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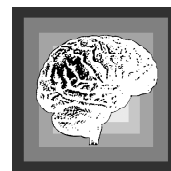
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Infectious insanities, surgical solutions: Bayard Taylor Holmes, dementia praecox and laboratory science in early 20th-century America. Part 1*

RICHARD NOLL**
DeSales University

After his 17-year-old son suddenly developed a chronic psychotic illness in 1905, Bayard Taylor Holmes (1852–1924), a Chicago physician and surgeon with no psychiatric training, conducted both library and laboratory research on dementia praecox, as described in Part 1 of this two-part study. By late 1915 he believed he had found support for a focal infection theory of its aetiology – an ergot-like toxemia caused by faecal stasis in the caecum. Holmes was also the editor of what is believed to be the first medical journal named after a psychiatric disorder: Dementia Praecox Studies. Part 2 will describe Holmes' adoption of a rational therapy (using it first on his son, who died), and his founding of a Psychiatric Research Laboratory.

Keywords: *autointoxication theory in psychiatry; Bayard Taylor Holmes; dementia praecox; focal infection theory in psychiatry; surgical treatments in psychiatry*

On 6 February 1905, Ralph Loring Holmes, a 17-year-old American boy visiting Jena, Germany, unexpectedly 'became sick',¹ and returned to the USA. The boy's father, although a noted Chicago physician, surgeon and medical professor, felt completely helpless when confronted with his beloved son's baffling condition. Following the advice of two physician colleagues,

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** Address for correspondence: Psychology Department, DeSales University, Center Valley, PA 18034-9568, USA. Email: Richard.Noll@desales.edu

the father placed Ralph in a private institution, 'where he was locked up, fed and restrained by pounds, actually pounds of sedatives'.² The diagnosis was dementia praecox. The boy would never recover from this illness, and it is listed on his death certificate as the official cause of his death at Lakeside Hospital in Chicago on 23 May 1916.³ Many death certificates of that era blamed dementia praecox for extinguishing the flame of life in mostly young, mostly male and mostly forgotten insane persons such as this one. However, unlike most victims of dementia praecox whose lives have faded into oblivion, the first psychotic break of Ralph Loring Holmes catalysed a chain of events in a heretofore lost chapter in the larger story of early twentieth-century American medicine: the laboratory science approach to discovering the causes of mental illnesses such as dementia praecox, and the development of rational treatments based on such laboratory findings.

The psychotic illness of Ralph Loring Holmes enters the history of American medicine and psychiatry through its influence on the life of the boy's father, Bayard Taylor Holmes (1852–1924).⁴ Holmes was personally devastated by his son's illness. His anguish was exacerbated by feelings of impotence, for although his professional life was devoted to improving medical education in Chicago, he had a complete lack of expertise in psychiatry. Holmes, however, had a combative nature and decided to tackle his ignorance and his son's illness head-on. Weary of relying on the advice of colleagues and some of the most respected psychiatrists in America while watching his son deteriorate further, Holmes semi-retired from his surgical practice and his position as Professor of Surgical Pathology and Bacteriology at the College of Physicians and Surgeons in Chicago to care for his son himself. He also vowed to use his scientific expertise to find both a cause and a cure for dementia praecox. He soon became a prominent advocate for reforms in the institutional care of the mentally ill, compiled a bibliographic collection of more than 8000 international scientific articles, dissertations and books concerning laboratory studies of dementia praecox, and from 1918 to 1922 was the editor of what is believed to be the first medical journal named after a psychiatric disorder: *Dementia Praecox Studies*.

Using equipment and bench space loaned by medical colleagues, in January 1915 Holmes began his own laboratory studies of dementia praecox. Within a few months, to his satisfaction, he hit upon a viable organic theory of the cause of dementia praecox. In the spring of the following year, 1916, he developed and experimented with a rational treatment based on this theory, applying it first on his own son who was suffering from dementia praecox, and testing it further on additional patients with dementia praecox between April 1917 and February 1918 at an experimental inpatient unit known as the Psychiatric Research Laboratory of the Psychopathic Hospital, Cook County Hospital, in Chicago, Illinois.

The organic aetiology of dementia praecox which Holmes believed he discovered was grounded firmly in medical theories that were popular during

World War I: autointoxication or focal infections located somewhere in the body that reached the brain and produced severe mental and physical disorders. His bibliography of publications in support of the autointoxication or focal infection theory of dementia praecox is perhaps the most comprehensive summary of this obscure literature in the history of psychiatry (Holmes, 1920). Holmes was not alone in positing such a theory: Emil Kraepelin (1856–1926) himself had speculated in the 5th–8th editions of his textbook, *Psychiatrie: Ein Lehrbuch für Studierende und Ärzte*, that such a process of autointoxication (*Selbstvergiftung*), possibly arising from the sex glands (and to which heredity made one vulnerable), was probably the true cause of dementia praecox (Kraepelin, 1896: 439; 1913, III/2: 931; 1987: 23; 1990: 154). The prominence of theories of autointoxication and focal infection in psychiatry in the early twentieth century has been surveyed elsewhere (Jahn, 1975; Noll, 2004; Scull, 2005) and need not be elaborated here.

The rational treatment that Holmes derived from his specific theory – abdominal surgery and daily colonic irrigations – claimed the life of the first dementia praecox patient in history to receive it as an experimental procedure. Ralph Loring Holmes died at the hands of his own father, a medical misadventure known at the time by family friends and some prominent medical colleagues, such as Adolf Meyer (1866–1950), but which has largely remained secret for almost 80 years.

In his recent book, *Madhouse: A Tragic Tale of Megalomania and Modern Medicine*, Andrew Scull (2005) details the story of Henry A. Cotton (1876–1933) of the Trenton State Hospital in New Jersey and his reliance upon radical surgical procedures to alleviate or ‘cure’ persons afflicted with severe mental disorders caused by focal infections arising in the mouth (from rotting teeth), the colon, the stomach, the thyroid, the cervix and other areas of the body. The story is a horrific one. However, although Scull’s tale is instructive about the reception and application of focal infection theory in America, it is incomplete. For example, although Cotton worked under Kraepelin in Munich for two years and certainly must have known of Kraepelin’s speculation that dementia praecox was probably caused by an autointoxication, this influence on Cotton’s later thinking is not explored. But more importantly for our purposes here, nowhere in Scull’s volume is there a mention of Bayard Taylor Holmes or the fact that it was Holmes – not Cotton – who was the first to attempt the surgical treatment of dementia praecox.

