first seen in 1952. Researchers collected urine samples from 19 schizophrenia patients and 10 healthy individuals. The samples were concentrated down to a single drop and applied to a strip of paper. Once spread out and dried, a pink spot appeared in 15 of the patient samples, but in none of the healthy samples. What was it? Biochemists found that it contained dimethoxyphenylethylamine, a substance that is structurally similar to dopamine, but not a dopamine breakdown product as initially thought. The pink spot was said to be present in acute cases but not in chronic cases, common in hallucinating patients but not in paranoid patients. Early reports lit up the psychiatric community, but the lights dimmed as subsequent results were inconsistent at best. In the end, the pink spot turned out to be just an occasional insignificant correlate of schizophrenia, in other words a false lead. Researchers failed to take into account the fact that schizophrenia patients drink more coffee, smoke more cigarettes and get fewer vitamins than non-patients, plus of course their medications.

In the face of such nonsense, two veteran twin researchers entered the fray. James Shields learned how to conduct twin studies from Eliot Slater after Slater returned to the U.K. from Ernst Rüdin's lab in Munich. He teamed up with Irving Gottesman, an American who started out in academic psychology but turned to genetics because someone close to him had schizophrenia. Gottesman and Shields began their collaboration at the Genetics Institute of Maudsley Hospital in London. Searching through around 45,000 admission records in the period 1948 to 1964, they found 57 cases in which one or both members of a twin pair had schizophrenia. Their 433-page report documented a double-hit rate of 58 percent for identical twins

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<sup>138</sup> A. Pauline Ridges, 'Biochemical research into schizophrenia in relation to pink spot excretion.' *Journal of Orthomolecular Psychiatry* 1:18-27 (1972).

compared to only 12 percent for fraternal twins.<sup>139</sup> Apart from its value as a convincing demonstration of genetic inheritance, Gottesman and Shields' study led directly to the concept of psychiatric endophenotypes.



Irving Gottesman [University of Minnesota]

Gottesman and Shields pondered how to connect genetics with the myriad of psychological and behavioral symptoms in schizophrenia. The symptoms are readily observable but complex, while the genetic risk factors are obscure and difficult to study. For Gottesman and Shields back in 1972, it was a gap seemingly too large to fill—and for the most part it still is. Looking for something that might lie *in between* genes and psychology, they came up with endophenotypes.<sup>140</sup>

An endophenotype in psychiatry is a biomarker that connects genes on one side with symptoms on the other side.<sup>141</sup> The word, ‘endophenotype’ has two roots, endo and phenotype. Phenotype (think phenomenon) refers to the observable traits of an organism, while endo means within or hidden. So, we are talking about hidden features like a biochemical flaw, a neurophysiological abnormality, or a structural brain defect. Endophenotypes are observable, but not obvious. Because an endophenotype is a single, tangible characteristic rather than the bundle of psychological and behavioral symptoms that together define the illness, it can be easier to find the few genes responsible for the endophenotype than the many genes responsible

<sup>139</sup> As explained in chapter 5, a double-hit is when both members of a twin pair have schizophrenia (or some other trait).

<sup>140</sup> Gottesman and Shields did not invent the concept of endophenotype. It was first used to explain the geographical distribution of grasshoppers.

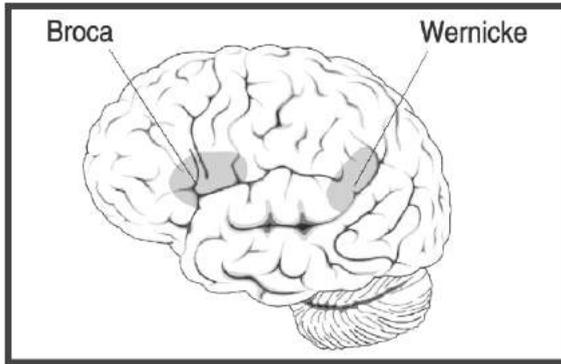
<sup>141</sup> I.I. Gottesman and T.D. Gould (2003). See suggested readings.

