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Mistakes I Have Made in My Research Career

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I started in psychiatry at the Maudsley Hospital and Institute of Psychiatry, London, in October 1972, and spent the next 3 years completing my basic training. I was then offered a research post studying the excretion of dimethyltryptamine (DMT) in patients with schizophrenia. DMT is a hallucinogen used by Amazonian Indians in their religious ceremonies, as well as a minor street drug, and the idea was that people with schizophrenia might be walking hallucinogenic factories. At the time, this idea, which appears bizarre in retrospect, was the main neurochemical alternative to the dopamine hypothesis.[1]

In the course of this project, I managed to offend the then Professor of Psychiatry at the Institute, Denis Hill, by writing an anonymous editorial in which I criticized the state of UK psychiatric research including his department.[2] Unfortunately 1 day soon after, when I got on the London underground, there was Professor Hill. He motioned me to sit next to him, and immediately demanded "Murray, do you know anything about this editorial in The Lancet?" I had to admit that I did. He was not pleased—so colleagues suggested I went to the United States for a year, to let him calm down. By the time I came back I was forgiven—he was a kindly man.

The Unrewarding Search for the Causes of the Brain Changes Underlying Schizophrenia

Psychiatry in the United States in 1976 was on the cusp of swinging from being wholly psychoanalytical to almost wholly biological. With all the lofty authority of nearly 4 years experience in psychiatry, I attempted to sum this up in a review in the Lancet entitled "A Re-appraisal of American Psychiatry."[3] While I was at National Institute of Mental Health, Bethesda, I attended the weekly journal club. One of the papers discussed was that by Eve Johnstone and Tim Crow, which demonstrated that people with chronic schizophrenia had cerebral ventricular enlargement.[4] This paper was dismissed in less than 5 min, mainly because nobody other than me had ever heard of the authors! I returned to the Institute of Psychiatry a few months later, to find the same paper again the subject of a journal club discussion. Once more, its findings were rejected, though it took an hour this time. The main objection, outlined in a letter to the Lancet by Denis Hill,[5] was that because schizophrenia was a functional psychosis, those cases with brain abnormalities, by definition, could not have true schizophrenia—a somewhat circular argument!

At the time, Tim Crow ran the best schizophrenia research unit in the world at Northwick Park in London. We spent a lot of time chasing after him to hear what his latest ideas were. A very interesting period in which Tim would put up a provocative hypothesis, but then, within a year or two, would produce new data which, as likely as not, would destroy his own theory; a truly Popperian attitude, sadly not often followed in psychiatric research.

The Johnstone et al paper was widely interpreted as validating the Kraepelinian view that schizophrenia was a neurodegenerative disorder. It kick-started the huge and ongoing endeavor of neuroimaging in psychosis. I myself worked with Adrianne and Michael Reveley to show that the identical co-twins of people with schizophrenia did not share the increased ventricular volume of their sick co-twin, thus indicating that it must be environmental in origin[6]; so we began hunting for the causes of these deviations.

Unfortunately, in the rush into neuroimaging, I paid no attention to another local objector to the conclusions of the Johnstone paper. David Marsden, Professor of Neurology at the Institute also wrote to the Lancet, pointing out that prolonged antipsychotic treatment can cause persistent changes in the sensitivity of striatal dopamine receptors,

with resultant tardive dyskinesia (TD). He therefore suggested that in a similar manner "long-term neuroleptic therapy could cause some of the cerebral atrophy and related cognitive changes demonstrated by Dr Johnstone and her colleagues."[7] Unfortunately, I, and most others, ignored his insight, and it was not until 30 years later, in 2008, that Ho et al[8] showed that long-term high-dose antipsychotics decreased cortical volume and increased lateral ventricular volume. This effect has been confirmed by other clinical and also animal studies.[9] So, in 2016, it is clear that high-dose antipsychotics contribute, not to the subtle brain changes present at onset of schizophrenia, but to the subsequent "progressive" changes thereafter; indeed, not only antipsychotics but probably also cannabis use, diabetes, and hypertension.[9,10] Amazingly, such is the power of the Kraepelinian model that some psychiatrists still refuse to accept the evidence, and cling to the nihilistic view that there exists an intrinsically progressive schizophrenic process, a view greatly to the detriment of their patients.

