of Mendeleev's periodic table. An account of the epistemological status of chemistry by Fredrich Paneth here, makes an interesting read.

Introducing Auguste Comte's concept of positivism, the authors then go on to question whether chemistry's adherence to facts constitutes positivism. Invoking the example of salt, they indicate how seventeenth century philosophers ascribed a positivist status to chemistry due to salt's chemical to metaphysical to positive journey. In due course, with experimental proof that salt in fact was a product of a reaction between an acid and an alkali, Comte's positive ideal, the authors note, was seen to provide parallels to Lavoisier's concept of an element.

Students of chemistry know enthalpy from entropy, and it is definitely with a sense of awe that one then reads of how Ostwald reduced chemistry and physics to the principles of thermodynamics giving rise to energetism, which in turn served to establish the opposition between positivism and realism in science.

The last section of the book gives an introduction to nanotechnology and ends with a note on ethical and professional guidelines to be followed by chemists in order to do responsible science.

In all, the authors have done a commendable job in preparing a good introductory book for beginners in Philosophy of Chemistry. Beginners with either a chemistry or a philosophy background, will find in this book, their initial sense of wonder multiplied manifold. And if you went into the book thinking of that distant land you always wanted to visit, you will realize somewhere along the pages that this is indeed the guidebook to your Shangri-la that you hoped to find. Much like a good travel book, the authors succeed in invigorating the reader's mind and make one yearn for more of this land.

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Annual Review of Pathology: Mechanisms of Disease, 2016. Abul K. Abbas, Jon C. Aster and Stephen J. Galli (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 11. vi + 649 pages. Price: US$ 102. ISBN 978-0-8243-4311-8.

The 2016 edition of *Annual Review of Pathology* continues to maintain the high standard that the series has had over the years. This volume begins with a favourite section of mine, the autobiographical essay. This time it is by Michael B.A. Oldstone, one of the pioneers of the field of viral pathogenesis. His article tells us about his research on Lymphocytic choriomeningitis virus (LCMV) and how it has become a 'Rosetta stone for solving several important puzzles in biology' and has helped clarify many concepts in virology and immunology. It sparkles with wit. He tells us about his introduction to anatomy dissection where he has a 'nameless cadaver and four classmates with names...' and how he has been wedded to LCMV, but has had a number of intense affairs with measles and influenza viruses. That he has had 77 postdoctoral fellows from his lab in his career should give one an idea of his legacy. The essay illustrates that along with focus and hard work, serendipity is essential for success. How serendipity helped is seen when Oldstone tells us that he was initiated into the world of infectious diseases on the third day of medical school. One of his classmates was the son of a friend of the chair of medicine who was an expert in infectious diseases. Because this professor wanted to personally coach his friend's son, but did not want the act of favouritism to look so blatant, he invited a couple of other students along with his friends son – one of whom was Oldstone!

Besides this article, there are 22 more chapters, some of which I shall cover in this review. While most of the articles are on pathogenesis of diseases, one deals with technology. That essay is on organoids. While much research is done on transformed cell lines, we are aware of the deficiencies with them – cell lines are 2-dimensional, lack a matrix and often contain additional mutations, all of which make analysis and interpretation daunting and possibly biased. Organoids seem to address some of these issues. They are cultures of transformed and normal human tissues, which are three-dimensional and consist of cells within a scaffold or a matrix. These organoids recapitulate organ architecture, multilineage differentiation and stem cells. Because the cells in the organoids are of wild type, the effects of additional genetic insults can be interpreted with better clarity. Thus, organoids can be used to evaluate tumour-suppressor genes and oncogenes, identify novel cancer loci and study tumour evolution and heterogeneity. The most exciting and novel thing about organoids, however, is their potential to enter the field of personalized medicine. Organoids created from patient tumour samples can potentially be used to evaluate response to targeted chemotherapy; further, multiple combinations and drug dosages can be evaluated simultaneously. Attempts are currently being made to incorporate immune cells and endothelial cells in organoids, so as to recapitulate, as much as possible, the *in vivo* environment.

