Potential confounds in psychiatric genetic research: the case of pellagra

Jay Joseph*

California School of Professional Psychology, Alameda, USA

Abstract

This paper looks at pellagra — a disease ultimately found to be caused by a vitamin deficiency, and manifested by skin lesions, gastrointestinal problems, and mental disorientation — as a way of demonstrating the potential for environmental confounds in psychiatric genetic research. Family and twin studies are commonly used research methods in psychiatric genetics, and constitute the main source of evidence supporting a genetic predisposition for many psychiatric conditions. Analysis includes a discussion of the early 20th century argument that pellagra carried a hereditary predisposition. Eugenists such as Charles Davenport reached this conclusion on the basis of family pedigree studies, but failed to appreciate the now widely held belief that genetic inferences from family studies are confounded by the common environment shared by families. It is also argued that a pellagra twin study, had it been performed, would have likely found monozygotic twins to be more concordant for pellagra than dizygotic twins. Studies are cited showing that monozygotic twins share a more similar environment and have more similar dietary preferences than dizygotics. In addition, it is argued that even among reared-apart monozygotic twins, high concordance would be expected on the basis of environmental similarity. Finally, pellagra is cited as an example of the potential harm of the “genetic predisposition” concept when environmental factors are unknown for a particular diagnosis.

Keywords: Genetics; Pellagra; Twin studies; Epidemiology; Eugenics; Psychiatry

1. Introduction

Pellagra is a disease that ravaged poor people in the southern part of the United States during the first half of the 20th century. Before then, it had been known in
southern Europe for almost 200 years. The often fatal disease, still found among the world’s poor, is characterized by severe skin rash, gastrointestinal problems, and mental disturbance. Between 1730 and 1930 pellagra claimed over half a million lives, including tens of thousands of poor black and white southerners (10,000 deaths in 1929 alone; Carpenter, 1981). On the basis of the pioneering work of Joseph Goldberger and others (Goldberger & Wheeler, 1915; Goldberger, Wheeler & Sydenstricker, 1918), it was firmly established that pellagra is caused by a dietary deficiency linked to malnutrition among the southern poor; in other words, pellagra was (and is) a disease of hunger and poverty. In spite of Goldberger’s discovery, it took 25 more years to finally wipe out pellagra in the United States. The reasons for the unnecessary and tragic period between discovery and effective action have been discussed elsewhere (Chase, 1980, Chapter 9; Etheridge, 1972; Roe, 1973).

This paper is about pellagra as the subject of genetic study. The condition presents a lucid example of how psychiatric genetic research methods are potentially confounded by environmental factors, and of the frequently irrelevant concept of “genetic predisposition”. Here, the discussion is limited to a published family pedigree study, and speculation about what a pellagra twin study might have found. Although adoption studies have been used by psychiatric genetics in the study of schizophrenia (Heston, 1966; Kety, Rosenthal, Wender & Schulsinger, 1968; Kety, Rosenthal, Wender, Schulsinger & Jacobsen, 1975; Rosenthal, Wender, Kety, Welner & Schulsinger, 1971; Tienari et al., 1994), there is evidence that the selective placement of adoptees invalidated these studies (Joseph, 1999a, b). A discussion of the possible results of a pellagra adoption study would take us beyond the bounds of reasonable speculation, and will therefore not be attempted — other than to point out that because of social conditions and agency placement policies, the socioeconomic status of biological and adoptive families is usually correlated. As discussed elsewhere (Joseph, 1999a), non-random placements would have likely confounded a pellagra adoption study:

In the early part of the 20th century, [pellagra] was thought to have a strong inherited component, based on its tendency to cluster in certain families. It was later shown that pellagra is caused by [a vitamin deficiency]. It had occurred mainly in poor families, whose members did not eat enough of the foods supplying this needed vitamin ... If an agency had placed adoptees into homes corresponding to the socioeconomic status of the adoptee’s biological family, then adoptees born into poor families would have been placed into poorer adoptive homes, where they would have been more likely to develop pellagra (p. 134).

While the schizophrenia adoption studies have been widely cited, the claim of important genetic factors for most psychiatric diagnoses is based on family and twin studies.

Although there is a widespread consensus that schizophrenia carries a genetic predisposition, the environmental factors thought to trigger it remain unknown, or are at least controversial. Fortunately, the cause of pellagra is known, and the author
will argue that psychiatric genetic methods would likely point to the operation of genetic factors in a condition known to be caused by an unhealthy environment.

