Part I

Introduction and general principles

1

Pathophysiology of nervous system diseases

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Since the last edition of this textbook, the field of Neurology and the Neurosciences has witnessed remarkable advances in the technologies available for the study of the brain and our concepts about the nervous system and its diseases. There has been progress in our ability to modify, prevent or treat these disease processes and to evaluate clinical outcomes, and in the resources available to handle and disperse data. There is, however, always a competition between the advancement of knowledge and the challenges of disease. We face challenges that demand that we put these advances to good use.

This introduction provides a brief, and necessarily incomplete, overview of some of the advances, and the many remaining challenges, for the study and treatment of diseases of the nervous system. A number of new therapeutic strategies have already been developed, and are already impacting on the quality of life of those with neurological disease. Many new treatments, both symptomatic and disease-modifying, are in the developmental pipeline. With the delineation of the human genome in 2001, a particular problem has emerged: the need to delineate protein production (proteomics) and protein modifications on a cellular basis. 'The emerging challenge in understanding the pathogenesis of the neurodegenerative disorders will be to characterize and elucidate aberrant protein interactions in the affected cells' (Martin, 1999). Future efforts will be focused on determining the tertiary structure of proteins which is currently determined using X-ray crystallography and nuclear magnetic resonance. Because of their relatively low through-put, complexity and high cost, these techniques have not generally been used for therapeutic targeting in drug discovery programmes. Recent technological advances, coupled with the information from human genome sequencing, are beginning to enable construction of a database to predict protein structure from sequence, and may be relevant for up to one-third of all gene targets (Christendat et al., 2000).

Global challenges in the developed and developing world

The world's aging population is increasingly affected by both acute and chronic neurological diseases. These include cerebrovascular disease, Alzheimer's disease and other dementias and Parkinson's disease. In the USA, the number of the very old (older than 85) is expected to increase sevenfold, from 2 million in 1990 to 14 million in 2040 and is increasingly vulnerable to chronic neurodegenerative disorders.

Since the original descriptions in the 1870s that microbes caused infections, specifically the discovery by Koch that *Bacillus anthracis* caused anthrax, major neurological complications of systemic infections continue to affect millions annually, particularly in developing nations. These infections include malaria, HIV-1 infection, tuberculosis, and leprosy, as well as 'new' infections that have emerged in previously unaffected areas. Malaria remains a major scourge across the world, with approximately 1.5 million deaths annually, many from cerebral involvement. Until recently, research efforts have been scattered and underfunded, with little coordinated effort for the development of a vaccine. In sub-Saharan Africa, the AIDS epidemic has produced an enormous sociopolitical crisis because it has literally decimated a generation, with seroprevalence rates exceeding 25% of the population, and an estimated 13.2 million 'AIDS orphans' (UNAIDS, 2000). Despite the availability of effective treatment, leprosy remains the commonest cause of peripheral neuropathy worldwide. Increasingly, developed and developing countries are linked by diseases which have spread because of the ease and speed of global travel. As

one recently developing example of 'emerging' infections, the appearance of West Nile encephalitis in the eastern USA in the past few years is thought to reflect the introduction of infected *Anopheles* mosquitoes from increased air travel (Lanciotti et al., 1999).

One of the major challenges facing our society will be how to equitably distribute therapeutic advances, many of which may be both costly and complex, particularly to underserved populations. The AIDS epidemic provides a stark warning of how an inadequate global response can fail to deliver currently available and effective treatments to millions. It serves as an example to avoid as improved pathogenesis-based treatments for neurological diseases such as Alzheimer's are developed (Steinbrook & Drazen, 2001).

The impact of imaging on neurosciences

No technology has changed the practice of the clinical neurosciences more than cranial imaging. Within the past two decades we have witnessed the development first of structural imaging (CT and MRI), then functional imaging (PET and fMRI), and now refined morphological and physiological imaging (diffusion-weighted and perfusion-weighted imaging), and biochemical characterization with magnetic resonance spectroscopy (MRS). Advances in imaging techniques during the past two decades have literally revolutionized our ability to localize pathology within the nervous system, establish diagnoses, and guide therapies. Rather than devalue the role of neuropathology in the clinical neurosciences, the improvements in imaging have facilitated an even closer integration of clinical neurology with pathology. We can now see the brain, ask what part is involved in neural and cognitive processing, evaluate the extent and distribution of injury, and characterize mechanisms of plasticity and recovery.

