The science of psychiatry has reached an impasse. The case of schizophrenia exemplifies the dilemma well. The introduction of chlorpromazine in the 1950's revolutionised psychiatry, beginning an era of neuropsychopharmacological research that would establish the theories of monoamine imbalance now central to psychiatric practice. The later establishment of computed tomography allowed detection of structural abnormalities in the brains of patients with schizophrenia. A wave of neuropathological research followed and numerous pathophysiological theories have propagated.

Decades of intense research later and schizophrenia is still a clinical syndrome of unknown aetiology. Today's antipsychotics offer few improvements to chlorpromazine, with varying efficacy and notable adverse effects. Just 11% of patients with schizophrenia are employed and 20% are considered homeless.

Whole genome association studies have been contradictory and fail to provide a unifying aetiology. These studies are not completely unyielding. In a small number of sufferers, associated penetrant genes exist. Many of these are not consistent either with each other or the syndrome at large. Interestingly they confer significant risk across a spectrum of psychiatric disorders, e.g. autism and bipolar disorder. This is suggestive of different pathological processes producing varied clinical symptoms within a spectrum of psychiatric disease and could account for the range of environmental and genetic aetiological factors, the wide variance in drug efficacy, and the varied validity of hypotheses regarding the role of different neurotransmitters.

This article presents the case that the future of psychiatric research lies in the redefinition of psychiatric disease away from the classical kraepelinion dichotomy enshrined in psychiatric practice.
Introduction

“It is in the admission of ignorance and the admission of uncertainty that there is a hope for the continuous motion of human beings in some direction that doesn't get confined, permanently blocked, as it has so many times before in various periods in the history of man.”

- Richard Feynman (Physicist and Nobel Laureate)

The science of psychiatry has reached an impasse. The “impasse” is a common feature within all scientific disciplines. As brief pauses between the leaps and bounds of scientific progress, they encourage us to step back and readdress the paradigm on which we build our knowledge.

Scientific method defines theory as fact when the supporting evidence is found to be both consistent and convergent. The amalgamation of the dark lines in figure 1 below converge to form an image we hold consistent with that of a duck. The evidence supports our claims, is this therefore a factual statement? Or does the image represent a rabbit? The likely answer being that the artist deliberately represented both animals. Science has no artist (...or so Darwin informs us). Fact is either true or false. While we hope that scientific method guides us to the appropriate conclusion, true certainty always remains evasive. A fact, as defined by science, is only ever true within a paradigm. Paradigms shift.

![Figure 1. A duck-rabbit illusion used by Thomas Kuhn to explain the paradigm shift. Taken within the public domain from 1](image)
Richard Feynman, famed physicist and nobel laureate spent his life addressing the “uncertain”. A physicist is fuelled by uncertainty. Uncertainty towards every law, theory and concept allows for the inevitable paradigm shift. Feynman aided the shift from classical to quantum mechanics.

In medicine, evolution, and not revolution, is king. Medical knowledge stands upon the shoulders of historical pioneers. Today’s ophthalmologists and plastic surgeons build upon the foundations created by Maharishi Sushrut (Suśruta), a mere 3500 years ago (with approximation)\(^2\). Paradigm shifts, present in nearly every academic discipline, are a rare entity in medicine. Psychiatry being the exception.

**Figure 2.** Statue of Suśruta in Haridwar, India. Taken with permission from\(^3\)

During the late 19th century, two strands of psychiatry were emerging. While neurologist Sigmund Freud pushed forward his concepts of psychoanalysis (healing the mind with the overt dismissal of the brain as a physical organ), Emil Kraepelin (Figure 3) was reinstating psychiatry as a biomedical science and creating a dichotomous syndromic method of psychiatric disease classification\(^4\).

Historically, psychiatry has drawn scholars from both the humanities and the sciences. Within the social sciences, numerous theories can coexist, and academics choose one over the other (e.g. Keynesian vs Austrian economics). Psychiatry however, behaves as a true science; A prevailing opinion, regarded (within the current paradigm) as fact, dominates a time period, only to be followed by a paradigm shift. In the early 20th century, psychoanalysis dominated and Kraepelin’s scientific psychiatry remained dormant. From periods of psychoanalysis to psychosurgery and institutionalisation, the largest paradigm shift followed the birth of neuropsychopharmacology after
the synthesis of chlorpromazine (the first antipsychotic)⁴. With the development of antipsychotics and antidepressants, a movement of deinstitutionalisation began, spurring the growth of community care and a burgeoning multidisciplinary team to support the previously ignored patient needs.