2. Family studies

“Running in the family” is commonly viewed by the general public as meaning that transmission is due to genetic factors. Although most epidemiologists and psychiatric geneticists nowadays acknowledge that family studies are confounded by environmental factors because families share both common genes and a common environment, several important researchers continue to point to family studies as evidence of genetic transmission. For example, Russell Barkley, a leading investigator of attention-deficit hyperactivity disorder (ADHD), has written, “Family aggregation studies find that ADHD clusters among biological relatives of children or adults with the disorder, *strongly implying a hereditary basis to this condition* [emphasis added]” (Barkley, 1998, p. 36). Like pellagra, ADHD clusters in families sharing both genes and environment. Barkley’s reasoning, however, is as false for ADHD as it is for pellagra. Simply put, “familiarity” does not equal “hereditary”.

The pioneers of the American eugenics movement were quite certain that pellagra had a hereditary basis. According to Charles Davenport (1916), “Pellagra is not an inheritable disease in the sense in which brown eye color is inheritable. The course of the disease does depend, however, on certain constitutional, inheritable traits of the affected individual” (p. 13). Davenport based his conclusions on the results of his family study, then known as a “eugenic family study” (Davenport & Laughlin, 1915). In fact, even before the advent of eugenic family studies, Davenport believed that “many physical, mental and moral traits have been proved to have an hereditary basis, and it seems probable that in practically all there is an hereditary factor of more or less importance”. He saw family studies as “afford[ing] the means of studying this [proven] hereditary factor” (Davenport & Laughlin, 1915, p. 3).

In support of the alleged hereditary basis of pellagra, Davenport (1916) provided 15 pages of the pedigrees of affected families. These diagrams showed that pellagra clustered in families at a rate far greater than would be expected in the general population. Although Davenport mistakenly believed that the condition was communicable, his fundamental position was that “the constitution of the organism must be held to be the principal cause of the diversity which persons show in their reaction to the same disease-inciting factors. This constitution of the organism is a racial, that is, hereditary factor” (p. 4). (Davenport mistakenly believed that African-Americans were constitutionally less susceptible to pellagra). In Davenport’s paper, one searches in vain for any mention of the fact that most pellagrins lived in dire poverty. Conspicuously absent from his study are words such as “poor”, “poverty”, “hunger”, or “malnutrition”, in spite of the fact that several researchers had pointed to nutritional factors in pellagra and that there were no reported cases of health care providers, working in close contact with pellagrins, who had come down with the disease. Above all, pellagra was known to be correlated with poverty and the consumption of corn.

That Davenport and others were blinded by hereditary theory and failed to pay serious attention to the possible environmental confounds in pellagra family pedigrees
is hardly an original observation; indeed, it is the classic example of the potential fallacy of reaching conclusions about genetic factors when studying people who share a common environment as well as common genes.

What sets pellagra apart from most psychiatric conditions is that, (1) its cause is known, and (2) there is no dispute that it is a physical disease of the body. Thus, we can look back today and recognize the fallacious thinking of Davenport and his associates. Psychiatric conditions such as schizophrenia and ADHD, on the other hand, are caused by unknown factors and involve no proven disease physiopathology (see Breggin, 1991, 1998), although biological psychiatry would dispute the latter claim. Because the known (although belatedly accepted) causes of pellagra predated the development of twin and adoption studies, no such investigations relating to pellagra have ever been published. The remaining portion of this paper thus performs a bit of historical speculation by asking the question: What would the results of a pellagra twin study have looked like? Following this discussion, we will examine the implications that these results might have for contemporary psychiatric genetic investigations.

3. Twin studies

Since the 1920s, twin studies have been cited by psychiatric geneticists and others as constituting important evidence in favor of the operation of genetic factors for a wide variety of psychiatric disorders. The primary method used has been the “classical twin method”, which compares the concordance rates of reared-together identical twins (monozygotic, or MZ) to the concordance rates of reared-together fraternal twins (dizygotic, or DZ). Because the environments of these two types of twins are assumed to be equal, while their genetic relationship differs, a significantly higher MZ concordance rate is typically attributed to genetic factors. Critics of the twin method (e.g., Jackson, 1960; Joseph, 1998a, b; Lewontin, Rose & Kamin, 1984; Pam, Kemker, Ross & Golden, 1996) have pointed to the implausibility of the equal environment assumption (EEA). These critics have argued that MZ twins would be expected to be more similar on the basis of a more common environment and the greater psychological association or “ego fusion” (Jackson, 1960) of MZ twins. MZs, therefore, are expected to be more concordant for psychiatric disorders on purely environmental grounds.

