

The Prehistory of Psychiatric Genetics: 1780–1910

Kenneth S. Kendler, M.D.

While psychiatric genetics has emerged as one of our most dynamic research fields, the historical context in which we view these developments is limited. To provide such a perspective, the author reviews 48 representative texts, published from 1780 to 1910, examining the inheritance of insanity. Six main conclusions emerge. First, most authors viewed heredity as among the strongest risk factors for insanity. Second, most writers concluded that a predisposition to illness rather than the illness itself was transmitted in families. Third, the probabilistic nature of the transmission was noted, as insanity often skipped generations or affected only a few of many siblings. Fourth, authors discussed the homogeneity versus heterogeneity of familial transmission of the various forms of insanities. Heterogeneous transmission was usually seen as the rule—with relatives of insane patients affected with a wide variety of psychiatric, and sometimes neurological, illnesses.

Homogeneous transmission (“like begets like”) was the exception. Fifth, writers noted that odd and eccentric personality features were common in the relatives of their insane patients. Finally, inheritance was commonly understood to include prior environmental parental experiences, and some authors noted that parent-offspring transmission of insanity could arise from psychological or intrauterine effects. Many of these conclusions, arising solely from clinical experience and without an understanding of biological mechanisms, statistical analyses, or necessary controls, are supported by later, more rigorous methods. Rather than entirely rejecting its value, we might view this literature as a complementary resource, likely more biased, but suffused with the extensive clinical knowledge of our forebears.

Am J Psychiatry 2021;178:490–508; doi:10.1176/appi.ajp.2020.20030326

Psychiatric genetics has, in recent years, been a key discipline driving scientific progress in psychiatry. However, we have a foreshortened historical framework within which to interpret these advances. Current work in psychiatric genetics rarely considers work done more than a decade ago. Our presentism is reinforced by the widespread belief that “real” genetics only began with the rediscovery of Mendel’s laws in 1900. In fact, psychiatric genetics has a long and rich history, having been a subject of interest from the beginning of modern psychiatry in the late 18th century. Having been unable to find a good introduction to this literature for modern audiences (but see Porter [1]), I decided to write one.

I began by reviewing available psychiatric textbooks from 1780 to 1910 originally in or translated into English or French. Our opening date marks the publication of Cullen’s major medical nosology (2), a good starting point for “modern” psychiatry. Our end date precedes by a year publications from Rüdin in Germany (3) and Rosanoff in the United States (4), which mark a new phase in the history of psychiatric genetics with the systematic application of Mendel’s laws. Most of the textbooks had a section on “causes of insanity,” all of which contained a discussion on heredity. Since I could find searchable pdfs for most texts (using the Internet Archive [<https://archive.org>] and the HathiTrust Digital Library [<https://www.hathitrust.org/>]), I also searched for other

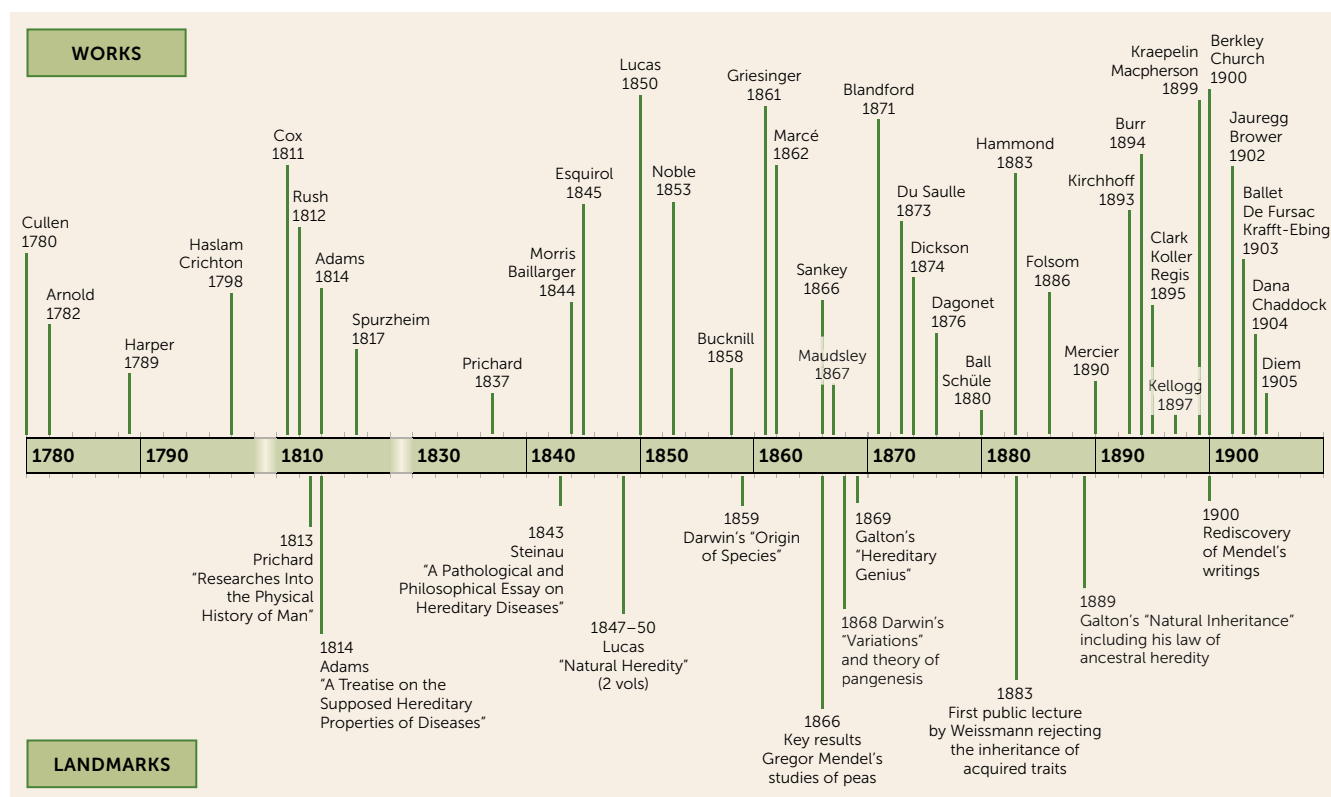
relevant discussions. I identified 48 texts with usable discussions on the role of heredity in the etiology of insanity.

As I reviewed the texts, I developed evolving tables of relevant quotations (Tables 1–5), divided by topic, around which I organize the discussion. Because many quotes dealt with multiple topics, I assigned them to the most relevant group. I then examined two additional texts to see if the views expressed on the role of heredity in the psychiatric literature were similar to those from outside the field (Table 6). I include the especially informative quotations in the text and encourage interested readers to study the other or more complete quotations in the tables. Figure 1 provides a timeline of the authors, along with major events in the history of genetics.

Before beginning, we need to review the understanding of human genetics in the late 18th and 19th centuries. Because inheritance had developed from the legal concepts of cross-generational transmission of property and wealth (5, 6), heredity was focused on direct parent-offspring transmission. Other forms of familial resemblance, such as in siblings, termed “collateral inheritance,” were of secondary interest.

Because the concept of the germ line being independent of somatic tissues was not demonstrated until the 1880s and not widely accepted until the early 20th century (7–9), belief in the inheritance of acquired characteristics was widespread. Many authors considered what are now known infectious

See related feature: **Editorial** by Dr. Sullivan (p. 475)

FIGURE 1. Timeline of publications and key discoveries^a

^a The authors and dates of publications of the texts reviewed in this article are presented in the upper section of the figure, and key publications or discoveries relevant to human genetics during this epoch in the lower section. For general histories of genetics during this period, consult references 6, 9, 68, 76, 87–89. References to the notable publications in the lower section are as follows: Prichard (90), Adams (21), Steinau (91), Lucas (60, 92), Darwin (93, 94), and Galton (95, 96). For the four authors who published before 1850 and are not likely well known to readers, the following may serve as some background. Prosper Lucas was a French alienist who wrote one of the most famous 19th-century works on genetics, reviewing exhaustively the field and proposing a theoretical explanation for the nature of inheritance (5, pp. 144–149). He was cited frequently by Darwin (94). Steinau authored one of the key early-19th-century texts on medical genetics and tried to distinguish between truly hereditary disorders and those due to noxious influences during pregnancy (68, pp. 57–58). Adams wrote one of the very first monographs in English on human heredity (68, pp. 54–55), which is quoted in this essay. Prichard was a British physician and ethnologist with broad interests in physical anthropology and alienism. His psychiatric work is quoted in this essay, but he was also, according to López-Beltrán, "the most important figure in the early 19th century British writers on hereditary transmission of physical and moral characters" (5, pp. 87–100).

diseases (e.g., tuberculous) to be hereditary (10). While many theories of heredity were proposed in this period, none came close to our modern understanding, and neither the laws of Mendel nor the biometrical theories of Galton and Pearson were applied to insanity until the 20th century (9, 11, 12).

Our authors had no general concept of statistics or controlled observations. Their main clinical tool was the family history, assessing the presence or absence of disorders in the close and sometimes more distant relatives of their patients. Only at the very end of our historical period of interest was the concern raised that to interpret their findings, parallel studies had to be made in the relatives of healthy individuals (13–15). In this essay, I focus on the broad diagnostic category of "insanity," as finer diagnostic categories varied widely over time and place.

THE IMPORTANCE OF HEREDITARY INFLUENCES IN PSYCHIATRIC ILLNESS

Table 1 presents quotations from 34 psychiatric texts discussing the role of heredity in the etiology of insanity. As illustrated by

eight representative quotations, the large majority of authors argued that heredity played an important causal role in insanity:

Arnold 1782: [I] cannot have the smallest hesitation in pronouncing that insanity is frequently communicated by parents to their children; and that, as there are family likenesses, and family tempers and dispositions, so this disorder, as well as the gout, and some others, affords abundant proof that there are family diseases (16, p. 290).

Cox 1811: At the head of the list [of remote causes of insanity] must be placed hereditary affections; these often descend from sire to son, and are transmitted to successive generations (19, p. 22).

Prichard 1837: That the predisposition to insanity, when it has once arisen, is frequently transmitted [within families], is a fact too well established to admit of doubt... (24, p. 122).

Esquirol 1845: Hereditary predisposition is the most common among the remote causes of insanity (27, p. 49).

Maudsley 1867: The more exact and scrupulous the researches made, the more distinctly is displayed the influence of hereditary taint in the production of insanity (34, p. 212).

