

have led to much theoretical work. This is the topic of ‘B flavor anomalies: 2021 theoretical status report’ by David London and Joaquim Matias. Since that article was written, many of these anomalies have disappeared due to large new data by the LHCb experiment in CERN. While the practical significance of the article is therefore diminished for the moment, it addresses in many ways the problems that fall into the ambit of ‘flavour physics’ where the Standard Model of particle physics does not offer sufficient insight.

A closely related topic is that of the article ‘Electroweak penguin decays of b-flavoured hadrons’ by Ulrike Egede *et al.* In the Standard Model, and because of the suppressed decay rate of the b-quark, the so-called penguin decays, which occur only at the one-loop level, are well observable. They provide a lot of information on the flavour-related structure of the underlying models – they are the drosophila of flavour physics. This article gives an extensive and useful overview of these decays.

An important and testable feature of the Standard Model is the occurrence of repeated ‘generations’ of particles with the same properties except for their masses. This issue is addressed in ‘Testing lepton flavour universality with pion, kaon, tau and beta decays’ by Douglas Bryman *et al.* The authors provide an exhaustive overview of the experimental situations and the implications for future theories.

While the long-standing belief that neutrinos are massless has been shattered, the exact masses are still not unknown. In ‘Probing the neutrino-mass scale with the KATRIN experiment’, Alexey Lokhov *et al.* describe the recent results and future plans of the KATRIN experiment, the world’s leading direct (electron)-neutrino mass measurement. While the present sensitivity stands at 0.8 eV, the goal is to reach 0.2 eV in the near future. Furthermore, they discuss the search for light sterile neutrinos.

Among the models beyond the Standard Model, some with enhanced couplings to the heavy particles of the Standard Model, like the Z, W, t, H, because of some unknown strong dynamics. In his contribution ‘Searches for heavy resonances with substructure’, Petar Maksimovic describes the observable effects of such scenarios and their signatures, distinct from the Standard Model.

Successful analysis at LHC requires difficult heavy-duty theoretical computations at the forefront of particle physics. Thomas Gehrmann and Bogdan Malaescu describe

the state of the art in ‘Precision QCD physics at the LHC’. QCD, or Quantum Chromodynamics, is the microscopic theory of strong interactions. The calculations in QCD have been constantly improved over the last decade; they are at the edge of the techniques of quantum field theory and use the most advanced concepts of information technology. The achievements described in this article are of the highest quality and a solid foundation for future work.

The difficulties of mastering the non-perturbative aspects of QCD have led to a numerical treatment based on discretizing space and time. In ‘Status of lattice QCD determination of nucleon form factors’, Aaron S. Meyer *et al.* review the status of this difficult field, which merges deep issues in field theory and numerical work. As can be seen, the properties of some of the most ubiquitous particles in the Universe, namely the proton and neutron, continue to be of interest to theoreticians as well as to experimentalists.

Apart from the issues concerning the two Standard Models, there remain unresolved puzzles at the subatomic level, some of which may also have repercussions at the more fundamental level. One area of interest is muonic atoms. Since the muon is much closer to the nucleus, one can probe light nuclei with high precision. Aldo Antognini *et al.* show in ‘The proton structure in and out of muonic hydrogen’ how to allow for precision measurements of fundamental constants, tests of QCD-bound states and even for searches of new physics.

The neutron has had its own riddles; for instance, its lifetime remained unknown for many years. But it also allows for tests of fundamental physics, such as CP-violation. Recent technological developments have allowed us to produce large samples of them, making precision measurement possible. The progress and outlook are described in the article ‘Fundamental neutron physics at spallation sources’ by Nadia Fomin *et al.*

Knowledge of the detailed nuclear structure in unusual conditions is important for understanding astrophysical objects like neutron stars and low-to-medium energy scattering, including neutrino oscillation effects in matter. John Arrington *et al.* review recent progress in the article ‘Progress in understanding short-range structure in nuclei’. The emergence of laboratory astrophysics and its implications is a fascinating new development.