There is no evidence that these two men met or corresponded. However, Holmes knew of Cotton’s work by the early 1920s and was supportive of it, although he criticized the emphasis on the removal of teeth, organs or tissues rather than the daily colonic irrigations that his method offered (Holmes, 1921a: 137). Cotton never mentions Holmes in his publications, but probably knew of Holmes through his many publications or from their mutual colleague,

Adolf Meyer. Like Holmes, Cotton produced two sons, performing abdominal surgery on the second, Adolf Meyer Cotton, in a preventive measure to halt the development of any mental disturbance later in life (Scull, 2005: 58). He had already extracted the permanent teeth of both sons and, later, his wife. Unlike Cotton, Holmes had a deeply personal stake in finding the cause and cure of dementia praecox. Unfortunately, he suffered the sacrifice of his own son to achieve it. But any parent of a child with a devastating chronic mental illness would understand his complex motivations, for what is done out of love is beyond good and evil.

What follows, therefore, is essentially a contextualizing preface to Scull's gothic tale: the biographical and scientific case history of a forgotten man in the history of psychiatry. An examination of the life and work of Bayard Taylor Holmes provides us with a narrative perspective through which to view the application of early twentieth-century laboratory medicine to the devastating problem of dementia praecox. The literature in the history of psychiatry currently lacks scholarly studies of the important experimental researchers of dementia praecox during that era. In order to comprehend the rationale for his aetiological theory of dementia praecox and his treatments for it, I explore the various stages of his research programme in great detail. Such a narrative, I believe, also gives us insight into the creative space opened in psychiatry by theories of autointoxication and focal infection, a rich field of possibilities for medical experimentation that, in the pre-antibiotics era, perhaps could have only logically ended with surgical tragedies such as those brought about by Holmes and Cotton. Perhaps the same case could be made for the rise and fall of psychosurgery, when surgical solutions rationalized by basic neuroanatomical and neuropathological research in animals and humans captured the imagination of psychiatrists in the mid-1930s (Pressman, 1998). It is useful to remember, as Joel Braslow (1997: 4) argued, that 'during their heydays ... most of the therapeutic practices ... generally conformed to standards that constituted legitimate evidence for efficacy.'

Additionally, the story of Bayard Taylor Holmes also documents the influential role played by Adolf Meyer in the tacit promotion of focal infection theory in American psychiatry through his personal contacts with Holmes and Cotton and his uncritical acknowledgement of their rational treatments. Meyer is anchored at the centre of the Holmes story just as he is in the Cotton story, with not only Holmes but two of the researchers working under him, Julius Retinger and H. M. Jones, reaching out to Meyer for support at various stages of their research on the causes and treatments of dementia praecox.

In the following, I allow the events of the story of Bayard Taylor Holmes to unfold without significant embedding in the secondary scholarly literature. To keep the focus on Holmes, I make only occasional reference to the activities of Cotton as provided by Scull (2005) in his illuminating volume of narrative history. My intention is to punctuate the need for future scholarly

studies of focal sepsis in early twentieth-century medicine, to link Holmes and Cotton, and to treat these two men equally as flawed pioneers of biological psychiatry.

Why have Holmes and his *Dementia Praecox Studies* been forgotten?

There is a revelatory silence in the literature of the history of psychiatry about Bayard Taylor Holmes, his journal, his laboratory studies of the aetiologic and pathologic processes of dementia praecox and the experimental treatment unit in Chicago. All the major histories of psychiatry completely ignore him (for example, Shorter, 1997, 2005), and there are no publications that acknowledge his role in the story of the American laboratory science response to dementia praecox. The last scholarly publication devoted to Holmes and his place in the history of medicine appeared more than 20 years ago, and it, too, ignores his scientific solutions to the cause and cure of dementia praecox (Beatty, 1981). Indeed, even in his own time, neither his publications nor those of his research team in Chicago were cited by prominent figures in psychiatry and neurology. Why?

First and foremost, his professional credentials as a surgeon and bacteriologist and his utter lack of formal training in psychiatry may have been reason enough for the prominent alienists of his day to disregard Holmes and his work. Hence, with the passage of time, the historical trail grew cold. 'I know very well that I have no education or University training, such as your colleagues have, and that it is ridiculous for me to tell you what I think of your letter', he wrote to his old acquaintance Adolf Meyer on 19 February 1912.⁵ But perhaps more distasteful to alienists than a surgeon dabbling in psychiatry, Holmes had made it quite clear in numerous opinion pieces in medical journals such as *The Lancet-Clinic* from 1910 until his death in 1924 that he detested the psychiatric profession for its lack of interest in laboratory science and for making false claims to the unsuspecting public about scientific knowledge of causes and effective treatments. The frustrating experience of trying to find competent help for his son led him to charge that the psychiatrists of his time were not true physicians, but merely 'keepers':

... I am shy at using psychiatrist for a man who devotes himself to the professional custody of the crazy and yet denies that they suffer of disease or that there is any need of pathological study of their condition or any hope of cure ... I prefer to term them keepers of the insane rather than physicians. It seems to me that a group that denies to dementia praecox a place among diseases and disparages it by relegating it to the 'reactions' can not claim to be psychiatrists in the medical sense. (Holmes, 1922a: 120)

This did not win him the respect of psychiatrists, and they responded by refusing to cite his published work and by leaving him out of the histories of

their profession that they would subsequently write. Additionally, Holmes was exceptionally out of step with the changing political tide in professional psychiatry by being a vocal sceptic of Sigmund Freud and psychoanalysis. 'It is a distinctly mystical theory,' he wrote in 1914, 'insusceptible of either proof or refutation' (Holmes, 1915a: 96). Holmes also rejected the Meyerian notion that dementia praecox, like all other mental disorders, was a 'reaction' to psycho-biosocial forces. He additionally believed Meyer used a deceptive style of idiosyncratic psychiatric jargon to divert attention away from the fact that little laboratory research on dementia praecox was being conducted in the best psychiatric institutions in the country. 'You are probably the most respected man in psychiatry in the United States and what you say ought to mean a lot to me', Holmes wrote to Meyer in 1912, just before accusing him of being deliberately evasive: 'As a matter of fact, I cannot understand hardly anything in your letter and I believe that some of it, in spite of its interrogatory form, is designed to deceive.'⁶ Holmes (1916a: 983) was also a critic of eugenics, which he referred to as a 'pseudoscience'. This, too, set him apart from contemporary trends in science and from prominent figures in psychiatry and neurology associated with the Eugenics Records Office such as Meyer and E. E. Southard (1876–1920), though he maintained superficial professional contacts with both these men.