## 13 The disconnected brain

In the year 1891, the best-known neurologist of the nineteenth century found himself embroiled in a scientific dispute with a young man who would later become the most famous psychiatrist of the twentieth century. The roots of the argument lay in a remarkable discovery made earlier by yet another man, Paul Broca. Broca was a French physician with wide scientific interests, including the study of skulls for understanding human racial groups. Broca was also a brain anatomist, intrigued by issues of function. One day, a stroke victim with speech problems came for a consultation. The man understood perfectly well what the doctor was saying, but he himself was unable to speak. Later, when the patient died, Broca dissected the brain and found a spot of obvious damage at the bottom of the left frontal lobe, near the posterior border and next to the temporal lobe. An additional eleven cases followed, all with the same speech deficit and the same lesion in what is now known as ‘Broca’s area’.

The famous neurologist mentioned above was the German neurologist, Carl Wernicke. He too was passionate about brain research and, like Broca, he examined his patients’ brains after death. He confirmed the location of Broca’s area and its association with speech deficits, but he found something different in his own patients who had other types of speech problems. In contrast to Broca’s patients, who could not speak, Wernicke’s patients spoke perfectly well, but had trouble understanding what people were saying. Wernicke found that his patients had healthy looking frontal lobes, but unmistakable lesions in the left temporal lobe, within a region now known as Wernicke’s area. So, there were now two distinct speech pathologies—called ‘aphasias’—each apparently caused by a different anatomical lesion.

For some time previously, Wernicke had been arguing that different functions must be located in different parts of the brain. Naturally, therefore, he took satisfaction in announcing that a seemingly single faculty of mind, namely speech, needs at least two separate centers. The theory of localization of function was not his alone, but he was its main proponent and its most vociferous defender against contrary views. His enthusiasm led



Two separate brain areas for speech production and speech comprehension [National Institute of Health, USA]

him to formulate hypothetical explanations for numerous neurological and psychiatric disorders. Detractors referred to his ideas as ‘brain mythology’.

Knowing that there is one speech area responsible for producing speech and another for understanding speech, Wernicke reasoned that there must be a neural connection between the two, and further, there must exist a particular type of aphasia caused by the destruction of the physical connection. He speculated that patients in whom that connection was broken would understand speech relatively well but would utter inappropriate words. He proposed the syndrome based on his examination of two patients, both of whom were still alive when he published the speculation. Later, other neurologists noticed something similar. Their patients understood speech, and they spoke reasonably well, but they too made frequent errors, especially when asked to repeat a sentence spoken by someone else. Wernicke named this new type of language deficit ‘conduction aphasia’, implying that it is caused by a failure of electrical conduction between Broca’s area and Wernicke’s area.

The second person referenced above, ‘the most famous psychiatrist of the twentieth century,’ was, of course, Sigmund Freud. While his reputation rests on the invention of psychoanalysis, he began his career as a neuroscientist. The first of his numerous books, published in 1891, was a critique of Wernicke’s ideas on language, and in particular, Wernicke’s interpretation of conduction aphasia. So far as we know, Freud had no aphasic patients, nor did he ever examine the post-mortem brain of an aphasic person. Nevertheless, he confidently asserted the following:

We reject the assumptions that the language apparatus consists of separate centers which are divided by cortical regions without function, furthermore that the images that serve speech are stored at particular cortical sites which are called centers... [T]he associations and transmissions upon which the language functions are based take place with a complexity that is beyond comprehension.<sup>155</sup>

Freud sided with the critics who opposed Wernicke's idea of local control over brain functions. He did not believe that any psychological disorder could be the result of damage to any particular nervous pathway. Instead, Freud assumed that the brain operates as a whole, with the mind dependent on unimaginably complex interactions amongst the brain's innumerable yet equivalent parts. Unwilling to confront the conundrum, Freud turned away from neuroscience and toward psychology.

Today, we commonly speak of localized functions in the brain. We say that the hippocampus is for memories, the frontal lobe is for planning, the amygdala is for emotions, the cerebellum is for balance. We also have the *visual* cortex, the *somatosensory* cortex, the *motor* cortex and the *auditory* cortex. While these are simplifying notions, there is a good measure of truth in them. Wernicke was largely right, Freud mostly wrong. And yet, for the greater part of the twentieth century, professionals tended to side with Freud. One prominent researcher argued that 'integration cannot be expressed in terms of connections between specific neurons ... the mechanisms of integration are to be sought in the dynamic relations among the parts of the nervous system rather than in details of structural differentiation.'<sup>156</sup> The author of these comments conducted experiments that proved—he said—the 'whole brain' concept. Others pointed to serious flaws in his methods and arguments.

