The Braggs and Astbury

Leeds and the Beginning of Molecular Biology

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William Henry Bragg

William Henry Bragg was born in Wigton, Cumbria in 1862.

He graduated in Mathematics from Cambridge in 1885. He came 3rd in the final examinations (a position known as 3rd Wrangler).

He had done some work in the Physics department and become known to J J Thomson (later a Nobel Laureate);

Shortly after graduating he applied for the position of Professor of Mathematics & Physics at the University of Adelaide at Thomson's suggestion.

Figure 1: Portrait of William Henry Bragg

The early Adelaide years

On his appointment in 1886, he found that, with just one assistant, he was entirely responsible for all the mathematics and physics teaching in the University, adding up to18 hours per week plus 6 hours evening FE classes.

In order for his students to do practical work, he apprenticed himself to a firm of instrument makers to make apparatus for his classes - and his interest in instrumentation was to prove important in later years.

But it was not all hard work - he was an excellent tennis player and joined in the social life of Adelaide. He met Charles Todd, who held the posts of South Australian Government Astronomer, Postmaster-General and Superintendent of Telegraphs. Todd had been responsible for constructing the telegraph line from Adelaide to Darwin and had named the staging post 'Alice Springs' after his wife.

Bragg got to know Todd's family and in 1889 he married Gwendoline Todd, with whom he had 3 children, William Lawrence, Robert and Gwendolen

Later Adelaide years

Initially, he had little opportunity for research, but he was very interested in the developing ideas about electromagnetism, wireless and, particularly, radioactivity; he constructed apparatus for demonstrating these phenomena.

Röntgen had discovered X-rays in 1895, but their nature was the subject of controversy. WHB took X-ray pictures of his hand and his son's elbow, hurt in a cycling accident.

It was not until 1903 that WHB carried out his first serious independent research (on radioactivity, alpha & beta particles and gamma rays).

He was a proponent of the idea that X-rays were particles, not waves, and had detailed correspondence with Rutherford and others. He became known internationally and was elected FRS in 1907. The following year, he was invited to the Cavendish Chair of Physics in Leeds.

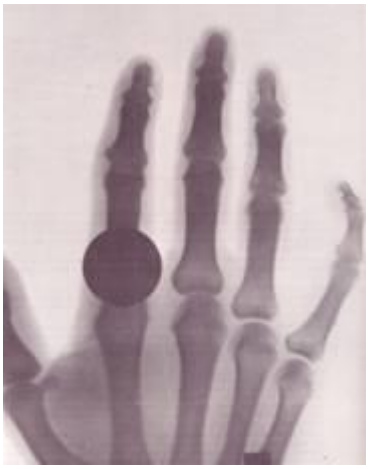


Figure 2: X-radiograph of William Henry Bragg's hand

W H Bragg in Leeds

Figure 3: Bragg's Laboratory was in this single-storey building. The Parkinson Building now stands at the corner site.

WHB continued to be engaged in a controversy with Barkla as to whether X-rays were waves or corpuscles. (In retrospect, Bragg had been studying high-energy rays and Barkla softer, low-energy rays, so they had been observing different properties.)

1912 was an important year: von Laue, Friedrich & Knipping shone X-rays on crystals and obtained a pattern of spots on photographic film.

Were the spots on the film due to corpuscles passing through channels between the atoms in the crystal or waves diffracted by the atoms?

WHB wrote to Schuster (a Cambridge physicist) enclosing this diagram.

Also in 1912, WHB's elder son (William Lawrence Bragg) graduated in physics in Cambridge.

