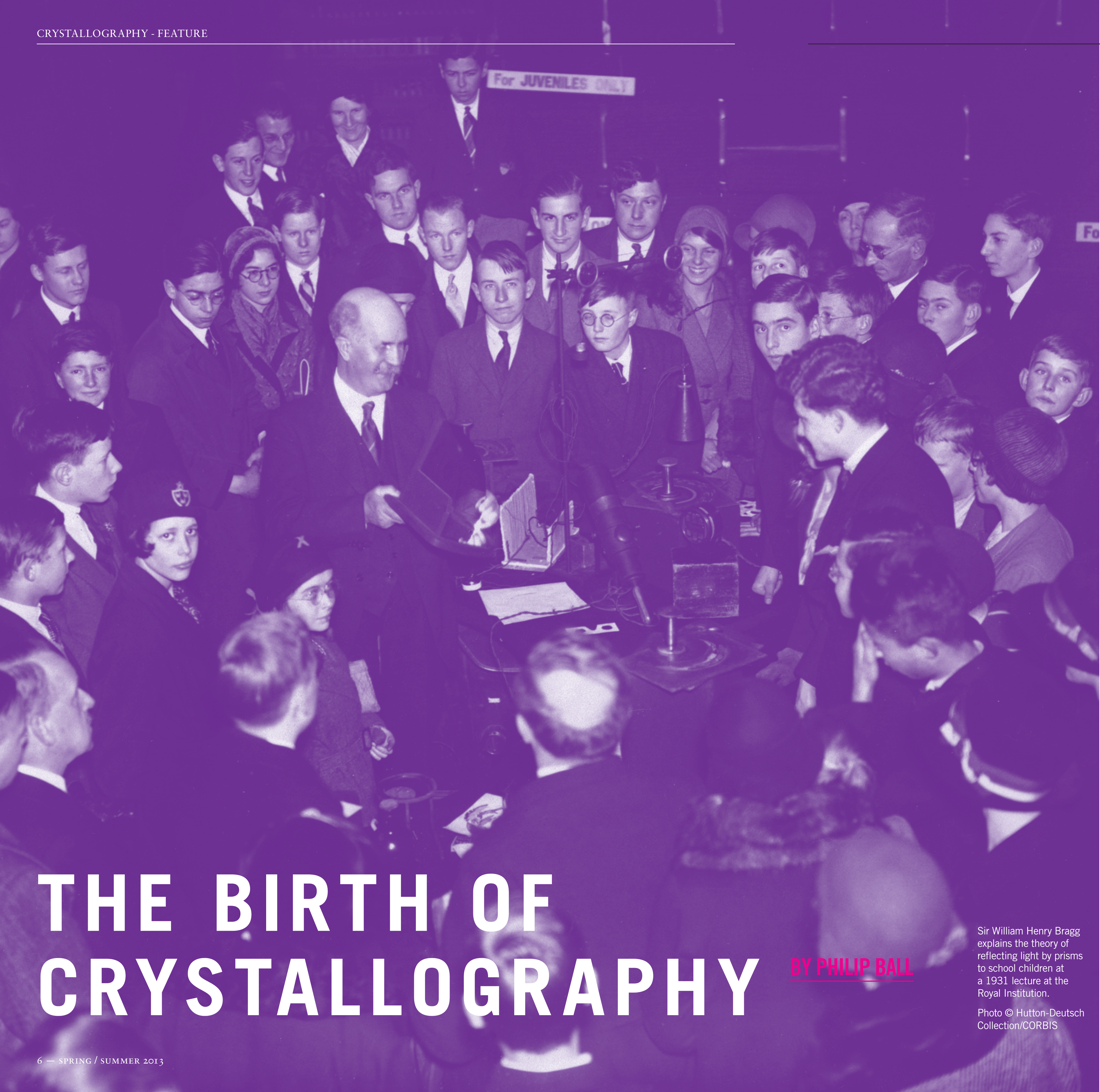
CRYSTALLOGRAPHY - FEATURE



THE BIRTH OF CRYSTALLOGRAPHY

BY PHILIP BALL

Sir William Henry Bragg explains the theory of reflecting light by prisms to school children at a 1931 lecture at the Royal Institution.

