The Scientific Status of Concepts of Mental Disorder, Community Concerns, and Precedents from the History of Science. Part II.

7. A Better Way Forward.

If psychiatry is *really* to become a fully scientific discipline, what is needed are robust explanations and disease theories, and robustly-validated concepts. Precedents from physics indicate that precise explanatory arguments depend on having precisely-defined basic concepts. These in turn depend on already having explanatory arguments in mind. There seems to be a total impasse at this point.

I do not regard this conundrum as insoluble; and I *am* drawing deliberate parallels with the way central concepts came to be defined in the natural philosophy tradition in the seventeenth century. There are several aspects to the analogy: It will be necessary: (i) to carefully distinguish the two traditions (natural philosophy and natural history) in what we are doing; (ii) to aim for a proper balance between empirical study and theory development; (iii) to aim for robust cross-level explanations of the relevant evidence known at a higher level in terms of lower level processes. The evidence to be explained may be psychological, behavioural, symptomatic and (with some caveats about interpretation) first person experiential accounts. The lower level premises for the explanation may be hypothetical rather than established facts, but are especially likely to be about brain biology. I believe these objectives are all within our grasp, eminently possible in many areas of psychiatry, on the basis of empirical evidence we already have. It will however need drastic reorientation of the focus of research.

I think that the analogy with early research in physics (a.k.a natural philosophy) is relevant for another reason. In the seventeenth century, apart from the struggle to define what "natural science" could be, there was a substratum of even more profound debate, on what are essentially metaphysical issues, about such things as the best meaning for words like "nature", and "causation", and the relation between religious notions of the time, and the nascent concept of natural science. Were scholars to continue using Aristotle's ideas about "final cause", or was there a more profitable way to conceptualise cause ("antecedent cause" as we might now call it). In psychiatry today, there are also underlying debates on metaphysical questions, about the relation between mind and brain (or equivalently between the subjective and objective worlds). In this sense, to define disease

theories in psychiatry is far more difficult, and far more fundamental than defining disease theories in other areas of medicine. The germ theory of infectious disease, or theories of autoimmune disease, neoplasia etc, do not require any original thinking at the metaphysical level. Thus, in psychiatry, the task is *very* fundamental, by comparison with much of today's "routine" biomedical science.

Although I draw the analogy with natural philosophy at the time of the origin of the natural sciences, the analogy should not be pushed too far. There are important differences. The major difference is that the brain and its psychological products (behaviour, thought etc) are vastly more complex than the physical systems dealt with by Galileo and Newton. No doubt those systems did seem formidably complex to those who were wrestling with these issues, as yet unsolved, at the time. The whole point of a good explanation is that it simplifies one's ways of thinking; and then we easily forget how complex it all seemed before the moment of illumination. Nevertheless, in the case of the brain we certainly need a vastly larger body of empirical data before precise reasoning can start to get traction. We *do* have a vast amount of factual information both about the normal brain, and about complex disorders such as schizophrenia. The problem is that very few individual scientists know about this except in small areas of their own research. In my view, at least in some areas of psychiatry, there *is* now sufficient empirical evidence to start to employ reasoning for theory development, but we need a dedicated body of researchers who try to get to know much more widely what is already known (by somebody).

The other major implication of the much greater complexity of the brain compared with most physical system studied in the natural philosophy tradition is that the scope for precise mathematical reasoning is likely to be far less than in physics. What is rather needed is a special style of scholarship. I do see *some* role for mathematics and computer modelling. However, in my view this is useful in special carefully-defined areas. Specifically, I think these methods can throw important light on the electrophysiology of single neurones, or the *abstract principles* of neural network interaction. Analysis using computer simulation or mathematical reasoning of the *reality* of complex biological systems, such as the *real* brains or structures within them, I think is not very helpful, and perhaps wasteful. There are far too many "floating" parameters, and the limits to exact reasoning set by chaos theory preclude exact predictions. Even in physics major theoretical advances sometimes have depended as much on sudden subjective insights in the prepared mind of the theoretician on how things "fit together", as on sophisticated formalized mathematics.

So, to, construct those cross-level explanations, the area where I see room for much greater emphasis is in very systematic, and very large scale scholarship, guided by reasoning which is often relatively straightforward. Only with such scholarship can one begin to get a feel for the full complexity of a biological system. Only with such thorough scholarship does the theoretician have a mind adequately prepared for those flashes of insight when new explanatory premises are conceived. Relatively simple reasoning then leads first to small-scale preliminary conjectures or predictions, which can then be checked against the wealth of published empirical information. Occasionally predictions are made on which no data exist, so then the ball is in the experimenter's court; and by repetition and extension, small-scale conjectures build up iteratively into larger theories.

