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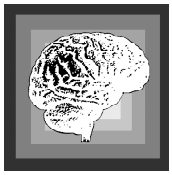

History of Psychiatry, 17(4): 395–418 Copyright © 2006 SAGE Publications (London, Thousand Oaks, CA and New Delhi) www.sagepublications.com [200612] DOI: 10.1177/0957154X06059440

The blood of the insane

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*The history of serological investigations of the blood of the insane is traced from the initial such study in 1854 by a solitary Scottish asylum physician, who counted the blood cells of his lunatic patients under a weak microscope, to the January 2005 announcement by an international team of geneticists of the development of a genomic blood test that can differentially diagnose schizophrenia and bipolar disorder. The story of the first claim of the development of a blood test for madness in 1912 – the Abderhalden defensive ferments reaction test – is related in detail. Studies of the blood of the insane have followed four general methodological paradigms: the corpuscular richness paradigm (1854); the metabolic paradigm (*c. *1895); the immunoserodiagnostic paradigm (1906); and the medical genomics paradigm (2005).*

Keywords: *Abderhalden defensive ferments reaction test; blood of the insane; dementia praecox; manic-depressive insanity; schizophrenia; serology and psychiatry*

In January 2005 an international team of researchers reported the results of a pilot study in which they claimed to have developed a blood test that could differentially diagnose schizophrenia from bipolar disorder and from normal controls. Collecting RNA from blood samples, the researchers found that schizophrenia and bipolar disorder exhibited unique expressed genome signatures. If the follow-up studies confirm the preliminary report (Tsuang, Nossova, Yager, Tsuang, *et al.*, 2005), this development signals not only a new paradigm in serological studies of mental disorders – that of medical genomics – but also promises the attainment of the holy grail of biological psychiatry: a blood test for madness.

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Given the potential revolution in psychiatry that may follow if a sero-diagnostic test has indeed been developed for schizophrenia and bipolar disorder, it is perhaps useful to reflect on the history of serological methods in biological psychiatry. In the discussion that follows I offer an introductory overview of experimental investigations of the blood of the insane from the first such study in 1854, acknowledging that a fuller scholarly history of these general methodological trends would easily surpass the page limitations of a standard journal article. My discussion should thus be viewed not as a definitive survey but as a starting point for future studies of serological methods in psychiatry. In identifying these general methodological trends in serological studies of the mentally ill, I give special emphasis to early twentieth-century experimental efforts to unravel the mystery of the organic basis of dementia praecox and schizophrenia. Manic-depressive insanity has always been secondary in concern to asylum physicians and laboratory researchers – a bias which continues to persist in the twenty-first century.[1]

For the present purposes I will sidestep the problem of the 'continuity hypothesis of schizophrenia' which assumes that researchers studying dementia praecox and schizophrenia applied their methods to the same 'object' through time. Indeed, I am in agreement with the 'discontinuity hypothesis' of Berrios, Luque and Villagran (2003: 111) that 'schizophrenia is not the result of one definition and one object of inquiry successively studied by various psychiatric groups but a patchwork made out of clinical features plucked from different definitions.' I am only interested in how researchers have tried to coax narratives of madness from blood, regardless of their chosen object of study.

Early laboratory science research into the causes and cure of insanity is a story still largely untold. Perhaps this has to do with the problems of story-telling that challenge all historians of science. 'Tales from the bedside' almost always make for more dramatic narratives than 'tales from the bench'. This is especially true in the history of psychiatry, where almost all the tales from the bench are about failed lines of research that explored hypotheses promising for their own historical era but which are obsolete in the present one. In almost all comprehensive works in the history of psychiatry, including the important compilation *Discovering the History of Psychiatry*, edited by Mark Micale and Roy Porter (1994), virtually no mention is made of early laboratory studies of insanity. Historians have neglected these literatures because these lines of research did not bear fruit. This situation has improved greatly with the arrival of *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (1997) by Edward Shorter, which places Germans such as Emil Kraepelin (1856–1926) and the history of biological psychiatry at the centre of the narrative, and with Jack Pressman's posthumous volume *Last Resort: Psychosurgery and the Limits of Medicine* (1998), which details the role of controlled experimental studies in the rise and fall of psychosurgery. Nevertheless, there are great gaps in our understanding of the details of the scientific

programmes of even the most famous of early dementia praecox researchers in Europe such as Kraepelin and his associates Alois Alzheimer (1864–1915) and Felix Plaut (1877– 1940), and the literature is virtually silent concerning early twentieth-century experimental research on dementia praecox conducted in American and British laboratories.

Serological studies of insanity were conducted within the context of distinct research paradigms, each reflecting not only the creativity of the medical imagination of its historical era, but also the limitations imposed by technology and the enormity of the task undertaken (evidenced by the fact that all their efforts failed). Historians of psychiatry who have constructed narratives of the rise, fall and resurrection of biological psychiatry in the past century have tended to focus on the neuropathological, neurohistological, psychopharmacological, psychosurgical and eugenics/genetics subplots of the story (Shorter, 1997). There are, however, other instructive tales in biological psychiatry that have been neglected, especially those framed by advances in serology, endocrinology and immunology. These textual remains of experimental dead-ends and dashed hopes are not only part of the larger story of the rise of 'scientific medicine', but they also impinge upon issues in the sociology of science and expose the problematics of histories of medical laboratory science in general.

For the history of psychiatry in particular, perhaps the most overlooked body of evidence – and it is indeed a gigantic one at that, with thousands of published reports in existence by 1920[2] – is the laboratory science response of the medical community to the enormous challenge posed by dementia praecox in the early twentieth century. First introduced as a chronic, deteriorating psychotic disorder by Kraepelin in the 4th edition of his textbook *Psychiatrie* in 1893, dementia praecox began to slowly gain general acceptance as a diagnostic entity after 1900 among British and American alienists and neurologists (Ion and Beer, 2002; Noll, 2004*a*). Although historians of psychiatry tend to interpret the 'reception' of a new mental disorder as its adoption as a diagnostic option, the true standard of reception is the point at which a diagnostic category frames experimental research. By World War I, dementia praecox would be acknowledged as one of the biggest problems faced by asylum physicians. Laboratories in America, Britain, Europe and Russia explored numerous experimental paths to unlocking the biological secrets of this terrible disease. My inquiry will centre on only one of the many dimensions of this response: the serological search in clinical laboratories for a blood test that could differentially diagnose insanity from 'health' and dementia praecox/schizophrenia from other mental and physical diseases.

