# Is psychiatry more mindful or brainier than it was a decade ago?*

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Academic psychiatry in the USA in the decade after the Second World War was dominated by psychoanalytic theory. Psychotherapy, most of it psychodynamic in orientation, was the principal activity of clinicians in office practice. Critics like myself who pointed out the lack of empirical validation for the theory or the practice were unavailing (Eisenberg, 1962).

This is less surprising when considered in context: there were *no* treatments of demonstrated effectiveness. Psychiatric diagnosis had low interrater reliability. The 'brain sciences' were largely irrelevant to clinical practice. To its credit, psychiatry made a virtue of the failure of its biomedical science by remaining the one medical speciality with a persistent interest in the patient as a person in an era increasingly dominated by organ-based medical subspecialities.

The chance discoveries of effective psychotropic drugs transformed the field in the mid-1950s. Because the new agents were relatively syndrome-specific, diagnostic categories were defined operationally and gained reliability. The search for an understanding of drug action stimulated research in neurobiology. Welcome as these developments were, they embodied a peril: psychiatry began to focus exclusively on the brain as an organ. Psychiatrists found it useful to emphasise their medical identity for purely economic reasons. Prescribing drugs and monitoring drug therapy require a medical licence, whereas psychologists, social workers and counsellors can compete in the psychotherapy market in the USA. Mindlessness had begun to replace brainlessness (Eisenberg, 1986).

In the 1940s and 1950s, just about all medical therapeutics was based on the claims of expert opinion and clinical experience (Doll, 1991). Not until 1948 was the first double-blind randomised controlled trial (RCT) in medicine carried out – the Medical Research Council trial of streptomycin for treating tuberculosis (Medical Research Council, 1948). With the advent of psychotropic drugs, RCTs entered psychiatric research. They undoubtedly improved matters, but they have not quite taken us to the promised land. Thornley & Adams (1998) reviewed for the Cochrane Collaboration the first 2000 controlled treatment trials in schizophrenia. Most trials were substantially flawed: they had inadequate sample size, or too short a duration, uncertain blinding, inconsistent methods of evaluation, or poor reporting. Only 20 (1% of the 2000) were rated at 5 on a 1–5 scale of quality. Clearly, we still have a long way to go.

Psychoanalysis, despite its inadequacies as science, made a powerful contribution to psychiatry. It taught trainees to listen to patients and to try to understand their distress – not simply to classify them, or shock them, or lock them up. It made psychiatrists aware of the importance of memory, its vulnerability to distortion, and its central role in patients' stories about themselves. Such narratives can be self-defeating, and a key task of therapy was defined as helping patients to reconstruct their autobiographies in such a way as to foster growth. That task, no less important today, is being squeezed out of clinical practice and residency training.

## THE EMPTYING OF MENTAL HOSPITALS

In the 1940s and 1950s, increasing numbers of severely disturbed patients were warehoused in understaffed mental hospitals (Deutsch, 1948). No treatments worked; Freud himself saw no role for analysis in treating the psychoses. Desperate times were thought to justify desperate measures. More than 20 000 patients were subjected to psychosurgery in the USA between 1935 and 1950. The procedure was carried out in private as well as public hospitals, and it was endorsed by leading academics because it sometimes 'worked'. What brought about the demise of psychosurgery was neither science nor compassion but the introduction in 1954 of chlorpromazine, the first in a series of drugs that made psychosurgery redundant (Pressman, 1998).

Good as they are, psychotropic drugs were vastly overvalued then, as they are now. They were credited with emptying the mental hospitals, although the onset of de-institutionalisation had preceded the introduction of the drugs. In catchment areas where 'open hospital' and 'community psychiatry' policies had been implemented, drugs had relatively little additional effect on length of hospital stay (Shepherd *et al*, 1961), but they *were* decisive in hospitals where patients continued to be warehoused (Odegaard, 1964). De-institutionalisation in the USA was driven more powerfully by economic forces (cost-shifting from state to federal budgets) than by theory or data. The decline of the mental hospital census was celebrated without finding out where the former patients were. Elderly patients were 'trans-institutionalised' to nursing homes; many long-stay patients were discharged to home addresses that no longer existed, and became street people. Calls to evaluate the community mental health movement (Eisenberg, 1968) were as unavailing as earlier critiques of psychoanalysis.