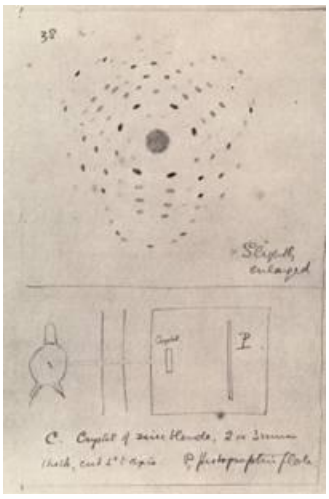


Figure 4: Scan of the diagram sent to Schuster

William Lawrence Bragg and William Henry Bragg in Cambridge and Leeds

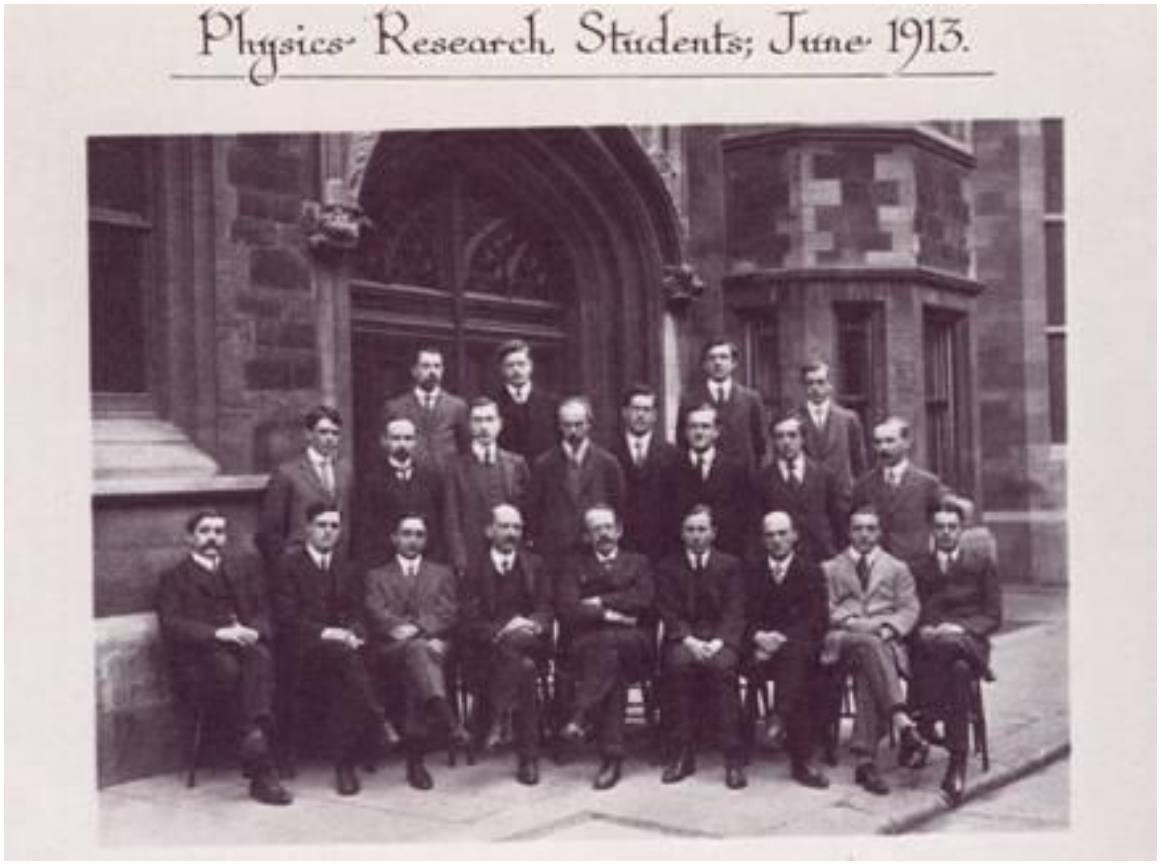


Figure 5: Cavendish Laboratory, Cambridge, 1913

Back Row: W D Rudge, R W James, W A Jenkins, J K Robertson

Middle row: W L Bragg, V J Pavlov, S Kalandyk, F W Aston *(known for his work on isotopes)*, H A McTaggart, H Smith, F Kerschbaum, A N Shaw

Front Row: R D Kleeman, A L Hughes, R Whiddington *(Professor of Physics in Leeds),* C T R Wilson *(invented the cloud chamber)*, J J Thomson *(1906 Nobel prize in Physics for discovery of the electron),* F Horton, R T Beatty, A E Oxley, G Stead

In late 1912, WLB had his "brain wave": the pattern of spots in the X-ray pattern from a crystal could be explained by "reflection" of waves from crystal planes, analogous to light rays from a mirror.

He wrote a paper "The diffraction of short electromagnetic waves by a crystal" in *Proceedings of the Cambridge Philosophical Society*.

WHB had constructed an X-ray spectrometer in Leeds, which gave much more reliable measurements than the Cambridge cameras and films.

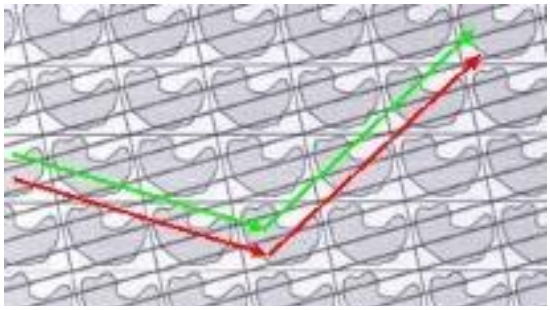
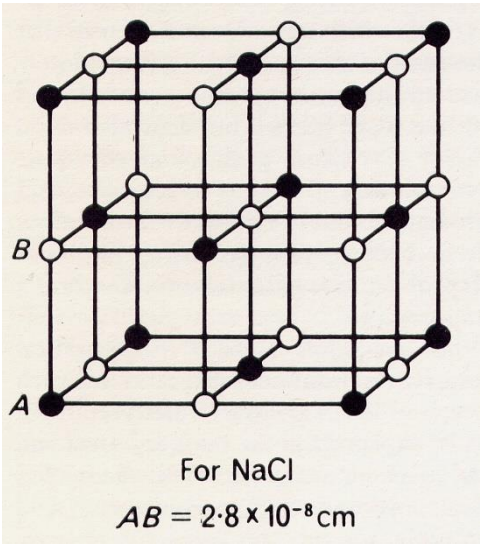


Figure 6: Sets of planes may be drawn through the crystal in many ways. The red line is a ray 'reflected' from one plane in a set. The green line is a ray 'reflected' from the adjacent plane. The rays will emerge in step if the extra distance travelled by the red ray is a whole number of wavelengths. Bragg's law: **nl =2d sin q relates wavelength l, spacing between planes d and direction of rays q.**

In 1912-13, the 2 men worked together and derived the arrangement of atoms in NaCl and KCl.

Sodium Chloride

For a long time, chemists refused to accept the fact that NaCl contains no NaCl molecules - crystals contain just an alternating array of Na and Cl ions.



Professor H E Armstrong, in a letter to Nature, 1927:

"Professor W L Bragg asserts that "in Sodium Chloride there appear to be no molecules represented by NaCl. The equality in number of sodium and chlorine atoms is arrived at by a chess-board pattern of these atoms; it is a result of geometry and not a pairing-off of the atoms.

This statement is more than "repugnant to common sense". It is absurd to the nth degree, not chemical cricket. Chemistry is neither chess nor geometry, whatever X-ray physics might be. Such unjustified aspersion of the molecular character of our most necessary condiment must not be allowed any longer to pass unchallenged. It were time that chemists took charge of chemistry once more and protected neophytes against the worship of false gods; at least taught them to ask for something more than chess-board evidence."

The war years

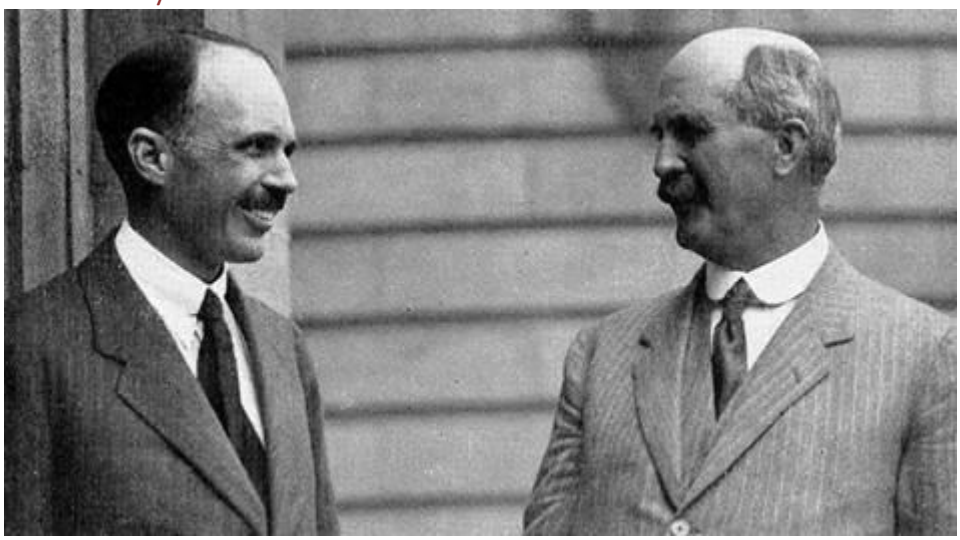


Figure 7: William Lawrence Bragg and William Henry Bragg

WHB became much involved with scientific advice to the government and decided to move from Leeds to University College London to be nearer the centre of national activity.