There are already a few areas where such cross-level explanations in the brain and behavioural sciences have emerged. Since this is the area on which my own work has focused in the last 35 years, I will mention some of that work in this section. My aim here is not to boast about these successes. As always, in real science, conclusions are for ever *sub judice,* always subject to challenge. Rather it is to show that a radically new approach, with great potential is not only possible, but promises great practical dividends.

(a) *The rubric of instrumental conditioning, the discovery of the self-stimulation phenomenon, and the impact of this on psychiatry.* In the first half of the twentieth century a great deal of work by psychologists in animals and humans analysed processes of learning using associationist paradigms. The rubric of instrumental conditioning, while far from a complete account of learning in any species, is nevertheless arguably an important component of learning systems, as described in psychological terms. Referring to the idea of cross-level explanations, this is the "higher level" in this example. What could be the lower level, that is, its neurobiological basis? In the early 1950s, James Olds and Peter Milner addressed this issue. (It is noted here that Peter Milner, the theoretician of the pair, was an engineer by training before becoming a physiological psychologist. He was no doubt used to analysing physical systems with built-in feedback loops.) As a result they reasoned that there must be an internal reinforcement system in the brain; and that by linking an animal's behaviour directly to this system (by-passing the sensory systems which normal activate it), behaviour could be reinforced, regardless of its usual motivational significance. The reasoning was thus a classic piece of cross-level explanation in the natural philosophy tradition. It led to the celebrated "self-stimulation", or "brain stimulus reward" experiment, published in 1954. Behaving animals, with electrodes implanted in the brain, were able to

lever-press to deliver electric pulses through the electrode. With some electrode placements, the animals would repetitively stimulate their own brains, regardless of other prevailing motivational drives. From this developed a vast body of experiments, examining the electrophysiological, anatomical and pharmacological aspects of the internal reinforcement system. In due course this had a major influence in psychiatry, as evidence accrued that a major part of this reinforcement system involved dopaminergic pathways linking the midbrain with the forebrain. I became aware of this literature in the early 1970s, and used the idea to explain a singular paradox about the effects of antipsychotic drugs: While they block dopamine receptors within, at most, a few hours, the beneficial clinical effects accumulate over weeks or even months. From that insight the idea grew that psychosis was an exaggeration of the reinforcement functions of dopamine, expressed mainly through distinctively human cognitive processes rather than necessarily through outward behaviour. My first paper on this was published in 1976[1]. In the early 1980s Rick Beninger from Queen's University (Kingston Ontario) independently came up with a very similar concept for psychosis, and, since we met in 1989, we have worked together, and published several jointly-authored papers. Nowadays it is becoming mainstream understanding of psychosis, although the terminology has been changed (to something like "aberrant salience" rather than exaggerated reinforcement). However, many of the subtleties of the reasoning have been lost, and few people know the origin of these ideas. If the full story were better understood, it would be clear that it has considerable practical implications for how antipsychotic drugs should best be prescribed, perhaps leading to more rational prescription than at present.

(b) To link psychological processes to underlying neurobiology, in a truly explanatory sense, we obviously need to know a great deal about the nerve cells of which the brain is composed. A great deal *is* known about nerve cell bodies and their biophysics, but so far, it has not proved very useful for cross-level explanations. However, one part of a neurone has been neglected, especially for central neurones, that is the humble axon. We have known the physical basis of action potentials in axons since the 1950s, and in the peripheral nervous system we have known about conduction properties (e.g., conduction velocity) for longer than that. However, in the central nervous system the evidence, especially on conduction velocity is scanty. As a post-doctoral student in Oxford in the early 1970s I was recording from single cortical neurones in the cerebral cortex of anaesthetised cats, and was able to

[1] Miller,R. (1976) Schizophrenic psychology, associative learning and the role of forebrain dopamine. *Medical Hypotheses* 2, 203-211.