The tide turned in favor of localization in the 1960s as laboratory research accelerated and clinical data accumulated. Wernicke's conduction aphasia came under renewed scrutiny, and the predicted disconnection was found to lie in the arcuate fasciculus, not the nearby insula as Wernicke had thought. But Wernicke's misidentification was a minor error compared to the uncontested confirmation of a physical disconnection between Broca's area and Wernicke's area. It didn't take long before psychiatrists began to

<sup>155</sup> Claus-W. Wallesch, 'History of aphasia: Freud as an aphasiologist.' *Aphasiology* 18:4, (2004), p. 394.

<sup>156</sup> Karl S. Lashley, *Brain Mechanisms and Intelligence*. Chicago, Illinois: Chicago University Press (1929), p. 176.

## 14 The plastic brain

What adjective comes to mind when you think of the brain? Is it *wrinkled*, because you've seen pictures? *Mushy*, because it cuts like tofu? Maybe *heavy* and *dense*. Actually, it is all of these things, but it is also *plastic*. Which is not to say that the brain is made of plastic, but rather, that it changes its shape like plastic. Fortunately, our brain doesn't need to be melted down before changing its shape. Life experiences, and sometimes simply will power, gets the job done.

Beginning in the embryo and continuing until late adolescence, the brain grows according to a predetermined plan, then late in life it deteriorates. All along the way, on every single day throughout our entire lives, it changes. The changes occur mostly at synapses, so they are tiny and invisible, unless examined with an electron microscope. Nevertheless, these small structural changes affect our minds, sometimes for the better, sometimes not. Neural plasticity has implications for psychiatry, including opportunities for reversing or repairing detrimental changes.

Hans Lukas Teuber, an American neuropsychologist, founded the Department of Psychology (later the Department of Brain and Cognitive Sciences) at the Massachusetts Institute of Technology in 1964. Revolutionary at the time, Teuber believed that to understand the mind, one must understand the brain. One of the first professors that he hired was his former student, Joseph Altman. Teuber had been studying the psychological effects of gunshot wounds suffered during WWII, and Altman was researching how the brain recovers from such injuries. Specifically, Altman wanted to know whether glia cells proliferate. Glia cells do not process information, but among other functions they were thought to clean up, and possibly repair, damaged nerve cells. As predicted, therefore, Altman found many new glia cells in the damaged brains of experimental animals. More surprising, startling in fact, he also found new nerve cells. The brains had changed by adding new neurons.<sup>168</sup>

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<sup>168</sup> Joseph Altman, 'Are new neurons formed in the brains of adult mammals?' *Science* 135:1127–1128 (1962).

Nerve cells are born when neural stem cells divide (mitosis). Since no dividing cells had been seen in any adult mammalian brain prior to Altman's discovery, it was assumed that all neurons are born during early development. Altman began his experiment by injecting adult rats with thymidine, a component of DNA. All new cells need to synthesize DNA, so they need thymidine, and they get it from blood. The thymidine that Altman injected into his rats was special, however, because he had made it radioactive. Later, when he found radioactive cells in post-mortem brain slices, he knew that they could only have been born subsequent to the injection. The reason why new neurons had not been noticed previously is because the stem cells that make them reside far away from where the new neurons eventually come to rest, and while migrating, the newly born cells undergo a drastic change of appearance from small and inconspicuous to fully formed neurons.

