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Neurology

Neurology

A Queen Square Textbook

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Second Edition

WILEY

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In memory of my beloved parents and elder brothers, whose blessings I count on and keep me moving.

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Foreword

The dilemma of rapidly emerging fields is that reviews are often outdated before they are printed. To make a contribution that would endure, we knew we had to go beyond a snapshot of the current state of fragment-based drug discovery and instead provide a framework for upcoming advances. To achieve this goal, we needed to convince leading scientists to take time from their busy schedules to write chapters. Fortunately, nearly all those we approached agreed; and what you hold in your hands is a virtual, although not comprehensive, "Who's Who" in fragment-based drug discovery. We are extremely grateful to all of our contributors for the quality of their chapters.

One striking feature of this book is that more than half of the chapters come from industry-based researchers; and even many of the academic contributors have close ties to industry. It has been alleged that the best science is done in academia; this book proves that this is not necessarily the case. Part of the reason may be that many of the techniques involved require expensive equipment and infrastructure as well as large collaborations between scientists from disparate disciplines – collaborations that would be difficult to set up outside industry. The multidisciplinary nature of fragment-based approaches shows in this volume: contributors include computational chemists, NMR spectroscopists, X-ray crystallographers, mass-spectrometrists, as well as organic and medicinal chemists.

Although fragment-based strategies for drug discovery have now pervaded laboratories across the world, the ultimate success of any drug discovery technology is measured in the quantity and quality of drugs that it produces. Fragment-based drug discovery has only been practical for the past decade, too soon to expect it to produce marketed drugs; but we believe these will come in time. Moreover, many of the techniques and concepts described in this book will alter drug discovery endeavors in subtle, tangential ways. Ideally, readers will be inspired to improve the methods described here, or even to develop fundamentally new methods for fragment-based drug discovery. But even if this book only changes the way medicinal chemists approach lead optimization, or persuades them to look more closely at weak but validated hits, it will have served its purpose.

Basely, March 2006

Wolfgang Jahnke
Daniel A. Erlanson

Part IV

Summaries and Visions

Bold Glance into the Future–Where no Man has Gone Before

6

Movement Disorders: Soviet Cinema and the Coming of Sound

Kailash Bhatia[1], Carla Cordivari[2], Mark Edwards[1], Tom Foltynie[1], Marwan Hariz[1], Prasad Korlipara[2], Patricia Limousin[1], Niall Quinn[1], Sarah Tabrizi[1] and Thomas Warner[1]

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Movement disorders are common causes of disability, especially in older people. They either cause poverty of movement or unwanted, involuntary movements. Much early work in the field was pioneered by Kinnier Wilson and Purdon Martin at The National Hospital, and many others elsewhere. David Marsden, in London and Stanley Fahn (the Neurological Institute, New York) founded the Movement Disorder Society and its journal *Movement Disorders*. It typically subsides or lessens with movement, to reappear after an interval when a new static position (e.g. arms outstretched) is achieved ('re-emergent tremor'). A number of patients can additionally, or instead, display a faster postural tremor. A classic rest tremor, particularly if accompanied by a jaw tremor, is a strong pointer to PD or drug-induced parkinsonism, but this combination can also be seen in dystonic tremor. Classic rest tremor is uncommon, and jaw tremor rare, in other degenerative forms of parkinsonism. To the above triad a fourth 'cardinal' motor feature of parkinsonism is sometimes added – postural abnormality. A classic rest tremor, particularly if accompanied by a jaw tremor, is a strong pointer to PD or drug-induced parkinsonism, but this combination can also be seen in dystonic tremor. These include particularly the pigmented brainstem monoaminergic nuclei, the substantia nigra (dopaminergic) and locus caeruleus (noradrenergic). However, the pathology is usually much more widespread, also involving serotonergic raphe nuclei, dopaminergic mesolimbic, mesocortical and tubero-infundibular pathways, the cholinergic nucleus basalis of Meynert (NBM), the cerebral cortex, the hypothalamus, the dorsal motor nucleus of vagus, the olfactory tract and sympathetic ganglia. It typically subsides or lessens with movement, to reappear after an interval when a new static position (e.g. arms outstretched) is achieved ('re-emergent tremor'). A number of patients can additionally, or instead, display a faster postural tremor. Classic rest tremor is uncommon, and jaw tremor rare, in other degenerative forms of parkinsonism. A classic rest tremor, particularly if accompanied by a jaw tremor, is a strong pointer to PD or drug-induced parkinsonism, but this combination can also be seen in dystonic tremor. To the above triad a fourth 'cardinal' motor feature of parkinsonism is sometimes added – postural

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abnormality. This chapter provides an overview of the different forms of parkinsonian and dyskinetic disorders[1].

6.1 Level 1 Heading

6.1.1 Level 2 Heading

Akinesia is the defining and principal disabling feature of parkinsonism (Table 6.1). It is a symptom complex, comprising slowness of movement (bradykinesia), poverty of movement and small amplitude of movements (hypokinesia), difficulty initiating movement or with simultaneous motor acts and, most specifically, fatiguing and decrementing amplitude of repetitive alternating movements, which distinguish true akinesia from pyramidal or cerebellar slowing. Almost all individuals with parkinsonism also display muscular rigidity to passive movement across a joint. Unlike spasticity, it is fairly equal in flexors and extensors, and may feel like bending a lead pipe; the presence of additional tremor (which may not be visibly evident) can add a ratchety 'cogwheel' feel to the rigidity (tremor alone can cause cogwheeling, but without rigidity).

Tremor is an optional feature of parkinsonism, and indeed of Parkinson's disease (PD) itself. Up to 80% of PD patients will display a tremor at some stage. Classically, this is in the form of a 4–6 Hz rest tremor which, in the hand, is 'pill-rolling' with flexion of the thumb. It typically subsides or lessens with movement, to reappear after an interval when a new static position (e.g. arms outstretched) is achieved ('re-emergent tremor'). A number of patients can additionally, or instead, display a faster postural tremor. A classic rest tremor, particularly if accompanied by a jaw tremor, is a strong pointer to PD or drug-induced parkinsonism, but this combination can also be seen in dystonic tremor. Classic rest tremor is uncommon, and jaw tremor rare, in other degenerative forms of parkinsonism. To the above triad a fourth 'cardinal' motor feature of parkinsonism is sometimes added – postural abnormality. Flexed posture may or may not be evident early in the disease, and postural instability is typically a late feature in PD, so this item is not usually useful for diagnosing PD, although if present early on can point to alternative causes of the syndrome.

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1 Enthusiasm for bioprospecting as incentive for conservation in the tropics peaked in 1991 when pharmaceutical giant Merck signed a 10-year, $1.3 million deal with the Costa Rican National Biodiversity Institute (INBio). But, InBio notwithstanding, bioprospecting has largely failed to deliver on its promises of both profits and conservation(Castree 2003; Mateo *et al*. 2001; Firn 2003; Burtis 2008; Dalton 2004; Clapp & Crook 2002). This is in part because the rates of discovery of viable biochemical compounds for medical research are extremely low, with the vast majority of natural products found in plants and microbes unlikely to contain the potent biological activity needed for pharmaceutical use (Firn 2003, 212). In drug development from natural products, only between 1 in 10,000 to 1 in 40,000 compounds screened is likely to yield a marketable product, and of those compounds that do reach clinical trials, fewer than 1 in 4 will be approved as a new drug (Clapp & Cook 2002). Others suggest that the conservation goals and poor business acumen of environmentalists further harm the economic viability of bioprospecting (Clapp & Crook 2002, Burtis 2008). A dedication to benefit sharing with local indigenous populations, for example, is cited as a significant contributor to Shaman Pharmaceutical's bankruptcy in 2001 (Clapp & Crook 2002). In a similar vein, Dalton (2004) suggests that the push for benefit-sharing agreements by indigenous populations has de-incentivized participation by large pharmaceutical investors (see also Burtis 2008). Others cite bureaucratic barriers in the post-Rio context as disincentives to profitable bioprospecting (See Dalton 2004).

