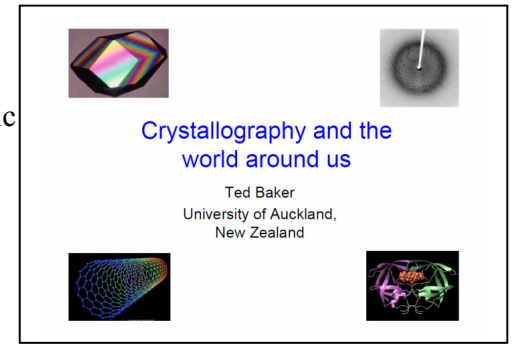
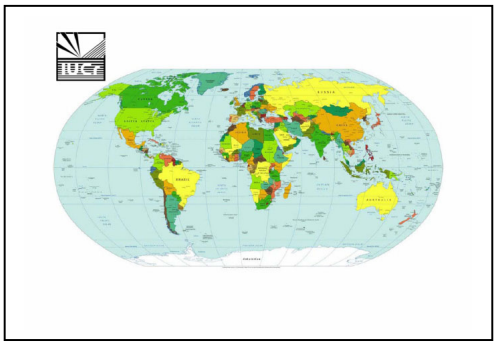
Crystallography and the World Around Us

Presentation for IUCr 60th Anniversary

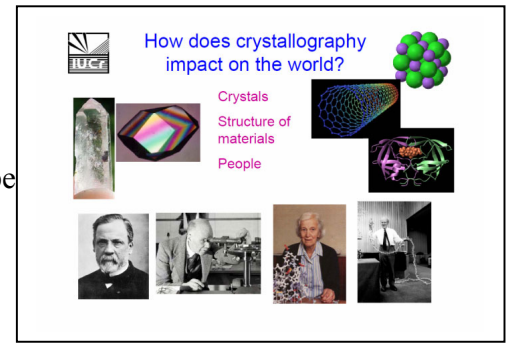
Ted Baker



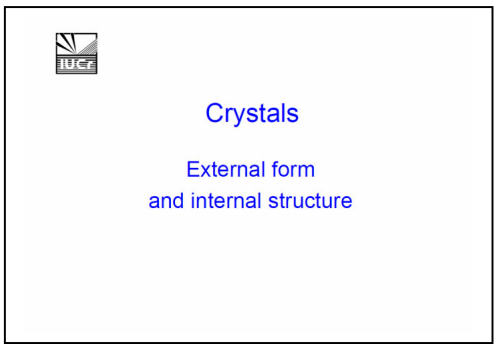
Slide 1.
Thank you for that very kind introduction, and thank you all for being here – this is a wonderful audience. My topic is "Crystallography and the world around us". I have found this very challenging, because crystallography is one of the oldest sciences and touches many areas. So I have had to be selective.



Slide 2.
My first comment is a personal one. For me one of the wonderful things about the IUCr is that it is international. For me, coming from a small country on the edge of the world it has meant great opportunities, even having the honour of serving as IUCr President. I have been introduced by Iris Toriani from Brazil. And here we are in Japan, to share in what I am sure will a great festival of science, hosted by Professor Yuji Ohashi as the current President of the IUCr.



Slide 3.
My lecture today will look at crystals. They are obviously very beautiful, But they also give insights into a whole range of materials from the physical, chemical and biological worlds. And most importantly I want to acknowledge some of the people who have helped to shape our science – here Louis Pasteur, Lawrence Bragg, Dorothy Hodgkin and Max Perutz, among others.



Slide 4.
I will start with crystals – which is where crystallography began.

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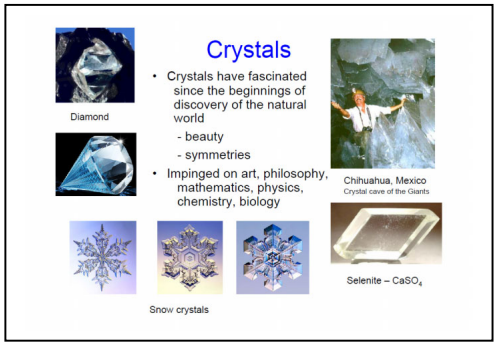

Crystals have fascinated people since the beginning of the exploration of the natural world – for their beauty and their symmetries. And they have impinged on art, philosophy, mathematics, physics, chemistry and biology. Here, for example is a diamond crystal in its natural setting. And when diamonds are shaped you see these wonderful faces. Next is a cave in Mexico, full of huge crystals, some as much as 20 metres high. These crystals are called selenite – a form of calcium sulphate, named after Selene, the Greek goddess of the moon. They are maintained in the cave by 100% humidity and atemperature of 70 degrees. And finally, here are snow crystals, in all their beauty. A fascinating question is: How do the external shapes arise?