Of all of the various imaging modalities: computerized tomography, positron emission tomography, angiography, arguably magnetic resonance imaging (MRI) has become the most widely used modality because of its sensitivity, and lack of radiation risk. The field of MRI has now taken on two new functions: (i) magnetic resonance spectroscopy, identifying the biochemical profile of the living brain through the identification of specific chemical spectra and (ii) the development of functional MRI using changes in deoxyhemoglobin to detect regional brain activation. Both of these techniques are non-invasive, repeatable, and involve no radiation risk. Specialized MR techniques such as diffusion-weighted imaging and perfusion-imaging have pushed forward our understanding of cerebrovascular pathophysiology. They allow for the identification of 'vulnerable' brain tissue within the first few hours after onset of stroke. The identification of diffusion–perfusion 'mismatch' can now lead directly to treatment with thrombolytic therapies or induced hypertension.

Table 1.1. Physiologic processes accessible in humans by functional and metabolic imaging

Physiologic processes	Methods
Glucose metabolism	FDG-PET[a]
Blood flow or volume	[^{15}O]H_2O-PET, perfusion MRI
Tissue oxygenation	nitroimidazole-PET, fMRI
Tissue pH	^{31}P-MRS
Protein synthesis	Amino acid-PET
Cell proliferation (mitotic rate)	Thymidine-PET
Receptor concentration or occupancy	PET
Enzyme kinetics	PET
Endogenous metabolite concentration	MRS(I)[a]
Water diffusion	DWI
Tissue anisotropy	DTI
Drug pharmacokinetics/dynamics	PET, MRS
Vascular permeability	Dynamic MR

Notes:
DTI, diffuse tensor imaging; DWI, diffusion-weighted MR imaging; FDG, [^{18}F]fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; MR, magnetic resonance; MRS(I), magnetic resonance spectroscopy–spectroscopic imaging; PET, positron emission tomography. [a]Technique used routinely in clinical practice for oncology.
Source: From Pomper, M.G. (2000). Table 27.3–1, p. 680. Reproduced with permission from the publisher.

These remarkable advances are incomplete. We are still not 'online' with the timing of the brain's processing of information. The dependence of current methods of functional imaging, both PET and fMRI, on changes in blood oxygenation and blood flow associated with neural activity remains a limiting factor. Other imaging techniques based on electrophysiological or magnetophysiological principles may provide further advances. Nonetheless, current physiological imaging as detailed in Table 1.1 can now permit the detection of a variety of metabolic alterations within the living brain, including blood flow, metabolism and perturbations in neurotransmitters (Fig. 1.1, see colour plate section). The recent development of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health will probably further facilitate and accelerate the progress of imaging research.

Neuropsychiatric disorders have been extensively studied using both structural and functional neuroimaging. Mood disorders have a neurochemical origin, but may also be associated with regionally selective alterations in brain structure. For example, a 40% reduction has been found in grey matter volume in prefrontal cortex in patients with bipolar disorders or familiar recurrent unipolar depression (Drevets et al., 1997). As an example of an investigative approach which combines genetic studies, neuropsychological testing and functional imaging, a specific gene variant in the dopamine-degrading enzyme, catechol-*o*-methyltransferase, is more common in schizophrenics and the prefrontal cortex appears to be metabolically more active (Egan et al., 2001). Positron emission tomography scans during reading tasks showed reduced activity in the left hemisphere in dyslexics from three different countries, suggesting that there is a universal neurocognitive basis for dyslexia (Paulesu et al., 2001). Multidisciplinary studies such as these will become more common and will undoubtedly facilitate an improved understanding of how genetic variation may influence brain behaviour in health and disease.

The genetics of neurological diseases

Over 50% of genetic disorders affect the nervous system and are detailed in the online textbook *Online Mendelian Inheritance in Man (OMIM)*. This database is a catalogue of human genes and genetic disorders authored and edited by Dr Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. OMIM contains 12 749 genetic disorders and 9365 established gene locations.

The elucidation of the genetic mechanisms of disease using molecular techniques has advanced rapidly, in large part because most neurogenetic disorders are inherited in a simple Mendelian fashion. Linkage analysis, positional cloning and searches for mutations in candidate genes have led to the identification of mutant genes in more than 50 disorders. The elucidation of the human genome through the Human Genome Project and the surprising observation that the number of identifiable human genes (26 000) is only a few thousand more than the number identified for a much smaller organism, the round worm, sets the stage for a detailed exploration of genes and proteins associated with specific neurological diseases.