Table 6.1 UK PDS Brain Bank diagnostic criteria for Parkinson's disease.

STEP 1. Diagnosis of a parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) – obligatory
And at least one of the following:
• Muscular rigidity
• 4–6 Hz rest tremor
• Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
STEP 2. Exclusion criteria for Parkinson's disease
History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis
Babinski sign
Imaging evidence of a cerebral tumour or communicating hydrocephalus
Negative response to large doses of levodopa if malabsorption excluded.
MPTP exposure
STEP 3. Supportive prospective positive criteria for Parkinson's disease
(Three or more required for diagnosis of definite Parkinson's disease)
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side of onset most
Excellent response (70–100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Source: Queen Square Brain Bank.

Molecular advances have revealed helpful schemata for classifying the principal degenerative parkinsonisms into alpha-synucleinopathies, including PD, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), and tauopathies, including progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD).

6.1.1.1 Level 3 Heading

- Myokymia of orbicularis oculi, an irritating twitch usually of the lower eyelid, is a normal phenomenon, but sometimes a cause of anxiety. More extensive facial myokymia, with persistent worm-like wriggling of the chin and other facial muscles is more sinister. This is typically caused by intrinsic brainstem pathology such as MS, or a pontine glioma, in both cases it is usually progressive. Facial myokymia is also a hallmark of some inherited ataxias, particularly spinocerebellar atrophy type 3 (SCA3).
- Tics and tardive dyskinesia frequently involve facial or perioral muscles.
- Neuro-acanthocytosis may cause prominent oro-facial dystonia.
- Blepharospasm is a form of focal dystonia affecting orbicularis oculi (Chapter 6). Fasciculation of facial muscles can develop in motor neurone disease (particularly Kennedy's disease).
- Focal motor seizures may affect facial muscles alone in some cases; epilepsy partialis continua (Chapter 7) is a cause of persistent clonic–tonic facial movements, which can be localised and difficult to recognise.

6.1.2 Parkinson's Disease

PD has traditionally been, and continues to be, defined as a clinico-pathological entity, in which progressive levodopa-responsive parkinsonism, without atypical features (see later), is associated, at postmortem, with neuronal loss and the presence of intracytoplasmic, eosinophilic, alpha synuclein containing inclusions known as Lewy bodies in specific central and autonomic nervous structures. These include particularly the pigmented brainstem monoaminergic nuclei, the substantia nigra (dopaminergic) and locus caeruleus (noradrenergic). However, the pathology is usually much more widespread, also involving serotonergic raphe nuclei, dopaminergic mesolimbic, mesocortical and tubero-infundibular pathways, the cholinergic nucleus basalis of Meynert (NBM), the cerebral cortex, the hypothalamus, the dorsal motor nucleus of vagus, the olfactory tract and sympathetic ganglia. The pathological criteria have been correlated in detail with the classic clinical PD phenotype lending support to the continued use of diagnostic criteria as elaborated in 1988 by the Queen Square Brain Bank (Table 6.1).

An analysis of these rare jugular foramen schwannomas found:

- Mean age at presentation was 40 years
- 2 : 1 left : right
- Common symptoms: hearing loss, tinnitus, hoarseness, dysphagia and ataxia, and
- Complete removal in 80%; recurrence in 7%.

Schwannomas arose from the glossopharyngeal nerve in 24%, vagus in 13% and cranial XI in 6%. Postoperative complications included facial and lower cranial nerve palsies occurred in around 25%.

The prevalence of PD in most countries is around 180/100 000. Overall, incidence rises steadily with age with an average age at onset of about 60 years, and fewer than 5% of cases starting before age 40. Despite modern treatment, life expectancy is still reduced, with a standardised mortality ratio of about 1.9.

Clinical heterogeneity has long been recognised within 'PD', and the concept of PD as a single entity has been turned upside down with the identification of individuals and familial kindreds carrying any of a variety of genetic mutations now known to be causally related to PD pathogenesis. For example, mutations in two genes (*alpha-synuclein* and *LRKK2*), or duplications or triplications of *alpha-synuclein*, can cause dominantly inherited or sporadic parkinsonism accompanied by Lewy bodies in the brain. On the other hand, mutations of three recessive genes (*parkin, DJ1* and *PINK1*) can present mainly in younger individuals with clinical PD without Lewy bodies. The list of *PARK* genes and loci is increasing exponentially, with more still to be identified. How many of these should still be called PD is a moot point. The phenotypes of these monogeneic 'PDs', especially of *LRKK2* cases, can be indistinguishable from typical sporadic PD. However, patients with *alpha-synuclein* mutations or triplications have somewhat younger onset, shorter survival and a higher incidence of dementia. *Although alpha-synuclein mutations are rare*, excessive levels of otherwise normal *alpha-synuclein*, as a result of gene duplications or triplications, are sufficient to cause dominantly inherited Lewy body parkinsonism. Furthermore, in meta-analyses of thousands of apparently 'sporadic' PD patients, the strongest whole genome association is with common variation in the alpha-synuclein gene. Evidence is emerging that exogenous fibrils of alpha-synuclein can enter neurones (by a form of endocytosis), and promote recruitment of endogenous alpha-synuclein leading to the formation of Lewy bodies. This reinforces the theory that Lewy body pathology is potentially 'transmissible' from one neurone to the next, as has been observed in the clinical trials of fetal cell transplantation for PD. Another rare cause of monogenic autosomal dominant PD are mutations in the *VPS35* gene.

One important constraint on mutual Si-O solubility in metallic iron can be understood by writing the reaction for dissolution of silica into metal as

$$\mathrm{SiO_2}^{\mathrm{Ox}} + 2\mathrm{Fe}^{\mathrm{M}} \rightarrow \mathrm{Si}^{\mathrm{M}} + 2\xi\mathrm{FeO}^{\mathrm{M}} + 2\left(1-\xi\right)\mathrm{FeO}^{\mathrm{Ox}}, \tag{6.1}$$

where ξ is the mole fraction of FeO that goes into the metal phase and can be expressed in terms of the equilibrium constant $K_{\mathrm{FeO}}^{\mathrm{M/Ox}}$ for the reaction $\mathrm{FeO}^{\mathrm{Ox}} \rightarrow \mathrm{FeO}^{\mathrm{M}}$ as

$$\xi = \frac{K_{\mathrm{FeO}}^{\mathrm{M/Ox}}}{1 + K_{\mathrm{FeO}}^{\mathrm{M/Ox}}}. \tag{6.2}$$

The recessive forms have younger onset, slower disease progression and present with leg tremor more often than sporadic PD. In independent populations mutations in the glucocerebrosidase (*GBA*) gene can cause either familial or seemingly sporadic PD. A mutation in a single copy is associated with an increased risk of PD, and of dementia within PD. Table 6.2 lists the currently identified *PARK* genes and loci. Overall, monogenic PD accounts for about 6–8% of all PD. However, different genetic causes vary in frequency in different populations (e.g. both *GBA* and *LRKK2*-related parkinsonism is particularly common in Ashkenazi Jews and *LRRK2*-related parkinsonsim in North Africans). Overall, incidence rises steadily with age, although recessive forms become less frequent with age.