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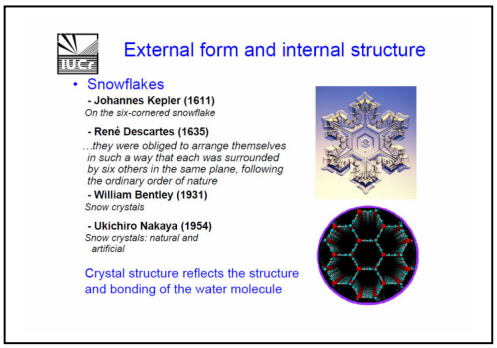

This leads to the question of how external structure is related to internal structure. Snow flakes provide a perfect illustration. Thus Johannes Kepler, the German astronomer and mathematician speculated on this in a book entitled "On the six-cornered snowflake". Rene Descartes, the French philosopher and mathematician, also wrote about this symmetry and hinted that it related to some basic structure. William Bentley, a self-taught American farmer produced a book – still in print – with the most wonderful collection of pictures of snow crystals. And Ukichiro Nakaya, a Japanese nuclear physicist – when he took up a position in Hokkaido and found he had no equipment for nuclear physics, devoted himself to snow crystals, documenting their shapes and finding out how to make them artificially. What all of them were looking for was a link between the internal structure of the crystals and their external shapes – and here we see how the hexagonal symmetry comes from the way the water molecules are arranged in the crystal, from their structure and bonding.

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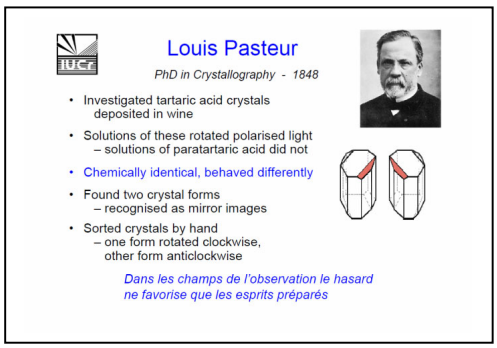

Probably the greatest demonstration that the external shape reflects internal structure came from the famous French scientist, Louis Pasteur. We usually think of him for his work in microbiology, but his PhD was in crystallography, and this was what made his name and won him international prizes. Pasteur was investigating tartaric acid crystals deposited in wine. It was known that when these were dissolved, the solution rotated polarised light. But there was another form, called paratartaric acid – which was chemically identical but did not rotate polarised light. Pasteur wondered why. There must be some difference. So he took paratartaric acid crystals, looked at them in the microscope – and realised that they were of two types! And they were mirror images! (The crystals here are related by mirror symmetry). So he sorted them into two piles, dissolved each pile, and showed that they both rotated light, but in opposite directions – one clockwise, one anticlockwise. It was this that

led to his famous quotation, which is translated as: “In the field of observation, chance favours only the prepared mind”.

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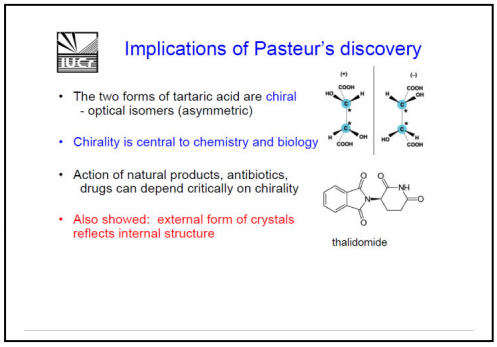

What were the implications of Pasteur’s discovery? He had discovered the phenomenon of optical isomerism. The two forms of tartaric acid are referred to as chiral – they are optical isomers. This form here cannot be superimposed on the other – they are chemically the same but structurally different. This is absolutely central to chemistry and biology – to the action of natural products, antibiotics and drugs – and to much of the natural world. As one example of its importance, you will remember the birth defects associated with the administration of thalidomide as a drug to control morning sickness in pregnancy. It turns out that thalidomide has optical isomer forms – one is safe and effective against morning sickness but the other binds to DNA and caused the birth defects. And for today’s lecture: what Pasteur’s discovery showed was that the external form of the crystals was linked to their internal structures.

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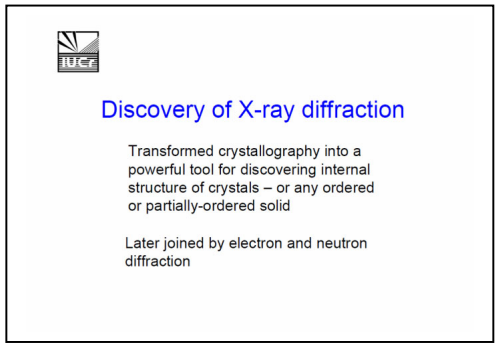

With this understanding, what then transformed crystallography as a science was the discovery of X-ray diffraction – later joined by electron and neutron diffraction. Because this transformed crystallography into the most wonderful tool for discovery – discovery of the internal structure of crystals.

