

Research into putative biological mechanisms of mental disorders has been of no value to clinical psychiatry

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FOR

In 1845 Griesinger declared that mental disorders were physical in origin (Kendell, 2001). The discovery of the bacterial cause of general paresis and the anatomical basis for Alzheimer's disease seemed to confirm this belief. However, is it still reasonable, a century later, to continue to devote increasing amounts of financial and expert human resource to pursuing further possible physical causes for mental disorders? The belief that there remain undiscovered and important biological causes for mental disorders continues to exert a major influence on the direction of research, practice and public education. But has it helped us to understand aetiology, improve management or destigmatise mental disorders?

Aetiology

Certainly there have been a multitude of biological findings reported in eminent psychiatric journals since they were founded, but conclusions about their significance continue to be conflicting and most evidence is non-specific, at least for the individual patient. Whether or which of these findings represent causative or epiphenomena remains in doubt or dispute even to the many resolute believers in the biological origins of mental disorder.

Genetic research, for example, has promised much. The search for the genes for individual mental disorders commenced and gained pace through the last century, but has failed to identify specific genes for schizophrenia, bipolar or other psychiatric disorders. This has now been substituted by the search for 'susceptibility genes of variable effect', although what clinical benefit could result from such a search for multiple interacting genes is unclear. At least where single genes were contemplated, discovering genes coding for single aberrant proteins might have had pharmacological implications.

There is, of course, strong support for a genetic basis for personality. There are also demonstrable links between mental disorders and personality, and thus for a vulnerability for mental disorder. Is the genetic vulnerability to mental disorder anything more than this? Research into the interaction between specific stressors, for example trauma (Read *et al*, 2003), hallucinogenic drugs (Hall, 2006) and sensitivity to stress (Myin-Germeys *et al*, 2005), and personality vulnerability has been more clinically productive. It is understandable to patients and the general public, fitting with their models of mental disorder, supports the development of psychosocial interventions and could provide a more comprehensible categorisation of psychiatric conditions (Kingdon *et al*, 2007).

Diagnosis

Has research into biological mechanisms assisted us in diagnosis? Urinary chromatography, the dexamethasone suppression test and neuroimaging have promised much but have produced nothing of value for individual patients. Changes found by neuroimaging have various explanations. For example, is hypofrontality in schizophrenia the cause or effect of reduced activity for social, psychological or biological reasons? Changes in brain functioning can occur with psychological treatments. Brain shrinkage is very non-specific diagnostically and given that neuroplasticity is well recognised (e.g. in relation to trauma) is of uncertain importance.

Treatment

So what about the contribution to treatment? Pharmacological discoveries have occurred as a result of observations by astute and observant clinicians, for example Laborit for chlorpromazine (Lopez-Munoz *et al*, 2005) and Kane for clozapine (Kane *et al*, 1988). The mechanisms of action of these drugs, not the mechanisms of the underlying disorders, were then used for

biochemical refinement. A review of guidelines from the National Institute for Health and Clinical Excellence (<http://www.nice.org.uk>) exposes the absence of influence of research into biological mechanisms. This contrasts with research into psychosocial mechanisms, which has been much more productive.

Destigmatisation

So has research into biological mechanisms assisted the cause of destigmatisation? It has certainly been very influential in relation to psychiatrists' attitudes, with almost half in the UK believing that, for example, schizophrenia has primarily biological rather than a combination of social and biological causes (Kingdon *et al*, 2004). However, the general public seems less convinced, and programmes based on adages such as 'Schizophrenia is a brain disease' have had no demonstrable effect on stigma and may have worsened it (Angermeyer *et al*, 2005). Similarly, psychoeducational programmes have been associated with increased suicidality (Cunningham-Owens *et al*, 2001) and acceptance of illness paradigms with increasing depression (Rathod *et al*, 2005). Presenting schizophrenia as primarily a disease caused by biological deficit – but we don't know what the deficit is – is unsurprisingly not a credible position to hold. It only confuses patients and carers, who have often recognised vulnerabilities and stresses relevant to the onset of the individual's problems. Such a biological approach to mental disorder has not even had a beneficial effect on recruitment into psychiatry, being quite unconvincing to medical students despite the interest in the mind as evidenced by the popularity of psychology degrees and clinical psychology.