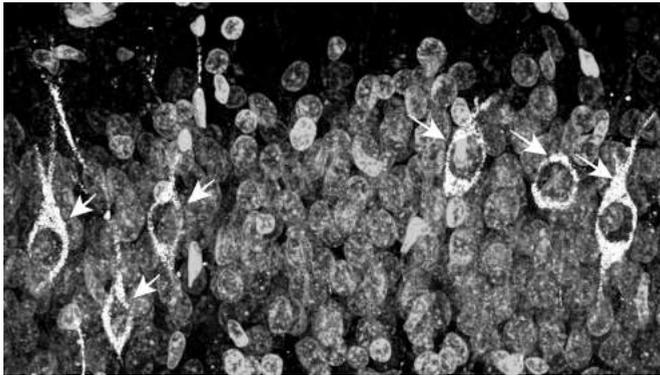


Joseph Altman [Shirley A. Bayer]

Altman announced his discovery in a series of papers published in the 1960s, but few scientists paid attention until 1998, when other investigators found neurogenesis in the adult *human* brain. Still, some scientists didn't believe it. They said the methods were inappropriate and the evidence inadequate. Then a group of researchers in Sweden, together with international collaborators, seized upon a clever test of Altman's claim. As mentioned, new cells need new DNA and thus, new thymidine. Now thymidine, like all organic compounds, contains carbon, which ordinarily has 6 neutrons and

6 protons (carbon-12). During the Cold War (1955–1963), however, above-ground bomb testing released enough energy to convert much of carbon-12 into an alternative isotope, carbon-14 (8 neutrons and 6 protons). Prior to the tests, carbon-14 was extremely rare, and it again became rare shortly afterwards, but in the meanwhile, huge amounts of carbon-14 entered the atmosphere and spread worldwide. Plants took up carbon-14, humans ate the plants, and all new biological cells born during that period incorporated carbon-14. When people who were adults in the bomb-testing years died fifty years later, they still had brain cells labelled with carbon-14, proving that the neurons had been born in their adult brains.

It was not just that neurogenesis occurs in humans— exciting in itself—but where, exactly, it occurs. The single beneficiary of new neurons, it turns out, is the hippocampus. A recent study counted newly born neurons in post-mortem brain slices.<sup>169</sup> Individuals with healthy brains at the time of death had tens of thousands of new hippocampal neurons per cubic millimeter. The number declined with increasing age at the time of death. By contrast, subjects who died with Alzheimer’s disease had fewer new neurons than even the oldest of the healthy subjects, regardless of age.



Newly born nerve cells (arrows) in the hippocampus of a 68-year-old man [Moreno-Jiménez, E.P., *Nature Medicine* 25, 2019]

Since the hippocampus plays an important role in the formation of memories, some scientists believe that neurogenesis participates in the process. Although unproven, it is possible that a decline in neurogenesis late in life accounts, at least in part, for memory losses. Low levels of neurogenesis

<sup>169</sup> Elena P. Moreno-Jiménez et al., ‘Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer’s disease.’ *Nature Medicine* 25:554–560 (2019).

## 15 An old diagnosis gets a bad prognosis

In Hans Christian Anderson's folktale, *The Emperor's New Clothes*, a pair of swindlers sell the emperor a magnificent, invisible outfit. The emperor steps out expecting to be greeted by an admiring crowd, but the room is silent until a gasping child cries out, 'The emperor has no clothes!' The story teaches the pitfalls of vanity and the fact that authority silences opposition.

Think now about Emil Kraepelin, the German psychiatrist whose name has appeared so often in this book. He has been described as the father of clinical psychiatry. The *Encyclopedia of Psychology* identifies him as the founder of modern scientific psychiatry, and, according to the distinguished medical historian Edward Shorter, 'It is Kraepelin, not Freud, who is the central figure in the history of psychiatry.'<sup>181</sup> It would be fair to conclude that Kraepelin's authority—within psychiatry—was as great as the emperor's. Moreover, Kraepelin's crowning achievement, schizophrenia, was a brilliant idea that no one dared to criticize. But now people are asking embarrassing questions.

Kraepelin first described schizophrenia in 1893. Some people say that he discovered schizophrenia, but it was really more of an invention. The real discovery—the one that merits inclusion in this book—is that schizophrenia is not the illness that Kraepelin thought it to be. It may not even be an illness. The emperor has no clothes. Kraepelin's schizophrenia is not an illness.

Schizophrenia is the quintessential madness, a highly debilitating condition that has long served as the testing ground for theories and treatments. In recent years, however, Kraepelin's grand conception has suffered one blow after another, to the point where many psychiatrists today question whether it serves any useful purpose. The reformers are picking up the shattered pieces of Kraepelin's edifice and reassembling them in ways that make us reconsider the very notion of discrete mental illnesses.