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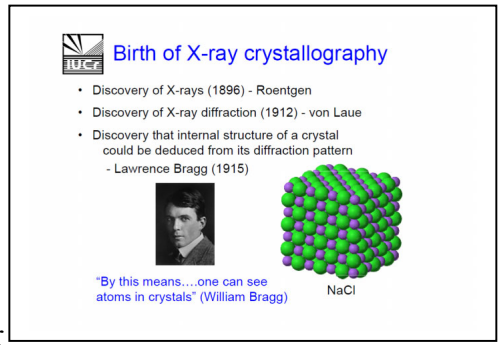
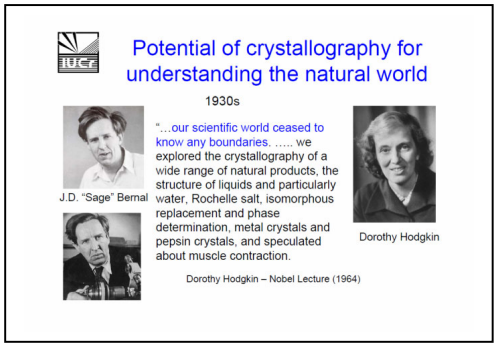


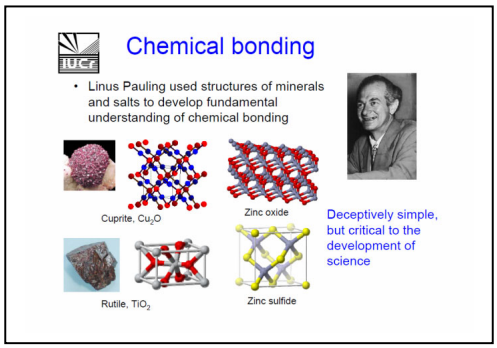
The key events here were the discovery of X-rays by Roentgen, followed by the discovery by von Laue that crystals diffract X-rays – both discoveries made in Munich, Germany. What transformed these discoveries was Lawrence Bragg’s discovery of a way of thinking about diffraction that led naturally to the determination of crystal structures. He solved the structure of sodium chloride – shown here – and immediately there was a surprise. Instead of molecules of sodium chloride there was an array of sodium ions and chloride ions. Not completely unexpected but of fundamental importance to understanding. Lawrence Bragg won the Nobel Prize at the age of 25 for this, together with his father William. And it was this quote by William Bragg, in a book written for school children, that inspired Dorothy Hodgkin – whom I will mention in a moment – and many others.

Slide 11.

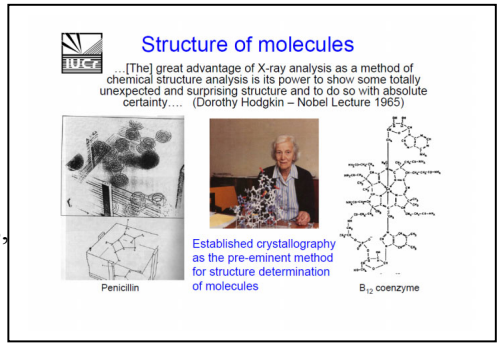
This quotation from Dorothy Hodgkin, taken from her Nobel Prize lecture captures the excitement of crystallography – and its potential for understanding the natural world. She wrote of going to Cambridge to work with J. D. Bernal – who was known as "Sage" because of his remarkable intellect and inexhaustible ideas. She wrote: "There, our scientific world ceased to know any boundaries. ….. we explored the crystallography of a wide range of natural products, the structure of liquids and particularly water, Rochelle salt (which is a salt of tartaric acid – referring back to Pasteur), isomorphous replacement and phase determination, metal crystals and pepsin crystals, and speculated about muscle contraction". So here is the vision – minerals, chemistry, biology. And all to be explored through crystallography.



Slide 12.
The contributions to the science of today is easy to underestimate. The fundamental ideas about chemical bonding – about covalent bonds, ionic bonds, hydrogen bonds and so on – were all developed by Linus Pauling through crystallography and the structures of salts and other small molecules. Here are an array of crystal structures – cuprite (cuprous oxide), zinc oxide, titanium oxide, zinc sulphide. They are deceptively simple, but were fundamental to the development of science.



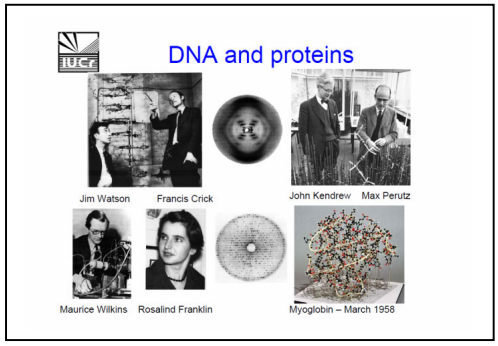
Slide 13.
Another quotation from Dorothy Hodgkin, again taken from her Nobel lecture, points to the power of crystallography. She refers here to "its power to show some totally unexpected and surprising structure and to do so with absolute certainty". Her focus was on natural products. The standard approach of organic chemists was to take a natural product, break it into small pieces, identify the pieces, showed that crystallography could do it with power and certainty. So here is penicillin – determined over the period 1942 to 1945 – and an incredibly important step forward for medicine. Here you see the 4-membered beta-lactam ring, which was very controversial – but plain for everyone to see. And here is the coenzyme form of vitamin B12. This was an amazing achievement, by far the largest structure solved to that point. One remarkable feature was a cobalt-carbon bond, which was again quite revolutionary. In fact, she was advised by a top chemist not to publish because "it must be wrong" – but she went ahead because the crystallography said it was true! Dorothy is shown with a model of the protein insulin in front of her – another of her life works – and she saw with great clarity what crystallography would mean for biology.



