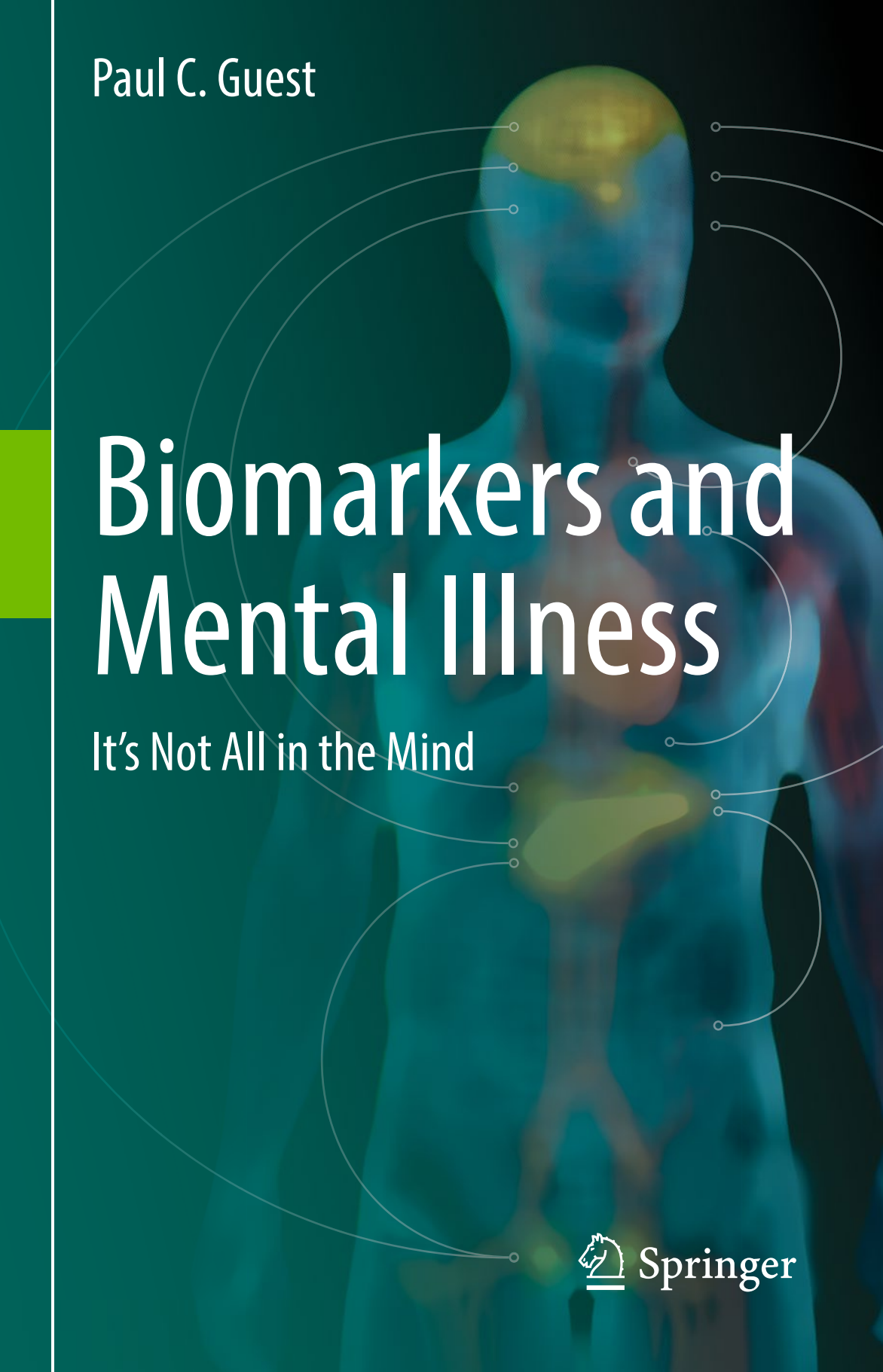
Paul C. Guest



Biomarkers and Mental Illness

It's Not All in the Mind

Springer

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ISBN 978-3-319-46087-1 ISBN 978-3-319-46088-8 (eBook)
DOI 10.1007/978-3-319-46088-8