Photo © Hutton-Deutsch Collection/CORBIS

STRUCTURAL BIOLOGY, GEOLOGY, ENGINEERING, CHEMISTRY, PHYSICS. BRAGG'S LAW. SPECTROMETERS. DIFFRACTOMETERS. PIONEERING WORK DONE AT LEEDS A CENTURY AGO STILL FEEDS INTO MUCH OF MODERN SCIENCE. THIS IS HOW IT STARTED

The birth of X-ray crystallography at Leeds in 1912-1913 through the work of Sir William Henry Bragg and his son Sir W. Lawrence Bragg was one of the culminating episodes in arguably the most extraordinary three decades in the physical sciences.

Between 1890 and the end of the First World War, X-rays and radioactivity were discovered, the theories of relativity and quantum mechanics developed, and the constitution of atoms first explained. During this period Marconi developed radio telecommunication, the Wright brothers made their first flights and Max Planck proposed quantum theory. These were, in other words, the formative decades of the modern age.

It is not often appreciated how important to that incipient modernity the Braggs' work was. William and Lawrence paved the way to countless scientific and technological breakthroughs by revealing the arrangement of atoms in crystals. Although it had been long suggested that crystals were made up of a regular pattern of atoms and molecules, there was previously no way of knowing precisely how these were arranged.

X-ray crystallography is the chemist's most reliable tool for deducing the shapes and arrangements of molecules. It tells us about the nature of terrestrial and extra-terrestrial minerals. Through an understanding of crystal structures, it became possible to develop new and better materials. When applied to the molecules of life, it ushered in the age of molecular biology and genetics – most famously as the technique that revealed the structure of DNA to James Watson and Francis Crick in 1953.

For their achievements, William and Lawrence Bragg were awarded the 1915 Nobel Prize in Physics. In 2013, the Braggs' work was named the third most important British innovation of the 20th century in an online vote of 80,000 people.

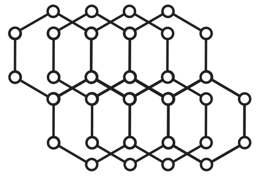
Yet research on crystallography had not even begun when the Braggs arrived in England from Australia six years before the Nobel award. Such immediate recognition is rare for Nobel Prizes, and it testifies both to the importance of their work and the clarity with which they explained and demonstrated its potential in many areas of science.

Cumbrian-born William came to Leeds from the University of Adelaide, Australia, where he had established a solid international reputation for his work on radioactivity and the nature of the new invisible 'emanations' from matter: X-rays, gamma rays and alpha particles. As Professor of Physics and Mathematics, William had found in Adelaide a meagre laboratory, so he set about making his own equipment by apprenticing himself to a local instrument maker.

When Leeds needed a new Cavendish Professor of Physics in 1907, the English chemist Frederick Soddy recommended William to the University, saying that, when he had visited Adelaide, "I was much struck with the spirit he has created around him." William was offered and accepted the post.

In January 1909 William and his family – wife Gwendoline, sons Lawrence and Robert and daughter Gwendy – boarded the coal-fired *Watarah* for the journey to England, arriving in Plymouth in March. They rented a house in fashionable Headingley as well as a weekend