WLB was on active service in France developing acoustic range-finding methods for directing gunfire and was invested with the Military Cross.

In 1915, they were awarded the Nobel Prize.

This is still the only example of the joint award of a Nobel prize to father and son and WLB remains the youngest recipient of a Nobel prize at the age of 25.

Post-war years

After the war, WHB and WLB continued their X-ray diffraction studies, but agreed to work on different aspects.

In 1919 WLB succeeded Ernest Rutherford in the Langworthy Chair of Physics in Manchester and for many years he concentrated mainly on metals and minerals, and on the development of diffraction methods.

WHB built up a research team at University College London, working largely on organic substances. While there, he wrote: "My son and I have been comparing notes and we find that we can only get a few hours each week for research" - an experience shared by most present-day academics!

In 1923, WHB succeeded Sir James Dewar at the Royal Institution, where he would be free from routine teaching, taking members of his UCL team, including William Astbury and Kathleen Yardley (later Lonsdale). Research workers at the R.I. included also J M Robertson (for many years a leading chemical crystallographer in Glasgow), E G Cox (later Professor of Structural Chemistry in Leeds) and J D Bernal, later an important innovator of structural studies of biological structures in Cambridge and London.

WHB re-established the series of R.I. lectures to lay audiences that had been started by Davy and Faraday and he asked Astbury to take an X-ray diffraction picture of a human hair for a lecture on "the imperfect crystallisation of common things".

Astbury Moves to Leeds

In Leeds, the Vice-Chancellor, James Baillie, had decided in 1928 that the Department of Textile Industries needed to be enlivened by the appointment of a Lecturer in Textile Physics. WHB was among the people consulted about the appointment and he wrote to Professor Aldred Barker:

"I have a man here who might possibly make you the research scientist you want W T Astbury. He is a really brilliant man, has done some first class work which is quoted everywhere. He has considerable mathematical ability and a very good knowledge of physics and chemistry. He is very energetic and persevering, has imagination, and, in fact, he has the research spirit. Although not trained in the workshop he is sufficiently skilful with his hands.

He is a most loyal colleague to me and I do not want to lose him at all but it is good for these people to make a move from time to time. He can lecture, though I do not call him a very good lecturer, he can write a great deal better than he can speak."

In those days, all textiles were made from naturally-occurring fibres such as wool, silk and hair. Astbury got the job in Leeds and set out to show that these were more than the "biochemically lifeless and uninteresting material" they were claimed to be.

Astbury in Leeds

Astbury was appointed as Lecturer in 1928 and became Professor of Biomolecular Structure in 1945. He died in 1961, aged 63.

In the opinion of his biographer, J D Bernal, Astbury was responsible for Leeds becoming the major centre of fibre research worldwide for more than 15 years following his appointment. He established the relationships between the gross (anatomical) structure of natural materials, their physical properties and their underlying molecular structures.

Figure 8: William Thomas Astbury

The Principle of X-ray diffraction

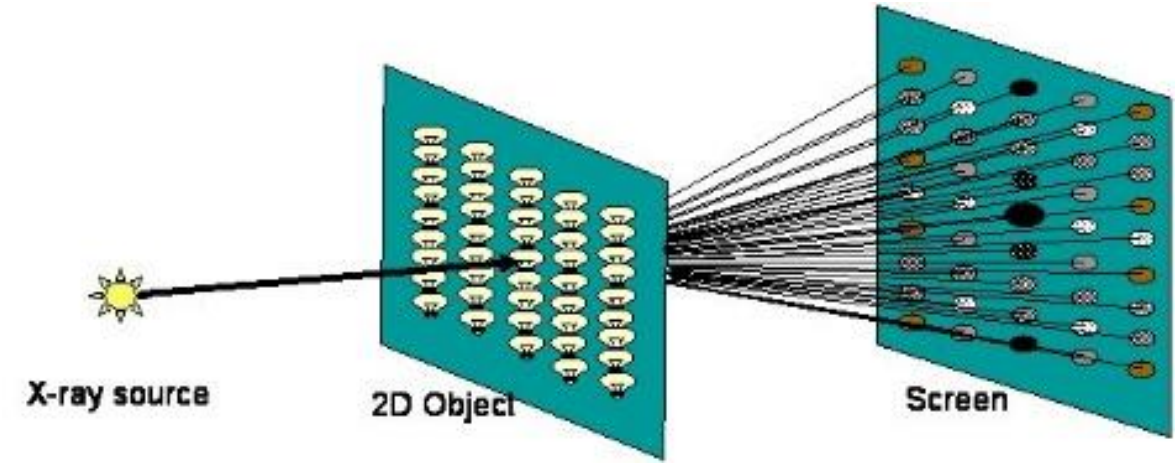


Figure 9: Diagram showing the process of x-ray diffraction through a two dimensional object.

X-ray diffraction occurs when X-rays fall on an object having regular repeating features of comparable size to the wavelengths of the X-rays.

An object that is regular in 2 (or 3) dimensions gives a pattern of rays spaced out in all directions.

Vertical features in the pattern relate to vertically-arranged features in the object and horizontal features in the pattern to lateral periodicities in the object.

The Nature of Crystals

Crystals are made up from a regular pattern of unit cells, of an identical shape and content, which fill space.

Each unit cell contains one or more molecules, packed together in a symmetrical way.

In this example, each cell contains two 'molecules'.

We can only show one layer of 'molecules' in this picture - the complete crystal would be formed by stacking layers one above the other.

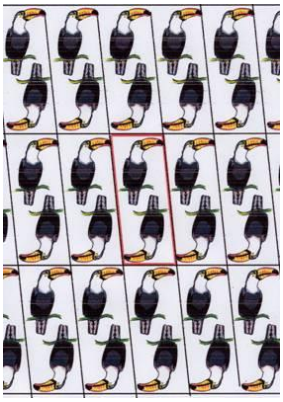


Figure 10: Diagram of a crystalline structure using toucans

The Nature of Fibrous Materials

Fibrous molecules such as the biological macromolecules like wool and silk are very long and, in the fibre, are parallel to each other.