Library of Congress Control Number: 2016952418

Printed on acid-free paper

This Copernicus imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

A 26-year-old female sees a psychiatrist because she has developed strange ideas and convictions. She believes that the world will end soon and she is the female embodiment of the messiah who can save everyone. She also believes that she receives advice from the president of the USA through the television on how to go about this task. The psychiatrist diagnoses her with schizophrenia and, as appropriate, treats her with an antipsychotic drug called quetiapine. After several weeks, the delusions and hallucinations disappear. However, there is now another problem. She slows down, talks less and believes that there is no hope and no future. She sees the psychiatrist again and he diagnoses her with negative symptoms of schizophrenia and possible depression. As a result, he treats her with an antidepressant called fluoxetine on top of the antipsychotic medication. After 1 week, the patient becomes agitated and her messianic beliefs begin to re-emerge. Also, there is now something new—she becomes sexually uninhibited and begins picking up men in bars. The psychiatrist changes the diagnosis to mania, which is basically the upwards part of the cycle of manic depression disorder. Consequently, he stops the antidepressant treatment and gives her a mood stabilizer known as valproate. After 3 weeks there is an almost complete recovery.

There are millions of cases around the world each year such as this one. The difficulties associated with psychiatric diagnosis stem from the fact that it is still based on fuzzy concepts. This fuzziness is not only due to a broad overlap of symptoms across the various psychiatric disorders, it is likely that the underlying biological causes of these conditions overlap as well. For example, the disorder that we know as schizophrenia is likely to consist of at least five separate diseases, each of which may require a different treatment. Given the complexities and difficulties surrounding current diagnoses, the question arises—how can the process be improved?

The answer: biomarkers.

I have written this book on the emerging use of biomarkers in the study of psychiatric diseases for a broad range of people including researchers, clinicians, psychiatrists, university students and even those whose lives are affected in some way by a psychiatric illness. The latter category is not trivial since a staggering one in

three people worldwide show the criteria for at least one psychiatric disorder at some point in their lifetime. The book lays out, in accessible language, the history of psychiatric research, the current state of the art in psychiatric practice, the systems affected in psychiatric illnesses, the whole body nature of psychiatric illnesses and the impact that this is having on emerging biomarker discoveries. It also gives descriptions of the major specific psychiatric disorders and the special challenges that surround the diagnosis and treatment of each one of these. The main concept behind this book that the reader should look for is that the brain does not work alone. Mood and behaviour actually result from integration of signals between the mind and the body, and many of these signals are borne by the bloodstream. This is important as this factor makes it possible to develop simple blood tests for diagnoses of these complex disorders. The final chapter drives home the way in which we can change the paradigm of how we treat patients with psychiatric disorders by incorporating biomarkers into clinical practice and even into the drug development pipeline. The ultimate goal is to incorporate personalized medicine approaches into these processes to help move psychiatric medicine into the twenty-first century.

I sincerely hope that the reader will find the contents of this book interesting on a subject that really matters and affects us all in some way.

Debden, Essex, UK Paul C. Guest

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Psychiatric Disorders as "Whole Body" Diseases

In the last decades of the nineteenth century "insanity" was postulated to be a set of discrete mental conditions, which were thought to exist alongside other diseases that are widely recognized by general medicine. However, anatomical studies which focused on the search for pathological processes in the brains of psychiatric patients found little or no evidence for a link with the common clinical signs or symptoms. Nevertheless, the new disciplines of endocrinology, immunology and biochemistry arrived on the scene, and began to offer new insights that pointed towards involvement of the whole body in the precipitation and course of psychiatric disorders. The assumption behind this research was that the brain was not separate from most of the physiological currents that surged throughout other organs and peripheral systems of the body. Thus, the source of insanity might reside not just in the brain, but elsewhere in the body. This chapter will briefly cover the history of physiological models of psychopathology with respect to what we now call schizophrenia, the major mood disorders and other psychiatric Illnesses. Over the past 60 years, most historical narratives have focussed on neuroanatomy, neurotransmitter systems and the genome. There is now an emerging concept that psychiatric disorders can be precipitated by various factors external to the brain, including exposure to certain drugs, infections, nutrient deficits, physical and emotional stress, and by other diseases such as autoimmune conditions and metabolic disorders. With the emergence of proteomic biomarker research at the start of the twenty-first century, whole body causes of psychiatric diseases are once again the prime suspect.

