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Having previously reviewed volumes of *Annual Review of Pathology*, which deal with pathogenesis of disease, I was curious to know what topics an *Annual Review of Medicine* would contain. After all, 'medicine' is a very broad term and encompasses a whole range of organ systems. As it turned out, the answer, I discovered, was just that: a wide spectrum. The volume under review contains articles dealing with cancer, cardiology, rheumatology, psychiatry and others.

Genetics forms the basis of the first five articles in the volume. Neonatal screening for disease is now well known, but Caskey *et al.* discuss the benefits and advances of adult genetic risk screening. We learn that there are about 150 reported genes, that, when mutated, cause vascular disease. Familial hypercholesterolaemia Type II is common but is now known to respond to statins; this illustrates how genetic risk identification can lead to therapeutic intervention. Further, the discovery of the cardiovascular risk gene *PCSK9* has led to the development of a monoclonal antibody, which, in clinical trials have been shown to reduce cholesterol levels in blood. Incidentally, Hippocrates, the father of medicine, seems to have been prescient as he had stated 'when a patient's unique idiosyncrasia is known, then it is feasible to custom tailor the treatment'!

Marfan's syndrome has now been known to be caused by a mutant *FBN1* gene. Identification of an index case in a family is important because it easily lends itself to genetic counselling. Aneurysms – caused by mutations in TGF β receptors 1 and 2 – are common in Marfan's syndrome. Conventionally, imaging studies followed by vascular engraftment were done to preempt vascular rupture. Of late, the drug losartan has been used to reduce the progression of vascular dilatation by its action on the TGF β pathway. A later essay on Marfan's syndrome further illustrates how the new findings in genetics have changed medicine. MicroRNAs have been shown, in recent years, to play a crucial role in all biologic processes. It is now likely that

microRNA modulation maybe a therapeutic option for abdominal aortic aneurysms in the future, based on our current knowledge that induction of *miR29* increases smooth muscle proliferation, whereas downregulation of *miR-29b* augments a profibrotic response in adventitial fibroblasts – this approach would help strengthen the weak wall of the aneurysm.

Neurodegenerative disorders, often, still have limited therapy options and the conventional thinking has been that screening for a neurodegenerative incurable disease is foolhardy because it would lead to considerable stress. However, a recent such screening study has indicated that this expected negative psychological impact was not realized. Though caution must undoubtedly be exercised still, perhaps the future does hold the possibility of whole-exome sequencing without undue adverse effects.

Male circumcision, that socio-religious-cultural act of minor surgery in childhood, was found to be beneficial a few years ago in reducing HIV-AIDS as well as HPV in men and HPV in women. So much so that male circumcision is now considered an important strategy in the prevention of heterosexual acquired HIV transmission in men. In fact, the WHO, the American Academy of Pediatrics as well as the American Association of Obstetrics recommend the procedure. Indirectly, because HIV in men can be prevented with this simple approach, if rates of HIV decrease, even the incidence of women being affected by HIV will decrease.

What is the mechanism of action? This is likely multifactorial. Viral infections (such as HSV2) may enter through microtears in the prepuce mucosa. In the absence of a prepuce (and consequently, the absence of a tear in the mucosa), the chances of a virus entering the tissue decreases. Further, when the foreskin retracts during intercourse, the prepuce is exposed to vaginal fluids that may penetrate the foreskin mucosa and infect it. Circumcision replaces the vascular tissue with keratin and scar tissue and protects it. A possibly thicker keratin thickness of the inner mucosa may be protective. Circumcision means that the presence of many Langerhans cells as well as CD4 and CD8 cells in the normal prepuce (cells which are attacked by HIV) which act as targets for the virus are no longer present.

The solution is however not easy, because rates of male circumcision have

been decreasing for the past half century. Low resources, technical and skilled, as well as other priorities have meant that most countries have not met the targets of male circumcision that have been recommended by the WHO.

In what is a curious twist, there is an article on a medical treatment for what has been a surgical disease for years – retinoblastoma being the example, while another article is on a surgical treatment for what has essentially been a medical disease, hypertension being the example. Refractory hypertension is defined as blood pressure that remains high despite the use of at least three drug classes, or that which is controlled with the use of four drugs. Leong *et al.* show how renal sympathetic denervation – a minimally invasive procedure can now be used to control hypertension. Thus, in what appears to be history repeating itself, a procedure – non-selective sympathectomy for severe hypertension, a procedure which was performed before the advent of anti-hypertensive drugs relegated this surgical approach – is now back, in a modified form and without the complications of non-selective sympathectomy, such as bladder and bowel dysfunction, erectile dysfunction, etc. An offshoot of renal sympathetic denervation for refractory hypertension is that the same procedure holds promise, in very early studies, for the treatment of chronic kidney disease, even without hypertension, as well as for insulin-resistance states and sleep apnoea.

In the same vein, we learn from another article, that transcatheter aortic valve replacement is now an option for patients with severe aortic stenosis, but who are poor surgical risks or are not candidates for surgical aortic valve replacement. This 'disruptive innovation', which is less invasive and has a shorter recovery period may, in future, be extended to patients with intermediate-surgical risk populations.