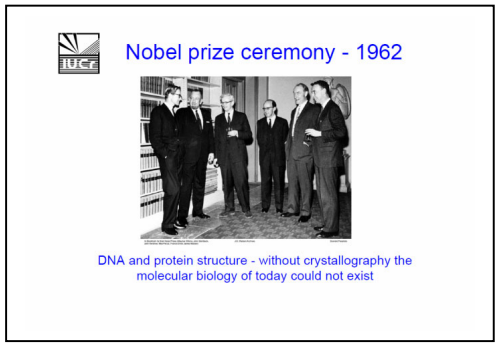
Slide 14.

The brings me to biology and here it is impossible to overstate the importance of the work carried out in Cambridge on both DNA and proteins – with the encouragement of Lawrence Bragg and ideas from Bernal, Dorothy Hodgkin and others.

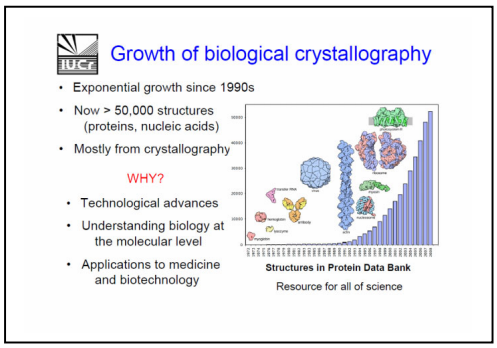
Slide 15.
Here you see the historic photo of Watson and Crick with their model of the DNA double helix. This was derived by knowledge of the fibre diffraction patterns obtained by Maurice Wilkins and Rosalind Franklin. They didn't have crystals – they couldn't obtain true crystals – but they had oriented fibres, and these patterns were critical to recognition of the structure. And here you see a picture of John Kendrew and Max Perutz with their model of myoglobin, the first protein structure to be determined – it was 50 years ago this year that the structure was determined, and it was revolutionary. Nobody expected how complex the structure would be, and this structure and the ones that followed showed how it is that a cell can contain tens of thousands of different proteins, all doing different things, and each having a structure that is absolutely specific for its particular function.



Slide 16.
The Nobel Prizes of 1962 were a milestone in the development of biology. Here you see John Kendrew and Max Perutz. And here are Maurice Wilkins, Francis Crick and Jim Watson. (The one interloper is John Steinbeck, the novelist). It can fairly be said that without these discoveries – through crystallography – of DNA and protein structure, today's molecular biology, the foundation of modern biological sciences, could not exist. And many other technologies, for example DNA fingerprinting, diagnostics, and many aspects of medicine, could also not exist. One other thing I should mention. Wilkins and Crick were physicists. Kendrew and Perutz were chemists. And Watson was a biologist. Indicating how crystallography stretches across the sciences.

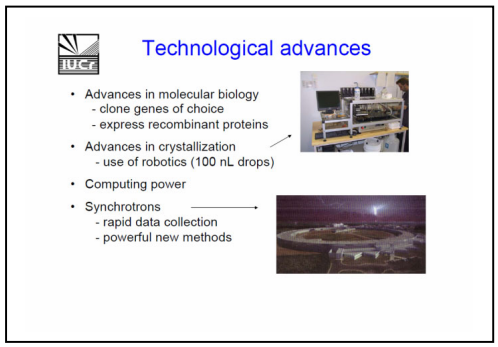


Slide 17.
This slide charts the growth of biological crystallography, through the number of structures in the Protein Data Bank. This is an international resource, with centres in the United States, UK and here in Osaka, in which all protein and nucleic acid structures are stored – a wonderful resource for the whole international community. You will notice that



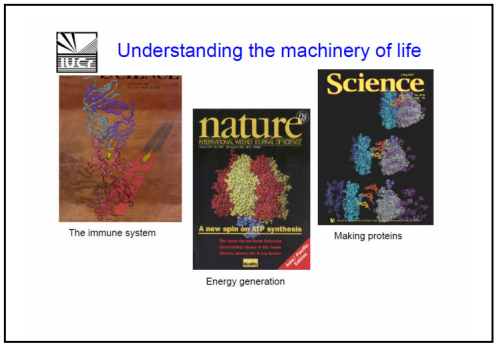
there has been exponential growth since the late 1990s – an extraordinary growth – with more than 50,000 structures now in this database, most of them determined by crystallography. Why is this? First, it is because of dramatic advances in technologies, which make it possible. Second, it is because these structures are such a wonderful window into biology – enabling us to understand biological processes at a molecular level. Third, it is because we can also use crystallography in applications to biotechnology and medicine. I'll give several examples of this.

Slide 18.



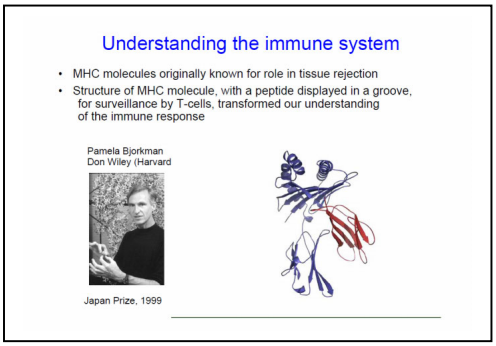
The technological advances include advances in molecular biology, which enable one to take a gene of choice – for example one implicated in a disease – clone it, and then produce the protein for crystallography. They include the use of robotics – for example in crystallization where we can now use very tiny drops, or in automated diffraction experiments. They include the massive advances in computing power. And they include the continued development of synchrotrons – such as Spring-8 near Osaka – which allow rapid data collection and very powerful new methods.