Extraordinary progress has been made in identifying specific genes that pose risk factors for many common neurodegenerative disorders and the ways in which proteins coded by these genes are associated with loss of function or gain of adverse properties (Price et al., 1998a; Hardy & Gwinn-Hardy, 1998; Price et al., 1998b). Even before the Human Genome Project was completed in 2001, the mapping and cloning of genes involved in inherited neurological disorders had been performed. It is now anticipated that the genomes of given individuals will be highly variable, as compared to the reference human sequence. Thus, it should be possible to analyse disease genes from studies of a single individual, rather than large kindreds, as has been required up to now. For a number of disorders long considered 'sporadic', the findings from genetics have changed our ways of thinking. Advances in Alzheimer's disease (AD) are illustrative, but we could equally have chosen Parkinson's disease (PD), frontotemporal dementia, or amyotrophic lateral sclerosis. It has been known for some time that rare families existed with an early onset of Alzheimer's disease (under age 60) and an apparently dominant pattern of inheritance. Evaluation of these families has yielded four genetic loci with numerous mutations, all involved in the processing of the protein beta amyloid. These findings not only strengthened the amyloid hypothesis as the underlying mechanism of Alzheimer's disease, but provided information leading to the development of transgenic mouse models. Allelic variation in apo-E appears to act as a time dependent susceptibility gene (Price et al., 1998a).

In an example of a multidisciplinary approach to improve the sensitivity of preventive treatment trials for AD, genetic testing has been combined with functional imaging in an innovative approach to more efficiently test preventive treatments. Positron emission tomography is used in cognitively normal apolipoprotein E4 heterozygotes to identify those with decreased glucose metabolism in several brain regions typically affected in AD. Those with PET abnormalities are considered to be at greatest risk for the development of AD and participate in the clinical trial (Reiman et al., 2001).

Alzheimer's disease also provides an example of the identification of genes associated with an increased risk of disease, rather than disease mechanisms. The first such genotype, Apo-E4, is associated with a fourfold increased risk of late-onset AD and appears to act as a time-dependent susceptibility gene (Price et al., 1998a). Two other genetic loci, A2M and LRPAP1 have also recently been reported as risk-associated genes (Sanchez et al., 2001; Nicosia et al., 2001), and perhaps only operate in selected populations. The concept of risk factor genes has been proposed for some time, but finally there is specific evidence for such a phenomenon. Manipulation of transgenic mice models has suggested therapeutic strategies for the much

larger group of patients with late-onset Alzheimer's disease through manipulation of the secretases involved in processing amyloid, or vaccines aimed against possibly toxic fragments of amyloid. As outlined in Chapter 115, similar strategies have been used to explore the role of the protein alpha synuclein in Parkinson's disease, and the protein tau in frontotemporal dementia.

The mechanisms of cellular injury for most neurogenetic disorders remain uncertain, even when a gene product can be identified. Another genetic abnormality, the triplet repeat mechanism for diseases such as Huntington's disease, fragile X syndrome, and various spinocerebellar ataxias, has focused attention on how proteins determine abnormal cellular function and ultimately cell death. There has been a shift away from thinking about enzymatic abnormalities to abnormalities of protein structure and function. This consideration of proteins as mechanisms of disease applies not only to the triplet repeat diseases, but also to other diseases involving proteins such as prion diseases and neurodegenerative diseases.

Common mechanisms may exist for a number of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Most neurodegenerative diseases have been linked to abnormal protein aggregates interfering with neuronal function and viability. Genetic errors and mutations may produce misfolded proteins which tend to accumulate within neurons and may impair the function of proteasomes, which is normally critical in the ubiquitin proteasome system for breaking down proteins. Further accumulation, over a prolonged period, may lead to additional accumulation and even more proteasomal dysfunction (Bence et al., 2001). In Huntington's disease, polyglutamine expansions in the huntingtin and atrophin-1 proteins can be identified, and have been proposed to lead to neuronal toxicity by interference with gene transcription (Fig. 1.2) (Nucifora, Jr. et al., 2001). Mitochondrial disorders can affect almost every tissue and organ system, typically with maternal transmission. Mitochondrial genetics have become increasingly important since the first descriptions of mutations in mitochondrial DNA in 1988 (Holt et al., 1988). A wide range of systemic and neurological diseases have now been linked to specific mutations, including chronic progressive external ophthalmoplegia (CPEO), Leber's optic atrophy, MELAS and MERRF. In addition, mutations in mtDNA may contribute to aging and neurodegenerative diseases.