The establishment of neuropsychopharmacology and the related theories of monoamine imbalance have now existed for over half a century. The treatments that arose from this period are dated in the face of modern medicine and recent improvements offer little other than to reduce certain side effect profiles. A meta-analysis of antidepressant efficacy data⁶ submitted to the FDA (Food and Drug Administration, United States) suggests that these drugs are efficacious only in the most severe cases and even then, their effect is small.

While there is no doubting the ability of antipsychotics to reduce the effects of acute psychosis, they are associated with severe side effects. Their use in schizophrenia involves a high 18-month discontinuation rate (above 70% with the exception of olanzapine - 64%)⁷ due to causes such as poor efficacy and low tolerance. This is coupled with questionable benefits, schizophrenia has remained a chronic disabling condition and despite long-term treatment, many patients cope with persistent positive symptoms (e.g. auditory hallucinations). Negative and cognitive features usually remain untouched. In europe, just 20% of sufferers are employed (UK - 12.9%; France - 11.5%; Germany 30.3%)⁸ and in the United States, 20% are homeless⁹.

Dissatisfaction of the current treatment range accompanies reservation over the validity of neurotransmitter based theories supporting their use⁹. Most importantly, 60 years of intensive
neuropsychopharmacological research has failed to deliver any solid evidence regarding the pathophysiology of psychotic and affective disorders.

This lack of scientific progress damages both the reputation and future of psychiatry. When surveyed, only 0.81% of medical students choose psychiatry as a future career. The two most commonly provided criticisms from students involve an apparent unscientific nature within psychiatry and a lack of efficacious therapeutic options\textsuperscript{10}.

Contrary to this perception, a historical review of psychiatric research reveals numerous pioneering studies ranging from the advanced techniques within neuroimaging and molecular pathology to large scale clinical trials and long-term cohort studies.

Scientific method is fundamental to psychiatry. This article will present the progress of science within schizophrenia from the advent of chlorpromazine to recent whole genome association studies. A review of our current knowledge of schizophrenia’s pathological basis leads us to ask whether it is not the lack of science in psychiatry that slows progress, but instead uncertainty of the very paradigm within which we develop this knowledge. What will the future hold? In this author’s opinion, the end of the nosological practices that stem from the historic krasepinian dichotomy.
Presenting an Uncertain Science; Schizophrenia

Schizophrenia is a severe neurological syndrome affecting 1% of the population and usually presenting in late adolescence to early adulthood. The so called “positive features” of this disorder involve hallucinations, delusions and paranoia. Cognitive deficits accompany the “negative features”; anhedonia, social withdrawal and a flat or blunted affect\textsuperscript{11}.

Importantly, schizophrenia is a syndrome of unknown aetiology. In psychiatric practice, to enable a standardised diagnosis, schizophrenia may be defined and sub-classified by a collection of clinical features dictated by the most recent DSM-IV\textsuperscript{12} (Diagnostic and Statistical Manual of Mental Disorders) and the ICD-10\textsuperscript{13} (International Classification of Diseases).

Before the 1950s, sufferers of schizophrenia were institutionalised and exposed to inhumane experimental procedures, e.g. insulin shock therapy and leukotomy. The recognition of chlorpromazine is arguably the greatest advance in the history of psychiatry. Originally synthesised as an antihistamine, then used as an anaesthetic, the phenothiazine derivative’s potential to calm patients was first identified by Henri Laborit, a french surgeon. Due to Laborit’s persistence, 1952 saw chlorpromazine trialled in a number of psychotic patients. The results were impressive, going beyond sedation and delivering improvements in both cognition and behaviour\textsuperscript{4}.

Figure 3. Early advert for chlorpromazine, the first antipsychotic which began a period of neuropsychopharmacological research developing our current knowledge regarding monoamine imbalance. Taken with permission from\textsuperscript{14}
Research into the mechanism of chlorpromazine, in particular its antagonism of D$_2$ receptors, coupled with the psychosis-inducing effects of dopamine agonists, led to the dopamine hypothesis. Initially simplistic, the dopamine hypothesis posited that the hyperactivity of dopaminergic neurones was responsible for the clinical features of schizophrenia. While offering an explanation for positive disease manifestations, this hypothesis did little to explain the negative features. Other flaws in the dopamine hypothesis involved the effects of the dopamine antagonists. Although D$_2$ receptor blockage is immediate, some therapeutic benefits take days to establish. Also, while the degree of D$_2$ blockade varies between patients, this does not correlate to the efficacy of the actual drugs$^{15}$.