Suppose that the twin method had been utilized in early 20th century Spartanburg South Carolina, a center of pellagra investigation, in order to determine the genetic basis of pellagra. The investigators would have likely identified subjects either by obtaining the names of pellagrins who were hospitalized and who also had a twin (commonly referred to as the “resident hospital method”), or by obtaining the names of all pellagrins admitted to a hospital for a particular time period, and then identifying the twins from this group (commonly referred to as the “consecutive admissions method”). Suppose that 50 MZ and 50 DZ pairs had been discovered in this manner. Given that we now know that pellagra is caused by a vitamin deficiency, what results would we expect to find among these twins? On the face of it, it might appear that we would not find a significant MZ/DZ difference on environmental grounds because, as Jackson (1960) argued was the case with schizophrenia, we would
not expect a higher MZ pellagra concordance rate on the basis of the greater psychological association of MZ twins. Association and “ego fusion” might compel a twin to behave like his or her co-twin, as acknowledged by a schizophrenia researcher as prominent as David Rosenthal (1960), but would not produce physical disease in the co-twin. However, several studies (e.g., Kringlen, 1967, p. 115; Smith, 1965; Wilson, 1934) have found that monozygotic twins are much more likely to spend time together and experience a similar environment than dizygotics. Looking specifically at food choices, Wilson (1934, p. 338) concluded that MZ twins “show the greatest similarity in food tastes” when compared to same- and opposite-sex DZ twins, and Smith (1965, p. 56) found that MZs had a significantly more similar preference for fruits and vegetables (but not for staple items). More recently, Fabsitz, Garrison, Feinleib and Hjortland (1978), in a large study of 455 pairs (232 MZ, 223 DZ), looked at differences in twin dietary intake and found that “Intraclass correlations are consistently and significantly higher for MZ twins for every nutrient” (p. 19). Confirming these findings, Falciglia and Norton (1994) found “a greater similarity in food preference between members of monozygotic twin pairs than between dizygotic twin pairs …” (p. 154). Of course, unlike the largely middle-class twins in these diet studies, impoverished southern MZ and DZ twins had few dietary choices and often went hungry. Thus, we cannot be sure that the greater MZ similarity in food preference could have been generalized to this population, but to the extent that MZ twins spend more time together, they will eat more similar foods than DZ twins and thus be more concordant for pellagra. There is also reason to believe that MZ twins would have eaten more similarly within the home. The 2–3 times higher pellagra rate among poor southern women than men has been explained on the basis that men, as the family breadwinner, were often given the best food available to the family, such as meat and eggs. To the extent that MZ twins are treated more similarly than DZ twins, which is acknowledged by most twin researchers (e.g., Bouchard, 1993a; Kendler, Neale, Kessler, Heath & Eaves 1994; Morris-Yates, Andrews, Howie & Henderson, 1990; Rose, 1991; Scarr, 1968; Scarr & Carter-Saltzman, 1979), they would have likely eaten more similar foods within the family than DZs.

It is therefore probable that an investigation of pellagra utilizing the twin method would have found a significantly higher MZ concordance rate on environmental grounds alone, but the difference, though significant, would not have been as great as most psychiatric conditions, where large differences were likely the result of common environment plus association and ego-fusion.\(^1\)

The concordance rate of reared-apart twins has been cited as evidence for the genetic basis of conditions such as schizophrenia. However, it is important to note

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\(^1\) In most twin studies performed prior to the 1970s, zygosity determination and diagnoses were not made blindly, and were often made by the researchers themselves. Because most twin researchers are proponents of the genetic position, twin studies have suffered from the bias these investigators brought into their study. For example, if Davenport and colleagues had performed a pellagra twin study, they would have expected to find a higher pellagra concordance rate among MZs when compared to DZs. Had Davenport and associates made diagnoses with the knowledge of the twin’s zygosity status, this would have introduced a serious bias into the diagnostic process. For a discussion of the problems introduced by non-blinded diagnoses in twin research, see Jackson (1960).
that because samples are too small to yield enough cases, there has never been a systematic study of separated twins looking at psychiatric conditions. Systematic studies of ostensibly separated twins assessing cognitive ability and personality similarity have been performed (Bouchard, Lykken, McGue, Segal & Tellegen, 1990; Juel-Nielsen, 1965/1980; Langinvainio, Kaprio, Koskenvuo & Lönnqvist, 1984; Newman, Freeman & Holzinger, 1937; Pedersen, Plomin, McLearn & Friberg, 1988; Shields, 1962), but suffer from serious methodological problems (see Farber, 1981; Joseph, 2000; Kamin, 1974; Taylor, 1980). What have been reported are the case histories of individual pairs of twins concordant or discordant for various psychiatric conditions. In schizophrenia, for example, the claim is generally made that the concordance rate of reared-apart monozygotic pairs in the literature is around 65% (Gottesman & Shields, 1982). Rather than discussing all of the reasons why these cases do not constitute strong evidence in favor of genetic factors, the author concentrates on only one — that reared-apart monozygotic twins (also known as MZAs) are usually placed in highly correlated socioeconomic environments, often in different branches of the same family, and most are poor. As Farber (1981) noted in her exhaustive review of the world MZA literature:

Twins are usually separated because of poverty or death in the family. Though the different cultures and time spans make exact rating of socioeconomic status impossible, it is clear that most of the cases were born to poor families and reared in conditions not greatly different. Many were reared by relatives. The sample, thus, is highly biased in the direction of lower and lower-middle-class rearing conditions (p. 18).

Thus, had an investigator searched the southern United States for pellagrins having a reared-apart monozygotic twin, it would not have been at all surprising to have found a sizable percentage concordant for pellagra for socioeconomic reasons alone.

While some (e.g., Bouchard, 1993b) have erroneously argued that correlated environments explain only a tiny fraction of MZA personality and IQ similarity, we would certainly expect that a correlated socioeconomic environment would affect MZA concordance rates for a disease like pellagra, where malnutrition based on socioeconomic status is the known cause. MZAs placed into separate impoverished families eating a pellagragenic diet would have both been at risk; MZAs living in separate middle- or upper-class homes would have been at no risk.

In general, because of the likelihood that twin studies are contaminated by environmental factors, their use in the study of pellagra would have probably led to conclusions as erroneous as those reached by Davenport and his co-thinkers on the basis of family pedigree studies.

4. Conclusion

We have seen how pellagra family studies were erroneously interpreted as showing that the condition had a genetic basis, and that twin studies would have likely
confirmed this conclusion. But suppose it had been shown that some people are genetically vulnerable to the disease. In spite of such a finding, the discovery of a genetic predisposition for pellagra would have been virtually meaningless. This statement is not true for all conditions, since the identification of a gene for phenylketonuria (PKU) calls for a critical time-limited dietary intervention in order to prevent mental retardation in an infant. Pellagra was wiped out in the United States by the relief programs of the 1930s, and more importantly, by a federally mandated World War II-era program requiring the enrichment of flour and corn meal with the vitamins needed to prevent pellagra. In other words, once the environmental factor was found and eliminated, any possible genetic predisposition had been rendered totally irrelevant. Or, suppose that a genetic factor had been proven, but the disease still prevailed today because the environmental component remained mysterious — which is how conditions such as schizophrenia, manic-depression, and ADHD are currently viewed. Like these diagnoses, pellagra would still be seen as having an important genetic component. Pellagra sufferers would be seen as the victims of a hereditary illness, and even their healthy relatives might be viewed as “heterozygotic taint-carriers” (as Kallmann (1938, p. 107) referred to the biological relatives of people diagnosed with schizophrenia). As opposed to this perspective, the author offers an alternative: For psychiatric conditions believed to carry a genetic predisposition requiring an unknown environmental trigger, the importance given to the alleged genetic predisposition represents little more than the acknowledgment of the failure to discover the environmental cause or trigger. There is often an inverse relationship between the belief in the importance of genetic factors for a given condition, and the knowledge of the environmental causes of that condition.

Let us imagine that the environmental factors for psychiatric disorders such as schizophrenia and ADHD are discovered, as was the case for pellagra. Our task would then be to remove these factors from the environment, and schizophrenia and ADHD would vanish along with the idea that they are genetic disorders. As Chase observed, “Pellagra has pretty much disappeared, without any apparent change in anyone’s genes” (Chase, 1975, p. 86) — and pellagra would have still disappeared even if some people were more susceptible than others. Chase also argued that the eugenists’ idea of pellagra as a hereditary-infectious condition delayed by 20 years the conquering of the disease in the United States. Of course, it is far easier to enrich bread with the proper nutrients than it is to “enrich” the frequently abusive and destructive childhood environments of psychiatrically diagnosed people.

As the example of pellagra shows, the claim of a genetic predisposition can delay the discovery of the true causes of a condition at the expense of unnecessary death and suffering, and can promote the unwarranted stigmatization of diagnosed individuals. For other diagnoses, the claim of a hereditary component — even if true — can have similar consequences.

References