The accurate diagnosis of many neurogenetic disorders is now possible; and both antenatal and presymptomatic disease diagnosis is also feasible. Genotypic diagnosis by DNA testing allows for precision in diagnosis, and facilitates genetic counselling and predictive testing. It can also identify patients with specific genetic disorders for natural history studies, and ultimately, for therapeutic interventions. These technological advances bring their own set of ethical concerns, however, including the potential misuse of genetic testing to screen 'at risk' individuals for employment or health insurance.

The field of gene therapy was introduced with tremendous fanfare over a decade ago, and had the potential to introduce functional genes into a diseased cell. There have been persistent technical challenges with the delivery systems used to deliver the genes, and the entire field suffered a major setback following an unanticipated patient death in one gene therapy trial. Nonetheless, the recent demonstration of a non-viral gene-transfer therapy for hemophilia A has generated renewed excitement at the potential to cure selected genetic diseases (Roth et al., 2001).

Ion channels and neurotransmitters in neurological disease

The study of ion channels and their distribution in muscle and nerve has expanded tremendously in the past decade, and has led to an improved understanding of the molecular basis for a collection of disorders termed 'channelopathies', including the familial myotonias and periodic paralyses. In epilepsy, different types of rare seizure disorders are now known to be inherited in either an autosomal dominant or autosomal recessive pattern. Mutations have recently been identified in a widely distributed sodium channel, SCN1A in an inherited form of epilepsy, Generalized Epilepsy with Febrile Seizures Plus type 2 (Escayg et al., 2000). The underlying mechanisms have now been clarified for febrile seizures inherited in an autosomal dominant pattern and have been linked to a point mutation in the beta subunit of voltage-gated sodium channel (Wallace et al., 1998). Identification of the mutant genes underlying rare forms of human epilepsy could facilitate recognition of molecular targets and the development of new treatments, for example, drugs acting on potassium channels to enhance potassium current and inhibit seizures. In other areas, the study of genetically determined dysfunction in ion channels has been productive. Several channelopathies with know genetic alterations have been identified in diseases as phenotypically diverse as familial hemiplegic migraine, episodic ataxia, benign neonatal epilepsy type I, and congenital myotonia. These can affect calcium, potassium or chloride channels, with molecular alterations ranging from point mutations, to prematurely truncated proteins, to pathological expansion of terminal sequences (Nappi et al., 2000).