obtain data on the range of conduction velocities in populations of axons connecting together different parts of the cortex. Some axons had conduction times much longer than anyone would have guessed at the time. The experiment certainly was biased against detecting neurones with such slow-conducting axons. Bearing in mind these likely biases, and scaling things up to brains the size of humans, it is very likely that different axons in a typical pathway have conduction times (from cell body to synapse) ranging from a few milliseconds (in rapidly-conducting axons) up to a few hundred milliseconds (in slowly-conducting ones). Harvey Swadlow, from the University of Connecticut has done much more animal experimental work on axonal conduction in the CNS, and, making similar inferences for humans, reaches much the same conclusion[2]. The slower-conducting axons have conduction times long enough to have major implications for the computation accomplished in the cortex, as might be revealed in psychological experiments in intact humans. Thus we are within reach of true cross-level explanations of psychological findings in terms of brain structure and cellular function. The first time I used this concept (in 1981[3]) to explain a psychological finding was as follows: Each consonant speech sound is, in acoustic terms, a brief succession of acoustic events occurring in sequence over a period of about 100 msec. It is known that human perception of consonant speech sounds is usually performed better with the left than the right hemisphere. The hypothesis I developed was that the left hemisphere has a richer repertoire of "long axonal delay lines" (which can represent patterns spread over intervals of time of ~100 msec) than the right (where conduction, hypothetically is faster, the hemisphere then being better for analysing *instantaneous* patterns). By the 1990s this simple idea had been worked up to produce a more comprehensive theory of cerebral asymmetry, the central hypothesis being that, in most pathways, the left hemisphere has axon populations whose range of conduction times spans longer time intervals than in the right. From there, I went on to explore an idea which had been around since the late 1960s, that there was some form of *abnormal* laterality in schizophrenia. In the end I was able to account for a very large number of non-psychotic traits associated with schizophrenia, in terms of the hypothesis that (regardless of the hemisphere) there is a relative lack of rapidly conducting axons in schizophrenia, these being replaced by slowly-conducting ones. My magnum opus on this subject was published in 2008. Anyone who wants to get a grasp of the full range of psychological functions for which explanations in terms of population-distributions of

[2] Swadlow,H.A., Geschwind,N. and Waxman,S.G. (1979) Commissural transmission in humans. *Science* 204, 530-531.
[3] Miller,R. (1981) *Meaning and purpose in the intact brain.* Clarendon press, Oxford.

axonal conduction times form the basic premises should look at three of my books[4]. The reasoning in these works, as well as the assumptions on which it is based have yet to be given a proper critique. I await that with interest.

There are several important general lessons to be learned from these two examples: (a) True cross-level explanations in the brain and behavioural sciences *are* possible, including ones related to mental disorders (where they may also be related to strategies for treatment), as well as to normal brain function. When such explanations are constructed, they may also serve to provide robust validation of the concepts used in the process; and these may cut across traditional concepts (such as concepts of disease) established in less rational fashion. (b) The two examples given employ two different principles from basic neuroscience. I am sure there are other principles coming from basic neuroscience, which may prove crucial for other explanatory frameworks, beyond these two. (c) Framing cross-level explanations is not possible unless *someone* is familiar with information at both the "upper level" (i.e. psychological findings, behaviour, symptoms or first-person accounts of experience) and the lower level (details of various aspects of brain biology). That means either that basic neuroscientists need to be educated about the fine clinical details of mental disorders, or that psychiatrists, clinical psychologists (etc) need to be educated about the fine details of neuroscience. This may require change in education in both areas. (d) There is no algorithm by which one can determine which upper level evidence is to be related to which lower level principles to form a cross-level explanation. Since the evidence at both levels is far more complex than in physical systems, any would-be theoretician in this area needs to be extremely well-read, before he has much chance of achieving the link. This, I believe, is far more important than expensive computer simulations or mathematical analyses (although occasionally those methods may be useful in theoretical work in this area).

It may well be said that we do not have yet have enough basic evidence to launch a large-scale, library-based theoretical branch in the brain and behavioural sciences, or in psychiatry. I disagree strongly with this view. The problem is *not* that we do not have enough information to commence theory building, but that too few people know enough of it to make any progress, have no confidence that real explanations can be found (because there are no traditions for this), and have no idea how to find them. The

[4] Miller,R. (1991) *Cortico-hippocampal interplay and the representation of contexts in the brain.* Springer, "Studies in Brain Function" series.
Miller,R. (1996) *Axonal conduction time and human cerebral laterality.* Gordon and Breach.
Miller,R. (2008) *A neurodynamic theory of schizophrenia and their disorders*, Lulu Enterprises, Morrinsville, North Carolina.

information that has been accumulated over the last 100 years at both the higher and the lower levels is immense, overwhelming, staggering, much of it (not all) very solid empirical data, if only we knew how to use it; but who reads it? Who tries to assimilate it even at one level, let alone across levels, or between different fields of experimentation?