Indeed whether the term mental disorder is meaningful or helpful in itself is doubtful. Disease classifications may work elsewhere but not with the circumstances psychiatrists face: anxiety and depression are not disorders in most instances but adaptations to stress. Even symptoms of psychosis, such as hearing voices and thought transference, can occur in a range of stressful (e.g. deprivation) states and other circumstances (e.g. trances and spiritual experience). Far more appropriate would be to develop classifications of mental and behavioural responses. Such classifications, which are not value based, are usual in the natural or social sciences (e.g. with fauna or flora or with social groupings).

Individuals then can select psychiatric, psychological and social interventions if they choose (or rarely, do so at society's behest). Rather than 'mental disorder' being 'what psychiatrists treat' as Kendell (1975) stated, a system that explicitly acknowledges individual variation, choice and need, and the role of the psychiatrist as one among others, including the criminal justice, housing and benefits system, can address or accommodate mental and behavioural responses more appropriately. By using inappropriate disease analogies, we have been hoisted by our own petard, contributing to continuing stigmatisation and the misunderstandings that, for example, underpin the current government's attempts to make psychiatrists responsible for all mental, including personality, disorders.

Conclusions

Research into biological mechanisms of mental and behavioural responses has failed to deliver anything of value to clinical psychiatrists and is very unlikely to do so in the future. Psychiatry will become credible and effective once it accepts this and broadens its focus to examine and value the breadth of human experience rather just the genotype and neuron.

David Kingdon

AGAINST

Professor David Kingdon is to be congratulated for proposing the motion with some enthusiasm. I will refute his contention by specifically addressing the points which he has raised. In addition, I will refer to flawed assumptions that form the bedrock of his case and the erroneous attitudes consequent to these. Finally I will suggest a reframing of the argument that will allow us to move our position to a more helpful and productive point of view. I shall also include an example of a broadly based approach which integrates various scientific disciplines and techniques, and is of current value to clinical psychiatry.

Aetiology

The term 'biological' is often misunderstood in psychiatry, sadly not only by the uninitiated trainee. The arguments have been well rehearsed before and the

interested reader is referred to Dr Guze's magisterial article (Guze, 1989). In brief, the error in thinking is that there are multiple different 'psychiatries'. One of these is 'biological', one 'psychosocial' and so on. Biological, in particular, is misused as being synonymous with either a neurological or physico-chemical psychiatry. The correct position is of course that biology is the study of life and psychiatry is a biological, more specifically a biomedical, discipline. This must be emphasised as it is a key rationale dictating the approach to research and care of mental ill health.

Biology of course does not just mean drugs or genes: Freud was aware of this and considered himself a biologist. Moreover, psychotherapeutic treatments are a key part of the approach to helping our patients. Indeed Professor Kingdon's own very distinguished work on psychotherapeutic approaches to schizophrenia occurs within a biological context (in the true meaning of the word) and has been of great benefit to clinical psychiatry. Another example is Alzheimer's disease. Alzheimer (working in a department of psychiatry) described the neuropathology of the illness which now bears his name approximately a century ago. Until very recently this was assumed to be a 'psychiatric' illness. It has only been since the acceleration of research in the past decade or so that this has been re-evaluated. The involvement of neurologists, gerontologists, neuroscientists and others in research into the biological mechanisms of Alzheimer's disease has given a great boost to this research. Clearly Professor Kingdon would not argue that research into the pathophysiological bases of Alzheimer's disease has been of no value, and even if he did few would agree with him.

Similar misconceptions are commonly held about genes. The old edition of *Companion to Psychiatric Studies* (Kendell & Zeally, 1988), which sits on my shelf and which I still refer to, states very clearly that the common psychiatric conditions are most likely to be due to multiple genes of small effect. These are now being discovered and will lead to benefits to clinical psychiatry eventually. Notwithstanding, the problems of discovering the genetic contribution to an illness such as depression are similar to those posed by other common medical conditions such as hypertension and diabetes. A similar toolkit should be used to approach both. If we forget the commonality between mental ill health

and other common illness we will impoverish our vision as to what might be discovered to benefit our patients.

