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Bayard Holmes (1852–1924) and Henry Cotton (1869–1933): Surgeon–psychiatrists and their tragic quest to cure schizophrenia

Jonathan Davidson

Abstract

Early 20th-century medicine was dominated by the infectious theory of disease. Some leading physicians believed that infection or the accumulation of toxic substances from bacterial stasis caused a wide range of diseases, including schizophrenia. In the case of schizophrenia, one theory held that intestinal stasis lead to the bacterial production of toxins that affected brain function, resulting in psychotic illness. This theory predicted that clearing the stasis by drainage or by removal of the offending organ would be curative. Bayard Holmes and Henry Cotton, surgeon–psychiatrists, achieved notoriety for their efforts to cure schizophrenia surgically. Their endeavours were not only a failure but resulted in tragedy to their families and to a wider population. Treatment of their own sons also represented a violation of the ethics of their time. This account describes the life and career of Holmes and Cotton and reappraises their work in the light of recent developments.

Keywords

Holmes, Cotton, schizophrenia, surgical treatment

Introduction

Autointoxication, focal sepsis and chronic intestinal stasis

The impressive triumphs of late 19th-century bacteriology offered a fruitful paradigm to understand disease. One theory to arise was that bacterial accumulation in one or more body organs caused a build up of toxic products. Such a notion was logically appealing since it predicted a method of cure by removal of the affected organ. Among the proponents of focal sepsis, or chronic bacterial stasis, were Charles Bouchard (1837–1915) in France, Sir William Arbuthnot-Lane (1856–1943) in Great Britain and Frank Billings (1854–1932) in the United States.[1] Bouchard considered the body was constantly fighting against what he termed *autointoxication*. The Nobel Laureate, Elie Metchnikoff (1845–1916), was a strong adherent of intestinal autointoxication and recommended the use of yoghurt to increase bowel transit time and sterilize the intestine. Arbuthnot-Lane rose to the highest ranks of British surgery but lost much of his credibility for enthusiastically championing bowel resection as the cure of illness; later in life he established the New Health Society which, although controversial at the time, espoused views that now command support, such as the importance of a high-fibre diet, rich in fruit and vegetables.[2] In the United States Frank Billings, Dean of the University of Chicago and Past President of the American Medical Association (AMA), wrote a widely read book on focal infection in which he advocated the removal of sources of infection such as the tonsils, adenoids and mastoids.

Against this background it is no surprise that others joined the bandwagon and invoked focal sepsis to explain a wide range of disorders, many of which are unrelated to infection. Although different body parts were held responsible, the intestine was one favourite and obvious organ of bacterial stasis which was often

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signalled through chronic constipation. The list of diseases that could arise from chronic intestinal stasis was staggering. For example, in 1919 Arbuthnot-Lane noted 'very clear evidence' that stasis contributed to 20 different conditions which he described and then went on to say that 'one may add largely to this list of diseases'.[3] Arbuthnot-Lane included schizophrenia in his inventory of diseases caused by intestinal stasis.

Schizophrenia (or dementia praecox), autointoxication and infection

Possibly the first to link psychosis to autointoxication were Theodore Deecke (1836–1905) in 1874 and François-Andre Chevalier-Lavaure (1863-) in 1893[4] but their ideas did not gain real attention at the time. Emil Kraepelin (1856–1926) remains one of the giants in modern psychiatry and perhaps is best known for distinguishing between depressive and manic-depressive illness (collectively, affective disorder) on the one hand and what he referred to as *dementia praecox* (now known as schizophrenia) on the other. In his mind the key feature of *dementia praecox* was its deteriorating nature and low likelihood of recovery. He too considered that *dementia praecox* could be the result of autointoxication although he regarded this as due to malfunction of the gonads or thyroid and not intestinal infection. However, Kraepelin's countrymen did not uniformly subscribe to this view, many holding true to the infectious origins of *dementia praecox*. For several decades in the early 20th century, authorities claimed that schizophrenia came about from autointoxication whether directly from microorganisms, indirectly from substances that accumulated due to bacterial stasis or from an endocrine origin.

It was in this context that Bayard Holmes and Henry Cotton can best be approached. These two men were united in their quest to find a surgical cure for schizophrenia in keeping with the germ theory of disease, yet in many other ways present a striking contrast from one another. Although their explanatory model of schizophrenia has long since been discarded, a close variant has resurfaced under the guise of the microbiome, inflammosome, probiotics and the world of alimentary pharmabiotics, giving renewed relevance to the work of Holmes and Cotton.