What I suspect has happened regularly over the last fifty years is that a new technique is discovered, experimenters rush to exploit it and many very good empirical papers are published, some not so good; but when the whole new area is reviewed it looks too messy and complicated to make *real* sense of it, and no-one knows enough in other fields or at other levels to do this. At this stage another new technique is invented, so researchers, always looking to publish good papers rather than achieve basic understanding switch to the new area; and then they do it again. . . and again . . . and again. Each time there is vast expense, and big profits for those who make the equipment, but little real progress in terms of understanding or at a conceptual level. The metaphor which comes to my mind is of a vast orchard, stretching way beyond the horizon; and wherever one takes a close look, one sees trees hanging low, overburdened with ripe fruit, ready for picking. Tending this orchard obviously took prodigious labours of many skilled and dedicated gardeners in times gone by; yet no-one picks the fruit, and hardly anyone knows of the existence, nor the size of this awesome orchard. No-one realises its wealth and enormous potential; and yet, since the fruit (all those research papers) are securely archived, the fruit will never become over-ripe and fall from the trees.

What this means is that a would-be theoretician should not expect to make a career out of *combining* theoretical work with experimental or clinical work (both of which may in themselves demand complete attention and commitment). S/he needs to be a dedicated theoretician, and we need a new discipline to emerge of theoreticians in brain/behavioural/psychiatric sciences, respected by and fully respectful of the experimental disciplines, both knowing that there is mutual benefit to come from close knowledge of each other's approaches, an alliance based on mutual respect, the one looking for predictions s/he can test, the other hoping to make predictions which the other *can* test. This also means that both sides should understand that (as in physics) good experimental researchers, and good theoreticians are quite different sorts of people, with different habits of thought, never to be evaluated on a single scale for "research assessment". This tradition of interplay between experiment and theory existed in the natural philosophy tradition ever since the time of Copernicus, Tycho Brahe and Kepler. It is now desperately needed if the brain and behavioural sciences are to make

further substantial progress. If it could be brought about, in my view, progress would then go further, faster, be more secure, and be *much cheaper.*

8. Some guiding concepts

A few more specific concepts are suggested to guide the construction of true disease theories in psychiatry.

(i) State versus trait. Research on schizophrenia clearly shows that, in addition to active psychotic states, there are many non-psychotic trait markers of the underlying predisposition. The distinction between state and trait aspects of mental disorders may apply to other disorders (bipolar disorder, depressive disorder, anorexia nervosa etc) although not yet defined so well as in schizophrenia. For disorders where traits, and their separation from corresponding states are not well-defined, there is need for more descriptive work. Abnormal *states*, being transient are likely to be based on dynamic aspects of brain function, such as transmitter release, or electrophysiological variables. The more dramatic and obvious symptoms (often aspects of transient states rather than enduring traits) may be the ones most accessible to explanation in the first instance. Their biological mechanism *may* emerge first, as a prelude to more fundamental understanding of enduring traits (as has occurred in schizophrenia research, where understanding of psychosis has been well ahead of understanding of non-psychotic traits). Traits, being long-lasting, are likely to be based ultimately on static aspects of the brain, that is on aspects of cellular structure or stable aspects of neuronal dynamics, and are therefore more fundamental to understanding those disorders. Therefore a focus on the relation between stable traits (symptoms, or psychological or psychophysiological traits) and evidence or hypotheses at the level of neuronal structure may be more fruitful in the long run than those which focus on transient, dynamic changes in the brain. The relation between the state and trait aspects of these disorders is also not to be neglected, but may be a more complex question, for which fundamental explanations may not easily be found, until explanations of both state and the trait features have been provided.

(ii) Concepts of pathology. If mental disorders are based fundamentally on divergence from normality in cellular properties, there is a distinction to be made which has an important impact on how we conceptualise those disorders: Divergence from normal, in a statistical sense, is not the same as pathology. Quantitative variation in cellular parameters need not mean that there is *pathology* at the cellular level. For instance, low conduction velocity

in axons is due to their having a fine calibre or being myelinated, and often with cells bodies of smaller size; yet there is nothing at all pathological about fine calibre or unmyelinated axons, or about small-sized neuronal cell bodies. The cerebral cortex in all of us contains a wide range of sizes of neuronal cell bodies, and a mix of large- and small-calibre axons, and of myelinated and unmyelinated ones. The shifts are in the quantitative aspects of populations of neurones and axons. At what level then is the pathology to be found? I would suggest that for most mental disorders it is at the level of large nerve networks, even the whole brain, in terms of their information processing, and resulting subjective experience, behaviour and symptoms. In other words, it is unusually *psycho*pathology, not *neuro*pathology or *cyto*pathology.