Diagnosis

History-taking and clinical examination remain the foundation of our practice in psychiatry – as they do in the rest of medicine. Diagnostic tests are of supplementary value in psychiatry, albeit to a lesser extent than in many other areas of medicine. This should not be viewed as a 'weakness' of psychiatry but rather as a particular characteristic; indeed many would argue that if history-taking is the basis of medicine psychiatrists are the best physicians. The diagnostic use of the dexamethasone suppression test is of course outmoded; however, the evolution of this into the dexamethasone/corticotrophin-releasing hormone test (Watson *et al*, 2006) is on the threshold of allowing us to specifically target some physical treatments (Kunugi *et al*, 2006).

Treatment

Many have been scathing about the paucity of truly new drug treatments in psychiatry and the role of the pharmaceutical industry in general. We must acknowledge the lag between primary research into disease mechanisms and the realisation of clinical benefits, as illustrated by the case of Alzheimer's disease. Drug treatments for this devastating illness only arrived many decades after the initial description of plaques and tangles. New drug treatment approaches are being pioneered in psychiatry, both by the pharmaceutical industry and by academic psychiatrists. An example of this is drugs which act on the hypothalamic-pituitary-adrenal (HPA) axis for mood disorders – these come after a long chain of diverse research which I shall briefly describe here.

HPA axis: model for an integrated approach

The HPA axis is of course a physiological system which is sensitive to psychological stress and is subject to modulation by factors such as social hierarchy. The function of the HPA axis in adulthood is very heavily influenced by adverse circumstances in early life and these early stressors alter gene function (Meaney & Szyf, 2005). Moreover, the HPA axis is abnormal in severe mood disorders and may be sensitive to drugs and psychotherapy (Watson *et al*, 2004). Thus 'biological' research of the

HPA axis utilises a wide variety of scientific approaches.

What about treatment? Excess levels of corticosteroid hormones (the end product of the HPA axis) impair the neurochemical actions of antidepressants and are associated with non-response in clinical populations (Gartside *et al*, 2003). Drugs which counteract the effects of corticosteroids show promise as treatments in mood disorders (Young *et al*, 2004). Research on the HPA axis thus illustrates the diversity of research approaches which need to be employed to tackle the tough problems of psychiatry; all of these however are 'biological'.

Destigmatisation

Stigma is one of the largest problems confronting mental health professionals. However, the notion that we could solve stigma by transforming mental ill health into something it is not is clearly wrong. Prejudice and injustice against those who suffer mental ill health should be addressed in the same way as other such unacceptable beliefs; the underlying assumptions need to be brought out into the open and the behaviours arising from these beliefs challenged. Stigma directed against mental ill health is as nasty and as morally wrong as racism, homophobia and all the other related prejudices. We as a profession need to challenge stigma on *a priori* grounds.

Kingdon quotes the late Professor Robert Kendell when he challenges the very conceptual basis of our existence as a medical specialty. I would suggest that all psychiatrists read Kendell's *The Role of Diagnosis in Psychiatry*, which it remains as relevant now as when it was first published. Kendell exhaustively reviews all the alternatives to our diagnostic system and concludes that none can currently replace it in clinical psychiatry. I agree with Professor Kingdon that many psychiatric disorders are stress related (after all I spend my life working on the HPA axis!), but many other diseases in medicine are also stress related and such an observation does not argue against our current model of clinical practice.

Reframing the argument

The notion that research into biological mechanisms of mental disorders has been of no value to clinical psychiatry is not only wrong but also potentially damaging to our patients. We should discard it forthwith.