Given the above background, is psychiatry 'more mindful' or 'brainier' than it was a decade ago? In an immediate sense, the answer is a self-evident 'yes'. A decade of imaginative research has taught us very much more about both brain and mind; the problem that continues to bedevil us conceptually is how to integrate the two domains into what, for lack of a suitable word, I shall have to call 'brain/mindedness'. The very elegance of neurobiology and the power of genetics dazzle us: knock out a gene and the effect stares you in the face; study a psychosocial phenomenon and the relevant variables require sophisticated statistical analysis before the meaning is clear. The psychosocial findings in a given case may be more important for patient care than finesse with genes in the laboratory, but they do not seem as 'real'. Add to the medical bias in favour of the tangible

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a market that understands doctors who prescribe pills but not those who listen (and talk) to patients and it is evident why the 'neurologising tautology' – that only those facts that can be reduced to terms of nerve cells are scientific – is growing apace (Eisenberg, 1986).

## MANAGERIAL FETTERS ON EFFECTIVE CARE

As a clinical discipline, psychiatry is thriving as it never has. Clinicians now command a range of therapeutic interventions whose efficacy has been demonstrated through RCTs. We have an array of proven psychosocial interventions: cognitive–behavioural therapy, interpersonal psychotherapy and problem-solving therapy; and, to reduce relapse in schizophrenia, family intervention, social skills training and rehabilitation. To the standard neuroleptic drugs have been added the 'atypical' antipsychotic agents which are effective in controlling negative symptoms. The existing stock of tricyclics and monoamine oxidase inhibitors has been augmented by the selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression. Nirvana, needless to say, is not quite here; a recent meta-analysis of the drug treatment of depression, while showing unequivocally that antidepressants are effective, found a response rate no better than 50% for active treatment by comparison with 32% for placebo (Agency for Health Care Policy Research, 1999). Treatment-refractory depression remains a major clinical challenge.

The sciences basic to psychiatry are advancing in dazzling fashion. New experimental techniques in neuroscience permit the exploration of fundamental aspects of cognition and emotion. Elegant imaging methods are demonstrating that experience shapes, as well as being shaped by, developing brain structures (Eisenberg, 1998). Epidemiology is providing reliable population data on the incidence and prevalence of mental disorders and on the extent of the illness burden they produce (Desjarlais *et al*, 1995).

At the very time that the intellectual and therapeutic competence of psychiatry has expanded, psychiatric practice has been sharply circumscribed. For-profit managed care dominates the medical market-place. Cost control has replaced health outcomes as the criterion for public policy. Office-based psychiatrists in the USA are spending less time with each patient, providing psychotherapy less often, and prescribing drugs more often than they did ten years ago (Olfson *et al*, 1999). Residency training programmes are narrowing their focus to DSM–IV (American Psychiatric Association, 1994) diagnosis and algorithms for drug prescribing; much less emphasis is placed on learning how to elicit the patient's story and how to do psychotherapy; psychological care in mental health 'carve-outs' is being farmed out to social workers and counsellors in order to save on costs. Just as the intellectual underpinnings of our field are becoming brainier and more mindful, practitioners are being pressed to reify DSM–IV categories and employ drugs as panaceas – strategies that are neither brainy nor mindful! I will not say more on this matter here, as I have addressed it elsewhere (Eisenberg, 1999*b*).

I now turn to the expanding science base of psychiatry and what it portends for understanding the relationship between mind and brain. I will highlight three research areas: the role of experience in constructing the anatomy of the brain; regeneration in the central nervous system (CNS); and gene effects in a social context.

## THE ROLE OF EXPERIENCE IN CONSTRUCTING THE ANATOMY OF THE BRAIN

The explosion in our knowledge of the neurobiological underpinnings of psychiatry has been extraordinary. The increase in membership of the Society for Neuroscience can serve as a proxy for the pace of change since its founding in 1971, when I joined and became member number 00091. By the end of the first year, membership totalled 1100. By 1986, the number had expanded ten-fold to 11 600; by the end of 1998, it had more than doubled again to 29 200.

Data are overthrowing dogma on all sides. The conceptual CNS is no longer a hard-wired telephone switchboard based on a blueprint in the genome. If the ground plan follows broad genetic specifications, the detailed pattern of connections results from stimulus-induced competition between axons for common target neurons. A review of the sequential construction of the visual system serves to make the point.

