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**Annual Review of Pathology: Mechanisms of Disease, 2014.** Abul K. Abbas, Stephen J. Galli and Peter M. Howley (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA94303-0139, USA. Vol. 9. vi + 386 pp. Price: US\$ 63. ISBN 978-0-8243-4309-5.

As usual and as expected, this volume of Annual Review of Pathology is marvellous. This volume does not contain what some issues begin with – an interview

with an authority on a particular subject, with the history and patterns of his/her research field highlighted in the interview. This is a pity because there are few journals which carry such articles – those from which students would benefit greatly.

Cancer (glioma, ovarian serous carcinoma, melanoma and chronic lymphocytic lymphoma among them) and autoimmune diseases (including IgG4 disease, Sjogren's disease and autoimmune thyroid disease) form a major part of the 17 chapters. Other essays are on atherosclerosis, *Cryptococcus neoformans*, reactive oxygen, etc.

Autoimmune pancreatitis, or to use the more recent term, IgG4-RD (IgG4 related disease) is a truly 21st century disease. Though first documented in the 1960s as an isolated case report, it is only in this century that the disease has come into its own, so to say. Briefly, it usually presents as a chronic pancreatitis; however, it needs to be distinguished from the other more common chronic pancreatitis (usually associated with gall stone disease or alcohol intake) because of some specific morphologic and biochemical associations and therapeutic implications. Histologically, the pancreas shows a dense infiltrate of plasma cells as well as obliterative phlebitis and fibrosis. Specifically, autoimmune pancreatitis is treated by steroids and not by major surgery and is thus a 'medical' rather than a surgical disease.

The discovery in 2001 that patients with this disease have elevated serum levels of IgG4 made diagnosis easier and ultimately also gave it its new name, IgG4-RD. Besides the pancreas, however, a whole range of organs is involved, including the salivary gland, ear, nose and throat, kidneys, lungs, aorta, stomach, retroperitoneum and lymph nodes.

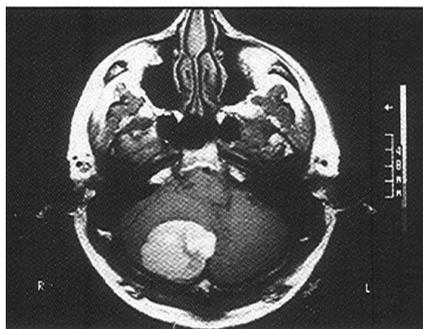
Yet IgG4 is more complex. Unlike other autoimmune diseases which are more common in women and often present in the young, autoimmune pancreatitis is more common in men, especially in the middle aged and old men. Besides, we do not know as yet, whether the raised IgG4 autoantibodies are a direct cause of the disease, or a mere association. Perhaps it is not autoimmune after all. The jury is still out on that and there is much work to be done on this entity – clearly material for a future issue of *Annual Review of Pathology*. I might add here that during the course of my review of this book, I saw a patient with a diffi-

cult-to-diagnose case of suspected IgG4-RD and the well-crafted essay helped me make a correct diagnosis – (not IgG4-RD, by the way) – much to the patient's benefit.

Sjogren's syndrome (SS) is a not uncommon autoimmune disease, which, fortunately, is relatively benign. However, SS has, among the autoimmune diseases, the highest incidence of lymphomas; 5–10% of SS patients develop Non-Hodgkin's lymphoma and have a higher mortality rate. Thus, SS is a model for the simultaneous study of autoimmune disease and malignant transformation. SS is histologically characterized by a mononuclear infiltrate in and around the epithelium of the ducts and acini of the exocrine glands. The organs most commonly involved are the salivary glands and the lacrimal glands. Because of the structural and physiologic alterations that take place in these organs, the symptoms of this disease are dry mouth and dry eyes ('keratoconjunctivitis sicca'). Besides these organs, the epithelium of the lungs, kidneys and liver can also be affected, leading to the new term for SS, 'autoimmune epithelitis'.

In SS, T cells predominate among the inflammatory cell populations that affect the organs. The disruption of the Th1/Th2 balance is believed to be a key event in the pathogenesis of SS. However, CD4+ T cells are seen mainly in the milder lesions, whereas the advanced cases of SS contain B lymphocytes. This automatically explains why the lymphoma that most commonly develops in SS is a B-cell lymphoma, specifically, the marginal B-zone lymphoma (a mucosa-associated lymphoid tissue type of lymphoma). Chronic antigenic stimulation of autoreactive B cells as well as t(14;18) translocation and mutations of the tumour suppressor gene *p53* are responsible for lymphomagenesis.

Autoimmune thyroid disease is of two types – Grave's disease and Hashimoto's thyroiditis. Remarkably, though both are characterized by lymphoid infiltrates in the thyroid and the production of thyroid autoantibodies, the clinical manifestations are quite different: Grave's disease presents as thyrotoxicosis, while Hashimoto's presents as hypothyroidism. As one would expect from the above facts, we learn from a Venn diagram that susceptibility genes for the two diseases include some common genes, but also some genes unique to each disease.



Melanocytoma of the central nervous system: hyperdense mass in the cerebellum.

