Annual Review of Medicine, 2021. Mary E. Klotman, Michael S. Parmacek and Howard A. Rockman (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 72. x + 510 pages. Price: US$ 118.

This volume of the *Annual Review of Medicine*, as in previous years, has stimulating and informative commentaries on diverse aspects of major human diseases. The 30 succinct reviews in the volume discuss disease mechanisms, novel therapeutic targets, routes for drug delivery and new approaches for prevention. Articles span recent advances in managing neurological, cardiovascular, pulmonary, gastrointestinal and endocrinal diseases.

The first four reviews relate to neurological disorders. The article by Ravi *et al.* (Johns Hopkins University School of Medicine, Baltimore, USA) provides an update on the various gene-targeting therapies for spinal muscular atrophy (SMA). SMA is associated with a complete loss of the survival motor neuron gene (*SMN1*) and alterations in exon 7 of the paralogous gene *SMN2*, which lead to the production of a truncated SMN protein that is rapidly degraded; these contribute to motor neuron degeneration. Efforts to increase the levels of SMN aim at (i) modification of SMN2 pre-mRNA splicing to facilitate exon 7 inclusion and (ii) *SMN1* gene replacement. Clinically successful gene-directed therapy in patients with SMA target either DNA through gene-replacement or gene-editing strategies and RNA using antisense oligonucleotides, short interfering RNAs or micro RNAs. The authors discuss these approaches and the outcomes of recent and ongoing clinical trials. They also throw light on novel biomarkers for monitoring the progress of the disease.

Ray and Buggia-Prevot (MD Anderson Cancer Centre, Houston, USA) delineate the emerging strategies for the treatment of Alzheimer's disease, thanks to progress in genetics and the lessons learnt from experience with anti-amyloid therapies. The discovery that microglial cells change into disease-associated microglia (DAM) and that apolipoprotein E gene polymorphism and TREM2 (triggering receptor expressed in myeloid cells) are involved in amyloid-independent cognitive decline have led to a search for TREM2 targeted therapies. These therapies are discussed in the article. Small molecules which can be administered orally and thus bypass the microglia are on the horizon. Jansens's JNJ-403465-27, NLRP3 inhibitors, cation channel P2X7 inhibitor and R1PK1 inhibitor seem promising candidates. The suggestion that brain inflammation could exhaust microglia, reducing their ability to convert to a DAM phenotype, has given the impetus for using gingipain inhibitor COR388 in phase-III trials in humans. The authors also introduce another concept of inducing microglia to change their phenotype, reduce amyloid burden and improve memory using gamma oscillations delivered through an external device. The device is already in phase-1 trials. Another futuristic drug target mentioned is the dysfunctional blood-brain barrier in APOE carriers. The article provides an update on various strategies to reduce Tau deposition through immunotherapy using vaccines and efforts to develop drugs to combat neurotoxicity from Tau.

Several neuropsychiatric disorders are associated with cognitive dysfunctions and hence require treatment to improve cognition. Grover *et al.* (Boston University, USA) give us an insight into the recent developments in the attempts to discover drug-free treatment modalities for the managing cognitive brain disorders. Circuit-based therapies for the improvement of cognition seem to be yielding good results. Transient synchronization among distinct brain rhythms is central in the coordination of brain activity. This mechanism forms the basis for intra- and inter-regional coordination of neural activity during cognition. Cross-frequency phase-amplitude coupling (PAC) and within-phase synchronization are responsible for smooth coordination of communication across the brain. Breakdown of any of them may affect the other and result in cognitive disorders. The authors describe the mechanisms underlying cognitive disorders such as schizophrenia, attention-deficit/hyperactive disorder (ADHD) and autism-specific disorders and speculate that targeting atypical synchrony patterns could improve the precise timing of communication among dysfunctional brain networks and thus increase cognition. Brain dynamics could be perturbed through transcranial alternating current stimulation (tACS), which is a promising technique for neuromodulation. Given the anatomical and physiological differences across individuals and the state of the brain during neuromodulation, a personalized approach is advocated. tACS is region-specific. Strategies for manipulation of inter-regional synchronization and cross-frequency PAC are currently under evaluation. The authors also discuss the issues that remain to be addressed in technologies for non-invasive neuromodulation.

There is strong evidence for the importance of physical exercise in treating mental health disorders. Those who exercise regularly seem to have protection from mental disorders, anxiety or depression. Experimental studies with aerobic and resistance training have indicated improvement in overcoming depression and anxiety-related problems. Smith and Merwin (Duke University Medical Centre, Durham, USA) provide an extensive review of the epidemiological studies that reveal a link between physical activity and mental health, and of treatment data on exercise interventions in patients with depression and anxiety. They also indicate directions for future studies to refine exercise-related treatment approaches.