'The laboratory will show up a false teacher in the shortest time'

Bayard Taylor Holmes found his way to medicine rather late in life. He was 30 years old when he entered the Homeopathic Medical College in Chicago in the autumn of 1882. Having spent the previous ten years teaching science in the schools of Kendall, De Kalb and La Salle counties in Illinois, Holmes began an aggressive self-education programme that went far beyond his formal training. He received his M.D. from the Homeopathic Medical College in 1884, interned for 18 months at Cook County Hospital, then entered the College of Physicians and Surgeons in the autumn of 1885 for further medical training. He received his second M.D. from this institution in the spring of 1888, just before his 36th birthday.

Holmes began his training just as the bacteriological breakthroughs of Robert Koch and others offered the possibility of challenging new career paths for scientifically ambitious medical students. Although he was already no stranger to microscopic work and was, of course, aware of the work of Pasteur and Koch, a single chance event steered him in the direction of bacteriology. While on his way to a series of histological lectures at the Rush Medical College in the summer of 1883, Holmes happened to see a notice for a lecture on tuberculosis accompanied by an autopsy to be given by W. T. Belfield at the County Hospital Morgue. Having just returned from Europe, Belfield summarized the latest developments in bacteriology. The lecture ended with Belfield inviting the medical students in the audience

down to his side to observe as he squeezed fluid from the lungs of a cadaver, smeared a specimen from it on a glass microscope slide, then gave these curious students their first look at *Bacillus tuberculosis*.

Profoundly moved by the experience, Holmes initiated a course of activity that eventually led to a position in 1885 as an assistant to Christian Fenger (1840–1902), a noted pathologist who had introduced Lister's antiseptic operative methods to the staff of Cook County Hospital in 1878 and who was then Professor of Surgery at the College of Physicians and Surgeons in Chicago (Herrick, 1941). Holmes had made an impression on Fenger in 1884 when he was the first to show Fenger microbes growing in nutrient material. Fenger had had no experience with the techniques of cultivating bacteria, and he responded to the sight with 'childlike delight' (Hektoen, 1937: 5). Holmes' bacteriological work and his association with Fenger opened doors for him in Chicago. In 1889 Holmes became attending surgeon at Cook County Hospital, and in 1891 he was appointed Professor of Surgical Pathology and Bacteriology at the College of Physicians and Surgeons. Holmes personally oversaw the design and construction of a six-storey laboratory building at the College, and his advocacy of laboratory science in medicine influenced medical training not only at the College but also at other medical schools in the USA. In the opinion of Holmes, a professor of medicine held little credibility unless he could hold his own at the laboratory bench. 'A man can easier preach without being converted', Holmes writes, 'than he can preach without being inspired, and the laboratory will show up a false teacher in the shortest time' (Beatty, 1981: 123).

Together with Fenger, Holmes wrote 'Antisepsis in abdominal operations. Synopsis of a series of bacteriological studies', published in the *Journal of the American Medical Association* in October 1887 (Fenger and Holmes, 1887). This was Holmes' second publication and it is remarkable for introducing two professional preoccupations that became very personal ones. Indeed, during the years of World War I, they would frame the fateful trajectory of his work on dementia praecox: infections as causes of disease and abdominal surgery as a cure of disease.

'130,000 pitiable wrecks'

Bayard Taylor Holmes married Agnes Anna George on 14 August 1878. Their first child, Bayard Taylor Holmes, Jr, was born in 1879 and, following in the tradition of his namesake, became a physician in Chicago. Their only other child, Ralph Loring Holmes, was born in Chicago in 1887. He was a highly intelligent young man who could read both German and Latin, and spoke German fluently in addition to his native English.⁷ Ralph, too, was expected to become a physician. However, it was during the middle of his first year of medical school that Ralph was unexpectedly disabled by his illness. Unfortunately, he then quickly became, as his father put it in 1918,



BAYARD HOLMES, M.D., 1889

(From *Medical Life*, 31 (1924), Issue 46, devoted to Bayard Holmes)

one of 'the 130,000 pitiable wrecks' suffering from dementia praecox who were periodic inmates in approximately 'four hundred hospitals for the insane' in the USA (Holmes, 1918b: 5).

The psychotic breakdown of his beloved younger child awakened Holmes to the extreme prejudice against the mentally ill, not only in society as a

whole but also among his colleagues, close friends and even his own family. Despite his disregard for Adolf Meyer's professional opinions, Holmes was grateful for a letter Meyer wrote in response to Holmes' increasingly polemical editorials and articles about the deficiencies in the care of persons with dementia praecox. In fact, Meyer's letter was the first response from anyone in the field of psychiatry. Holmes' reply to Meyer, dated 19 February 1912, is worth quoting at length here.

I am grateful to you for the first letter which my editorials or reprints have brought forth. At the end of your letter you refer to the calamity to my son Ralph. A few days after the boy was taken away to Jacksonville, I had a beautiful and helpful letter from Doctor Bertram Sippey [Sippy, a Chicago physician], who had undergone a similar experience. Yours is absolutely the second letter from any person, except Ralph's attendants, in which his existence or misfortune has been mentioned. My own scattered family in their numerous and intimate letters to me have never once during these six terrible years mentioned his name or recognized by holiday token or birthday present his past or present existence. Not one of my medical friends in Chicago and elsewhere, many of whom in their family bereavements or professional misfortunes, have called upon me for sympathy and sometimes for succor, rendered at my own great risk, not one of them have volunteered me by letter or by word of mouth in all these terrible years, one single inquiry for my boy or one suggestion of sympathy or token of support. The dozens of internes and assistants and the hundreds, even thousands of students, and I may say, the public itself which has been entertained so freely at my house, not one of them has ever once written me one word of sympathy or recognition of the catastrophe which ruined my son and has taken away my own zest of life.