BRAGG X-RAY SPECTROMETER
ENGLAND, 1910-1926



BRAGG EXPLAINED THE IDEA OF SHEETS OR PLANES OF ATOMS WITH REFERENCE TO THE ROWS OF VINES IN A VINEYARD

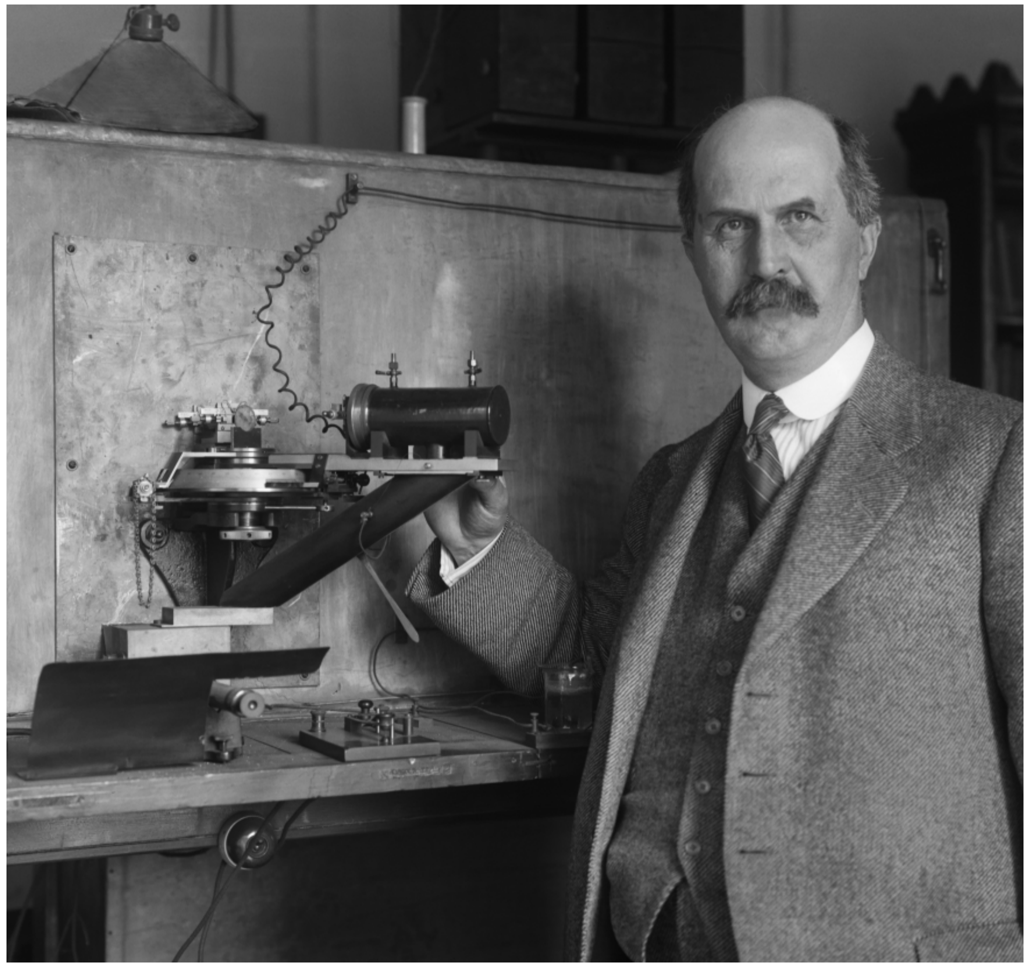


PHOTO:
WILLIAM HENRY BRAGG WITH HIS SPECTROMETER, C1910. WILLIAM ENJOYED THE SERVICES OF AN EXCELLENT WORKSHOP AT LEEDS, LED BY HEAD MECHANIC CH JENKINSON

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cottage near Bolton Abbey 20 miles north of the city. Lawrence enrolled, as his father had 28 years earlier, at Trinity College, Cambridge.

William was deeply interested in the nature of X-rays. At the time a vigorous debate raged among physicists about whether X-rays were 'corpuscles' or 'pulses' – particles or waves – the latter widely believed to travel through an invisible medium called the ether. Although William preferred the particle interpretation, X-rays are in fact electromagnetic waves, like light, but of a very much smaller wavelength. Yet Albert Einstein argued in 1905 that light can also be considered to be like a stream of particles, called photons: this 'wave-particle duality' was one of the first fruits of the nascent quantum theory.

Given this interest, the Braggs, father and son, were fascinated by news of work in Munich by Max Laue, a student of Max Planck. Laue found that when a narrow beam of X-rays was directed at a crystal, the scattered rays formed a geometric pattern of bright spots on a photographic plate placed behind the sample. Laue attempted to interpret the pattern but could not account for all the spots. Lawrence, still at Cambridge, recalled that he and his father discussed Laue's findings intensely "when we were on holiday at Cloughton on the Yorkshire coast."