Bayard Taylor Holmes

Bayard Holmes entered medicine relatively late in life, graduating from the Chicago Homeopathic Medical College in 1884 at the age of 32. Even at this early stage, Holmes showed an interest in bacteriology (Figure 1). His obvious aptitude in this field impressed

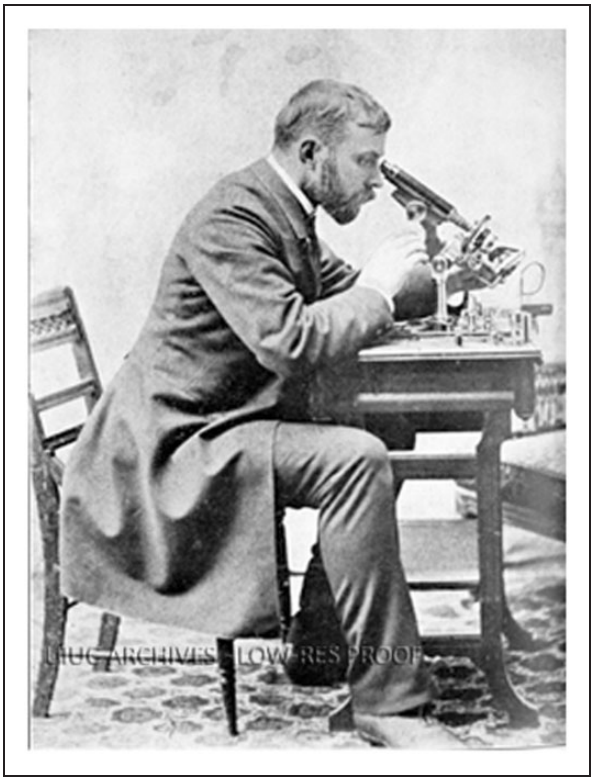


Figure 1. Image of Bayard Holmes at the microscope (Medical Life 1924; 31: 252).

Christian Fenger (1840–1902), a prominent Chicago surgeon and bacteriologist who offered Holmes a prestigious internship at Cook County Hospital upon graduation in 1884. To be offered such an appointment with a mere homeopathic degree was a sterling achievement.[5] While serving as an intern, Holmes set up a small bathroom laboratory to investigate bacteriology and incurred ridicule from his fellow interns for what they erroneously regarded as high-potency homeopathic research.[6] Subsequently homeopathy played little or no part in Holmes' career but he remained supportive of its presence in American medicine and towards the end of his life he published two reviews of his ideas about autotoxicity in the homeopathic literature.[7,8]

In 1887 Holmes coauthored a paper on antisepsis in abdominal surgery in the *Journal of the American Medical Association* (*JAMA*).[9] This publication aroused interest in Europe and was reproduced in its entirety as a German translation in the *Centralblatt fur Bakteriologie und Parasitenkunde*.[10] At the time of his *JAMA* publication, Holmes was studying for a second medical degree at the Chicago College of Physicians and Surgeons from which he graduated in 1888 and where he took the student prize for surgery.