In the decades following 1976, I spent more time and energy than I like to recall, trying to find what caused the brain changes in schizophrenia. Sadly, I did not realize that the effects of risk factors such as adverse obstetric events, on brain structure and function, which can be readily seen in nonschizophrenic samples,[11] are obscured in people with established schizophrenia by the effects on antipsychotics and other nonspecific factors.

The Runaway Rise of the Neurodevelopmental Hypothesis

Here I should backtrack to say that in the late 1970s, I had gone on a short tour of research centers in Scandinavia, and I had met Tom McNeil in Lund who had shown that people who go on to develop schizophrenia have suffered an excess of adverse obstetric events.[12] My seniors and betters at the Institute laughed at the idea that such early developmental hazards might be causal but fortunately one of my junior colleagues didn't. Shon Lewis reviewed all the CT scans we had carried out on people with schizophrenia and found an excess of developmental lesions such as cavum septum pellucidum[13] or agenesis of the corpus callosum. Shon and I,[14] and Dan Weinberger in the United States, separately suggested in 1987 that the abnormalities, or more correctly deviations, might be neurodevelopmental rather than degenerative.

Within a few years, other evidence such as childhood developmental problems came in to bolster the hypothesis,[15] and to my surprise the neurodevelopmental theory of schizophrenia achieved widespread acceptance; indeed, perhaps too much. It is now common to read or hear experts confidently stating that schizophrenia is a neurodevelopmental disease. This is clearly an overstatement as subsequent work has demonstrated![16]

In 1990, I had long discussions about the way forward with an Irish research fellow, Eadbhard O'Callaghan, who maintained that epidemiology would be crucial. I retorted that this was old-fashioned and that the future obviously lay in molecular genetics and brain imaging. Eventually, I gave in, and let Eadbhard try and replicate Mednick's finding that the 1957 influenza pandemic was followed by an excess of births of people who later developed schizophrenia. We did indeed find evidence for this,[17] and went on to suggest that there could be a human leucocyte antigen × prenatal influenza interaction resulting in antibodies to neurotransmitter receptors,[18] though we suggested antibodies to the dopamine, rather than to the currently fashionable *N*-methyl-D-aspartate receptor.

I Ignored Social Factors for 20 Years

So almost by accident, I got into epidemiology, and then was confronted by the evidence that one of the most consistent epidemiological findings in the United Kingdom is the high incidence of schizophrenia in the African-Caribbean population. Having excluded genetic and other biological causes, we were forced to look at the role of social factors such as migration, social isolation, and discrimination.[19]

It is odd that it took me until the mid-1990s to take social factors seriously as component causes of schizophrenia because when I trained in the 1970s, social psychiatry was predominant at the Institute. Indeed, one of the first researchers that I worked for was Jim Birley who, together with George Brown, had demonstrated the importance of adverse life events in schizophrenia.[20] However, by 1990 the predominant view, including my own, posited that schizophrenia was a brain disease influenced by aberrations in developmental genes[20] and early environmental insults.[21,22] Social psychiatrists, including our local experts such as Paul Bebbington and Julian Leff, confined themselves to saying that social factors contributed to relapse. Indeed even as late as 1998, we took a sociologist, Rosemary Mallet, to the winter workshop on schizophrenia in Switzerland. Unfortunately, she was miserable because she didn't ski, and apart from her own poster, there was no mention of social factors in the whole conference!

In the last 2 decades, it has become obvious that child abuse, urbanization, migration, and adverse life events contribute to the etiology of schizophrenia and other psychoses. This has been a big shift for me! Indeed about 5 years ago, after I had given a lecture on the subject of social factors in schizophrenia, one listener stood up and said "Professor Murray, I last heard you talk abut social factors in schizophrenia in 1982. Then you were against them, now you are for them." The audience fell about laughing! I spluttered that one must change one's mind if the data change. However, the truth was that my preconceptions had made me blind to the influence of the social environment.

