

# Biotechnology, the brain and the future

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**Several new approaches to illness, inspired by recent advances in molecular biology, informatics and nanoscience, are readily applicable to diseases of the central nervous system. Novel classes of drugs will widen the scope of therapeutic action beyond merely modifying transmitter function and stem cell and gene therapies could offer an even more selective mode of targeting. Further into the future, nanotechnology has the potential to allow development of new medicines and novel access routes via miniaturized monitoring and screening devices: these systems, together with increasing use of carbon-silicon interfacing, will challenge traditional neuropharmacology. As the 21<sup>st</sup> century unfolds, the structure and function of the brain, which is incomparable with any other organ, will present unique technological and ethical questions.**

The brain presents the most significant challenge to biomedical science in this century. Not only are more of us living healthier and longer lives thanks to advances in preventative medicine, healthier habits, and of course medical and surgical breakthroughs, but in addition we have increased expectations of a comfortable and happy lifestyle. The old distinction between mental and physical, between 'organic' versus 'affective' disorders is being eroded as we realize the degree to which stress, anxiety and depression can feature as a factor in general health [1]. Moreover, brain imaging has offered new insights into the physical basis of previously elusive thought processes, such as the perception of pain [2-7] and the placebo effect [8], which is itself over-due for more rigorous investigation and eventual exploitation. This review summarizes the impact that some of the new biotechnologies will have on our understanding of brain function and dysfunction in the near future: inevitably, it cannot be exhaustive but instead will use particular developments, mostly in neurodegeneration, as illustrations of the problems and the potential that the biotechnologist will need to grasp.

## Beyond neurotransmission

### *The impact of genetics*

The new technologies, particularly the genetic-based approaches, are opening up new possibilities that go beyond targeting neurotransmission. In general, although there are only some 400-500 molecular targets throughout the body, there could soon be some 4000. Of these, one broad, new class of drugs will be proteins. As well as insulin, used for many years to treat diabetes, treatments using human proteins promoting blood vessel growth [12]

and wound healing [13] are now established. Direct application of protein-based therapeutics to the brain could soon include variations of diphtheria toxin to combat refractory glioblastomas [14] and engineered anti-apoptotic factor (FNK) with powerful cytoprotective activity, to protect against ischemia [15]. In addition, therapeutic monoclonal antibodies to combat brain cancers are also being developed [9,16]. As for neurodegeneration, one seemingly attractive new therapy has been the use of growth factors, such as glial-derived neurotrophic factor (GDNF) as a potential means of reducing the depletion of certain key populations of cells lost in Alzheimer's or Parkinson's diseases [17]. The particular difficulty for

### Box 1. The constraints of classic neuropharmacology

The principle action of a drug might be to enhance the presence of a transmitter either by blocking its uptake (e.g. Prozac for serotonin) or by increasing its synthesis (e.g. L-DOPA for dopamine) or by blocking the relevant catalytic enzyme (e.g. Aricept for acetylcholine), to act as an impostor directly on the relevant receptor (e.g. morphine at enkephalin receptors), or to enhance action by acting at an allosteric site at that receptor (e.g. minor tranquilizers at the GABA receptor), or conversely, to block the receptor to prevent excessive stimulation (e.g. the major tranquilizers at the dopamine receptor) [9]. However the central problem that has dogged neuropharmacology until now is that the transmitter systems in the brain are very diffuse, hence any drug modifying an abnormality in one part of the brain will inevitably have an effect on another brain region where the transmission was previously functioning normally thereby giving rise to side effects. Perhaps the most obvious example would be of manipulation of the dopamine systems: blockade of the dopamine receptor as a treatment for schizophrenia can lead to Parkinsonian-like motor impairments, and enhancing the brain dopamine of Parkinsonian patients with L-DOPA risks causing psychotic-like symptoms [10]. Over the decades, the traditional way around this problem could only be to develop increasingly selective agents for targeting increasingly specific (dopamine) receptors: clozapine is a well-known example of how an 'atypical' antagonist of a specific receptor sub-type can do much to reduce side-effects. The conventional approach to tackling brain disorders is to modify the functional availability of a transmitter or class of transmitter. Nonetheless it could be argued that manipulation of transmitter function, even though it might nowadays be more selective, is still not the ideal strategy. Receptors are notoriously capricious and will change in sensitivity as soon as they are over- or under-stimulated. Hence any drug could have limited use as the receptor re-adjusts its response to it. A more profound concern still is that abnormal transmitter levels are usually a reflection of the problem, not the problem itself. Hence the deficiencies in dopamine and acetylcholine that traditionally characterize Parkinson's and Alzheimer's diseases, respectively, are the result of the death of key neuronal populations. Increasing the levels of these substances is only temporarily alleviating the ongoing symptoms, not arresting the all-important cell death. In fact in the case of enhancing endogenous dopamine in Parkinson's disease, there is even some suggestion that such treatment might, be exacerbating the aetiology of the disease in the long-term [11].