Somewhat outside the focus is the contribution ‘Something can come of nothing: Surface approaches to quantum fluctuations

and Casimir force’ by Giuseppe Bimonte *et al.* Since the pioneering calculation by Casimir in 1948, who showed that vacuum fluctuation indeed gives rise to a measurable force, there are many extensions, including the work on material, surface or temperature dependence, with possible application in nanotechnology. This article reviews these developments and points to open the problems in this domain.

In this lengthy review of the *Annual Review of Nuclear and Particle Science*, we have attempted to relate to the prospective readers the essence of this collection of articles and their setting in the fields of elementary particle physics, nuclear physics and cosmology. We believe that these articles provide valuable overviews for young researchers, motivate them to explore the fields in greater detail, and provide them and experienced researchers with an extensive bibliography. This volume is a useful addition to every reference library in the world with a readership in the field covered, and we encourage libraries to procure copies.

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Yet another edition of *Annual Review of Medicine* is here. Given that all of 2020 and 2021 seemed to revolve around only one thing – COVID-19 – it comes as no surprise that COVID-19 dominates even in this volume. Whereas the 2020 edition that I had reviewed (*Curr. Sci.*, 2022, **123**(11), 1394–1395) had 392 pages, this one has as many as 602 pages. Of these, 166 pages are devoted to articles related to COVID-19/SARS-CoV-2 and include the topics of

vaccines (mRNA, adenoviral, whole inactivated and protein-based) as well as articles on pulmonary aspects, neurologic manifestations, critical illness, diabetes and myocarditis; and on neutralizing antibodies for prevention and treatment of COVID-19. As always, there is material from the cutting edge of science as well on advances in age-old diseases. Examples of the former include articles on organoids, the microbiome, on undiagnosed diseases and others. As for better established diseases where we continue to learn more, we have the examples of *Helicobacter pylori* gastritis, thyroid diseases, fatty liver, diabetes, brain tumours, etc.

Peptic ulcer disease has been around for centuries, but the discovery in the early 1980s that it was caused by a bacterium, now called *Helicobacter pylori*, was a startling one and one that entirely changed our approach to the management of the disease. This is most obvious when you read the article that discusses methods of diagnosis and therapy – and note that surgery does not feature in it at all! When I was a young medical student, not too long ago (relatively speaking!), surgery was often the only option for complicated peptic ulcer disease. A combination of various drugs (proton pump inhibitors, antibiotics, etc.) is now the means of treating patients with this disease. However, it is a bit of a surprise to learn that the success rate of therapy is only about 80%. Equally surprising was the statement that it was only ‘in 2015, that the gastroenterology community formally recognized *H. pylori* gastritis as an infectious disease and recommended that whenever *H. pylori* infection was diagnosed, it should be eradicated’. Gastric cancer is the most feared complication of *H. pylori* gastritis and hence, the need for treatment of the infection. However, for some reason, the authors, in this chapter, do not consider MALT lymphomas of the stomach, which are also caused by *H. pylori*. In fact, low grade MALT lymphomas can and are treated by antibiotics and are a unique example of cancers being treated by antibiotics. Empirical treatment has been widespread and has contributed to antibiotic resistance. To explain this, the authors explain that use of concomitant therapy (a four-drug regimen) will, at minimum, produce 14,000 kg of unneeded antibiotics per one million successful treatments and 28,000 kg per one million treatment failures! Ideally, susceptibility to the organism must be confirmed before initiating therapy. These investigations are now available in the West and

should, if utilized, contribute to better cure rates and reduced antibiotic resistance.

Further research on *H. pylori* – and other infectious diseases – will likely be on organoids. Organoids, like most significant advances in science at the time the progress is made, appear to be the stuff that science fiction is made of. They consist of human stem cell-derived cultures, with an additional extracellular matrix, such that they model the organ at a micro-level. In fact, the gastric organoid actually has chief cells, parietal cells, mucous cells, endocrine cells, etc. Besides gastric organoids, there are also intestinal organoids (where *Clostridium difficile* is being studied, among other organisms) as well as organoids in various other systems too such as respiratory system organoids and nervous system organoids. SARS-CoV-2 is an example of a virus that involves both of the last two named organs and organoids. Organoids, of course, are still not the absolute same as the organ itself because endothelial cells, mesenchymal cells and the entire population of the immune system are absent.