Slide 19.



I could take many examples of the importance of crystallography in biology. Here I give you just three, taken from the front covers of leading international journals over the past 10 years. Here, for example, is an image of the molecules involved in the cellular immune response – which allows the body to destroy infected cells. Here is one showing the large protein complex called ATP synthase which powers the processes the take place in cells. And here is perhaps the most spectacular of all the ribosome – crystal grown first by some Russian scientists, structures solved by scientists in Israel, USA and UK. This is the machinery in the body that makes proteins – over and over again, without mistakes. These systems are made up of hundreds of thousands of atoms, and we now know exactly how they are arranged and how these systems work. I find this truly amazing and inspiring. I'll spend just a few minutes giving you a closer look.

Slide 20.



The cellular immune system provides a perfect example of the power of crystallography to completely transform some area of science. The proteins we call MHC molecules were first identified as having some role in tissue rejection during organ transplants. When Pam Bjorkman and Don Wiley solved the structure of an MHC molecule it immediately showed how they work, and it changed immunology completely. The MHC molecule shown here is attached to

the cell membrane. At its top is a groove. If a cell is infected by a virus or bacteria, it displays a peptide from the foreign organism in this groove – human T-cells recognise it as foreign and bring in the immune response. This is so profound that Don Wiley received the Japan Prize. You can see in this movie how it works.

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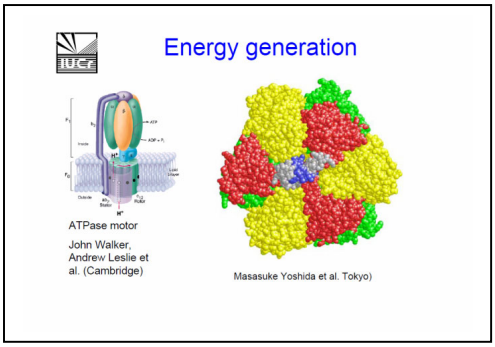
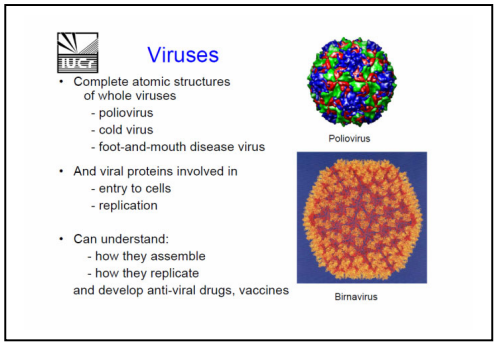


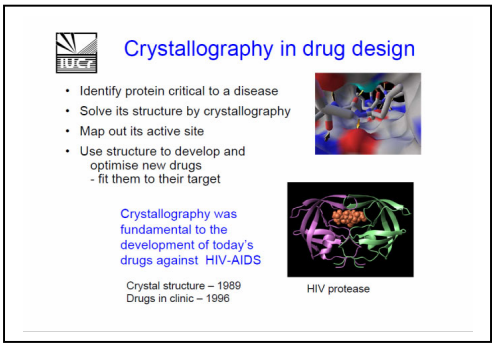
Here is the a diagram of the ATP synthase, the machine that makes ATP which fuels processes in the cell. John Walker received the Nobel Prize for his work, with Andrew Leslie, in figuring out its structure and how it works. Japanese scientists, led by Masasuke Yoshida from Tokyo, also made crucial contributions by showing how the parts that make the ATP – the alpha and beta subunits, shown here in green and orange and here in red and yellow – rotate about a central axle – the gamma subunit shown in the centre. This is just like a rotary engine, and we are now beginning to understand how all these parts are coordinated – again in atomic detail through crystallography. This move will give you a view of the movement – looking down on top of it – again through a series of crystal structures of different states.

Slide 22.



While we are looking at biological machines, I want to move towards human health by looking at viruses. Again, one of the successes of crystallography has been its ability to understand the structures of viruses, which have the potential to cause huge loss of life. So we now know the structures of viruses such as poliovirus, the common cold virus, or foot and mouth disease virus – in each case their coats are made of proteins packed together (poliovirus has 180 protein subunits) – hundreds of thousands of atoms, arranged in minute detail. Here is another example – a chicken virus called birnavirus and you see all the proteins that make up its coat. We know the structures of the proteins that allow the viruses to get into cells, and the proteins that allow them to replicate. So we can understand how they assemble and how they replicate and develop drugs against them.

Slide 23.