In my first helplessness I called on two colleagues, who advised in a cold and fateful manner, and withdrew. I followed implicitly their advice, yet they have never asked me how this advice eventuated. Ralph was put in a private institution, where he was locked up, fed and restrained by pounds, actually pounds of sedatives, as his history shows.

At this time I wrote a letter to the two acquaintances whom I considered most likely to offer helpful advice. They were both men most distinguished in their particular spheres. It would be hard for you to imagine with what anxiety I watched for days and weeks for some answer to those two letters which might relieve my imprisoned hopes, but until today none ever arrived. Professor Jacques Loeb, of California, likely thought my request impertinent, and in your letter today you say that you sent me literature at the time.

It seems hardly likely to me that had I had a daughter and she had blazonly gone into public prostitution, would my colleagues have been as silent.⁸

During the first year of his son's illness, Holmes threw himself into his work and relied on his 'most distinguished colleagues in the United States' for advice rather than doing any reading on dementia praecox himself.

They gave one cheerless and discouraging reply, if they did not hedge or neglect to answer. They agreed to a man that the disease was of unknown pathology, unknown etiology and of an invariably unfavorable prognosis. Hopeless custody was the substitute for treatment.

But when Ralph returned home after spending 8 months in a private sanitarium, Holmes decided to use his expertise to find the cause of his son's devastating illness and to save him by finding a cure. He began visiting psychiatric institutions and was horrified when he finally saw the inmates on the 'back wards':

When at last I discovered the result of the disease, the realization of the victims' pathetic condition threw me into a new frenzy. Terrible as my affliction was already my agony had not yet begun. So this was to be my son's end! (Holmes, 1921a: 120)

Holmes gradually retired from teaching but continued his medical practice and began a review of the medical literature on dementia praecox. His first impression of the scientific status of psychiatry appalled him.

It will be impossible for you to imagine my astonishment and confusion on reading text books, journals and monographs to find that in this branch of medical literature, the same method, the same argument and the same obscurity prevailed as in the literature of religion and occultism.⁹

By 1920 Holmes had compiled more than 8000 references on the pathological, biochemical, histological and bacteriological laboratory findings on dementia praecox. He kept these references in a card catalogue which he donated to the John Crerar Library at the University of Chicago. This database would prove to be of decisive importance to Holmes when he returned to the laboratory to do the critical work himself. Holmes never lost his certainty that clues to the aetiology, prophylaxis, therapy and eventually cure of dementia praecox were somehow buried in this gigantic and seemingly disconnected body of evidence. To Holmes, continual consultation of the medical literature was as necessary for a practising physician as clinical experience and basic laboratory skills (Holmes, 1893). The problem that plagued him for years, however, was how to discern which of the thousands of published laboratory findings on dementia praecox led to the truth about this disease. One new lead after another was followed and then abandoned in favour of the latest new laboratory technique or organic finding. As Holmes frantically tried to master this immense literature and begin his own laboratory studies, the years rolled by and Ralph Loring Holmes continued to deteriorate.

Dementia Praecox Studies

Holmes turned his revulsion for the psychiatric treatment of his son into a public crusade. He was temperamentally well suited for this. As a man of

rather benign rural origins, Holmes had been appalled at social conditions in Chicago when he moved there to attend medical school. He was especially angered by the living and working conditions of immigrants and the poor. He involved himself in issues such as the education of illiterate workers, the inspection of safety conditions in factories, and child welfare. He founded an organization called the National Christian Citizenship League which recruited volunteers to engage in various social welfare projects among the destitute of Chicago. His social conscience led him into politics, and in 1895 he was the unsuccessful Chicago mayoral candidate for both the People's Party and Socialists of Eugene Debs, coming in third behind George Bell Swift. 'He is a man of moods', reported a Chicago newspaper in the days following Holmes' nomination, continuing:

The doctor's personal peculiarities are intense. He is a fighter when aroused, and frequently it takes very little to arouse him. He has been known mercilessly to flay with tongue or pen those with whom he differed or whom he thought deserved a flaying as a matter of principle.¹⁰

Three years after his son Ralph became ill, Holmes published his first clinical article with a psychiatric theme when he wrote a warning about the use of chloroform with dementia praecox patients' (Holmes, 1908a). However, it would be several years before he published further clinical contributions in psychiatry. Instead, he used the pages of the Cincinnati-based medical journal *The Lancet-Clinic* as his bully pulpit and wrote one short essay after another deploring the conditions in state hospitals, demanding more state funding for laboratory research on dementia praecox, and denigrating just about every prominent school of thought in psychiatry. The first eight of these essays appeared in 1910, but Holmes, mimicking Sir William Osler (Tigertt, 1983), used the pseudonym 'E. Y. Davis, M.D.' for them. He continued writing editorials for this journal until 1916. These essays were collected and published under his actual name in two volumes: *The Friends of the Insane, The Soul of Medical Education, and Other Essays* (Holmes, 1911) and *The Insanity of Youth and Other Essays* (Holmes, 1915a). Beginning in 1914, Holmes sent out reprints of his articles as circulars under the heading *Dementia Praecox Studies*. He also became peripherally involved in the mental hygiene movement.

During the annual meeting in Chicago of the Alienists and Neurologists Association, held 10–12 July 1917 – the year after his son's death – Holmes lobbied for the creation of an organization to study dementia praecox (Holmes, 1917). However, although several prominent conference participants signed the initial petition, only Holmes' Illinois colleagues committed themselves to the proposed organization. On 13 July 1917 Holmes was joined by two Illinois physicians, Hermann Campbell Stevens of Chicago and George Michell of Peroria, as elected officers of the Society for the Study of Dementia Praecox. The purpose of the society was 'to stimulate further

research and to co-ordinate work already in progress in different parts of the world' (Holmes, 1918a: ii). The main method for achieving these goals was the publication of a quarterly scientific journal that would be distributed internationally: *Dementia Praecox Studies: A Journal of Psychiatry of Adolescence*.