But they are not always lined up longitudinally with their neighbours on either side.

We can still have “unit cells” (red outline), but now with the molecules passing through from one cell to the next along the chain.

As with normal crystals, we still have regular lateral spacings between unit cells and regular spacings along the chain, but we have lost some of the regularity of a normal crystal when the chains are not in register sideways, as shown here.

Figure 11: Diagram of a fibrous structure using toucans

X-ray Diffraction from Fibrous Polymers

X-ray fibre diagrams from naturally occurring fibrous materials (These diagrams are not all to the same scale.)

Figure 12: Alpha keratin (wool)

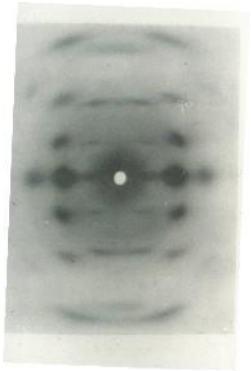


Figure 13: Beta keratin (silk)

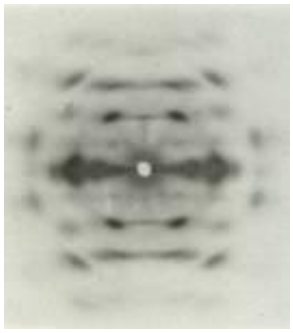


Figure 14: Cellulose

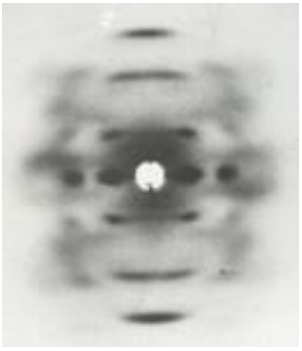


Figure 15: Collagen (tendon)

The fibres were placed with their lengths vertical, and the X-ray beam at right angles to the plane of the X-ray film.

The spacing of spots in the vertical direction relates to regular distances along the length of the fibres and horizontal spacings relate to lateral distances in the fibres.

Cellulose has the simplest and most regular chemical structure with identical chemical units, whereas the structure of wool has a less regular sequence of amino acids. Silk and collagen have more regular sequences than wool.

The Structure of Cellulose Fibres

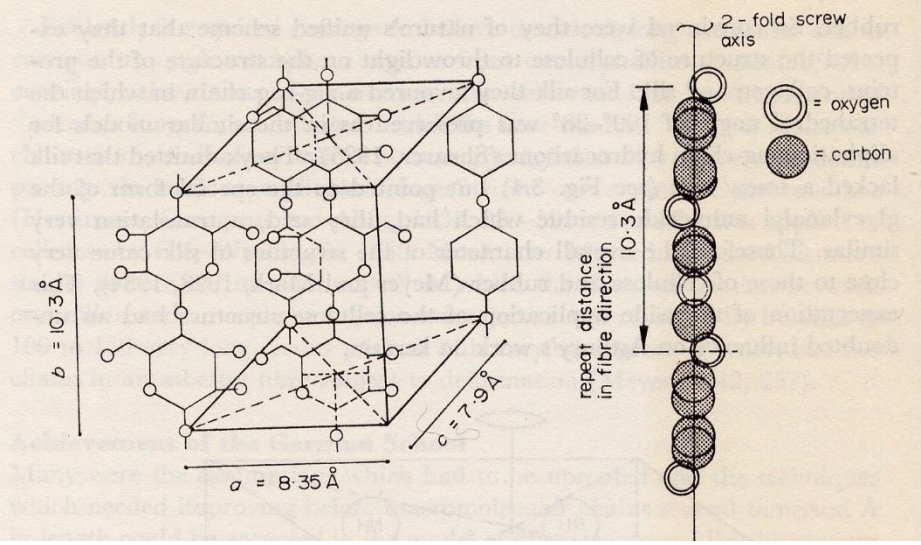


Figure 16: Diagram showinf the structure of cellulose fibres

Cellulose, the major structural polymer of plants, is an unbranched polymer of identical glucose units, which face in alternate directions. Each unit is 5.15Å long, giving an exact repeat of 10.3Å along the fibre axis.

The Structure of Protein Chains

Protein molecules are polymers of 20 different kinds of monomer - the amino acids. As the chain is synthesised on the ribosome, each additional amino acid is added to the carboxyl end of the growing chain with the elimination of a water molecule (bottom left).

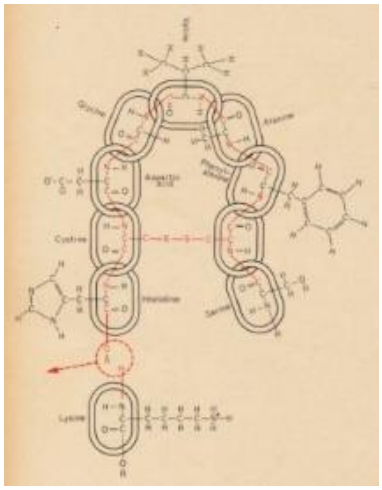


Figure 17: Diagram showing the structure of protein chains

The amino-acid side chains have widely differing sizes and properties:

- positively charged, e.g. lysine
- negatively-charged, e.g. aspartic acid
- neutral polar, e.g. serine
- non-polar aliphatic, e.g. alanine, valine
- non-polar aromatic, e.g. phenylalanine

cystine, which cross-links two different parts of the chain, stabilises (but complicates) the overall chain fold.

