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EDITORIAL

X-rays, Crystals and Diffraction: Illuminating the Structure of Matter

Students of science, in the final years of school, and those who continue to study physics in college, confront the famous equations of physics, at times with trepidation. Newton's $F = ma$ makes an early appearance; mechanics seems to relate to everyday experience, although a little reflection might lead to the conclusion that most individuals are comfortable with an Aristotelian world view. Einstein is inextricably linked, in the popular mind, with $E = mc^2$; the mass–energy equivalence conjuring up the dramatic image of mushroom clouds after a nuclear explosion. There are many other immortal equations, easy to remember but harder to relate to, like Schrödinger's $H\psi = E\psi$, which introduces us to the uncomfortable idea that everything may not be what it seems to be; its symbols representing a hidden complexity that eludes common understanding. There are other equations like Boltzmann's $S = k \log W$, an equation of 'compact and penetrating beauty' in Jacob Bronowski's words, which are striking for their simplicity of form and remarkable for the deep insights into nature that have been derived from them. It is easy to gauge which equations have imprinted themselves in the minds of students, who have little intention of pursuing a career in science, during casual questioning at interviews. There is one, a favourite in the many committees in which I have been a spectator, which appears embedded in the memories of students, in the years after exposure to college physics – Bragg's $n\lambda = 2d \sin\theta$. Bragg's law is simple in form, but spectacular in the insights that it provides on the interaction of X-rays with crystals; laying the foundations for building the edifice of X-ray crystallography, a technique, which more than any other, has contributed to our understanding of the structure of matter over the last century. Bragg's equation appeared almost exactly a century ago in November 1912, an anniversary highlighted with characteristic elegance by John Thomas, in an essay which notes that 'the seminal work begun in Yorkshire that summer of 1912 still resonates worldwide'. He draws attention to the title of a lecture scheduled at the Cambridge Philosophical Society, to mark the occasion, to be delivered by Venki Ramakrishnan, which says it all: 'Seeing is believing: how a century after its discovery, Bragg's law allows us to peer into molecules that read the information in our genes.' Crystallography is, in Thomas' words, 'still the single most powerful tool for scientists in physics, biology, medicine, materials and Earth sciences as well as for many breeds of engineer' (Thomas, J. M., *Nature*, 2012, **491**, 186). Ironically, Thomas forgets to mention chemistry, a Freudian slip. Indeed, most scientific advances that critically depend on X-ray crystallography have been recognized with Nobel prizes in chemistry.

Röntgen's discovery of X-rays is also a November event that dates back to 1895. The serendipitous discovery of a mysterious radiation that appeared to penetrate soft matter has probably had a greater impact on medicine and chemistry than any other finding of the 19th century. Radiology's origins may be traced without any difficulty to Röntgen's famous X-ray images of his wife's ringed hand. A year after a reluctant Röntgen, known for his reticence, spoke about his discovery, X-rays entered medical diagnosis. In the early years, patients encountered X-ray machines that appeared formidable and intimidating, a sharp contrast to modern day facilities. A commentary on 'First-generation radiography: The patient's perspective' provides a fascinating account of what it was like 'to undergo radiography in the first generation'. The authors quote extensively from Thomas Mann's novel, *The Magic Mountain*, that appeared in 1927. Mann, the 1929 Nobel prize winner for literature, was a patient at a tuberculosis sanatorium when he encountered X-rays. 'His wife had been a student of Röntgen at Munich' (Gunderman, R. B. and Tritle, B. A., *Radiology*, 2011, **259**, 321). One of Mann's characters in the book is permitted to view 'his own form through the lens of the X-ray'. He sees 'precisely what is hardly permitted man to see, and what he had never thought it would be vouchsafed him to see: he looked into his own grave… and for the first time he understood that he would die'. Gunderman and Tritle note that 'for centuries the skeleton has symbolized death'. X-rays strip away the flesh allowing us, in the authors' words, to perceive 'the same skeleton, symbol of the ineluctable mortality that lurks inside every human being'. Indeed, Röntgen's wife described the view of the skeleton of her hand as 'a premonition of death'. The early amazement and fear of X-rays quickly gave way to wide acceptance. A light hearted retrospective on Röntgen rays draws attention to poetry and limericks inspired by the discovery.

A doggerel that appears in a 1970s physics book is a sample (Rowe, R. C., *Drug Discovery Today*, 2003, **8**, 60)

'*I'm full of daze,*
Shock and amaze;
For nowadays
I hear they'll gaze
Thro' cloak and gown – and even stays,
These naughty, naughty, Röntgen Rays.'

What were X-rays? Were they particles or waves? These are questions that occupied physicists in the years following Röntgen's discovery at a time when the edifice of classical physics seemed on the verge of crumbling under the pressure of impending revolution.