Cardiac disease is dealt with in five separate articles which include spontaneous coronary artery dissection (SCAD); silent atrial fibrillation; hypertrophic cardiomyopathy; cardiac failure with preserved ejection fraction; and the effects of pollution on the cardiovascular system. SCAD is now being increasingly recognized as a cause of acute myocardial infarction, especially in young and middle-aged women. SCAD takes place due to a separation between the tunica media and the tunica adventitia and results in the formation of an intramural haematoma. As many as 90% of the patients are women and this suggests an association with sex hormones. Yet, hormonal contraception, hormone replacement therapy and parity do not seem to have an effect. The usual cardiac risk factors do not seem to apply to this disease. However, fibromuscular dysplasia is a common pathology that is noted in the blood vessels. Accurate diagnosis of this disease is possible because of angiography – and is essential because of the considerable differences in management, compared to the usual atherosclerosis-induced myocardial infarction.

One associates air pollution with pulmonary effects, but it is perhaps startling to learn that cardiovascular effects of particulate air pollution are severe and are linked to morbidity and death. We now know that particulate matter of <2.5 micrometres in diameter (PM_{2.5}) are associated with an increase in the systolic as well as diastolic

blood pressures; with an increase in the risk of dyslipidaemia; and the risk of type II diabetes; and with increased thrombosis. Not surprisingly, then, this is also associated with increased mortality to ischaemic heart disease, stroke, heart failure and atrial fibrillation.

Atrial fibrillation – whether related to the air pollution referred to above or otherwise – is a common problem. However, we now know, because of the use of implantable devices, that there is the entity of silent or subclinical atrial fibrillation (SCAF) as well. Because symptomatic AF is an important cause of morbidity and mortality, it stands to reason that even the asymptomatic variety would result in health issues. How exactly one should deal with a newly detected case of SCAF is not yet clear, however, much research is under way to assess what the predictive factors are and indeed, which the clinically significant SCAF cases are.

Seven essays are devoted to various types of cancers. Immunotherapy is among the great recent advances in the treatment of cancers. We learn the specifics as well as about other advances in chapters on the treatment of glioblastoma and of hepatocellular carcinoma. Hepatocellular carcinoma is the third leading cause of cancer deaths the world over. Single agent immunotherapy in the form of checkpoint inhibitor treatment has not been a success and currently, a combination of checkpoint inhibitors with anti-vascular endothelial factor (VEGF) is under investigation.

Brain tumours such as glioblastoma (GBM) are among the most aggressive tumours and despite much research, the median overall survival is a dismal 15 months. There are many reasons for this and some of them include the genetic heterogeneity among the tumour cells, presence of the blood-brain barrier, lack of lymphatics, etc. And yet, there is always hope and there are always surprises in science. The brain is an immunologically cold organ and it was expected that immunotherapy may not be effective in GBM. Yet, the fact that metastatic tumours in the brain do respond to immunotherapy and because there are now doubts about the existence of the blood brain barrier, suggests that immunotherapy may be useful in GB, too. That basic research is considerably different from the real world is clear when you read that veliparib and temozolamide were effective on GBM cell lines – and yet, resulted in severe and toxic thrombocytopenia as an adverse effect in a clinical trial, when combined with radiation.

Hypoxia is a key feature of aggressive cancers and this is because of disrupted vasculature in the tumour, fibrosis within the tumour microenvironment, as well as increased oxygen consumption by the tumour cells. Hypoxia results in increased resistance to chemotherapy, radiotherapy and immunotherapy. This suggests that reversing the tumour hypoxia would possibly benefit patients by improving their response to various therapies. Evofosfamide, a hypoxia-activated prodrug is one such prodrug which gets activated in the presence of hypoxia. In murine models of prostate cancer, Evofosfamide has been shown to diminish hypoxia and reduce tumour progression; reduce hypoxia in metastatic nodes in orthotopic head and neck squamous cell carcinoma model and augment immunotherapy in syngeneic models. Of course, whether this will translate into a repetition in real life needs to be seen.