Over the summer and autumn of 1912, William and Lawrence collaborated in the Leeds Physics laboratory. Writing in 1961, Lawrence pointed out how adept William was in the laboratory. "My father was supreme at handling X-ray tubes and ionization chambers. You must find it hard to realize these days what brutes X-ray tubes then were." At Leeds, William had rather better technical support than Lawrence did in Cambridge, which still pursued a "sealing wax and string" approach to experimentation. William, in contrast, enjoyed the services of an excellent workshop led by head mechanic C H Jenkinson.

It was Jenkinson who built, from William's design, a revolutionary instrument that could be used both to measure X-ray wave lengths (the technique of X-ray spectrometry) and to measure reflections from crystal plains (X-ray diffraction). The instrument, used both as a spectrometer and a diffractometer, partly superseded Laue's photographic technique in that it enabled precise measurements of the angles and intensities of the diffracted beams.

Adhering to William's 'corpuscular' view of X-rays, the Braggs at first sought to interpret Laue's bright X-ray spots on the basis that X-ray 'particles' were being channelled along 'avenues' between rows of atoms, an idea they described in a paper published in October 1912 in the journal Nature.

But later that month, shortly after his return to Cambridge for the Michaelmas term, Lawrence hit on a novel explanation. "The idea suddenly leapt into my mind," he later wrote, "that Laue's spots were due to the reflection of X-ray pulses by sheets of atoms in the crystal." What Lawrence understood was that the beam behaves as though it has been reflected by these sheets, or layers, as light is reflected by a mirror.

William explained the idea of sheets or planes of atoms in 1915 in the Leeds student magazine The Gryphon with reference to the rows of vines in a vineyard – not an obvious Yorkshire reference, but wine had been made in the Adelaide Hills since the early nineteenth century. As you walk through the rows of vines, every so often they align and you can see them stretching away in parallel formation.

On this basis, Lawrence worked out how the reflection angles of the spots depend on the distances between sheets and the wavelength of the X-rays. He expressed this in a formula now known as 'Bragg's law,' which first appeared in a paper presented to the Cambridge Philosophical Society in November 1912 and was reported in Nature in December. Here he also showed that, by assuming a particular kind of arrangement of atoms in crystals of zinc sulphide, he could account perfectly for the X-ray pattern.

The Braggs' crucial realisation was that, if the X-ray diffraction pattern could be accurately predicted from a crystal structure, then one could also work backwards, deducing from the experimentally measured pattern, the structure of the crystal itself.

Of all the crystals whose structures were worked out principally during 1913 (sodium chloride, potassium chloride, calcium fluoride, zinc sulphide and diamond) it was the structure of iron sulphide which gave Lawrence "the greatest thrill," as he recorded long afterwards. This was the first structure in which the positions of the (sulphur) atoms were determined from the intensity (brightness) of the reflections. Lawrence recalled that "I worked it out in the drawing room of our house in Leeds and was so excited that I had to tell my aunt who was sitting in a corner all about it, with indifferent success."

The collaboration between father and son continued throughout the whole of 1913 and until the outbreak of war in 1914. Lawrence spent part of the spring and summer terms in 1913 at Cambridge but the rest of the year at Leeds. The Braggs' work, for which they jointly were awarded the Nobel Prize, was published in a series of papers by the Royal Society in London, marking the birth of X-ray crystallography.

William delivered talks on this new science around the country, at the British Association and in particular at the Solvay Conference. The conference – a roughly triennial gathering of Europe's top physical scientists – was a particularly prestigious platform, and at the 1913 meeting on "The Structure of Matter" William discussed his work with Albert Einstein and Marie Curie, along with several scientists, such as Leon Brillouin and Frederick Lindemann, who went on to make important contributions to the understanding of diffraction and crystal structure.

Late in 1914, William wrote a long letter to the Leeds Vice-Chancellor Michael Sadler, pointing out the University's pre-eminence in X-ray diffraction. "The practical applications are likely to be of no less importance than the theoretical," he wrote. Although his request for funds was supported, Leeds couldn't match the offer in early 1915 of a professorship from wealthy University College London (UCL). William at first refused the offer, but by the time he accepted their second offer he had decided he needed to be in London at the centre of the war effort.

William's departure was not necessarily the tragedy for Leeds that it might have seemed at the time. The Braggs' seminal work here inevitably left a legacy. In 1929 William's student William Astbury, who worked with him at UCL and later at the Royal Institution in London, came to Leeds as a 'textile physicist.' Textiles was the manufacturing base on which Leeds had grown prosperous, and the hope was that research on wool and other economically important fibres might one day improve the manufacturing process.