A Brief History of Psychiatric Disease: The Curse of the Gods?

In prehistoric times, many individuals believed that mental diseases came from magical beings that disrupted the minds of unsuspecting and innocent victims (Fig. 1.1). Ancient shamans used spells and rituals in an attempt to cure the afflicted

P.C. Guest, *Biomarkers and Mental Illness*,
DOI 10.1007/978-3-319-46088-8_1

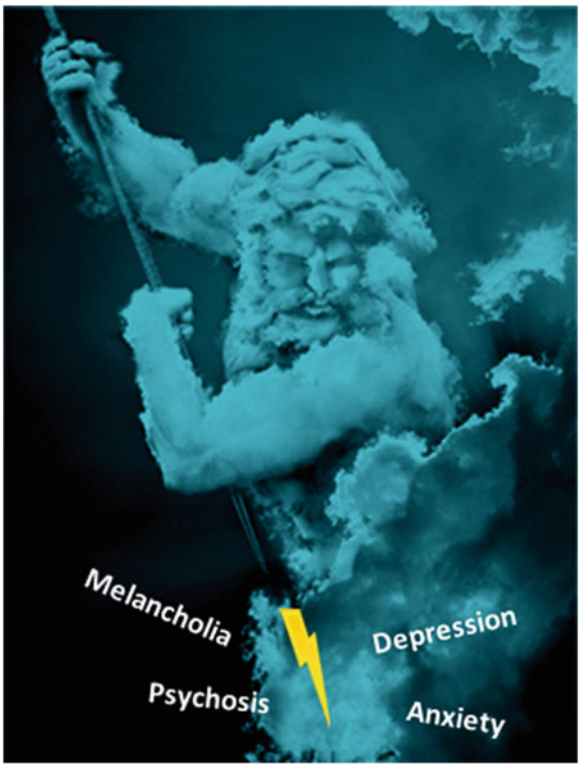

Fig. 1.1 Many people in ancient times believed that mental illnesses were caused by the gods

of their mental illnesses This often took the form of an exorcism, which involved the shaman attempting to drive the invading spirit away from the body. In other cases, a crude form of brain surgery was used which was called trepanation. This involved drilling a hole through the skull to allow the spirits trapped inside the skull an easy escape route to the outside world. Skulls with these holes have been found in Europe and South America, dating back some 10,000 years (Fig. 1.2). Amazingly, the technique is still in use today for conditions such as epidural and subdural hematomas, and for allowing surgical access for particular procedures such as intracranial pressure monitoring.

The ancient Egyptians brought about many changes in the treatment of the mentally ill. However, they still regarded these conditions as resulting from magic or that they were brought about by the gods. For example, they believed that normal mental health required a strong interaction with the *khat* (the body), the *ka* (the guardian spirit) and the *ba* (a bird symbolising the connection with heaven). Concepts similar to these forces can be found in many cultures, such as chi or qi in china, *mana* in Hawaiian culture, *lüng* in Tibetan Buddhism, as well as ideas in popular culture (e.g. "The Force" in the *Star Wars* films and books). The obsession of the Egyptians with life after death revolved around the belief that the well-being of the mind and soul was critical for overall health of each person. For this reason,

Fig. 1.2 Ancient skull showing a skull subjected to trepanation—a drilling process used to let the bad spirits out

they focussed on the health of the soul and they carried out specific purposeful treatments for erratic behaviour as early as 5000 years ago. Typical cures for those suffering from any form of insanity included treatment of the afflicted with opium, performance of ritual prayers to the gods, along with dream interpretation to discover the source of the illness.

Is It All in the Blood or Other Body Fluids?