I never had a proper epidemiology training—but a succession of younger fellows in my group spent a year at the London School of Hygiene and Tropical Medicine. There

they learnt how to use epidemiological techniques to examine risk factors for psychosis, whether they were social or biological. So, for example, Peter Jones and Mary Cannon were interested childhood hazards be they infection or abuse, David Castle and Nori Takei studied effects of urbanization, Jane Boydell and Craig Morgan researched migration and ethnic minority status, while later Marta Di Forti examined the effects of cannabis. Jim Van Os in particular taught me, and then European psychiatrists as a whole, that it's oversimplistic to regard schizophrenia as just a brain disease. Asthma may be a lung disease but it is one which can be precipitated by environmental toxins (eg, pollution) and allergens. Just as the lungs process air, so the brain processes external stimuli; consequently, its healthy function can be harmed by noxious factors in the social environment such as childhood abuse or adverse life events.

Dopamine Supersensitivity; Another Old Idea I Dismissed for too Long

Recent Positron Emission Tomography studies have demonstrated that the final common pathway underlying psychosis is excess synthesis of presynaptic dopamine. Furthermore, most of the environmental risk factors for schizophrenia facilitate dopamine dysregulation.[16,23]

Unfortunately, our pharmacological treatments don't address the excess synthesis of dopamine but rather rely on blockade of the D2 receptor.[23] But can one continually block this receptor without causing changes in it? David Marsden had raised this question back in 1976,[7] and then again in 1983 when he and his colleagues pointed out that "Long-term antipsychotic treatment causes the proliferation of dopamine receptor sites, accompanied by an exaggerated response to DA agonists and a decreased response to antipsychotics i.e. "the dopamine receptor population is supersensitive."[24] Sadly I paid no more attention to his views in 1983 than I had 7 years earlier.

However, many subsequent animal studies have confirmed his findings. With continuous administration, antipsychotics progressively loose their efficacy in suppressing amphetamine-induced locomotion and conditioned avoidance in rats; this can be reversed temporarily by a further increase in dose of antipsychotics. The failure of efficacy is linked to an increase in post-synaptic D2 receptor density.[25]

One might be forgiven for dismissing findings from animal research. But in 1978 the Canadian psychiatrist Chouinard had also noted that antipsychotics can induce supersensitivity of the motor system with resultant TD, and described what he termed "drug-induced psychotic relapses" associated with TD after long-term high doses of first-generation antipsychotics.[26] He and his colleagues proposed that this supersensitivity causes tolerance to antipsychotics, such that eventually they no longer control psychotic symptoms.

All of this points to an intrinsic problem with studies comparing continued antipsychotics with placebo. This was noted by Carpenter and colleagues[27] when they stated "once patients are placed on medication, they are less vulnerable to relapse if maintained on neuroleptics. But what if these patients had never been treated with drugs to begin with? ……..We raise the possibility that antipsychotic medication may make some schizophrenic patients more vulnerable to future relapse than would be the case in the natural course of the illness." Moncrieff[28] carried out a meta-analysis of patient withdrawal studies, and was convinced that "antipsychotic discontinuation may also increase the risk of relapse over and above the risk because of the underlying disorder."

So, in treating schizophrenia with antipsychotics, do we sometimes compound what is essentially a disorder of presynaptic dopamine by causing secondary dopamine supersensitivity? There is no doubt that antipsychotics are necessary in acute active psychosis. But do have to continue to prescribe them in some patients because we have rendered the D2 receptor supersensitive to the excess dopamine released? I, and indeed most investigators, have neglected this vitally important question.

What Have I Learned?

If I had the chance to have a second career, I would try harder not to follow of the fashion of the herd. The mistakes I have made, at least those into which I have insight, have usually resulted from adhering excessively to the prevailing orthodoxy. Fortunately, I have often been rescued from this by the arrival of a brilliant young research fellow who has proposed a novel approach; I have usually resisted her/his idea initially before eventually come round to its merits. Sadly, this reliance on the corrective influences of younger colleagues has its limits. For example, David Marsden was already a famous professor when I met him; he must have been too senior for me to take seriously his insightful comments on the effects of antipsychotics on the brain! Consequently, I sailed on, believing the same false dogma for several decades.

It is curious that as I grow older, I find myself increasingly asked to give my predictions for future directions in psychiatry. This is likely to be as productive as asking Mick Jagger to comment on likely new trends in Hip-Hop. I shall therefore confine myself to saying that if I was starting afresh, I would throw myself into examining gene × environment interactions and epigenetics, as ways of elucidating the mechanistic pathways through which the environment contributes to the onset of psychosis. However, one has to be very good at statistics to succeed in this area. So if I wasn't clever enough, I would instead go into neurochemical imaging; it is true that the maths is still complicated but at least the pictures of the brain are pretty.

