carbon dioxide at –80°C, which was at least twice as strong as the line 1388 cm^{-1}. They attributed the line to the intermolecular oscillation in loosely polymerized groups at low temperature. Sirkar and S. N. Sen studied benzene, carbon tetrachloride, glycerine, acetone, and xylene with continuous radio waves in the range of wavelengths 55 to 100 cm. They found that different polar molecules in the liquid state exhibit anomalous absorption in different radiofrequency regions, and non-polar liquids do not show this phenomenon.

Chapter 7, 'Studying the Jute Fibre and Cosmic Rays' describes the ingenuity of SCS to study the quality of Jute fabric under the direction of Professor M. N. Saha, the Palit Professor of Physics at Calcutta university. The aim of the investigation was to find out how to improve the strength of high quality varieties of green jute fibre by treatment with chemicals. Under the guidance of Saha, SCS and his associates began their cosmic ray research. The American scientists, H. V. Neher and W. H. Pickering, helped them in constructing an apparatus (counter telescope) for this study during their visit to the University of Calcutta. SCS and S. K. Ghosh investigated the production of mesons by non-ionising agents in cosmic rays in lead absorbers using an anticoincidence circuit. They found that at sea level, about 2% of the total meson intensity was produced by non-ionising rays rather than photons in a lead absorber. Their results were not in accord with that of L. Janossy and G. Rochester, who performed experiments with similar instruments. SCS did not continue his work on high energy particles despite reasonably good results.

Chapter 8 is based on research publications of S. C. Sirkar. It includes 110 research papers, bulk of them published in Indian journals, 24 general articles and book reviews, and two books. He published his book *Cosmic Rays* in Bengali. It is a mere coincidence that when I ventured to prepare reading material in Punjabi language during my service in Punjabi University, Patiala, my first book was also on cosmic rays, titled *Brahmandi Kirna Di Kahani*. SCS proved to be one of the most widely published scientists of Calcutta School (IACS) amongst the students of CV Raman, who carried his legacy forward.

The author has published an exhaustive bibliography to augment the historical worth of his volume. It also shows the painstaking effort made by the author to prepare this monograph on S. C. Sirkar, who suffered neglect at the hands of his own countrymen. Despite the best efforts of the author, some minor mistakes of technical nature are visible in the text: on page 14, electric moment written as 'electric movement'; on page 107, precision misspelt as 'precession'; and on page 150, lead absorber written as 'lead observer'. Overall, one has to appreciate the hard work by the author to bring to light the rare quality of work done by S. C. Sirkar.

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This issue of Annual Review of Nutrition (ARN) deals with many unusual nutrients as also with the complex interactions between nutrients. While the nutritional significance of fat-soluble vitamins is well-documented, most researchers tend to focus on the more popular areas, such as vitamin A and vision or vitamin D and bone health. Usually the other vitamins such as vitamin E and vitamin K get downplayed – and this issue of ARN attempts to bridge this gap. Shearer and Okano focus on vitamin K, which is classically known for its role in blood coagulation. The Vitamin K cycle involves its utilization as a cofactor for a microsomal enzyme, γ-carboxyglutamyl carboxylase (GGCX), and its subsequent regeneration by the enzyme Vit K epoxide reductase (VKOR). The article highlights novel predictive insights into specific mutations in these enzymes and their clinical phenotypes. Vitamin A and its derivatives belong to a group of organic compounds called apocarotenoids, which are cleavage products of parent carotenoids such as β-carotene. Interest in apocarotenoids has spiked in recent years primarily due to their antioxidant properties, which can be attributed to the unique conjugated double bond system in their structure. The article by Harrison and Quadro describes many nonretinoid apocarotenoids, and attempts to elucidate the molecular mechanisms underlying the various beneficial effects they have on almost all organs in the human body. While many apocarotenoids regulate gene transcription by interacting directly with nuclear receptors, others also appear to have nongenomic activities. It is clear that further studies are needed to understand the bioavailability of these compounds, and if necessary, to define dietary requirements of the same. Studies suggest that there is high inter-individual variability in the bioavailability of all fat-soluble vitamins including apocarotenoids. Borel and Desmarchelier attempt to describe how this variability is mainly due to single nucleotide polymorphisms (SNPs) in or near genes involved in intestinal uptake or efflux of these compounds, and in genes involved in their metabolism and transport.