How are the ocular alternation layers in the geniculate and cortex formed? Early in embryogenesis, axons from both eyes migrate to, and intermingle in, the geniculate nuclei. The segregation of separate layers results from bursts of electrical activity arising in unstable retinal ganglion cells. Neither the genes governing the retina nor the genes governing the geniculate specify the ocular alternation layers; they result from *interaction* between neurons in the course of development (Penn *et al*, 1998). At the next relay, the precise targeting of projections from the lateral geniculate to occipital cortex in turn depends on geniculate activity. Abolishing geniculate action potentials leads axons to project to cortical areas that they ordinarily bypass, and leads many fewer axons to project to the striate cortex (Catalano & Shatz, 1998). Finally, post-natal stimulation is required for the formation of ocular dominance columns in the occipital cortex (Wiesel, 1982). Both eyes of the newborn must receive precisely focused stimulation from the visual environment during the early months of post-natal life in order to produce a fine-tuned cortical structure.

Experience moulds the brain in a process that continues throughout life. Finger representation in the cortex is larger on the right in professional violinists, where it is greater than it is in the rest of us (Elbert *et al*, 1995); it is also enlarged in Braille readers (Sterr *et al*, 1998), and it shrinks after deafferentation (Mogilner *et al*, 1993). Brain function and structure are constantly in flux.

Psychotherapy that makes a difference changes brain function. What is the evidence? The symptoms of obsessive–compulsive disorder (OCD) are associated with changes in cerebral metabolism in the basal ganglia, the limbic system, and the cortical projections from both. OCD symptoms are reduced by cognitive–behavioural therapy about as effectively as they are by SSRIs. When the patient improves, what happens to cerebral activity? When treatment produces improvement, whether by drug or by psychotherapy, the clinical change is associated with a relative 'normalisation' of brain metabolism (Baxter *et al*, 1992). The bidirectionality of the process is evident from the results of symptom provocation. Psychological stimuli identified by individual patients as capable of provoking obsessions lead to an increase in regional blood flow in the affected areas (Rauch *et al*, 1994). Brain imaging techniques reveal linkages between mind and brain not imagined a decade ago.



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## REGENERATION IN THE CENTRAL NERVOUS SYSTEM

Do changes in function reflect modifications in existing neurons or can neurons multiply as well as die? The very question would have been heretical not so long ago. In 1913, the great Ramon y Cajal declared that nerve paths in adult brain are "fixed, ended, immutable. Everything may die, nothing may be regenerated" (Lowenstein & Parent, 1999). Everyone believed this until the past few years. Investigators have uncovered a previously unrecognized potential for producing new neurons in the mammalian CNS. Progenitor cells within the dentate gyrus of the hippocampus continue to produce new granule cells throughout life in human brains (Eriksson *et al*, 1998). Granule cell proliferation is diminished by stress (Gould *et al*, 1998) and enhanced by environmental enrichment even in aging animals (Kempermann *et al*, 1998*a*,*b*). Not only are new cells produced, but they migrate throughout the appropriate cell layers and extend axon arbours into the furthest reaches of their normal targets (Lowenstein & Parent, 1999). Although the evidence of his time led Cajal to conclude that "nothing may be regenerated", he did urge future scientists "to work to impede or moderate the . . . decay . . . and to re-establish normal nerve paths when disease has severed centers that were intimately associated".

In keeping with that plea, Evan Snyder's laboratory has isolated stable clones of neural stem cells from the human foetal telencephalon, clones that give rise to all of the fundamental neural lineages *in vitro* (Flax *et al*, 1998). Transplanted into germinal zones of a newborn mouse brain, the stem cells migrate along established pathways, differentiate into multiple developmentally and regionally appropriate cell types, and intersperse with host progenitors. Neural stem cells are more plastic and are distributed more widely throughout the adult CNS than anyone had thought. Cells within the ependymal lining of the adult brain ventricle are multipotent and can generate new neurons and glia (Johansson *et al*, 1999). They seem to lie dormant, waiting for an activating stimulus. Potentially, their secretory products can replace enzymatic deficits in patients with inherited metabolic abnormalities. In tissue culture, cultivated stem cells secrete enough functional hexosaminidase-A to correct the deficiency in 'Tay–Sachs' mutant mouse cells.

