A road less travelled by

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David J King, MD, FRCPsych, FRCP(I), DPM

A ROAD LESS TRAVELLED BY

"Two roads diverged in a wood, and I took the one less travelled by, And that has made all the difference."

Robert Frost (1874-1963)

In his book "Genome" Matt Ridley has said "scientists are not interested in knowledge – only ignorance and mysteries". My review will therefore be unlikely to inform but rather to bewilder!

My title is taken from Robert Frost’s famous poem and indeed I believe I have explored not one but many rarely frequented avenues of research in neuropsychopharmacology. Looking back over 30 years, however, I think I can discern a pattern of sorts which, I trust, I will be able to persuade you to see as well. The total "journey" is summarised in Table 1.

The story started with an aspect of my MD thesis (“Some aspects of the role of cortisol in relation to affective disorder”, 1971) in which I examined a possible link between elevated cortisol (a known finding in depressive illness) and decreases in brain serotonin (5HT). The idea was that raised cortisol levels by inducing a liver enzyme, tryptophan oxygenase, diverted circulating tryptophan down the kynurenine pathway, so reducing the amount of tryptophan available for 5HT synthesis in the brain, thus leading to depression. Since the rate limiting enzyme in 5HT synthesis was tryptophan hydroxylase I first demonstrated that there was a reduced level of this enzyme in the brain of rats which had been injected with cortisol in comparison with those which had not: an effect which was prevented by the co-administration of allopurinol (which inhibits tryptophan oxygenase in the liver). I was further able to show, in a longitudinal study in

| Year | Title |
|------|-------|
| 1969-87 | Neuroendocrinology (Transcortin and dexamethasone suppression in depression; cortisol and tryptophan hydroxylase in rat brain). |
| 1975-82 | Pharmacovigilance (inter and intra-regional differences in psychotropic drug prescribing). |
| 1979-89 | Viruses and mental illness (Serum and CSF viral antibodies in psychiatric patients). |
| 1979-2001 | Biological Psychiatry (CSF amines, peripheral adrenergic receptors, neurological soft signs, CT scans, eye movements). |
| 1980-97 | Drug trials of new/novel antipsychotics (propranolol, ondansetron, remoxipride, quetiapine, sertindole, zotepine, ziprasidone, M100907). |
| 1982-95 | Pharmacokinetics of antipsychotic drugs in patients (haloperidol, remoxipride, zotepine). |
| 1985-2001 | Pharmacodynamics of antipsychotic drugs in healthy volunteers (eye movements, "McCollough Effect", EEG, psychomotor function, cognition, auditory and visual latent inhibition, pre-pulse inhibition, heart rate variability). |
| 1993- | *Neuropharmacology (animal studies using latent inhibition, *in vivo* microdialysis, quantitative autoradiography). |
| 2000- | *Functional neuroimaging (SPECT studies of acute tryptophan depletion in patients and healthy volunteers). |

*Combined programme: “The role of the pre-frontal serotonin system in cognition”.

The Queen’s University of Belfast, Department of Therapeutics and Pharmacology, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL.

DJ King, Professor of Clinical Psychopharmacology.

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which rats were sacrificed every two hours for a twenty four hour period, that this effect could be explained by a phase shift in the activity of tryptophan hydroxylase. This was particularly interesting since the abnormality in cortisol levels reported in mood disorders was an exaggeration of the normal diurnal variation or a phase shift in this circadian rhythm.

At this point I had to leave laboratory research but was eventually very fortunate in being able to combine my interest in biochemistry and pharmacology with clinical psychiatry, by being appointed jointly to the Department of Therapeutics and Pharmacology at Queen’s University, Belfast (perhaps the only pharmacology department in the country with its own psychiatrist!) and a local general adult psychiatric hospital (Holywell Hospital, Antrim). Building on the earlier work of Owen Wade and Peter Elmes in that department I took an interest in monitoring the use of psychiatric drugs in the community from GP prescribing data. It was clear, and the cause of some alarm at the time, that this was rising, particularly the use of benzodiazepines and antidepressants. This was in the early 1970s at the peak of our civil unrest, and there were many newspaper headlines suggesting that our increased use of these drugs was an inappropriate response to the troubles and was producing a “tranquilised province”. Careful analysis of our data showed, however, that these trends continued long after the worst of our troubles; were similar in England and other Western European countries; and could just as readily be explained by the increase in the availability of new compounds. Indeed the rise in antidepressant prescribing continues and has now exceeded that of benzodiazepines. We now believe much depressive illness was previously being recognised and is now more often successfully treated by family practitioners in the community, rather than as a specialist disorder requiring psychiatric in-patient treatment.