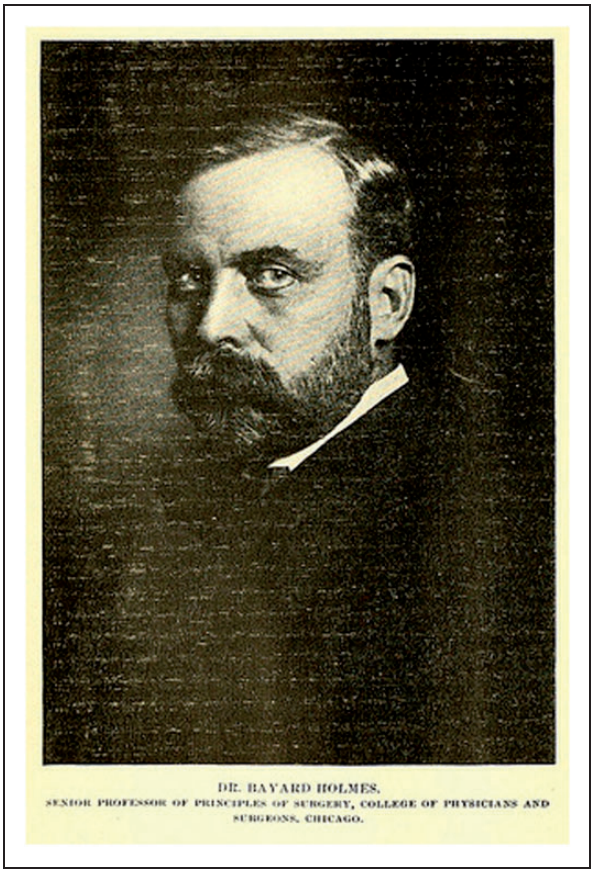
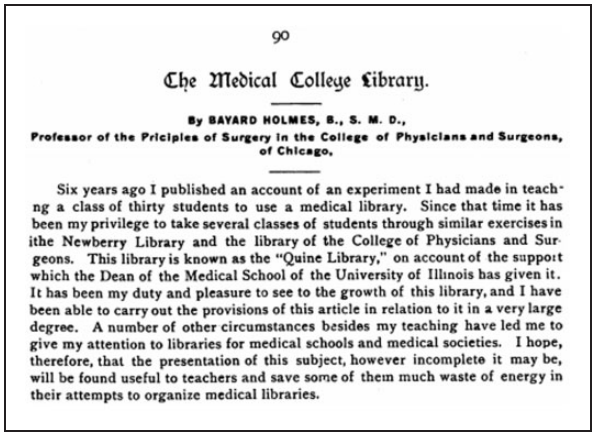


Figure 2. Bayard Holmes. Senior Surgeon, Chicago College of Physicians and Surgeons. Image in public domain. The P&S Plexus. Chicago. 1897; 3: 78. www.archive.org/details/plexus14coll.

Soon afterwards, he was appointed to teach the first bacteriology course in a Chicago medical school.

For many years, Holmes pursued his surgical and bacteriological career as Professor at the College of Physicians and Surgeons (Figure 2) but branched out into other areas including medical education, social reform and politics. In the nascent field of medical education, he oversaw the construction of a large laboratory building, an expression of his personal commitment to making medical training more laboratory-based and less didactic. As Secretary of the College, Holmes led its reorganization in 1891 and recruited some outstanding faculty.

Chicago lacked an adequate medical library. To remedy this deficiency, in 1889 Holmes created the Medical Library Association. Starting from a small collection he had assembled, Holmes secured cooperation from the Newberry Library that pledged to create a medical section. In due course this collection was taken over by the John Crerar Library and it continues today at the University of Chicago as one of the major American medical libraries (Figure 3).


90

The Medical College Library.

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Six years ago I published an account of an experiment I had made in teaching a class of thirty students to use a medical library. Since that time it has been my privilege to take several classes of students through similar exercises in the Newberry Library and the library of the College of Physicians and Surgeons. This library is known as the "Quine Library," on account of the support which the Dean of the Medical School of the University of Illinois has given it. It has been my duty and pleasure to see to the growth of this library, and I have been able to carry out the provisions of this article in relation to it in a very large degree. A number of other circumstances besides my teaching have led me to give my attention to libraries for medical schools and medical societies. I hope, therefore, that the presentation of this subject, however incomplete it may be, will be found useful to teachers and save some of them much waste of energy in their attempts to organize medical libraries.

Figure 3. Bayard Holmes (Medical Libraries 1899; 2: 90–94).

Holmes as social activist

Being deeply disturbed by the effects of industrialization on health, Holmes campaigned to improve health conditions of exploited garment industry workers. In 1894 he published in *JAMA* an attack on the Chicago Health Department for its pusillanimous attitude to sweatshop regulation in the midst of a smallpox epidemic.[11] Holmes accused the manufacturers and health board of collusion to protect the interests of the former and asserted that if the medical profession failed to protect the consumer at a public health level then it would be futile to expect other groups to take any serious interest in the matter. To advance the health of oppressed groups in society, Holmes founded the National Christian Citizens League. He became a well-known figure in Chicago and was persuaded to run for Mayor in the 1895 election, finishing a distant third even though he received strong backing from supporters of Eugene Debs (1855–1926) and Henry Demarist Lloyd (1847–1903). This proved to be Holmes' last sortie into politics and social reform, for his energies subsequently became channelled into improving the welfare of people with mental illness.

