The Continuum of Psychosis — 1986-2010

The shadow of Kraepelin stands over psychosis nosology like a colossus. The reason is that Kraepelin made an attempt to systematize diagnosis in a rational, pathophysiological manner. But, to this day, no one has done better. The tragedy is that one can say of Kraepelin that the measure of his stature is the extent to which his influence has delayed progress since his death. With such a judgment, we may be sure he would be distressed. By 1920, he had formulated reservations about the dichotomous scheme to which his name is attached. The quotation that summarizes the paper is: “No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis … Nevertheless it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect ...”

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The meaning is crystal clear, as is the context. Kraepelin himself had doubts about the validity of his dichotomous separation of manic-depressive insanity from dementia praecox. There were cases that were intermediate, and they challenged the whole concept.

But such was the power of a simple binary classification that a century of clinicians, textbook writers, and examiners adopted the system with uncritical enthusiasm and regardless of the reservations of its progenitor. Some will say it does not matter; etiology supersedes nosology. We can press ahead, and etiological investigations will solve our nosological problems. I incline to the contrary view, that if we get nosology wrong, we have no basis for proceeding with investigation in other domains.

Perhaps the first after Kraepelin to appreciate that all was not well was Kasanin, who in 1933 put forward the concept of schizoaffective psychosis. Born of clinical necessity rather than theory, the concept seems not to have spawned any great revision of the dichotomous framework. It survived relatively isolated from serious discussion in the textbooks or elsewhere for almost 40 years.

It is true there were those who never were committed to the Kraepelinian binary system. Among these were Menninger, Beck, and, outside the English-speaking world, Rennert and Llopis, but none developed an idea that competed with the Kraepelinian prototypes.

**KENDELL AND GOURLAY, 1970**

Perhaps the first serious challenge to the Kraepelinian orthodoxy to follow Kasanin was the paper by Kendall and Gourlay, which took data from the U.S.-U.K. diagnostic project and subjected it to discriminant function analysis. The outcome was that the symptoms were distributed as a trimodal plot, (ie, with a maximum at the midpoint between schizophrenia and manic-depressive psychosis). On replication, the peak of the distribution was again in the middle, but the form was unimodal. The conclusion was a contradiction of the Kraepelinian binary system.

My memories of this article are subjective testimony to the resilience of the binary system enshrined in the textbook account. I read the paper and can remember clearly concluding that this could not be true. It must be some form of statistical artifact. When I formulated the two-syndrome concept, it was in part a reaction to the failure of the efforts of myself and colleagues to encompass what we thought we knew about the pathophysiology of schizophrenia within the scope of a single entity. I was not at that time thinking of a dimension that included affective illness. Indeed, I was committed to the viral hypothesis of etiology, following Torrey and Hare, and was not yet convinced of an evolutionary perspective.

**FAMILY STUDIES**

Kendall and Gourlay’s article certainly had little effect on me, and as far as I can tell, on the literature as a whole for some years. It needed collateral support from another discipline, and this came from the family genetic studies of Jules Angst. With his co-workers, he set out to determine whether schizoaffective psychosis was genetically related to schizophrenia or to manic-depressive illness, or whether some part was related to one and some part to the other. Angst and colleagues concluded that no non-arbitrary line could be drawn, therefore, we are dealing with a continuum.

Later, Gershon and colleagues reached the same conclusion, having studied the first-degree relatives first of those with manic-depressive illness and secondly of those with chronic schizophrenia. Individuals with schizoaffective illness were to be found in both sets of relatives, and the form of the illness did not depend on that in the proband. At the time when I believed in a gene environment interaction, the environmental component being a virus, the nature of the genetic component was not of great interest to me. It was only when I was deprived of the viral hypothesis by a study of age of onset in pairs of siblings (but I was aware of the result 2 years earlier) that I became convinced that the genetic component and its nature were of overriding importance and that an evolutionary theory was required.

**LATERALITY**

Thus, the continuum concept emerged first from phenomenological and then from family studies. Two other workers had reached a similar conclusion. They were Penrose, on the basis of his survey of familial mental illness in Ontario, and Odegaard, from his case register studies in Norway. Later Maier et al confirmed the earlier results in a systematic study with criteria defined according to the Diagnostic and Statistical Manual of Mental Disorders, third edition (DMS-III). I summarized my conversion to the continuum concept
in a review. This put together the genetic and phenomenological evidence as I understood it, but also included data on season of birth that I now regard as a statistical artifact as outlined by Lewis. Sometime that year, I gave a talk in the Edinburgh Department when, as I recollect, Bob Kendell welcomed the conclusions warmly. I also included the notion that I had come to 2 years earlier that the genetic factor was the asymmetry or cerebral dominance gene. By that time we had results from our first post-mortem study that included thinning of the parahippocampal gyrus selective to the left side. When I saw that finding, I recalled the findings of Flor-Henry that when psychosis develops in temporal lobe epilepsy and the lesion is on the left side, the form of the illness is schizophrenic, but when the lesion is on the right side, the form of the illness is affective. I was fortunate to have spent 6 months at the Maudsley Hospital in 1966 before I joined the Physiology Department in Aberdeen. I had met Bob Kendell and Pierre Flor-Henry and valued their collegiality in subsequent years. But in 1969 and 1970, I disbelieved Kendell on the basis that his findings were in serious conflict with a long-established and unchallengeable consensus. I disbelieved Flor-Henry on the basis that his findings did not fit with what else I thought I knew; for example, that psychosis was basically a disorder of chemical neurotransmission. By 1986, and maybe earlier, I was convinced that their respective discoveries were necessary ingredients of a solution to the problem of psychosis.