What then? We need to clarify our underlying assumptions. Psychiatry is a biomedical discipline which rests on scientific, empirical and eclectic foundations. We should acknowledge that a variety of approaches are required and may contribute to better outcomes for our patients and inform our research. Each should be judged on its merits and not disqualified by a sweeping generalisation. Clinical psychiatry requires a broadly based research approach. We should devote our energies to arguing for more funding to be devoted to tackle the problems of mental ill health overall as research in this area is still grotesquely underfunded (Kingdon, 2006a). Although progress in medicine is often slow and may come from unexpected directions, it does inexorably come. However, for people with mental illness to fully benefit from the application of modern medical science, both clear thinking and greater resources will be required.

Allan H. Young

FOR: REBUTTAL

Professor Young's response is an eloquent exposition of the theoretical basis for biological research. However, it fails to address the motion proposed and to compensate he suggests that the motion be changed to 'Clinical psychiatry requires a broadly based research approach'. He provides not one individual instance where research into putative biological mechanisms of mental disorders has led to developments in clinical psychiatry. Work on Alzheimer's disease leading to memory-enhancing drugs is the arguable exception. However, unlike schizophrenia, depression and other mental disorders, the explicit biological basis of Alzheimer's disease has been known since the 1800s and the condition has for decades been regarded as a neurological disorder in most European countries.

The argument that distinguishing biological psychiatry from other areas is erroneous seems difficult to sustain and would imply, for example, disbanding the Biological Psychiatry Section of the Royal College of Psychiatrists. Biology may be the study of life but so is sociology and psychology. Yet they are clearly not the same and giving pre-eminence to biology is precisely the concern that I and many others

have. Guze's article (Guze, 1989) is worth reconsideration because it illustrates, in its final paragraph, so clearly the way in which social context is distinguished from biology, and viewed as peripheral:

'No thoughtful and knowledgeable individual advocates an approach to psychiatry . . . that isolates it from its social and cultural context. But . . . biological concepts and approaches remain central and indispensable.'

Psychological therapy is only set in a biological context in the sense that it occurs in human beings and may be used alongside physical treatments. The argument that the clinical value of such therapy is a justification for biological research into putative mechanisms of mental disorder is entertaining but untenable.

Again the centuries-old assertion that genetic research has potential is made, but yet again there is no actual evidence of it being of any value. Seduction by emerging new technologies is understandable but exactly how is research into genetics going to assist us in clinical psychiatry? Multiple interacting genes seem unlikely to provide discrete pharmacological targets for intervention. Knowledge of such genes also seems unlikely to be helpful for meaningful genetic counselling or screening. Phrenology had its advocates but lack of results and clinical application led to refocusing. Although it was justifiable to seek answers initially, when is it time to look elsewhere?

Professor Young accepts that the dexamethasone suppression test is outmoded but the statement that the dexamethasone/corticotrophin-releasing hormone test is on the 'threshold of allowing us to specifically target some physical treatments' has a sadly familiar ring to it. Treatments are asserted to exist that arose from biological research into the HPA, but these are still described as 'showing promise'. Discrimination we agree is noxious and should be fought, but biological models appear to make matters worse (Cunningham-Owens *et al*, 2001; Angermeyer & Matschinger, 2005; Rathod *et al*, 2005). Solving the problem of stigma might be helped if we did not contribute to it in the first place by assigning incoherent and inaccurate terminology and conceptualisations: 'dementia praecox' replaced by 'schizophrenia' – semantically inaccurate and essentially meaningless, with increasingly damagingly associations (Teskey, 2006) – and worse, 'the deficit state'; 'personality disorder' is a similarly devastating term and is over-inclusive; 'bipolar disorder' is a confused

concept – it is not mood bipolarity, especially elation, that is the problem but damaging behaviour from mania and devastating depression – dichotomous illness models fundamentally fail to address management especially of hypomania. Is the person ‘ill’ at the time, or responsible for their actions, or a bit of both? How do you explain illness models to a relative who has suffered the consequences? ‘It wasn’t their responsibility because they were ill’? It also leads to nihilism – websites describing schizophrenia and bipolar disorder often state that little is known about their origins, which is true in relation to putative biological mechanisms of mental disorders but is certainly not true when relevant psychological and social mechanisms are considered (Bentall, 2004).