TABLE 1. The magnitude of heritable influences on the occurrence of insanity

Author, Year, Reference	Text
Arnold 1782 (16, vol 2)	Before I pass from the consideration of bodily to that of mental causes, it may be proper to say something concerning hereditary predisposition.... the term ought to be considered as merely relative, and as rather expressive of the peculiar origin, and generation, of a cause, than of its specific quality. It points out a general question relative to causes; not any one particular cause. That the gout, scrofula, consumption of the lungs, insanity, and some other disorders, may be derived in some respect from our parents, seems so plainly proved by the frequent occurrence of striking, and indubitable facts, that, in a proper and limited sense, it cannot, I think be denied by any man of much experience and observation: and to refuse to diseases capable of being so communicated the title, which they have long possessed, of hereditary disease, seems but objecting to a name, while we allow the reality of the thing which it is intended to signify. But that diseases of any sort are hereditary is to be admitted only in a very limited sense. They do not pass from parents to their offspring with the certainty of hereditary estates. A variety of circumstances, to us totally unknown, may probably in many instances disturb the succession: or, at least, may prevent the actual appearance of the disease in some fortunate individual, notwithstanding that the latent disposition to it may be some way transmitted by him to his posterity. It is indeed a common remark, which appears to be verified by fact, that the disease of the parent may appear in some of the offspring, and not in others; or may lie dormant in the immediate descendant, and break out again in the next generation.... [W]hatever may be thought of the strict propriety of calling any disease hereditary, which is not certainly transmitted, and inherited, it cannot have the smallest hesitation in pronouncing that insanity is frequently communicated by parents to their children; and that, as there are family likenesses, and family tempers and dispositions, for this disorder, as well as the gout, and some others, affords abundant proof that there are family diseases (pp. 286–290).
Harper 1789 (17)	Whether Insanity be hereditary or not? And what it is that constitutes real Insanity? In the course of inquiry, the extreme absurdity of the common opinion, that Insanity is an hereditary disease, will plainly appear. It is true that every constitution is naturally calculated for the reception of particular impressions and passions, and when the incidents of human affairs and peculiar habits of living happen to conspire too powerfully to fan the native spark, the flame of Insanity may possibly be kindled; but still the cause can only be accidental, and not by any means hereditary (p. vi).
Crichton 1798 (18, vol 1)	Of those remote causes which are not only themselves concealed from our senses, but whose mode of operation is greatly obscured, are to be reckoned all those which proceed from hereditary disposition to insanity... (p. 149). Every medical man possessed of a moderate share of experience, must have observed that the children of those who have been insane are more liable to attacks of delirium, and alienation of mind, than the descendants of other people; insomuch that where a numerous family has sprung from parents who are tainted, it rarely happens that insanity is not produced in some of that family during part of their lives, by any slight exciting causes. If they marry and beget children, the same thing is also observed among them. This fact makes us conclude that many have an hereditary right, or in other words, are born with a predisposition to the complaint (pp. 184–185).
Cox 1811 (19)	At the head of the list [of remote causes of insanity] must be placed hereditary affections; these often descend from sire to son, and are transmitted to successive generations (p. 22).
Rush 1812 (20)	A peculiar and hereditary sameness of organization of the nerves, brain, and blood-vessels, on which I said formerly the predisposition to madness depended, sometimes pervades whole families, and renders them liable to this disease from a transient or feeble operation of its causes (p. 48).
Adams 1814 (21)	Gout and madness are, by almost universal consent, considered hereditary; yet, if we admit the general implication as to their immediate causes, both these diseases, and particularly the former, should be considered as only hereditary in predisposition (p. 16).
Spurzheim 1817 (22)	Considerable diversity of opinion has prevailed, whether insanity be hereditary or not; and much is said on both sides. With [Erasmus] Darwin, Crichton, Cox, Haslam, Hallaran, and many others, I consider insanity as hereditary. It is indubitable, that children inherit from their parents the constitution of body, and the dispositions of mind ... the internal viscera, such as lungs, stomach, intestines, kidney, bladder, uterus, &c. with their various dispositions, participate of inheritance, why should it not be the case with the brain? Numerous facts, indeed, are unfortunately too well ascertained, that the offspring of insane parents are more liable to insanity than those whose parents have never shown any deranged manifestations of the mind (pp. 102–103).
Heinroth 1837	Insanity is the loss of moral liberty; it never depends on a physical cause; it is not a disease of the body, but of the mind; it is a sin. It is not, and it cannot be, hereditary, for the thinking ego, the soul, is not hereditary (quoted in Hammond [23, p. 80]).
Prichard 1837 (24)	That the predisposition to insanity, when it has once arisen, is frequently transmitted [within families], is a fact too well established to admit of doubt.... There is reason for believing that this one circumstance of constitutional tendency to mental derangement is by itself more important, in respect to the origination and the frequent occurrence of the disease, than all the other causes ... taken together (pp. 122–124).

continued

TABLE 1, *continued*

Author, Year, Reference	Text
Morris 1844 (25)	Hereditary predisposition — This is a very frequent remote cause of insanity, for if insanity [as I believe] be always preceded and accompanied by a peculiarly debilitated state of the constitution, can we wonder if the children of such parents should partake of that debility? [He then discusses gout and scrofula and concludes] ... these three diseases, perhaps more than any others, have been said to arise from hereditary predisposition (pp. 22–23).
Baillarger 1844 (26)	Everyone is aware of the influence of heredity in the production of madness. Among those who run institutions devoted to insane persons, he would have to be unqualified if he did not observe a sufficient number of facts to establish his conviction in this regard. It is besides a popular and very old opinion on the heredity of insanity, and the published statistical records of these twenty years only confirmed it. But if the very fact of heredity of madness no longer need to be proven, it remains to be studied in detail... (p. 158). I think I must point out that the study of madness may, better than any other disease, be used to the advancement of the general history of heredity and to the determination of the laws that it follows (p. 168).
Esquirol 1845 (27)	Hereditary predisposition is the most common among the remote causes of insanity (p. 49).
Noble 1853 (28)	The first noticeable fact having reference to the predisposition to mental derangement, is its hereditary character. I very much doubt whether any other class of diseases exhibits this feature so remarkably.... I am of opinion, indeed, that no pathological state exemplifies more strikingly the communicability by generation of morbid tendencies, than Insanity... (pp. 231–232). Gout, scrofula, affections of the heart, and certain other diseases, are undoubtedly hereditary. Their causation, in many instances can be made out; but very often their origin can neither be accounted for nor explained; and yet, by generation, they become the characteristics of particular families. It is just the same thing with insanity (pp. 242–243).
Bucknill 1858 (29)	Among the most important predisposing influences are hereditary predisposition... (p. 240).
Griesinger 1861 (30, 31)	Hereditary Predisposition—Statistical investigations strengthen very remarkably the opinion generally held by physicians and the laity, that in the greater number of cases of insanity a hereditary predisposition lies at the bottom of the malady; and I believe that we might, without hesitation, affirm that there is really no circumstance more powerful than this (p. 150).
Marcé 1862 (32)	Heredity is a provision under which the parents transmit to their children certain states or certain physiological or pathological dispositions. Of all the predisposing causes of madness, heredity is unquestionably the most important. It dominates the pathogenesis of mental illnesses (pp. 102–103).
Sankey 1866 (33)	An hereditary tendency to insanity is admitted as a well-observed fact by nearly every writer on the disease.... [A]fter all, I entertain no doubt of the fact that hereditary influence is a predisposing cause of insanity (pp. 191–192).
Maudsley 1867 (34)	Hereditary Predisposition. —The more exact and scrupulous the researches made, the more distinctly is displayed the influence of hereditary taint in the production of insanity.... Whatever, then, may be the exact number of cases in which hereditary predisposition is positively ascertained, it may, I think, be broadly asserted that, in the great majority of cases, whether there has been observable madness or not in father or mother, or some remoter relative, there has been some constitutional instability or infirmity of nervous element in the individual whereby he has been unable to rally against adversity, and has broken down in insanity (pp. 212–213).
Blandford 1871 (35)	The first tendency which demands your attention is hereditary transmission, for it is of all [causes] the most potent and ought always to be kept in view by those aware of its existence, whether medical men, parents, or guardians. Here is a cause of insanity which cannot be got rid of, a part and parcel of the individual's constitution and being (p. 118).
Du Saulle, 1873 (36)	[After reviewing prior studies] These authors provided a good deal of material. They established irrefutably that mental illnesses can be transmitted from ancestors to descendants by means of procreation and based on laws that are often very complex (pp. 2–3).
Dickson 1874 (37)	The operation of predisposing causes is markedly seen in insanity, and perhaps the most powerfully marked is hereditary tendency (p. 13).
Dagonet 1876 (38)	Hereditary predisposition must be placed at the top of the special causes [as opposed to "the general causes," such as sex and age], it plays an important role in the production of mental illnesses.... Heredity fixes alienation in families and makes it transmissible from generation to generation (p. 474).
Ball 1880 (39)	And if I were asked to condense, in a word, everything we know about the origins of madness, I would gladly answer: "There is only one cause of insanity—that is heredity" (p. 354).
Hammond 1883 (23)	The hereditary transmission of peculiarities of form, mental character, manner, idiosyncrasies, habits, and proclivity to disease, is no longer a matter of doubt with those best qualified to form an opinion on the subject... (p. 75). Like the transmission of the physical and mental qualities, the transfer of pathological tendencies from parents to offspring must be accepted as a fact amply capable of demonstration, but not susceptible of explanation... (p. 77). That insanity is often transmitted by hereditary influence is a fact scarcely requiring discussion (p. 80).
Folsom 1886 (40)	In general, it may be said that the more individuals of both branches in whom insanity and its allied diseases are found, just so far may a larger proportion of the children be expected to suffer [from insanity].... Undoubtedly, a great portion of the mental and nervous disorder commonly attributed to heredity is largely caused or aggravated by imitation and by vicious training of children (pp. 115–116).

continued

TABLE 1, continued

Author, Year, Reference	Text
Burr 1894 (41)	Under this head [constitutional causes] come all causes of insanity which operate because of some innate defect in constitution or development of the individual. Here hereditary tendency figures to a great extent.... There is known hereditary tendency to mental diseases, either remote or immediate, in about fifty per cent. of all cases under treatment in large institutions. Probably if the facts were invariably discoverable, the percentage would be found vastly greater (pp. 30–31).
Meynert 1885 (97)	Dissatisfied with the statistical method, which laid inordinate stress upon hereditary predisposition to disease, I have considered predisposition as a form of disease and not as a condition antecedent to it. I have above all referred to the anatomical peculiarities constituting predisposition. I was not content, as others have been, to accept the mystical conception of heredity, but have insisted on the anatomical peculiarities in patients which constitute predisposition (p. viii).
Clark 1895 (42)	Heredity is the most potent cause of insanity in its predisposing tendency (p. 244.)
Mercier 1890 (43)	That the children of insane parents are apt to inherit a tendency to insanity is what might be expected and is a well-established fact (p. 144).
Krafft-Ebing 1903 (44, 45)	As a rule, however, it is not sufficient to know the individual history of life and development; usually we must go further to the physical and mental peculiarities of progenitors, for, with the exception of tuberculosis, there is no disease that is so far grounded in heredity, in physical and mental anomalies of organization, and in the life and conditions of progenitors, as insanity... (p. 137). By far the most important cause of insanity is transmissibility of psychopathic dispositions or cerebral infirmities by way of heredity (p. 157).
Berkley 1900 (46)	Of all the varied inciting causes of mental infirmities, heredity and alcohol are the most important (p. 105).
Brower 1902 (47)	First among all predisposing factors of insanity must be reckoned heredity, or the hereditary transmission of a liability to mental breakdown or failure ... [I]t may be considered as one of the most hereditary of diseases (pp. 18–20).
Ballet 1903 (48)	The role of heredity in mental pathology is well established.... There is no illness ... wherein the action of heredity is better demonstrated (p. 22).
Dana 1904 (49)	Heredity is the most serious and important of these predisposing causes.... A nervous disease, however, is rarely directly inherited (p. 23).
De Fursac 1903 (50, 51)	Congenital predisposition exists in more than half or in about two-thirds of the insane. A morbid heredity constitutes its most frequent cause... (p. 8).

Dagonet 1876: Hereditary predisposition must be placed at the top of the special causes [as opposed to “the general causes,” such as sex and age], it plays an important role in the production of mental illnesses... (38, p. 474).

Hammond 1883: That insanity is often transmitted by hereditary influence is a fact scarcely requiring discussion (23, p. 80).

Ballet 1903: The role of heredity in mental pathology is well established.... There is no illness ... wherein the action of heredity is better demonstrated (48, p. 22).

While the opinion expressed in these examples—that hereditary factors contributed strongly to risk for insanity—was very common in our texts reviewed, it was not universal. Three of our authors were skeptical:

Harper 1789: Whether Insanity be hereditary or not? And what it is that constitutes real Insanity? In the course of inquiry, the extreme absurdity of the common opinion, that Insanity is an hereditary disease, will plainly appear. It is true that every constitution is naturally calculated for the reception of particular impressions and passions, and when the incidents of human affairs and peculiar habits of living happen to conspire too powerfully to fan the native spark, the flame of Insanity may possibly be kindled; but still the cause can only be accidental, and not by any means hereditary (17, p. vi).