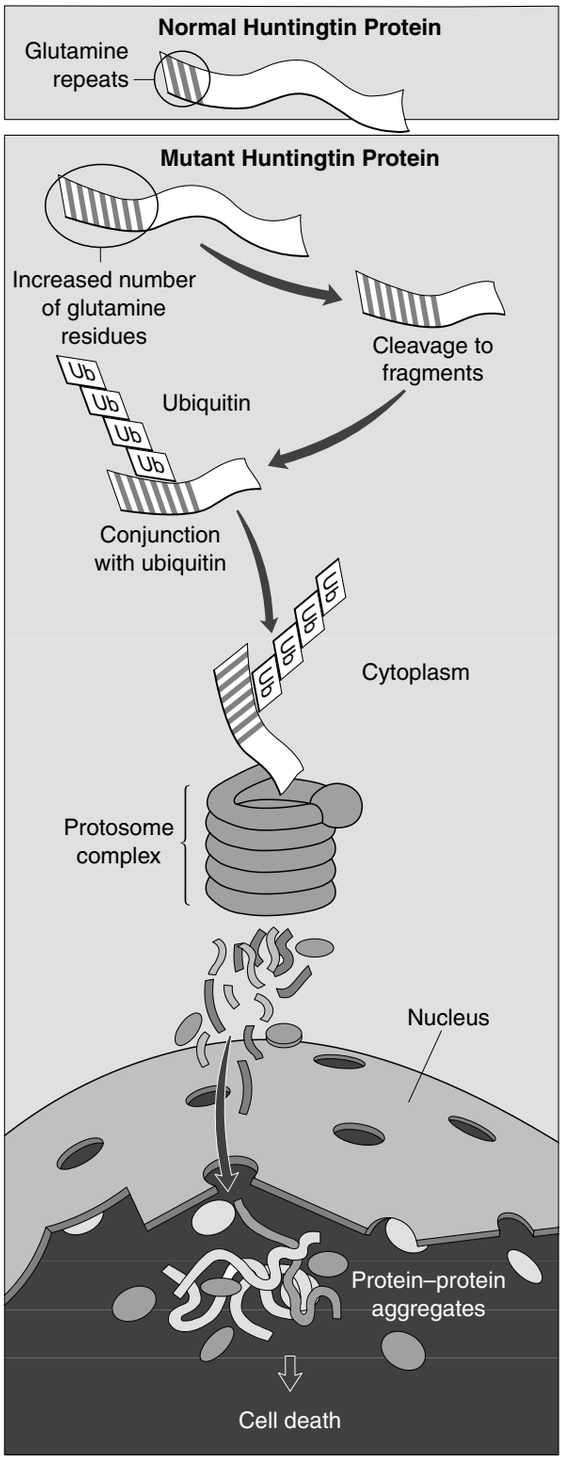


Fig. 1.2. Proposed mechanism of huntingtin-induced death of neuronal cells. The mutant huntingtin protein produced by an increase in the number of CAG repeats in the DH gene is cleaved to fragments that retain the increased number of glutamine residues. These fragments are conjugated with ubiquitin and carried to the proteasome complex. Subsequent cleavage is incomplete, and components of both huntingtin and the proteasome are translocated to the nucleus, where aggregates form, resulting in intranuclear inclusions. Over time, this process leads to cell death. (From Martin, 1999.)

With the description of the neurotoxicity of glutamate in 1957, there has been an explosion in our understanding of the biology of neurotransmitters in the CNS. Much of this work has focused on glutamate, the principal excitatory neurotransmitter, and its inhibitory counterpart gamma-amino butyric acid (GABA). To date, five high-affinity glutamate transporters have been cloned, with differential cellular and anatomical localization. In addition to its neurotoxicity, glutamate plays important roles in synaptic plasticity, learning, and development (Maragakis & Rothstein, 2001).

The molecular pathways underlying learning, memory and drug addiction have begun to converge with the recognition that drugs of abuse can cause long-lasting neural changes in the brain (Nestler, 2001).

The impact of stem cells for neurological diseases

Most of us were brought up with the concept that individuals are born with all of the neurons that they are ever going to have, and that neurons are gradually lost with aging. This concept has now been clearly proven wrong, at least for specific areas of brain such as the hippocampus. The adult brain and spinal cord contain neural stem cells that have the capacity to form neurons, astrocytes, and oligodendrocytes from cells in the ependyma and subventricular zone. Although widely viewed as a 'new' observation, in fact progenitor cells were identified in the periventricular zones in the 1950s. What functional significance this neurogenesis has in later life for the processing of memories or in response to injury remains to be determined. In addition, marrow stroma cells transplanted to the brain are able to generate astrocytes (Kopen et al., 1999). Cell lines developed from pluripotent human fetal or embryonic stem cells have now been developed (Shihabuddin et al., 1999), and successful transplantation has been achieved in animal models of Parkinson's disease, motor neuron disease, and spinal cord injury. The

long-term efficacy of such treatments, particularly in Parkinson's disease, is a particularly active area of investigation. Stem cells are usually derived from aborted fetuses or embryos, and in the USA, ethical concerns have effectively halted the public funding of stem cell research using these embryonic stem cells. The field of stem cell transplant has achieved even greater promise, both scientifically and politically, through the recognition that pluripotential embryonic stems cells can develop into a wide range of differentiated tissues, including neurons and muscle cells. Although embryonic stem cells appear to proliferate much more efficiently than adult stem cells, these cells are being actively developed and may avoid some of the ethical issues of the use of embryonic tissue. There are many questions still to be answered regarding the relative potential of embryonic stem cells and adult-derived progenitor cells. The exciting possibility exists, however, that these cells could be used as therapeutic agents, either as cell transplants, as sources of trophic factors or gene products to modify neurodegenerative processes in the brain or spinal cord. Functional recovery has been achieved in damaged spinal cords with some restoration of neurological function after injury (Kocsis, 1999) and early human trials have been completed in stroke with positive results.

The development of animal models

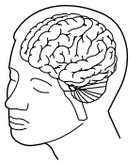
Animal models have, of course, been available for the study of neurological diseases for many years. These models usually occurred spontaneously and were utilized when an astute observer realized their implications for neuroscience research. The development of molecular biological techniques has allowed the insertion and removal of genes at the will of the investigator, particularly in easily manipulated species like the mouse and the fruit fly. This has permitted the development of reproducible animal models of common neurological diseases. Transgenic animals engineered to express human genes linked to Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease have produced critically valuable advances in our understanding of the pathophysiological mechanisms. Although the exact pathophysiological mechanisms of Alzheimer's disease remain unclear, several transgenic animal models have already been used to delineate discrete pathways of injury. The application of transgenic technology should allow us to modify tumour-suppressor genes and to test pharmacological, biological, or genetic manipulations to prevent progression or even reverse the neurological disease. Small animal models will also allow for the efficient testing of new therapies for PD and other chronic neurodegenerative disorders. For example, in Parkinson's disease, animal models have been developed in the fly and mouse, which duplicate many of the cardinal features of Parkinson's disease (Fig. 1.3) (Dawson, 2000). Transgenic mice or flies over-expressing alpha synuclein develop pathology within dopamine neurons and age-dependent motor deficits (Masliah et al., 2000; Feany & Bender, 2000). Shimura et al. (2001) showed that the products of two genes, Parkin and alpha-synuclein, functionally interact and may lead to Parkinsonian degeneration.