The ancient Greeks were probably the first culture in known history to overcome the belief systems that diseases were caused by supernatural events. In fact, they came to realize that afflictions of the mind did not differ from those of the body. Following on from this, they developed a system which saw all sicknesses as being due to natural phenomena and the cause may reside in the blood and other fluids (humours).

For thousands of years, the blood has been used as a source of information on illness and health in human beings. Ancient Greek doctors believed that most illness was caused by an imbalance in the four body humours known as black bile (earth), yellow bile (fire), phlegm (water) and blood (Air) (Fig. 1.3). More specifically, they believed that fever was caused by an imbalance of the yellow bile and they would therefore try to increase the opposite humour phlegm (water), for example by immersing the afflicted in a cold bath. In the case of mental illnesses, an excess of phlegm (water) was thought to render a person emotionally unresponsive. The father of medicine, Hippocrates, believed that an excess of black bile led to irrational

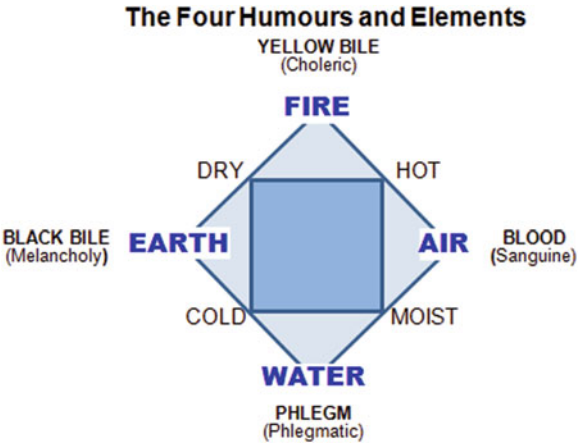

Fig. 1.3 Ancient Greek doctors believed that most illnesses are caused by an imbalance in the four body humours known as black bile (earth), yellow bile (fire), phlegm (water) and blood (air)

thinking or depression. So as a response, the Greeks would use bleeding and purging to rebalance the blood and black bile.

> *Aristotle, who used the image of wine to expose the nature of black bile. Black bile, just like the juice of grapes, contains pneuma, which provokes hypochondriac diseases like melancholia. Black bile like wine is prone to ferment and produce an alternation of depression and anger….* (From Linet's, *The History of Melancholy*)

Again, these four humours have analogues in other cultures. For example, the Chinese concept of qi revolves around five elements: wood, fire, earth, metal and air. These are thought to function in a cyclical sequence that represents the natural flow of qi. Furthermore, these elements are thought to represent many qualities. In terms of emotion, wood represents anger versus patience, fire is hate versus joy, earth corresponds to anxiety vs empathy, metal equals grief versus courage and water represents fear versus calmness. The Chinese developed a number of exercises, such as qi gong and tai chi, to help the qi keep flowing to maintain physical and mental health and to rebalance these elements during sickness.

> *Author's note: I have tried both of these at various times and found them to be both relaxing and stimulating. In the case of qigong, I managed to improve my ability to stand still like a tree (with arms outstretched at a 90 degree angle from the body) from 5 minutes to 20 minutes.*

What Went Wrong in the Middle Ages?

By the time the Middle Ages came around, such progressive ideas about the cause of psychiatric disorders were discarded. People who were mentally ill were now treated with fear, disgust and shame. Also, hospitals known as asylums began to emerge in Egypt and Iraq around the thirteenth century and these were not very hospitable places. These were used to isolate the mentally ill or the socially

ostracized from society, with purpose of removing them as a problem. In fact, asylums did not offer any form of treatment to help the afflicted to reintegrate into society. Europe's oldest asylum was the Bethlem Royal Hospital of London, which became known as the infamous Bedlam. Bedlam began housing the mentally ill in 1403. The first asylum in the Colonial USA was built in Williamsburg Virginia around the year 1773. Pictures from some of these institutes revealed that the "patients" were often bound with rope or chains to beds or walls, or restrained in straitjackets.