There are six articles on novel therapies. Naggie and Lok summarize the limitations of current therapies for hepatitis B virus (HBV) infection and explain new approaches to HBV cure. The new agents with unique mechanisms of action comprise targeted antivirals and immunomodulatory agents, including vaccines. Hirten and Sands (Icahn School of Medicine at Mount Sinai, New York, USA) point out the promising treatment approaches for ulcerative colitis. Inhibitors of Janus kinase and phosphodiesterase, sphingosine receptor modulators, anti-adhesion molecules and anti-interleukin antibodies are the hopeful drugs for ulcerative colitis. The authors indicate that foecal microbiota transplantation and hyperbaric oxygen may evolve as useful adjuvant therapies. Thompson and Powell (Johns Hopkins University School of Medicine) examine the potential of adenosine pathway inhibition to bolster cancer immunotherapy. They review the status of clinical trials targeting multiple constituents of the adenosine pathway. These trials employ anti-CD73, A2aR antagonists, dual A2aR/A2bR inhibitors and anti-CD39, anti-CD38 as well as approaches combining adenosine blockade with blockade of the immune check-point. Early results of clinical trials, however, reveal only modest results.

Yet another new therapy on the horizon targets mutations in the viral oncogene RAS (rat sarcoma). RAS mutations are the best known and most prevalent genetic alterations in human cancers. Kirsten RAS (KRAS) is the most frequently mutated (about 85% of all cancers) among the three RAS isoforms. Several novel, small, covalent molecules that specifically inhibit KRAS, are being developed. Early phase

trials reveal that inhibitors such as AMG 510 and MRTX849 have potential. Approaches to target KRAS, clinical trials of novel KRAS inhibitors and further challenges in the fight against KRAS mutant tumours are the theme of the article by Thein *et al.* (Oregon Health and Science University and University of Texas MD Anderson Cancer Centre, Houston, USA).

The role of lymphatics in treating diseases is the subject matter of the article by Xu *et al.* (University of North Carolina, Chapel Hill, USA). They enumerate the targets to generate functional lymphatics, modulate lymphatic function, limit immune responses related to lymphatics and the factors to be considered in designing drugs targeted at lymphatics. They point out the need to develop non-invasive sensitive tools to image lymphatics as they can aid clinical evaluation of the latter in diseases and the efficacy of therapies targeted at lymphatics.

Another new therapeutic under development is the engineered interleukin-2 (IL-2). This is an appealing target for treating cancers such as metastatic melanoma, renal cell carcinoma and autoimmune diseases. Re-engineered IL-2 formulations preferentially bind to different conformations of the IL-2 receptor and stimulate specific T-cell subsets. They thus are more efficacious and less toxic than IL-2. The potential of engineered IL-2 is discussed in the article by Overwijk *et al.* (Nektar Therapeutics, San Francisco, USA).

Three reviews discuss organ or cell transplantation. One of them is on the progress and barriers in organ transplantation from donors with HIV infection following the implementation of the HIV Organ Policy Equity (HOPE) Act. The second article highlights the advances in clinical, translational and basic science studies related to lung transplantation in humans. These studies have focused on allograft dysfunction, the most important graft-limiting complication in patients who undergo lung transplantation. The advances have led to prolonged survival and better quality of life in patients with pulmonary fibrosis, chronic obstructive pulmonary disease and cystic fibrosis. The third article provides recent data on supportive evidence for autologous haematopoietic stem cell transplantation (HSCT) in patients with autoimmune diseases such as multiple sclerosis, rheumatologic diseases and Crohn's disease. HSCT is currently endorsed by the European autoimmune diseases societies as a standard treatment option.

Diabetes is historically classified into two types, based on whether there is a lack of endogenous production of insulin or whether the defect is in insulin sensitivity in tissues that regulate energy metabolism. Recognition of clinical and phenotypic heterogeneity in both types of diabetes, as well as of new forms with overlap between the classical two types indicates the drawback of the current system of classification of diabetes. Molecular genetics, metabolomics, bioinformatics and machine learning have provided opportunities to identify different causal factors and pathophysiologic pathways and classify patients based on them. Balasubramanyam (Baylor College of Medicine, Houston, USA) examines the possibilities for precise classification of patients with diabetes for targeted and efficacious treatment.