Heinroth 1837: Insanity is the loss of moral liberty; it never depends on a physical cause; it is not a disease of the body, but of the mind; it is a sin. It is not, and it cannot be, hereditary, for the thinking ego, the soul, is not hereditary (translated in Hammond [23, p. 80]).

Folsom 1886: In general, it may be said that the more individuals of both branches in whom insanity and its allied diseases are found, just so far may a larger proportion of the children be expected to suffer [from insanity] ... Undoubtedly, a great portion of the mental and nervous disorder commonly attributed to heredity is largely caused or aggravated by imitation and by vicious training of children (40, pp. 115–116).

Their reasons for denying an etiologic role for heredity in insanity differed. Later in his monograph, Harper argues that insanity results from disturbances of the mind, not physical disorders of the body or brain. Heinroth believed that insanity resulted from sin. Folsom, by contrast, accepted that insanity runs in families but suggested that the causes were largely psychological.

NATURE OF THE HEREDITARY TRANSMISSION OF INSANITY

Many of our authors considered the question of what precisely was passed within families that predisposed to insanity (Table 2). Was the disease itself transmitted or was only a predisposition? We begin with an insightful early passage from one of the first monographs in English on hereditary diseases:

Adams 1814: Madness, as well as gout, is never hereditary, but in susceptibility; and those who have paid the greatest attention to the subject, must admit the two degrees of susceptibility. When we perceive ... several children of the same

TABLE 2. The nature and mode of transmission of insanity in families

Author, Year, Reference	Text
Adams 1814 (21)	Madness, as well as gout, is never hereditary, but in susceptibility; and those who have paid the greatest attention to the subject, must admit the two degrees of susceptibility. When we perceive, (an event by no means uncommon) several children of the same parents, and sometimes in different branches of the same family, seized with madness about the age of puberty, we cannot but admit a disposition to the disease; for though some mental irritation is usually assigned, yet the cause is often so trivial, that we cannot doubt whether the supposed effect has preceded it.... But when the susceptibility amounts only to a predisposition, requiring the operation of some external cause to produce the disease, there is every reason to hope, that the action of the disease may be for the most part much lessened, if not prevented altogether... (pp. 26–27).
Spurzheim 1817 (22)	Those who deny hereditary diseases must at least admit hereditary predisposition to diseases. As weakness of certain parts runs through whole families, so at least a predisposition to insanity is propagated from parents to children.... This object [hereditary transmission] is involved in deep obscurity, and I do not intend to hazard an explanation; but the fact is indubitable. On the other hand, it must be admitted that children born from insane parents may escape, as is the case in other hereditary complaints and that insanity may be produced in every person, born from the strongest and most healthy parents.... The hereditary dispositions cannot be explained by the mind itself, which we consider as a free agent. If it could, it certainly would escape such miserable situations.... I think it more natural to explain hereditary insanity, like all other hereditary dispositions, by the corporeal conditions by which the powers of the mind are manifested (pp. 103–105).
Noble 1853 (28)	When hereditary tendency to insanity exists, then, it becomes necessary to assume that some peculiar proneness to disordered action inheres in the cerebral and nervous structures, not compromising sensibly the organization at large; but of the precise nature of this tendency we are as yet ignorant... (p. 233). There is good reason for believing that, in the case of insanity, as in other forms of inherited disease, even if the tendency to disordered action in the brain and nervous system do not display itself at birth or in early life, the slightest injury may give effect to it so as to produce derangement of mind. And a predisposition once established, the liability may be communicated to succeeding generations, just as happens with regard to constitutional maladies in general (pp. 236–237).
Morel 1857	We do not mean exclusively by heredity the very complaint of the parents transmitted to the children, with the identical symptoms, both physical and moral, observed in the progenitors. By the term heredity we understand the transmission of organic dispositions from parents to children. Mad doctors have, perhaps, more frequent occasion than others for observing this hereditary transmission, as also the various transformations which are exhibited in the descendants. They are aware that a simple neuropathic state of the parents may produce in the children an organic disposition which will result in mania or melancholy nervous affections which in turn may give rise to more serious degeneracy, and terminate in the idiocy or imbecility of those who form the last links in the chain of hereditary transmission (quoted in Ribot [52, p. 210]).
Moreau 1859	It shows an incorrect conception of the law of heredity to look for a return of identical phenomena in each new generation. There are some who have refused to subject mental faculties to heredity, because they would have the character and intelligence of the descendants exactly the same as those of the progenitors; they would have one generation the copy of the other that went before it, the father and son presenting the spectacle of one being having two births, and each time leading the same life, under the same conditions. But it is not in the identity of functions, or of organic or intellectual facts that we must seek the application of the law of heredity, but at the very fountainhead of the organism, in its inmost constitution. A family whose head has died insane or epileptic, does not of necessity consist of lunatics and epileptics; but the children may be idiots, paralytics, or scrofulous. What the father transmits to the children is not insanity, but a vicious constitution which will manifest itself under various forms, in epilepsy, hysteria, scrofula, rickets. Thus it is that we are to understand hereditary transmission (quoted in Ribot [52, pp. 209–210]).
Marcé 1862 (32)	Instead of being direct, heredity can be collateral. So, for many insane, there are no traces of affected ancestors but only an affected cousin, uncle, or aunt. In other cases, heredity jumps one degree, the disease being transmitted from grandfather to grandson and sparing the middle generation. Sometimes heredity follows the sexes; we observed families in which the women become insane, while the men keep their reason intact. Finally, there is sometimes variation in the children who succumb to hereditary transmission: between two children one is struck with illness, while one is born who remains unscathed from all madness until the end of his life. Such are the odd varieties that the law of heredity can offer (p. 104).

continued

TABLE 2, *continued*

Author, Year, Reference	Text
Sankey 1866 (33)	No doubt mental individuality is transmitted from parent to offspring as well as physical resemblances, and morbid processes as well as what is called the "constitution" of a man. Indeed, we can see propensities transmitted. Hereditary influences may act not only through the physical condition in producing a liability, but the "force of example," — as a constant impression present in the mind may give a bias to action, not only in health but in disease. The child whose ancestors one after another have immolated themselves in different ways, must have that fact ever present in his mind (pp. 193–194).
Krafft-Ebing 1903 (44, 45)	The physical and mental organization and peculiarities may be transmitted from the first generation to the third, without making their appearance in the intervening generation.... Only in rare cases is the actual disease transmitted by heredity (congenital insanity, hereditary syphilis); as a rule, it is only the disposition to it that is transmitted. Under such circumstances actual disease occurs only when accessory injurious influences make themselves felt (p. 158).
Clark 1895 (42)	The factor which is inherited cannot be insanity per se, but may be an instability or disordered arrangement of nerve tissue, which allows insanity to occur, and we must look for the bequeathed antecedents of insanity, not in insanity itself as existing in progenitors, but in all maladies, which display evidence of undue instability or disorder of the highest nerve arrangements (p. 238).
Maudsley 1895 (53)	What is it that he inherits who inherits a predisposition to insanity? How far is he the thrall victim of an evil fate? In the first place, it is certain that he does not inherit actual madness, since no one is born mad; he inherits only a predisposition to it, which may be either strong or weak: so strong in a few instances as to burst forth and wreck the mind in childhood; so weak in some instances as to lie dormant and not issue in actual derangement; of such force in other instances as to be kindled into flame by the evil troubles and vicissitudes of life.... [H]e who inherits a predisposition to insanity does not necessarily get it from a parent who happens to be insane; no, not even though his father was insane when he was begotten or though in madness his mother conceived him. He gets it from where his parent got it—from the insane strain of the family stock.... Thus it comes to pass, on the one hand, that the child of an insane parent is perhaps never insane at all, and on the other hand that the child of a sane parent, who has an insane uncle or aunt, becomes insane... (pp. 47–48). A predisposition to insanity not being the heritage of something definite and known passing from one generation to another in a definite and constant way, but rather of an uncertain bundle of obscure tendencies which break up into various distributions, therefore it is impossible even to guess with any confidence what the issue shall be in a particular case (p. 51).
Mercier 1890 (43) (nature of transmission)	What is inherited from an insane person is not insanity itself, it is an undue instability of nervous organization; and hence, whenever there is undue instability of nervous organization in the progenitors, there will be liability to insanity in the offspring... (p. 145). The stability or instability of a person's highest nervous arrangements depends primarily and chiefly upon inheritance.... Every man is the outcome and the product of his ancestry... Doubtless every man is to some extent molded into conformity with circumstances by the influence of circumstances upon him; but the small amount of new character that circumstances can produce in any individual, in comparison with the characters transmitted to him by his ancestry, may be gathered from the length of time that circumstances can act upon him, in comparison with the aggregate length of time [of] ... the long line of his ancestry.... [B]ut the fact remains that, for the great majority of people, the question of the stability or instability of their highest nervous arrangements resolves itself into a question of the kind and degree of organization that they have inherited from their ancestry (pp. 142–143).
Mercier 1890 (43) (mode of transmission)	Latency and Reversion. Among the most remarkable of the many remarkable occurrences of heredity are the complementary phenomena known as Latency and Reversion. When an attribute exists in an individual, is absent in his offspring, and reappears in the third or some subsequent generation, it is said to be latent in those generations in which it does not appear; and the individual in whom it at length appears is said to revert, in so far as that attribute is concerned, to the ancestor in whom it was present (p. 149).
Regis 1895 (54)	Heredity is most frequently from the parents, that is, it is immediate. It may be on the side of both father and mother, and in that case, it is called double, or from convergent factors. Generally, it is from one parent, either father or mother, and then it is simple heredity, either paternal or maternal.... The heredity may be traced from the grandparents, having passed by the immediate ancestors. It is then mediate heredity. It may also have existed for many prior generations and in that case it is called cumulative. Heredity is either direct or collateral according as it is observed in parents or grandparents or in collateral branches of the family. Hereditary insanity may appear in children at the same time that it appeared in the parent, and it is then called homochronous. It may also appear in children a longer or shorter time before it is seen in the parent. It may then be called anticipatory as regards the parental disease, which has so far remained latent (p. 39).
Kellogg 1897 (55)	It may be well to say here that diseases are never inherited, but only tendencies to disease. In the case of Insanity it is the instability of nervous centers, the tendency to vasomotor and nutritional disorder, and the susceptibility to functional mental disturbance which are inherited (p. 84).

continued

TABLE 2, *continued*

Author, Year, Reference	Text
Kraepelin 1899 (56, 57)	Only in the most severe forms of hereditary degeneration are morbid states as such transmitted; as a rule on the predisposition to disease, to an insufficient mental stability, is hereditary, which only leads in turn to real insanity when unfavorable influences exercise their harmful effect on the basis of the hereditary predisposition (p. 68).
Macpherson 1899 (58)	It is not as a rule the special pathological characters themselves which are transmitted, but a predisposition—manifested usually by a morbid affection of nutrition, a feebleness of development, and certain functional incompetencies—which is capable of engendering under unfavorable influences diseases of very different appearances. This morbid hereditary deviation from the normal type, whether grave or light, is always associated with a corresponding change in some function of the nervous system (p. 5).
Brower 1902 (47)	There is, however, as is well known, no fatal certainty of the transmission of mental or other defect; the children of insane parents may escape altogether, or it may appear in only one or two members of a family, or may skip one or two generations (p. 19).
Dana 1904 (49)	Parents do not pass down special [psychiatric] maladies, but only a general tendency to nerve disease, which is not developed into any distinct trouble unless some disturbing cause arises (p. 23).
Chaddock 1904 (59)	Hereditary predisposition to insanity is proved by the history.... An insane ancestry casts suspicion on descendants, and this suspicion is called hereditary predisposition. When certain neuropathic symptoms are present in an individual they justify a diagnosis of a predisposition to insanity. The signs of a neuropsychopathic predisposition may be indicated rather than defined ... night-terrors ... striking eccentricity of character not due to education; lack of development of normal moral feeling ... hysteria; hypochondria; general nervous weakness devoid of sufficient cause; illogical suspicions ... these are some of the many ways in which predisposition to insanity may be indicated, but which may or may not be followed by insanity (pp. 91–92).

parents, and sometimes in different branches of the same family, seized with madness about the age of puberty, we cannot but admit a *disposition* to the disease; for though some mental irritation is usually assigned, yet the cause is often so trivial, that we cannot doubt whether the supposed effect has preceded it.... But when the susceptibility amounts only to a *predisposition*, requiring the operation of some external cause to produce the disease, there is every reason to hope, that the action of the disease may be for the most part much lessened, if not prevented altogether... (21, pp. 26–27; italics added).