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administering protein drugs for brain diseases is the lack of access because of the blood–brain barrier.

There are, however, various ways around this problem: one strategy is to deliver the medication via implants [18], which still involves a high level of hospital care, risk, unpleasantness and expense. Another technique has been to exploit the transferrin receptor – which, as its name implies, transports iron from blood to brain, transcytosing back and forth across the blood–brain barrier. Monoclonal antibodies to the transferrin receptor [19] can then actually act as a carrier to potentially therapeutic agents, such as epidermal growth factor (EGF) [20,21]. A further means of introducing trophic factors into the brain has been to harness gene therapy techniques [22–24].

Molecular biology has, in general, inspired a variety of new approaches to tackling the endogenous proteins and peptides thought to underlie the process of neurodegeneration, for example a lentiviral vector expressing neprilysin, which in turn degrades amyloid- $\beta$ , reduces amyloidosis in transgenic mice models [25]. Another idea has been to target the formation of amyloid plaques by inhibiting proteases, such as gamma secretase, that generate amyloid from its precursor [26]. Yet a further strategy has been to develop a vaccine [27] – the most well known example has been based on the 1–42 $\beta$ -amyloid peptide, pioneered by Elan [28] to combat accumulation of amyloid ss-protein. Although the treatment performed well in animal models, and indeed passed Phase 1 trials, the project was halted in Phase 2 owing to the onset of encephalitis in some patients. Unfortunately, the trial did not last long enough to establish efficacy or otherwise against Alzheimer's disease [29].

However, the problem in this case is that such strategies are predicated on the assumption that amyloid formation is indeed the predisposing, crucial cause of Alzheimer's disease. Although the association of amyloid accumulation with Alzheimer's is well established, a direct causal link has not yet been demonstrated. Although amyloid accumulation into fibrils will disrupt neuronal membranes, such a process on its own, without any other constraining factors, would not account for the regional and indeed neuronal selectivity that characterizes neurodegeneration (Box 2).

An alternative idea from our own laboratory is that, although fibril toxicity might aid and abet the degenerative process, a more specific mechanism is responsible for the characteristic highly selective progressive neuronal death. We have suggested that a peptide derived from acetylcholinesterase (AChE) might be a pivotal molecule in development, and that degeneration is aberrant and inappropriate activation of this system (Figure 1); hence targeting the peptide, or more easily, its interaction with the relevant receptor, could offer a new therapeutic strategy [30]. A detailed discussion of the merits or otherwise of this idea are outside of the scope of this review. Rather, the issue is that new, non-transmitter-related approaches are being inspired by new suggestions regarding the crucial neuronal mechanisms underlying brain dysfunction. The important point is, of course, the validity of the underlying hypothesis in the first place. Currently there are no

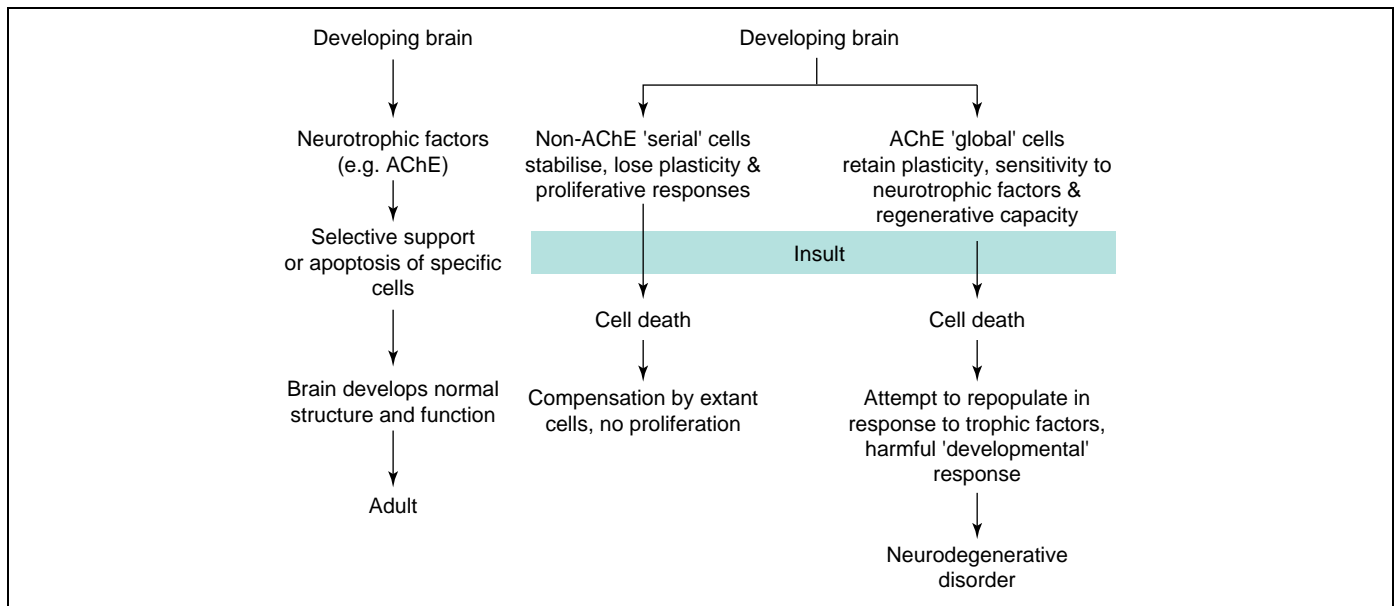
## Box 2. The proteomics of tau protein in Alzheimer's disease