Over the last few years, the focus of papers in the ARN has been on obesity and its associated cardiovascular risks. In this issue, the focus is shifted to the other major global non-communicable disease, viz. cancer. High intake of carbohydrates has been implicated strongly in obesity and diseases such as CVD and type 2 diabetes, however the data on cancer is less obvious. It has long been speculated upon that sugars are the main source of energy for malignant cancer cells, but the review by Makarem indicates that the association between dietary sugars and cancer varies by the type of sugar, by cancer site and also by gender. The authors do provide a note of caution that there are a number of methodological issues with such studies, mainly with respect to self reporting of sugar intakes, and with extrapolation of such intake data over long periods of time. Nevertheless it does appear advisable to limit sugar intake, especially in the form of added sugars and sugar-sweetened beverages. One form of sugar, whose consumption has increased dramatically over the last 50 years is fructose, mainly due to the use of additives such as high fructose corn syrup. Ferraris *et al*. elucidate the process of absorption of fructose through the GLUT5 receptor, and discuss how high uptake of fructose could potentially

compromise bone health by reducing intestinal Ca^{2+} and Pi transport.

Although the effects of sugar consumption on cancer appear to be inconsistent, one thing that all nutritionists appear to agree upon currently is that sugar consumption is strongly correlated with body mass index (BMI) and obesity. In this context, the article by Cespedes Feliciano, exploring the relation between obesity and cancer appears very timely. The key message in this article is well worth highlighting, i.e. BMI should not be used as an index of obesity. The so-called obesity paradox, whereby both underweight as well as obesity increases the risk for cancer mortality, compared to being overweight (BMI of 25 to <30), can be attributed mainly to the ratio of adipose to muscle mass in the body. BMI is a poor index of muscle mass, and overweight patients often have higher muscle mass. Since both cancerous cells as well as cancer therapy contribute to muscle loss, the presence of higher muscle mass at the time of cancer detection considerably improves the odds of survival. However the picture changes in obesity, wherein the percentage of adipose increases over muscle mass, resulting in increased inflammation and metabolic dysregulation in cancer patients.

Another important nutrient that behaves as a two-edged sword is iron. This has been a hotly debated topic especially in the last few years, with the focus on the universal iron supplementation programmes for pregnant women. The main issue has been the possible deleterious effects of excess iron intake, especially in women who are already iron-sufficient[1,2]. In this issue of ARN, Torti *et al*. have explored the role of high levels of iron in cancer initiation. A number of epidemiological studies point to the clear association between heme iron ingestion (in the form of red meat) and certain cancers such as pancreatic, lung and colorectal cancers. It is well known that dietary iron is poorly bioavailable and its metabolism in humans is strictly regulated, however tumour-initiating cancer stem cells appear to subvert this process resulting in enhanced intracellular iron acquisition and retention. This excess iron now fosters tumour growth, leading to metastatic spread as well as treatment resistance. This characteristic of most tumour cells has led to a new strategy in targeted cancer therapy, by chelating circulating iron to reduce iron availability, or by using the excess iron to cause oxidative stress, resulting in cell death.

Yet another deleterious effect of excess iron lies in its ability to promote viral infections, mainly because iron is an essential nutrient for almost all infectious microorganisms. The article by Wessling-Resnick helps to understand how many viruses use the transferrin receptor as the main route to enter cells. This occurs through a canonical clathrin mediated endocytosis. This delivers the virion to low-pH endocytic compartments, helping in the eventual invasion of the virion into the cytoplasm. Furthermore, the recycling of the transferring receptor may actually allow for superinfection to occur.

Having talked about iron excess and its fallout effects, the fact remains that iron deficiency is a much larger problem than iron overload, and iron deficiency anemia continues to be a global risk especially for children and pregnant women. WHO prescribes a dose of 30–60 mg/day iron daily during pregnancy, in combination with 0.4 mg folic acid. Folic acid is a B vitamin that plays a key role during early embryonic development, and in combination with vitamin B12, folate has been unequivocally shown to prevent neural tube defects in the developing foetus. However, the molecular mechanisms underlying the role of folic acid and birth defect etiology remains elusive. Field *et al*. describe the role of folate in 1-carbon metabolism, especially the partitioning of methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) between the cytosol and the nucleus, which ensures that 1-carbon units are available for de novo thymidylate (dTMP) synthesis in the nucleus.