X-ray crystallography had been initially applied to inorganic crystals, and the challenge of applying the same technique to the study of the large biological molecules found in fibres was considerable. Yet Astbury met the challenge and, thanks to a series of breakthrough papers on the structure of proteins and to his energetic proselytising, Leeds became famous as the "X-ray Vatican" and the home of molecular biology.

CRYSTALLOGRAPHY - FEATURE

A PLAQUE OUTSIDE THE PARKINSON BUILDING COMMEMORATES THE WORK OF THE BRAGGS AT LEEDS

AFTER ONLY SIX YEARS THE BRAGGS WERE AWARDED A NOBEL PRIZE FOR THEIR WORK. NOT EVERYONE RECOGNISED THE IMPORTANCE OF THEIR WORK HOWEVER. "I WAS SO EXCITED THAT I HAD TO TELL MY AUNT ABOUT IT, WITH INDIFFERENT SUCCESS," WROTE LAWRENCE

PHOTO:
W. LAWRENCE BRAGG, WHO WORKED WITH HIS FATHER AT LEEDS WHILST A STUDENT AT CAMBRIDGE

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"AT THE 1913 MEETING ON "THE STRUCTURE OF MATTER" WILLIAM BRAGG DISCUSSED HIS WORK WITH ALBERT EINSTEIN AND MARIE CURIE"

A LEEDS GRADUATE: FROM LEEDS TO MARS

Would the Braggs ever have looked up at Mars and imagined that, one day, an X-ray spectrometer would be there, gathering data on the planet's surface? Although only the size of a tin can, the Alpha Particle X-ray Spectrometer (APXS), developed by the Canadian Space Agency (CSA), MDA robotics and Professor Ralf Gellert's science team at University of Guelph, Canada, is sending an enormous amount of data about the geology of Mars back to Earth. Attached by an arm to NASA's Curiosity rover, the instrument determines the chemical composition of the rocks and soil in the red planet's Gale Crater.

CSA's mission scientist for Curiosity is a physicist who studied at Leeds. Vicky Hipkin (PhD Atmospheric Physics 2000), Senior Program Scientist, Planetary Exploration, says "Curiosity's APXS is amazingly sensitive given its small size. William Henry Bragg's spectrometer at Leeds has been miniaturised using modern technologies – the silicon drift detector and sensitive electronic circuitry for pulse detection. APXS data are very important to geochemists on the Curiosity team. Ratios of trace abundances of soluble elements like chlorine and bromine can tell us about the water history of Mars, and ratios of sodium, potassium and silicon oxides can be used to understand rocks of volcanic origin."

A LEEDS GRADUATE: STILL LEADING THE WAY

A leading pioneer in electron microscopy, Ondrej Krivanek FRS (BSc Physics 1971) is developing a new generation of electron microscopes and other electron-optical instruments. Nion, a company he co-founded 15 years ago near Seattle, USA, makes the world's leading scanning transmission electron microscopes, which are able to focus a beam of electrons on one atom at a time to determine its chemical type, its precise location in a complex structure and its atomic environment.

Both the Bragg apparatus and the electron microscope use a radiation with a wavelength short enough so that individual atoms can be distinguished. Compared to the X-rays used in the Bragg instrument, the electrons used in electron microscopes have an additional advantage: they can be focused into a beam that's narrower than a single atom. Such precise focusing requires highly perfected electron lenses. These have only become available due to a recent breakthrough in electron optics called aberration correction, a technique pioneered by Nion.

Nion's instruments have many other features such as an unprecedented stability that allows them to keep the beam centred on each single atom for several minutes. They are found in only a few laboratories around the world. Two are located at the UK SuperSTEM laboratory, based at a very stable vibrational site in Cheshire. Bragg's diffractometer showed that matter is made of atoms, and led to figuring out how the atoms are arranged. SuperSTEM is now able to image the individual atoms and analyse them one atom at a time.