As amyloid deposits grow in the Alzheimer brain, they induce another protein, tau, to accumulate intracellularly, creating a lethal tangle. The tau protein plays a key role in healthy cells, stabilizing microtubules in a polymerized state, and allowing the transport of materials from one part of the neuron to another. However, in Alzheimer's disease, the tau protein becomes abnormally modified such that it can no longer stabilize microtubules, which disappear, and the tau itself aggregates, forming the intracellular twisted paired helical filament structures (PHF) characteristic of Alzheimer's sufferers' cells. These cells will then perish, owing to the lack transport of key chemicals, such as those needed for manufacturing the relevant transmitter.

One important question now is to understand this process of transition from a normal microtubule network to a twisted aggregate of tau. There is a single gene for tau but six different forms of the protein can be produced by different splicing events, resulting in six different isoforms. Some forms of dementia have tau deposits but no amyloid plaques, owing to a tau gene mutation that prevents some splicing resulting in an excess of one form of tau isoform. We know that the abnormal tau isolated from Alzheimer brains differs from normal brain tau by having an excess amount of phosphate attached to it. We also know that phosphorylation of tau regulates the ability of tau to stabilize microtubules and that when tau is phosphorylated to an extent similar to that in Alzheimer brain, it can no longer stabilize the microtubules. Thus identifying all of the phosphorylation sites on tau is a first step to identifying the enzymes – protein kinases – that are responsible for excessive tau phosphorylation in Alzheimer's disease. Mass spectrometry can be used to identify phosphorylation sites on the PHF-tau protein. This allows information on the protein sequence to be obtained from a very small sample. Thirty-six potential phosphorylation sites on this protein have been identified but this protein is very heterogeneous and not all Tau proteins isolated have the same sites phosphorylated [10] (and pers. commun. – Brian Anderton). Phosphorylation is rapid and can be long or short lasting. As such it is an excellent candidate for a role in learning and memory, addiction and the biological basis of belief. It is central to the biological basis of behaviour. Quantitative mass spectrometry allows us to find out about gradation of phosphorylation.

universally accepted theories for the neuronal mechanics and dynamics of Alzheimer's disease – it would be unwise for any single biotechnological dogma to become so fashionable that, even in the absence of clinching evidence, it would nonetheless become a bandwagon that precluded any other ideas.

Two other strategies that reach beyond modification of neurotransmission, and that are gaining increasing attention are: first, the identification of factors that could help in preventative medicine and second, the development of surrogate markers. A good illustration of a candidate preventative factor in Alzheimer's disease is based on the notion that the pernicious cycle of neurodegeneration is triggered by cell death in a key brain area, and that such cell death might be caused by a small, clinically silent stroke. One brain region particularly vulnerable to conditions such as hypoxia and high blood pressure is the medial temporal lobe, and the theory is that local neurodegeneration would then spread by an as yet unknown mechanism, to other parts of the cortex [31]. It follows that any measure that can be taken to reduce the risk of stroke will reduce the risk of eventual Alzheimer's disease. For example, folic acid is now proposed for use in combating the high homocysteine levels associated with Alzheimer's disease [32,33].