Table 6.2 *PARK* genes and loci.

Park number	Chromosome	Gene	Inheritance pattern	Clinical features	Comments
PARK1[*]	4q21	*SNCA*	AD	EOPD	Missense mutations, genomic multiplication
PARK2	6q26.2-q27	*Parkin*	AR	YOPD	
PARK3	2p13	Unknown	AD	Classic PD	Unconfirmed
PARK5	4p13	*UCLH1*	?	Classic PD	Unreplicated mutations in a single sibling pair
PARK6	1p36	*PINK1*	AR	YOPD	
PARK7	1p36	*DJ-1*	AR	YOPD	
PARK8	12q12	*LRRK2*	AD	Classic PD	
PARK9	1p36	*ATP13A2*	AR	Juvenile parkinsonism, pyramidal signs, dementia	
PARK10	1p32	Unknown	Risk factor	Late onset parkinsonism	Unconfirmed
PARK11	2q37	Unknown	Risk factor	Late onset parkinsonism	
PARK12	Xq21-25	Unknown	X-linked	Late onset parkinsonism	Unconfirmed
PARK13	2p12	*HTRA2*	AD or risk factor	Late onset parkinsonism	Unconfirmed
PARK14	22q12-q13	*PLA2G6*	AR	Early onset parkinsonism-dystonia	
PARK15	22q12-q13	*FBXO7*	AR	Juvenile parkinsonism and pyramidal signs	
PARK16	1q32	Unknown	Risk factor	Late onset parkinsonism	Unconfirmed
PARK17	16q11.2	*VPS35*	AD	Classic PD	
PARK18	3q27.1	*EIF4G1*	AD	Classic PD	Unconfirmed

AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset Parkinson's disease; YOPD, young onset Parkinson's disease (usually before 40 years).
[*] *PARK4* is an erroneous locus; the family was subsequently proven to have an *SNCA* triplication (i.e. *PARK1*).

Molecular advances have introduced alternative schemata for classifying the principal degenerative parkinsonisms into alpha-synucleinopathies (Lewy body diseases and MSA), tauopathies (including PSP and CBD), and others (e.g. cases with parkin mutations).

PD has been traditionally defined as a motor disorder, but the frequency and importance of premotor and non-motor features is increasingly recognised.

6.2 Ecologists and Economists Unite!

I found myself to be at Stanford the same time as Partha Dasgupta. And that led to … these evening get-togethers for the first time, on campus, of people in ecology and evolution, and economics. Ken Arrow was [also] there, David Sterritt, I ended up working with both of them quite a bit. Larry Goulder was a young new faculty member. … This was a fun new thing.

I got to know them personally. … I was an early graduate student at the time, and … this never became a focus of my PhD work, but I started getting to know some of the issues and some of the people.

Gretchen Daily, interview

6.2.1 Premotor Features of PD

All neuronal systems have built-in reserves which allow a degree of neuronal loss to be tolerated, and which can be compensated for by up-regulation of surviving neuronal function before a threshold is reached at which point symptoms become apparent. Thus,, Braak *et al.* (2006), based on examination of Lewy body pathology in a large number of brains of individuals with and without clinical parkinsonism in life, postulated 6 'stages' of PD. Thus, back-extrapolation from fluorodopa PET scans can only, at best, tell us when stage 3 might begin. Clinically, constipation, dysphagia, olfactory impairment, cardiovascular autonomic involvement and REM sleep behaviour disorder (RBD) can precede, by many more years, the appearance of the motor disorder in PD. In RBD there is loss of the usual muscle atonia that accompanies dreaming, such that the individual is able to 'act out' usually frightening dreams, often striking or injuring their bed-partner, and often with vocalisations. In one sleep laboratory study, 38% of 29 men with (at that time idiopathic) RBD went on to be diagnosed with a parkinsonian disorder an average of 3.7 years after the diagnosis and 12.7 years after the onset of their RBD.

$$\left(\mathrm{Mg,Fe}\right)\mathrm{SiO_3}^{\mathrm{Br}} + \mathrm{Fe}^{\mathrm{M}} \rightarrow \mathrm{MgSiO_3}^{\mathrm{Br}} + \mathrm{FeO}^{?} + \mathrm{FeSi}^{?}. \tag{6.3}$$

The identification of premotor PD features has led to great interest in the detection of cohorts of individuals with premotor features of sufficient sensitivity and specificity for predicting the future development of PD. The main purpose is to enable trials of candidate neuroprotective agents to be applied as early in the disease process as possible, when they may be most likely to modify the neurodegenerative process.

6.2.1.1 'Typical' Motor Presentation of PD

Most patients with PD only present to medical attention following the onset of the well-known motor features of the disease. PD is classically an asymmetric disease, remaining so throughout its course. It more commonly starts in the arm, with impaired dexterity on fine tasks, and often with a tremor at rest (e.g. holding a newspaper). Other patients present with a tendency to drag one leg or shuffle. The spouse may have noticed a general slowing down, a change in facial expression or impaired arm swing. Direct questioning may reveal a change in voice or micrographia, but these symptoms as presenting complaints are less common, and raise the possibility of atypical disease. The patient may admit to aching or sometimes pain in the affected limb, and presentation with or development of a frozen shoulder or worsening back discomfort is well recognised.

Examination will reveal akinesia, usually with rigidity and often tremor, which can be difficult to bring out. The patient should be asked to relax their hands in their lap or over the arms of a chair, and deliberately put under stress by being asked to count backwards with the eyes closed, then repeated with the arms outstretched, then with the fingers in front of the nose. Often the earliest tremor to be observed may be an adduction–abduction tremor of the fingers. Sometimes, the only time a rest tremor is observed is on walking, when reduced arm swing, flexed posture (initially of one arm) and gait abnormality can be seen.

> It made me realize first of all that many of them cared just as deeply as the biologists I knew cared about the natural world, and the future of human well being… they made me appreciate how carefully they had studied a lot of these things…So I slowly came to appreciate what economists can do and what they think about and how useful some of their approaches are. It is not just slapping a price tag on something, but they really have huge sub-disciplines on the effects on different sectors of society, or different types of people in a household of alternative policies. They thought … about much more aspects of environmental problems that I have ever heard of from anybody else. It was clear that we needed to team up. They [the economists] were also missing things…they didn't know the science very well. And they were sceptical of some of the science because of the way it had been presented in the media. But as they got to know us, they were respectful. And soon we became all one group.