Astbury's models for keratin

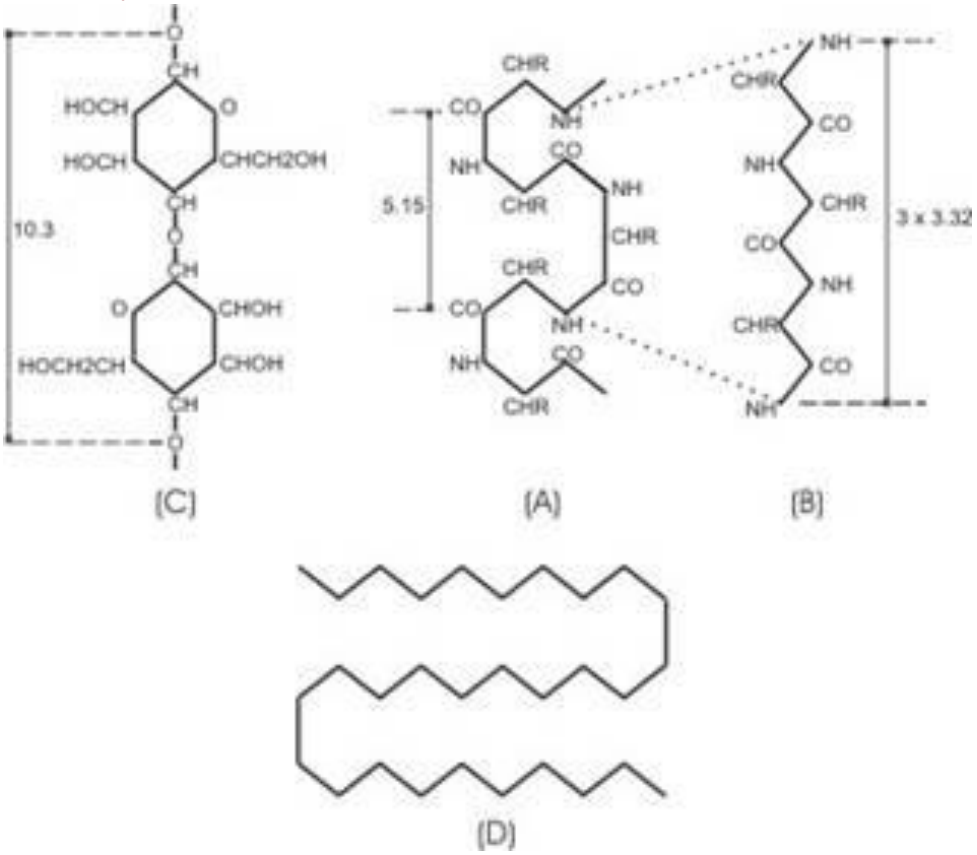


Figure 18: Astbury based his model for the 'contracted' form of wool keratin (A) on the structure of cellulose (C), having been struck by the similarity of the axial periodicity of wool (5.15Å) to half that of cellulose (10.3Å). For the 'stretched' form of wool (and that of silk) the chain was nearly fully extended (B). In the 'cross-beta' structure, the chain is folded with its axis perpendicular to the fibre direction (D).

Astbury's classification of fibrous proteins

By consideration of their density, mechanical properties and X-ray diagrams, Astbury was led to the following classifications:

- collagen (the protein of tendons and the matrix of bone and skin)
- the k-m-e-f group:
    - keratin (the protein of wool, hair and silk)
    - myosin (one of the principal muscle components)
    - epidermin (a skin component)
    - fibrinogen (the blood clotting agent)

Members of this group can exist in 2 forms, alpha and beta - the alpha form can be converted to beta by stretching, with the gross change in length being accompanied by a change in the molecular conformation evidenced by the change in X-ray diagram.

A third form of structure was found in some sources, including a component of bacterial flagella, the egg-stalk of the lacewing fly and fibres produced from denatured proteins.

This form was termed "cross-beta" because the X-ray diagram showed that the protein chain, while in the beta form, ran at right angles to the length of the fibre.

The alpha-beta transformation

Astbury thought that the alpha - beta transition might be the basis of muscle contraction, but we now know that this was wrong; muscle contraction is due to filaments of myosin sliding past filaments of actin.

But it does explain the shrinking of wool and 'permanent waves' are formed when hair is treated with appropriate chemicals while it is wound round a former, so that the some of the molecules are stretched into the beta form, while others remain in the alpha.

The crystallographer A L Patterson, a Canadian who had worked in W H Bragg's lab. at the Royal Institution, wrote:

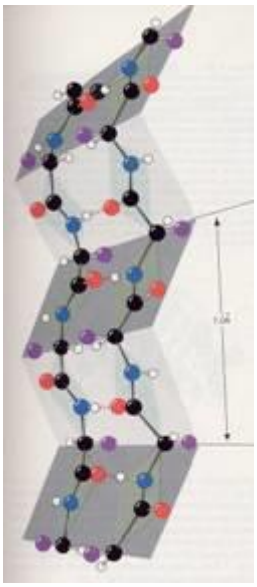
Amino acids in chains
Are the cause, so the X-ray explains,
Of the stretching of wool
And its strength when you pull,
And show why it shrinks when it rains.

Protein chain folds

The correct conformations for the alpha and beta structures were derived by Linus Pauling and Robert Corey. They had realised that the atoms in each peptide group (CONH) should be coplanar and that the structures should be stabilised by hydrogen bonds in which the N-H...O atoms would be nearly linear.

The alpha helix (left) is very different from Astbury's flat ribbon, and it is stabilised by hydrogen bonds between adjacent turns of the helix.

But the beta sheet (right) is quite similar to Astbury's beta structure, with the strands not fully extended, but crimped. The hydrogen bonds link adjacent strands. The pleats in the resultant sheets are responsible for the elasticity of silk and stretched wool.



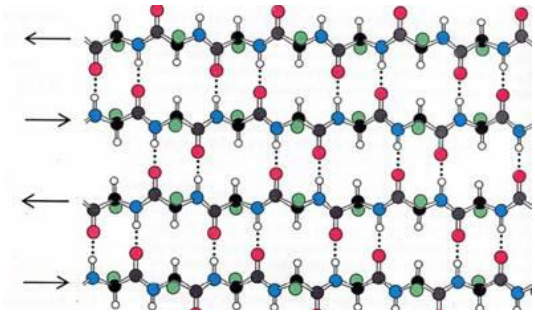


Figure 20: In the beta sheet adjacent strands may go in alternate directions (as shown here) or they may all be pointing the same way.

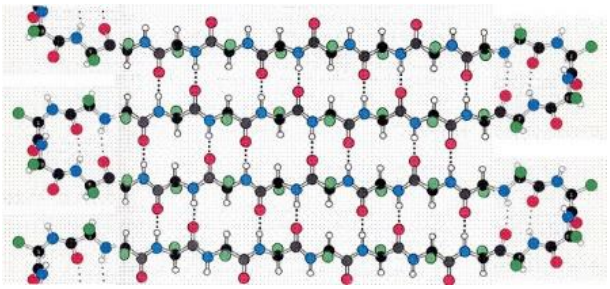


Figure 19: In the 'cross-beta' fold (first given that term by K M Rudall), the strands weave their way back and forth across the width of the fibre.