In the opening pages of the inaugural issue (1 January 1918) of *Dementia Praecox Studies*, the editors unabashedly expressed their 'faith' in the hypothesis that 'disease of the mind is the result of organic disease of the body', and as 'in spite of the magnitude of this problem there is a great scarcity of books and monographs dealing with the physical, chemical and biologic conditions of the unfortunate victims of this disease', they 'urge the publication of a journal devoted exclusively to the study from the organic point of view, of one part of the field of mental disease, viz., dementia praecox' (Holmes, 1918a: ii).

Dementia Praecox Studies continued to be published through five volumes, ending in 1922 when Holmes' health began to fail. During these five years it included a wide range of articles on dementia praecox, many of them republished or translated from international journals. Unfortunately for Holmes and his colleagues, the journal had little impact in accelerating research. But fortunately for historians, it chronicles the path of his own research in the cause of dementia praecox, the rise and fall of one dementia praecox research laboratory and the failed plans for two others, and the results of the experimental treatment that Holmes devised and believed until the day he died was more effective than anything psychiatry had to offer.

'The blood crisis ... is sudden, almost explosive'

Like many physicians of his era who were trained in the new science of bacteriology, Holmes believed that each disease had a single cause and single cure. Rationally discover the cause of the disease in the chemical, bacteriological, haemolytic or physiological laboratory, and a rational treatment or even a cure would soon follow. Dementia praecox would yield its secrets just as tuberculosis, syphilis, yellow fever, typhus and cholera had done in Holmes' lifetime. He was convinced from his earliest bibliographic researches that dementia praecox was a physical disease with an organic, mechanistic aetiology. Psychogenic causes for dementia praecox were not rational ones in his opinion, and therefore he completely discounted them. Holmes could not discount the role of heredity in the insanities, but he felt that these distal influences were secondary to more powerful, ongoing proximal causes in dementia praecox that could be found in living bodies and effectively treated. The theory of the hereditary cause of dementia praecox should, he felt, therefore be taken with a grain of salt. He often illustrated his position by arguing that heredity also had been considered the greatest aetiological factor in pulmonary tuberculosis and syphilis until the discovery of their respective pathogenic bacteria led to the abandonment of that theory.

By the winter of 1909, Holmes' literature review of laboratory studies of dementia praecox had led him to conclude that 'most of the investigations came to zero for their aggregate result' (Holmes, 1921a: 121). However, he felt that there were eight firm findings in the literature: (1) the identifying symptoms of the disease were well described and could lead to a reliable diagnosis after a single observation of the patient; (2) the prognosis for recovery was uniformly poor; (3) spontaneous recoveries were rare; (4) many dementia praecox sufferers improved, and some completely recovered, following an acute infectious disease accompanied by a high fever; (5) brain weight was heavier in dementia praecox than normal; (6) chronic cases of dementia praecox often manifested left-sided internal hydrocephalus; (7) no fundamental histopathology of dementia praecox had been discovered and its existence was often denied; (8) in several highly suggestive cases, rapid polycythæmia (an increase in the number of red cells in the blood) resulted in an alleviation of symptoms in dementia praecox, especially if the red cell count increased by 2 million within an hour.

This last finding particularly intrigued Holmes. He had been following with fascination the transformation of the clinical laboratory since 1900 brought about by the serological and immunological contributions of Karl Landsteiner (1868–1943) and those of others, such as August Wasserman (1866–1925) and Emil Abderhalden (1877–1950), who followed in his wake. When Much and Holtzmann (1909) published their study of differences in reactivity to cobra venom of the blood of dementia praecox patients when compared with normals, Holmes was encouraged. Blood changes measured in dementia praecox victims were, in Holmes' mind, convincing evidence – especially to himself – that persons such as his son Ralph were 'really sick' due to a recognized organic disease rather than a psychogenic mind twist or hereditary taint (which, of course, would locate the cause of his son's illness directly in Holmes himself).

Blood held the secret to solving the mystery of dementia praecox. Therefore, in congruence with his training as a bacteriologist, between the years 1909 and 1916 Holmes largely followed a *serological* programme in his search for a cause of dementia praecox.¹¹ From this point on he was intrigued by spontaneous rapid changes in the relative numbers of red and white cells in the blood – a phenomenon termed a 'blood crisis' – particularly if they were linked to specific diseases and not found in normals. Holmes found the work of two dementia praecox researchers particularly relevant in this regard. The first, Halvar Lundvall of Lund, had reported in Swedish publications as early as 1907 some initial success in improving the symptoms of dementia praecox patients by injecting them with sodium nucleate (salts of yeast acids used in the treatments of anaemia, rheumatism and gout) (Lundvall, 1915). Sodium nucleate had long been known to increase the number of white blood cells (leucocytosis) and had been used by others with success in the treatment of septicaemia and paresis, and the fact that it

seemed to work in dementia praecox suggested its symptoms, too, might be due to an infectious process, perhaps even a bacterial one (for a review of this literature, see Holmes, 1915*b*). The second, Gunnar Kahlmeter (1914) found that very abrupt changes in the relative numbers of white blood corpuscles, red blood corpuscles, and the percentages of the neutrophile leucocytes, lymphocytes and eosinophile cells could be directly correlated to disturbed mental states. 'The blood crisis of Lundvall and Kahlmeter is prognostic of change in the mental symptoms and this crisis is sudden, almost explosive', wrote Holmes (1916*b*). Holmes was also fascinated by the studies of Willi Schmidt (1914) in which the typically low blood pressure of dementia praecox patients (or so it was assumed at the time) could not be raised by an intramuscular injection of 0.5 cc of 1:1000 adrenalin solution. Holmes (1915*c*) suggested that adrenalin injections could be a possible diagnostic test for dementia praecox since they produced this paradoxical response.