Leukocoria, also known as the cat's eye reflex. The cancer is directly visible behind the dilated pupil.

Because medicine deals with people and not disease, there are articles which revolve around areas that many of us do not know much about – and which are not taught in medical school. Some such examples include clinical trials, health care expenditure and reducing hospital readmission rates.

As the costs of healthcare spiral, with the USA leading this charge as well, calls are being heard to reduce the costs, but to maintain the quality of health care. Information technology can analyse data and trends better than could be done in the past. The increase in expenditure is due to increasing prosperity, private and public insurance players, defensive medicine, better technology – and because many previously untreatable diseases can now be addressed successfully by modern medicine. The increase in the incidence of diabetes and obesity has also added to this. Adherence to evidence-based guidelines in management has been shown to improve survival and response to medicine while increasing the quality of the outcome – and reducing the expenditure.

Clinical trials have of course been very much in the news in India for the past decade, for multiple reasons, ethical as well as commercial. The author, Shein-Chung Chow, does not of course discuss such issues; however, we are informed that advances in drug development have not kept pace with expenditure on research and trials. Among the fixes that have been suggested are to use ‘adaptive clinical trials’. An adaptive trial is one that uses accumulating data to decide how to modify aspects of the trial as it continues without undermining the validity and integrity of the study. There are many ways of doing it – adaptive randomization design, adaptive group sequential design, flexible sample size re-estimation design, drop-the-losers design, adaptive dose-finding design, biomarker-adaptive design, adaptive treatment-switching design, adaptive hypothesis design (yes, this too!) and phase I/II (or phase III/IV) adaptive seamless design. The benefits of adaptive trials is that it allows the investigator to correct erroneous assumptions made before the trial, can help the investigator use information that may be available during the study (either from the same study or from other sources) and may reflect a real life situation in a clinical trial. The limitation, of course, is that great care must be taken not to

unintentionally – or intentionally! – introduce bias into the study.

I have earlier referred to the chapter on retinoblastoma – which, to me, was the most fascinating one! Retinoblastoma is a unique cancer because it affects the eye/eyes of children and leads to blindness and often, subsequent death. Many of those who survive the cancer suffer from a second, non-ocular cancer. Though not very common, the fact that it is a paediatric cancer increases the poignancy of the disease; thus retinoblastoma has been the subject of an award winning Marathi movie a few years ago; users of Facebook would also remember that there appeared in 2010, an incident of a nurse who detected a ‘cat’s eye’ appearance in the eyes of a friend’s daughter on Facebook and alerted her (the mother) about the possibility of retinoblastoma. Abramson begins his essay with a brief account of the history of this disease, where we learn that enucleation of the eye was the first form of treatment offered in the early nineteenth century and that the ‘pattern of advocacy for an unproven treatment criticized by contemporaries was to be repeated often during the next 200 years in the history of retinoblastoma treatment’.

Subsequently, in the early twentieth century, radiation – of different types – was employed as a means to control the disease. Systemic chemotherapy was advocated as a treatment in the second half of the twentieth century, but was soon abandoned because the side-effects were more harmful than the disease. However, the use of intraarterial chemotherapy – selective chemotherapy into the carotid artery on the side of the disease produced better results. The Japanese were among those who worked on this – because of religious reasons. The Japanese belief that removal of an eye prevented humans from proceeding to the next and more important phase of existence, meant that families would rather have a child die with a diseased eye than live with removal of an eye. Abramson’s group has now initiated ‘superselective infusion of chemotherapy’ where the tip of the catheter is placed into the ophthalmic artery for introduction of the chemotherapeutic drug. This new form of treatment has eliminated the side effects of radiation as well as of systemic chemotherapy, preserved the eye and often produced a cure! The future for children with the misfortune of having a retino-

blastoma – and for the parents – seems brighter and this made, for me, this essay the most inspiring chapter in the volume.

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The present volume of the *Annual Review of Nuclear and Particle Science* is a collection of 16 articles on topics in Particle Physics and Field Theory and some topics on what has now come to be known as ‘Beyond the Standard Model’ physics. The articles are by the leading experts in the field and bear a magisterial stamp. One may even say that each of the articles is basically the last word on the subject at the time of the writing of the articles. Nevertheless, each of the topics is an active and growing subject, which requires a summation of the state of the art at various points in time, and the present collection is absolutely one such.

As is often the case, the series honours the lifetime achievement of an outstanding subject in the field, in the form of an article by an eminent person or as an article by the person himself or herself. In this volume, the reader is treated to an article by the Nobel Laureate James W. Cronin who was one of the discoverers of the phenomenon of CP violation (C stands for charge conjugation which relates the laws governing the interactions of particles with those that govern their anti-particle counterparts, and P stands for parity or mirror symmetry which governs the laws of physics in our world with that of a posited mirror world, and CP stands for their joint action on the laws of physics, the violation of which is not forbidden by the laws of relativity, but is today known to occur only in the physics of certain unstable particles known as mesons. On the other hand, this when combined with T, or time reversal to yield CPT must be conserved as a consequence of the special theory of relativity). Cronin has two distinct phases in his life, one between 1955–85 when he worked on particle