With the emergence of techniques in experimental physiology and medicine in the middle of the nineteenth century, investigations into the biological nature of mental illness began to re-emerge. In an amazing venture well before its time, many studies were conducted which attempted to determine whether or not there were physical characteristics in blood that could be used to distinguish the diseased state from the normal one. In addition, questions arose as to whether blood characteristics could be used to determine whether insanity was a continuum of one disease or a variety of discrete disease entities that could be identified and sorted into different clinical categories. According to Richard Noll in his paper "The blood of the Insane" in the *History of Psychiatry*, these investigations comprised four phases based on different concepts (summarized below).

Phase 1

In 1854, the first microscopic investigations of blood cells from psychiatric patients were carried out in a Scottish asylum by W. Lauder Lindsey. He basically used a low power microscope to count the numbers of different blood cells in samples from the patients in comparison to those of his staff members. However, this investigation did not yield any earth shattering results as Lindsey found no differences associated with different types of mental illness or between the patients and the staff members. However, approximately 30 years later, S. Rutherford Macphail reviewed a number of subsequent related studies and came to the conclusion, albeit a tentative one, that there was an overall "deficiency of corpuscular richness of the blood" in the early stages of mental illness. This meant that he thought there may be a lower number of red blood cells in psychiatric patients. Similar blood studies of patients at various stages of insanity continued up to the 1920s with mixed results and no firm conclusions.

Phase 2

As the new field of endocrinology began to emerge in the 1890s, the scientists of that time jumped on the band wagon and began to study blood to detect and measure "inner secretions" in an attempt to increase our understanding of many medical

conditions, including mental illnesses. Thus, this endocrinological approach was adopted by the first modern biological psychiatrists who were looking for a new approach in understanding the physical causes of psychiatric disorders. This was driven by the assumption that if an over or under production of "inner secretions" could lead to diseases such as diabetes (this secretion was identified as insulin in 1921 by Frederick Banting and Charles Best), which were accepted as diseases of a physical nature, then the same might be true of one or more of the psychiatric disorders. One German psychiatrist in particular, Emil Kraepelin (1856–1926), followed this approach doggedly and eventually developed the concept that severe psychotic disorders (he first called these "dementia praecox") were the result of a persistent whole body metabolic disease process which led to effects on the brain in the later stages, resulting in chronic mental "deterioration". It was from these ideas that Kraepelin became regarded by historians as a central figure in the history of modern psychiatry. Then, in 1908, a Swiss psychiatrist named Eugen Bleuler (1857–1939) proposed the new term "schizophrenia" as an expanded version of Kraepelin's dementia praecox. However, schizophrenia was meant to have a more favourable disease outcome. Nevertheless, only the term schizophrenia and not the original disease concept of Bleuler are accepted in the present day. For more than 100 years changes in the function of hormones and hormonal abnormalities in various psychiatric disorders have been detected and this remains a frequent finding today. The endocrinological paradigm also provided a direct link to the discovery of acetylcholine as the first neurotransmitter, by German biochemist Otto Loewi in 1921. We will see later how an upset in the balance of neurotransmitters plays a key role in the development of various psychiatric conditions.

Phase 3

In 1906, an immunoserodiagnostic paradigm emerged in psychiatric research. This was basically looking at immune factors in blood to help distinguish psychiatric patients from "normal" healthy subjects. This followed the development of the Wasserman reaction test for neurosyphilis, which was considered a breakthrough in biological psychiatry. This was important as it actually marked the first occasion in which a diagnostic blood test was used to identify a specific mental illness, commonly observed in asylums and known as "general paralysis of the insane". Following this, two German psychiatrists injected cobra venom into dementia praecox and manic-depression (bipolar disorder) patients. This showed that some patients had reactions to the toxin compared to healthy control subjects. However, these results were never replicated and their findings were later refuted.

Author's note: replication of results is paramount in all scientific studies. If they cannot be replicated, they never really happened.