Nevertheless, I was primarily concerned with the biological substrates of psychiatric illness and began a series of studies on the neurotransmitter metabolites found in cerebral spinal fluid (CSF) of patients with psychotic disorders. Lumbar puncture studies would now be regarded as unjustifiably invasive but this was the best we could do before the advent of in vivo neuroimaging. Together with Dr Stephen Cooper, we were able to show that ECT (Electroconvulsive Therapy) and a standard antipsychotic drug, haloperidol, were both associated with a transient increase of the dopamine metabolite (HVA) in the CSF of schizophrenic patients.\(^3\) ECT, despite its detractors, is still the “gold standard” by which other treatments for severe psychotic depression have to be measured. It is also effective, albeit temporarily, in otherwise treatment-refractory schizophrenia. We had thus demonstrated that ECT was having an antipsychotic action through a similar effect on the dopamine pathways as standard antipsychotic drugs. An interesting sequel to these CSF studies was a follow up carried out on the subsequent course of those schizophrenic patients who had had lumbar punctures eleven years previously.\(^4\) We found that ten of the original thirty patients had subsequently made a suicide attempt and that these had had significantly lower CSF levels of the 5HT metabolite, 5-HIAA, at the time of the original illness. This was consistent with the previous depression literature, but seemed to point to a link with the depressed mood itself rather than impulsivity, since there was no association between low CSF 5-HIAA and more violent suicide attempts or other forms of violent behaviour.

We were driven by two convictions: (1) the need to find an objective, measurable correlate of psychotic illness and (2) that new antipsychotic drugs could be found which would be both more effective and better tolerated than existing treatments.

We did indeed confirm that neurological “soft signs” were present in schizophrenic patients and, in collaboration with John Waddington, correlated the cognitive impairment in these patients with increased lateral ventricular size on CT (Computerised Tomography) scans.\(^5\) We also replicated by objective measurement, an observation which had first been made in 1908,\(^6\) that these patients had abnormal eye movements when carrying out simple “smooth pursuit”\(^7\) or “antisaccade”\(^8\) tasks. We measured both smooth pursuit tracking and saccadic eye movements using a simple electro-oculographic (EOG) system. Saccades are rapid eye movements which occur when visual attention is switched between objects of regard and are the fastest movements of which the body is capable, reaching peak velocities of up to 600°/sec. The speed of these is unchanged in schizophrenia but when the task is to inhibit the tracking and instead to look in an...
equal and opposite direction (the antisaccade paradigm), schizophrenic patients make many more errors. We were not, however, able to distinguish between treatment responsive and treatment refractory patients using this method.

Our quest for new and better treatments led us to try new compounds, or new uses of old compounds (propranolol) and also to explore the possibility that pharmacokinetic differences between patients led to their resistance to treatment. The propranolol story demonstrated that its apparent efficacy in schizophrenia was due to a positive or beneficial pharmacokinetic interaction whereby the addition of propranolol, by inhibiting the metabolism of the adjunctive antipsychotic, increased the plasma levels of those drugs. This encouraged us to embark on a somewhat “heroic” study of very high levels of haloperidol in an attempt to improve treatment refractory schizophrenic patients — perhaps this is where the toxicology comes in! There was, however, a negative result in that, although we achieved somewhat hazardous serum haloperidol levels of up to 100 ng/ml, there was no additional response with levels above 20 ng/ml. This has repeatedly been found with subsequent studies which show that there is no additional response to haloperidol in doses above 20 mg per day.

The other drug studies carried out at Holywell Hospital over this period of time are listed in Table 2. Clozapine, the first “atypical” antipsychotic which had been shown to be effective in otherwise treatment-resistant patients and to have a low incidence of adverse extrapyramidal side-effects, but which also carried a substantial risk of potentially fatal agranulocytosis, was re-introduced in the United Kingdom under limited licence procedures in 1990. We started using it in February of that year and published the first series of 24 patients to be given clozapine in Ireland. 71% of these previously, very disturbed and treatment-resistant patients improved, one third markedly. However, because of the risks with this drug a range of “new atypicals” were being developed and we participated in the early trials of a number of these. An example is the remoxipride study. Remoxipride is a selective D₂ antagonist which was subsequently withdrawn due to aplastic anaemia. Crucial to its development was a multicentre study which we carried out in Northern Ireland, which proved to be the only placebo controlled trial to be done with this drug. We demonstrated that when chronic schizophrenic inpatients were randomised to remoxipride or placebo the relapse rate was significantly reduced in the remoxipride group. This study was deemed to be ethical at the time since the patients had had a minimal response to standard treatment and had shown no signs of relapse during a previous one month placebo “wash out” phase. These studies underline the great change that has come about in the organisation of drug trials within the last twenty-five years. It is even more remarkable to read Heinz Lehmann’s account of the first trial with chlorpromazine about fifty years ago as recorded by David Healy in his book on “The Psychopharmacologists” (1996).