More recent research has allowed for a new, more plausible theory of dopamine imbalance. Key to this is the observation that ketamine, an NMDA (N-methyl D-aspartate) antagonist, recreates select features (particularly the negative facets) of schizophrenia. Numerous studies have implicated deficits in glutamate transmission (the natural agonist of NMDA receptors) in schizophrenic traits$^8$.

Central to current thoughts regarding neurotransmitter imbalance, are the findings of numerous neuropathological studies. Until the rise of computed tomography (CT) in the 1970’s, it was widely thought that patients with schizophrenia lacked any structural neurological deficits. This was shown incorrect and further improved data obtained from magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission tomography (SPECT) inspired a new wave of neuropathological research$^{16}$.

Combining neuropsychopharmacological, neuropathological and neuroimaging studies, a new dopaminergic and glutaminergic hypothesis is posited. Schizophrenia involves excessive striatal D$_2$ stimulation. However, there is also a hypodopaminergic state specifically involving prefrontal D$_1$ receptors associated with decreased prefrontal glutamate signalling. The reduction in glutamate and dopamine signalling within the prefrontal cortex are responsible for the negative symptoms of schizophrenia while episodic mesolimbic hyperactivity at D$_2$ receptors account for positive symptoms$^{17,18}$.

It is this theory which backs the actions of newer partial antipsychotic D$_2$ agonists (e.g. aripiprazole), which are thought to stabilise the dopaminergic system during both periods of deficiency and excess$^{15}$.

Other significant neuropathological findings not directly associated with the dopaminergic hypothesis exist. The dorsolateral prefrontal cortex (DLFC) of patients with schizophrenia demonstrates reductions in GABAergic (gamma-Aminobutyric acid) interneurons$^{19}$. This is
accompanied by deficiencies in glutamic acid decarboxylase (a GABA synthesising enzyme) and up-regulation of the GABAa receptor. Combined, these findings point to a potential role for GABA deficiency in schizophrenia’s pathology.

Synaptic and dendritic abnormalities are also been implicated. This is particularly true within the DLFC where dendritic spines exhibit both reduced volume and length. Additionally, raised GTPases of the Rho family (Cdc42 and Duo) potentially contribute to altered dendritic dynamics. Supporting this theory, microarray analysis of gene expression within the prefrontal cortex demonstrates multiple reductions in synaptic gene products.

Some authors have suggested that schizophrenia may primarily be a disorder of neurodevelopment with heterogenous genetic factors conferring susceptibility to some environmental insult (of which numerous are candidates). Data from a cohort of 1037 individuals born in 1972 in Dunedin, New Zealand, highlighted persistently low IQs amongst children destined to develop schizophrenia. Additionally, other longitudinal studies have identified subcortical and cortical loss prior to the onset of clinical symptoms. Whether this is part of a prodromal phase or a longer period of maldevelopment is unknown.

Inspired by the heritable nature of schizophrenia (81% in a meta-analysis of twin studies), and advances in DNA sequencing speeds, research is currently shifting away from neuropsychopharmacology and neuropathology to an extensive search for genetic markers of risk.

Unfortunately, many early candidate gene studies have been disappointing, failing to show replicable results. Several genome wide association studies have been conducted both for hypothesis-free detection of new risk-predicting genes and confirmation of previous findings surrounding particular common genetic variants. While two studies have failed to find any genome wide significant associations, those that identified variants noted only small contributions to the disease process, and many have failed to replicate. Nonetheless, several genes have been identified that may be implicated in later studies (most notably DISC1, ZNF804a, COMT, RGS4, DTNBP1 and NRG-1).