Psychiatry remains focused on biomedical models. Despite the fundamental inadequacies of current classification systems based on these models, as described by Kendell (1975), 30 years later we are no further towards a coherent and credible system (for example, using broad-based clinically relevant vulnerability–stress models). Psychiatry should more actively embrace psychosocial research and intervention. Does that really ‘challenge the very conceptual basis of our existence as a medical specialty?’ The argument is not that biological research cannot be of value to clinical psychiatry; it is that it has not been. The focus on biology has distorted practice and research, and devalued other areas which are proving much more promising (Kingdon, 2006b).

David Kingdon

AGAINST: REBUTTAL

Professor Kingdon has produced a passionate defence of his motion, unfortunately it is riddled with factual errors and conceptual flaws. He states that the work on Alzheimer’s disease leading to memory-enhancing drugs is an ‘arguable exception’ to his case but that this has been thought to be a neurological disorder ‘for decades’. Alois Alzheimer described the case of Auguste D. in the early 20th century and added important neuropathological evidence to the earlier clinical description of the illness by Kraepelin. Nobody, surely

not even Professor Kingdon, would dispute that Kraepelin was a psychiatrist.

Professor Kingdon further states that research into ‘putative biological mechanisms’ has not led to developments in clinical psychiatry. An example which defeats Professor Kingdon’s argument is that of lithium. John Cade’s original work on lithium was based on research into a ‘putative biological mechanism of mental disorder’ – the role of urea in the pathophysiology of severe mental disorder. These enquiries evolved greatly from initial animal work through to the seminal publication on the use of lithium in patients (Cade, 1975). It is of course ironic that Cade’s initial notion about urea is now held to be wrong but, nevertheless, this was research which was initiated into a ‘putative biological mechanism of mental disorder’ and thus disproves Professor Kingdon’s case. It is also now quite clear that this resulted in ‘developments in clinical psychiatry’; more specifically a treatment of great benefit to many patients worldwide. Lithium has a sound evidence base backing its use in bipolar disorder and as an augmenting agent to antidepressants in unipolar depression (Bauer *et al*, 2003; Geddes *et al*, 2004). There is also convincing evidence that lithium reduces suicide and suicidality in severe affective disorders (Baldessarini *et al*, 2006). All of this derives from the initial research over half a century ago into ‘putative biological mechanisms of mental disorder’.

Professor Kingdon also makes a factual error when stating that distinguishing biological psychiatry from other areas is erroneous and would imply, for example, disbanding the Biological Psychiatry Section of the Royal College of Psychiatrists. As far as I am aware the Biological Psychiatry Section of the College is no more for precisely the reasons that Professor Kingdon states! Perhaps the more serious conceptual flaw however is the notion that psychology, sociology and biology are mutually incompatible and that one of these ‘ologies’ must somehow have primacy. Our strength as a medical discipline lies in our ability to utilise all of these approaches in an empirical manner to the maximum benefit of our patients.

Professor Kingdon is particularly exercised by genetics and repeatedly returns to attack this approach; one which, admittedly slowly, is paying dividends throughout diverse medical fields and increasingly in multifactorial illnesses. Of course some have

been ‘seduced’ by genetics, but this is a phenomenon which is familiar in other approaches to psychiatric problems, perhaps most especially psychological treatments.

Molecular genetics supplies tools to help us identify the biological systems that are involved in psychopathology. This will allow development of treatments targeted at the systems (and in most cases not targeted at the genes or risk variants). It will also provide an approach to validating diagnosis, something which Professor Kingdon concedes is clearly necessary. Professor Kingdon reminds us that the late Professor Robert Kendell described the fundamental inadequacies of current classification systems a generation ago. However, he neglects to mention that Kendell pointed out that, like democracy, our current diagnostic system may be considered the worst – apart from all the others! Inadequate though it is, nobody, especially not Professor Kingdon, is proposing anything better.

Biological psychiatry has clearly been of value. It is worthwhile recalling that 2005 marked the centenary of the discovery of the *Treponema pallidum* by Schaudinn & Hoffmann. This was a milestone in the cure of general paralysis of the insane, one of the most frequent causes of devastatingly severe mental ill health until the first half of the 20th century (Nitrini, 2005). Before this happened, no doubt there were psychiatrists such as Professor Kingdon arguing that all the focus should go on the best social/psychological management as biological research had not been of value.