“So the next morning, which was a Monday, the first resident I met was Dr Hanrahan and I asked him ‘Do you want to start some research with me on a new drug?’ and he said ‘yes’. So we did it... We decided we would try it out on about 70 or 75 patients. Nowadays, of course, this would take years but in those days it didn’t take very long. We just chose 70, and we did them all, practically simultaneously, within one or two months. Also, I didn’t have to ask permission from the Director of the Hospital. I didn’t have to get permission from the FDA or the Government. There were no ethical committees at the time, no guidelines, laws or regimentations...I don’t remember – this was in 1953 – whether I even asked the patients. Certainly there was no such thing as informed consent at that time. I might have, but I don’t think so. I just ordered it. I might have told the families if they visited... We started in May and by August we had written the paper...”

Increasingly, however, I was becoming persuaded that psychotic illness was associated with a localised brain abnormality and that a full understanding of the condition required a proper description both of the psychological function that was disturbed and the location of this abnormality within the brain. This, of course, raises the old Cartesian chestnut but we are beginning to see that a true account of pathophysiology will avoid separating “mind” from “body” by understanding that the integration of all somatic, endocrine and neural functions provides the subjective experience of consciousness. I was also convinced that a proper understanding of the mode of action of antipsychotic drugs would lead to important clues about the nature of the illness itself.
The great challenge was to understand how it was that antipsychotic drugs could have profound effects on such a fundamental human function as thinking. So I embarked upon a review of the effects of antipsychotic drugs on cognition and found that the literature was in a real mess. It was quite clear there was no general agreement as to what was meant by “cognition” and in particular there was no consistency in the way trials were being carried out. Pharmacologists controlled the pharmacological aspects of their studies but used very simplistic measures of cognition and took no account of neuropsychological subtleties such as practice effects, while on the other hand psychologists had sophisticated measures of cognition but no proper control over or understanding of the importance of controlling for dose and the timing of their tests. It was quite clear also that many of the studies in patients were confounded by these and other variables particularly the severity and nature of the illness itself. There was also an apparent paradox in that those drugs which improved thought disorder in patients generally had adverse effects on cognitive function in normal healthy people.

Thus I embarked on a series of studies of the effects of antipsychotics in healthy volunteers. This was not without its hazards, because, as was well known, healthy volunteers tolerated such drugs poorly. In particular haloperidol caused very unpleasant dysphoria and akathisia. Nevertheless, it was interesting that the dose at which we found these effects emerging was very similar to the “neuroleptic threshold” i.e. the dose at which there were the first signs of parkinsonian adverse effects in patients, i.e. 3.7 mg. Among other things these studies led me to realise that a great deal of “dysphoria” was being dismissed in psychiatric patients as part of their illness rather than an adverse drug effect. We found that healthy volunteers could in fact tolerate most other antipsychotics, including chlorpromazine as well as the newer atypicals, quite well. We started with studies of saccadic eye movements, demonstrating that peak saccadic velocity was a good correlate of the sedative properties of these drugs. We then went on to show that the antisaccade paradigm, which recruited a “cognitive” component, was paradoxically spared any impairment in spite of clear evidence of slowing of the saccadic velocity and of substantial subjective sedation. This “sparing” of cognitive function was very similar to that which had been previously observed by Miersky and Kornetsky in the 1960s using a simple digit symbol substitution test (DSST). We also confirmed that memory was largely unaffected by single doses of antipsychotics in healthy volunteers. More recently we have attempted to replicate an animal model of the attention deficit seen in schizophrenia, known as “latent inhibition”, and have, once again, found that this is relatively unaffected by antipsychotic drugs. Indeed, chlorpromazine actually improved selective or focused attention as measured by this task. However a limitation of all these studies was that we could not give the drugs chronically for long enough in healthy volunteers to simulate the situation of therapeutic dosing in patients.