Atypical features should also be sought. The 'bedside' examination of eye movements should be normal (except for some limitation of convergence or of up-gaze with normal saccadic velocity), and there should be no evidence of limb or gait ataxia or dysdiadochokinesis, no apraxia and no pyramidal signs. The so-called striatal toe can mimic a Babinski response, but is often present spontaneously or on walking and is not accompanied by other pyramidal features. Sometimes (particularly younger) patients may present with 'dystonic claudication' (exercise-induced leg dystonia) on prolonged walking. Early postural stability or freezing of gait, although sometimes seen in PD, should raise other possibilities. Of note, patients who are unsteady for whatever reason may not swing their arms, and abnormal arm swing is also common in patients with dystonia.

Unilateral PD (stage 1 on the non-linear Hoehn and Yahr scale) progresses, through stage 2 (bilateral), which typically lasts for 5–10 years, until postural instability (stage 3) appears. Over time, fully developed disease (stage 4) develops, and after many years the patient may eventually become chair- or even bed-bound (stage 5). However, this progression is influenced by treatment, so that a patient on chronic levodopa treatment can fluctuate between stage 4 or even 5 when 'off', to stage 2 or 3 when 'on'. Freezing of gait is usually a late feature.

$$\mathrm{FeO}^{\mathrm{Ox}} \rightarrow \mathrm{Fe}^{\mathrm{M}} + \mathrm{O}^{\mathrm{M}} \tag{6.4}$$

and

$$\mathrm{SiO_2}^{\mathrm{Ox}} \rightarrow \mathrm{Si}^{\mathrm{M}} + 2\mathrm{O}^{\mathrm{M}}. \tag{6.5}$$

6.2.1.2 Non-motor Features of PD

Beyond the premotor symptoms, a host of other non-motor features occur in, and can be the most disabling features of PD so should be routinely enquired about:

- Sialorrhoea is particularly a problem in later disease; only a few patients can tolerate centrally acting anticholinergics such as scopolamine because of the risk of confusion, but some can be helped by peripherally acting drugs, or botulinum toxin injections. As this is caused by reduced frequency of swallowing rather than excessive saliva production, simple tricks such as chewing gum to promote swallowing can be effective in controlling this problem.
- Drenching sweats usually occur in levodopa-treated patients, often as wearing off or 'off' phenomenon. They are poorly understood and no effective pharmacological treatment exists, other than adequate dopaminergic replacement. Anxiety, and sometimes panic, can also be a major problem, and can occur acutely in the wearing off or off state.

Box 6.1 In their own words

Primary Deviance: Student Cheating*

Sure I've cheated. Everybody has. I don't make it a habit, but sometimes it's necessary in order to stay competitive. It's kind of like in the NFL or in major league baseball, or something. If everybody is taking steroids, and you're not, it doesn't matter how great an athlete you are, you don't stand a chance. Sometimes you have to cheat just to make things fair.

INTERVIEWER: So, you are a modern-day witch.
SARAH*: First of all, I do not like being called a "witch." I am a Wiccan. I worship Wicca, the goddess of the earth and nature. Some Wiccans believe Wicca is both male and female, but I see her as female.
INTERVIEWER: But, in class when the topic came up, you identified yourself as a "modern-day witch," did you not?
SARAH: Well, yes, but that's only because I knew that the rest of the class wouldn't know the difference between Wiccans and witches and that they didn't know anything about what they were talking about – just parroting what they had seen and heard on TV or somewhere. Plus, in some ways, Wiccans are a form of witch, in that we practice what most people consider to be witchcraft.
INTERVIEWER: So, what is the difference, and why are the two confused by most people?
SARAH: There are lots of different types of witches and warlocks, and different covens believe in different things. I don't profess to know everything about witches or witchcraft. I can tell you about modern-day Wiccans though, and what we believe, or at least what I believe. I don't profess to speak for all Wiccans. Wicca is like any religion – it means different things to different people.

How do the comments of this student reflect primary deviance? If this student had been caught cheating, given a failing grade and expelled from school, do you think he would still view himself as "an honest person and a good student?"

*This interview involved a 20-year-old male honor student at a medium-sized regional state university.

- Urinary urgency and frequency are common, as a result of detrusor hyper-reflexia, and can be helped by a peripherally acting anticholinergic such as trospium.
- Depression, usually minor rather than major, affects about 40% of patients before, at, or after diagnosis. The symptomatology of this minor depression overlaps with abulia, and lack of initiative and drive, which is also common in PD. In numerous studies, depression has been shown to be the most important factor correlating with impaired quality of life, so it should be actively sought, and treated if found. Clinical depression can be treated with nortriptyline, with an SSRI such as citalopram, or with a serotonergic noradrenergic re-uptake inhibitor (SNRI) such as mirtazapine or venlafaxine.
- Pain is also common in PD. It may be a presenting feature or can arise in established disease, often as a wearing off or off phenomenon, sometimes in conjunction with dystonia. It is usually lateralised to the side more affected by PD.
- Cognitive impairment can occur early in PD but is usually a very mild dysexecutive syndrome which is detectable only when specifically sought using neuropsychological tests. As the disease progresses, other cognitive problems can emerge including more obvious disturbances of memory and attention, and presence of hallucinations and visuospatial deficits. After surviving 20 years of disease, 80% of PD patients will have developed dementia (see Dementia in association with Lewy body pathology).

Many of these non-motor features appear only when the patient's dose of levodopa is wearing off, or in the off state, but can represent the patient's biggest problem. Appropriate management is to take measures to minimise time 'off' (e.g. by appropriate adjustment of dopaminergic medications), rather than necessarily resorting to antidepressants or analgesics. A whole range of neuropsychiatric disturbances resulting from the disease or its treatment can also occur (see later).

Box 6.2 Resources

If you are in crisis or you know someone who is hurting, *please* contact these FREE resources.

Resource	Phone number	Website
National Suicide Prevention Lifeline	1-800-273-8255	http://www.suicidepreventionlifeline.org/
Contact: From breaking point to turning point	(972) 233-2233	http://contactcrisisline.org/
Crisis Call Center	1-800-273-8255 OR Text ANSWER to 839863	http://crisiscallcenter.org/crisisservices.html
The Trevor Project (for LBGTQQ youth)	1-866-488-7386 OR Text the word "Trevor" to 1-202-304-1200	http://www.thetrevorproject.org/
Veterans Crisis Line	1-800-273-8255 and Press 1 OR Text 838255	http://veteranscrisisline.net/

Figure 6.1 Hypointensity in the posterior putamen in multiple system atrophy (MSA) (T2-weighted magnetic resonance imaging; MRI T2W). *Source:* Sample text sample text.

Figure 6.2 'Hot cross bun' appearance (arrow) in the pons in MSA (MRI T2W).

6.2.1.3 Monoamine Oxidase B Inhibitors

Selegiline and rasagiline are irreversible inhibitors of monoamine oxidase B (MAO-B), the iso-enzyme responsible for catabolising dopamine to homovanillic acid (HVA). Unlike MAO-A inhibitors, they can safely be given together with levodopa. Used alone in early disease, selegiline has been shown, probably through a mild symptomatic effect, to delay the need for levodopa by about 9 months. Symptomatic effects are modest. Oral selegiline is partly metabolised to metamphetamine, so should be given in the morning to avoid insomnia. Zelapar, a buccally absorbed preparation of selegiline, avoids first-pass metabolism and hence this problem. Otherwise, these drugs have very few side effects when given alone, but can potentiate any of the symptomatic side effects of levodopa. Safanamide, a new MAO-B inhibitor (but also dopamine reuptake and glutamate inhibitor), has recently been licensed for use in the United Kingdom and the EU.