**Figure 1.** Possible process underlying neurodegeneration. Scheme for selective degeneration of certain groups of neurones in Alzheimer's, Parkinson's and motor neurone disease. In the developing brain most neuronal groups will transiently express neurotrophic factors, such as AChE, which will ensure the development of specific cell circuitry that characterizes the adult brain. Once mature, the majority of these serial circuits will no longer express AChE and, indeed, lose much of their plasticity and proliferative responses. If there is an insult, the cell death that ensues will ensure a functional compensation that characterizes, in many cases, recovery or partial recovery in stroke. However, the global AChE-containing neurones, because they have retained their ability to regenerate and their sensitivity to trophic factors, will respond to a local insult in a different fashion. In this case there will be an exuberant axonal regeneration in an attempt to repopulate leading to enhanced release of AChE. AChE, acting in a non-cholinergic capacity, or a fragment derived from AChE, will then trigger calcium entry, both within the local global cell population as well as on to target serial cells of hippocampus and cortex. Whereas a certain degree of calcium would be beneficial in development, the mature cell is less able to handle intracellular calcium levels, which therefore become toxic. The death of the cells will then constitute a further insult, leading to a pernicious cycle of events – neurodegeneration. Adapted, with permission from [30]. © 2002 by the Society for Neuroscience.

The development of a surrogate marker for brain diseases, in particular for neurodegeneration, is another potentially fruitful approach. The idea is to develop a simple blood or urine test whereby those at risk can be screened in the presymptomatic stage of a potential illness, and those already diagnosed can be readily monitored. An example of just such a test has been proposed by 'AlzheimAlert' (Nymox Pharmaceutical Corporation, [www.nymox.com](http://www.nymox.com)) which monitors urine levels of neural thread protein (NTP), which seem to be correlated with severity of dementia [23,34].

One argument against this strategy is that it has little benefit, at least while there is no appropriate therapy. It will only depress the patient to learn that they have an incurable disease. Although the closeness of the relationship between NTP and Alzheimer's disease is not yet understood, and hence offers little chance for novel therapeutic application, any faithful monitor of the course of an individual's degeneration could still be welcome. An accurate surrogate marker, be it NTP or another molecule, would enable not just the patient, but also the carers, to plan the remaining stage of their lives. Moreover, if the marker were sufficiently sensitive, it would reflect individual aetiology and enable the patient to serve as their own control, thereby facilitating clinical trials. For example, at present drug trials in motor neuron disease (MND) patients use survival as the primary end-point. They take up to 18 months, require up to 1000 patients to show a 10% benefit, and could cost up to £20 million. The problem is even greater in Parkinson's and Alzheimer's diseases, in which fluctuations in motor function and

memory mean that even larger numbers must be studied over a longer period of time. A biomarker that reliably measured 'disease activity' would mean that compounds could be screened in a much smaller number of patients, and in a shorter time.

### Beyond genes

#### *From genes to function: the bridge too far?*

Molecular biology coupled with advances in informatics, and indeed in automation at the bench, has enabled the swift analysis and mapping of genes in both healthy and diseased states. The strategy of targeting rogue genes (i.e. gene therapy) is far from novel and is reviewed concisely elsewhere [35]. However, this approach has floundered from the original optimism of a decade ago, owing to the problem of accessing DNA in somatic cells. Strategies to overcome this problem include marrow transplants [36], virus vectors [37], and 'bolistics' [38] in which DNA is mixed with tungsten and fired into cells at high speed. Such techniques might become obsolete in the future with the advent of 'one generation' germ-line engineering [39]. As its name suggests, this technology exploits the ease of access to germ cells (eggs and sperm) without the dubious ethical, and currently illegal, process of immortalizing that change in the trait forever [40]. In this regard, the brain presents no more, and no less, of a problem for access than any other body tissue. Instead, the problem is a more theoretical one concerning the relation of genes to brain function in the first place.

If a therapeutic strategy is to be based on certain genes, the central assumption is that a gene or genes are indeed