Turning once again to animals we followed up the theme of cognition by first establishing the latent inhibition paradigm. This is supposed to have “construct” validity in that it appears to model a key deficit in schizophrenic thought disturbance, namely the inability to ignore extraneous and largely irrelevant stimuli. This is done by having parallel groups of rats one of which is “pre-exposed” to a flashing light while the other is not. Following this training both groups are exposed to an aversive stimulus which had previously been linked with the “pre-exposed” stimulus. The response to the aversive shock is much less in the “pre-exposed” rat and the difference is “latent” inhibition. We found that both haloperidol and clozapine were effective in this model and also some novel compounds such as antagonists of cholecystokinin, a neuropeptide co-transmitted with dopamine, but
We by two areas devoid of extrapyramidal the antipsychotics and differentialeffectsof antipsychotics, the after and the selective subtypes.31' the brain was exposed to antipsychotic compounds we decided to look at the effects of these compounds on the neurotransmitter release in the core and shell of the nucleus accumbens using in vivo microdialysis. The shell of the nucleus accumbens links with the mesolimbic areas of the brain while the core is closely linked with the nigrostriatal areas. Thus the parkinsonian extrapyramidal adverse effects of antipsychotics are linked with increased dopamine turnover in the core of the nucleus accumbens while we believe that the beneficial effects are associated with a similar increased turnover in the shell. Robert Moran, who set up this technique, was then able to demonstrate a separation between the effects of haloperidol and clozapine (the first “atypical” antipsychotic drug which is virtually devoid of extrapyramidal side effects) on these two areas of the nucleus accumbens.29, 30

We have also established another way of looking at receptor pharmacology in rat brain through radioligand binding in membrane homogenates and by quantitative receptor autoradiography, and Marie Cahir is currently looking at the differential effects of typical and atypical antipsychotics on α₁ and α₂ noradrenergic receptor subtypes.31, 32, 33 In the autoradiography technique, after animals have been treated with different antipsychotics, the brain is removed and sectioned by microtome. The sections are incubated with a radioligand (in this case tritiated prazosin, a selective α₁ adrenoceptor ligand), washed, dried and then apposed to a radioactive sensitive film for up to 6 weeks. The resulting images are examined by a computer linked digital camera system (Computer Assisted Image Analysis), which produces colour-coded pictures revealing the distribution and density of the receptors of interest. Marie has shown that clozapine causes an increase in α₁ receptors in a wide range of cortical regions, which may reflect part of the mechanism of its “atypical” action. Comparisons with other atypical antipsychotics and with chlorpromazine are ongoing. We will now be starting to use this technique to examine the effects of manipulating brain 5HT by tryptophan depletion, on both serotonin, noradrenergic and dopamine receptors in rat brain.

Finally in collaboration with Dr Stephen Cooper, we are currently developing functional neuroimaging with Single Photo Emission Computerised Tomography (SPECT), with the hope of also being able to use Position Emission Tomography (PET) scanning in Belfast in the near future. We have been manipulating central 5HT using acute tryptophan depletion in both healthy volunteers and schizophrenic patients, and, using 99mTc-HMPAO SPECT, have demonstrated that this procedure causes similar decreases in regional cerebral blood flow (rCBF) in healthy volunteers as have been previously demonstrated in depressed patients, but without the concomitant subjective reaction of depression.34 Thus a fall of serotonin seems to be a necessary but insufficient explanation for depression.

In schizophrenic patients, however, we found increases rather than decreases in rCBF in those same prefrontal areas following acute tryptophan depletion.35 Since these rCBF changes principally reflect glutamatergic function, these findings are consistent with the theories of a glutamatergic abnormality in this condition.

Furthermore, we have recently gathered evidence that this fall in serotonin following acute tryptophan depletion is associated with improved rather than impaired cognitive performance using a “gambling” or decision making paradigm, which is probably associated with increased activity in the orbital frontal cortex or the ventro-medial pre-frontal cortex. This is the area of the brain which when damaged leads to undirected and uninhibited behaviour, as in the classical case of Phineas Gage and many others now referred. It may also be impaired in psychiatric disorders with cognitive dysfunction such as schizophrenia and even, perhaps, in psychopathic personalities. Intriguingly, a recent study has found elevated kynurenate (a metabolite of kynurenine and ultimately of tryptophan) levels in one of these prefrontal areas (Brodmann area 9) in schizophrenic brain.36 Since kynurenate is a glutamate receptor antagonist, tryptophan depletion might improve cognition by reducing the levels of this metabolite.

We are now combining our animal work with these more recent human neuroimaging studies and have set ourselves the task of defining “The role of the pre-frontal serotonin system in cognition”, and this programme of research has
been funded as part of a recently successful bid to establish a Recognised Research Group (RRG) in Neuroscience by the R & D Office of the Northern Ireland DHSSPS. We hope to demonstrate using the animal studies exactly what happens following acute tryptophan depletion not only to 5HT but also to other neurotransmitter systems. We trust that this will map on to the changes we see in regional cerebral blood flow in healthy volunteers after tryptophan depletion. We will then be in a position to interpret the changes in regional cerebral blood flow in schizophrenia.

Thus I have come full circle, back to tryptophan, serotonin and psychosis: a road now more travelled by!. It has been a fascinating journey. I do not know what it all means and I am just as puzzled as I was 30 years ago, but I still have the conviction that this is one of the greatest challenges we face in medical science and that further exciting glimpses of the truth about the brain and its most important functions lie ahead.

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