Great publicity surrounded the publication of the DATATOP (selegiline) and the TEMPO and ADAGIO trials (rasagiline) which sought to evaluate whether these agents can have neuroprotective properties. The rasagiline trials adopted a delayed start design deliberately to try to disentangle the known symptomatic effects of these drugs (observed in DATATOP) from possible disease-modifying effects. Although small benefits appeared to emerge as a result of earlier introduction of rasagiline at a dose of 1 mg, the data on the 2-mg dose were negative, casting doubt on the overall reliability of the trial findings, and prompting the US Food and Drug Administration (FDA) to conclude that no neuroprotective effects had been demonstrated.

Figure 6.3 Clinico-genetic correlations in dystonia phenotypes.

When first introduced, at low dosage, dopamine agonists can also have a paradoxical effect of worsening parkinsonism by shutting down endogenous dopamine release, before higher dosages that stimulate the postsynaptic D2 receptors are reached. Agonists are often used in suboptimal dosage, commonly because the patient stops increasing the dosage at the end of a 'starter pack', or because of confusion about what is meant by 'minimum effective dose' – this can be construed as the dose that is effective, but is usually the minimum dose that has any useful effect.

If one oral agonist fails to have any useful effect at maximum dosage, there is usually little to be gained by switching to another. If one agonist is poorly tolerated because of somnolence, one may switch to another, although risking the same problem again.

The coexistence of parkinsonism and dystonia should prompt imaging looking for the presence of metal deposition in the basal ganglia. A range of conditions can cause neuronal degeneration with brain iron accumulation (NBIA) – listed in Table 6.3 and also discussed in section on dystonia. These can be distinguished using genetic tests. Iron deposition is best revealed during T2* sequence MRI, while CT imaging usefully demonstrates basal ganglia calcification. The presence of abnormal deposition in the absence of evidence to suggest iron, calcium or copper deposition, and especially with the coexistence of cirrhosis, should raise the suspicion of hypermanganesaemia, and can be associated with mutations in the SLC30A10 manganese transporter.

6.2.1.4 Diagnosis

The emergence of parkinsonism, dystonia or a tremor in an adolescent or young adult with slurred speech should always raise the possibility of WD, particularly if there is a family history of hepatic, psychiatric or neurological disorder in childhood. Consanguinity should be enquired about. Suspected cases should be referred to an experienced ophthalmologist for slit-lamp examination.

The combination of a movement disorder with emotionalism, a risus sardonicus and a K-F ring makes the diagnosis highly likely but biochemical confirmation is required. Unfortunately, there is still no one single fail-safe test.

A low serum caeruloplasmin level is consistent with WD and is diagnostic when K-F rings are present. Low levels of caeruloplasmin also occur in hereditary acaeruloplasminaemia and Menkes' disease. Some WD heterozygotes have a reduced caeruloplasmin level, while a few WD patients with decompensated liver disease can have normal levels.

Figure 6.4 Classic 'eye of the tiger sign' (central hyperintensity with surrounding hypointensity in globus pallidus) in a patient with neurodegeneration with brain iron accumulation (NBIA) caused by a *PANK2* mutation (MRI T2W).

In females, the oral contraceptive pill can raise an otherwise low level to within the normal range. In WD, a hepatic copper concentration greater than 250 μg/g dry weight is usual. Serum aminotransferase levels are also usually abnormal. However, a lower hepatic copper value does not absolutely exclude WD and long-standing cholestasis can also cause high copper levels. The biochemical results therefore need to be taken in the context of the clinical picture and the histological changes. Although genetic testing is not available as a routine service test, in ambiguous cases it can be extremely helpful to at least screen for the more common mutations. Urinary copper, derived from the free non-caeruloplasmin-bound copper circulating in plasma, is elevated in WD. An excretion rate greater than 100 μg/24 hours (0.6 mmol/L in 24 hours) is considered diagnostic but levels above 40 μg/24 hours can be significant in a neurological presentation. Wide-necked bottles with copper-free disposable polyethylene liners are recommended. Urinary copper excretion after penicillamine loading can be a useful ancillary test.

In neurological cases, brain MRI can show high signal abnormalities on T2-weighted images and low intensity lesions on T1 in the putamen, globus pallidus, thalamus, midbrain, pons and cerebellum. White matter abnormalities are also common and cortical atrophic changes also occur. Proton density MRI sequences can be particularly sensitive. Once WD has been diagnosed, screening of all first degree relatives is essential.

6.2.1.5 Treatment

The first chelation treatment, parenterally administered British anti-Lewisite (BAL), was introduced in 1951. In 1956, John Walshe first reported clinical benefit with penicillamine and half a century of use has confirmed its efficacy in most cases. However, some patients cannot tolerate the drug and about 20% of patients with neurological presentations can deteriorate markedly on its introduction. Regular monitoring with a full blood count and renal function tests is recommended. Adverse events include fever, rash, lymph gland enlargement, neutropenia, thrombocytopenia and proteinuria. Nephrotoxicity, a lupus syndrome, bone marrow suppression, skin changes including elastosis perforans serpiginosa and a myaesthenic syndrome are late complications. Children and pregnant women should be given weekly pyridoxine.

Figure 6.5 Clinical assessment of the choreic patient.

Table 6.3 Neurological examination findings in the choreic patient.

	Peripheral neuropathy	Cerebellar signs	Amyotrophy	Oculomotor dysfunction	Motor impersistence	Tics/ vocalisations	Parkinsonism	Dystonia	Myoclonus	Orolingual dystonia	Psychiatric disorders
Huntington's disease				•	•	•	•*	•*	•*		•
Neuro-acanthocytosis	•	•	•			•				•	•
Macleod syndrome	•	•	•			•					•
Friedreich's ataxia	•	•									
Mitochondrial disease	•	•		•				•	•		
Ataxia telangiectasia	•	•		•							
Spinocerebellar ataxias	•†	•		•							•‡
DRPLA		•									
Prion disease		•							•		
Wilson's disease				•		•	•	•			•
NBIA							•	•			
HDL2						•		•	•		•

DRPLA, dentatorubro-pallidoluysian atrophy; NBIA, neurodegeneration with brain iron accumulation.
* Juvenile and Westphal variants of Huntington's disease.
† Typically SCA2.
‡ Typically SCA17.

Table 1.4 Results for the comparison of processes.

R of functional molecule[a]	Cycle	Catalyst[b]	Conversion (%)	M_n (kg mol_{-1})	M_w/M_n	Reference
CH_3, $CH{=}CH_2$, $(CH_2)_3COOH$	D_4	SR	~90	10–43	–	[87]
$CH{=}CH_2$, $(CH_2)_3NHSi(CH_3)_3$, $(CH_2)_3$-acrylate,$(CH_2)_3$ COOH	D_4	SR	80–90	0.8–1.2	1.4–1.9	[57]
H	D_4	AC	80	8	1.9	[88]
H, CH_3, $CH{=}CH_2$, $(CH_2)_3COOH$	D_4	SR	–	–	–	[89]

a) The chain-terminating agent has the following structure: R–$Si(CH_3)_2$–O–$Si(CH_3)_2$–R, unless stated in the table.
b) SR: sulfonic resin; AC: activated clay.