The recent announcement of the development of a possible blood test for schizophrenia and bipolar disorder is actually the *second* time in the history of psychiatry that such a claim has caught the world's attention (and held it for any significant length of time). The first occurred in 1912 when an immunoserodiagnostic procedure know as the 'Abderhalden defensive ferments

reaction test' was believed by many for several years to be a valid method for differentially diagnosing those with dementia praecox from healthy persons and those with other mental disorders. The rise and rapid fall of the first blood test for insanity will be chronicled in detail. We can only hope that a similar fate does not befall the second.

Is there something different about the blood of the insane?

Blood has always been regarded as a carrier of information about the essence – physical, mental, spiritual – of the individual person. Humoral medicine, of course, posited blood as one of the primary causative factors in disease and offered rational treatments, such as bloodletting, for the cure of physical and mental maladies. For asylum physicians and researchers intrigued by the stories that blood may reveal, there were at least four questions that needed to be addressed: (1) Is the blood of diseased persons different from the blood of healthy ones? (2) Can specific diseases be diagnosed by specific changes in the blood? (3) Is the cause of madness in the blood itself? In other words, is 'mad' blood 'bad' blood? (the question of *aetiology*). (4) Are differences in the blood of the insane merely clues to the hidden causes of madness that are to be found elsewhere in the body? (the question of *pathophysiology*). Or, to translate Ludwig Fleck's (1979: 98) identification of the central problem of the perfection of the Wasserman reaction for syphilis into the terms of biological psychiatry, the question for these researchers became: How does one define mental illness and set up a blood test, so that after some experience almost any research worker will be able to demonstrate a relation between them to a degree that is adequate in practice?

The iconic story of the events following the May 1906 announcement of the development of the serodiagnostic Wasserman reaction test for syphilis (Wasserman, Neisser and Bruck, 1906) – the subsequent demonstrated relation of positive Wasserman reactions and the presence of *Treponema pallidum* in the brain tissue of mentally disordered persons diagnosed with general paralysis of the insane, and finally the development of treatments for GPI such as fever therapy – is well known in histories of psychiatry (Shorter, 1997; see also Plaut, 1911) and need not be recounted here. The hopes raised a century ago for the development of analogous serodiagnostic tests for dementia praecox, manic-depressive insanity and other mental illnesses cannot be overestimated.

But the success story of the development of the blood test for syphilis proved to be an elusive model for biological psychiatrists to emulate. The identification (in 1905) of the spiral organism that caused syphilis gave researchers a clear basis for developing the Wasserman blood test and the later redefinition of general paralysis of the insane as neurosyphilis. Clinical syndrome, cellular pathology and aetiology were tightly linked in less than a decade in this instance. Unclear about the exact parameters of the clinical

syndromes confronting asylum physicians, and not knowing how to operationally define mental illnesses such as dementia praecox or manic-depressive insanity except as vaguely 'organic' or 'biological', most laboratory researchers simply applied methods inspired by the latest conceptual or technological innovations in the various medical sciences and hoped there would be a serendipitous payoff in the search for the aetiology, pathophysiology and treatment of psychiatric disorders.

In the past 150 years four general approaches to the examination of the blood of the insane have framed experimental research: the corpuscular richness paradigm (1854); the metabolic paradigm (*c.* 1895); the immunoserodiagnostic paradigm (1906); and the medical genomics paradigm (2005).

The corpuscular richness paradigm

The first quantitative laboratory investigation of the blood of asylum patients was conducted in 1854 by W. Launder Lindsay, then an assistant physician at the Crichton Royal Institution at Dumfries, and published in January 1855 just as he assumed a new position as Superintendent and Chief Medical Officer of James Murray's Royal Asylum for Lunatics in Perthshire, Scotland. Lauder Lindsey created the initial paradigm for this type of laboratory research in psychiatry by focusing on the relative numbers or proportions of the structural elements of blood as counted through microscopic observation. In doing so, Lauder Lindsey was applying laboratory logic – but not the time-consuming procedures – inspired by Karl Vierordt's (1852) pioneering publication in which the first blood cell counts were reported. Lauder Lindsay mentions Vierordt in his article, and reveals a command of the literature on microscopic examinations of the blood. The studies of Vierordt and Lauder Lindsay were conducted within the context of the first phase in the history of modern haematology in which the focus was on the quantification of various cell types within the blood (Sabine, 1940). Staining techniques that could more accurately reveal the structural characteristics of the blood only came into general use sometime after 1877 when Paul Ehrlich (1854–1915), while still a medical student, developed a triacid stain that enabled the clear microscopic definition of the nucleus, cytoplasm and other details of cells in thin films of dried blood on glass slides.

In his unprecedented experiment, Lauder Lindsay used a needle to prick the fingers of 236 insane patients and 36 officers and attendants of the Crichton Royal Institution and Southern Counties Asylum at Dumfries. Simple blood smears on glass slides were examined using a microscope from Nachet in Paris, with a magnifying power of '180 to 380 diameters'. His procedural remarks are colourful:

> As a general rule, the insane are extremely bad subjects for such experiments. . . . They are extremely sensitive, restless and suspicious of

> operative interference, even of a slight nature. Many obstinately refused to allow their fingers to be pricked. Some did so from a firm conviction that a deep-laid conspiracy against their lives or welfare lurked under the cloak of apparently simple experiment; others simply objected to becoming tools of experiment or amusement; some declined on the plea that in their greatly debilitated condition they could ill afford to spare even a single drop of blood; others lacked courage to submit to the operation; some demanded full explanations of the motives which led to my making the singular request of allowing their finger to be pricked by a needle; in others this formed the keynote of their delusions, delirium or vituperation, for days or weeks after the experiment was attempted in them. On the other hand, many, who could not appreciate the objects of experiment, submitted cheerfully . . . some presented their fingers under the impression that, from the single drop of blood, the state of their constitution, the chances of cure, and the period of their removal, could infallibly be predicted; others from curiosity to see the appearance from which their own blood, or that of their companions, presented under a microscope . . . some carried this laudable curiosity to a great extent, begging most earnestly not only to see their own blood at different periods of the day, but that of fellow-patients and attendants, evidently strongly impressed with the belief that between their own blood and that of companions who exhibited most different traits of character or conduct, or between that of insane patients and sane attendants, there should exist a perceptible difference. On various occasions, I was obliged to demonstrate the condition of my own blood under the microscope, to satisfy the curiosity thus awakened. (Lauder Lindsay, 1855: 82)