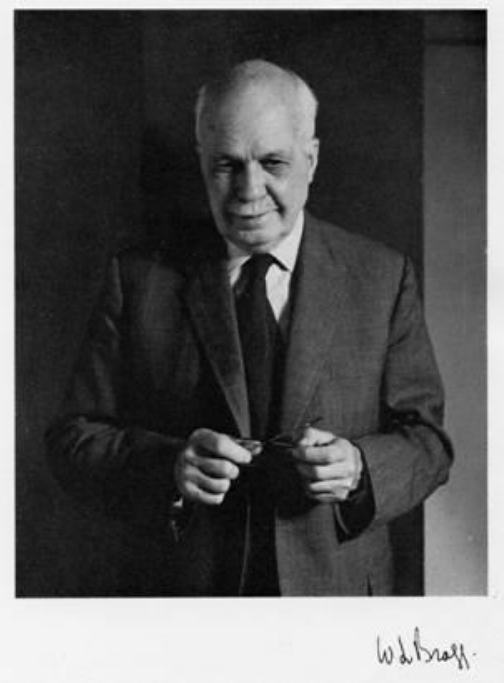
Astbury's and Bragg's ideas on globular proteins

Astbury naturally wondered about the structures of globular proteins and he expected them to be more highly ordered than molecules such as rubber, so he proposed that they would be formed of regularly folded sheets built up from the types of fold he had proposed for the keratins.

The determination of the actual 3-dimensional structures of the first globular proteins took place in the laboratories of W L Bragg (by now Sir Lawrence).

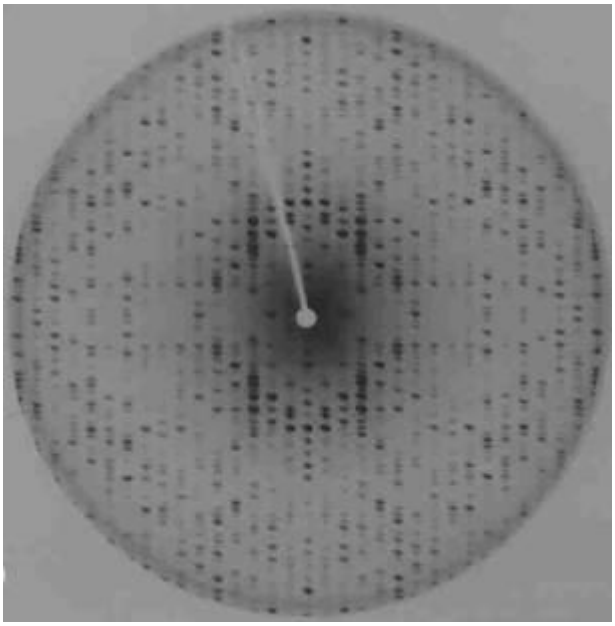
WLB had moved to the Cavendish Laboratory in Cambridge in 1938 where he obtained support from the Medical Research Council, initially to support the work of Max Perutz on haemoglobin and John Kendrew on myoglobin - the first 2 protein structures to be determined.

WLB's final move was to the Royal Institution in 1954, where, in addition to re-invigorating the lecture programmes as his father had done a generation before, he oversaw the solution of the 3-d structure of lysozyme, the first enzyme to have its catalytic activity explained on the basis of its atomic arrangement.



X-ray Diffraction from Crystalline Globular Proteins

Unlike fibrous proteins, globular proteins can form true crystals which give highly detailed X-ray diagrams (an example is shown here). J D Bernal and Dorothy Crowfoot Hodgkin had found that the crystals must not be allowed to dry out, water being essential to pack out the gaps between molecules in the crystal.



It was still not easy to derive the atomic positions from the X-ray data which lack information about the phases of the 'reflected' X-ray waves. These may be found by making a series of complexes in which atoms of high atomic number have been attached to the protein molecules.

Protein chain folds

The first 3-d structure of a globular protein was that of myoglobin, the oxygen storage protein abundant in muscles.

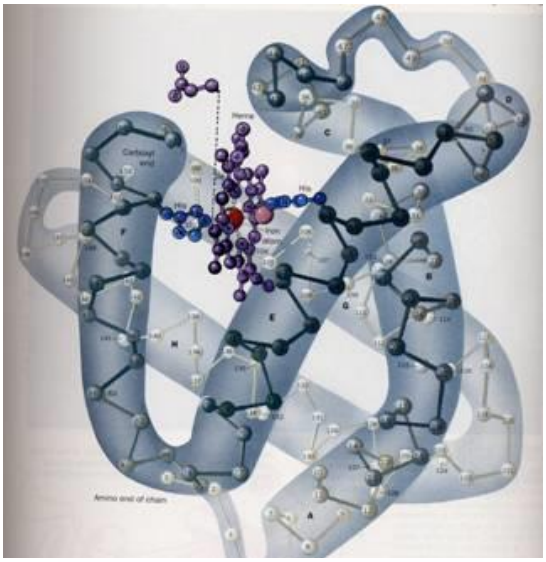


Figure 21: myoglobin

Astbury had been right in surmising that the structure of a globular protein would be like a fibrous protein chain folded up - and indeed most of the myoglobin chain has an alpha-helical form, but it is folded in a much less regular pattern than Astbury (and many others) had expected.

The fold of the chain encloses the haem group whose function is to bind an oxygen molecule.

Haemoglobin, whose role is to transport oxygen in the blood, comprises 4 sub-units, each very similar to a myoglobin molecule.

The enzyme lysozyme contains 3 alpha-helical segments, but it also has several beta strands in which the chain doubles back on itself to form miniature beta sheets.

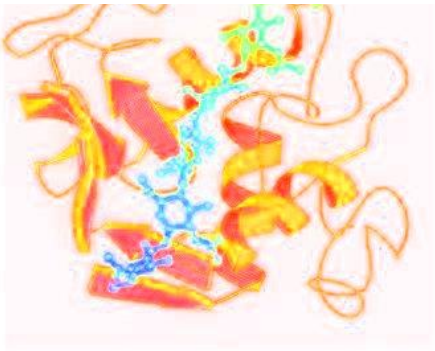


Figure 22: lysozyme

However, parts of the lysozyme chain are folded in a rather irregular form.