If this is accepted it will have considerable impact on how mental illness are conceived, and how they are portrayed to the public, and to individual patients. In particular, many divergences from the statistical norm will be seen as being in complete continuity with the range of normal personality variations; and they may then turn out not to be truly pathological, except in certain environmental situations (such as in some social contexts). There are serious questions to be faced here for the broad concept of "mental illness". Do we have a proper definition for mental illness, which would withstand scientific scrutiny? . . .or as some antipsychiatrists have claimed, are we misusing the concept of "illness" to pathologise something which is really deviance against *social* norms, rather than illness as conceived elsewhere in medicine?

(iii) Across how many levels should we seek explanations? There are many levels at which mental disorders can be studied, all the way from the basic "alphabet" laid out as nucleotide sequences, through "words" and "sentences" (amino acid sequences in proteins, and growth factors), to cellular properties, tissues, organized brain structures, whole brains, and their functional expressions in physiological, psychological, symptomatic or experiential ways. Undoubtedly *correlations* can be discovered which are many levels apart, and linked only distantly in causal terms, but these are not *explanations*. The reasoning needed for cross-level explanations initially has greatest chance of success if it does not cross too many levels. The two examples given above reached downwards from psychological findings of symptoms, to link, in one case with effects of the dynamics of a neurotransmitter (but not its determinants in terms of molecular genetics), and in the other to functional properties of axons, closely linked to their structure (but not to *their* genetic determinants). I suspect that this is a profitable avenue to explore - between the psychological/symptom domain

and cellular properties. Sometimes the known beneficial effects of a medicine acting on a transmitter in reality signifies a fundamental abnormality not in the transmitter itself (or in its receptors or gene), but in cellular properties which can be normalised by a shift in activity of a neurotransmitter or neuromodulator. Focus on molecular origins may thus be cutting too many corners, along the road to an explanation. There *may* be cross-level explanations to be found between gene sequences and developmental processes in the brain. Although this is not my field, it seems to me *un*likely that this would throw much light on mental disorders in explanatory terms (although correlations may no doubt emerge). To seek explanations of symptoms or other psychological findings in terms of nucleotide sequences is I suggest, attempting too much. As one psychiatrist has said, genes do not code for "auditory verbal hallucinations in the third person"; nor, if we were trying to understand the meaning of Shakespeare's writing, would we get much success by analysing the frequency of different letters of the alphabet, or single words (or even phrases) in his text. As already mentioned, genes interact in immensely complex ways to produce tissue structures, and we have scarcely begun to unravel the principles of such interaction

(iv) Neurodevelopmental disorders. Many psychiatric disorders emerge during adolescence, and have some degree of genetic determination. This implies that they are something to do with brain developmental processes, as specified genetically, perhaps as trajectories of brain development somewhat different from the normal or optimal. Hence, we can call these disorders "neuro-developmental". One aspect of normal development which we know about is axonal maturation, especially myelination. While some axonal pathways myelinate relatively early in post-natal life, those connecting together the different structures in the hemispheres myelinate progressively between birth and early adulthood, at different rates in different pathways, and perhaps continuing slowly in some regions or pathways into the twenties, or even later. Therefore, alterations in the developmental program for myelination of forebrain axonal connections is an important area where subtle divergence from the normal developmental trajectory may occur, which could underlie neuro-developmental psychiatric disorders. The potential of this area is indicated by the fact that myelination, via the variable it controls (axonal conduction velocity) affects neurocybernetic function and therefore psychological function; and since myelinated axons have larger calibre axons plus the myelin sheath, abnormality in the degree of myelination (if it affects large populations of axons) will have detectable

effects on gross structure, as might be revealed in structural MRI or diffusion tensor imaging.

(v) Similarities and differences between neurological and psychiatric disorders. Historical parallels have already been referred to in the debates in psychiatry and neurology in the context of phrenology, the concept of cerebral localization of function, and the alternative more holistic approach to the brain, as an organized whole. Likewise the inference that schizophrenia, or other mental disorders are a form of disconnection syndrome draws a direct parallel to neurologists' ways of thinking. For mental disorders, however, there is hardly ever a real lesion, and no direct evidence for disconnection, so the statement is an inference from functional evidence, or even just a metaphor. Here we can extend the comparison by pointing out further differences (and similarities) between neurology and psychiatry. Most of neurology is based on identifiable pathology in the form of loss or damage to nerve cells in specific locations in the brain. In psychiatry, this is seldom the case, yet there *are* some similarities in symptoms profiles, especially in comparing milder neurological deficits with trait aspects of psychiatric disorders. One possible basis for these similarities comes from the suggestion that abnormal myelination underlies a number of neurodevelopmental psychiatric conditions.