By 1912, Paul Ewald's work on crystals and their optical properties was becoming known, leading Max von Laue to suggest the famous experiment, carried out by Friedrich and Knipping, which revealed that ZnS crystals acted like a diffraction grating when a beam of X-rays struck the material. X-ray diffraction was born and the Braggs, father and son, armed with the insights from Bragg's law, quickly began to determine the structures of simple inorganic crystals. Sodium chloride succumbed first, quickly followed by the potassium halides and finally diamond, all in 1913. A century later it is hard to imagine the excitement that must have been caused in the physics and chemistry communities at that time, although World War I must have undoubtedly limited the impact to a great extent. Within fifteen years after their institution, three Nobel prizes in physics were awarded for the discovery of X-rays and their abilities to lay bare not only the human skeleton in living people, but also to uncover the arrangements of atoms in crystals. Röntgen in 1901, von Laue in 1914 and William and Lawrence Bragg in 1915 were honoured for their work, with Lawrence Bragg at 25 being the youngest ever Nobel laureate. Crystallography became a discipline that made major inroads into the study of minerals and inorganic materials by the 1920s and the first steps towards the structure determination of small organic molecules were evident by the 1930s. For the practitioner, the 'phase problem' loomed large; a technical hurdle that impeded the progression from an X-ray diffraction pattern to a crystal structure. Specific techniques developed to overcome the obstacles to three-dimensional structure determination allowed some major battles to be won in the 1940s and 1950s. The conquest of penicillin, not long after the antibiotic era began in the mid-1940s, and vitamin-B12 revealed molecular structures unprecedented in chemistry. Crystalline fibers, less ordered than the perfect single crystals of chemistry, provided limited diffraction data but together with model building allowed X-rays to breach the barriers between the 'small' molecules of chemistry and the 'large' molecules of biology. The alpha-helix in fibrous proteins, the DNA double helix and the collagen triple helix (an Indian triumph) appeared in the years between 1951 and 1954. Size barriers were truly breached when the structures of the proteins myoglobin and hemoglobin appeared, revealing for the first time the formidable complexity of molecular structures in biochemistry. Crystallography had given birth to structural biology. The 1962 Nobel prizes in chemistry and physiology or medicine recognized the structures of proteins (Kendrew and Perutz) and DNA (Watson, Crick and Wilkins). The hard won successes of penicillin and vitamin-B12 were recognized a couple of years later (Dorothy Hodgkin). Even in the late 1960s and early 1970s X-ray diffraction remained the domain of specialists. The advent of the direct methods of phase determination coupled with the development of immensely efficient computer programs for structure solution and refinement, together with the availability of automated diffractometers with intense X-ray sources and sophisticated detectors, opened the floodgates of molecular structure determination, X-ray diffraction was an essential analytical tool in chemistry by the mid-1980s. The 1985 Nobel prize in chemistry to Jerome Karle and Herbert Hauptman recognized the key catalytic role of the mathematical approaches that led to this transformation. The esoteric, probabilistic methods that formed the core of the direct solution of the phase problem were not readily assimilated in the years immediately following their publication. In Hauptman's assessment the initial reactions were skeptical, if not hostile. He says: 'In hindsight I think this reaction was due, first, to the strong mathematical flavour of this early work, not well understood by most crystallographers, as well as the ingrained and almost universal belief that the phase problem was unsolvable in principle and that any claim to the contrary must therefore be flawed' (Hauptman, H. A., *Struct. Chem*., 1990, **6**, 617).

Crystallography in India traces its origins to C. V. Raman's laboratory at the Indian Association for the Cultivation of Science in Calcutta in the late 1920s leading to the publication of the structures of naphthalene and anthracene by Kedereshwar Banerjee in 1930. The highpoint was reached in Madras in the 1950s and 1960s when the structure of collagen was determined by G. N. Ramachandran, culminating in the pathbreaking work on the conformations of protein chains. 2014 has been declared as the International Year of Crystallography, marking the 100th anniversary of von Laue's Nobel prize. In reflecting on the evolution of crystallography over a century I was drawn to an unusual article entitled 'Domesticating the crystal: Sir Lawrence Bragg and the aesthetics of X-ray analysis' which argues that Bragg's science preferred 'aesthetics over mathematics'. The author goes on to conclude that 'placing X-ray crystallography in this category will give us a richer view of modern physics, too often seen as relatively plus quantum mechanics' (Black, S., *Configurations*, 2005, **13**, 2007). Early X-ray images of human bodies evoked a premonition of death. When Röntgen's rays are trained on inanimate crystals, they bring them to life. X-rays have truly illuminated the structure of matter.

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