In 1987, *Lancet* published an editorial on the continuum of psychosis that gave me more credit than I deserved. It was generally favorable to the concept: “Doctor TJ Crow has now proposed an alternative hypothesis — he suggests that psychotic illness should be regarded not as separable disease entities but as a single illness with a spectrum of symptoms. Moreover, this formulation has been linked to a particular hypothesis of genetic causation that appears to account for other biological findings in the psychoses.

“Crow postulates an abnormal gene controlling cerebral lateralization that exists in several aberrant forms and can be modified by insertion of viral DNA. The latter suggestion of a viral gene persists from an earlier synthesis in the same literature.”

The leader went on: “What then is the value of linking the notion of a continuum of psychosis with an eccentric genetic hypothesis? … Is it likely to do harm? The issues Crow raises are far more interesting than those habitually addressed in many departments and institutes of academic psychiatry that do no innovative research.”

These were encouraging words. One can ask what progress has been made in the intervening 20 years on the basis of the concept formulated then. Has there been progress either in gathering empirical evidence, or formulating concepts so that they can be tested and perhaps eliminated?

**X-Y HOMOLOGY**

The *Lancet* leader pointed to linkage findings with respect to schizophrenia on the X chromosome and with respect to affective disorders on chromosome 11 and implied that this already constituted a problem for the continuum theory: there should be a single locus.

I accepted this point and was vexed by the apparent strength of the evidence. But neither linkage has survived. One of these (unusually) has been withdrawn by a subsequent publication. By 1984, I was beginning to think about the implications of the sex differences in the schizophrenic and affective illnesses. I was aware of the same-sex concordance effect that had been drawn attention to by Penrose and Rosenthal, apparently first noticed by Mott for review of sex differences in relation to the continuum see 16). I wondered how a locus could appear to be sex-linked and autosomal at the same time. I became aware of work that had been done on the pseudoautosomal region and proposed that a locus for psychosis within this region would have some merit in explaining the sex differences. Several groups, including ourselves, applied themselves to testing this theory by linkage, ultimately with negative result. The theory had the merit of explaining the same-sex concordance effect. It also explained the association between sex chromosome aneuploidies and deviations in cerebral asymmetry that I had cited in favor of a locus for cerebral asymmetry in a region of XY homology. But what it did not explain is a sex difference, as I should have appreciated earlier than I did. Within the pseudoautosomal region, there is strict homology between genes on the X and genes on the Y because there is regular recombination between the chromosomes in male meiosis. Given that the objective of the theory was to explain a sex difference in the first place, this was a fatal defect.

**XQ21.3/YP11 DUPLICATION**

By 1993, I had realized the error, and a much better theory was feasible. Meanwhile, I had been talking to Nabeel Affara and Carole Sargent in Cambridge about the work they had done on XY homologous genes. At the Y chromosome workshop, I presented an abstract outlining what I now believe to be true that the cerebral dominance gene is located in a sex-specific region of homology, specifically the Xq21.3/Yp11 sapiens-specific region. I had earlier formulated an evolutionary theory in an attempt to answer Huxley et al’s question: if schizophrenia is genetic in origin and is associated with a biological disadvantage, why are the genes not selected out? By 1984, I saw this as a serious problem. Huxley et al’s own answer was flawed, but there must be a balancing ad-
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ies, and therefore, we are left with no definite findings from this approach. What is the alternative? From the above result, it is apparent that a new source of variability, which is species specific, is generated by the process of meiotic suppression of unpaired chromosomes (MSUC) in the hominid specific Xq21.3 region of homology. The rule is that parts of the chromosome that do not pair are subjected to an epigenetic process of suppression. The obligatory pairing and recombination occurs within the pseudoautosomal region and much less frequently (perhaps 1 in 40 times) in pseudoautosomal region. It is clear that there is a likelihood of pairing, but highly stochastic within the Xq21.3/Yp region. Insofar as this is transmitted to the descendant X and Y chromosomes, it may be supposed to influence expression in the next generation. Therefore, we have a form of species-specific variation as envisaged by Bateson.

My hypothesis, therefore, is that in this mechanism is a source of variation that specifically relates to cerebral asymmetry and language. Herein lies the variation, not only of the continuum of psychosis but other aspects of human diversity.

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