While it is well accepted that folic acid is required during pregnancy for proper brain development of the foetus, we tend to forget that the brain requires additional nutrition even after the first 1000 days. The adult human brain is only 2% of the weight of the body, but consumes about 20–25% of the body's total energy consumption. Although this sounds very high, the fact remains that in the first decade of life, the glucose consumption by the brain is double that of an adult. It is becoming more and more apparent that the brain cells continue to grow and 'mature' far longer than previously believed, and this requires not just glucose, but a whole host of vitamins, minerals and micronutrients such a long chain *n*–3 and *n*–6 fatty acids. The composition of the gut microbiota is another important modulator of brain development. In this context, Goyal *et al.* argue that considering such a high nutrient requirement by the brain, discussions of dietary nutritional requirements ought to focus on brain requirements as the principal determinant, while simultaneously taking into account cultural, agricultural and socioeconomic features of different countries.

At the other end of the spectrum lies the field of geroscience, an interdisciplinary field that seeks to define the biochemical mechanisms involved in ageing. Nutritionists have often looked at diets and lifestyles of centenarians in order to determine if there is any such thing as a specifically 'healthy phenotype'. Franceschi *et al*. introduce a new term – inflammaging – which refers to chronic, low grade inflammation that contributes to the pathogenesis of age-related diseases. It appears that centenarians have a unique combination of genetics and epigenetics, which in combination with disciplined nutritional habits and lifestyle, results in a younger biological phenotype. In many aspects, they seem to be similar to individuals on calorie restricted diets[3], especially with respect to the increased levels of fibroblast growth factor 21 (FGF21), a master mitokine in metabolism. FGF21 is an endocrine hormone derived from the liver, and studies in the past decade have shown it to be a critical regulator of nutrient homeostasis. The review by Bon Durant and Potthoff examines the various functions of FGF21, especially its role in metabolic diseases such as obesity and diabetes. The metabolic effects of FGF21 are mediated through actions in the CNS, through regulating macronutrient preference, sweet taste preference as well as alcohol intake.

The articles in this issue of ARN also give us an insight into why the effects of individual dietary nutrients should never be considered in isolation. For example, dietary tryptophan has recently been the focus of attention due to its role in serotonin production in the brain, resulting in improved mood and cognition[4]. However, the article on centenarians suggests that a Trp-restricted diet can actually promote longevity and reduce age-dependent deterioration[5]. Similarly, calorie restriction (CR) has been shown to be the most effective intervention to extend longevity and to protect against chronic

and degenerative diseases. However, while CR has clearly been shown to decrease tumour growth, it can paradoxically increase the number and proliferation of intestinal stem cells, thus boosting the rate of malignant transformation. The article by Alonso and Yilmaz describe the effects of nutrient sensing pathways such as the mTORC pathways on intestinal stem cells, and their potential application in the development of therapeutic interventions.

Finally, the role of individual variations in the dietary management of obesity and overweight is highlighted in the article by Hjorth *et al*. Numerous randomized controlled trials have compared various diets for treating overweight and obesity, and have failed to provide strong evidence for the efficacy of any particular one. A more well-defined classification of participants by combinations of glycemia and insulinemia status might help to provide better and more personalized nutrition and lifestyle interventions. This would go a long way in resolving the never-ending argument on which diet is the best.

The issue ends with a very controversial and hot topic – genetically modified (GM) or genetically engineered (GE) foods. The increasing use of genetic modifications to improve crop yields has led to numerous controversies worldwide among individuals, governments and companies. The last chapter in this volume of ARN by Scot *et al.* is a succinct presentation of the complexity of the issue – whether dealing with the advent of technological advancements such as the CRISPR/Cas9 techniques, or with the belief in the lay public that GE foods present a 'moral' violation of nature. There is no simple solution to this problem especially as this juggernaut continues to race ahead with not just plants but also animals coming within its purview.

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