A brief comment on how crystallography fits into modern approaches to drug design. The idea is that first of all you identify a protein that is critical to the disease. It might be a protein from a bacterium or a virus. You then solve its structure by crystallography and map out its active site. The idea is to block this active site with a drug to block the activity of this protein target – so you use the structure to help develop and optimise new drugs by fitting them exactly

to their target. I will give an example soon, but one that is of huge importance to medicine today is the anti-HIV drugs that were developed to control the AIDS epidemic. Crystallography was critical to this. The target was an enzyme called HIV protease, shown here, with a drug molecule bound to it – here in orange. The structure of HIV protease was determined by crystallography in 1989 and the first drugs were in the clinic in 1996 – very fast progress – and these have saved countless lives.

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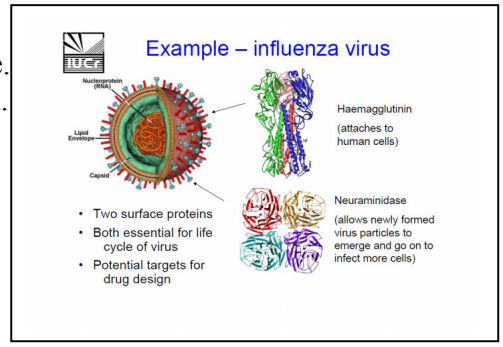

Here is my second example – influenza. The virus has two proteins on its surface, which are important for its life cycle. This one, looking like a spike, is called the haemagglutinin. It allows the virus to attach itself to human cells and get into them, to replicate. The second protein, called the neuraminidase, cleaves sugar molecules called sialic acid, and allows new virus particles to get out of human cells – to escape – and go on to infect more cells. Both proteins are essential to the virus, and both are potential targets for the design of anti-influenza drugs.

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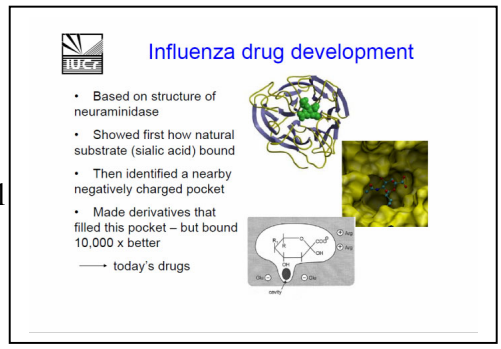

Here is how today's anti-influenza drugs such as Zanamivir (Relenza) and Tamiflu were developed. I think it's a great story, because much of the work was done in Australia, by a very small group by world standards, and it depended in a very beautiful way on crystallography. Peter Colman led this work – and he's here at this meeting and can tell you all about it. The drugs were based on the structure of the influenza virus neuraminidase. First they showed how the natural substrate sialic acid binds – here – in a small cavity in the surface of the protein. They then looked closer and saw that there was a nearby pocket that was negatively charged. So they made molecules the filled the cavity like sialic acid but had additional positively charged groups that filled this pocket – they bound much better (10,000 times better) and now form the basis of today's drugs.

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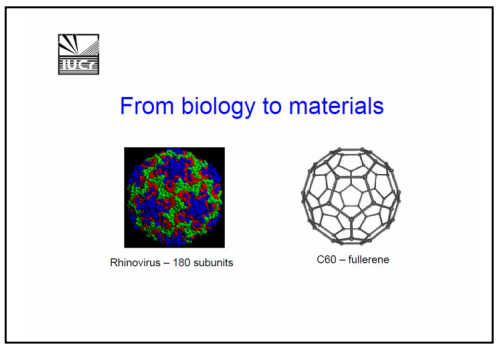
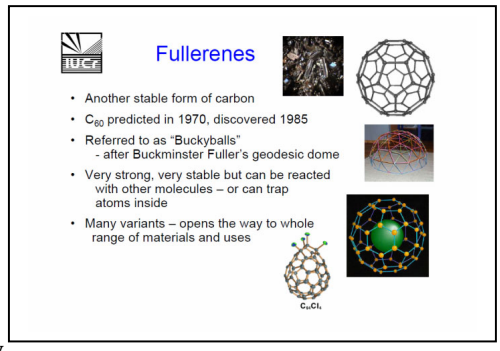


I showed you some spectacular biological structures, and it's easy to think that they are very different from other materials. But they are not. So here is a virus – it is the common cold virus whose structure was solved by Michael Rossmann. And here is a molecule made entirely of carbon – 60 carbon atoms arranged in an icosahedron, called a f ullerene. Both are built on the same principles – and this brings me back towards materials.

Slide 27.



This form of carbon was predicted in 1970 and finally discovered in 1985. The crystals are shown here. It is very stable, and its structure, with 60 carbon atoms joined up in an icosahedron, is shown here. You will see that it has hexagonal rings of atoms and pentagonal rings (5 sided) and these give its curvature. It's like a soccer ball, and they are sometimes called "Buckyballs" after the architect Buckminster Fuller, who designed his geodesic domes. There are many things you can do with these materials, including trap atoms inside – here is an example – or modify them to get different shapes and properties. Here is a pineapple fullerene!