A genetic model of Tauopathies has been developed by expressing human wild type and mutant Tau in the nervous system of the fruit fly. Transgenic flies die early after developing progressive neurodegeneration, but, at least in this model, show no signs of the large filamentous aggregates of Tau that compose neurofibrillary tangles (Wittmann et al., 2001).

Even more complex functions and neurological disorders can now be evaluated in large animal models. These have traditionally been used for physiological experiments, but are now being developed for the study of neuropsychiatric disorders such as schizophrenia. For example, by disrupting the development of fetal pigs brains chemically with a toxin that impedes cell division, pathological changes can be induced that mimic the abnormalities evident in the brains of some schizophrenics (Anon, 2001).

Mechanisms of cellular injury

Work since the last edition of this book has delineated more clearly how neurons and astrocytes may be injured during neurological diseases. The role of excitotoxic substances including glutamate has been studied extensively and the 'traditional' dichotomous model of two forms of cell death (necrotic or apoptotic) has been challenged. Substantial advances have been made in understanding the pathophysiological mechanisms underlying neuronal cell death in diverse neurological disorders. Great efforts have been made both in dissecting the cellular mechanisms mediating neuronal death, and in developing therapeutic strategies to prevent this, broadly defined as 'neuroprotection'. The two basic mechanisms of neuronal death, necrosis and apoptosis (or programmed cell death), have been extensively researched. In excitotoxic cell death, exposure to exogenous toxic substances, including glutamate, leads to an energy-independent cell destruction. Glutamate exposure can trigger neuronal death within the brain and has been implicated in the pathogenesis of numerous CNS diseases, including ischemic brain injury,



Human	Mouse	Fly
Age-dependent onset with chronic progression	Age-dependent onset – unknown	Age-dependent onset with chronic progression
	Inclusions get larger with age	
Dopamine neuronal cell loss in select brain regions	Dopamine neuronal cell injury	Dopamine neuronal cell loss
Lewy bodies (cytoplasmic inclusions containing α-synuclein and ubiquitin with a core and radiating fibrils)	Cytoplasmic inclusions (containing α-synuclein and some ubiquitin without fibrils); nuclear inclusions	Cytoplasmic inclusions (containing α-synuclein with fibrils; ubiquitin not determined)
Motor deficits	Motor deficits	Motor deficits
Mitochondrial complex 1 deficits	Unknown	Unknown
Increased markers of oxidative stress	Unknown	Unknown

Fig. 1.3. A comparison of animal models of PD. Recent molecular advances have enabled the engineering of mice and flies that carry wild-type or mutant versions of the protein α-synuclein, which is implicated in PD. A comparison of the features of the fly and mouse animal models of PD and how they correlate with the characteristics of the disease in human patients is shown. (From Dawson, 2000.)

amyotrophic lateral sclerosis, trauma, and seizures (Choi, 1988). NMDA receptors appear to be critical in acute glutamate neurotoxicity, for example, in ischemic brain injury. Hypoxic–ischemic brain injury may lead not only to excitotoxic cell death, but also to apoptosis or programmed cell death wherein cells die with negligible inflammation. Lee and Choi (Lee et al., 1999) have proposed that ischemic brain injury most likely represents an 'admixture' of morphologic features of both excitotoxicity and apoptosis. In apoptosis, caspase activation results in cell death through the destruction of critical molecules and the activation of others which mediate an energy-dependent 'suicide programme'. Mediators of apoptosis have been defined and several genes identified, including a family of 'cell death' sustained proteases, the caspases. Activation of caspase1 occurs in diverse models including cerebral ischemia, cerebral trauma, and neurodegenerative diseases such as ALS and Huntington's disease (Hara et al., 1997; Ona et al., 1999). Caspase inhibition may therefore be yet another avenue for targeted therapies, both for acute and chronic neurological disorders. Caspase activation also occurs in cerebral trauma, amyotrophic lateral sclerosis and Huntington's disease. Caspase pathways are activated in territories subjected to moderate hypoxia and lead to apoptotic cell death over a more prolonged period than that occurring with necrotic cell death. The importance of this is that apoptosis can be aborted either by timely reperfusion of the brain or by caspase inhibition (Friedlander, 2000). Despite the clear effectiveness of NMDA antagonists in experimental models of stroke, numerous clinical trials have unfortunately failed to show any clinical efficacy. Rather than being the result of faulty trial design or poor outcome measures, it seems more likely that other forms of cellular injury may play critical roles in ischemic brain injury. These may include AMPA/kainate receptor-mediated toxicity and extracellular zinc.