The genetic, pathological and environmental heterogeneity of schizophrenia may disappoint those hoping to unify the syndrome by aetiology. Schizophrenia is a syndrome defined only by its clinical features and therefore it is plausible that those features may be a product of many different disease processes.
The potentially incorrect labelling of schizophrenia as a single disease entity may explain our inability to identify solid aetiological factors. For example, when James Parkinson first described paralysis agitans (now labelled Parkinson’s disease, PD) he was in fact describing parkinsonism (the syndrome), not PD. This distinction has not slowed progress in the elicitation of the disease’s aetiology solely because it accounted for the vast majority of parkinsonism cases. The rarity of alternative causes, e.g. progressive supranuclear palsy were less likely to disrupt the findings of PD research. However, if the various causes of atypical PD occurred with the same incidence of typical PD, researchers would undoubtedly be facing a similar dilemma (gross aetiological variance) as those considering schizophrenia.

**Beyond the Kraepelinian Dichotomy**

Recent genetic studies suggest the case of schizophrenia may actually be more complex than the PD example. The small number of schizophrenia associated genetic variants noted with high penetrance also appear to increase the risk of other psychiatric disorders e.g. DISC1 has high penetrance and is involved with both schizophrenia and bipolar disorder. ZNF804A, DTNBP1, COMT, BDNF and NRG1 are also associated with disease risk across the bipolar-schizophrenia divide.

Considering that psychosis is frequently a feature of bipolar disorder, and schizophrenia often accompanies an affective disorder (schizoaffective disorder), it is not so implausible that these two syndromes may represent the outcomes of different disease processes capable of producing clinical features along the same spectrum. To add strength to this argument, a Swedish study involving 2 million families confirmed that the heritable risk involved in the two conditions is transferable.

These genetic overlaps are not unique to schizophrenia and bipolar disorder. Variants at numerous genetic loci appear to predispose to both autism and schizophrenia. This accompanies a potentially diametric relationship with deletions or duplications at the same loci predisposing to either autism or schizophrenia.

This new wave of genetic research provides us with good evidence that our classification system is not representative of the real disease processes. Genetic associations are conferring risk as much across the boundaries created by the current dichotomous classification as those within. As described in the PD example, an incorrect classification system threatens research and may explain the varied response rates of current psychiatric treatments.
This genetic overlap will not command surprise. Extensive clinical overlap is easily observable in most psychiatric disorders. Within the DSM and ICD there is the tendency to encapsulate overlapping features into unique entities (e.g. the creation of schizoaffective disorder as distinct from schizophrenic and affective disorders). This method of trying to simplify and standardise diagnosis was useful in the 20th century to establish a basis for research. Without differentiating between schizoaffective disorder and schizophrenia, how can a researcher be sure they are dealing with uniform experimental groups? Unfortunately disease, like most physiological variants, tends to occur upon a spectrum and a simplified classification does little to change the complexity of the underlying pathology. An incorrect classification however, could suggest the presence of more complex and heterogenous pathology then actually existent.

A Conclusive Op-Ed

Any nosological practitioner would consider classification by pathophysiology or aetiology preferable. Emil Kraepelin had to do without. His syndromic grouping allowed him to apply scientific method to psychiatry, redefining it as the speciality we know today. Both the ICD-10 and the DSM-IV are built upon the Kraepelinian dichotomy. The diagnostic practices stemming from these systems are the cornerstones of psychiatric practice. They not only define psychiatric disease, but also psychiatry as a profession. Criticising their presence feels like a criticism of the speciality.

Criticism is also far easier than the suggestion of a replacement. Should there even be a replacement? The sole purpose of disease labelling is to aid treatment. If the label fails that goal, then no purpose remains. The concept that we will establish separate genes and pathophysiological pathways for different syndromes seems unlikely. Perhaps the future lies in a genetic based classification predicting the responses of individual clinical features, (e.g. anhedonia) to particular therapies.

Currently, single classes of medication (namely antidepressants and antipsychotics) are used across a range of different psychiatric syndromes. The separating diagnostic labels merely provide official access to care, drugs and social stigma. With the majority of psychiatric healthcare revolving around the organisation of adequate social support, psychiatrists are becoming sidelined, providing the label and monitoring the drugs.

This is not a criticism of psychiatry. It is a criticism of the nosological practices that have created this paradigm. Psychiatry is not a nosology, it is a science structured around clinical expertise. It's development relies on both clinical and scientific research for the sole aim of improving the countless number of lives unfortunate enough to experience a mental illness.
The science of psychiatry is uncertain, but then all good sciences are. The current pause in scientific progress must be met with reassessment of the paradigm in which it exists.

The future for psychiatry will begin in the admission of uncertainty, uncertainty of the very definitions on which we practice, as it is only though this uncertainty, can the paradigm shift.
References