There is, of course, a great distance between a demonstration in a Petri dish and clinical success in human infants. However, the possibility can now be dreamt of. Will it prove possible to implant pluripotent stem cells derived from foetal telencephalon or ventricular ependyma stereotactically into the brains of patients with Parkinson's disease or Alzheimer's disease or after stroke and have function restored in part or in whole? Only careful laboratory and clinical research will yield the answer. Will that research be done? Not if 'right-to-lifers' have their way. Proposals to ban research on foetal tissue have been introduced before many parliamentary bodies.

## GENE EFFECTS IN A SOCIAL CONTEXT

The completion of the Human Genome Project will result in a quantum jump in our ability to identify the hereditary components of mental diseases. Most psychiatric disorders are non-Mendelian in inheritance; most are probably polygenic, and triggered by gene–environment interactions. Under such circumstances, identifying genes that confer risk (or protection) is a formidable task. The National Human Genome Research Institute expects to produce a working draft of the human genome by the spring of this year and the full sequence by 2003 (Collins *et al*, 1998). The availability of an accurate display of the DNA base-pair sequence in all 46 human chromosomes will make it feasible to identify incompletely penetrant risk-conferring genes.

At a practical level, prescribing practices will benefit significantly. No longer will drug dosage be based on the average response of a heterogeneous patient population. Screening by DNA chip before treatment will enable clinicians to individualise the dose to the metabolic pattern of the patient (Kleyn & Vessell, 1998). Microchips with tens of thousands of snippets of DNA will identify the genetic variation in the *N*-acetyltransferase alleles that underlie differential drug responses (Service, 1998). Patients who are 'slow acetylators' clear psychotropic drugs like isoniazid and phenelzine slowly and thus suffer greater toxicity at a given dose. The likelihood of such outcomes will be minimised.

The ability to screen the genome will be a major step towards the goal of prevention, but it will be no more than a first step. The genotype is not the phenotype. To know completely the norm of reaction for a given genotype requires placing the carriers of that genotype in all possible environments and observing the phenotypes that develop. That is clearly impossible because the existing variety of environments is immense and new environments are constantly being produced. As the geneticist Dobzhansky (1995, p. 75) pointed out: "Invention of a new drug, a new diet, a new type of housing, a new educational system, a new political regime introduces new environments". Statements about the heritability of a given trait without having parsed the relevant environmental variables are meaningless. If a particular strain of wheat yields different harvests under different conditions of climate, soil and cultivation, how can we assume that the much more complex human genome would yield identical behavioural phenotypes under different circumstances of nurture?

We need to know what distinguishes the gene carriers who manifest clinical disease from those who do not. To know that a particular allele is a necessary condition for the appearance of clinical disease does not establish that it is a sufficient condition. Take the case of familial haemochromatosis, an inherited disease of iron metabolism. If not recognised and treated in time, iron deposition in the liver causes fatal cirrhosis. If the diagnosis is made before major organ damage has occurred, treatment by periodic phlebotomy is effective and relatively simple. When the putative gene was identified in 1996, enthusiasts endorsed population screening in order to permit early identification. As testing proceeded, it became apparent that only a fraction of gene carriers manifest the clinical disease. Without knowledge of the co-factors, screening would yield unacceptably high false positive rates and lead to intervention where none is needed. Progress awaits population-based research defining the prevalence of the mutations causing haemochromatosis, the age- and gender-related prevalence of the various alleles, and the interactions between genotypes and environmental modifiers (Burke *et al*, 1998).

The case for schizophrenia, depression or Alzheimer's disease is much more complex. Twin and family studies demonstrate unequivocal genetic roots for schizophrenia and depression, yet there has been a secular increase in the lifetime prevalence for both disorders during this century (Cross-National Collaborative Group, 1992)



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(further details available from author upon request). This increase cannot be due to shifts in the gene pool; the time interval is far too short. The challenge is to identify the relevant environmental risk factors. A recent Danish population-based study of variables associated with risk for schizophrenia found that family history of the disorder in a parent or a sibling increased relative risk nine-fold, but that being born in an urban as opposed to a rural area doubled it, and that risk was greater for births in February and March and lower for those in August and September (Mortensen *et al*, 1999). Such a pattern suggests the presence of multiple genetic as well as non-genetic co-factors (Andreasen, 1999).

Similarly, although depression is clearly familial, Brown *et al* (1995) have demonstrated that experiences of humiliation and entrapment after a severe life-threatening event are major risk factors and that positive events involving hope are instrumental in recovery from depression (Brown, 1993). The same team of investigators found that 'befriending' – that is, providing to depressed women a female volunteer willing to meet and talk on a weekly basis, to go on excursions, and to promote 'fresh-start' experiences capable of creating new hope – improved outcome to a significant degree (Harris *et al*, 1999).