Adams argues that insanity is itself never directly inherited, but familial risk can come in two “strengths.” Those with a strong family burden have a *disposition* whose onset occurs with only a “trivial” proximal cause. Those with a weaker familial background have a *predisposition*, so that insanity will arise only with a strong “external cause.” Here are four other authors supporting the concept that only a predisposition to insanity is inherited:

Spurzheim 1817: Those who deny hereditary diseases must at least admit hereditary predisposition to diseases. As weakness of certain parts runs through whole families, so at least a predisposition to insanity is propagated from parents to children... (22, p. 103).

Noble 1853: When hereditary tendency to insanity exists, then, it becomes necessary to assume that some peculiar proneness to disordered action inheres in the cerebral and nervous structures (28, p. 233).

Morel 1857: By the term heredity we understand the transmission of organic dispositions from parents to children (quoted in Ribot [52, p. 210]).

Kraepelin 1899: Only in the most severe forms of hereditary degeneration are morbid states as such transmitted; as a rule on the predisposition to disease, to an insufficient mental stability, is hereditary (56; 57, vol. 1, p. 68).

A number of these authors offer a “metaphor” for the transmitted predisposition (e.g., “weakness in certain parts” or “proneness to disordered action”). Of interest, one author wonders, in line with Folsom’s views, whether along with biological forms of heredity, psychological factors could contribute to the transmission of insanity across generations:

Sankey 1866: Hereditary influences may act not only through the physical condition in producing a liability, but the “force of example,”—as a constant impression present in the mind may give a bias to action, not only in health but in disease (33, p. 193).

In a similar vein, Du Saulle, writing in 1873 (36), described the potentially contagious nature of delusional beliefs (Table 5).

MODE OF TRANSMISSION

Several authors examined more specifically how insanity was transmitted within families (Table 2). Traditionally, heredity in Europe from the 17th century onward implied parent-offspring transmission (6). The variety of patterns is well illustrated in this passage:

Marcé 1862: Instead of being direct, heredity can be collateral. So, for many insane, there are no traces of affected ancestors but only an affected cousin, uncle, or aunt. In other cases, heredity jumps one degree, the disease being transmitted from grandfather to grandson and sparing the middle generation. Sometimes heredity follows the sexes; we observed families in which the women become insane, while the men keep their reason intact (32, p. 104).

Brower (47) comments (see Table 2) on the uncertainty involved in the familial transmission of insanity, and how often, for example, it skips a generation, whereas Arnold and Marcé note the apparent randomness of inheritance:

Arnold 1782: That diseases of any sort are hereditary is to be admitted only in a very limited sense. They do not pass from parents to their offspring with the certainty of hereditary estates. A variety of circumstances, to us totally unknown, may probably in many instances disturb the succession (16, p. 287).

Marcé 1862: [T]here is sometimes variation in the children who succumb to hereditary transmission: between two children one is struck with illness, while one is born who remains unscathed from all madness until the end of his life. Such are the odd varieties that the law of heredity can offer (32, p. 104).

SPECIFICITY OF TRANSMISSION WITHIN FAMILIES

Twenty of our authors commented on the nature of the psychiatric and nervous conditions that co-occurred in families with insanity (Table 3). They were particularly interested in the degree to which the familial transmission was homogeneous (i.e., the disorder “ran true” within families) or heterogeneous. Far more authors observed familial heterogeneity, starting with Benjamin Rush:

Rush 1812: A predisposition to certain diseases seated in parts contiguous to the seat of madness often descends from parents to their children. Thus, we sometimes see madness in a son whose father or mother had been afflicted only with hysteria, or habitual headache. The reverse of this remark likewise sometimes takes place (20, pp. 52–53).

Many authors noted the wide variety of disorders often found in the relatives of the insane:

Maudsley 1867: [N]ot insanity only in the parents, but any form of nervous disease in them—epilepsy, hysteria, and even neuralgia—may predispose to insanity in the offspring, as, conversely, insanity in the parent may predispose to other kinds of nervous disease in the offspring (34, p. 213).

Burr 1894: One inherits a susceptibility, so-called, to mental disease from intemperate, vicious, insane, or delicate ancestors (41, p. 158).

Berkley 1900: Only exceptionally ... is the type of insanity developed in the descendant identical with that present in the forefather (46, p. 106).

De Fursac 1903: Heredity is ... similar when the anomaly present in the descendant is the same as that in the ascendant; in the opposite case it is dissimilar. The latter form is by far the most frequent (50; 51, p. 9).

Krafft-Ebing 1903: It is only exceptionally that one and the same disease in progenitors and descendants develops as a result of hereditary transmission of abnormal disposition. On the contrary, there is a remarkable changeableness of the disease-pictures that has almost the significance of a law (polymorphism or transmutation) (44; 45, p. 9).

However, others note that homogeneous transmission can frequently occur:

Schule 1880/1888: The transmission of disorders may be grouped according to form. Most often, the nature of the disorder is the same as in the ancestors, that is to say that a melancholy of the descendants may appear in succession from the melancholy of the parents, frequently with the same ideas

and same tendencies. Thus, suicide is also transmitted from one generation to another (61; 62, p. 409).

Kraepelin 1899: The clinical form as well as the course of the mental disorder [often] faithfully repeats in each individual case the clinical picture of the ancestry from whom the characteristics are inherited (56; 57, p. 69).

Finally, some authors note that both forms of transmission are common:

Griesinger 1861: Sometimes hereditary mental disorders present essentially the same character in parents and children, and occasionally also in a whole line of brothers and sisters, appearing at the same age and terminating in the same manner—as, for example, by suicide. Frequently, however, this is not the case; the psychical disorder manifests itself in different ways (30; 31, p. 155).

Marcé 1862: Hereditary affections can be transmitted either in a complete or an incomplete manner. It is rare that a mental illness is found in children exactly with the same form, the same nuances as was seen in the parents. However, science has shown instances in which the transmission is as perfect as possible (32, p. 106).

Regis 1895: The hereditary taint may reveal itself in the children by a mental disorder identical with that of the parent. This occurs in cases of suicidal impulse and sometimes also in certain forms of alienation, such, for example, as circular insanity. It is then similar or homologous. It is dissimilar or transformed, on the other hand, when it is modified in passing from one generation to another. This is generally the case (54, pp. 38–40).

PERSONALITY AND AN “INSANITY SPECTRUM”

A number of our authors commented on the kind of traits and peculiarities they frequently saw in the relatives of their insane patients (Table 4). We begin with the first two of our authors to note this:

Cox 1811: There is a connate predisposition [to insanity], where certain peculiarities are exhibited, which mark men as characters who delight in oddity, in singularity of manner, modes of thinking and reasoning, such as often accompany the different temperaments when they are exquisitely marked, when extreme mobility of body and mind, or torpidity of either, takes place... (19, pp. 23–24).

Prichard 1837: In many instances it has been observed that, while some members of a family are manifest lunatics, others are only eccentric in character, displaying peculiarities of habit, conduct, and disposition (24, p. 124).

Typical comments from other authors include the following:

Griesinger 1861: An original anomalous disposition is also not to be denied in those cases where one or both parents, although not suffering under insanity, present a striking eccentricity or extravagance of character, and a morbid exaltation of the passions, which strongly approach to insanity (30; 31, p. 153).

Ball 1880: For others finally, and I frankly agree with their opinion, it is necessary to take into account not only madness [in relatives of the insane], but other material or moral [psychological] deviations parallel to it: neurosis, the

TABLE 3. Homogeneous versus heterogeneous transmission of mental illness within families

Author, Year, Reference	Text
Rush 1812 (20)	A predisposition to certain diseases seated in parts contiguous to the seat of madness often descends from parents to their children. Thus we sometimes see madness in a son whose father or mother had been afflicted only with hysteria, or habitual head-ache. The reverse of this remark likewise sometimes takes place (pp. 52–53).
Prichard 1837 (24)	In many instances one particular form of mental disorder seems to be transmitted in families.... As the particular form of insanity is determined in a great measure by the natural temperament, and as peculiarities of temperament are hereditary, the predisposition to mental disease, where it exists in a family, is likely to be determined in its type or character. This, however, is not uniformly the fact. There are many instances in which one individual is affected with melancholy dejection and a tendency to monomania, while another of the same kindred is subject to attacks of raving madness (p. 124).
Lucas 1850 (60, vol 2)	The inheritance of this nature of madness is displayed in the inheritance of all the various diseases accompanying, preceding or following it, such as epilepsy, hysteria, cerebral congestion, meningitis, encephalitis, apoplexy, paralysis, all, as we have seen, transmissible by the way of generation (p. 764).
Griesinger 1861 (30, 31)	We do well not to conceive of a family predisposition to mental diseases as limited to these alone, but rather to consider it as a disposition to serious cerebral and nervous diseases generally... (p. 153). Sometimes hereditary mental disorders present essentially the same character in parents and children, and occasionally also in a whole line of brothers and sisters, appearing at the same age and terminating in the same manner—as, for example, by suicide. Frequently, however, this is not the case; the psychical disorder manifests itself in different ways, partly dependent on external circumstances (p. 155).
Marcé 1862 (32)	Hereditary affections can be transmitted either in a complete or an incomplete manner. It is rare that a mental illness is found in children exactly with the same form, the same nuances as was seen in the parents. However, science has shown instances in which the transmission is as perfect as possible (p. 106).
Maudsley 1867 (34)	[N]ot insanity only in the parents, but any form of nervous disease in them—epilepsy, hysteria, and even neuralgia—may predispose to insanity in the offspring, as, conversely, insanity in the parent may predispose to other kinds of nervous disease in the offspring... [T]he disorders of the different nervous centers may occasionally blend, or combine, or replace one another in a remarkable manner, so as to give rise to varieties of disease intermediate between those which are commonly regarded as typical. Now this circumstance, manifest enough in individual life, is much more plainly displayed when we trace the history and progress of nervous disease through generations (pp. 213–214).
Du Saulle 1873 (36)	The simplest case is that in which ancestors transmit to their descendants the illness that they themselves suffered, with all of its accompanying symptoms.... When heredity assumes these characteristics, we say that it is similar. It is rare among mental pathology phenomena.... We don't usually see such an invariable uniformity in the transmission of mental illnesses; most often, the illness that transmits itself transforms itself. There is, however, one sort of madness that transmits from parents to children with a constant similarity: I speak of suicidal madness.... Similar heredity is as common in suicidal madness as it is rare in other forms of insanity (pp. 7–9).
Schüle 1880/1888 (61, 62)	The transmission of disorders may be grouped according to form. Most often, the nature of the disorder is the same as in the ancestors, that is to say that a melancholy of the descendants may appear in succession from the melancholy of the parents, frequently with the same ideas and same tendencies. Thus, suicide is also transmitted from one generation to another... [But] well-defined mental affections need not be alone transmitted; the cerebral, nervous, and mental affections can alter form in the offspring. Thus, a first generation may be struck with mental disorders, the second may be affected by chorea and epilepsy, and the third by melancholy and mania (p. 409).
Blandford 1886 (63)	The first remark to be made is that children may inherit insanity from parents who are not insane; and this we can explain in two ways: first, although the parents may not have been insane, insanity may have existed in their parents and reappeared in the grandchildren, skipping a generation; secondly, though the parents may not have been insane, they may have been the subjects of neuroses, which in their progeny become insanity; they may have been chronic drunkards, epileptics, hypochondriacs, weak-minded, or have indicated their nervous condition by chorea, stammering, and the like. The reverse of this is also true: insane parents, either or both, may have of a number of children some insane, others idiots, others epileptics, deaf mutes, or nervous, and some perfectly sane and sound... (p. 118). If we have the opportunity of knowing and observing all the children in a family tainted with insanity, it will not be difficult to point out, even at an early age, those individuals in which it is most likely to be developed. Children may show signs of a nervous temperament almost from birth. Convulsive attacks, night horrors, a tendency to spasmodic ailments, chorea, or epilepsy, mark out those who inherit, beyond others, the hereditary weakness (p. 122).
Hammond 1883 (23)	It is a peculiarity of nervous affections that they are not necessarily transmitted to descendants in the same form in which they appear in the ancestors. Thus, the latter may have epilepsy and the progeny neuralgia, migraine, or some variety of mental alienation, or the reverse may occur. Neither when insanity itself is clearly due to hereditary influence is it always the case that a like type of disease is transmitted. The ancestors, for instance, may have had general paralysis, and the descendants will exhibit the several forms of mania or melancholia (p. 85).