Three reviews discuss colorectal cancer. They address (i) how to deal with disparities in outcomes of colorectal cancer screening through well-designed multicomponent interventions, (ii) clinical applications for blood-based assays of cell-free DNA in the management of patients with colorectal cancer, and (iii) the role of aspirin in chemoprevention of colorectal cancer, mechanism of the action of aspirin and the emerging role of the microbiome in the mode of action of aspirin.

Three more articles relate to cancer. One of them details the biological determinants of cancer health disparities. These determinants consist of ancestry-related mutations, immune responses to tumours and responses to cancer therapy, gene fusions, differentially expressed or spliced RNAs, differentially expressed miRNAS or IncRNAs, and differential epigenetic patterns. The authors outline the implications of these factors for precision oncology in relation to cancer registries, databases and biobanks, as well as race and ethnicity stratified clinical trials.

Lopez *et al.* (University of North Carolina and Appalachian State University, Chapel Hill, USA) delineate the experimental evidence for the impact of microbiota on initiation, promotion, and progression as well as related specific mechanisms for cancer development. They also discuss the important questions that remain to be answered on host–microbe interactions in carcinogenesis.

Hereditary diffuse gastric cancer is featured in one review. The authors provide recommendations for screening, surveillance and treatment of asymptomatic persons at risk and patients with early disease. They also sketch the future directions for research related to pathogenesis, diagnosis and management of the disease.

Four articles narrate the advances in our knowledge on disease pathogenesis and mechanism-based treatment. They pertain to (i) chronic obstructive pulmonary disease, (ii) eosinophilic esophagitis, (iii) autoimmune endocrinopathies secondary to anti-cancer treatment using immune checkpoint inhibitors and (iv) toxicities such as lymphodepletion, cytokine release syndrome and encephalopathy associated with adoptive transfer of T lymphocytes modified with chimeric antigen receptors (CAR-T cells) in patients with haematologic malignancies.

One of the reviews analyses the benefits and risks of testosterone treatment of older men with low hormone level. While testosterone trials have indicated several benefits in men with age-related decline in hormone levels, the treatment is also associated with adverse effects. Since the safety and efficacy of long-term treatment are under debate, a patient-centric approach is recommended for decision on testosterone treatment in older men with hormone deficiency.

In another article, the authors assess the value and risk of direct-to-consumer genetic testing. They discuss various concerns such as psychosocial impact, effects on the healthcare system, privacy and investigative genetic genealogy. They also consider the issues related to future possibilities, such as merger with traditional modes of healthcare delivery or the DTC genetic system continuing as a parallel system driven by patients.

The last three reviews pertain to cardiovascular diseases. Hussain and Ballantyne (Baylor College, Houston, USA) outline the emerging therapeutic approaches to further reduce low-density lipoprotein cholesterol, apo-lipoprotein B containing lipoproteins, lipoprotein(a) and thus decrease events related to atherosclerotic cardiovascular disease in patients with dyslipidemia. They also summarize the outcomes and status of clinical trials of the emerging therapies which target the triglyceride pathway and immune-modulatory therapies. Musunuru (Perelman School of Medicine, Philadelphia, USA) discusses new therapies which modify lipid traits and inflammation in patients with coronary artery disease. Target genes and pathways have been validated through genetic studies. Many new drugs are monoclonal antibodies, ani-sense oligonucleotides or si RNAs. These have the disadvantage of short half-lives. Musunuru predicts that future development of gene

therapies and genome editing techniques would be similar to vaccination, providing prevention which needs only a single administration. Mizuno and Patel (University of Pennsylvania, USA) and Changolkar (University of Michigan Medical School, USA) appraise on the wearable devices used to detect cardiac arrhythmias and monitor pulse, blood pressure, heart and respiratory rates, physical activity and sleep. These devices aid remote patient monitoring, tracking their health behaviours and evaluating strategies to change health behaviours.

The final article is on the well-known antipyretic and non-steroidal anti-inflammatory drug aspirin. Both preclinical and clinical studies indicate that aspirin may decrease the incidence of deaths from sporadic colorectal cancer (CRC) and perhaps other cancers. The evidence for cancer prevention by aspirin is convincing in patients with Lynch syndrome, an inherited disorder resulting from mutations in one of the DNA mismatch repair genes and increases the risk of CRC, endometrial cancer and several other cancers. Rocciotti and Fitz-Gerald (Perelman School of Medicine, Philadelphia, USA) review the results of randomized clinical trials of aspirin in primary prevention of hereditary CRC and conclude that the benefit of aspirin for primary prevention of CRC is unproven as of now. Their article also provides a history of medical use of aspirin, pharmacology and mechanism of action of the drug, and a summary of the results of randomized clinical trials of aspirin in both primary and secondary prevention of cardiovascular diseases. While aspirin has a clear benefit in the secondary prevention of myocardial infarction and stroke, the beneficial effects for primary prevention are counterbalanced by a significant increase in risk for intracranial and gastrointestinal bleeding.