Chronic traumatic encephalopathy (CTE) was very much in the news in 2016. First, in March 2016, the National Football League in the USA accepted, at a congressional hearing that there was a direct link between football and CTE. Then, in June 2016, Muhammad Ali, the greatest heavyweight boxer of all time and one of the greatest sportsmen ever, died. As we all know, Ali did not 'float like a butterfly' for the past three decades, as a result of his Parkinson's disease, a disease likely to have been an occupational hazard. The earliest reports of repetitive trauma to the brain appeared in 1928 and was soon termed Dementia pugilistica, as the autopsied brains were those of boxers. We now know that other sports which lead to repeated brain injury – and surprisingly, even single episodes of moderate to severe brain trauma can lead to CTE. As one would expect, there are similarities and differences between brains subjected to single episodes of trauma and those subjected to repeated trauma. Deposits of hyperphosphorylated tau protein have been seen in the two brains of boxers which have been studied. These tau proteins are similar to those seen in brains of Alzheimer's disease. However, the tau protein is deposited in the superficial layers of the cortex in CTE, but in the deeper layers of the cerebral cortex in Alzheimer's disease. Diffuse axonal injury, as evidenced by

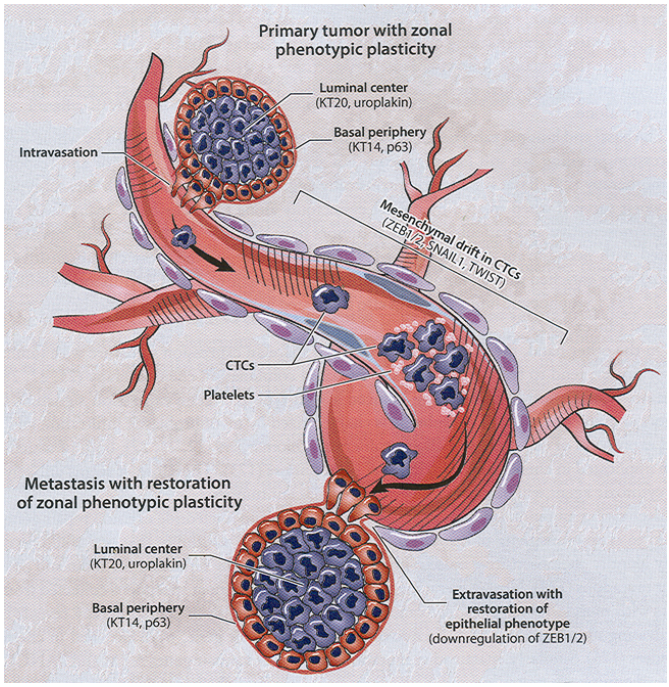
the presence of Amyloid precursor protein is also consistently detected in these brains. The effects of CTE include aggression, poor judgement, dementia, depression and even suicide – a very poor advertisement for contact sports such as boxing and rugby! Our understanding of this preventable disease is likely to improve vastly in the future as many American football players have pledged to donate their brains for research (the number, as of 3 February 2017, is 1647 ex-athletes and military veterans, since 2008 – and as many as 647 in 2016 alone).

Bronchiectasis is an uncommon, debilitating obstructive lung disease in which the bronchi are abnormally and permanently dilated and is characterized by recurrent lung infections and lung damage. First described by the great French physician Laënnec in 1819, the incidence of bronchiectasis declined in the twentieth century because of vaccinations and antibiotics, but is now again on the increase. Remarkably, the pathogenic organisms that cause the infections are consistent and similar across geographic locations and climates and with differing host polymorphisms. The most common organisms implicated are *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Interestingly, most of the *H. influenzae* are nontypeable, i.e. unencapsulated and hence not affected by *H. influenzae* type B vaccination. I learnt, to my surprise, that bronchiectasis has an association with inflammatory bowel disease (a lung-gut axis) and is, in fact, the leading pulmonary manifestation of inflammatory bowel disease. Changes in diet which lead to change in the gut microbiome also lead to change in the lung microbiome! Further, patients who have undergone colectomy as treatment for their inflammatory bowel disease often develop bronchiectasis. Vitamin D deficiency – also in the news nowadays – is linked to bronchiectasis and vitamin D supplementation may benefit patients with bronchiectasis.