**Table 1. Mouse transgenic lines with Alzheimer's disease-like pathology (data from [43])<sup>a</sup>**

Transgenic line	Mouse strain	Mutation	Promoter used	Pathology
PD-APP	Swiss Webster B6D2F1	V717F	PDGF- $\beta$	A $\beta$ deposits, neuritic plaques, synaptic loss, astrocytosis and microglia
Tg2576	C57BL/6-SJL	K670M/ N671L	Hamster Prp	Behavioural, biochemical and pathological abnormalities
TgAPP23	C57BL/6-DBA/2	K67-M/N671L	Murine Thy-1	Congophilic senile plaques that are immunoreactive for hyperphosphorylated tau
TgCRND-8	C57BL/6-CH3	K67-M/N671L and V7171	Hamster PrP	A $\beta$ amyloid deposits, dense-cored plaques and neurite pathology, early impairment in acquisition and learning reversal
TgR1.40YAC	C57BL/6-DBA/2 129S3/sim	K670M/ N671L	Human APP	A $\beta$ deposits, accelerated mating to homozygosity and/or to mutant PS-1 YAC transgenic mice
PS/APP PS-1xTg2576	Swiss Webster B6D2F1/SJL b156	PS-1 M146V or L+APP K670M/N671L	PDGF/prp	Fibrillar A $\beta$ deposits in the cerebral cortex and hippocampus, reduced spontaneous alternation performance in a 'Y' maze
Alz27	B6D2F1	Wild type (4R,2+,3+)	Murine Thy 1.2	Tau present in nerve cell bodies, axons and dendrites was phosphorylated at sites that are hyperphosphorylated in paired helical filaments
JNPL3	Swiss Webster B6D2F1	P301 (4R, 2-,3-)	Murine PrP	Motor and behavioural deficits with age- and 34 gene-dose-dependent development of neurofibrillary tangles
hTau40	FVB/N	Wild type (4R,2+,3+)	Murine Thy 1.2	Axonal degeneration in brain and spinal cord, axonal dilations with accumulation of neurofilaments, mitochondria and vesicles
Htau	Swiss Webster B6D2F1	Wild type (genomic transgene – all isoforms, on mouse tau knockout background)	Murine tau promoter	Hyperphosphorylated tau accumulating as aggregated paired helical filaments in the cell bodies and dendrites of neurons in a spatiotemporally relevant distribution
PS1/APP/Tau	C57b16	PS-1 M146V (knock in) APP K670M/N671L TauP301 (4R,2-,3-)	Murine Thy 1.2	Development of plaques and tangles; synaptic dysfunction, including LTP deficits, manifesting in an age-related manner (before plaque and tangle pathology)

<sup>a</sup>Abbreviations: PD-APP, Parkinson's disease-amyloid precursor protein; Tg, transgene.

the 'cause' of the illness. Again, Alzheimer's disease is a good illustration that such an assumption is far from straightforward. Leaving aside the small (5%) cases of 'familial' Alzheimer's, the more common 'sporadic' condition seems to be highly polygenetic [41]. Accordingly, there is a range of transgenic mouse 'models' of Alzheimer's disease [42], yet each expresses a different phenotype. See Table 1 (see [43]). This plethora of models highlights two problems for relating aberrant genes to mental function.

First, a model, be it transgenic or otherwise, is only powerful when it does feature the salient factor in that disease. As yet, although there are many theories as to the primary mechanism in Alzheimer's disease (see preceding section) none has been unequivocally validated. As it stands, the impairments expressed in current transgenic models might be focussing on epiphenomena, or indeed features that occur later in the disease as a consequence of an initial, and still unidentified, insult or perturbation. The fact that such a range of models exists, and that cognitive deficits can be dissociated from molecular or histological markers, strongly suggests that the truly faithful animal model of Alzheimer's disease remains to be found.

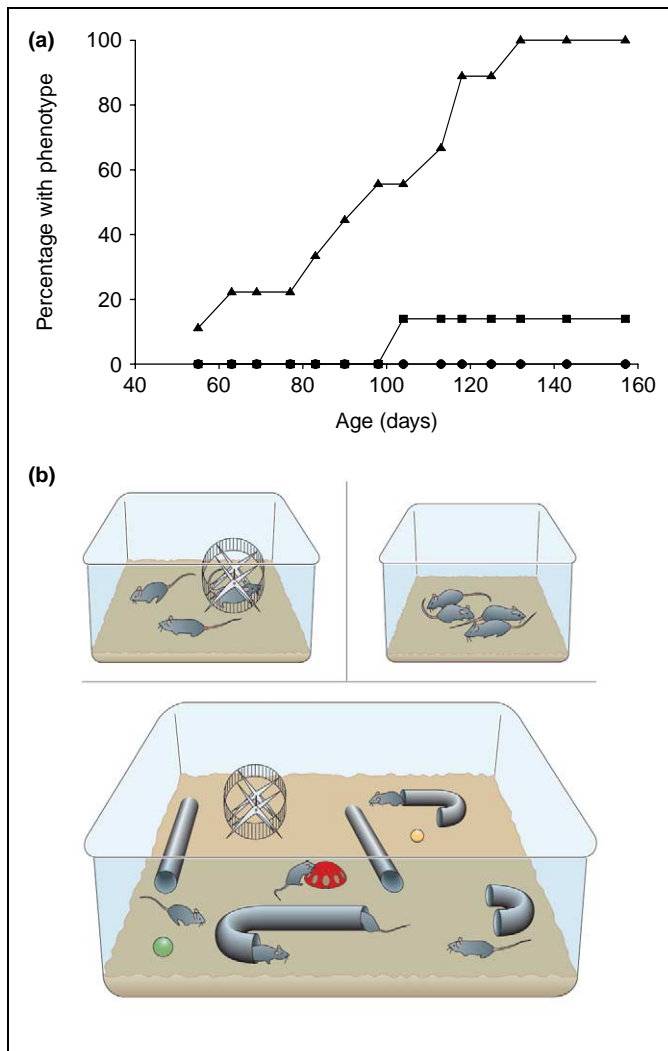
The second problem illustrated by transgenic models is that the steps from malfunctioning genes to final phenotype are far from clear. A gene, after all, can only express a protein, and it is still necessary to then trace how an aberrant protein might lead to sophisticated mental impairments. A striking illustration of this problem can be seen in a study of transgenic mice engineered to develop

the murine equivalent of Huntington's chorea. In animals exposed to an 'enriched' environment the age of onset of symptoms was far later, and even then the degree of eventual impairment far more modest, than in the group of genetically identical counterparts maintained in standard housing [44] (Figure 2).