A little detail is needed here: If a pathway contains axons whose conduction times range over the population of axons between (say) 5 and 20 msec, impulses which start off at the same time, will be dispersed a little in time when they reach their destination, but nevertheless most will arrive within the same "neuronal integration time" (order of 10-15 msec) and so can effectively summate in the post-synaptic neurones. If a corresponding pathway has conduction times all four times longer (ranging from 20-80 msec), far fewer impulses will arrive at their destination in any single integration time, and summation in post-synaptic neurones will be much less. The result may be deficits similar in some way to an actual disconnection syndrome, due to physical damage to cells or interruption of their axons. There may thus be considerable overlap between traits of mental disorder, and neurological problems due to actual brain damage, although at the cellular level, the causes are quite different. However, slowly-conducting axons *do* still conduct impulses, and for some functions, this may show up as *better than normal* performance (as is the case for some non-psychotic schizophrenia traits).

Another implication is that when neurological and psychiatric syndromes overlap they may be more dramatic subjectively for the neurological than the psychiatric patient, because in the former case, impairment is very often the

result of actual head injury, or other forms of brain damage. Thus, if the person so affected is capable of reflective insight into his or her impairment, it may be more informative than in psychiatry, because there is more likely to be a striking "before and after" comparison. In contrast, in psychiatry, the present state of impairment may be the only subjective reality a person knows. There may thus be much to learn from dialogue between neurology and psychiatry, and their respective patients. There may also be much to learn from German physicians and researchers, where the separation between psychiatry and neurology did not occur as it did in the English-speaking world, and many specialists combine training and experience in both specialities.

(vi) "Specific energies", and the overlap between trait aspects of different psychiatric disorders. In 1826, Johannes Peter Müller proposed the law of "Specific Nerve Energies", which states (in modern terms) that the function (and subjective impact of) activity in a nerve pathway depends on what it is connected with rather than what initiated the activity (be it a sensory stimulus, an applied electrical or chemical stimulus, or whatever). An adaptation of this principle is directly relevant to the preceding argument, with major implication for classification principles in psychiatry. If there is abnormality in an axonal pathway in the forebrain (whether that is an interruption of the pathway, or a change in the range of conduction velocities in a population of axons) the functional impact depends not so much on the cause of the change, but on what the pathway is connected to, upstream and downstream. This means that underlying factors at the cellular level causing the change (whether genetic, or environmental) are not directly related to either the details of symptoms and other functional abnormalities, or the supposed disease entity of which they are a part. A similar cause of change (slowing of the range of conduction velocities, or actual damage to axons) may produce quite different symptoms (and be put into quite different disease entities), according to which region or which pathway is involved.

This fact is more relevant to trait aspects of mental disorders than to the state aspects (whose theory is likely to be more difficult to derive from fundamental causes). However, from my knowledge of schizophrenia traits I can give some rather tentative examples of disorders which might be similar at the cellular level, but quite different at the symptom level. *(a)* The historic separation between schizophrenia and manic-depressive illness coming from Kraepelin was known even by him (in his later years) not to be a sharp separation, and has been questioned by later writers ever since. Nevertheless, there *are* some differences between the two disorders as conventionally

defined (as well as many similarities). There may be similar processes at work at the cellular level, but in different parts of the hemispheres. (b) If one looks at traits associated with dyslexia, many of them overlap with those of schizophrenia. There are however two major differences, that schizophrenia is associated with vulnerability to psychotic episodes, which do not occur in dyslexia; and in dyslexia there are usually striking disturbances of visual perception, not seen in schizophrenia. This leads to a hypothesis worth investigating, that the abnormality in both disorders is similar at the cellular level, but affects the anterior parts of the hemisphere more than the posterior parts in schizophrenia, the opposite in dyslexia. (c) Similar questions arise from two more examples of co-occurrence of syndromes: Schizophrenia is sometimes associated with noise sensitivity, sometimes not. Likewise, I recently met a person who had the dual diagnosis of schizophrenia and OCD/Tourette's syndrome. Such instances of overlap between supposedly-separate disorders may be quite common, and more than chance coincidence. They need better documentation: There is need for much more epidemiological work on co-morbidity especially for enduring traits or trait-like symptoms. Such research may point to underlying commonalities at the cellular level, while the details of functional abnormalities or symptoms are determined by which region or pathway is primarily involved.