An important new concept in pathology is the description of the role of inflammation in diseases previously thought not to involve an inflammatory component. For example, in Alzheimer's disease there are now clear descriptions of local microglial activation, cytokine release, reactive astrocytosis and a multiprotein inflammatory response (McGeer & McGeer, 1995; Eikelenboom et al., 1994). Whether these responses are critical, or simply reflect an epiphenomenon, remains to be determined, but

already clinical trials of anti-inflammatory agents are in progress, and their results eagerly awaited.

Multiple sclerosis has traditionally been referred to as an inflammatory demyelinating disease and most of us were taught in medical school that it 'spared CNS axons'. Though degeneration of axons in multiple sclerosis lesions was first recognized by Charcot in 1877, recent elegant work has reinforced the frequency with which axonal transection and both neuronal and axonal loss occurs in multiple sclerosis. Axonal pathology has been identified as a determinant of irreversible disability (Matthews et al., 1998; Davie et al., 1995). This has led directly to change in treatment philosophy, ie, to begin treatment early before there is irreversible axonal injury. Refinement of non-invasive MR-based techniques to quantify underlying pathological lesions in MS will be relevant to the rational development of new treatments.

Plasticity in adult brains

In the past three decades, there has been an increased understanding of the synaptic and molecular basis of plasticity within the adult human brain. Current research indicates that experience-dependent plasticity may not decrease dramatically with age, as had previously been thought. This research may produce effective remediation for neurological impairments following trauma, stroke, or surgery. Functional magnetic resonance imaging has been widely used to examine the neural mechanisms underlying the acquisition of skilled behaviours. In epilepsy, the development of circuitry with recurrent excitatory synapses has emerged as common to numerous experimental models of epilepsy and could potentially occur within the sclerotic hippocampus of humans (McNamara, 1999).

Dendrites may have the capacity to synthesize proteins, thus could modulate the strength of connections between neurons, ultimately influencing neural activities including learning and memory. Protein synthesis occurs in intact dendrites, and this local protein synthesis could facilitate the ability of synapses to make synapse-specific changes (Aakalu et al., 2001).

Information processing and computational neuroscience

The ability to store, integrate and rapidly analyse large amounts of data has been a crucial advance in facilitating the progress in areas such as genomics and imaging. Data management, data handling, and statistics have all advanced to a point where more than adequate computational power is available on the average laptop computer. In addition, the Internet has revolutionized how most neuroscientists access, publish and disperse information, making use of large publicly available databases. One exciting application is the potential for the Internet to enhance remote or long-distance collaborations, without the need for travel or telephone communications. Systems are now in place which can permit the control of experimental equipment remotely in real time. For example, the Great Lakes Regional Center for AIDS Research facilitates telemicroscopy, distance learning, and video conferencing with real-time document and image sharing (Teasley & Wolinsky, 2001).

The objectives of computational neuroscience span the development of alternative test systems to model biological processes to the working of physiological systems, such as explaining how the brain might process information. This field has obviously been advanced by the revolution in affordable computers, which can be applied to produce neural networks and artificial intelligence, or systems which 'learn' how to address a neurobiological problem. The concept of neural networks has increasingly focused on attempts to understand complex human behaviour. For example, complex human memory is likely mediated by assemblies of interconnected neural networks with different components contributing towards memory function and dysfunction. At the same time, our patients and non-scientists have become our partners because they have the potential to tap into the same information sources as clinicians and scientists. In this new era, there is increasing need for clinicians and investigators to be sources of understandable, accurate and unbiased information.