This work was followed by a more influential immunoserodiagnostic test produced by a Swiss biochemist named Emil Abderhalden (1877–1950) and one developed by

the German psychiatrist August Fauser (1856–1938). Both of these tests were aimed at diagnosis of dementia praecox and manic-depressive conditions in comparison to healthy subjects. Again, none of these findings could be replicated and these tests were also cast into doubt. Nevertheless, over the last 100 years or so, changes in immune function and inflammation which can be detected in the blood have been linked to various psychiatric disorders through many lines of evidence and there remains no doubt about their involvement (at least at some level) in psychiatric disorders.

Phase 4

The development of blood tests for psychiatric illnesses in the twenty-first century has been attempted based on breakthroughs in the fields of genomics (the study of genes) and proteomics (the study of proteins). The way it works is that all cells of a particular organism contain the same genes (the genome). However, only specific sets of genes are expressed as proteins (the proteome) and this depends on specific factors such as the type of cell, the developmental stage of the organism or the presence of external factors like disease. As far as the genes are concerned, heredity has been shown to play in role in the development of different psychiatric disorders to varying extents. However, efforts at developing genetic-based diagnostic tests for most medical diseases including psychiatric illnesses have met with disappointment. Despite 20 years of extensive efforts, no single gene, or combination of genes, have been identified that could be linked to an increased probability of an individual developing any psychiatric disorder. Likewise, no studies carried out thus far have implicated a single protein as being causative in any of the major mental illnesses. However, a number of recent studies have suggested that such an effect may occur through effects on protein networks. This means that not one but multiple proteins may be affected in specific disorders. Therefore, there is considerable hope that specific patterns of altered proteins (proteomic fingerprints) can be found and linked to different psychiatric disorders (see later chapters).

Famous People with Psychiatric Disorders

The commonality of mental disorders is perhaps best illustrated by the number of famous individuals, past and present, who have been afflicted. Throughout history and contemporary times, many people with so called mental illnesses have contributed immensely to society and human culture. Despite their accomplishments, many faced stigma within their lives. One reason why many of these individuals may not be known to the reader is due to the fact that many of them have learned to cope and even conquer their demons. On the list below are many individuals who have made amazing contributions to the arts, sciences or the world of politics. There are of course many others but space limitations prohibit a more comprehensive list.

SCIENTISTS

Isaac Newton (25 December 1642–20 March 1727)
Field: Mathematician/scientist of the seventeenth Century, responsible for many scientific discoveries
Condition: suspected bipolar disorder, schizophrenia.
Nikola Tesla (10 July 1856–7 January 1943)
Field: physicist/inventor
Condition: suspected obsessive compulsive disorder
Albert Einstein (14 March 1879–18 April 1955)
Field: Physicist (Nobel Prize winner)
Condition: suspected Asperger syndrome
John Nash (June 13, 1928–May 23, 2015)
Field: Mathematician (Nobel Prize winner)
Condition: schizophrenia

ARTS/LITERATURE

Leo Tolstoy (9 September 1828–20 November 1910)
Field: Writer
Condition: depression, hypochondriasis, alcoholism and substance abuse
Vincent Van Gogh (30 March 1853–29 July 1890)
Field: Painter/artist
Condition: suspected major depressive disorder or bipolar disorder (death by suicide)
Louis Wain (5 August 1860–4 July 1939)
Field: Painter/artist
Condition: schizophrenia
Virginia Woolf (25 January 1882–28 March 1941)
Field: Novelist
Condition: bipolar disorder (death by suicide)
Ernest Hemingway (July 21, 1899–July 2, 1961)
Field: Novelist/Short-story writer/journalist (Pulitzer Prize and Nobel Prize winner)
Condition: depression (death by suicide)
Jack Kerouac (March 12, 1922–October 21, 1969)
Field: Novelist
Condition: dementia praecox (older term for schizophrenia)

MUSICIANS/COMPOSERS

Wolfgang Amadeus Mozart (27 January 1756–5 December 1791)
Field: Composer
Condition: suspected autism spectrum disorder (Asperger syndrome)
Ludwig van Beethoven (baptized 17 December 1770–26 March 1827)
Field: Composer
Condition: bipolar disorder
Brian Wilson (born June 20, 1942)
Field: Songwriter/musician
Condition: schizophrenia (although diagnosis later retracted)