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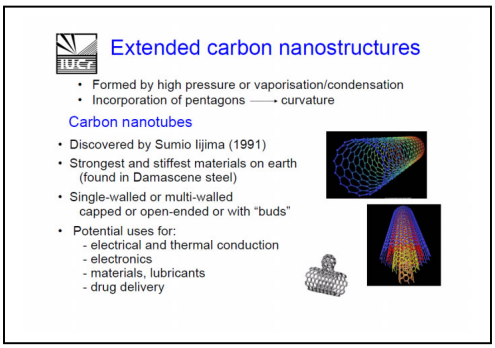

Some related carbon structures have also been developed, based on the same principles, called carbon nanostructures. They are formed at high pressure or by vaporising and condensing carbon on surfaces. Again they are based on hexagons and pentagons. I believe they were discovered in Japan, by Sumio Iijima at NEC, and the form the strongest materials on earth. In fact there was a form of steel, made in India more than 1000 years ago, and often referred to as Damascene steel – it was used in Arab swords from Damascus. The recipe to make it seems to have been lost, but crystallographic analysis suggests that it contains similar carbon nanotubes. These kinds of structures can be made in many forms – with single walls, or double walls, with bubbles or with caps on the end. And there are all kinds of potential uses – for electrical and thermal conductions, for electronics, for drug delivery, for materials and lubricants.

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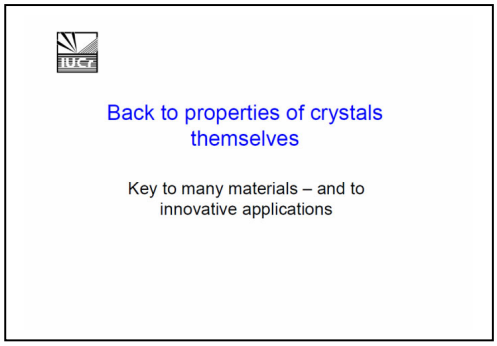
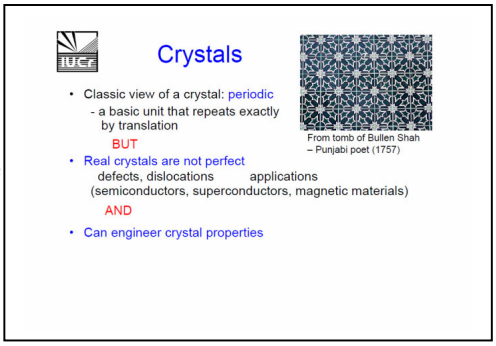


Finally, I started this lecture with crystals and then showed how crystallography can be used to discover the structures of important molecules. I have now moved back towards materials and I would like to finish by briefly considering how we can use the structures of crystals themselves.

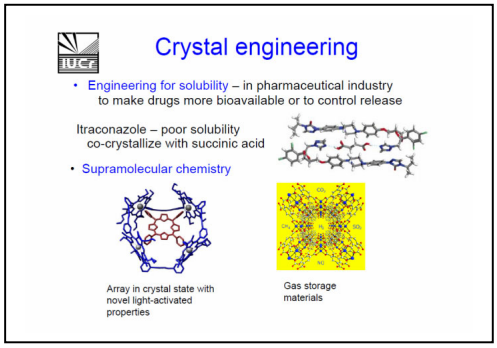
Slide 30.



So now let us look at crystals again. The classic view of a crystal is that it is periodic. It has a basic unit which repeats in three dimensions by translation. Here is an Islamic design, from Pakistan, that shows it perfectly – a basic unit that repeats exactly through the whole array. But real crystals are not perfect. They have defects, holes and dislocations. This gives unexpected properties that lead to useful

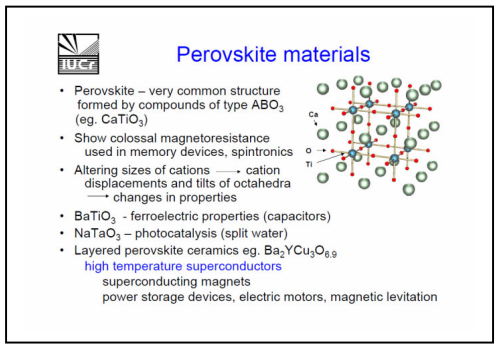
applications – as semiconductors, superconductors or magnetic materials. Also – there is a developing field of crystal engineering in which the properties of crystals are deliberately engineered to give new properties. I will give several examples.

Slide 31.



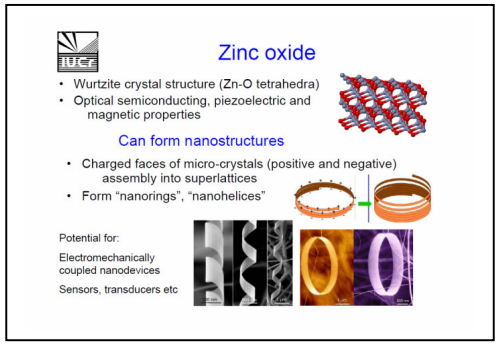
Here are some examples from chemistry. One of the problems in the pharmaceutical industry is that a drug may be potentially very effective, but it simply does not dissolve properly inside the body and so it is not effective – it is not bioavailable. One approach to overcome this is to form crystals in which it is combined with something else, to make it dissolve better. Here is an example. An anti-fungal drug called itraconazole which has very poor solubility on its own. But when crystallized with succinic acid you get a crystal in which the succinic acid molecules fit between the drug molecules – and this dissolves much better. Then we have the area of supramolecular chemistry where molecules are designed to give crystalline arrays with useful properties. Here is one that has novel light activated properties. And there are a whole variety of materials being developed that can trap gas molecules in crystal arrays – which could be very important for future hydrogen-based fuels, or for trapping toxic gases.