In January 1915 Holmes returned to the laboratory to do his own serological work on an intermittent basis with a colleague, Peter Gad Kitterman (1877-?). Holmes and Kitterman (1914) had co-authored a short amateurish monograph on ancient Egyptian medicine. At first they had no laboratory of their own, nor any money for their own equipment, so from 1 January to 1 April 1915 they used a laboratory room at the Ricketts Laboratory in Chicago belonging to Dr H. Gideon Wells, Director of the Otho S.A. Sprague Institute and a researcher at the University of Chicago. This work was conducted during off hours whenever they could steal the time from their busy lives. Holmes knew it was to be the beginning of a long research programme: 'My first thesis was to demonstrate the first evidences of disease in dementia praecox patients and the absence of the same evidence in other patients.'¹²

The decisive factor in the return of Holmes to the laboratory was his discovery in late 1913 of the techniques of the Abderhalden defensive ferment reaction and the fact that it has been used diagnostically with some success by European researchers in Germany and Italy. Holmes was particularly convinced by the claims of Stuttgart researcher August Fauser (1856-1938) that Abderhalden's test could differentially diagnose dementia praecox from other disorders and from healthy controls (Fauser, 1912, 1913*a*, 1913*b*, 1913*c*). 'Here then, it seems that we have found an almost certain, if not absolutely certain, method of diagnosing dementia praecox', Holmes (1914*a*: 250) enthused in a short medical report published on 12 February 1914. The dialysing method of Abderhalden purported to recognize in the blood specific defensive ferments (enzymes) connected with specific protein molecules that formed the basis of specific organs or glands. If cells of an organ or gland are injured (such as the brain, liver, heart, lungs, appendix, thyroid or gonads), molecular detritus ends up in the blood and this arouses a reaction, that is, production of the defensive ferments which catabolizes or breaks down these molecules into ones small enough to be eliminated by the body. The specificity of the 'positive reaction' of the

ferment in the Abderhalden dialysis method was thought to be directly linked to damage to specific parts of organs, including very specific areas of the brain. For example, a colleague of Holmes consistently found positive reactions in 'the lower part of the motor area in the cortex corresponding to the trunk shoulders, arms and in a lesser degree that representing the head.'¹³ Therefore, just through drawing the blood of a patient and analysing it, it was assumed one could 'see' into the living body without opening it surgically and be able to discern focal areas of disease.

At the Ricketts Laboratory, Holmes reported he 'examined the blood of seventy lodging house tramps by the defensive ferment reactions of Abderhalden' and found that 'the blood of the average tramp does not contain ferments that would lead to the diagnosis of dementia praecox' because 'these bloods did not give reactions to the cerebral cortex or to testicle' as had been found and reported in the European studies.¹⁴ From 1 April to 1 August 1915 Holmes continued his studies in a laboratory at Lakeside Hospital in Chicago, but added a new experiment: taking blood from a dementia praecox patient (probably his own son, Ralph) and injecting it into a goat and a rabbit to see if the 'passive transmission of the defensive ferments' could be accomplished. It was. However, since Holmes did not have any blood from a 'recovered patient', the defensive ferment against the cause of dementia praecox could not be injected into an animal for the purposes of producing a serum against the disease to be used later in humans if the animal also began producing these same defensive ferments.¹⁵

However, by his own admission, his application of this complex technique was rather crude. This problem was soon rectified. On 1 August 1915 they were joined by a skilled biochemist, Julius Retinger, PhD (1885-?), who had received his degree from Leipzig in 1913 for a thesis on a method of preparing ninhydrin, an essential component of one of the various procedures for the Abderhalden reaction test. Holmes was given the money to pay for Retinger's services by a grateful former patient. But it was only a small amount, and also Retinger could only work part-time on finding the cause of dementia praecox. The hiring of Retinger coincided with Holmes' move to the laboratory of the Psychopathic Hospital of Cook County Hospital at the invitation of Adam Szwajkart, M.D., its Director. The Psychopathic Hospital, which had opened in 1914 and which occupied a corner of the Cook County Hospital grounds at Wood and Polk Streets, averaged about 80 psychiatric admissions per week who remained only a few days before being released or transferred to various Illinois state hospitals.¹⁶ Thus, Holmes and his new colleague Retinger now had daily access to a rich supply of dementia praecox subjects for their studies.

During the last five months of 1915, Retinger devised an 'improvement' on the Abderhalden method and examined 30 dementia praecox patients, concluding 'it can now be seen that the organs mostly involved in dementia praecox are the cerebral cortex, pons, optic thalamus, genital organs, and the

small intestine.¹⁷ With reliably replicated results such as these, the Abderhalden reaction seemed to be a breakthrough in psychiatric research.

The problem with the Abderhalden reaction test, as many researchers soon discovered, was that it was not a quantitative test, but a subjective one. The reaction was 'real' only if tissue from a particular organ gave off a bluish or purplish colour during the process. Some researchers always saw the colour, a few more sometimes saw the colour, but many others never did – and the doubters eventually began to speak out against Abderhalden (Deichmann and Müller-Hill, 1998). By 1920 Abderhalden's defensive ferments had fallen into general disrepute in the USA, although the test continued to be used in Germany for several more decades (Kaasch, 2000) and, until the end of his life, Holmes would never lose his faith in the method. But by the end of 1915 the Abderhalden test had already outlived its usefulness as a source of new knowledge. Based on Retinger's research, Holmes believed it had repeatedly confirmed which internal organs were implicated in the aetiology or pathophysiology of dementia praecox. Its further use would be redundant. Also, it had not led to the development of a serum that would cure dementia praecox, as had been hoped (Holmes, 1914*b*). Other methods were needed to detect the true *vis morbi* of dementia praecox, the cause of the 'blood crisis' and other unusual physiological phenomena.

How Holmes found the cause of dementia praecox

In January 1915, the month that Holmes began his laboratory studies and completed his preface to *The Insanity of Youth and Other Essays*, he was confident that he had identified a cluster of five organic signs that, taken together, were pathognomonic of dementia praecox: (1) adrenal mydriasis (pupil dilation produced experimentally by two or three drops of adrenalin solution); (2) cyanosis, particularly in the hands; (3) the blood crisis of Lundvall; (4) the positive reactions of the defensive ferment test of Abderhalden for the sex glands, thyroid and cerebral cortex; and (5) the positive response to artificial hyperleucocytosis induced by injections of sodium nucleate (Holmes, 1915*a*: 44–53). What was missing was an adequate pathologic '*disturber*', as Holmes often put it, that would link all these physical phenomena to an underlying cause.