The above argument is illustrated mainly with the idea of statistical differences from normal in range of conduction velocity in populations of axons. However, if there were other statistical deviances at the cellular level, the same might apply to them also: The expression of cellular abnormality in terms of symptoms and signs is conditional on the region and pathway in the brain so affected.

(vii) Symptoms versus Syndromes versus Disorders: Approaches to a new classification, based on robust theory. This line of argument has major implication for how psychiatric disorders are to be classified. Here my comments are about the possibility of defining mental disorders in terms of principles from brain science; but I admit that this can only be part of the story. Some mental disorders are inevitably bound closely to the particular society and culture in which they occur; and since this is not to be encompassed within the universal language of the natural sciences, these aspects of classification cannot be universal. However, for classification related to brain science, current approaches, based on a group of wise persons sitting round a table - or a random sample of 500 wise people surveyed on-line - and then reaching some sort of consensus, are definitely *not* the way to establish an enduring system of classification. We need one based on reasoning from causal principles, and definite disease theories.

However, as in neurology, disease classes (and diagnoses) may require to be done at two levels, which are largely independent of each other - one at the level of cellular processes or abnormalities, the other defining the regions or pathways most affected. In any case, trait aspects of mental disorders are likely to be more fundamental for classification than the state aspects, because they are more directly liked to underlying stable cellular abnormalities. Another consequence for classification follows from the fact that abnormalities at the cellular level are more in the nature of statistical deviance than definite pathology: State aspects of mental disorder may be sharply defined categories (e.g. active psychosis, depression, mania, acute aspects of anorexia nervosa). However, the trait aspects are likely to merge with complete continuity into normal variation of psychological profiles and personalities in the general population. They are then better represented in a dimensional than a categorical typology. Furthermore, given that similar abnormalities at the cellular level may give rise to quite different disorders at the whole-person level, dependent on the brain region affected, means that the initial stages for developing explanatory arguments and classifications of mental disorders might better focus on trait-like symptoms and their groupings as syndromes, rather than on disorders, as currently classified.

9. A Personal Invitation to Theoretician/Scholars Interested in Collaboration Leading to more Robust Concepts of Mental Disorder:

(i) My proposal: I am now aged sixty seven. For the last ten years I have been a "freelance researcher", but have retained my links with Otago University, in the South Island of New Zealand. My health is good, and my mind is working far better than when I was younger. I have no intention of "retiring"; but I won't be here for ever, and I hear the clock ticking. The bounty of empirical data in the libraries could keep me busy as a theoretician for the next 100 years even if nothing was added to it; but that is not the best way to go.

I probably have the experience to guide other people keen on exploring the unknown, and finding real explanations, developing real disease theories in psychiatry, which in due course could be fed back to the empirical researchers for testing, refinement or refutation. Academia provided me with little opportunity to do this, because it had no interest in research unless big grants were involved (due to the fact that there is usually a big top-slice from the grant, to support the institution). I currently live in Masterton, a small town of 20,000, within easy reach of the capital of New Zealand Wellington. I have electronic access to the excellent library of Otago University, and have all I need to continue this work. I would feel honoured to collaborate

with researchers around the world in fundamental research to derive robust theories for mental disorders. These may be psychiatrists or psychiatrists-in-training, neuroscientists, or people in other walks of life, with some experience either in neuroscience, psychology or in some areas of the mental health professions. Collaborators could also include persons with lived experiences of mental illness, or with their family members, friends, carers (etc). Much of this work can be done by e-mail correspondence. However, if keen young researchers in psychiatry, or related fields wanted to join me in Masterton for periods, and later to work together via e-mail correspondence, I would feel privileged. This is a serious offer. If you are interested, please make contact, along the lines of the invitation attached below. I will give an honest response on whether, and in what ways a collaboration could proceed.

(ii) Implications for personnel and other resources, and administrative style. What are the resource implications of this proposal? *First,* and most essential is the researchers themselves. This sort of work probably needs young people, energetic in mind, with active imaginations, yet knowing how to do rigorous reasoning, which can refute as well as support their favoured ideas, capable of large-scale, meticulous and detailed scholarship, and above all, people consumed by fierce curiosity, a desire for real progress in psychiatry to benefit those who suffer from mental disorders, and guided by a secure faith that the world is comprehensible. These, rather than a desire for fame and wealth, are the requirements for this sort of work. I do not see mathematical ability, or facility in computer simulation as so important, though sometimes it might play a subsidiary role. These people need to be able to work in a climate of intellectual freedom. It would be an advantage for such persons to have access to a reasonably good academic library, which may or may not be electronic. The work I am envisaging would require a great deal of free time. The possibility of travel to meet other researchers, especially those who can do empirical studies relevant to their own work would also be an advantage. I would *not* expect to provide such persons with projects for me to supervise. Instead I look for people who have already formed their own questions, perhaps finding them too daunting, but in any case hoping for guidance from someone who has spent the last thirty-five years reading many thousands of papers. In the first instance, money is less important (except for travel) provided that one can identify the right people. However, further down the track, raising money may become important.