continued

TABLE 3, *continued*

Author, Year, Reference	Text
Kirchhoff 1893 (64)	As regards the form of mental disturbance, heredity acts in two ways, each of which is sharply defined, and only rarely do we find transitional forms. The more extensive group embraces symptom-complexes which are distinguished, not alone by variability as regards each one, but also by the fact that they are apt to pass into one another. This group has taught the multifarious relations of heredity; all the neuroses already mentioned and allied conditions, such as inebriety, criminal impulses, etc., lead to the most manifold symptoms as the result of heredity. In the second group there is inheritance of the same form of mental disturbance as that presented by the ancestor, but this form is very much rarer than the preceding variety. The disease may appear in the children at the same age as it did in the parents, or under similar conditions—for example, when mother and daughter are attacked in childhood. The most striking phenomenon in this respect is the inheritance of the tendency to suicide (p. 30).
Burr 1894 (41)	One inherits a susceptibility, so-called, to mental disease from intemperate, vicious, insane, or delicate ancestors (p. 31).
Regis 1895 (54)	The source of this predisposition may be not merely mental alienation in the ancestors, but other related diseases, eccentricity, neuroses, alcoholism, certain diatheses, consanguinity, etc.... The hereditary taint may reveal itself in the children by a mental disorder identical with that of the parent. This occurs in cases of suicidal impulse and sometimes also in certain forms of alienation, such, for example, as circular insanity. It is then similar or homologous. It is dissimilar or transformed, on the other hand, when it is modified in passing from one generation to another. This is generally the case (pp. 38–40).
Maudsley 1895 (53)	Except in melancholy and in dipsomania, it is unusual for the disease to pass by descent in the same form. Nor need the unsound strain in the stock show itself in any form of actual insanity; it may appear in some allied nervous disorder—in hypochondriasis, in suicide, in epilepsy, in dipsomania, in weakness of mind, in neuralgias, in stammering, in chorea, in spasmodic asthma, in some periodical nerve-storm of abnormal character; as, conversely, these disorders of one generation may in their turn forebode some form of insanity in the next generation (p. 51).
Kraepelin 1899 (56, 57)	The clinical form as well as the course of the mental disorder [often] faithfully repeats in each individual case the clinical picture of the ancestry from whom the characteristics are inherited (homogeneous inheritance).... I will even go a step further and suppose that a number of even closer groups can be distinguished which represent a pronounced tendency to homogeneous inheritance. The manic-depressive diseases, for instance, are likely to form such a group, another the psychoses of the involuntal period.... On the other hand, we likewise observe quite frequently a transforming heredity which in particular may take the most varied directions.... All these forms of inheritance have the pathological basis in common, whereas the development of the disorders seems to be determined in particular by various accidental causes (p. 69).
Macpherson 1899 (58)	In morbid heredity, diathetic and nervous conditions are seldom transmitted in the same form from parent to offspring. The morbid basis persists and it only is transmitted, the neuroses being transformed in each succeeding generation, and being different in members of the same family. This is known as dissimilar heredity or heredity by transformation.... In a certain number of cases, however, the neuroses are transmitted by heredity in the same form from parent to offspring. This is known as analogous or similar heredity (p. 6).
Berkley 1900 (46)	Only exceptionally ... is the type of insanity developed in the descendant identical with that present in the forefather; transmutations usually take place, so that among the children of neurotic parents we are apt to find various forms of mental alienation. Occasionally the same forms of insanity crop up from generation to generation... (p. 106).
Brower 1902 (47)	If besides the heredity of mental disease itself we take account of other neurotic and degenerative conditions, we greatly enlarge the scope of hereditary influence in the causation of insanity. Eccentricity, epilepsy, hysteria, "nervousness," intemperance, vagabondage, and criminality, as well as various organic and functional (so-called) neurotic disorders, are very often met with in the family histories of the insane, and there are certain disorders, the liability to which is inherited, that may alternate in the generations with mental disorder (p. 20).
Ballet 1903 (48)	Transmitted pathological characters are not always the same. A hysteric can engender a hysteric, and a case of melancholy a case of melancholy. But it is more common that the transmitted defects are different from those seen in the agents of transmission [i.e., the parents].... This is expressed by saying that heredity is sometimes similar, sometimes dissimilar. In mental pathology, similar heredity is the exception, dissimilar heredity the rule (p. 23).
Krafft-Ebing 1903 (44, 45)	It is only exceptionally that one and the same disease in progenitors and descendants develops as a result of hereditary transmission of abnormal disposition. On the contrary, there is a remarkable changeableness of the disease-pictures that has almost the significance of a law (polymorphism or transmutation). The transmutations are innumerable. The most various neuroses and psychoses appear in families affected with heredity, side by side and one after another, through generations; and they teach us that from a biologic-etiologic standpoint they are branches of but one and the same pathologic tree (p. 158).
De Fursac 1903 (50, 51)	Heredity is ... similar when the anomaly present in the descendant is the same as that in the ascendant; in the opposite case it is dissimilar. The latter form is by far the most frequent (p. 9).

TABLE 4. Role of personality/temperament/spectrum

Author, Year, Reference	Text
Cox 1811 (19)	There is a connate predisposition, where certain peculiarities are exhibited, which mark men as characters who delight in oddity, in singularity of manner, modes of thinking and reasoning, such as often accompany the different temperaments when they are exquisitely marked, when extreme mobility of body and mind, or torpidity of either, takes place.... Persons thus predisposed should carefully avoid the exciting causes. Wherever singularity of natural temper is strikingly obvious, there exists a connate predisposition to insanity (pp. 23–24).
Prichard 1837 (24)	In many instances it has been observed that, while some members of a family are manifest lunatics, others are only eccentric in character, displaying peculiarities of habit, conduct, and disposition (p. 124).
Esquirol 1845 (27)	This predisposition, which manifests itself by the external conformation, by the moral and intellectual character of individuals, is not more surprising with reference to insanity, than to gout, phthisis pulmonalis, etc. It is noticeable, even from infancy. It will explain a multitude of whims, irregularities, and anomalies of character, which should betimes have put the parents on their guard (p. 50).
Esquirol 1845, quoted in Lucas (60)	Lypemania [broadly analogous to melancholia] is ... often hereditary; Those with lypemania are born with a particular temperament, the melancholy temperament, which disposes to lypemania (vol. 2, p. 784).
Noble 1853 (28)	In what particular temperament, or constitution of body, this vicious tendency [to insanity] inheres, or in what manner it comes first into existence, are questions involved, to a great extent, in difficulty and uncertainty (p. 232).
Griesinger 1861 (30, 31)	An original anomalous disposition is also not to be denied in those cases where one or both parents, although not suffering under insanity, present a striking eccentricity or extravagance of character, and a morbid exaltation of the passions, which strongly approach to insanity (p. 153).
Marcé 1862 (32)	[We observe] intellectual quirks ... defiant, mobile, elusive sad prerogatives of some parents of the insane. They deny the most obvious facts, judge them incorrectly, and try to provide explanations for their most unreasonable actions. This is not yet madness, but there is already an abnormal state of intellect which serves as a transitional state to more serious conditions and offers a very serious and dangerous problem from the point of view of transmission (p. 107).
Ball 1880 (39)	[After discussion of various statistics for the proportion of cases of insanity with affected relatives] For me, I do not hesitate for a moment to take the broadest basis, and I say that hereditary predisposition is found in the vast majority of cases, provided that you know how to look for it.... For others finally, and I frankly agree with their opinion, it is necessary to take into account not only madness, but other material or moral [psychological] deviations parallel to it: neurosis, the neuropathic constitution, eccentricities, vices, crime, and sometimes genius (p. 360).
Schüle 1880/1888 (61, 62)	Underlying transmitted inherited disease, we can define an abnormal constitution, a defective nervous or psychic constitution; this imperfection can be physiological (lack of proper balance in the different intellectual functions; pathological exaggeration of a faculty, the others being weakened or developmental delay), or it may be a morphological deformity of the head and brain (p. 411).
Church 1900 (65)	In determining the factor of heredity we must not be content with ascertaining the existence of psychoses in the ascendants, but must seek, by careful interrogation of various members of the family, for some of the hereditary equivalents, such as epilepsy, chorea, hysteria, neurasthenia, somnambulism, migraine, organic diseases of the central nervous system, criminal tendencies, eccentricities of character, drunkenness, etc., for these equivalents are interchangeable from one generation to another, and are simply evidences of instability of the nervous system. It is the unstable nervous organization that is inherited, not a particular neurosis or psychosis, and it must be our aim in the investigation of the progenitors to discover the evidence of this (p. 611).
Brower 1902 (47)	It is not infrequently observed that the parents of the insane on one side or the other are themselves on the borderland of insanity; while not exactly over the boundary-line, they are erratic, peculiar, "nervous," or otherwise manifest a degenerative neurotic tendency. We have in these cases what has been called the insane diathesis; a condition that tends to insanity, if not in the individual himself, at least in his descendants (p. 21).
Krafft-Ebing 1903 (44, 45)	The hereditary influence of abnormal character in predisposing to insanity has been demonstrated (p. 159).

neuropathic constitution, eccentricities, vices, crime, and sometimes genius (39, p. 360).

Brower 1902: It is not infrequently observed that the parents of the insane on one side or the other are themselves on the borderland of insanity; while not exactly over the boundary-line, they are erratic, peculiar, "nervous," or otherwise manifest a degenerative neurotic tendency (47, p. 21).

Krafft-Ebing 1903: The hereditary influence of abnormal character in predisposing to insanity has been demonstrated (44; 45, p. 159).

Insanity can, these authors suggest, be transmitted from relatives who demonstrate a range of personality-like

traits described in terms such as eccentric, peculiar, and odd.

MISCELLANEOUS OBSERVATIONS

Several other observations of interest on the nature of the hereditary risk for insanity were noted by our authors (Table 5). Six are noteworthy. First, as observed by Haslam (1798), insane relatives often demonstrate a similar age at onset:

Although I have made no exact calculation, yet, from a great number of cases, it appears to be the time, when the hereditary disposition is most frequently called into action; or, to speak

more plainly, it is that stage of life when persons, whose families have been insane, are most liable to become mad (66, p. 117).

Second, Kellogg commented, in 1897, on the strength of hereditary influences in different classes of relatives:

Other things being equal, the nearness of the kinship determines the degree of the heredity, counting first in direct line parents and grandparents, and then in indirect line uncles, aunts, and cousins.... Convergent heredity, that is to say from both parents and of like kind, is apt to be very strong (55, p. 87).