It was Holmes' careful reading of the medical literature that provided him with the clues. While searching the literature for parallels to the paradoxical lowering of the already chronically low blood pressure in dementia praecox patients with adrenalin injections, Holmes found an animal study in which this phenomenon could be produced – but only if the injection of adrenalin followed a prior dosing with ergotoxine (tyramine). Since ergot was then commonly used to induce uterine contractions, Holmes found this same paradox occurred in obstetrical cases. Women who had been given ergot or peturiterin and then injected with an adrenalin solution (5 cc of 1:1000) had

their blood pressure lowered. Thus, in the winter and spring of 1915, Holmes began an intense study of the chemistry of ergot and the history of epidemic ergotism. It was this latter literature that led him to consider a connection between the toxic amines of ergot and the symptoms of dementia praecox – an analogical transfer familiar in studies of the history of science in which a previously solved medical problem (in this case, ergotism) serves as a source for solving a new target problem (Thagard, 1999: 134–47), in this case the illness of his son and others diagnosed with dementia praecox.

Of the ten or more toxic amines in ergot described in the biochemical literature of that time, Holmes seized upon histamine (beta-iminazolyethylamine) and indolethylamine as possible pathogens capable of producing the symptoms of dementia praecox. But it was histamine in particular that attracted his attention. In June 1915 he published a paper in which he detailed the striking similarities of the physiological effects of histamine on the body to the symptoms of dementia praecox (Holmes, 1915*d*). Histamine lowered the blood pressure and produced various effects on the conditions and number of the red and white corpuscles in the blood, similar but perhaps not identical to the blood crisis of Lundvall. And since cyanosis and adrenal mydriasis also occurred in persons who had ingested ergot, four of their five core pathognomonic signs of dementia praecox could be explained by the actions of the toxic amines found in ergot, particularly histamine. The fifth sign, the results of the Abderhalden test, could not be used to detect toxic amines in the blood. Other research methods needed to be found.

Serological analysis allowed for the detection of evidence of an excess of indolethylamine in the blood, but not for histamine. Urine tests were inconclusive. Holmes and Retinger – who had been hired specifically to pursue the ergot-like toxic amine hypothesis of Holmes – found literature documenting the presence of catabolized products of indolethylamine in the urine but, again, histamine could not be detected. Since their theory of the cause of dementia praecox depended heavily on the assumption of ‘hyper-histaminemia’, they were running out of options. Finally, in work conducted during the latter half of 1915 and early 1916, as Holmes and Retinger told it: ‘The examination of the feces alone was left to us. If there had been excessive production of histamine in the intestine from any cause, bacterial or non-bacterial, “endogenous” or “exogenous,” some moiety of this excess might be found entangled in the stool.’ And so it was. Retinger found no histamine in normal controls and in ‘one perfectly sane patient’ who had spent three years in an asylum with catatonic dementia praecox. However, in seven patients from the Psychopathic Hospital of the Cook County Hospital, the six dementia praecox patients had excessive amounts of histamine as did one patient with the ‘gastric crisis of tabes’ (Holmes, 1921*a*: 130; see also Holmes and Retinger, 1916*a*). When this last patient was injected with adrenalin the gastric pain stopped immediately and the blood pressure dropped – the same paradoxical effect found in people who had ingested

ergot and in dementia praecox patients. This patient provided another clue: they found a tender spot on the right side of the patient's abdomen. Was this the locus of an infectious process that sent poisons to the brain?

Evidence found in the medical literature supported their hypothetical locus of infection. They also learned that other researchers had found that *Bacillus aminophilus intestinalis*, a bacterium discovered in the caecum, reduced histadine to histamine. All the pieces fitted.

Holmes was now on familiar territory. He was a specialist not only in bacterial infections but also in the organs of the abdomen. His 10-year quest to find a cause and a cure for dementia praecox that had begun in 1906 brought him right back to his major areas of expertise as a physician and scientist. His autodidactic mastery of the gigantic and confusing medical and psychiatric literature, his years of consultations with alienists, neurologists and other medical colleagues, his data resulting from the adoption of new laboratory methods – all of these disparate sources of evidence now made sense when Holmes assimilated them to his pre-existing cognitive schema. Perhaps this trajectory was inevitable. Indeed, as early as 1908 Holmes speculated that, 'It is my opinion that there are many cases of insanity which are due to exogenous toxemia that should be sought for in the infection of some of the natural cavities of the body' and that the infection may be 'possibly of bacterial origin' (Holmes, 1908*b*: 8).

Similar odysseys by laboratory researchers looking for the causes and cures of dementia praecox had all ended in shipwrecks. The vast majority of those scientists moved on to other, more fruitful voyages at the bench. But not Holmes. Because of the constant reminder of his son Ralph's illness, Holmes was simply not going to give up. He was going to *comprehend* dementia praecox. And with this knowledge he was going to save his son.

With these new clues to the puzzle, Holmes worked fast. Getting the co-operation of Cook County Hospital for technical support, during the late months of 1915 he and his colleagues began to use the (then) relatively new technique of the fluoroscope to observe barium meals being passed through the digestive system. It was quickly determined that in dementia praecox patients it took 60–120 hours to pass a barium meal, but only 4–6 hours for normal controls. The barium meal tended to be stuck in the caecum and proximal colon for this abnormally long time in dementia praecox patients. A spasm of the sphincter of the colon – the 'ring of Cannon' – was blocking the passage of the meal. Holmes believed to the end of his life that this was his greatest single scientific contribution to the world, and in the article 'The relation of cecal stasis to dementia praecox' (sent to *The Lancet-Clinic* in April 1916 but not published until 12 August), Holmes and Retinger (1916*b*: 147) wrote: 'Therefore, *the time necessary for the development of the toxic amines is furnished by the stay of the residue in the cecum*' [original italics]. This article confirmed identical theoretical speculations they had made in print as early as January of that year (Holmes and Retinger, 1916*a*).