Holmes' ire was aroused by the power monopoly in the AMA. He joined forces with other reformists in the organization who bucked against exclusion of the rank and file from the workings of the AMA. In 1899 Holmes was one of the four shortlisted candidates for the position of AMA Secretary.[12]

Schizophrenia: searching for a surgical cure

A watershed occurred in Holmes' life when his second son, Ralph, who was a medical student, developed schizophrenia in 1905. Holmes' experience in seeking help for Ralph left him disillusioned with psychiatrists.

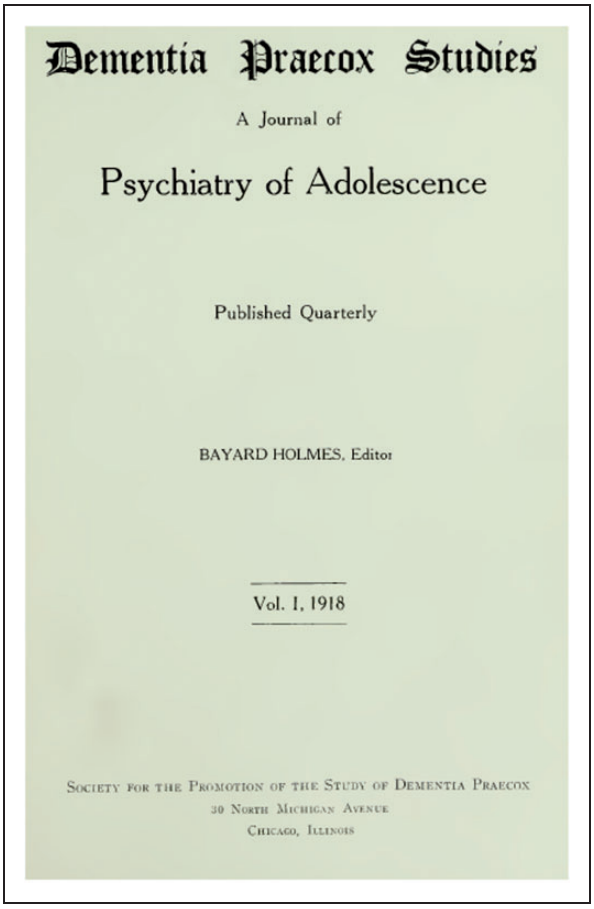


Figure 4. Dementia praecox studies. Bayard Holmes, founding editor. In public domain. http://archive.org/details/39002086349223.med.yale.edu.

After a demoralizing hospitalization during which Ralph was sedated by 'pounds of sedatives',[13,14] Holmes relinquished his academic career in surgery and devoted the rest of his life to find the cause and cure of schizophrenia. After visiting a number of mental asylums, where conditions left him appalled, he published exhortations on the need for better institutional care of the mentally ill.[15,16] To familiarize himself with the extant literature, Holmes assembled a bibliography of more than 8000 articles on *dementia praecox* and in 1918 founded *Dementia Praecox Studies*, believed to have been the first journal to focus on a psychiatric disorder (Figure 4).

In 1915 Holmes obtained funding for a research laboratory and in 1916 claimed he had discovered the cause of *dementia praecox*. Radiographic barium studies demonstrated to Holmes' satisfaction that barium transit was delayed in the large colon due to spasm at the sphincter of Cannon, leading to build up of material in the caecum. Holmes and his colleague Julius Retinger (1885–unknown), Professor of Chemistry at the University of Chicago, had shown high faecal histamine levels in schizophrenic subjects and he became convinced that this toxin accumulated in the intestine because of excess degradation of histidine through the action of *bacillus aminophilus intestinalis*. A reservoir was created that ultimately found its way to the brain, producing symptoms of psychosis. Holmes believed in a surgical approach to treat the problem whereby an opening would be made in the appendix (appendicostomy) and a program of daily colonic irrigation then implemented five hours after the last meal of the day and maintained for months or years thereafter. Driven by urgency to help his son, Holmes operated first on Ralph in May 1916 but with catastrophic consequences. Four days after surgery, Ralph died from gastric distension. Holmes spoke to very few people about the tragedy although his mentor Adolf Meyer (1866–1950) was one in whom he confided; he even expunged the case from his medical reports. In total, Holmes or his associates operated on 22 patients between 1916 and 1919, claiming several good successes as well as two fatalities. However, Holmes was unwilling to look critically at his findings and when Horry Jones, one of his research colleagues, could not replicate Holmes' radiological and bacteriological results,[17] Jones fell from grace and was fired.