Immediately after writing that Kraepelin is the 'central figure' in the history of psychiatry, Edward Shorter defended the judgment, stating that Kraepelin 'provided the single most significant insight that the late nine-

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<sup>181</sup> Edward Shorter, *A History of Psychiatry*. Toronto: John Wiley & Sons (1997), p. 100.

teenth and early twentieth centuries had to offer into major psychiatric illness: that there are several principal types ...<sup>182</sup> That is not to say there were no types of psychiatric illness before Kraepelin. In early times, there were two types: mania and melancholy. The number grew to six in 1801 when Philippe Pinel recognized mania with delirium, mania without delirium, melancholia with elevated moods, melancholia with depressed or anxious moods, dementia and idiocy. For the remainder of the nineteenth century, French psychiatrists obsessed with identifying and classifying even more types.

The classification of data under clear and distinct rubrics was the *sine qua non* of enlightened scientific method in France at the end of the eighteenth century. With respect to psychiatry, that meant—and continued to mean throughout the nineteenth century—drawing up and periodically overhauling ... classificatory systems of mental disease, in which each disease was defined by the cluster of symptoms it regularly presented, and the ensemble was presumed to exhaust all the pathological possibilities.<sup>183</sup>

The enterprise of psychiatric classification spread around the world. Benjamin Rush, the leading American psychiatrist in the early 1800s, thought that madness was either partial (disorders like hypochondriasis, tristimania and amenomania) or general (disorders like mania, mania and manalgia). The Scottish psychiatrist, David Skae, named mental disorders after the part of the body from which the malady arose, for example mania of masturbation, mania of pregnancy, sunstroke mania and metastatic mania. Some authors used Latin names, some used vernacular names, and some organized their disease types in complex schemes copied from Carl Linnaeus's biological taxonomies. Every classification was different.

Most troubling for practicing psychiatrists was the multitude of diagnostic terms meant to encompass the most severe cases. These were named madness or insanity in Britain, craziness in America, *manie* in France and *Wahnsinn* in Germany. On top of that, an Austrian doctor coined a new term, *Psychose*, in 1845. Initially a term for purely psychological disorders, psychosis later came to imply brain damage. Asylums dealt with their psychotic patients as best as they could, usually with physical restraints, iso-

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<sup>182</sup> Ibid.

<sup>183</sup> Jan Ellen Goldstein, *Console and Classify: The French Psychiatric Profession in the Nineteenth Century*. Cambridge, England: Cambridge University Press (1987), p. 5.

lation and punishment. Meanwhile, in the universities, professors argued over whether psychosis constitutes a single disorder or multiple related disorders. One year after the word *Psychose* was introduced, a textbook listed no less than thirteen synonyms, all commonly used in clinical practice.

Enter Emil Kraepelin. Hard-working and highly ambitious, his career first took off after being appointed head of an asylum in Heidelberg. Later, as director of a large psychiatric hospital in Munich, he gained international fame. Although he was a man of wide interests, his passionate attention was focused on psychosis. His widely consulted textbook expressed the view that mental illnesses are real diseases, just like any physical disease. Each mental illness has its own psychological profile but also a unique biological basis. The way forward, he wrote, is to design treatments that address the underlying causes, most probably germs and toxins. But first, psychiatry had to properly identify the various diseases.



Emil Kraepelin and the psychiatric clinic at Heidelberg, c. 1900 [Heidelberg University Library, Graph. Slg. A\_0775]

Kraepelin approached psychiatry as a scientist, and he likely learned to think that way from his older brother, Karl. The family lived in a region of northern Germany surrounded by patches of untamed nature. Karl, who later became a botanist, took Emil for walks in the woods. He showed Emil how to identify the different plants. Each species, he explained, possesses certain unique features which together constitute its essence. Later, when the young doctor confronted insanity in all its bewildering variety, he recalled his brother's teachings. What sets this patient's illness apart from that other patient's illness? What are its essential features? He may have recalled Karl telling him about giraffes. Karl would have told him, 'If you