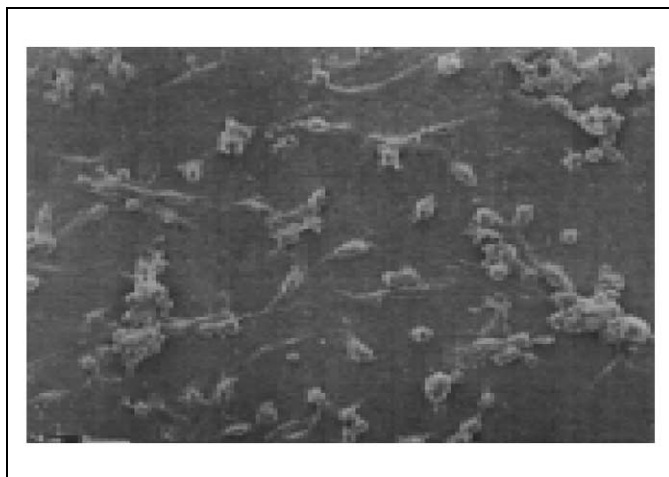
#### Proteomics

A central difficulty in extrapolating from gene malfunction to brain dysfunction is not only a problem in tracing the consequences of expression of a single aberrant protein, but in the number of aberrant proteins that could be expressed as a result of activation of a single gene. For example, in yeast alone with a paltry 6000 or so genes compared with our 30 000 or more, a single mutation can alter the expression of over 300 further genes, while differential mRNA splicing can give rise to a whole range of different compounds. In the fruit fly alone, a single gene could be 'the gene for' a staggering 38 000 different proteins. In the light of such imperfect matching of gene to eventual mental function, and given the importance and variety of the mediating proteins, it is not surprising that proteomics, which has only been recognized properly in the last four to five years, is becoming central to the understanding of diseases.

The only current problem of proteomics is that there is no method for amplifying the amount of protein isolated: hence good analysis is dependent on the quantity of protein that can be isolated. Moreover, mass spectrometers cannot handle entire proteins and rely on the protein being fragmented by an enzyme. These fragments



**Figure 2.** Effects of housing in transgenic Huntington's Chorea (HC) mice, on motor performance. Effects of differential housing conditions (a) on motor performance in transgenic mice with Huntington's Chorea repeat. Severity of impairment is shown by failure on rod test, plotted against age. Reproduced with permission from Nature Reviews [70] ([www.nature.com/reviews](http://www.nature.com/reviews)). Those from enriched housing have significantly later onset, with markedly more modest phenotype (b). Figure kindly supplied by M. Hannan, University of Melbourne, and adapted from [43].



**Figure 3.** Human nerve cell growing on integrated circuit. B50 neuron cells grown on nanostructured silicon.

can then be put into the mass spectrometer where they will fragment further as high energy breaks the peptide bonds between the amino acids. Each of the fragments will yield a particular read out on the mass spectrometer trace. It is possible to find fragments that differ in size by one amino acid, or even by one phosphate. Because the weight of each of these amino acids is known, the amino acid sequence of the protein can be determined by comparing the fragments produced from a sample of the protein.

Proteomics could be used to study long-term potentiation. These techniques could allow protein changes, such as phosphorylation, to be followed and thereby enable us to gain a better understanding of the mechanisms of learning and memory. But then again, such phenomena can only be fully appreciated in the context of the whole brain.

### Beyond the molecular level

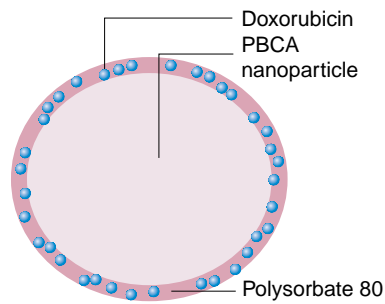
#### Stem cell therapy

One approach featuring in the news currently, and in which eventual success relies on understanding more about whole-brain organization, is stem cell therapy. These precursor cells, if introduced into an appropriate neuronal environment, will themselves become neurons, and hence provide the possibility of replenishing the loss occurring in neurodegeneration. Although stem cells have been used in animal models of Alzheimer's disease [45,46], significantly more attention has been paid to Parkinson's disease in which the primary site of the lesion is far more discrete, and thus far easier to target with an implant of stem cells [47].