Holmes was never accepted by American psychiatry, due largely to his embittered attitude towards the profession and the numerous scathing editorials he authored. He was, moreover, untrained in the discipline. Holmes' many positive attributes were at times overshadowed by his confrontational manner and he became so enmeshed with his son's plight that it affected his scientific objectivity and academic career. Although the outcome was not as he would have wished, Holmes may still be seen as a pioneer in biological psychiatry and an early advocate for better care and more accepting public attitudes towards schizophrenia, causes that remain as important today as a century ago. Bayard Holmes was eulogized by Graham Taylor (1851–1938), a prominent contemporary social reformer, as a man who 'had the courage not only of his convictions, but also of his sympathies. He was unafraid and not ashamed to think ahead of his time ... or to stand alone and dare to fail ... He served his generation by seeking the coming of the better day, and died not until he saw its early dawning'.[18]

Henry Cotton

Henry Cotton (Figure 5) graduated from the University of Maryland Medical School in 1899 and then accepted a position at the Worcester (Massachusetts) State Psychiatric Hospital as a junior psychiatrist. Cotton's ambition was evident at an early stage: his supervisor at

Figure 5. Henry A. Cotton, Sr. MD. 1932. Credit and permission, New Jersey State Archives, Department of State.

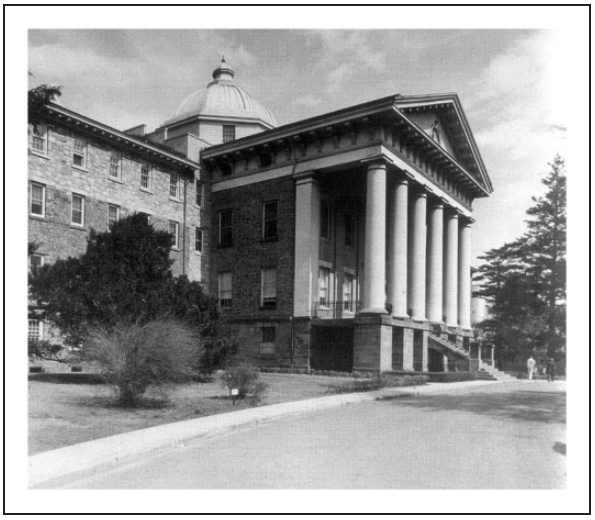


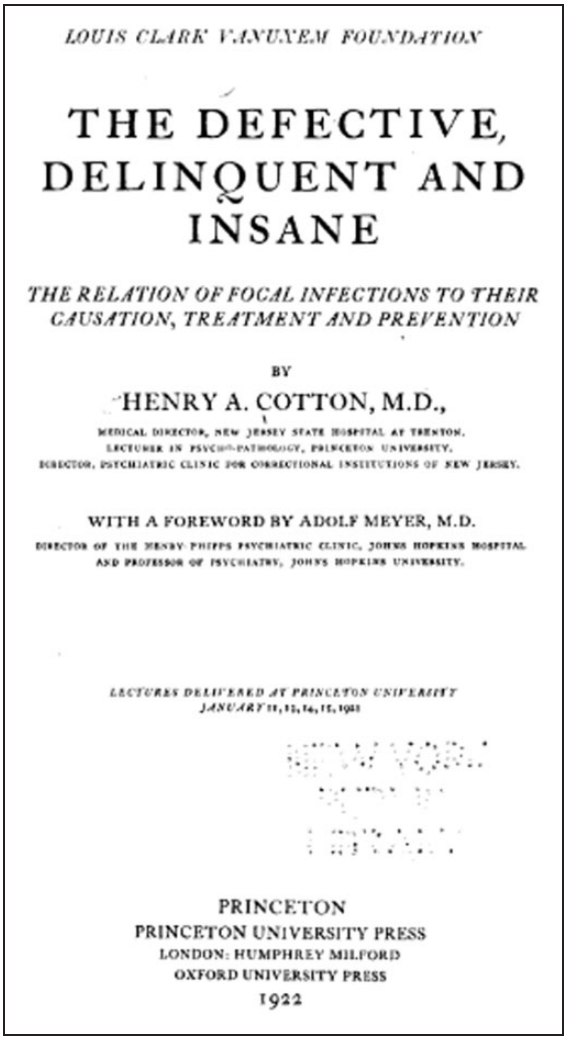
Figure 6. Trenton State Hospital. Image in public domain. www.asylumprojects.org.