Lysozyme is an anti-bacterial enzymes which breaks down the polysaccharide chains of bacterial cell walls; it is found in many body fluids including tears and egg-whites.

The surface of the protein has a cleft into which fits 6 units of the polysaccharide chain of the cell wall; 2 acidic side chains of the protein act like wire-cutters to cleave the bond linking the 4th to the 5th unit down (red arrow in this diagram).

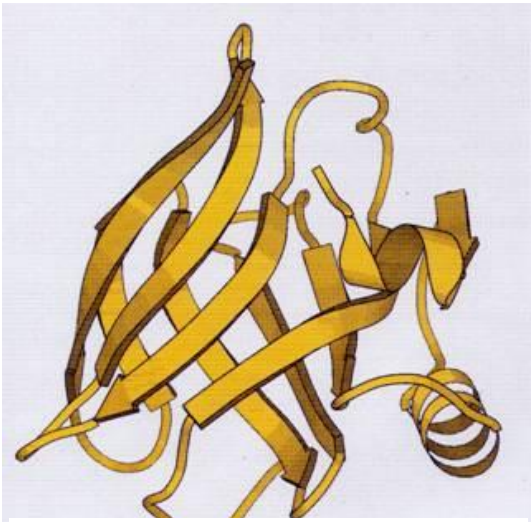


Figure 23: Beta-lactoglobulin

Beta-lactoglobulin, whose structure is shown here, is a member of a family of lipid-carrying molecules whose structures have been determined in Leeds in recent years.

Its structure contains just one alpha helix and it is mainly in the form of beta strands which form two sheets.

The gap between the sheets makes a pocket within which the lipid molecule can be carried.

Beta-lactoglobulin is found in milk -other proteins of the family include retinol-binding protein and rodent urinary proteins, which carry odorant molecules.

The combination of alpha helices, beta strands and less-ordered regions, with the beta strands often forming sheets, has been found to be widespread throughout the range of of protein molecular structures and of macromolecular assemblies, such as the satellite tobacco necrosis virus shown here and being studied in Leeds by Peter Stockley, Simon Phillips and their colleagues.

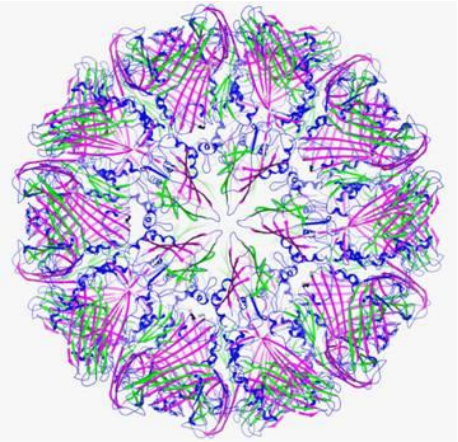


Figure 24: satellite tobacco necrosis virus

Astbury on protein denaturation

It had long been known that both fibrous and soluble globular proteins could be 'denatured' by heat or chemical treatment, resulting in an irregular molecular conformation. But it had also been found that in appropriate conditions, fibres could be drawn from the resulting mass, and Astbury was fascinated by the relationships between the different classes of proteins and their properties.

On wearing a pullover made of a yarn spun from a globular protein, he wrote:

“Only the other evening, I was watching my daughter knitting yarn spun from monkey-nut protein - a protein, I repeat, with round molecules that once seemed to bear no relation whatsoever with fibres - and as I touched the knitting, again the wonder of it all flooded over me”.

(Astbury, 1936)

Protein denaturation & Amyloid diseases

In recent years, it has become clear that protein denaturation and mis-folding are important factors in a number of degenerative disorders, including:

- Alzheimer’s
- CJD
- Primary systemic amyloidosis
- Type II diabetes
- Lysozyme amyloidosis
- Dialysis-related amyloidosis

Protein folding mechanisms are currently being studied in the Astbury Centre by Sheena Radford and her colleagues. Remarkably, it has been found that the mis-folded amyloid proteins often have a fibrous nature in which the strands adopt the cross-beta conformation first identified by Astbury, as shown in the diagram on the right by Blake and Serpell.

Figure 25: The fibre axis is vertical and there are 24 beta strands marked in the length

Astbury's ideas on nucleic acids

DNA extracted from cells is in the form of a gel; if a needle is poked into the gel and then withdrawn slowly, a fibre is formed in which the molecules are aligned.

X-ray diagrams of DNA fibres obtained by Astbury and his colleagues showed a regular axial repeat of 3.34 Å.

This is similar to the thickness of flat molecules such as benzene and Astbury deduced that the DNA bases are stacked on top of each other "like a pile of pennies". This deduction was correct.

He also thought that the similarity to protein periodicities was significant, but there is no evidence that this is so.

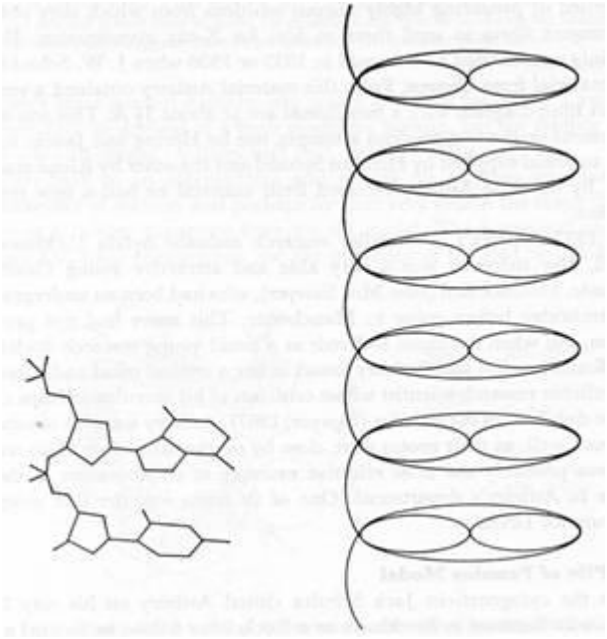


Figure 26: Astbury's "pile of pennies" diagram for a single strand of the DNA molecule

It must be remembered that in the 1930s, the genetic role of DNA had not been established and it was just thought to be a rather uninteresting molecule that acted as 'scaffolding' in the chromosomes.