## CAN EDUCATION DELAY ALZHEIMER'S DISEASE?

The interplay between genes and environment in Alzheimer's disease once again illustrates the complexity of the interaction. Early-onset Alzheimer's disease is associated with defects in one of three identified genes – the amyloid precursor protein gene on chromosome 21, and the presenilin genes on chromosomes 14 and 1. However, the great majority of cases are not familial.

In late-onset Alzheimer's disease one of the four alleles of the gene for apolipoprotein ε4 (APO ε4) on chromosome 19 confers a four-fold increase in risk, an association found in multiple ethnic populations worldwide. Yet a full half of Alzheimer's disease patients do not carry APO ε4 at all, and only one in six has two copies. The allele is neither necessary nor sufficient to cause Alzheimer's disease (Blacker, 1998).

At the same time, epidemiological studies in the USA, France, Italy, Sweden, Finland, Israel and China reveal a robust inverse correlation between the amount of schooling received in youth and the prevalence of dementia in old age (Katzman, 1993). At present, there are no published data on whether there is an interaction between APO ε4 and number of years of schooling.

What accounts for the relationship between education and the prevalence of Alzheimer's disease? Three possibilities suggest themselves. First, is selection at work? Do individuals who will develop dementia have fewer cognitive resources early in life, causing them to drop out of school? Second, is poor education merely a proxy for brain damage resulting from poverty and repeated episodes of malnutrition, trauma, alcohol abuse, poor health care and the like? Third, is it possible that the intellectual stimulation provided by greater schooling leads to increased synaptic density during development and yields a brain reserve that delays the appearance of clinical symptoms even after amyloid protein has been deposited? Disentangling these alternatives is a task for inter-disciplinary research.

Once we can identify vulnerability in a gene-based disorder, does providing information about risk to families necessarily lead to prevention? Disappointingly, the answer is no. A Swedish clinical trial of counselling parents of infants with an inherited disorder revealed toxicity without benefit. Alpha-1-antitrypsin deficiency increases susceptibility to chronic obstructive pulmonary disease (COPD) from cigarette smoke. Detecting the gene in infancy should make it possible to diminish the likelihood of clinical disease by advising parents not to smoke and thus avoid passive exposure for their children. On evaluating a community trial of anticipatory parental counselling, Theilin (1985) found that parental smoking persisted unabated, even though the mothers had become much more anxious about their children than mothers in the control group. Mothers saw their children as condemned to COPD rather than as being at risk for it. The intervention was discontinued.

The very power of the genetic 'paradigm' will almost certainly reinforce biological reductionism in medicine. Moreover, information can come at a heavy cost. The woman who is told that she is positive for BRAC 1 or 2 (and thus at much increased risk for breast cancer) has learned that she faces a hazard without a certain remedy and has been given information that will, if it becomes public knowledge, make her uninsurable and unemployable, or will, if she conceals it, possibly void her insurance cover. Until there is some action that can reduce that risk, learning that one carries a gene or genes that increase risk for mental disorder will add to stress and confer stigma without bringing benefit. Ethnic groups express alarm at being targeted as different when they are identified as carrying a disproportionate load of harmful genes. The notion that genes are destiny, although it is utterly untenable scientifically, is used to rationalise racism. Medical care, especially in the USA now that the profit motive dominates, is less available to patients from minority groups, even when ability to pay is not at issue because patients are covered by insurance (Eisenberg, 1999*a*).

## CONCLUSION

Nature and nurture stand in reciprocity, not opposition. Children inherit – along with their parents' genes – their parents, their peers and the places they inhabit. Neighbourhood and neighbours matter, as do parents and siblings. The distribution of health and disease in human populations reflects environmental factors (where people live, what they eat, the work they do, the air and water they consume, their degree of connection with others, and the status they occupy in the social order) as well as what they inherit, namely their relative vulnerabilities and resistances to environmental pathogens.

Biomedical knowledge is essential for providing sound medical care but it is not sufficient; the doctor's transactions with the patient must also be informed by psychosocial understanding. Neither mindlessness nor brainlessness can be tolerated in medicine. The unique role of psychiatry will be its contribution to a new paradigm: brain/mindfulness, integrating neurobiology with behaviour in its social context. That is the intellectual challenge ahead.

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