Worcester, Adolf Meyer, recalled that Cotton would discuss his plans to make a mark in psychiatry and achieve major administrative responsibility.[19] A subsequent appointment as Assistant Superintendent at the Danvers Hospital was followed by two years of study with Kraepelin and Alois Alzheimer (1864–1915) in Munich between 1905 and 1907. Upon returning to the United States, Cotton was offered the medical directorship of Trenton State Hospital (Figure 6), an institution famous for its association with Dorothea Dix (1802–1887) who founded the facility and spent her final years in retirement on the campus.

As noted in Scull's masterful biography,[20] Cotton immediately made sweeping changes at Trenton, many of which were laudable such as abolishing the mechanical restraint of patients, introducing training for nurses and courses on preventing staff violence towards patients, improving safety in the facility, increasing the staff-to-patient ratio and adding occupational therapy to the available treatments. Cotton was determined to establish psychiatry as a scientific discipline and he initiated research studies and experimental treatments, including the treatment of general paresis of the insane by lumbar and intraventricular injections. As Meyer put it, 'From this it was but a short step to what made Cotton the protagonist of the focal infection theory and . . . the working out of the surgical treatment of his patients'. In order to carry out his ideas, Cotton lobbied state politicians for funds which he used to increase staff, install a laboratory and provide surgical facilities and an aftercare programme. In exchange, the state believed the new biological treatments would provide value for state expenditure by curing psychosis and reducing the costs of long-term hospitalization.

As a proponent of the focal infection theory, Cotton concluded that the cure for schizophrenia (and other mental illnesses) lay in removing sources of infection. Initially, Cotton relied on the surgeon JW Draper but after Draper's death Cotton took full responsibility for the work of the surgical service although tooth extractions continued to be performed by a dental surgeon, Dr Ferdearle Fischer (1897–1996) and gynaecological procedures by Robert Stone who eventually succeeded Cotton as Hospital Director.[20] Unlike Bayard Holmes who limited his interventions to the intestine, Cotton removed teeth, tonsils, gall bladders, cervices, colons, thyroids and other body parts. All told, Cotton performed 645 colectomies at Trenton,[20] with approximately 33% each being for schizophrenia, manic-depressive and mild disorders.[21] Cotton claimed astonishingly high success rates of over 80% but also acknowledged a mortality rate of 25–30%, explaining it away as due to the poor physical condition of patients with chronic psychosis. In some colectomy series the mortality exceeded 40%. To add insult to injury, at times Cotton operated in the absence of consent or in defiance of family wishes.

Despite the poor outcome of his surgical interventions, Cotton was *fêted* as a psychiatric hero in some circles, being invited to give prestigious lectures and to


LOUIS CLARK VANUXEM FOUNDATION

THE DEFECTIVE, DELINQUENT AND INSANE

THE RELATION OF FOCAL INFECTIONS TO THEIR CAUSATION, TREATMENT AND PREVENTION

BY

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WITH A FOREWORD BY ADOLF MEYER, M.D.

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LECTURES DELIVERED AT PRINCETON UNIVERSITY JANUARY 11, 12, 14, 15, 1921

PRINCETON
PRINCETON UNIVERSITY PRESS
LONDON: HUMPHREY MILFORD
OXFORD UNIVERSITY PRESS
1922

Figure 7. Title page, Vanuxem Lectures given by Henry Cotton, 1922. Image in public domain. http://archive.org/details/defectivedelinqu00cottuoft.

visit Great Britain on more than one occasion.[22] One of the highest honours accorded Cotton was an invitation from Princeton University to give the Vanuxem Memorial Lectures in 1922, resulting in publication of a book titled *The Defective Delinquent and Insane* (Figure 7). Other invitees to this series included Thomas Mann, Robert Oppenheimer, AN Whitehead, Edwin Hubble, Francis Crick and Harold Urey – Cotton was indeed in exalted company. Not all were persuaded as to the merits of Cotton's *oeuvre*, however, and in 1923 a group in New York reported what seems to be the first quasi-randomized controlled trial in psychiatry[23] to test Cotton's theories. This study failed to show any difference in outcome between the surgical group and the untreated controls, with response rates being 38% and 47% respectively.[24] Kopeloff and Kirby accused Cotton of being remiss in failing to compare his results against a control group, a very early understanding that control groups are important, as well as concealing data; they regarded his conclusions as not credible. Many of Cotton's colleagues also took issue with the manner in which he presented his work. Although Cotton published many papers in the peer-reviewed literature, he was perceived more as engaging in self-promotion through the public media. While Cotton's reputation was clearly damaged by the New York study, as well as similar findings by others including Englander,[25] he continued to pursue his work. He was scarred by two investigations, one by Phyllis Greenacre (1894–1989), a young psychiatrist sent by Adolf Meyer, and the other by a committee of the New Jersey Senate, led by Senator William Bright. Cotton reacted to the Greenacre Report with anger but the Bright investigation led to a serious psychotic reaction.