Ovarian cancer is a lethal disease; this has meant that much research has gone into it. Yet, the survival rates for this disease have remained pretty much the same over the past 50 years. This is despite screening for ovarian cancer. Theoretically, an early diagnosed ovarian cancer would have better survival rates compared to late diagnosed conditions. However, early detection is not easy. A study has shown that in spite of intensive annual screening for ovarian cancer, 70% present with advanced-stage cancer and that there is no difference in the stage at detection between screened and non-screened groups.

Our understanding of the origins of ovarian cancer got a fillip – and an unexpected surprise, recently. After the discovery of BRCA-1/BRCA-2 and their mutations, and their relation to breast and ovarian cancers, some women in the West underwent prophylactic oophorectomy for the prevention of ovarian cancers. Pathologists examining the ovaries and fallopian tubes were surprised to find that it was the fallopian tube that harboured the features of early cancer. It was later hypothesized that tumour cells from these fallopian tube cancers were shed onto the ovary, and simulated primary ovarian cancer.

The current thinking is that there are two kinds of ovarian serous carcinomas – low grade and high grade. Low-grade tumours are genetically stable, unlike the high-grade tumours. Low-grade tumours are often indolent, and chemo-resistant, while high-grade cancers are at an advanced stage when discovered and are chemotherapy-sensitive. It is this latter group that must be detected early.

Of course, the path from understanding a disease to curing it, is more complex than one would imagine. The

chapter on glioblastomas exemplifies this. Mammalian target of rapamycin (mTOR) is one such potential target in gliomas. mTOR exists in two complexes – mTORC1 and mTORC2 – which promote growth, survival and chemotherapy resistance of glioblastomas. Because of the importance of mTOR signalling in glioblastoma pathways, it was expected that the allosteric mTOR inhibitor rapamycin would be an effective therapy. However, phase I and phase II clinical trials showed no such benefit. It turns out that there is incomplete inhibition of mTOR signalling and insufficient suppression of mTORC1 signalling. This failure of rapamycin to achieve its intended target is similar to the resistance seen in glioblastoma patients treated with EGFR tyrosine kinase inhibitors.

Neutrophils are the soldiers of the body, a fact known to all of us right from our school days. Yet, most of us do not know much more about the functions of these cells. The complex nature of the neutrophil is elucidated in an essay, where, among the many things that we learn, is that there is now some doubt about the life span of neutrophils – they probably live for up to 5 days rather than 8–12 h, as has been believed all these years. Though neutrophils are the cells of the acute inflammatory response, they are also involved in diverse conditions. Neutrophils are involved in the regulation of dendritic cells, B and T lymphocyte function, macrophage and natural killer cells. They act on endothelial and epithelial cells as well. Finally, they have been implicated in chronic lesions such as atherosclerotic lesions (where in addition to initiation and progression of the plaque, neutrophils may contribute to thrombosis, stroke and myocardial infarction through intravascular thrombus growth), as well as in autoimmune conditions such as systemic lupus erythematosus and surprisingly, in allergic diseases as well as in anaphylaxis. Finally, inflammatory bowel disease and cancer are other groups of diseases in which neutrophils play an important role. In inflammatory bowel disease, overproduction of reactive oxygen species (ROS) by neutrophils may contribute to the development of malignancy.

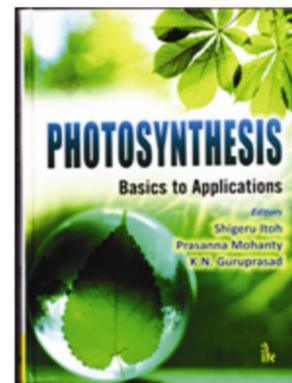
Pathogen killing by neutrophils is done by phagocytosis, generation of ROS and degranulation. A new mechanism, NETosis (neutrophil extracellular trap) is a fascinating phenomenon that has been

described only in the past decade. NETosis is the process by which neutrophils extrude a meshwork of chromatin fibres which are decorated with granule-derived antimicrobial peptides and enzymes such as neutrophil elastase and MPO. However, there is a flip side to NETosis: excess NET formation is related to different conditions, including vasculitis, sepsis and lupus nephritis. Thrombosis and endothelial cell injury and pre-eclampsia of pregnancy are also associated with it.

Not without good reason is the *Annual Review of Pathology* a journal that I and thousands of researchers around the world look forward to every year.

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**Photosynthesis: Basics to Applications, Second Edition.** Shigeru Itoh, Late Prasanna Mohanty and K. N. Guruprasad (eds). I.K. International Publishing House Pvt Ltd, S-25, Green Park Extn, Uphar Cinema Market, New Delhi 110 016. 2015. 308 pp. Price: Rs 200. ISBN: 978-93-84588-54-0.

This book was inspired by an International Conference on Photosynthesis held at the University of Indore in November 2008, in honour of Govindjee, an inspirational and indefatigable teacher and a distinguished researcher, who is known internationally for his contributions to photosynthesis research. Selected participants from the conference were invited to contribute research and review articles. The first edition of this book was published in 2012 entitled *Photosynthesis* –