The correct structure for DNA

The correct structure for DNA was deduced by Francis Crick and James Watson, working in W L Bragg's department in Cambridge, using X-ray diffraction data obtained by Maurice Wilkins, Rosalind Franklin and their colleagues, working in J T Randall's department at King's College London (Randall himself had been a student of W L Bragg in Manchester).

The evidence that had not been available to Astbury included the following:

- The X-ray data indicated that the the DNA molecules were in pairs, running in opposite directions along the fibre, and that they had a helical form.
- Erwin Chargaff had found that, in a wide range of DNA samples, there was a striking ratio of the contents of the 4 types of DNA bases, A, T, G and C with A=T and G=T.

With the aid of molecular models, Watson and Crick found that the bases could be put together in pairs held together by hydrogen bonds.

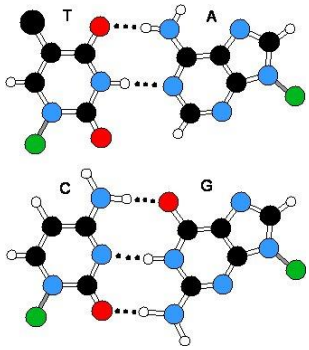


Figure 28: A:T and G:C base pairs can be linked by hydrogen bonds, shown by dotted lines and these pairs may be exactly superimposed

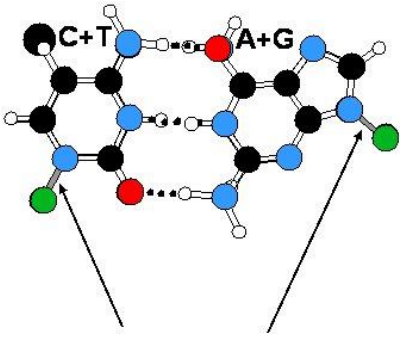


Figure 27: A:T and G:C base pairs can be linked by hydrogen bonds, shown by dotted lines and these pairs may be exactly superimposed

DNA Models

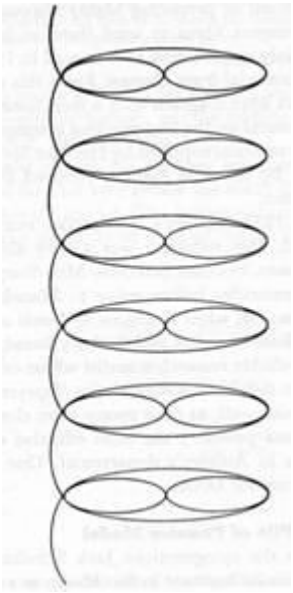


Figure 31: Astbury's sketch

Figure 29: Crick's sketch

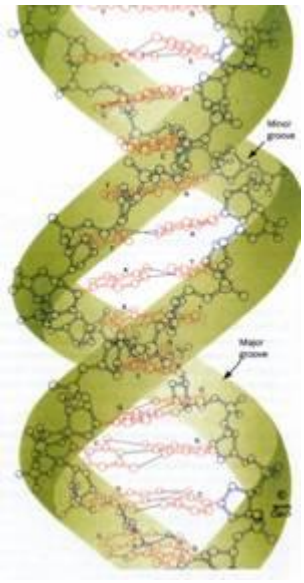


Figure 30: DNA as published in Voet & Voet's Biochemistry

The final models for DNA were determined by Wilkins's group, following the obtaining of much better X-ray fibre diagrams and extensive 'refinement' of the structural parameters.

The term "Molecular Biology"

While it may have been used earlier, the first recorded use of the term 'Molecular Biology' seems to be in a report by Warren Weaver, director of the Rockefeller Foundation's natural sciences programme, in 1938:

"Among the studies to which the [Rockefeller] Foundation is giving support is a series in a relatively new field, which may be called molecular biology, in which delicate modern techniques are being used to investigate ever more minute details of certain life processes."

Astbury gave the following definition in 1961:

"Molecular biology implies not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below the large-scale manifestations of classical biology for the corresponding molecular plan. It is concerned particularly with the forms of biological molecules and is predominantly three-dimensional and structural which does not mean, however, that it is merely a refinement of morphology it must at the same time enquire into genesis and function."

Although "Molecular Biology" has a rather wider connotation nowadays, it remains the case that it is founded on a structural basis of understanding molecular structure and function.

Astbury's conception of his role in science

When he was promoted to Professor, Astbury asked to be entitled 'Professor of Molecular Biology', but this request was turned down, apparently on the grounds that, while he knew all about molecules, he did not know sufficient biology - so he became 'Professor of Biomolecular Structure'. The criticism seems

harsh, because he was continually interested in the implications of structure at the molecular level throughout biological organisms.

His work may be criticised because, while he initiated molecular structural studies on a wide range of materials, it was largely other people who brought them to a successful conclusion. Perhaps he realised that his main contribution had lain in establishing foundations, when he gave the following quotation in assessing his career:

> "The which observ'd, a man may prophesy,
> With a near aim, of the main chance of things
> As yet not come to life, which in their seeds
> And weak beginnings lie intreasured."
>
> (Shakespeare, King Henry IV, part 2)

Summary

The work of the Braggs in 1912-1913 laid the foundations of X-ray crystallography as a method for the determination of the structures of materials.

Astbury's work, from his arrival in Leeds in 1928, was seminal in developing our belief that the innermost secrets of living things may be explained from a knowledge of the structures and properties of their constituent molecules.

John Locke wrote in 1620 in his Essay Concerning Human Understanding:

"Did we know the mechanical affections of the particles of rhubarb, hemlock, opium and a man, as a watchmaker does those of a watch … we should be able to tell beforehand that rhubarb will purge, hemlock kill and opium make a man sleep"

The work of the Braggs and Astbury, significant parts of which were carried out in Leeds, have surely provided a basis for the understanding that Locke and others have sought through the ages.

Acknowledgements

Source material may be found in:

Biographical Memoirs of Fellows of the Royal Society:

> J D Bernal: *William Thomas Astbury*
> Sir David Phillips: *William Lawrence Bragg*

G M Caroe: *William Henry Bragg* [Mrs Caroe was WHB's daughter & WLB's sister]

John Jenkin: *The Bragg Family in Adelaide*

Robert Olby: *The Path to the Double Helix*

Graeme Hunter: *Light is a Messenger: the Life and Science of William Lawrence Bragg*

Information about the science referred to is of course to be found in many of the standard texts, such as Blundell & Johnson *Protein Crystallography*, Voet & Voet *Biochemistry* and Stryer *Biochemistry*.