In summary, the book is a good read for medical professionals and biomedical scientists who want to improve their awareness of the frontiers in medicine. The articles in the book also indicate the gaps in the knowledge in several sub-specialities of medicine and are thus useful for the readers to identify topics for their scientific pursuits.

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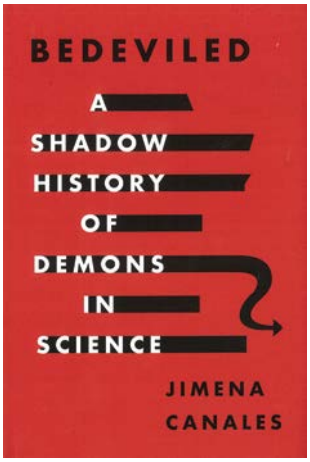

Bedeviled: A Shadow History of Demons in Science. Jimena Canales. Princeton University Press, Princeton, USA. 2020. x + 398 pages. Price: US$ 29.95. ISBN: 978-0-691-17532-4.

This detailed and insightful book traces the history of the conceptual demons that the modern sciences have invented even as they exorcised spirits from the domain of scientific investigation. It simultaneously chronicles the role these demons have played in advance of the sciences. But while science has been successful in exorcising demons, spirits and superstition, the march of science, as the title of the book suggests, is shadowed by demons of another kind. The demons that scientists invoke in their theories and experiments travesty the provisional rules and principles of the sciences and manifest themselves in scenarios and theories that escape the prevailing imagination of science. Over 10 chapters, an introduction, conclusion and postscript, the author takes us through a journey spanning more than three centuries. The first part of the book covers the demons encountered in physics, and then discusses demons in cybernetics, the computer and biological sciences and finally, the economy itself.

While the book begins more or less with the emergence of modern science in the 17th century, it must be noted that the demons discussed are modern ones. The term 'demon' is employed as an analogy to make an important point about the nature of the scientific quest. Consequently, the analogy is not to be taken literally but understood in the nuanced way that the author elaborates. The irony here is that while the faculty of reason, in tandem with experiments, exorcised premodern demons, scientists introduced imaginary creatures or beings in thought experiments in the scientific realm. These creatures as devices were helpful not just in exploring the physical realm, but led to breakthroughs at the frontiers of science.

More than half the chapters in the book discuss the demons encountered in the realm of physical theory, from Laplace's mechanistic intelligence to Maxwell's demon to those encountered in quantum theory – and 'Bohm's demon' or 'Bohmian demons' is played out in the discussion on hidden variables. We are familiar with the demons evoked by Laplace and Maxwell and, in the latter case, we have a theoretical entity that could, in principle, 'stop entropy, put an end to decay and make the world run in reverse'; the explorations of Einstein, Marie Curie and Planck's reflections on the quantum realm throw fascinating light on the attempts to understand the new realm of physical theory. Thus while the author discusses the imaginary creatures at work in other disciplinary and interdisciplinary endeavours, the demons evoked by physics are widely known and indirectly played a role in the evolution of the scientific understanding of the world. However, these scientific demons did manifest themselves differently in thought experiments and theories. Thus, as the author Canales points out: 'If Laplace's creature was law-abiding and Maxwell's demons were law breakers, quantum demons were law benders.'

In any case, commencing with Descartes' 'evil genius', Canales discusses the philosopher's familiarity with automata and his fixation with one who might create an alternate reality that would mislead our senses, blurring the boundary between the real and spectacle. Descartes must find his way back to reality with the *Cogito ergo sum*. Canales trails how scientists invented several of these now-familiar demons as by products of their theoretical or technological constructions (Laplace's demons and Lovelace's reflections on machines and thinking beings) have enabled the scientists to make important discoveries and invent technological solutions. But the genealogy of these demons unfolds from the precision of Newton's theory to the Laplacian demon, who, given the trajectory and location of a particle as well as the forces acting on it, could compute both its past and future. Every subsequent demon surpassed its predecessor, for example, by sorting out fast from slow-moving gas molecules into separate chambers, one warmer and the other cooler respectively, in violation of one of the fundamental laws of thermodynamics. Each of these, as Canales points