Documenting the relative proportion of serum, fibrin and globules in the blood of the insane and non-insane, as well as a comparison of the form and structures of the red and white corpuscles, he attributed differences in the blood of the insane to the presence of other physical diseases that were equally present in non-insane persons. Diagnostic differences among the insane did not yield corresponding differences in the blood. His negative findings are summarized more succinctly in his June 1857 annual report as Superintendent and Chief Medical Officer of Murray's Royal Asylum for Lunatics: 'insanity and the different types and phases thereof are not characterised by a particular morbid state of the blood, and tend to show that insanity must be placed in the category of ordinary physical diseases' (Lauder Lindsay, 1857: 15).

Lauder Lindsay was a Scottish precursor to what Shorter (1997) referred to as 'the first biological psychiatry' launched in the 1860s by Germans such as Wilhelm Griesinger (1817–68). Additionally, Lauder Lindsay expressed his faith in laboratory medicine as a means not only to discover the causes of mental disorders, but also as a medium for dispelling discrimination against the mentally ill:

> Researches of this nature will tend greatly to break down the unfounded

> prejudices still existing in the public mind regarding the special nature of insanity, and to propagate, among the profession as well as the public, more correct opinions of the mutual relations of the healthy and morbid states of mind and body, and more particularly the reaction of physical disease on mental phenomena. It will hereby be found that insanity is much more a corporeal disease than is at present believed, or, at least, is more intimately connected with, or inseparable from, various of the ordinary physical diseases to which human flesh is heir (Lauder Lindsay, 1855: 78).

Reflecting the assumptions and practices of the 'morphologic era' in the early history of haematology, subsequent innovators in biological psychiatry also focused on the 'corpuscular richness' of the blood (Wintrobe, 1980). Blood was taken from insane persons, diluted, and then the corpuscles in a certain volume of that dilution were counted using such instruments as Gower's Haemacytometer. The relative proportion of red and white blood cells (blood dyscrasias) was of particular interest, as was the amount of haemoglobin, and many who followed this research paradigm claimed these amounts differed before, during and after an individual's bout of madness. By 1892 S. Rutherford Macphail could review the extant literature up to that time and conclude that there was an overall 'deficiency of the corpuscular richness of the blood met with in the first stages of insanity', and that a 'close connection' exists 'between improvement in the quality of the blood, and mental recovery, the converse of which exists in cases of persistent and incurable dementia' (Macphail, 1892: 140). Macphail was careful to emphasize the tentativeness of the conclusions to be drawn from the experimental literature and acknowledged that more work needed to be done in blood investigations of the insane. The corpuscular richness paradigm continued to be followed not only by American and British researchers, but also by those in Germany and France (Klippel and Lefas, 1906; Schultz, 1907).

Following the division of dementia praecox from manic-depressive insanity by Emil Kraepelin in the 6th edition of his *Psychiatrie* (Kraepelin, 1899), serological studies focused on distinguishing these two diseases from each other and from normals. Experiments designed to test the corpuscular richness hypothesis were, not surprisingly, often contradictory. This was especially true with regard to manic-depressive illness. However, a 1920 review by Bayard Taylor Holmes (1852–1924) – an ardent American proponent of biological psychiatry and the founder (in 1918) of *Dementia Praecox Studies*, the first medical journal named after a mental disorder – concluded that the blood in dementia praecox 'is at times highly concentrated, exhibiting polycythemia [an excess of red blood cells] with leucopenia [a decrease in white blood cells]' and that 'the morphological changes in the blood are excessively rapid, almost instantaneous, and when the ratio of corpuscles approaches the normal, there is often a betterment in the mental condition of the patient' (Holmes, 1920: 33). This latter statement by

Holmes referred to a phenomenon known as the 'blood crisis' in which the exacerbation of psychotic symptoms was correlated with a rapid diminishing of white blood cells and an overproduction of red blood cells, the reversal of which accompanied a return to relative normalcy. A rational treatment for dementia praecox derived from this experimental observation involved the injection of patients with sodium nucleate (salts of yeast acids used in the treatments of anaemia, rheumatism and gout) to increase the white blood cell count (Holmes, 1916; Kahlmeter, 1914; Lundvall, 1915).

By the 1920s, serological studies in psychiatry were no longer conducted within the corporeal richness paradigm. Two more promising serological paradigms – the metabolic paradigm and the immunoserodiagnostic paradigm – captured the imagination of researchers after 1900 following advances in endocrinology and immunology.

The metabolic paradigm

Throughout the latter half of the nineteenth century, physiologists sought to understand the mechanisms of metabolism. For most of that time, physiological changes in the body were explained by theories of *nervous regulation.* Between 1890 and 1905 – the year Ernest Starling first proposed the modern concept of 'hormone' (Welbourn, 1993) – metabolism was increasingly explained by theories of *chemical regulation* through secreting organs such as glands. In April 1891 the French physiologist and neurologist C.-E. Brown-Sequard (1817–94) and his assistant Arsene d'Arsonval (1851–1940) proposed for the first time that disease could result from the lack of production of 'internal secretions' in animal tissues. Evidence in support of the hypothesis of internal secretions was provided in the work of British physiologists such as George Redmayne Murray (1865–1939), who discovered the cure of myxoedema by subcutaneous injection of thyroid extract in 1891, and George Oliver (1841–1915) and Edward Schaefer (1850–1935), who discovered the vasosupressor effects of adrenal extract in 1894 (Borell, 1976).