Advances in neuroepidemiology and clinical trials

Here, neurological clinical trials research has advanced on several different fronts. At a national level in the USA, programmes and resources sponsored by the NIH to train and develop well-trained clinical researchers have been expanded. One example of this is the NIH-funded K23 programme, which is designed to foster the career development of clinician–investigators in patient-oriented research. The widespread application of evidence-based neurology in the past two decades has greatly improved clinical practice, the quality of patient-oriented neurology publications and the education of neurologists. Many neurological therapies and interventions have been submitted to rigorous and systematic analyses and meta-

analyses to examine both the efficacy and effectiveness of therapies. Detailed literature reviews and practice guidelines have been developed for most neurological disorders and their treatments through mechanisms such as the *Cochrane Review* and the *American Academy of Neurology.*

The design of clinical trials has improved markedly with the more accurate modelling of sample size calculations to ensure that clinical trials are adequately powered to show statistically significant differences, where they exist. The interactions of neuroscientists and statisticians have led to new strategies to more efficiently test new therapies in controlled clinical trials. As an example, it is now recognized by clinical trialists that even small overestimates in the efficacy of an intervention can lead to a significant reduction in the statistical power of a trial. Cost-effectiveness modelling techniques can be used to better define minimum clinically important differences (Samsa & Matchar, 2001). Finally, new outcome measures have been developed and refined both for the study of central and peripheral nervous system disorders in clinical trials. For example, in multiple sclerosis, clinical trials now routinely incorporate magnetic resonance imaging as one of the important outcome measures. In the study of painful peripheral neuropathies, skin biopsy, a technique originally developed in the 1960s has now been 'rediscovered' and is now being used as an outcome measure in trials of regenerative agents for sensory neuropathies.

Some of the great successes in clinical neurosciences have actually been in prevention with the development of effective vaccines. Thus, we rarely encounter poliomyelitis, postrubella mental retardation, or postinfectious demyelination after measles (at least in the developed world). Recognition of risk factors and changes in life style have led to a significant decline in cardiovascular and cerebrovascular diseases, but strategies for preventing or delaying neurodegenerative diseases are still lacking. Possible protective effects of estrogens, antioxidants, and non-steroidal anti-inflammatory agents for neurodegenerative diseases are promising, but firm recommendations can still not be made.

The ultimate value of deciphering pathophysiological processes at a molecular level will arise in the development of targeted therapies. These should both reduce toxicity and permit a direct attack on disease process. Examples include the development of Herceptin, a 'monoclonal antibody', which has been proved useful for treatment of metastatic breast cancer which has been linked to the over-expression of the HER-2 allele. More recently, a targeted treatment for CML has been approved which blocks the expression of AB-1, a 'tumour promoting gene' (Druker et al., 2001). Gene and cell-based therapies are being developed for stroke, anoxic brain injury and other neurological disorders. In global ischemia models in gerbils, it appears that new neurons are produced within the hippocampus, raising the possibility that recovery after brain ischemia may, in part, reflect neurogenesis (Frank R. Sharp, University of Cincinnati, personal communication 2001). Fetal stem cells have been implanted in rodent models and continue dividing for several weeks. Cell lines in a marmocet model of stroke have restored some functional recovery (Svendsen & Smith, 1999; Ostenfeld et al., 2000).

At the same time, clinical research has come under closer scrutiny. Potential conflicts of interest by investigators, adequacy of informed consent procedures and the adequacy of monitoring of ongoing studies are subjects of concern, not only among investigators, but among the general public as well. As we proceed into the intervention phase of neurologic disease research and care, it is essential that investigators maintain their credibility for accurate, unbiased clinical research trial design, implementation and interpretation.

Therapeutic impact of translational neurosciences research

The concept of translational research, the delivery of laboratory discoveries to patient-oriented applications has many examples in neurological diseases. One increasingly important aspect of translational research is the development of new therapies, focused on pathogenic mechanisms. There are now FDA-approved agents for neurological diseases for which, until recently, we had no therapeutic options. These include Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis, with agents that, at least for ALS and MS, are truly 'disease modifying', rather than symptomatic. One intervention which has changed clinical practice substantially is the introduction of TPA in appropriately selected patients with acute ischemic stroke. Acute ischemic strokes are now considered, like myocardial infarction, as 'brain attacks' requiring urgent evaluation and consideration for specific treatment. In stroke, the concept of neuroprotection has been tested successfully in ischemic animal models, but has failed to translate successfully to human trials. In fact, the last 15 years have seen a series of failures for a variety of treatments for ischemic stroke. Some of these failures may have been due to underpowered trials, or incorrect estimates of treatment effect (Samsa & Matchar, 2001) In Alzheimer's disease, transgenic models have been used to probe possible effectiveness of disease-modifying therapies, including inhibitors of beta secretase, the enzyme