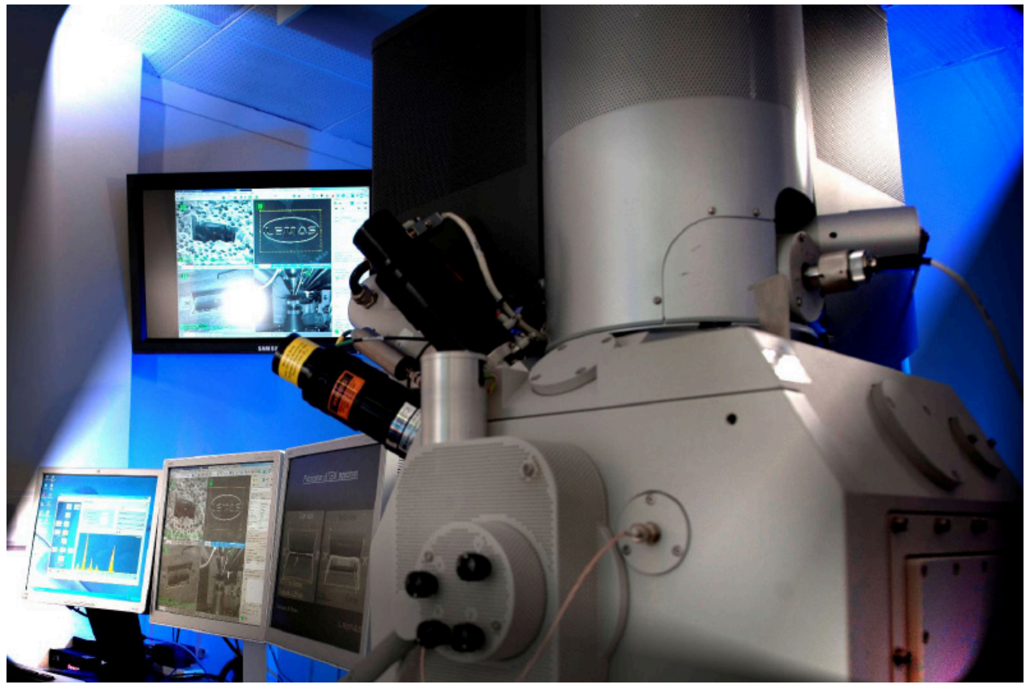

PHOTO: A HIGH RESOLUTION FIELD EMISSION GUN SCANNING ELECTRON MICROSCOPE IN THE LEEDS ELECTRON MICROSCOPY AND SPECTROSCOPY CENTRE

> “THE BRAGGS' CRUCIAL REALISATION WAS THAT, IF THE X-RAY DIFFRACTION PATTERN COULD BE ACCURATELY PREDICTED FROM A CRYSTAL STRUCTURE, THEN ONE COULD ALSO WORK BACKWARDS, DEDUCING FROM THE EXPERIMENTALLY MEASURED PATTERN, THE STRUCTURE OF THE CRYSTAL ITSELF”

In 1938 one of Astbury's research students, Florence Bell, produced the first X-ray diffraction image of DNA, a crucial step that led in 1953 to one of the most important discoveries of the 20th century: the double-helical structure of DNA.

Astbury's work is one example of the significance of the Braggs' research not only within the confines of crystallography, but more broadly across science, engineering and societal boundaries. It has been fundamental to the development of various scientific fields within industry, including microelectronics, pharmaceuticals, aerospace and power generation.

The influence of William Bragg's time at Leeds continues to resonate at the forefront of science a century later.

LEEDS TODAY

MOLECULAR BIOLOGY

The Astbury Centre of Structural Molecular Biology brings together around 250 researchers from across the University to understand the molecular basis of life, and much of this work is based on X-ray crystal structures.

Thomas Edwards, Deputy Director of the Centre, uses X-ray crystallography in much the same way as the Braggs, but on a vastly different scale. Instead of using diffraction to determine the structure of sodium chloride (which has two atoms), the lab team is working with biological molecules made up of hundreds of thousands of atoms.

They determine the 3-D structure of proteins that perform normal tasks within living organisms, and can identify how this is different to a protein that causes disease. “In biology, structure is function,” says Thomas. “By seeing the shape of a protein, we understand better how it works or, in some cases, doesn't.”