Endocrinology emerged from physiology in a recognizable form in the years following British physiologist Edward Schaefer's address 'On internal secretions' to the British Medical Association in Physiology in London on 2 August 1895. 'Internal secretions' was a term introduced by physiologist Claude Bernard in 1855, but reframed by Schaefer in terms of clinical medicine. Metabolic diseases as a separate category of illness were caused by the over- or under-production of internal secretions in the glands with ducts (liver, pancreas and kidneys), those without ducts (thyroid, adrenals, pituitary) and the sex glands (gonads). As Schaefer proposed in his famous lecture, secreting organs, both with and without ducts, return secreted materials to the blood. The ductless glands, however, produce only internal secretions. Blood thus became the medium through which to detect and measure internal secretions, or, later in the twentieth century, hormones and neurotransmitters.

This emerging new endocrinological paradigm was immediately seized upon by the first biological psychiatrists. If an over- or under-production of internal secretions could produce physical diseases such as diabetes, why not also insanity? Since it was clear that the brain was the organ underlying mental diseases, perhaps the true aetiology of the insanities originated elsewhere in the body, places where substances toxic to the brain (internal secretions, ptomaines, bacteria and so on) were produced and then transmitted to the central nervous system via the blood. This autointoxication theory of mental disorders first became prominent in France in 1893 and influenced a generation of alienists, neurologists and laboatory researchers (Noll, 2004*b*).[3] And indeed the most prominent among them was Emil Kraepelin.

Shorter (1997: 109) emphasized the irony that Kraepelin, the icon of the first biological psychiatry, was instrumental in putting an end to it because he was 'agnostic about cause' and had 'declared [brain] anatomy to be unimportant'. This is only partially correct. Although Shorter correctly reports that Kraepelin introduced dementia praecox in 1896 as a 'metabolic disorder', the close connection between metabolic disorders and auto-intoxication theory in Kraepelin's medical cognition was not explored by Shorter. Kraepelin is perhaps better characterized as having been 'tentative about cause' rather than agnostic. From the 5th edition of his *Psychiatrie* in 1896 until the 8th edition in 1913, autointoxication (*Selbstvergiftung*) arising from a metabolic disturbance, probably in the sex glands – and not heredity – was Kraepelin's prime candidate for the cause of dementia praecox.[4]

Kraepelin was keenly aware of the new research on internal secretions, and from 1895 onwards he linked dementia praecox conceptually to the 'myxedematous insanity' caused by thyroid disease. In both the 5th and 6th editions of his *Psychiatrie* (Kraepelin, 1896, 1899), discussions of dementia praecox immediately follow those of thyroid autointoxication diseases such as myxoedema and cretinism.

Myxoedema was, to some degree, Kraepelin's aetiological model for dementia praecox. It was arguably the inspirational source of an analogical transfer Kraepelin made to dementia praecox when trying to discern its biological essence – a cognitive process that Paul Thagard (1999: 134–47) argues is typical in the explanation of new diseases. Kraepelin noted a cluster of physical anomalies in dementia praecox patients that, taken as a whole, pointed to an underlying metabolic disease such as myxoedema. These were: enlargement of the thyroid gland, brady- and tachycardia, skin changes similar to those found in myxoedema, tremor, changes in the sizes of the pupils, and exophthalmos. By 1900 the over- or under-production of 'internal secretions' in the glands of the body were posited as the cause of a wide variety of diseases, both physical and mental. It was this metabolic form of autointoxication theory that most intrigued Kraepelin.

It has been forgotten by scholars that Kraepelin applied a rational somatic treatment for dementia praecox based on Murray's work on myxoedema.

Kraepelin experimented with a form of organotherapy. As he put it in the Volume 3 of the 8th edition (1913) of *Psychiatrie*, 'Many years ago I endeavoured for a long time to acquire influence on dementia praecox by the introduction of preparations of every possible organ, of the thyroid gland, of the testes, of the ovaries and so on, unfortunately without any effect' (Kraepelin, 1919: 278).

The early experimental literature on the search for traces of internal secretions in the blood of the insane reflects the confusion in the emerging field of endocrinology regarding the nature of hormones and their similarities to enzymes, general metabolites, drugs, toxins, antitoxins and vitamins. These studies are too numerous, perplexing and contradictory to summarize here. Perhaps the most extensive early review of this literature was conducted by the Russian psychiatric researcher Aleksandr Ivanovich Iushchenko (1869–1936) in a series of lectures delivered in 1911 and then translated into German and published in 1914. He hypothesized that dementia praecox was caused by glandular dysfunctions, especially disease processes in the parathyroid (Justschenko, 1914: 52). Holmes, a major proponent of the auto-intoxication theory of dementia praecox, published a massive bibliography of works relating to the 'toxaemia of dementia praecox' that remains the best source for the metabolic paradigm of early serological studies of the insane (Holmes, 1920). A comprehensive and cogent review of the German literature concerning serological and endocrine research on dementia praecox was provided by Gabriel Langfeldt (1926) in the report of his own laboratory studies in this area from 1923 to 1925, at the Neevengaarden Asylum in Bergen, Norway.

Modern endocrinological research into the biological substrates of dementia praecox/schizophrenia began in the 1920s, increased in number from the 1960s to the 1980s, and then declined somewhat in the past 20 years. One of its major American proponents, Nolan D. C. Lewis (1889–1959), believed the thyroid, adrenal and gonads were implicated in dementia praecox (Lewis, 1923). Roy Hoskins (1880–1964), one of the pioneers of endocrinology in the USA, devoted more than two decades of his life to this problem as Director of Research at the Worcester State Hospital in Massachusetts beginning in 1927, but earned very few returns on his investment (Hoskins, 1946). Nor did it achieve its larger aim: the development of a treatment that might cure Stanley McCormick[5] (1874–1947) who suffered from a lifelong chronic psychotic illness (Fields, 2003; Noll, 1999). In fact, most of the research into the metabolic disorder hypothesis of schizophrenia that followed Hoskins' work yielded little of value (Meltzer, 1979). The past half-century of research has been confounded by the fact that endocrine abnormalities in schizophrenia may be due to stress caused by the illness itself or the effects of antipsychotic medications. Today, the best evidence for an endocrine link to schizophrenia involves the anterior pituitary gland (Garver, 1988). The anterior pituitary

contains gland cells that respond to releasing- or inhibiting-factors from the hypothalamus, which eventually may be found to be the source of the myriad confusing findings of endocrine dysfunction in schizophrenia.