Cotton encountered new problems with the state authorities in the late 1920s due in part to his profitable private practice. Although he made no effort to keep it a secret, the authorities had turned a blind eye for several years until the economic depression forced them to look into the matter. It was asked how a full-time state employee could be permitted to 'double-dip'. This problem, together with the general disquiet surrounding Cotton's work, led the New Jersey Health Commissioner and Board of Managers to remove Cotton from his position on 1 October 1930[20] and make him Medical Director Emeritus as well as Director of Research, thereby enabling Cotton to continue with his clinical research at Trenton.

Despite being shunted aside, Cotton did not meekly accept the new order at Trenton. He protested at staff reluctance to perform dental extractions and colectomies, appealing to the legislature where he still had support. He lobbied for the state to restore the old practices at Trenton. At his private hospital Cotton modified his technique to lower the mortality rate. He also advocated even more vigorously for full dental extraction before performing abdominal surgery. At the same time, a third investigation was undertaken into Cotton's practices, this time by Emil Frankel (1886–unknown), Director of Research for the New Jersey Department of Institutions and Agencies. Like the others, Frankel's report was a serious indictment yet it failed to reach the public's attention and was ignored by Cotton who continued to preach his message of focal sepsis. Late in 1932 he prepared a summary of his ideas about the causes of insanity which he sent to HL Mencken (1880–1956) for publication in Mencken's widely read journal, *The American Mercury*, where it appeared in June 1933. By the time of its publication Cotton had died, passing away on 8 May, and he was saluted in the local newspaper as one

of 'few men in the public life of the State who could point to a record so replete with notable accomplishments' and to whom mentally ill people owed such a debt for 'displacing confusion and despair with hope and confidence'.[20]

Holmes and Cotton compared

It is instructive to compare parallels between the two men and, on a personal level, to explore the nexus that existed between father and son in each case. Holmes unquestionably preceded Cotton in applying surgery to treat the presumed focal infection for schizophrenia, but Cotton nowhere acknowledged Holmes' work. Holmes was aware of Cotton's practice and broadly supported it, at least as it related to the intestine. Despite overlap in their careers and a shared quest, it appears the two never met.

Both men were adroit in working the local political system, each was fixated on focal sepsis as the cause of psychosis and each came to lose his capacity for objectivity in the pursuit of his goal. Neither man was open to criticism or disagreement. Both were professional crossovers – Holmes was trained in surgery and bacteriology but took up psychiatry as an autodidact. The reverse was true for Cotton, a trained psychiatrist and self-taught surgeon. Both men became enmeshed as caretakers of their sons' mental health. On the positive side, one of Holmes' sons, Bayard Jr, and one of Cotton's, Henry Jr, became a physician. Yet tragedy visited sons in both families. Holmes' other son, Ralph, died from postoperative complications at the hands of his own father who was attempting to treat his psychosis. Cotton, who had once suffered a psychosis, also 'treated' his sons prophylactically by removing all their permanent teeth to ward off major mental illness; Cotton's wife also yielded to his demands that she have her teeth removed. The younger son, Adolf, also underwent abdominal surgery for symptoms which his father interpreted as due to infection.[20] But all this preventive psychiatry was for naught since both boys died by suicide – the younger son, Adolf, disappearing off a steamship in 1934 and the older son, Henry Jr, dying from a drug overdose in 1948. At least Henry Cotton Sr. was spared the anguish of living through these events.