A not-so-new disease, but now an epidemic in the USA is obesity and it is estimated that more than 40% of Americans in 2018 were classified as being obese. Bariatric surgery (which was covered in the 2020 volume and was discussed in my book review mentioned above) has offered a way out to many, yet the fact is that bariatric surgery can be offered to only about 1% of this population. Besides, there are adverse effects to the surgery and also, weight gain in almost 40% of the patients at 10 years post-surgery. Thus, medical means of management are now being attempted. These include use of intragastric balloons (of which there are three types as well as others in the pipeline), endoscopic sleeve gastroplasty, aspiration therapy and superabsorbent hydrogel. The small bowel is also a target and duodenal mucosa resurfacing and endoluminal bypass sleeves are currently under investigation.

IgG-related disease (IgGRD) is truly a 'new' disease as it was first described in 2003. This is a unique disease in that almost

all organ systems can be affected by the disease process. The disease is potentially curable, but the very broad spectrum of symptoms combined with the histopathology and other laboratory findings that are essential for diagnosis and are yet neither sensitive nor specific, make it a challenge for physicians to suspect or diagnose. Thus, the publication of key exclusion criteria for the disease, is a step forward. For instance, the presence (among many criteria) of fever (clinical), leukopenia and thrombocytopenia (laboratory findings), and the presence of granulomas or necrosis or numerous neutrophils (histopathology findings) should lead the physician into considering the possibility of other diagnoses, instead of IgGRD. Steroids have always been the treatment of choice. However, now, even the anti-CD20 monoclonal antibody Rituximab has been shown to be effective.

Phage therapy is discussed too and is an example of a possible resurgence of thought. Phages are viruses that infect bacterial hosts. First discovered a little over a 100 years ago, they were investigated for possible anti-bacterial use. However, the subsequent discovery of antibiotics resulted in phage therapy being put on the backburner – until now, when antibiotic resistance has become common. The authors describe three specific cases (personalised, compassion-use): one, a patient with multidrug-resistant *Acinetobacter baumannii* infection, a second with *Pseudomonas aeruginosa* infection on a Dacron aortic arch graft and the third, a patient with *Mycobacterium abscessus* infection in lung transplant for cystic fibrosis. The success of these cases has led to multiple clinical trials. Some of these are discussed – all of which have resulted in 'failure'. The word 'failure' is in inverted commas because while the expected and hoped-for success did not see light of day, there were many learnings from these carefully performed trials, all of which are being put to good use in current and future

trials. A pity that *Annual Review* is dedicated purely to cutting edge research: one wishes that there would be the occasional bit of wit and pop history as well. For instance, the chapter on phage would have been the appropriate place to inform readers that a much earlier example of phage treatment was on Tom Mix, a leading Hollywood actor of the 1930s. Equally interesting is the fact that his image is seen on the cover of the iconic album by The Beatles, 'Sgt Pepper's Lonely Hearts Club Band' (as elucidated recently, in the book *Invisible Empire*, by Pranay Lal).

The quest to conquer disease knows no bounds and so it is heartening to know about the creation of The Undiagnosed Diseases Network (UDN) in 2014 in the USA. Fifteen leading centres participate in it, and the UDN uses whole-exome sequencing, chromosomal microarray, metabolomics and model organism screening as well as newer technologies such as whole-genome sequencing, RNA sequencing and long-read sequencing to diagnose complex, previously undiagnosed cases. About a third of such cases ultimately do reach a diagnosis. Each of these methods has advantages and some disadvantages – technical as well as economic. Further, only about 4400 genes of the about 20,000 genes in the human genome have been mapped. Finally, because of changing concepts – about 250 new gene-disease associations are detected annually – and because of changing guidelines, it often makes scientific sense to re-evaluate data before performing alternate or new or more expensive testing.

As ever, *Annual Review of Medicine* keeps you informed and also fascinates.

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