Slide 32.



Finally, two examples of inorganic materials. The first is based on a very common type of mineral structure called perovskite – name after a Russian mineralogist called Perovski. This is formed typically by materials with two cations of different sizes plus an anion such as oxide – with a formula ABO_3. Here is an example, with large atoms (calcium, in grey) on the corners, smaller atoms (titanium, in blue) in so-called octahedral holes surrounded with six oxygens – the red balls. These show huge variations in their electrical resistance when placed in a magnetic field, and so are used in many electronic applications – for example memory devices. Importantly if you alter the sizes of the cations, they can change their positions and orientations of the octahedral – so you get changes in properties. This gives materials such as BaTiO3 which is ferroelectric, used in capacitors; NaTaO3 which is photocatalytic – can split water into oxygen and hydrogen; and layered compounds such as this one – which have small proportions of other cations or anions. Some of these form high temperature superconductors and they have huge potential applications in superconducting magnets and for such things as power storage devices or electric motors.

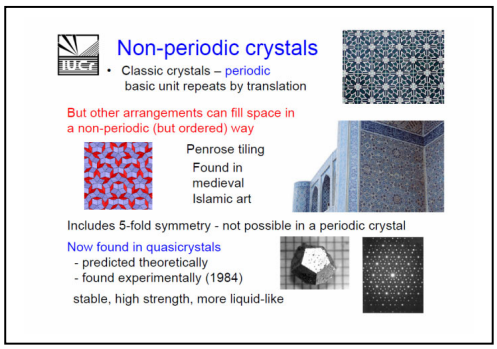
Slide 33.



My second example is a simple compound I mentioned earlier – zinc oxide. This has layers of zinc and oxygen atoms and has optical semiconductor, piezoelectric and magnetic properties. But in its crystal structure you get positively and negatively charged faces (because of the

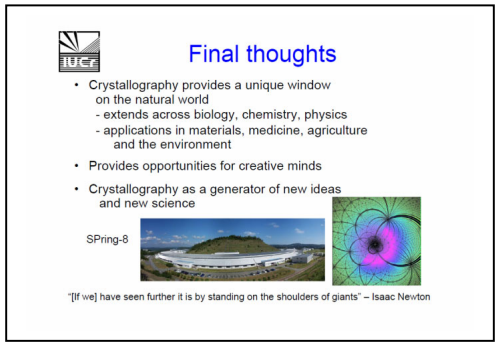
zinc and oxide layers) and Zhong Lin Wang from Georgia Tech (USA) has shown that this simple compound can form nanostructures, formed of tiny microcrystals that assemble into rings and helices. See these rings here with the positive and negative charges that make them assemble. And helices shown here. So this has the potential for a whole range of applications based on exploiting their structural and electrical properties – sensors, transducers and so on.

Slide 34.



One final and very intriguing example. I mentioned that classical crystals are periodic and this is what crystallography is traditionally concerned with. The example is this Islamic design. However, there are other arrangements that can fill space in a non-periodic way. An example is in the Penrose tiling arrangements for which the English mathematician Roger Penrose received the Nobel Prize. Here there are pentagons – five sided shapes – which cannot properly fill space on their own, but when combined with other shapes they can. It turns out that these patterns are also found in Islamic design – for example in mosques in Iran and Uzbekhistan. So Islamic scholars had worked this out 500 years before. But the important thing is that these patterns include 5-fold symmetry, which is strictly not possible in a classical periodic crystal. Interestingly, it was predicted that similar arrangements might be found in nature – and they have been, in so-called quasi-crystals. They are found for certain metal alloys. So this crystal has five-fold symmetry and it gives a diffraction pattern with five-fold symmetry. These quasi-crystals, too have different properties from conventional crystals.

Slide 35.



There are a few things I would like to say in conclusion. The first is that crystallography provides a unique window on the natural world that extends across biology, chemistry, physics, and has applications in materials, medicine, agriculture and the environment. This gives it a rather unique place in science – it truly does stretch across all the disciplines. Secondly, being able to "see" into the natural world – to see molecules, to see where atoms are, to see how materials are constructed – gives huge opportunities for creative minds. You can use your imaginations and develop new ideas. So I see crystallography as a generator of new ideas and new science – and we have already seen it in biology, in chemistry and in materials science.

I will not try to gaze into the future – that is for you, especially the young scientists here. I would say, though, that many of these new sciences are likely to take place around synchrotrons, such a Spring-8 and the KEK here in Japan. One area which I do think is ready to develop very fast is in following dynamic changes – for example reactions in crystals. Professor Ohashi, our current President, is one of those who has helped pioneer this area. In biology we have seen that wonderful diffraction patterns can be obtained with a single burst of X-rays at a synchrotron. There is still great potential for following biological reactions by crystallography – which have only been exploited to a small extent so far.

I will finish with a quote from Isaac Newton. I have mentioned the contributions of some of the great scientists who have developed crystallography. We all now have the opportunity to stand on their shoulders and exploit this potential.