Endocrinological research provided a direct and important analogical bridge that led to the discovery of neurotransmitters in the brain. Following the 1921 discovery by Otto Loewi (1873–1961) of a substance in the peripheral nervous system, later identified as acetylcholine, 'neurohormones' or 'neurohumors' were the terms applied to the proposed internal secretions of nerve cells. Indeed, the term 'neurotransmitter' did not come into use until the 1960s, only after the revolutionary decade between 1955 and 1965 when the 'electrical brain' became the 'chemical brain' (Valenstein, 2005). Neurohumoral and neurotransmitter theories of the pathophysiology of schizophrenia (*not* the aetiology – an important distinction to remember) involving the measurement of serotonin (1954), dopamine (1976), glutamate (1980), and so on, in the blood or cerebral spinal fluid (CSF), evolved directly from the metabolic paradigm in studies of the blood of the insane.[6]

The immunoserodiagnostic paradigm

By 1890 the discovery of 'reactions' in the blood to foreign organisms or substances, as evidenced by the production of detectable 'antitoxins', 'antigens', 'defensive ferments' or 'antibodies', led to the rise of immunology in medicine. Following the general acceptance of the germ theory of disease by 1880, and advances in bacteriology that demonstrated micro-organisms could directly or indirectly cause disease, between 1890 and 1910 the development of serologic tests such as agglutination, the precipitin reaction and complement fixation revolutionized the diagnosis of infectious diseases (Silverstein, 1985). The development of the Wasserman reaction test for neurosyphilis in 1906 was a turning point for biological psychiatry. It had long been suspected that the many asylum patients with 'general paralysis of the insane' were suffering from the long-term effects of the syphilis bacterium in their nervous systems. For the first time there was a blood test for madness – at least for one variety of madness, anyway. Could such immunosero-diagnostic tests for the other insanities be developed? Could one serologic test be developed that could differentially diagnose the major forms of insanity, dementia praecox and manic-depressive illness?

In 1909 two German researchers from Eppendorf created a minor sensation when they injected patients with cobra venom and found that all the dementia praecox patients and a portion of the manic-depressive subjects invariably reacted to the toxin while other psychiatric patients and normals did not (Much and Holzmann, 1909). Their discovery was reported in newspapers around the world, including *The New York Times*. But the excitement about the 'Much-Holzmann psycho-reaction' was over within two years: 'Unfortunately the original claims have not been substantiated,

and it is definitely known that as a diagnostic measure the Much-Holzmann test is of little value' (Fitzgerald, 1911: 693). Even Kraepelin felt compelled to discount the finding in the 8th edition (1913) of his *Psychiatrie* (Kraepelin, 1919: 255). Although the 'Much-Holzmann psycho-reaction' was quickly discredited by other researchers, it was the first promising differential diagnostic immunoserologic finding for dementia praecox and manic-depressive insanity.

In an era in which autointoxication theory influenced medical and psychiatric cognition, researchers posited that bacteria in the intestines spread throughout the body and caused damage to internal organs (Jahn, 1975). These damaged organs would release debris such as 'toxic albumins' into the bloodstream which would then be carried to the brain and cause the symptoms of insanity. Such theories were many and varied, as were the hypothetical substances that could be detected in the blood of the insane. As just one example, Holmes of Chicago believed he had produced experimental support for the theory that faecal stasis in the cecum led to the bacterial production of the same toxic amines that were implicated in ergotism, resulting in the poisoning of the brain and eventual psychosis. An excess of histamine in the blood was claimed as evidence for this mechanism (Holmes and Retinger, 1916).

The immunologic paradigm continues to this day in schizophrenia research, with not only the blood but cerebral spinal fluid examined for antibodies to possible pathogens. Evidence for allergic reactions to foods, viruses transmitted from cats to humans, and a lengthy list of other possible pathogens is weak. Viruses in particular are suspected to be involved in the aetiology of some forms of schizophrenia and bipolar disorder, although no confirmatory antibodies have yet been detected (Yolken and Torrey, 1995).

In the late 1990s there was renewed interest in the immune system response in schizophrenia and other mental disorders. A review of this literature by researchers from the Netherlands (Gladkevich, Kauffman and Korf, 2004) led to the hypothesis that lymphocytes – which make up about 20 per cent of all white blood cells – might carry information that reflects the metabolism of brain cells and might be utilized as an indirect probe of a limited number of cellular functions, including gene expression. They proposed focusing on the T (thymus-derived) cell, B (bone-marrow-derived) cell and NK cell subpopulations of lymphocytes. Other increases or decreases in specific lymphocytes have been found in schizophrenia (Mueller, Riedel, Ackenheil and Schwarz, 1999). The return of interest to numerical or morphological changes in the white blood cells harks back to the early twentieth-century research by Lundvall, Holmes and others intrigued by correlating changes in the blood with changes in symptoms in dementia praecox.

The story of the first blood test for dementia praecox (1912)

In May 1913, at the annual meeting of the German Psychiatrists Association

in Breslau, a presentation of experimental research findings by August Fauser (1856–1938), a psychiatrist from Stuttgart, created an international sensation that would capture the imagination of medical researchers for the next several years. At that conference, Fauser reported that he had used a recently invented immunodiagnostic test in an examination of the blood of 250 psychiatric patients and found that it could differentially diagnose dementia praecox from other psychiatric disorders. Furthermore, Fauser claimed that this blood test could also differentiate normal controls from persons suffering from severe mental disorders (Fauser, 1913*a*, 1913*b*, 1913*c*). As with the Much-Holzmann 'psycho-reaction' of 1909, Fauser's claim was reported in *The New York Times* and other world newspapers.

Fauser's stunning announcement of the discovery of a blood test for madness held out the promise that psychiatry would now share in the success of other medical sciences that had been revolutionized by laboratory studies in bacteriology, endocrinology and serology. This remarkable new immuno-serodiagnostic tool was known as the Abderhalden defensive ferments reaction test, originally developed in 1909 by the Swiss biochemist Emil Abderhalden (1877–1950) as a purported method of diagnosing pregnancy.[7] Abderhalden continually refined his procedure and central concept – that of the 'defensive ferments' (*Schutzfermente* or *Abwehrfermente*) – and a 1912 book on his discovery went through two more editions by 1914 (Abderhalden, 1912*a*, 1913, 1914). The 3rd edition of 1913 included a bibliography of more than 400 published studies using his serodiagnostic technique.