6.2.1.6 Differential Diagnosis of Huntington's Disease

6.2.1.6.1 Level 4 Heading

Before the advent of genetic testing for HD, diagnosis was based on clinical evaluation and neuropathological examination. Now, genetic diagnosis allows definitive confirmation of the disease. Genotype–phenotype studies have increased our understanding of disorders that can present like HD (HD phenocopies) with similar cognitive, psychiatric and motor features, but are HD gene negative (Table 6.12). HD phenocopies occur in approximately 1% of large genetic screens of individuals with clinical signs of HD. An approach to genetic testing of HD phenocopies is suggested in Figure 6.8.

6.2.1.7 Spinal Myoclonus

Two different patterns of spinal myoclonus are recognised: proprio-spinal myoclonus and segmental myoclonus. Myoclonus is most often positive, but negative myoclonus also occurs.

Table 1.2 Propagation rate constants (k_p) and the selectivity parameters ($\beta = k_p/k_{tr1}$) for the polymerization of ε-caprolactone [95].[a)]

Active species	$\frac{k_p}{L\ mol^{-1}s^{-1}}$	$b = \frac{k_p / k_{trl}}{L\ mol^{-1}}$
…–$(CH_2)_5O^-Na^+$	≥1.70	1.6×10^3
…–$(CH_2)_5$O–Sm[O$(CH_2)_5$–…]$_2$	2.00	2.0×10^3
…–$(CH_2)_5$O–Al$(C_2H_5)_2$	0.03	4.6×10^4
…–$(CH_2)_5$O–Al[$CH_2CH(CH_3)_2$]$_2$	0.03	7.7×10^4
…–$(CH_2)_5$O–Al[O$(CH_2)_5$–…]$_2$	0.50	3.0×10^5
…–$(CH_2)_5$O–AlO_2SB[b)]	0.35	$\approx 10^6$

a) Polymerization conditions: 20°C, THF solvent.
b) Polymerization conditions: 80°C, THF solvent, SBO2: (S)-(+)-2,2′-[1,1′-binaphthyl-2,2′-diylbis-(nitrylomethylidyne)]-diphenolate ligand (A. Duda and A. Kowalski, unpublished results). SB=Schiff's base.

Proprio-spinal myoclonus is characterised by arrhythmic sequences or runs of axial jerks producing flexion or extension of the trunk. Bursts of muscle activity vary from 50 ms to 4 s. EMG jerks arise from abdominal or cervical spinal segments and slowly spread rostrally and caudally at <10 m/s. Cranial muscles are not involved, with the exception of the neck. It can be stimulus-sensitive. It is important to keep in mind psychogenic myoclonus and look for premovement potential in these cases.

Segmental myoclonus is described as regular or irregular repetitive jerks, involving a group of muscles innervated by one or two spinal segments.

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7

Carcinoembryonic Antigen

Marlies Keijzers, Peyman Sarda Nia and Jos G. Maessen

CHAPTER TABLE OF CONTENTS/INDEX

Life is pretty simple: You do some stuff. Most fails. Some works. You do more of what works. If it works big, others quickly copy it. Then you do something else. The trick is the doing something else.

Leonardo da Vinci

Book Title: Subtitle, First Edition. Edited by Author/Editor Name.

In Canto 29, which is set in the ninth sphere of heaven, a *primum mobilum* or crystalline zone beyond space and time (cf. *Paradiso*, Canto 27, 106-117), Dante Alighieri drew on this Thomistic conception of the simultaneous production of the matter and form in an unforgettable account of how the world was created all at once:

> Forma e materia, congiunte e purette,
> usciro ad esser che non avia fallo,
> come d'arco tricordo tre saette.
> E come in vetro, in ambra o in cristallo
> raggio resplende sì, che dal venire
> a l'esser tutto non è intervallo,
> così 'l triforme effetto del suo sire
> ne l'esser suo raggiò insieme tutto
> sanza distinzione in essordire.
>
> Then form and matter, either separately
> or in mixed state, emerged as flawless being,
> as from a three-stringed bow, three arrows spring.
> And as a ray shines into amber, crystal,
> or glass, so that there is no interval
> between its coming and its lighting all
> so did the three – form, matter, and their union –
> flash into being from the Lord with no
> distinction in beginning: all at once [Mandelbaum trans.]
>
> *(Dante Alighieri - 1978)*

Although the poet was describing angelic knowledge of the first creation of the world in abstract, metaphorical terms, the idea of a simultaneous creation of form, matter, and their union was resonate with the visual arts. In the early thirteenth century, a composition was developed for representing the formation of man from the earth without the use of hands. The visual idea was derived from images of Eve rising directly from the side of the sleeping Adam. At Elne Cathedral on a capital (ca. 1200–20) and in a window at Bourges Cathedral (ca. 1210–15), a fresco in the Cloister Church at Wienhausen (1306) and the Grabow Altarpiece by Master Bertram of Minden (1379–83), the creation of Adam was rendered by a living, half-figure of the man rising from a mound of earth or a hole

7.1 Space Heating and Cooling Loads

Define terrorism in accordance with the U.S. Code. Even here there is a bit of divergence, as the code in question, 18 U.S. Code § 2331, recognizes two forms of terrorism: international terrorism and domestic terrorism. Consider the following definitions taken from that code:

1) the term "international terrorism" means activities that—
   a) involve violent acts or acts dangerous to human life that are a violation of the criminal laws of the United States or of any State, or that would be a criminal violation if committed within the jurisdiction of the United States or of any State;

b) appear to be intended—
   i) to intimidate or coerce a civilian population;
   ii) to influence the policy of a government by intimidation or coercion; or
   iii) to affect the conduct of a government by mass destruction, assassination, or kidnapping; and
c) occur primarily outside the territorial jurisdiction of the United States, or transcend national boundaries in terms of the means by which they are accomplished, the persons they appear intended to intimidate or coerce, or the locale in which their perpetrators operate or seek asylum…

2) the term "domestic terrorism" means activities that—
   a) involve acts dangerous to human life that are a violation of the criminal laws of the United States or of any State;
   b) appear to be intended—
      i) to intimidate or coerce a civilian population;
      ii) to influence the policy of a government by intimidation or coercion; or
      iii) to affect the conduct of a government by mass destruction, assassination, or kidnapping; and
   c) occur primarily within the territorial jurisdiction of the United States.

7.1.1 Geothermal Power Plants

7.1.1.1 Overview

The first geothermal power was generated at Larderello, Italy in 1904. According to Lund (2007), the first commercial power plant (250 kW) was commissioned in 1913 at Larderello, Italy. Due to the impurity of the geothermal fluids, steam was generated in a secondary loop isolated from the geothermal fluids by a heat exchanger. In the United States, an experimental 35 kW plant was installed at The Geyers geothermal field, California, in 1932, and provided power to the local. My qualitative interviews showed that FOE groups recognized that they were in a position for potential brokerage. But they also suggest the reasons why FOE offices did not want to take on the broker role in the context of this competitive and divided.