The ethical debate over stem cell research is beyond the scope of this review, as are the current immediate difficulties that the requisite surgery would present. However, even assuming that the procedure was neither unpleasant nor hazardous, and assuming the socio-economic issues had been resolved, along with the technical problems of implanting with minimal loss of tissue *en passant*, stem cell therapy still presents fundamental problems (see [48]). In the case of Parkinson's disease, there is the very real issue that the cells might produce too much dopamine, and psychotic symptoms ensue (see Box 1). Moreover, unfettered cell proliferation, as could occur following stem cell introduction into the brain, could constitute a tumour – which is after all no more than excessive cell division [49]. One way around this problem might be for the stem cells to divide only at temperatures a few degrees hotter than would normally be the case in the living brain. In any event, more research is needed to find ways of ascertaining the desired levels of dopamine, in the case of Parkinson's disease, for an individual brain, and then for ensuring that the new neurons are of the appropriate quantity and quality to deliver those optimum levels.

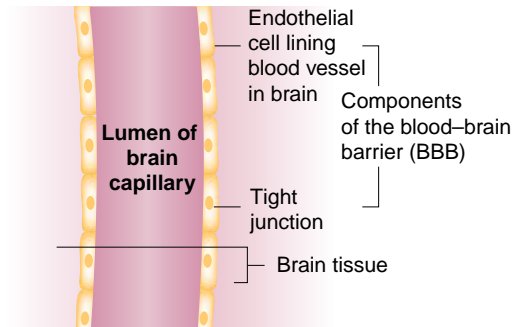
An alternative strategy to stem cell therapy that nonetheless promotes the supply of new neurons is to exploit the relatively newly discovered phenomenon of adult brain neurogenesis. Contrary to traditional dogma, it is now widely accepted that the adult brain is capable of creating new neurons [50]. Indeed it seems that astroglia could be important in this process, by an as yet unknown mechanism [2,51]. Were such a mechanism to be identified, and particularly if it were site-selective, it could be

## (a) Mechanisms of action of drugs in development at NanoCure Corporation

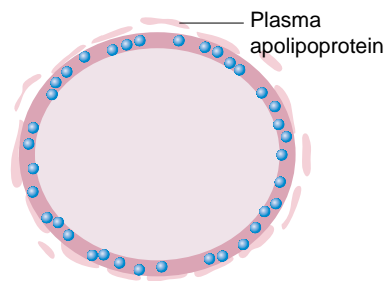


Drugs in development consist of a Poly(ButylCyano Acrylate) PBCA nanoparticle coated with a layer of drug (doxorubicin), and a layer of polysorbate 80.

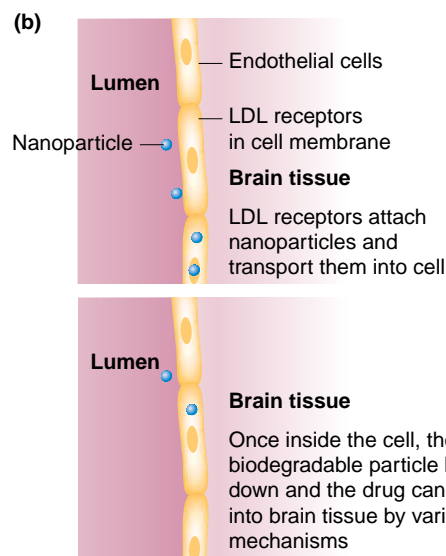
Drugs in development are injected intravenously into the patient and circulates through the blood stream.



The blood-brain barrier – a protective barrier between the brain and the circulative system – separates the brain from the central nervous system. The barrier consists partly of a tight seal of endothelial cells that line the blood vessels in the brain. These cells prevent the normal transport of most drugs into the brain.



Once the drug enters the blood stream, the outer coating of polysorbate 80 attracts plasma apolipoproteins. These packaging units used by the blood stream to carry lipids adhere themselves to each individual particle of the drug. Once these particles are coated, they are camouflaged from the body. This camouflage tricks the blood-brain barrier into thinking that these particles are LDL (a form of cholesterol).



The drug is transported through the blood-brain barrier by LDL receptors. These receptors are there to bring lipids into the brain from the blood stream. Gliomas often have more LDL receptors than normal brain tissue. This would allow a higher rate of accumulation in the tumor cells.

The drug breaks down and allows the diffusion of doxorubicin into the brain tissue where it begins to treat the brain tumor. This process can work better in tumors because the blood-brain barrier is often disrupted in a tumor.