Holmes had found the mechanisms of dementia praecox: ergot-like toxic amines produced in the caecum that poisoned many organs of the body, including the brain. The poisoning of the brain resulted in a mental disorder with psychotic symptoms. All the sufficient links in the mechanistic causal chain were present. And in Chicago some very important physicians, politicians and benefactors had noticed and were offering to help Holmes fulfil the next logical step: the establishment of a laboratory and experimental unit where new treatments or even a cure for dementia praecox could be realized. This will be described in Part 2

Notes

1. This is the expression used by the parents of Ralph Loring Holmes on the elegantly printed 3×5-inch linen card announcing his death: 'Ralph Loring Holmes / son of / Dr. Bayard T. Holmes and Agnes A. George Holmes / Born May 25th 1887 in Chicago / Became sick February 6th 1905 in Jena / Died in Chicago May 23rd 1916.' Adolf Meyer Collection, The Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions, Baltimore, MD [hereafter AMC].
2. Bayard Holmes to Adolf Meyer, 19 Feb. 1912. AMC.
3. State of Illinois, State Board of Health, Bureau of Vital Statistics, Standard Certificate of Death, Registered No. 15352. The 'Standard Certificate of Death' of Ralph Loring Holmes indicates he died at 1 a.m. on 23 May 1916 at Lakeside Hospital in Chicago. He had been attended there from 16 May to 23 May by A. R. Johnstone, M.D., who signed the certificate. The cause of death was listed as 'dementia praecox'. But under the section for 'contributory (secondary)' causes of death, Johnstone wrote: 'Cecostomy – acute dilatation of stomach (Duration) 4 ds.'
4. Biographical details on Holmes can be found in the following: Beatty, 1981; Malone, 1932: 161; Watson, 1896: 48. Holmes contributed biographical as well as autobiographical pieces to the monthly journal *Medical Life*, edited by Victor Robinson, M.D. The July 1924 issue of *Medical Life* (Volume 31, Issue 46) was designated the 'Bayard Holmes Number' and contains two autobiographical papers by Holmes.
5. Bayard Holmes to Adolf Meyer, 19 Feb. 1912. AMC. Meyer spent two years (1893–95) in Illinois as a Docent in Neurology at the University of Chicago and as a pathologist for the Eastern State Hospital for the Insane in Kankakee, Illinois, and knew Holmes and other major figures in Chicago medicine. Adolf Meyer had written to Bayard Holmes, 17 Feb. 1912: 'Somehow I have always maintained a warm feeling for you as one of my early acquaintances. ... When I heard your son was ill, I really thought often of what might be done for him.' AMC.
6. Bayard Holmes to Adolf Meyer, 19 Feb. 1912. AMC.
7. Bayard Holmes to John Spurgeon, 31 Mar. 1916. Crerar Ms. 099, Special Collections Research Center, University of Chicago Library, Chicago, IL [hereafter SCRC].
8. Bayard Holmes to Adolf Meyer, 19 Feb. 1912. AMC. Meyer told Holmes in subsequent correspondence that he did not remember where he had first heard of Ralph's illness, and offered to review Ralph's treatment records from the Psychopathic Ward of the University of Michigan Hospital in Ann Arbor, Michigan. Both Holmes and Meyer then contacted its director, Albert M. Barrett, for his clinical notes on the case. See Adolf Meyer to Bayard Holmes, 21 Feb. 1912; Holmes to Meyer, 24 Feb. 1912; Meyer to Holmes, 27 Feb. 1912, Crerar Ms. 093, SCRC.

9. Bayard Holmes to Adolf Meyer, 19 Feb. 1912. AMC.
10. An unidentified and undated clipping from a Chicago newspaper ('He Is A Man Of Moods – Dr. Bayard Holmes, the Populist Candidate is A Remarkable Person') in the scrapbook Holmes compiled containing flyers for political events, newspaper clippings and other memorabilia from his unsuccessful 1895 Chicago mayoral campaign, Crerar Ms. 096, SCRC.
11. Holmes (1911: 37–42, 43–50) had argued for the application of modern serological techniques to psychiatry in two early essays, 'Serology in psychiatry', and 'The condition of the blood in the insane'.
12. Bayard Holmes, 'Dementia Praecox Studies. Report of One Year of Work in Research in Dementia Praecox' in 'First Annual Report of Dementia Praecox Studies Conducted by Bayard Holmes, M.D., Chicago, December 21, 1915', p. 2. Other contributions to this report are: J. Retinger, 'Report of laboratory work from August 1st to December 30, 1915', pp. 8–21; and W. H. Solle, 'Literary propaganda', pp. 22–9. Unpublished typescript, 55 pages; John Crerar Library, University of Chicago.
13. Julius Retinger to Adolf Meyer, 13 Nov. 1917. In his 15 Nov. 1917 reply to Retinger, Meyer reveals that he and his colleagues at Johns Hopkins 'have done some work with the Abderhalden method and I am very much interested in it.' AMC.
14. Bayard Holmes, 'First Annual Report ...' [see Note 12], p. 2.
15. Bayard Holmes, 'First Annual Report ...' [see Note 12], p. 5.
16. Although the 5-storey, 300-bed unit was to follow the trend of psychopathic hospitals such as those in Boston and at the University of Michigan and provide innovative treatment and research, the Psychopathic Hospital of Cook County Hospital never realized its full potential. In a November 1920 report prepared by Bayard Holmes, H. I. David and Edward Ochsner it was revealed that, 6 years into its operation, 'This institution has never been used as a psychiatric hospital.' Instead, since opening, it had only been used 'as a detention hospital for disturbed and insane patients awaiting the necessary ten days before commitment to the State Hospitals.' Unpublished typescript (1920) 'Report of the Committee on the Psychopathic Hospital from the City Club of Chicago'. Crerar MS. 092, folder 8, SCRC.
17. Julius Retinger, 'Report of laboratory work from August 1st to December 30, 1915', in Bayard Holmes, 'First Annual Report ...' [see Note 12], p. 11.

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