Third, a number of authors noted the consequences of “inheritance of acquired characteristics,” which was accepted by virtually all medical experts and most biologists up to the 1880s, including Charles Darwin (67). Most commonly, they noted that the risk to offspring from an affected parent would be much less prior to rather than after the onset of illness in the parent. This was because the active insanity in a parent was assumed, typically by a process termed pangenesis (67), to contribute to the egg or sperm, thereby increasing illness risk in offspring:

Rush 1812: Children born previously to the attack of madness in their parents are less liable to inherit it than those who are born after it (20, p. 51).

Ball 1880: [C]hildren born to sick parents, but before the onset of madness, are infinitely less exposed [to risk] than those who have the misfortune to be born later (39, p. 362).

Fourth, one author was concerned about intrauterine effects as a special form of familial transmission:

Dagonet 1876: Striking psychological moral impressions, suffered by the mother during the gestation, can also come to exert a pernicious effect on the child that she carries in her womb and can cause in them a nervous disposition (38, p. 482).

Fifth, Dagonet also commented on the premorbid features that indicated a high hereditary risk for insanity:

Signs of hereditary predisposition.... [O]ne can notice from childhood an excessive impressionability, irritability, driving quirks, some eccentricities, nervous tics, etc.... Later, around the age of puberty, we observe a kind of hypochondria, an exaggerated nervous temperament, resulting in neuroses of various kinds, attacks of hysteria ... [and] finally, a particular moral idiosyncrasy [which often] ... disturbs the tranquility of the domestic home (38, p. 482).

Finally, Kraepelin was the only author reviewed who opined on the degree of heritable influence on different psychiatric syndromes:

Manic-depressive insanity, epileptic, hysteric mental disorders ... and lastly *Verrücktheit* (paranoia) ... develop most frequently on an hereditary basis. Infection psychoses, states of exhaustion, insanity of the involutional period, and progressive paralysis appear relatively little influenced by heredity, whereas dementia praecox, idiocy, and chronic intoxications occupy an intermediate position (56; 57, p. 68).

WHITEHEAD AND RIBOT

Having reviewed texts written by and largely for alienists/psychiatrists, I wondered whether similar views were adopted by experts outside this field. I consulted two: James Whitehead, a British physician and author of one of the few 19th-century English texts on heredity (68, 69), *On the Transmission From Parent to Offspring of Some Forms of Disease and of Morbid Taints and Tendencies*, published in 1857 (69), and the French psychologist/philosopher Théodule Ribot, author of *Heredity: A Psychological Study of Its Phenomena, Laws, Causes, and Consequences*, published in 1873 (70) and translated in 1875 (52).

As seen in Table 6, Whitehead and Ribot both offered views on the transmission of insanity consistent with the majority of our authors. Whitehead's views on the role of personality and Ribot's on “eccentricity” were also congruent with our review. Ribot emphasizes the frequent heterogeneity of the disorders in the families of insane patients.

DISCUSSION

I provide an overview of the major themes in psychiatric genetics in Western psychiatry from 1780 to 1910. Of the many topics discussed in this rich literature, I emphasize six. In addition to summarizing them, I here review the degree to which they have been replicated by the more sophisticated methods of modern psychiatric genetics.

First, most reviewed authors were convinced that hereditary factors were important in the etiology of insanity, a number of them considering it the single most important cause. There were, however, a few doubters, some on metaphysical grounds, and a rare clinician who was concerned that psychological factors might contribute substantially to the transmission of insanity in families. Recent research clearly supports the strong etiologic role of genetic risk factors for most psychiatric disorders (56).

Second, our authors were concerned with whether insanity itself was directly transmitted within families, or only the predisposition. Some background is in order here. In the 18th and 19th centuries, it was widely believed that to be truly hereditary, traits or diseases had to be manifest at birth, such as skin color, or that they at least had to run in families with high consistency (6). Insanity met neither of these criteria. Indeed, authors puzzled over the apparently random nature of inheritance. Onset was typically in early or middle adult life, and patients were often seen whose parents were well but who had more distant relatives (grandparents, aunts, uncles, etc.) who were affected. In siblings, some would become ill while others led mentally healthy lives. These patterns could be explained by assuming that the heritable trait was a predisposition that could be quiescent over development or even across generations. A further common observation encouraged this conceptualization. Many clinicians observed that onsets of insanity occurred soon after adversities, yet that many others experienced similar stressors without becoming insane. So they developed a model, articulated in the quotation from Adams above (see Table 2), in which the level of hereditary predisposition was related to the severity of stressor needed to

TABLE 5. Special topics in the hereditary transmission of insanity

Author, Year, Reference	Topic ^a	Text
Haslam 1798 (66)	AAO	Although I have made no exact calculation, yet, from a great number of cases, it appears to be the time, when the hereditary disposition is most frequently called into action; or, to speak more plainly, it is that stage of life when persons, whose families have been insane, are most liable to become mad (p. 117).
Rush 1812 (20)	AAO	It [insanity] generally attacks in those stages of life in which it has appeared in the patient's ancestors.... Children born previously to the attack of madness in their parents are less liable to inherit it than those who are born after it (p. 51).
Prichard 1837 (24)	AAO	Another observation relating to the hereditary transmission of this morbid tendency [to insanity] is, that the disease is apt to show itself in different individuals of a family at a particular period of life (p. 122).
Baillarger 1844 (26)	Sex-specific transmission	This research [the inheritance of madness] would lead to the conclusion that the transmission of intellectual and moral faculties is far more often from mother to daughter than from mother to sons and this transmission, on the contrary, takes place much more frequently from father to boys than from father to girls (pp. 167–168).
Noble 1853 (28)	IAC	Another circumstance determining the origin of constitutional predisposition, is the moral conduct of the father or mother, or both. It is something more than plausible speculation, which makes out that the physical and moral condition of parents, at the commencement of embryonic existence, influences, in some degree, the integrity of the offspring... (p. 234). It is certain, moreover, that injurious excitement of the mind, and particularly of the moral nature, especially when this is long continued and painful, has much to do with originating cerebral disease, not only in the direct subject of such excitement, but also in the offspring (p. 237).
Du Saulle 1873 (36)	Psychological contagion	Certain people suffering from delusions of persecution sometimes convert those around them to their delusions. When a person, a mentally healthy one, for that matter, lives constantly with one of these ill people, and when he/she is present at the beginning of their delusions, he/she first finds their ideas strange, then in certain cases excuses their errors in reason, shares one by one as the delusions give rise to all of their aberrations and obsessive/pathological ideas, so that after a certain time he/she has accepted and appropriated a systematized delusion created out of the blue by the sick person! (p. 10)
Dagonet 1876 (38)	IAC	If we examine the morbid conditions in parents that, apart from insanity itself, can become for children a cause of hereditary predisposition, the most prominent would be alcoholism.... [C]hildren conceived during the drunkenness of the father, even if the father was not a drunkard, produces a strong predisposition to insanity... (p. 478). Striking psychological moral impressions, suffered by the mother during the gestation, can also come to exert a pernicious effect on the child that she carries in her womb and can cause in them a nervous disposition (p. 482).
Dagonet 1876 (38)	"Infectious" transmission	[E]pidemics of madness that appear from time to time under the influence of certain conditions of general overexcitation, and which can arise because of the widespread hereditary predispositions in the country.... It is, indeed, enough for some highly predisposed people to attend to the pernicious spectacle of eccentric and extravagant acts, to receive a deep impression that could, in turn, become the starting point of their own disorders.... [S]uch examples cannot be lost; they must lead to measures of wise prophylaxis. It would be a useful caution to order to move away from the sad sight of unfortunate people who have lost their reason, people in whom we notice a strong susceptibility ... a lively and mobile imagination, an abnormal impressionability; in a word, any predisposition to alienation (pp. 475–476).
Dagonet 1876 (38)	Precursors	Signs of hereditary predisposition.... [O]ne can notice from childhood an excessive impressionability, irritability, driving quirks, some eccentricities, nervous tics, etc. The child sometimes shows a wild nature, is unsociable: he can be of weak intelligence; he is sometimes, on the contrary, endowed with a strong and precocious intelligence. Later, around the age of puberty, we observe a kind of hypochondria, an exaggerated nervous temperament, resulting in neuroses of various kinds, attacks of hysteria ... [and] finally, a particular moral idiosyncrasy that becomes the source of incessant sorrows, and which, in most cases, disturbs the tranquility of the domestic home (p. 482).
Ball 1880 (39)	IAC	Finally, note that children born to sick parents, but before the onset of madness, are infinitely less exposed [to risk] than those who have the misfortune to be born later (p. 362).
Hammond 1883 (23)	Maternal effects	That the tendency to certain diseases is derived from the seminal fluid of the male, and in an equal or perhaps greater degree from the ovaries of the female, does not admit of a reasonable doubt; but that there are other agencies at work capable of influencing the child while yet unborn is quite as certain. And this fact demands that a distinction shall be made between those diseases or other peculiarities which are connate and those which are purely hereditary. By a connate disease we understand one which the child possesses when born, not necessarily the result of any similar taint or impression received from the system, either of the father or mother, but due to accidents or mental influences operating through the mother. For instance, a child may be born idiotic, not because either of the parents or other ancestors were similarly affected, but through the influence of some severe mental or physical shock received by the mother during her pregnancy.... Such cases are, of course, not due to hereditary transmission, for a disease cannot be communicated hereditarily which has not affected either of the parents or any other ancestor (p. 77).

continued

TABLE 5, *continued*

Author, Year, Reference	Topic ^a	Text
Clark 1895 (42)	Methodological problems	In estimating the influence of heredity in producing a tendency to insanity, regard has to be had to the number of instances of insanity that have occurred among the relatives, direct or collateral, and of the taint of the patient under consideration. Heredity has been considered to exist in those cases, and in those only in which a record of insanity has been found among the near relatives. [However,] first this estimate is liable to error. The insanity of the relative may not have been heritable, or at least remotely so, as, for example, in general paralysis of the insane. Second, the insanity of the relative and that of the patient under consideration may arise from different sources, and not from a common cause (p. 238).
Kellogg 1897 (55)	Potency of various relations	Other things being equal, the nearness of the kinship determines the degree of the heredity, counting first in direct line parents and grandparents, and then in indirect line uncles, aunts, and cousins.... Convergent heredity, that is to say from both parents and of like kind, is apt to be very strong (p. 87).
Kellogg 1897 (55)	IAC	A child born after the parents' Insanity will be affected more likely than one born before the attack. The heredity will be strongest in those born nearest and after the attack, provided the parent's recovery is complete, but the children of imperfectly recovered patients may have decided heredity. Heredity is apt to be intense in children begotten in the acute incubatory stage of mental diseases... (p. 87). A somewhat similar direct origin of morbid heredity proceeds from physical or psychical influences active in the parents at the moment of the conception of the child. These influences may be exhausting diseases, toxic, and specially alcoholic, conditions, and powerfully distressing emotions, which, like the maternal impressions of gestation, may be followed by bodily or mental abnormalities in the offspring (pp. 88–89).
Macpherson 1899 (58)	IAC	Pathological influences, acting on the germ-plasm and sperm cell, tend to break the continuity of physiological inheritance and to create new characteristics, which, being abnormal, are less in harmony with the environment, and consequently hamper the individual in the struggle for existence (p. 5).
Kraepelin 1899 (56, 57)	Different degrees of heritability	Manic-depressive insanity, epileptic, hysteric mental disorders ... and lastly <i>Verrücktheit</i> (paranoia) ... develop most frequently on an hereditary basis. Infection psychoses, states of exhaustion, insanity of the involuntal period and progressive paralysis [general paresis of the insane] appear relatively little influenced by heredity, whereas dementia praecox, idiocy, and chronic intoxications occupy an intermediate position (p. 68).
Brower 1902 (47)	IAC	[T]he insanity of the parent is no insurance of that of the child, and ... if it has occurred after the birth of the latter, there is a better chance of its escape. In that case the offspring inherits only the general weakness that caused the breakdown of the parent, not the added injury to the brain from the parental insanity itself (p. 20).
Ballet 1903 (48)	Pregnancy effects	It is also necessary to take into account in the search for transmitted defects, the condition of the mother and any physiological or pathological incidents that may have occurred during pregnancy, the emotions, the fears, the illnesses of various natures can in fact exert an unfortunate influence on the development of the child during pregnancy (p. 27).
Dana 1904 (49)	Pregnancy effects and AAO	Injuries or even severe shock to the mother during the early months of pregnancy sometimes leads to nervousness in the offspring. The mother transmits neuroses more often than the father.... Morbid traits that have become fixed in a family reappear at about the same age in the descendants (pp. 23–24).