I expect to see the end of the concept of schizophrenia soon. Already the evidence that it is a discrete entity rather than just the severe end of psychosis has

been fatally undermined. Furthermore, the syndrome is already beginning to breakdown, for example, into those cases caused by copy number variations, drug abuse, social adversity, etc. Presumably this process will accelerate, and the term schizophrenia will be confined to history, like "dropsy."

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References

1. Rodnight R, Murray RM, Oon MC, Brockington IF, Nicholls P, Birley JL. Urinary dimethyltryptamine and psychiatric symptomatology and classification. *Psychol Med*. 1976;6:649–657.
2. A Wellcome boost. *Lancet*. 1976;2:29.
3. Murray RM. A reappraisal of American psychiatry. *Lancet*. 1979;1:255–258.
4. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;2:924–926.
5. Hill D. Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;2:1132.
6. Reveley AM, Reveley MA, Clifford CA, Murray RM. Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*. 1982;1:540–541.
7. Marsden CD. Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;2:1079.
8. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry*. 2003;60:585–594.
9. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;39:1363–1372.
10. Vita A, De Peri L, Deste G, Barlati S, Sacchetti E. The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. *Biol Psychiatry*. 2015;78:403–412.
11. Karolis VR, Froudist-Walsh S, Brittain PJ, et al. Reinforcement of the brain's rich-club architecture following early neurodevelopmental disruption caused by very preterm birth. *Cereb Cortex*. 2016;26:1322–1335.
12. McNeil TF, Kaij L. Obstetric complications and physical size of offspring of schizophrenic, schizophrenic-like, and control mothers. *Br J Psychiatry*. 1973;123:341–348.
13. Lewis SW, Mezey GC. Clinical correlates of septum pellucidum cavities: an unusual association with psychosis. *Psychol Med*. 1985;15:43–54.
14. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *Br Med J (Clin Res Ed)*. 1987;295:681–682.
15. Jones PB, Rodgers B, Murray RM, Marmot M. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344:1398–1402.
16. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*. 2014;383:1677–1687.
17. O'Callaghan E, Sham P, Takei N, Glover G, Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet*. 1991;337:1248–1250.
18. Wright P, Laing P, Donaldson PT, Murray RM. Schizophrenia: the teratogenic antibody hypothesis. In: Müller N, ed. *Psychiatry, Psychoimmunology, and Viruses. Key Topics in Brain Research*. Wien, Austria: Springer Verlag; 1999:89–99.
19. Sharpley M, Hutchinson G, McKenzie K, Murray RM. Understanding the excess of psychosis among the African-Caribbean population in England. Review of current hypotheses. *Br J Psychiatry Suppl*. 2001;40:s60–s68.
20. Birley JL, Brown GW. Crises and life changes preceding the onset or relapse of acute schizophrenia: clinical aspects. *Br J Psychiatry*. 1970;116:327–333.
21. Jones P, Murray RM. The genetics of schizophrenia is the genetics of neurodevelopment. *Br J Psychiatry*. 1991;158:615–623.
22. Murray RM, O'Callaghan E, Castle DJ, Lewis SW. A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull*. 1992;18:319–332.
23. McCutcheon R, Murray RM, Owen M, Howes O. The role of genes, stress and dopamine in the development of schizophrenia [published online ahead of print August 6, 2016]. Biol Psychiatry. doi: 10.1016/j.biopsych.2016.07.014.
24. Rupniak MN, Jenner P, Marsden CD. The effect of chronic neuroleptic administration on cerebral dopamine receptor function. *Life Sci*. 1983;32:2289–2311.
25. Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci*. 2007;27:2979–2986.
26. Chouinard G, Jones BD, Annable L. Neuroleptic-induced supersensitivity psychosis. *Am J Psychiatry*. 1978;135:1409–1410.
27. Carpenter WT, McGlashan TH, Strauss JS. The treatment of acute schizophrenia without drugs: an investigation of some current assumptions. *Am J Psychiatry*. 1977;134:14–20.
28. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand*. 2006;114:3–13.