In a lecture on 27 October 1912 in Halle at a congress of German Psychiatrists and Neurologists, Abderhalden himself had suggested that his new blood test might be applied to the study of nervous and mental disorders (Abderhalden, 1912*b*). Fauser, under the direct guidance of Abderhalden, carried out this research plan and published a short research report on his findings at the end of the same year (Fauser, 1912). But it was Fauser's presentation at the May 1913 meeting of the German Psychiatrists Association that caught the world's attention. For a very brief – but exciting – period in the history of psychiatry, many researchers in Europe and North America believed that psychiatry now had the equivalent of the Wasserman reaction test for dementia praecox.

Fauser's claim to have found a blood test that could differentially diagnose dementia praecox from other psychiatric illness and from healthy persons was, for a time, internationally accepted as valid because of the congruence of his specific findings with Kraepelin's aetiological speculations. He believed the disease was caused by 'a tangible morbid process in the brain (*einen greifbaren Krankheitsvorgang im Gehirn*)'. Furthermore, Kraepelin speculated that the brain is affected by 'an autointoxication (*Selbstvergiftung*)' which originated elsewhere in the body. Rejecting notions prevalent in medicine at the time that bodily autointoxications primarily arose from the intestines, Kraepelin held to the notion that dementia praecox was caused by a

metabolic disturbance originating in the sex glands (Kraepelin, 1896: 439; 1896/1987: 23).

One of the major claims of Abderhalden's defensive ferments reaction test was that it could identify diseased internal organs in the body through a reaction of hypothesized 'defensive ferments (*die Abwehrfermente*)' in the blood of a patient when it came into contact with tissue from corresponding human organs taken from a cadaver. The assumption by Abderhalden was that debris from a diseased organ, toxalbumins, would end up in the bloodstream. Since such material was poisonous to the blood, and not excreted through the kidneys, the blood produced 'defensive ferments' or enzymes which dissolved this debris, catabolizing it and making it into a peptone and amino acid. Specific defensive ferments would be produced in the blood only when coming into contact with tissue from specific organs, and this process could be experimentally replicated in a test-tube outside a living body. An experimental reaction indicating the creation of defensive ferments in the blood in response to contact with corresponding tissue would result in a bright violet colour. Such a colour would confirm which organ in a patient's body was diseased.

Thus, Fauser found that defensive ferments in the blood of all persons with severe mental disorders caused a reaction against tissue from the cerebral cortex, thereby supporting Kraepelin's contention that dementia praecox is caused by a tangible morbid process in the brain. Fauser further corroborated Kraepelin when he reported that he found defensive ferments reacted against sex glands tissue only in the blood of persons with dementia praecox and not in those diagnosed as manic-depressive, hysteric or purely degenerative insanity. The serum of male patients reacted only with testicular tissue and the serum of female patients only with ovarian tissue.

Fauser's report, and subsequent research publications from his clinic, immediately inspired replication efforts around the world. The most notable of these was a study conducted with the blood of 106 psychiatric patients at the Sheppard and Enoch Pratt Hospital in Baltimore by the noted virologist Charles E. Simon (Harvey, 1978). In an article published in *The Journal of the American Medical Association*, Simon provided a critical review of the work of Fauser and subsequent researchers who did not confirm Fauser's findings, pointing out possible flaws in their use of Abderhalden's complex methodology as a reason for conflicting results. In Simon's own study, the sex-gland reaction was found in nearly all dementia praecox patients, but he directly rejected Fauser's claim that such a reaction is exclusive to dementia praecox. Simon also directly accused Fauser of manipulating his data to achieve the expected outcome. According to Simon (1914: 1703):

> In surveying the literature just outlined, one cannot help being impressed … by the wonderful apparent uniformity of the results reported by Fauser, and … by the total lack of uniformity of those obtained by others

> … The thought naturally suggests itself that two factors may have been operative to this end, namely that Fauser was carried away by his enthusiasm and allowed himself to be influenced unduly in the direction of his own wishes, and that [others] lacked complete control of the technic. As a matter of fact, there is good ground for the belief that both factors were operative.

Despite an acute awareness of the chaos in the medical literature on what Simon renamed the 'Abderhalden-Fauser Reaction', he insisted on the reality of Abderhalden's proposed 'defensive ferments' and on the method for detecting them: 'It is my firm conviction that ... Abderhalden's basic work in this field should be viewed as one of the most important contributions to modern experimental science' (Simon, 1914: 1702).

Simon never again mentioned the 'Abderhalden-Fauser Reaction' in any subsequent publications – and for a very good reason. In the four months before Simon's paper appeared in print, a series of devastating critiques of Abderhalden's defensive ferments reaction test began to appear in German medical journals.[8] Serious criticisms of Abderhalden's methods and even the veracity of the 'defensive ferments' continued in English language journals (Van Slyke, Vinograd-Villchur and Losee, 1915).

With the wisdom of hindsight at our disposal, all of us know why the Abderhalden defensive ferments reaction test did not revolutionize biological psychiatry: Abderhalden's defensive ferments simply do not exist. They never did. All the reports of positive results with the Abderhalden reaction test were based on error – if not worse. Indeed, in an article published in *Nature*, two German scholars accuse Emil Abderhalden of outright fraud rather than incompetence (Deichmann and Muller-Hill, 1998). The issue of error versus fraud was explored in depth by Kaasch (2000).

But surely the hundreds of published experimental reports of positive findings using Abderhalden's test were not fraudulent? There is, of course, another explanation: human fallibility. Since the reaction depended on the ability to perceive a particular colour, the method was not quantitative. Instead, it was highly subjective. Some researchers saw the colour all the time, some saw the colour some of the time, and some never saw it no matter how carefully they followed Abderhalden's procedures. The story of the rise and fall of Abderhalden's blood test is more akin to a social psychology experiment on perceptual bias and the consensual nature of reality rather than fraud perpetuated on a massive international scale. August Fauser and his colleagues in Stuttgart clearly saw the colour every time it fitted their preconceptions about the locus of the diseased organs in dementia praecox. Because of this highly subjective element, the hundreds of experimental reports often conflicted wildly in their results. Simon was therefore correct in his suspicion of experimental bias on the part of Fauser, but failed to discern the essential weakness in Abderhalden's method. By 1917 it was clear to most of the world that Abderhalden's defensive ferments did not exist and

that the method purported to detect them was flawed. In 1920 Jacques Loeb could write to a biochemist colleague, 'Nobody speaks of the Abderhalden reaction any more in the United States and I am very much surprised to see that in his journal Abderhalden still continues that myth' (cited in Deichmann and Muller-Hill, 1998: 110). However, scientific articles reporting the use of Abderhalden's test continued to appear in German publications for several more decades (Kaasch, 2000).

