book reviews

Parkinson's disease

By DG Grosset, KA Grosset, MS Okun and HH Fernandez. Manson Publishing, London 2009. 160 pp. £40.00.

This easy-to-read book ably summarises Parkinson's disease (PD), an enigmatic condition with promising genetic and toxic clues that, when solved, may answer other site-specific diseases linked to senescence.

The authors begin by discussing the uncertain epidemiology of the disease as nobody is sure if the incidence is rising, how long the condition has been around, or whether or not it is a disease of affluence – rates in Africa/China are low but may be increasing. What did seem certain was that it is a disease of ageing but incidence peaks at 70 so it is a localised central nervous system senescence that is the problem, not age as such. Non-motor symptoms get emphasised whether dementia, behavioural, mood, autonomic or circadian related, such as the rapid eye movement sleep disorder, that can all antedate the motor symptoms as of course does the pathology (that may not even start in the substantia nigra). Given the typical motor asymmetry, a classic sign of developmental instability, the origins of PD date back to early life history.

Multidisciplinary management of PD has evolved since the landmark discoveries of levodopa replacement and dopamine agonists, including apomorphine. Environment enrichment with 'use it or lose it' and 'low stress but not no stress' hormetic approaches are championed as is PD imaging as a diagnostic aid. Stem/fetal cell and gene therapies are mentioned but are not yet practical. They have, however, taught us that cell implants catch the disease implying that something is wrong initially with the local microenvironment not with the nigral dopaminergic cells. Antioxidant regimes have disappointed but the 50-year-old mitochondrial-radical theory of ageing (and PD) has not been superseded (all PD clues, whether genetic, environmental toxins or biochemical, point in that direction) and improving radical sinks may not work whereas turning off the tap upstream at redox NAD(P)H oxidation sites might. Electrical stimulation of the subthalamic nucleus does work for selected patients and is fully covered here as is apomorphine the chief alternative along with duodopa infusions for dyskinetic and fluctuating patients.

These are striking examples of applied physiological translational research, originally inspired by Claude Bernard, that work in practice and, when combined with the known acquired cellular pathology and recent genetic breakthroughs, perhaps enlightenment is around the corner. If not, there may be a conceptual block to understanding multifactorial diseases in general.

Among the excitement (10 PD genes listed with proposed mechanisms) evolutionary theory spoils the fun as ageing and ageing diseases are not programmed. Rather they are side effects of energy trade-offs made earlier in life to survive/reproduce that led to skimping on reserves or repairs, or when energy levels are high innovative syntheses, that are pleiotropic seeds for later trouble. Stretched energy microenvironments may cause cells to compensate by autocarnivory/autophagy or reversions to energy exporting fermentations, as seen in cancer, creating a fog of pathology hiding its basic bioenergetic and homeostatic nature, with at risk genes relegated to determining the site and age of onset.

Caloric energy restriction, a major clue, involves the nutrient suppliers glucose and nicotinamide forming NADH and utilises nutrient-responsive signalling molecules, that link current and predicted energy levels, using circadian and stress responses, such as NAD consuming SIRT1, mTOR and PGC-1 alpha that regulate metabolic paths and mitochondrial biogenesis.[1] Caloric restriction spares primates (and yeast, worm, fruit fly or rodent) from premature senescence and models of neurological (including PD), metabolic and cancerous disease, suggesting common mechanisms.

Perhaps we need to emerge from disease-specific bunkers, cross-fertilise and engage with the common ecologically derived redox gradients affecting cell differentiation and survival and realise that Darwinian principles during development (the highest rate of neuronal loss happens by apoptosis if connections with the energy environment fail) and during decline (as autophagy or as stem cells are chosen to proliferate) are utilised to stabilise energy landscapes. Parallel Bernardian principles emphasise outer and inner microenvironments viewing ourselves (less anthropocentrically) as super-organisms with co-evolved diets and symbionts with many inner ecosystems and that it is these delicate interfaces that may breakdown rather than the cell first targeted.

While the fog of pathology clears and we delay the onset of diseases of ageing such as PD by attending to bioenergetic inner and outer ecosystem homeostasis, this book, that does not pretend that PD management is simple, is highly recommended as a model of clarity.

ADRIAN WILLIAMS
Professor of clinical neurology
University of Birmingham

Reference

1 Colman RJ, Anderson RM, Johnson SC *et al.* Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 2009;325:201–4.