^a AAO=similarity of age at onset in affected relatives; IAC=inheritance of acquired characteristics, most typically increased risk for children born after versus before parental onset of illness.

provoke the onset of insanity (71). Molecular genetic methods have shown definitively that psychiatric disorders are not full penetrant “genetic diseases” but rather are highly polygenic, so that what is inherited is indeed a liability to illness (57, 72). Many empirical studies have supported the existence of gene-by-environment interaction in the etiology of psychiatric disorders (73–75).

Third, the probabilistic nature of the transmission of insanity was often noted as a concomitant of the liability theory. This explained why insanity would often skip generations or occurred in only a few of many siblings. The first of these observations would now be explained by the “incomplete” penetrance of the transmitted liability. The second of these observations could be explained the same way, but also by Mendel's law of segregation, rediscovered in 1900, toward the very end of our historical period (76).

Fourth, despite the varied and informal diagnostic approaches practiced over this period, it was widely observed

that, with respect to severe mental illness, like often did not beget like. However, several authors did comment that in some families, syndromes did “run true,” particularly suicide and what we would now call bipolar illness.

The rise of systematic family and twin studies has repeatedly demonstrated that the hope that psychiatric disorders, “properly diagnosed,” would run true within families has failed to materialize. Repeated studies have shown that close relatives of carefully selected patients with one given disorder typically have an increased risk for a range of psychiatric disorders (77). Using a related method, now confirmed by molecular genetic studies (78), most of our disorders have quite substantial genetic correlations with other psychiatric conditions (79, 80). A consensus might be that a moderate proportion of genetic risk for most disorders is unique to that disorder, but considerable sharing of genetic risk is seen across groups of disorders (e.g., internalizing, externalizing, psychotic) (58–60, 72).

TABLE 6. Quotations from Whitehead (1858) and Ribot (1873) on the role of heredity in the etiology of insanity

Author, Year, Reference	Topic	Text
Whitehead 1858 (69)	Transmission of insanity	The hereditary tendency to insanity appears to be so general, that it has not escaped the notice of any author who has written on mental pathology (p. 41).
	Role of personality	As there is no physical peculiarity more liable to transmission than that of temperament, so the several types of disease peculiar to such condition must be expected to influence any specific idiosyncrasy or diathesis derived from the parent.... [I]n the nervous temperament, disturbances of the cerebral system must be expected as a complication, convulsive affections, epilepsy, hysteria, chorea, [and] mania (pp. 43–44).
Ribot 1873 (70)	Transmission of insanity	Does the study of mental diseases contribute its quota of facts in favor of heredity? The answer must be in the affirmative. The transmission of all kinds of psychological anomalies whether of passions and crimes, of which we have already spoken, or of hallucinations and insanity, of which we are next to speak is so frequent, and evidenced by such striking facts, that the most inattentive observers have been struck by it, and that morbid psychological heredity is admitted even by those who have no suspicion that this is only one aspect of a law which is far more general (p. 119).
	Polymorphic heredity	The metamorphoses of heredity are still more perplexing. Nervous disorders are often transformed in their transmission. Convulsions in the progenitors may change to hysteria or to epilepsy in the descendants. A case is cited where hyperaesthesia in the father branched out in the grandchildren into the various forms of monomania, mania, hypochondria, hysteria, epilepsy, convulsions, spasms. Facts of this kind are very numerous. To confine ourselves to psychological metamorphoses, nothing is more frequent than to see simple insanity become suicidal mania, or suicidal mania become simple insanity, alcoholism, or hypochondria (p. 121).
	Eccentricity in transmission of psychiatric illness	Just as real insanity ... may be hereditarily reproduced only under the form of eccentricity, may be transmitted from progenitors to descendants only in modified form, and in more or less mitigated character, so a state of simple eccentricity in the parents, a state which is no more than a peculiarity or a strangeness of character, may in the children be the origin of true insanity. Thus, in these transformations of heredity we sometimes have the germ attaining its maximum intensity; and, again, a maximum of activity may revert to the minimum (p. 212).

Fifth, a number of authors expanded the range of conditions frequently present in the relatives of the insane to include personality traits reflecting eccentricities and behavioral oddities. They understood such conditions to bear a close familial relationship with classical insanity. The results from the famous Danish adoption study of schizophrenia (81, 82) and several subsequent family studies (83, 84) confirmed these impressions, providing evidence for a familial/genetic link between classical schizophrenia and a personality disorder characterized by odd speech, behavior, and beliefs along with poor rapport and social isolation. Evidence for personality-like diagnostic spectra have also been seen in family members of individuals with other psychiatric disorders, including bipolar illness and autism (77, 85).

Sixth, inheritance for the early workers in psychiatric genetics was commonly understood to include prior environmental parental experiences (67) and, for some authors, parent-offspring transmission arising from psychological effects. The first of these theories did not stand the test of time. In the final decades of the 19th century, August Weissmann showed that in multicellular organisms, inheritance takes place only by means of the germ cells, thereby disproving the widely held theories of Lamarckian inheritance of acquired characteristics (9). Interestingly, the early generation of adoption studies of major psychiatric disorders, often with modest sample sizes, typically found evidence only for genetic transmission across generations (61, 67). However, consistent with the claims of some of our 19th-century authors, larger and more

powerful adoption designs have recently reliably detected evidence for environmental parent-offspring transmission across a range of psychiatric disorders (68, 69).

Limitations

This essay should be viewed in the context of five potential limitations. First, texts were chosen because of language and availability from online and library resources and not by content. However, bias may have affected this process. Second, space limitations precluded details of background features of particular authors, for example, Heinroth's views on sin in the etiology of insanity (57). Third, the reviewed texts were entirely from English/American, French, and German/Austrian authors. Fourth, I strove to select quotations objectively, but cannot rule out a bias, for example, focusing preferentially on certain topics. Finally, while this study was not designed to examine differences of author viewpoints during the period of 1780–1910, no striking trends were observed. For example, the rise of infectious disease theories in general medicine in the late 19th century produced a commensurate reduction in interest in hereditary theories (56). I saw no such trend among our authors.

CONCLUSIONS

I have provided, through a review of a large, hopefully representative set of primary sources, an overview of the commonly expressed views of the role of heredity in the etiology of insanity from 1780 to 1910. What has been learned?

First, we have gained insight into what our predecessors understood about the role of heredity in the etiology of insanity on the basis of their extensive clinical experiences with patients and their families. Second, what about their specific conclusions? Is there any reason to take their findings seriously compared with results from the far more methodologically rigorous reports of our own era?

A first reaction might be that the collective wisdom of the work of these authors is scientifically useless. Perhaps they result from biased observations based on faulty preconceptions, since no controlled studies were done. I am skeptical of this approach for two reasons. First, having read this literature for many hours, I find that such an approach would reflect a radical devaluation of the experiences of earlier practitioners of our discipline. Second, as the brief review above suggests, our more refined scientific methods appear to have largely, albeit not entirely, verified their conclusions.

I suggest an alternative approach. Recent work in the philosophy of science has valued “triangulation,” where different kinds of methods are used to address an empirical question (86). The value of a congruence of observations is seen as stronger the greater the differences in methods. Unlike replication, converging results from quite divergent methods are unlikely to arise from similar methodologic failings. In summary, this inquiry has sought to provide a historical context in which to understand the development of the modern field of psychiatric genetics. It provides us a window on their empirical findings obtained by methods quite different from those we now use, which, I suggest, can usefully complement our own views on several key issues within our field.

AUTHOR AND ARTICLE INFORMATION

Virginia Institute of Psychiatric and Behavioral Genetics and Department of Psychiatry, Virginia Commonwealth University, Richmond.

Send correspondence to Dr. Kendler (kenneth.kendler@vcuhealth.org).

The author reports no financial relationships with commercial interests.

Received March 22, 2020; revision received June 16, 2020; accepted July 27, 2020; published online Oct. 15, 2020.

REFERENCES

- Porter TM: Genetics in the Madhouse: The Unknown History of Human Heredity. Princeton, NJ, Princeton University Press, 2018
- Cullen G: Synopsis Nosologiae Methodicae, 3rd ed. London, Edinburgh Press, 1780
- Rudin E: Einige Wege und Ziele der Familienforschung, mit Rücksicht auf die Psychiatrie. Z Gesamte Neurol Psychiatr 1911; 7:487
- Rosanoff AJ, Orr FI: A study of insanity in the light of the Mendelian theory (Bulletin 5). Cold Springs Harbor, NY, Eugenics Records Office, 1911
- López Beltrán C: The medical origins of heredity, in Heredity Produced: At the Crossroad of Biology, Politics, and Culture, 1500–1870. Edited by Müller-Wille S, Rheinberger H-J. Cambridge, Mass, MIT Press, 2007, pp 105–132
- López-Beltrán C: Human heredity 1750–1870: the construction of a domain (doctoral dissertation). King's College London (University of London), 1992
- Churchill FB: From heredity theory to Vererbung: the transmission problem, 1850–1915. Isis 1987; 78:337–364
- Meloni M: Political Biology: Science and Social Values in Human Heredity From Eugenics to Epigenetics. New York, Palgrave Macmillan, 2016
- Robinson G: A Prelude to Genetics: Theories of a Material Substance of Heredity: Darwin to Weismann. Lawrence, Kan, Coronado Press, 1979
- Worboys M: From heredity to infection? Tuberculosis, 1870–1890, in Heredity and Infection: The History of Disease Transmission. Edited by Gaudillière J-P, Löwy I. London, Routledge, 2001, pp 81–100
- Heron D: A First Study of the Statistics of Insanity and the Inheritance of the Insane Diathesis. London, Dulau and Co, 1907
- Rudin E: Studien über Vererbung und entstehung geistiger Störungen. I. Zur vererbung und neuentstehung der Dementia praecox (Studies on the inheritance and origin of mental illness. I. The problem of the inheritance and primary origin of dementia praecox), in Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie, Number 12. Berlin, Springer, 1916
- Koller J: Beitrag zur Erblichkeitsstatistik der Geisteskranken im Canton Zürich; Vergleichung derselben mit der erblichen Belastung gesunder Menschen durch Geistesstörungen u dergl. Arch Psychiatr Nervenkr 1895; 27:268–294
- Jauregg JWv: Ueber erbliche Belastung. Wien Klin Wochenschr 1902; 15:1153–1159
- Diem O: Die psycho-neurotische erbliche Belastung der Geistesgesunden und der Geisteskranken: Eine statistisch-kritische Untersuchung auf Grund eigener Beobachtungen, I Teil, vol 2. Archiv für Rassen- und Gesellschaftsbiologie, 1905, pp 215–252
- Arnold T: Observations on the Nature, Kinds, Causes, and Prevention of Insanity, Lunacy, or Madness. Leicester, UK, Printed by G Ireland, for G Robinson, 1782
- Harper A: A Treatise on the Real Cause and Cure of Insanity: In Which the Nature and Distinctions of the Disease Are Fully Explained and the Treatment Established on New Principles. London, C Stalker, 1789
- Crichton A: An Inquiry Into the Nature and Origin of Mental Derangement: Comprehending a Concise System of the Physiology and Pathology of the Human Mind and a History of the Passions and Their Effects. London, T Cadell, Junior, and W Davies in the Strand, 1798
- Cox JM: Practical Observations on Insanity: To Which Are Subjoined Remarks on Medical Jurisprudence as Connected With Diseased Intellect. Philadelphia, Thomas Dobson, 1811
- Rush B: Medical Inquiries and Observations, Upon the Diseases of the Mind. Philadelphia, Kimber & Richardson, 1812
- Adams J: A Treatise on the Supposed Hereditary Properties of Diseases. London, Printed for J Callow, 1814
- Spurzheim JG: Observations on the Deranged Manifestations of the Mind or Insanity. London, Printed for Baldwin, Cradock, and Joy, 1817
- Hammond WA: A Treatise on Insanity in Its Medical Relations. New York, D Appleton and Company, 1883
- Prichard JC: A Treatise on Insanity and Other Disorders Affecting the Mind. Philadelphia, Haswell, Barrington, and Haswell, 1837
- Morris BR: A theory as to the proximate cause of insanity. Prov Med Surg J 1844; 7:303–306
- Baillarger JGF: Recherches statistiques sur l'hérédité de la folie. Paris, Bourgogne et Martinet, 1844
- Esquirol JED: Mental Maladies: A Treatise on Insanity. Translated from the French, with additions, by Hunt EK. Philadelphia, Lea and Blanchard, 1845
- Noble D: Elements of Psychological Medicine: An Introduction to the Practical Study of Insanity, Adapted for Students and Junior Practitioners. London, John Churchill, 1853
- Bucknill JC, Tuke DH: A Manual of Psychological Medicine: The History, Nosology, Description, Statistics, Diagnosis, Pathology, and Treatment of Insanity. Philadelphia, Blanchard and Lea, 1858
- Griesinger W: Die Pathologie und Therapie der psychischen Krankheiten: für Aerzte und Studierende. Stuttgart, Germany, Verlag von Adolph Krabbe, 1861