Despite the general rejection of Abderhalden's defensive ferments and the test purporting to detect them, a minority of physicians in the USA continued to believe in them and in their promise to revolutionize biological psychiatry. These physicians were Albert Sterne of Indianapolis, Bayard Taylor Holmes of Chicago and Henry A. Cotton of Trenton.[9] What united these men in their continued trust in Abderhalden and his test was their strong belief in autointoxication and focal infection theories of the cause of dementia praecox and other mental disorders.

All of them initially used the Abderhalden reaction test to confirm sources of autointoxication or focal infection in dementia praecox patients, and two of them eventually resorted to major surgery to remove them. Surgery was viewed as a therapeutic measure that followed rationally from theories of autointoxication and focal infection. A 'cure' for dementia praecox by performing surgical procedures on the thyroid gland was attempted by Newdigate Owensby (1882–1952) at the Bay View Asylum in Highlandtown, Maryland (near Baltimore), and this was reported in *The New York Times* on 19 December 1907. Like Kraepelin, Owensby's explicit analogue for dementia praecox was myxoedema. Beginning in 1909, surgical removal or alteration of the thyroid to treat dementia praecox was reported occasionally in the literature, but with no clear success indicated (Kanavel and Pollock, 1909). The first physician to perform abdominal surgery specifically to cure autointoxication in dementia praecox was Holmes, a professor of medicine and a specialist in abdominal surgery in Chicago (Noll, 2006). As avid supporters of Abderhalden's blood test, Holmes and his associates found defensive ferment reactions in the blood of dementia praecox patients to the cortex, sex glands and cecum. In 1915 Holmes hit upon a focal infection theory of the aetiology of dementia praecox – an ergotism-like toxaemia caused by faecal stasis in the cecum. The following year Holmes began performing cecostomies and appendicostomies, constructing a stoma in the side of his subjects to allow daily irrigations of the colon with water and magnesium sulphate to eliminate psychotic symptoms. Between 1916 and 1918, in private hospitals and in his short-lived (1917–18) Psychiatric Research Laboratory of the Psychopathic Hospital at Cook County Hospital in Chicago, Holmes and his associates performed major surgery on at least 22 persons suffering from dementia praecox. The first one was his own son, Ralph Loring Holmes, who had developed dementia praecox at age 17 while in his first year of medical school. Ralph never recovered from his

cecostomy in May 1916 and died four days after the experimental surgical procedure.[10]

The second physician to advocate surgery as a treatment of dementia praecox was Henry A. Cotton (1876–1933), the Superintendent of the New Jersey State Hospital at Trenton from 1907 to 1930. Cotton was an innovative psychiatrist who had studied with Kraepelin and Alzheimer in Munich for two years. In his annual reports for the years 1914 to 1917, Cotton recorded the use of Abderhalden's defensive ferments reaction test on the inpatients at Trenton. He specifically referred to the work of Simon in Baltimore as a validation for the use of this procedure to find organs diseased by focal infections.[11] In other words, contrary to the impression provided by Scull (2005) in his recent book on the tragedy that ensued, Cotton had a legitimate rationale for his experiments.

Heavily influenced by the dental theory of focal infection, starting in 1918 Cotton routinely had all the teeth removed from the psychiatric patients to stem the production of psychotic symptoms. By the following year he began even more radical procedures, removing part or all of the colon, cervix, ovaries, testes or appendix of dementia praecox patients and claimed enormous success. More than 2000 persons received dental work or experimental surgery as psychiatric treatment at the State Hospital in Trenton and in Cotton's private clinic, although the pace of this endeavour slowed considerably after a political investigation into Cotton's excesses led to a public scandal and his own mental breakdown (Scull, 1987, 2005). A third physician to treat dementia praecox through dental and abdominal surgery was Thomas C. Graves, the Medical Superintendent of the Rubery Hill and Hollymoore Mental Hospital in Birmingham, England (Graves, 1927).

Holmes died in obscurity in 1924. Prior to his demise and death, the claims of Cotton were rejected in their controlled experimental test by Nicholas Kopeloff of the New York Psychiatric Institute (Kopeloff, 1923; Kopeloff and Cheyney, 1922). Although Graves continued to play a prominent role in British medical circles until the mid-1940s, the focal infection theory of mental illness did not.

The medical misadventures of Holmes, Cotton and Graves illustrate how a faulty diagnostic blood test directly led to rational treatments that were dangerous in the extreme and, as we now know, based entirely on erroneous assumptions. The impulse to develop rational treatments from blood findings should give us pause as biological psychiatry undergoes a new paradigmatic shift.

The medical genomics paradigm

It has been known for some time that both schizophrenia and manic-depressive illness (bipolar disorder) have a significant genetic component. Blood relations of persons with schizophrenia or bipolar disorder are more

likely also to have the same disorder than persons with whom there is no genetic relatedness. The promise of medical genomics for finding the causes and potential treatments for schizophrenia and bipolar disorder has long been promoted by pharmaceutical and genomics companies. But the genetic heterogeneity of both disorders, and the complex environmental factors that surely must also be involved in the aetiology of these disorders, has seemed to push the pay-off of basic genetics research further and further into the future. This is why the January 2005 report of a pilot study of a gene-based diagnostic blood test for schizophrenia and bipolar disorder is so stunning.