Program Listing 7.1 Definition of the iteration loop subroutine in the file g_DEMSystem.f90

```
subroutine DEMS_iterate(this, numiter)
 implicit none
 class(DEMSystem) this
 integer(IK),intent(in):: numiter ! number of time steps
 . . . some code. . .
 do i=1,numIter
  call this%m_total_timer%start()
  ! pre-iteration adjustments
  call this%m_pre_iter_timer%start()
     call this%preIteration()
  call this%m_pre_iter_timer%finish()
```

```
  ! predicts position and velocity based on the previous
time steps
  call this%m_prediction_timer%start()
     call this%Lin_Integration%predict()
     call this%rot_Integration%predict()
  call this%m_prediction_timer%finish()
  ! finds contacts between particels
  call this%m_ContSearchPP_timer%start()
     call this%Cont_Search%FindContacts()
  call this%m_ContSearchPP_timer%finish()
  ! finds contacts between particles and walls
  call this%m_ContSearchPW_timer%start()
     call this%Cont_Search_PW%FindContacts(this%numPrtcl,
this%prtcl_dpos, this%prtcl_ids)
  call this%m_ContSearchPW_timer%finish()
  ! calculates contact force and torques between particles
  call this%m_ForcePP_timer%start()
     call this%m_cont_force%AllContactForce_PP()
  call this%m_ForcePP_timer%finish()
  ! calculates contact force and torques between particles
and walls
  call this%m_ForcePW_timer%start()
     call this%m_cont_force%AllContactForce_PW()
  call this%m_ForcePW_timer%finish()
  ! calculates linear and angular accelerations
  call this%m_Acceleration_timer%start()
     call this%clc_Acceleration()
  call this%m_Acceleration_timer%finish()
  ! corrects position and velocities
  call this%m_integration_timer%start()
     call this%Lin_Integration%correct()
     call this%rot_Integration%correct()
  call this%m_integration_timer%finish()
  ! moves walls if a wall is moving
  call this%m_Geometry%move_walls(this%prtcl_dt)
  this%iterNumber = this%iterNumber + 1
  ! writes result to the output file (code is not presented
here)
  . . .some code. . .
  call this%m_total_timer%finish()
  ! output to log file and terminal/command window (code is
not presented here)
  . . .some code. . .
 end do
end subroutine
```

In the United States, an experimental 35 kW plant was installed at The Geyers geothermal field, California, in 1932, and provided power to the local. My qualitative interviews showed that FOE groups recognized that they were in a position for potential brokerage. But they also suggest the reasons why FOE offices did not want to take on the broker role in the context of this competitive and divided.

Sidebar 3: What's In Your Genes?

Genes are part of the building blocks of human cells. They are arranged along pairs of chromosomes, and each parent contributes one side of the pair. Some diseases are caused by anomalies in genetic structure. While these anomalies can be inherited from one or both parents, they can also occur with no family history as spontaneous mutations. Breakthroughs in the study of molecular genetics have revealed the specific anomalies responsible for various forms of muscular dystrophy, as well as other inherited disorders such as sickle cell disease, Marfan syndrome, hemophilia, and osteogenesis imperfecta.

Inherited diseases have three variations: they can be autosomal dominant, autosomal recessive, or X-linked disorders.

- **Autosomal dominant** inheritance means that one parent has a defective gene and the other does not. Each child has a 50% chance of inheriting the defective but dominant gene, which causes the disease. Males and females are at equal risk for autosomal dominant inheritance.
- **Autosomal recessive** inheritance means that each parent carries one defective gene, but it produces no symptoms. Each child has a 25% chance of inheriting both defective genes and developing the associated disease. Alternatively, each child has a 50% chance of inheriting only one gene and becoming a carrier for the next generation.
- **X-linked** inheritance means that a woman carries a defective gene on one X chromosome. Each of her sons has a 50% chance of inheriting the faulty gene from her. Each of her daughters has a 50% chance of carrying the faulty gene to her sons. It is rare for females to be severely affected by X-linked diseases. Women who carry these genetic defects are at increased risk for developing some but not all of the characteristics of the genetic disease. Men who have X-linked mutations may pass the genes onto their daughters, who may become carriers, but no sons are directly affected.

Notes

1 We use the terms "domestic" to refer to terrorist attacks where the country location and the nationalities of the perpetrators and targets of the attack are all the same. For example an attack in the United States by a terrorist organization based in the US on a US target is a domestic attack; if the nationality of any of these three elements is non-US we consider it an "international" attack.

2 In their pioneering books *Superhighway Robbery* (Newman & Clarke, 2003) and *Outsmarting the Terrorists*, (Clarke & Newman, 2006) Clarke and Newman demonstrated how Situational Crime Prevention (SCP) could be adapted to explain cybercrime and terrorism respectively and, more importantly, how its unique approach to crime problems could provide detailed accounts of how to respond to these problems and to counter them

2

The Molecular Characterization

Abstract

The molecular characterization of tumor-associated antigens recognized by T cells [1] revolutionized the field of tumor immune biology providing conclusive evidence that CD8+cytotoxic T cells (CTLs) specifically recognize and kill autologous cancer through recognition of molecularly-defined calixarenes is usually explained by the presence cancer-specific elements. Since then a myriad of TAA have been identified that has triggered their utilization as anti-cancer vaccines [2–8].

Keywords *The molecular; characterization; of tumor-associated; antigens*

The molecular characterization of tumor-associated antigens (TAA) recognized by T cells [1] revolutionized the conformational.

2.1 Animal Models for CEA

Delivery of radio-nuclides to tumors using murine and human anti-CEA antibodies has been studied for many years. The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing the delivered therapeutic dose by separating the antibody targeting to the tumor from the subsequent delivery of the therapeutic radionuclide that binds to the tumor-localized antibody. The conformational flexibility of calixarenes is usually explained by the presence of intramolecular hydrogen bonds, which is related to the number of free phenol groups.

Definition 2.1 The position of a body along the x axis, in metres, is given by the equation $x = t^3 - 30t^2 + 5$, where t is the time in seconds. Find its velocity and acceleration as a function of time.

Delivery of radio-nuclides to tumors using murine and human anti-CEA antibodies has been studied for many years. The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing the delivered therapeutic dose by separating the antibody

Instrumental Box 4

Numerical Data Analysis

The incorporation of these techniques has provided a rapid prototyping technique, essential for the commercial development of current minimum feature-sized semiconducting integrated circuits. However, the production of these devices has been achieved at a high price, with the primary challenges currently faced by high-throughput fabrication laboratories including the high cost of laborers and instruments, high-temperature reaction conditions, and a surplus in generated waste [1].

The versatility of biology's incredible portfolio encourages researchers to develop modified syntheses derived from Nature. Hence, their findings have been successfully organized into the field of biomimetics, or bioinspired research technological applications [8].

Source: The versatility of biology's incredible portfolio encourages researchers to develop modified syntheses derived from Nature

targeting to the tumor from the subsequent delivery of the therapeutic radionuclide that binds to the tumor-localized antibody.

Example 2.1 The position of a body along the x axis, in metres, is given by the equation $x = t^3 - 30t^2 + 5$, where t is the time in seconds. Find its velocity and acceleration as a function of time.

Velocity $\mathbf{V} = \dfrac{dx}{dt}$

Acceleration $a = \dfrac{d^2x}{dt^2}$

$$x = t^3 - 30t^2 + 5$$

$$a(t) = \frac{d^2x}{dt^2} = 6t - 60$$

The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing the delivered therapeutic dose by separating the antibody targeting to the tumor from the subsequent delivery of the therapeutic radionuclide that binds to the tumor-localized antibody.