The sort of person I am describing is rare, but I would think that trainee or recently qualified psychiatrists include some such. Others may be

working in academic institutions, as neuroscientists, biological psychologists and others. Fostering partnerships with institutions may become important. I admit that (usually) really good theory has to come from a single mind; yet unless those minds have detailed knowledge of critical evidence, their reasoning cannot have a solid base. Therefore the possibility of free exchange of information and ideas between psychiatrists and researchers with other backgrounds would be important. Opportunities for researchers with a non-clinical background to meet patients may also provide the stimuli which can fire the imagination and reasoning in those single minds. Some of the most strongly-motivated persons may be those within service-user communities, who are trying to understand their own experiences. It would be a pleasure to work with them too.

(iii) Difficulties. I anticipate some difficulties: Some people may think the intellectual difficulties would prove insuperable. For me, that is not the major problem, and if, for a would-be theoretician, it seems to be so, s/he is probably not the right person for this task. The real problems are political ones, that "research" is now almost synonymous with money, many universities having forgotten what their real mission with regard to research *is,* the shibboleth of "science" having been thoroughly debased. It is not just university attitudes which hold back this sort of venture, it is attitudes of funding agencies, learned journals, conference organisers, and government officials. I am also aware that the sort of research I advocate does not fit easily into the typical career structures assumed for either academics or health service researchers. It may therefore be that some collaborators in this venture might have other means of earning their living, and work on *this* in a freelance capacity, as I have done for ten years. I have met a few such persons, and the increasing accessibility of academic library material to the general public may make this a more feasible possibility in the future.

(iv) Avenues of publication: A major problem for the intensive library-based theoretical research advocated in this essay is that it requires a different form of publication from those currently fashionable. In former times research monographs were an acceptable form of scientific communication, and sometimes were the vehicle for definitive statements of major new works. In the last generation, for various reasons, journal articles have become the sole prestige form of academic publication in the natural sciences. In the physical sciences, whether empirical or theoretical, and for empirical work in the biomedical fields they probably serve their function fairly well. However theoretical work in biomedicine requires a bigger canvas, to cope with all the scholarly detail of more complex systems. In this respect the sort of work I advocate is similar to that in the humanities,

although it differs from humanities research in that it is assumed that there is a coherent answer to the questions posed, a definite explanation to be found, and predictions are to be made to testing such explanations. Such work may therefore often require publication in the form of monographs, not journal articles. I do have experience in both writing and editing such monographs. If the proposal made in the previous section could somehow be set in motion, there is then a likely corollary: The result should usually be published as monographs, not as papers. If a coalition of researchers working on various topics in theoretical psychiatry could emerge, one possibility for the future is that a publisher be approached with a view to starting a monograph series. On-line publication is another way to go. I might be able to edit it myself, but it would be much better if coordinated and edited by a small team, collectively with wider expertise.

I cannot do what I propose by myself. If I continue to work as a lone wolf, I will probably make some progress, but that work could go further and faster, if there existed a coalition of keen fellow theoreticians especially those from a younger generation. We may then be able to start a fruitful new tradition, which many people now know is needed, but, to my knowledge, has never been developed to the point where it has real momentum in any country.

Robert Miller
13.10.10.

For persons who want to respond to the invitation in the last section of this essay:

Please write to me, telling me a bit about yourself, your experience as a research student, scientist, clinician, family member, or person with lived experience of mental disorder. Give me a brief account of the areas of your interests and expertise. If you have writings you would like to share with me, let me know the reference (if they are in regular academic journals), or e-mail me a copy if they are in books, chapters in books or unpublished manuscripts. (Once e-mail correspondence has started, I can also give you a mailing address.) I am more interested in works of scholarship, even if they have not have reached the stage of a fully formed theory, than in purely empirical papers. I do however hope for referencing to sources of relevant empirical studies. I am not able to offer any financial support, but initial stages of this endeavour (which are all that I can envisage at present) are likely to have few costs other than your (and my) time.

My e-mail address is: robert.miller@stonebow.otago.ac.nz