31. Griesinger W: *Mental Pathology and Therapeutics*. London, New Sydenham Society, 1867
32. Marcé L-V: *Traité pratique des maladies mentales*. Paris, J-B Baillière et Fils, 1862
33. Sankey WHO: *Lectures on Mental Diseases*. London, J Churchill and Sons, 1866
34. Maudsley H: *The Physiology and Pathology of the Mind*. New York, D Appleton and Company, 1867
35. Blandford GF: *Insanity and Its Treatment: Lectures on the Treatment, Medical and Legal, of Insane Patients*. Edinburgh, Oliver & Boyd, 1871
36. Du Saulle L: *La folie héréditaire: leçons professées à l'École pratique*. Paris, Adrien Delahaye, 1873
37. Dickson JT: *The Science and Practice of Medicine in Relation to Mind: The Pathology of Nerve Centres and the Jurisprudence of Insanity Being a Course of Lectures Delivered in Guy's Hospital*. New York, D Appleton and Company, 1874
38. Dagonet H: *Nouveau traité élémentaire et pratique des maladies mentales: Suivi de considérations pratiques sur l'administration des asiles d'aliénés*. Paris, Librairie J-B Baillière et Fils, 1876
39. Ball B: *Leçons sur les maladies mentales*. Paris, Asselin, 1880
40. Folsom CF: *Mental Diseases. American System of Medicine*, vol 5. Boston, 1886
41. Burr CB: *A Primer of Psychology and Mental Disease*. Detroit, George S Davis, 1894
42. Clark D: *Mental Diseases: A Synopsis of Twelve Lectures Delivered at the Hospital for the Insane, Toronto, to the Graduating Medical Classes*. Toronto, William Briggs, 1895
43. Mercier C: *Sanity and Insanity*. London, Walter Scott, 1890
44. Krafft-Ebing Rv: *Lehrbuch der Psychiatrie: auf klinischer Grundlage für praktische Ärzte und Studierende*, 7th ed, revised and expanded. Stuttgart, Germany, Enke, 1903
45. Krafft-Ebing Rv: *Text-Book of Insanity: Based on Clinical Observations (for Practitioners and Students of Medicine)*. Translated by Chaddock CD. Philadelphia, FA Davis, 1904
46. Berkley HJ: *A Treatise on Mental Diseases*. New York, D Appleton and Company, 1900
47. Brower DR, Bannister HM: *A Practical Manual of Insanity for the Medical Student and General Practitioner*. Philadelphia, WB Saunders, 1902
48. Ballet G: *Traité de pathologie mentale*. Paris, Octave Doin, 1903
49. Dana CL: *Text-Book of Nervous Diseases and Psychiatry: For the Use of Students and Practitioners of Medicine*, 6th revised and enlarged ed. New York, William Wood, 1904
50. De Fursac JR: *Manuel de psychiatrie*. Paris, Felix Alcan, Editeur, Ancienne Librairie Germer Baillière et Cie, 1903
51. De Fursac JR: *Manual of Psychiatry*. New York, John Wiley & Sons, 1905
52. Ribot T: *Heredity: A Psychological Study of Its Phenomena, Laws, Causes, and Consequences*. New York, C Appleton and Company, 1875
53. Maudsley H: *The Pathology of Mind: A Study of Its Distempers, Deformities, and Disorders*. London, Macmillan and Company, 1895
54. Régis E: *A Practical Manual of Mental Medicine*, 2nd ed. Philadelphia, P Blakiston, Son & Company, 1895
55. Kellogg TH: *A Text-Book on Mental Diseases for the Use of Students and Practitioners of Medicine*. New York, William Wood & Company, 1897
56. Kraepelin E: *Psychiatrie: Ein Lehrbuch für Studierende und Aerzte*, 6th ed. Leipzig, Barth, 1899
57. Kraepelin E: *Psychiatry: A Textbook for Students and Physicians* (translation of the 6th edition of *Psychiatrie*; vol 1 translated by Metoui H; edited by Quen J). Canton, Mass, Science History Publications, 1990
58. Macpherson J: *Mental Affections: An Introduction to the Study of Insanity*. London, Macmillan and Company, 1899
59. Chaddock CG: *Outlines of Psychiatry: Introductory Lessons Designed for the Use of Students of Medicine*. St Louis, Commercial Printing Company, 1904
60. Lucas P: *Traité philosophique et physiologique de l'hérédité naturelle dans les états de santé et de maladie du système nerveux: avec l'application méthodique des lois de la procréation au traitement général des affections dont elle est le principe*, vol 2. Paris, JB Baillière, 1850
61. Schüle H: *Handbuch Der Geisteskrankheiten*. Leipzig, Verlag Von FCW Vogel, 1880
62. Schüle H: *Traité clinique des maladies mentales*. Paris, Lecrosnier et Babe, 1888
63. Blandford GF: *Insanity and Its Treatment: Lectures on the Treatment, Medical and Legal, of Insane Patients*, 3rd ed. New York, William Wood and Company, 1886
64. Kirchhoff T: *Handbook of Insanity for Practitioners and Students*. New York, William Wood & Company, 1893
65. Church A, Peterson F: *Nervous and Mental Diseases*, 2nd ed. Philadelphia, WB Saunders, 1900
66. Haslam J: *Observations on Insanity: With Practical Remarks on the Disease, and an Account of the Morbid Appearances on Dissection*. London, Printed for F and C Rivington, and sold by J Hatchard, 1798
67. Zirkle C: The early history of the idea of the inheritance of acquired characters and of pangenesis. *Trans Am Philos Soc* 1946; 35: 91–151
68. Rushton AR: *Genetics and Medicine in Great Britain, 1600 to 1939*. Bloomington, Ind, Trafford Publishing, 2009
69. Whitehead J: *On the Transmission, From Parent to Offspring, of Some Forms of Disease, and of Morbid Taints and Tendencies*, 2nd ed. London, John Churchill, 1858
70. Ribot TA: *L'hérédité, étude psychologique sur ses phénomènes, ses lois, ses causes, ses conséquences*. Paris, Ladrangé, 1873
71. Kendler KS: A prehistory of the diathesis-stress model: predisposing and exciting causes of insanity in the 19th century. *Am J Psychiatry* 2020; 177:576–588
72. Smoller JW, Andreassen OA, Edenberg HJ, et al: Psychiatric genetics and the structure of psychopathology. *Mol Psychiatry* 2019; 24: 409–420
73. Sigvardsson S, Bohman M, Cloninger CR: Replication of the Stockholm Adoption Study of Alcoholism: confirmatory cross-fostering analysis. *Arch Gen Psychiatry* 1996; 53:681–687
74. Kendler KS, Kessler RC, Walters EE, et al: Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry* 1995; 152:833–842
75. Tienari P: Interaction between genetic vulnerability and family environment: the Finnish Adoptive Family Study of Schizophrenia. *Acta Psychiatr Scand* 1991; 84:460–465
76. Olby RC: *Origins of Mendelism*. London: Constable, 1966
77. Weissman MM, Gershon ES, Kidd KK, et al: Psychiatric disorders in the relatives of probands with affective disorders: the Yale University–National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry* 1984; 41:13–21
78. Cross-Disorder Group of the Psychiatric Genomics Consortium: Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013; 381:1371–1379
79. Kendler KS, Aggen SH, Knudsen GP, et al: The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *Am J Psychiatry* 2011; 168:29–39
80. Anttila V, Bulik-Sullivan B, Finucane HK, et al: Analysis of shared heritability in common disorders of the brain. *Science* 2018; 360: eaap8757
81. Kety SS: The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. *J Psychiatr Res* 1968; 6:345–362
82. Kendler KS, Gruenberg AM, Kinney DK: Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. *Arch Gen Psychiatry* 1994; 51:456–468
83. Baron M, Gruen R, Asnis L, et al: Familial relatedness of schizophrenia and schizotypal states. *Am J Psychiatry* 1983; 140:1437–1442

84. Kendler KS, McGuire M, Gruenberg AM, et al: The Roscommon Family Study, III: schizophrenia-related personality disorders in relatives. *Arch Gen Psychiatry* 1993; 50:781–788
85. Sucksmith E, Roth I, Hoekstra RA: Autistic traits below the clinical threshold: re-examining the broader autism phenotype in the 21st century. *Neuropsychol Rev* 2011; 21:360–389
86. Munafo MR, Davey Smith G: Robust research needs many lines of evidence. *Nature* 2018; 553:399–401
87. Rushton AR: *Genetics and Medicine in the United States: 1800 to 1922*. Baltimore, Johns Hopkins University Press, 1994
88. Stubbe H. *History of Genetics: From Prehistoric Times to the Rediscovery of Mendel's Laws*. Cambridge, Mass, MIT Press, 1972
89. Sturtevant AH: *A History of Genetics*. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 2001
90. Prichard JC: *Researches Into the Physical History of Man*. London, John and Arthur Arch, 1813
91. Steinau JH: *A Pathological and Philosophical Essay on Hereditary Diseases, With an Appendix on Inter-marriage and the Inheritance of the Tendency to Moral Depravities and Crimes*. London, Simpkin, Marshall, & Co, 1843
92. Lucas P: *Traité philosophique et physiologique de l'hérédité naturelle dans les états de santé et de maladie du système nerveux: avec l'application méthodique des lois de la procréation au traitement général des affections dont elle est le principe*, vol 1. Paris, JB Baillière, 1847
93. Darwin CR: *On the Origin of Species by Means of Natural Selection*. London, Murray, 1859
94. Darwin C: *The Variation of Animals and Plants Under Domestication*, vol 2. London, Murray, 1868
95. Galton F: *Hereditary Genius: An Inquiry Into Its Laws and Consequences*. London, Macmillan and Company, 1869
96. Galton F: *Natural Inheritance*. London, Macmillan and Company, 1889
97. Meynert T: *Psychiatry: A Clinical Treatise on Diseases of the Fore-Brain, Based Upon a Study of Its Structure, Functions, and Nutrition*, part I: The Anatomy, Physiology, and Chemistry of the Brain. Translated by Sachs B. New York, GP Putman's Sons, 1885