**Figure 4.** Application of nanotech to biotech and the brain: a means for drugs to gain access to the brain, despite the blood-brain barrier. Adapted from <http://www.nanocure.com/index.html>.

exploited pharmaceutically, perhaps even with a systemic treatment, so that the number of cells created and indeed the levels of transmitter they released, had more likelihood of being in the physiological range.

### Brain implants

Nonetheless, for certain brain malfunctions, implant surgery might prove inevitable. Already, an implant of nerve growth factor into the brain has enabled a

quadriplegic patient to 'will' a cursor to move on a computer screen [52] and as such offers hope of restoration of function for those with spinal cord damage [53,54,55]. In fact, pioneering work in rats [56,57] and monkeys [58] might lead to the development of a vastly improved treatment for those with spinal injury and ensuing paralysis by circumventing not only the motor system, but the incoming (currently defective) sensory signals too [59,54,57]. Perhaps a similar technology could be developed, not interfacing thoughts with motor or sensory systems, but instead intercepting the as yet poorly understood traffic between the CNS with the immune system, that presumably underlies the placebo effect. In fact, we now know that isolated neurons will function on integrated circuits by interfacing readily with silicon electronic components [60–63] (Figure 3). This work could have two major implications for biotechnology, not just an increased possibility for implant therapy, but also an application beyond healthcare, the development of a completely different type of computer based on a 'neurochip' [64].

Still further into the future, yet again departing from purely carbon-based technologies, is the application of nanoscience to medicine in general. Nanoparticles could deliver molecules to specifically targeted sites, including places that standard drugs do not reach easily. An alternative application is to reveal what sets of genes are active under certain conditions, for example with gold particles bound to a DNA-probe; if the DNA in question is operative they will bind, with a resulting change in colour. DNA linked to gold nanoparticles has been developed by several companies for diagnostic purposes [e.g. to replace microarrays for single nucleotide polymorphism (SNP) analysis]. These include Nanosphere ([www.nanosphere.com](http://www.nanosphere.com); for technical details see [http://www.nanosphere-inc.com/2\\_tech/1\\_nanopobes.html](http://www.nanosphere-inc.com/2_tech/1_nanopobes.html)) and Nanoplex Tech ([www.nanoplextech.com](http://www.nanoplextech.com); for technical details see <http://www.nanoplextech.com/technology/index.htm>). The gold nanoparticle is used as a tool to detect target binding to oligos (or other biomolecules) linked to the surface of the nanoparticle. The properties of the gold nanoparticle that are exploited include silver deposition on the particles, colour changes owing to nanoparticle aggregation and surface plasmon resonance of gold.

Another device might enable quick diagnostic screens. Antibodies labelled with magnetic nanoparticles and exposed to a magnetic field will respond with a strong magnetic signal if they are reacting with certain substances. Alternatively, gold nanoshells linked to specific antibodies that target tumours could, when hit by infrared light, heat up to destroy growths selectively. Although these applications are far from specific to diseases of the brain, it is clear that they would have particular value in this organ, where access has proved particularly problematic. On the other hand, a further application of nanotechnology, 'NanoCure™' (NanoCure™ Corporation, [www.nanocure.com](http://www.nanocure.com)), is designed specifically to overcome the problem mentioned earlier, of crossing the blood–brain barrier, and thereby deliver antagonist drugs to brain tumours (Figure 4).

However, perhaps the most profound problem with the treatment of the brain in the future lies in the very nature of the organ itself. Any change in brain function will amount to

a change in the individual mind. Hence as the advances outlined here become a reality, and as the trend for high expectations of individual and society escalate [65], there will be an increasingly blurred distinction between 'curing' a disease, and changing the type of thoughts and feelings an individual might experience. Already some are taking *Ginkgo biloba* to improve and maintain their memory [35,66], while paroxetine might combat social anxiety [67], and of course Prozac banishes depression [68]. In addition a society in which there is still the prevailing fiction of a 'gene for' a specific mental trait could drift towards further, even more radical, lifestyle treatments inspired by genetic technologies, including artificial chromosomes [69,62] which make the notion of 'enhanced' genes more feasible, at the practical if not at the much-desired functional level.

## Conclusions

The biotechnology of the brain is now reaching beyond conventional neuropharmacology, beyond genetic manipulations, and beyond the targeting and/or general use of isolated molecules. To appreciate to the full the additional potential, not just for therapy, but also for diagnosis, screening and monitoring – as well as the non-pharmacological opportunities offered by the traditionally physical sciences – we must develop a much greater multidisciplinary that extends across different branches of the physical and biomedical sciences and also spans the different levels of brain operations, from the genetic to the cognitive. Above all however, as biotechnologists manipulate the human mind with increasing precision, we must be realistic not only about what is achievable, but what we actually wish to achieve.

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