Ming T. Tsuang, Director of the Institute of Behavioral Genomics at the University of California, San Diego, and his international team of colleagues from the USA, Canada and Taiwan used a procedure for using RNA derived from white blood cells. This procedure – known as 'the Sentinel Principle' – was invented and patented by C. C. Liew, Chief Scientist ChondroGene, a private genomics firm in Toronto, Canada. They took blood from 30 subjects with schizophrenia, 16 with bipolar disorder and 28 normal controls. Using a microarray analysis, they found that each disease state exhibited a unique expressed genome signature, allowing for the objective biological differential diagnosis of mental disorders for the first time (perhaps) in history. They examined eight candidate biomarker genes and with 95–97% accuracy were able to use them as blood biomarkers to discriminate between schizophrenia, bipolar disorder and normal controls. As they conclude in their abstract: 'We therefore propose that blood cell-derived RNA may have significant value for performing diagnostic functions and identifying disease biomarkers in schizophrenia and BPD' (Tsuang *et al.*, 2005: 1).

Is this the dawning of a 'third biological psychiatry'? The trajectory of history from a solitary Scottish asylum physician counting the blood cells of his lunatic patients under a weak microscope in 1854 to this recent report by a team of geneticists in three different countries is nothing less than breathtaking.

Notes

1. Volumes reviewing the experimental literature on dementia praecox and schizophrenia have appeared with great regularity since the 1920s (Davis and Riley, 1928; Lewis, 1923, 1936), with Leopold Bellak editing such compilations each decade from the late 1940s to the late 1970s. The most recent series seems to be the successive editions of *Schizophrenia* by Hirsch and Weinberger (2003). Between 1950 and 2000 only three comprehensive reviews of manic-depressive illness appeared (Bellak, 1952; Campbell, 1953; Goodwin and Jamison, 1990). Another point of contrast is worth noting here: whereas there were more than one hundred neuropathological studies of dementia praecox published after 1897, only six such studies of manic-depressive illness of any significance appeared in print prior to 1988 (Jeste, Lohr and Goodwin, 1988). The modern era of neuro-pathological studies of mood disorders began only in 1998 (Harrison, 2005).

2. A library card collection of bibliographic citations of more than 8000 international scientific articles, dissertations and books concerning laboratory studies of dementia praecox (1909 to 1924) was compiled by Bayard Taylor Holmes, a surgeon and Professor of Surgical Pathology and Bacteriology. He donated his collection to the John Crear Library at the University of Chicago, but it was subsequently discarded in the decades after his death. Holmes was a prominent advocate of serological methods in psychiatric research (Holmes, 1910) and used such techniques to arrive at a theory of the aetiology of dementia praecox (Noll, 2006).
3. On 1 August 1893, at the Fourth Session of the French Congress of Psychological Medicine held in La Rochelle, 'Rapporteurs' Francois-Andre Chevalier-Lavaure, a physician from Aix-en-Provance, and Emmanuel Regis, a physician from Bordeaux, drew attention to the value of autointoxication as a possible organic cause of madness by organizing and leading a panel on 'Auto-intoxication in Mental Disease'. This topic had been the subject of Chevalier-Lavaure's doctoral dissertation (1890), the first substantive treatment of this issue in the history of psychiatry. In the presentation by the 'Rapporteurs', they argued that it was difficult to distinguish between cases of auto-intoxication and those of infection from sources outside the body, but that a clear diagnostic distinction should be made between 'infectious' insanity (mental disturbances following acute infectious diseases, such as meningio-encephalitis) and 'visceral insanity', which is 'associated with disease of the internal organs' and is 'also very probably due to autointoxication' (Regis and Chevalier-Lavaure, 1893).
4. See: Kraepelin, 1896: 439; 1896/1987: 23; 1899/1990: 154; 1913, III/2: 931. I have documented this point more fully elsewhere (Noll, 2004*b*).
5. The husband of the woman who funded the research, Katharine Dexter McCormick (1875–1967), and an heir to the International Harvester Company fortune of the McCormick family of Chicago
6. Reviews of the role of neurotransmitters in the pathophysiology of schizophrenia can be found in several selections in the edited volume by Hirsch and Weinberger, 2003.
7. Abderhalden's long career and prominent place in German science is chronicled in the uncritical biography by Gabathuler, 1991.
8. The 1913–14 controversy over Abderhalden's concept of 'defensive ferments' and his methods for detecting them is well documented by Kaasch (2000: 168–78).
9. See: Cotton, 1917; Holmes, 1914*a*, 1914*b*, 1914*c*, 1914*d*, 1914*e*, 1914*f*; Sterne, 1914.
10. The death certificate of Ralph Loring Holmes lists his cause of death on 23 May 1916 at Lakeside Hospital in Chicago as 'dementia praecox,' but under the section for 'contributory (secondary)' causes of death, his physician wrote: 'Cecostomy – acute dilatation of stomach (Duration) 4 ds.'; State of Illinois, State Board of Health, Bureau of Vital Statistics, Standard Certificate of Death, Registered No. 15352.
11. In his annual report for 1914 as Medical Director of the New Jersey State Hospital at Trenton, Cotton (1915: 20) wrote: 'The introduction of the so-called Abderhalden tests in the domain of psychiatry seems to point to some definite lead in the direction of studying the secretions of internal organs. The methods are complicated and difficult, and really require the services of a trained physical chemist. The work done by Charles E. Simon, at the Sheppard and Pratt Hospital, has shown the value of this method of attacking some of the difficult problems, especially Dementia Praecox. Besides the method of Abderhalden we believe that the metabolism relating to the glands of internal secretion should also be the subject of intensive investigation'. According to his annual reports, Cotton used the Abderhalden test routinely at his hospital from 1914 to 1917 but

discontinued its use in 1918. It should be mentioned that this absolutely critical link in Cotton's logic between the Abderhalden test and the presumed infection of specific organs is not mentioned in the recent book on Cotton by Scull (2005). Indeed, the use of the Abderhalden defensive ferments reaction test at Trenton is not mentioned at all. Without an appreciation of the role that Abderhalden's test played in convincing Cotton of the correctness of focal infection theory, and thereby emboldening him to perform surgery, Cotton is perhaps a bit unfairly maligned as a madman from the very first. In fact, it could be argued that both Holmes – who was the first to perform surgery as a remedy for dementia praecox – and Cotton were administering rational treatments that were entirely consistent with influential trends in medicine during World War I. In this respect Joel Braslow's caveat is worth remembering: 'For the most part, I will take a given remedy's efficacy for granted … During their heydays, however, most of the therapeutic practices that are the subject of this book generally conformed to standards that constituted legitimate evidence for efficacy' (Braslow, 1997: 4).

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