Because the volume deals with recent advances, there are chapters on fairly recently described diseases too. Two of these are non-alcoholic fatty liver disease (NAFLD) and eosinophilic oesophagitis (esophagitis, as the Americans spell it; hence, EoE). EoE has been described as a specific disease for just less than a quarter of a century now, but is being increasingly diagnosed, partly because of being able to recognize the entity and partly because of an increase in endoscopic procedures. It has overlapping microscopic features with reflux oesophagitis – a disease which has markedly different treatment (dietary change and use of steroids for EoE, but not for reflux oesophagitis) and is the lesser of the two evils. EoE, for instance, can lead to fibrosis of the oesophagus. While the diagnosis is essentially a microscopic diagnosis, the development of a EoE diagnostic panel, a set of 94 genes that are differentially expressed in these patients has now been developed. This panel has over 96% sensitivity and specificity and can be done on only one biopsy unlike four biopsies which are required for conventional microscopic diagnosis. The eosinophil is, of course, crucial to the diagnosis and to the pathogenesis of the disease. Eosinophil products such as major basic protein and eosinophilic cationic protein are cytotoxic to oesophageal epithelium; besides, major basic protein increases smooth muscle reactivity and can trigger mast cell degranulation while eosinophilic cationic protein can make cell membranes porous. Cytokines play a role as well. IL-5, for instance, regulates eosinophil expansion and eosinophil survival. It also leads to mast cell induction. Mast cells, too, degranulate and contribute to the disease process. Anti-IL-5 therapy has shown reduction in oesophageal mast cells and eosinophils – but not in the patient's symptoms, suggesting that we have some way to go before we can translate laboratory-based findings in the clinic as well.

The same, sadly, appears to be true for NAFLD. It is a condition associated with obesity, insulin-resistance and dyslipidaemia (metabolic syndrome). Despite much understanding about the disease, we are no closer to developing better biomarkers or treatments for NAFLD. How severe is it as a disease? Suffice it to say that it is predicted to be the leading indication for liver transplantation in the coming decade in many countries. Our research into the complex world of NAFLD is hindered by at least two things – animal models (*ob/ob* mice and *db/db* mice and others) have striking differences from man in the mechanisms of development of their NAFLD, resulting in concerns that at least some of our beliefs about the mechanisms of this disease may be misplaced. As for studies in humans, the issue is that the diagnosis can only be made by liver biopsy – which is an invasive procedure and cannot be performed repeatedly.

Yet, how the 'new biology' is changing medicine is clear from the essay on brain tumours which informs us that the classification, which for most of the past



Epithelial-to-mesenchymal transition in metastasis.

90 years was based on microscopy, is now yielding way to combined morphology and molecular data diagnosis.

Blue sky research aside, the entire basis of biomedical research is to alleviate health problems. Thus, better understanding of physiology and pathology has meaning only if it contributes to better patient management. One particularly good example of this is in the chapter on genomic instability and cancer. The numerous types of genomic instability include single nucleotide variations and small insertions/deletions, copy number alterations, structural variations and chromosomal instability. An example of nucleotide-level instability is microsatellite instability and mismatch repair defect (MMR). Microsatellites are short tandem repeat sequences in the human genome, which often undergo strand slippage during DNA replication. Microsatellite instability (MSI) is a hypermutation phenotype which involves many insertion/deletion mutations in microsatellites, because of defective MMR. In the early years of this century a profound discovery was made that patients with MSI colorectal adenocarcinomas have a better prognosis; more importantly, they do not benefit from 5-FU based chemotherapy. Thus, a basic discovery was soon converted into practical medicine in the clinic.

The surgical pathology report forms the crux of treatment decisions in cancer medicine. Thus, the essay on the role of surgical pathology in guiding cancer immunotherapy was of particular interest to me. The immune system plays a defensive role against cancer. The clinical evidence for this lies in the fact that immune-deficient patients have higher rates of cancer (albeit specific cancers and not a generalized tumourigenesis). The role of tumour-infiltrating lymphocytes was shown in malignant melanoma when Mihm *et al.* and Clark *et al.* showed that patients with melanomas which were lymphocyte-rich had less aggressive cancers. Similarly, in colonic carcinoma too, the presence of a lymphoid infiltrate strongly correlates with better disease-free survival and overall survival. An immune score has been developed, which assesses the CD3 and CD8 cells by immunohistochemistry on tumour sections. Again, a high immune score correlates with better prognosis. The significance of T-cell infiltrates has also been demonstrated in many other carcinomas. Besides these, immune checkpoint inhibitors (e.g. Ipilimumab) have been developed for the treatment of malignant melanoma. Likewise, monoclonal antibodies (e.g. nivolumab and pembrolizumab) have been developed against PD-1 ligand 1, which have successfully been used to treat lung and renal cell carcinoma as well as relapsed or refractory Hodgkin lymphoma. Detecting further immune checkpoint proteins in diagnostic pathology material will be part of the responsibility of the surgical pathologists, so that the treating physician can treat the patient appropriately. Personalized medicine and immunotherapy will clearly be part of the future of medicine.

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