Allan H. Young

FOR: CONCLUSION

Professor Young’s further spirited response is a delight to critique. He seems to make the case that Alzheimer’s disease emerged in the early 20th century, not the 1800s, which accords with when Alzheimer described it. However, the neuropathological basis of dementia was recognised long before that date and indeed even before the descriptions of that acclaimed, if rather misguided psychiatrist, Kraepelin (Craddock & Owen, 2005). Moreover, is it really ironic that John Cade’s original work on the possible role of urea in mental disorder led to the discovery of the effects of lithium or wasn’t he simply wrong? The serendipity

that led to lithium being found to be of value in the treatment of bipolar disorder, eloquently described by Professor Young, has been of unquestioned benefit to many people, but is this really the only evidence of the benefit of systematic research into putative biological mechanisms?

I am indeed particularly exercised by the emphasis on genetics, as I would contend are most psychiatric journals and funding bodies internationally. It is just that after decades of research, I fail to see any dividends emerging in psychiatry; not slowly, not at all. If it were to assist in validation of diagnosis, that would be valuable but when will it? Other multi-axial classification systems based on vulnerability–stress models seem more likely to be clinically valuable (e.g. as we have begun to describe for psychosis; Kingdon & Turkington, 2005) and also relevant to resource usage. They certainly need further exploration. Incidentally I am also delighted to hear that the Biological Psychiatry Section of the Royal College of Psychiatrists has been disbanded.

Finally, before celebrating the discovery of *Treponema pallidum*, isn't it appropriate to reflect on whether the research strategy of a century ago – heavily biologically based – now needs rethinking? My argument is not that we should, in principle, proscribe any research area – including that into putative biological mechanisms of mental disorder – but that any such area, especially where it has been so dominant a force in psychiatry for so long, should at least begin to demonstrate its clinical relevance.

David Kingdon

Declaration of interest None.

AGAINST: CONCLUSION

Over the preceding few pages Professor Kingdon and I have debated the motion 'Research into putative biological mechanisms of mental disorders has been of no value to clinical psychiatry', with Professor Kingdon supporting the motion, and arguments against being put forward by myself. What lessons might we draw from this exchange or has it been simply a form of occupational therapy for two academic psychiatrists with nothing better to do, a form perhaps of ping-pong with obscure facts taking the place of a ball? I would respectfully suggest that a number of points

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emerge, some of which Professor Kingdon and I may even agree upon.

First, not only do psychiatrists enjoy debating (these two seem to at least!) but a debate such as this is clearly important. It is perfectly correct and proper to question the value of any avenue of research in psychiatry; indeed one might go further and say that it is legitimate to question any aspect of psychiatry whatsoever and of course this frequently happens. Unfortunately, those asking the questions are only rarely as well informed as Professor Kingdon and many are driven by ignorance or base motives. Nevertheless, psychiatrists must be prepared to engage in debates about the nature of our trade; to stay silent is not an option.

Second, many of the concerns voiced in this debate are widely held. Professor Kingdon is particularly exercised by the current emphasis on genetics but so, in one way or another, is most of the medical research community internationally. He is correct to state that after decades of research, we see few, if any, dividends yet emerging in psychiatry. He is sceptical of the 'jam tomorrow' argument, even though for some areas, such as pharmacogenetics, most of us accept this. However, these issues pertain to many other areas of medicine, reinforcing (at least to my mind) the commonalities and continuities between psychiatric problems and those dealt with by the rest of medicine. Professor Kingdon also argues (perhaps somewhat against himself) that he would not 'proscribe any research area – including that into putative biological mechanisms of mental disorder'. We are finally entirely agreed upon something: every possible means of advancing knowledge to the end of greater clinical benefit in psychiatry should be open. From genetics through neuroimaging and psychopharmacology to psychosocial research and psychotherapy, all should be pursued and scrutinised equally based upon relevant merits. It's all biology after all!

Allan H. Young

Declaration of interest

None.

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