Differences can be seen in their medical backgrounds. Holmes came into medicine at a late age through the sectarian pathway of homoeopathy and always preserved a measure of support for the discipline. Cotton received an orthodox training and arguably made greater use of the media whereas Holmes was more inclined to deliver his message through medical journals. Furthermore, Holmes founded the first journal dedicated to a single psychiatric disorder and did much to promote awareness of the neglect and stigma affecting the mentally ill. His commitment to social reform and democratization of the AMA might suggest a more altruistic side in contrast to Cotton's self-aggrandisement. However, Holmes was not untarnished by self-promotion since he would publish revealing personal information about his successfully treated patients further to boost his program. At death, one was saluted as a great pioneer while the other was largely ignored.

Conclusion

Lessons can be learned from considering the lives of these two physicians who remind us of the eternal appeal of medical theories that promise to reduce stigma or provide a simple answer to complex problems; the notion of 'detoxifying' the body is long-standing and continues to the present day. The idea that psychosis was caused by focal infection was plausible at the time until efforts were made to actually prove it scientifically – although Holmes thought he had shown it, his Chief Assistant published negative results, showing how important the publication of results that do not support a thesis can be. Similarly for Cotton when independent evaluation of his records failed to support his claims. To continue with such a harmful practice in the face of negative or flawed evidence is more a sign of hubris than of scientific courage.

A second lesson concerns the enmeshment of these two eminent physicians in the health of their sons. Holmes and Cotton both transgressed the normal boundaries that exist today and certainly existed 100 years ago, discouraging a doctor from treating a family member. As early as 1803, in his book *Medical Ethics* Thomas Perceval (1740–1804) enjoined doctors not to treat their relatives. This injunction became part of the AMA Code of Ethics upon its founding in 1847. The code stated that the emotional ties 'obscured … judgment, and produce[d] timidity and irresolution in [their] practice'. This precept was retained in revisions of AMA *Principles of Medical Ethics* in 1901, 1912 and later, although it was relegated to neglect in the mid-20th century before beginning to be revived in recent times. Cotton and Holmes should have been aware of this ethical principle yet proceeded in violation, with disastrous consequences.[26]

Third, it is apparent that checks, balances and monitoring processes failed to work, particularly in the case of Cotton, reflecting, inter alia, self-serving motives by Adolf Meyer, the New Jersey State Legislature and other bodies, as well as the absence of any critical self-appraisal by the two principal characters when faced with contradictory data. However, the controlled

clinical study by Kopeloff and Kirby acted as a significant brake on Cotton's wider influence.

We may also ask whether Holmes and Cotton were far off base? Has focal sepsis truly been discarded as an explanation of psychiatric illness? At the dawn of the 21st century a reappraisal seems due. Although removal or drainage of the colon would not find support today, awareness is growing that modification of gut microbiota by other means may come to play a part in treating mental illness. It is now recognized that the human gastrointestinal tract is occupied by ten times as many microorganisms as there are cells in the body and that these organisms contain 150 times as many genes as in the human genome. Cryan and Dinan report evidence that gut microbiota regulate anxiety, mood, cognition and pain and that 'the emerging [or as Holmes and Cotton might have said, ''re-emerging''] concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders'.[27]

Other strands of evidence can be marshalled. In 2007 a team of Japanese doctors reported that minocycline, a tetracycline-related antibiotic, improved symptoms of psychosis in two patients who received the drug for concomitant infection. Upon stopping the drug after the infections had healed, psychotic symptoms returned, only to disappear again when the drug was reintroduced.[28] Further studies have confirmed this finding and a large multicentre trial of the drug is now underway. It is not yet known how minocycline could benefit schizophrenia but anti-inflammatory and neurotrophic effects of the drug are major candidates. Nevertheless, Sir Robin Murray has opined that 'infection or inflammation might be involved in a minority of people with acute psychosis and minocycline might counter this'.[29] The last word on sepsis in schizophrenia has not been written. As to Holmes' fascination with histamine, it should not pass unnoticed that in 2013 the histamine H_2-antagonist famotidine was shown to be more effective than placebo in an augmentation trial of patients with schizophrenia[30] and that a theory of abnormal histamine metabolism in schizophrenia had previously been articulated.[31] Although Holmes and Cotton have long been *personae non grata* within psychiatry, and while the methods they espoused lead to horrible tragedy, the underlying theories that drove them are now reappearing in psychiatry in transformed fashion. The words Holmes wrote in 1921 could well be echoed by those who today are exploring the role of gut microbiota in mental illness: 'For some years I have held and expressed the view that dementia praecox is caused by toxins that are produced by the action of bacteria in the intestinal tract'.[8] How this idea is to be understood is today's challenge.

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