Developing drugs to stop malfunctioning proteins, Thomas says, is “a bit like a lock needing a key. Once we see the shape of the lock, we'll look for a small molecule that will fit into it.” Using crystallography to find the exact shape of the lock can speed up drug design by five to ten years.

Thomas is part of an Astbury Centre team of structural biologists and virologists that recently discovered how the Schmallenberg virus, which causes birth defects and still births in some animals, could be targeted by anti-viral drugs. They deciphered the 3-D shape of the Schmallenberg virus nucleocapsid protein and saw the proteins bind together in a ring-like structure, held together by contacts between the protein units, a bit like people holding hands in a circle. Thomas says: “We are now designing small molecules that could block ring formation and could therefore become an effective antiviral drug.”

MATERIALS ENGINEERING

Professor Rik Brydson leads the Leeds Electron Microscopy and Spectroscopy Centre (LEMAS) as well as coordinating the National Facility for Electron Microscopy (SuperSTEM). Based at Daresbury Laboratories in Cheshire, SuperSTEM houses the UK's best electron microscopes (see Ondrej Krivanek sidebar) and was formed by a consortium of five universities and four collaborating partners.

The diffraction and scattering of high energy electrons rather than X-rays makes it possible to actually directly image the planes of atoms that give rise to the reflection or diffraction of the electron or X-ray waves.

SuperSTEM has contributed to an atomic level understanding of the structure of many advanced materials used in electronics, chemical catalysis and in the application of nanotechnology to healthcare. Notably it has made a significant contribution to the understanding of the new material called graphene (a single layer of hexagonally bonded carbon atoms) for which researchers at Manchester received the Nobel Prize for Physics in 2010.

Piezoelectric ceramics are all around us in sensors and actuators and are the irreplaceable heart of modern devices such as SONAR, medical ultrasound, fuel injection valves and parking sensors. Without using X-ray diffraction to inspecting the atomic structure in piezoelectric materials, researchers would be unable to observe the results of their atomic manipulation and engineering efforts.

Because current commercial piezoelectric materials only work well up to around 200°C, their development has been limited. Ionix Advanced Technologies, a spin-out company based on work done in the Institute of Materials Research by Dr Tim Stevenson and Dr Tim Comyn, is creating novel piezoelectric materials that can operate at high temperatures and in extreme environments. If these materials could be used in valves and transducers for cars and aero-engines at temperatures in excess of 500°C, they would enable the development of cleaner, more efficient transport systems.

> “IN BIOLOGY, STRUCTURE IS A FUNCTION. BY SEEING THE SHAPE OF A PROTEIN, WE UNDERSTAND BETTER HOW IT WORKS, OR IN SOME CASES, DOESN'T”

CENTENARY BRAGG CHAIR

To mark the Braggs' achievements, the University is creating a new Professorial post (the Centenary Bragg Chair) in collaboration with the Royal Academy of Engineering, Diamond Light Source and Infineum UK. This aims to advance engineering applications of crystallography using one of the most intense X-ray sources in the world – the Diamond Synchrotron – for studying changes in the structural arrangements of atoms in crystals in the manufacture and use of engineering materials. — (*l.*)

A LEEDS GRADUATE: SAVING LIVES WITH X-RAY SPECTROMETRY

The study of the structure of protein receptors in cancer cells and how they react to drugs is at the heart of how one Leeds graduate has saved women's lives around the world.

V Craig Jordan OBE (BSc Pharmacy and Pharmacology 1969, PhD Pharmacology 1973, DSc 1985, DMed 2001), an eminent specialist in drugs for breast cancer treatment and prevention, is known as “the Father of Tamoxifen” after doing his PhD on the oestrogen receptor (ER) binding with oestrogen or antioestrogen.

Today, Craig is Scientific Director and Vice Chairman of Oncology at the Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC. He uses conformational analysis of molecules binding to the ER to understand breast cancer cell death. “With conformational analysis we're still applying the Braggs' and Astbury's X-ray crystallography, this time to see how one shape of the complex causes survival and another death” says Craig. “This knowledge will help us help patients.”

Craig's new book Estrogen Action, SERMs and Women's Health (Imperial College Press) includes a chapter on X-ray crystallography.