Theorem 2.1 The position of a body along the x axis, in metres, is given by the equation $x = t^3 - 30t^2 + 5$, where t is the time in seconds. Find its velocity and acceleration as a function of time.

Velocity $\mathbf{V} = \dfrac{dx}{dt}$

$$x = t^3 - 30t^2 + 5$$

$$a(t) = \frac{d^2x}{dt^2} = 6t - 60$$

Delivery of radio-nuclides to tumors using murine and human anti-CEA antibodies has been studied for many years [70].

Lemma 2.1 The position of a body along the x axis, in metres, is given by the equation $x = t^3 - 30t^2 + 5$, where t is the time in seconds. Find its velocity and acceleration as a function of time.

Velocity $\mathbf{V} = \dfrac{dx}{dt}$

Acceleration $a = \dfrac{d^2x}{dt^2}$

Proof: Proof for the above Lemma

$$x = t^3 - 30t^2 + 5$$

$$a(t) = \frac{d^2x}{dt^2} = 6t - 60$$

Delivery of radio-nuclides to tumors using murine and human anti-CEA antibodies has been studied for many years [70]. The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing the delivered therapeutic dose by separating the antibody targeting to the tumor from the subsequent delivery of the therapeutic radionuclide that binds to the tumor-localized antibody.

Corollary 2.1 The position of a body along the x axis, in metres, is given by the equation $x = t^3 - 30t^2 + 5$, where t is the time in seconds. Find its velocity and acceleration as a function of time.

Velocity $\mathbf{V} = \dfrac{dx}{dt}$

Acceleration $a = \dfrac{d^2x}{dt^2}$

$$x = t^3 - 30t^2 + 5$$

$$a(t) = \frac{d^2x}{dt^2} = 6t - 60$$

Delivery of radio-nuclides to tumors using murine and human anti-CEA antibodies has been studied for many years [70].

Techniques described in this book Moreover, many of the techniques and concepts described in this book will alter drug discovery endeavors in subtle, tangential ways. Ideally, readers will be inspired to improve the methods described here, or even to develop fundamentally new methods for fragment-based drug discovery. But even if this book only changes the way medicinal chemists approach lead optimization, or persuades them to look more closely at weak but validated hits, it will have served its purpose

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11

Carcinoembryonic Antigen

Decoding the CEA-Related Cell-Cell Adhesion Molecule

The molecular characterization of tumor-associated antigens (TAA) recognized by T cells [1] revolutionized the field of tumor immune biology providing conclusive evidence that CD8+ cytotoxic T cells (CTLs) specifically recognize and kill autologous cancer through recognition of molecularly-defined cancer-specific elements. Since then a myriad of TAA have been identified that has triggered their utilization as anticancer vaccines [2–8].

11.1 CEA Biology

11.1.1 CEA Gene Family, Genomic Localization, Protein Structure

CEA is encoded by the CEA-related cell-cell adhesion molecule 5 (CEACAM5) gene, which belongs to the CEA gene family and in humans consists of 22 expressed members and 12 pseudogenes [3,4]. The CEA family has been subdivided into the CEACAM and pregnancy-specific glycoprotein (PSG) subgroups.

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11.1.2 CEA as a Tumor Marker for Prognosis and Post-surgery Follow-up

11.1.2.1 Animal Models for CEA

Antibody Delivery of Radionuclides, Drugs and Effector Molecules Using Murine and Human Anti-CEA Antibodies Delivery of radio-nuclides to tumors using murine and human anti-CEA anti-bodies has been studied for many years [70]. The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing the delivered therapeutic dose by separating the antibody targeting to the tumor from the subsequent delivery of the therapeutic radionuclide that binds to the tumor-localized antibody. The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing. The use of low molecular weight single chain antibody fragments and pre-targeting has been found to enhance the sensitivity of tumor visualization as well as increasing the delivered therapeutic dose by separating the antibody targeting to the tumor from the subsequent delivery of the therapeutic radionuclide that binds to the tumor-localized antibody.

Student's t-test is the number of replicates sufficient to detect the fold change that you are interested

Welch's test is the number of replicates sufficient to detect the fold because it does not conversion efficiency change that you are interested permutation tests.

Taking the perspective that it is the human activities that require management rather than the biological systems that we disturb, this chapter will describe an adaptive management approach to environmental management.

Step 1: Generate random paths through the graph.
Step 2: Keep only those paths that begin with V_{in} and end with V_{out}.
Step 3: If the graph has n vertices, then keep only those paths that enter exactly n vertices.
Step 4: Keep only those paths that enter all of the vertices of the graph at least once.
Step 5: If any paths remain, say "Yes"; otherwise, say "No."

The versatility of polyurethanes is derived in large part from the wide selection of building blocks available to materials designers.

The adaptive management process is iterative, so that new information on the response of the ecosystem to our management activities is used to improve the next round of decisions. Using technological advancements such as remote sensing and geographic information systems, ecologists can determine the most successful ways to harmonize human disturbances with natural ones and identify feasible biological targets for the system of interest.

CLAUDIO: To make you answer truly to your name.
HERO: Is it not Hero? Who can blot that name With any just reproach?
CLAUDIO: Marry that can Hero!

Understanding the scale of the system and its processes is critical, and using large-scale data sets along with remote sensing can help ecologists determine where the system is, where it needs to be, and whether preservation is the right management decision or if more active restoration or rehabilitation is necessary.

Multiple Choice Questions

Questions Different types of question i.e. Multiple Choice Questions, Extended Matching Questions. Accordingly, calixarenes containing four phenol groups 39a–e exist as cone conformers. These are quite often put on a website but may still be typeset - Requirementsare:

1 Multiple choice questions

For each question below, what is the most likely answer? Select ONE option from the answers supplied.

1.1 Ion Channels and Currents

1.1.1 Potassium

1 In a diagram of AP shown below, which one of the following currents is active where answers arrow is pointing?

A Ito
B IK1
C INa
D ICa

2 In a diagram of AP shown below, which one of the following currents is active where answers arrow is pointing?

A Ito
B IK1
C INa
D ICa

3 In a diagram of AP shown below, which one of the following currents is active where answers arrow is pointing?

A Ito
B IK1
C INa
D ICa

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9 In a diagram of AP shown below, which one of the following currents is active where answers arrow is pointing?

A Ito
B IK1
C INa
D ICa

10 In a diagram of AP shown below, which one of the following currents is active where answers arrow is pointing?

A Ito
B IK1
C INa
D ICa

11 In a diagram of AP shown below, which one of the following currents is active where answers arrow is pointing?

A Ito
B IK1
C INa
D ICa

Glossary

account classification The way in which suppliers of electricity, natural gas, or fuel oil classify and bill their customers. Commonly used account classifications are "Residential," "Commercial," "Industrial," and "Other." Suppliers' definitions of these terms vary from supplier to supplier. In addition, the same customer may be classified differently by each of its energy suppliers.

account of others (natural gas) Natural gas deliveries for the account of others are deliveries to customers by transporters that do not own the natural gas but deliver it for others for a fee. Included are quantities covered by long-term contracts and quantities involved in short-term or spot market sales.

accounting system A method of recording accounting data for a utility or company or a method of supplying accounting information for controlling, evaluating, planning and decision-making.

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Subject index

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