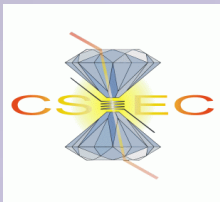


Some History of Protein Crystallography

A few random jottings on the subject of macromolecular crystallography

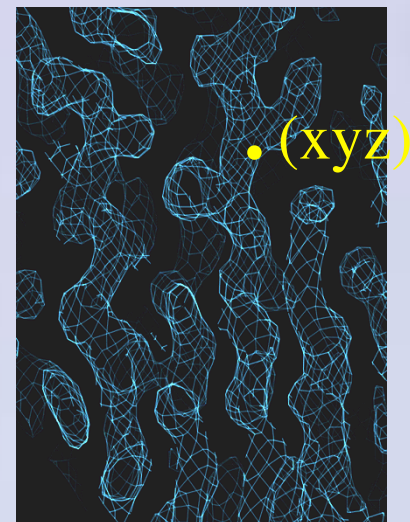
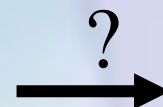
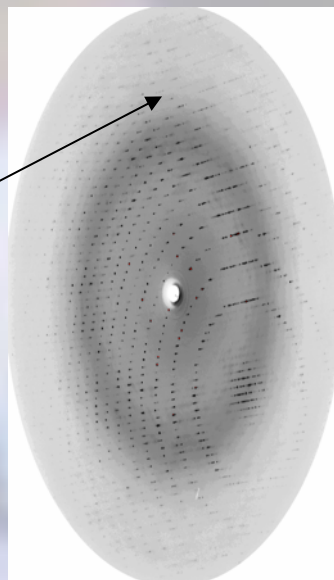
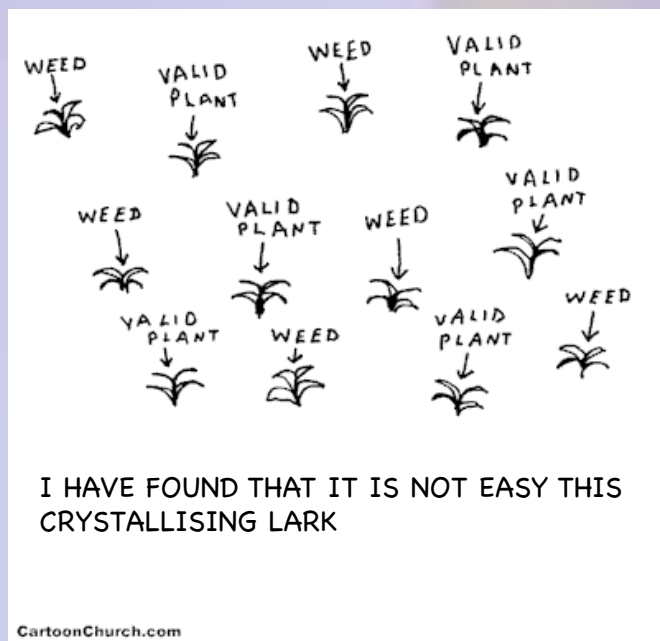
Lindsay Sawyer

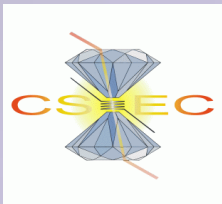
Institute of Structural & Molecular Biology
School of Biological Sciences
The University of Edinburgh



Outline

Some random, largely historical thoughts concerning the X-ray experiment





What are crystals?



Naturally occurring crystals have been valued by man for years, presumably their symmetry helped.

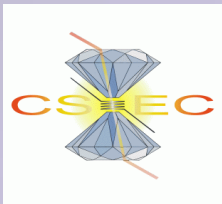
In the 17th century, Steno, Kepler, Hooke and Huygens started considering the nature of crystals scientifically, showing the formation of crystal shape by packing of spheres.

Steno noticed the 'constancy of interfacial angles' - Steno's Law

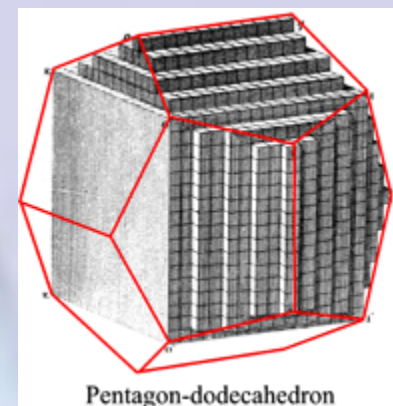
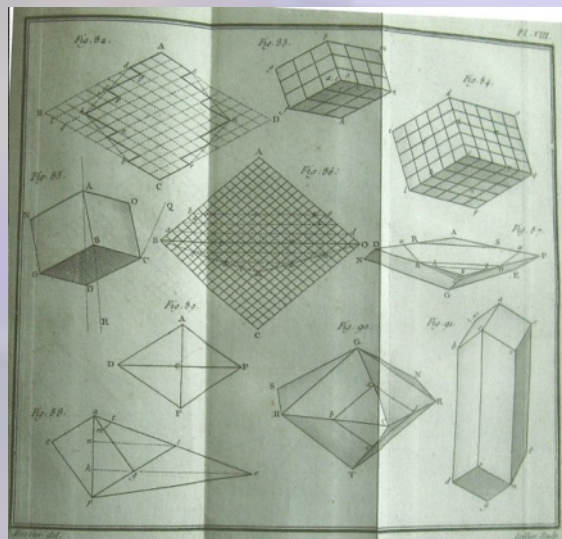
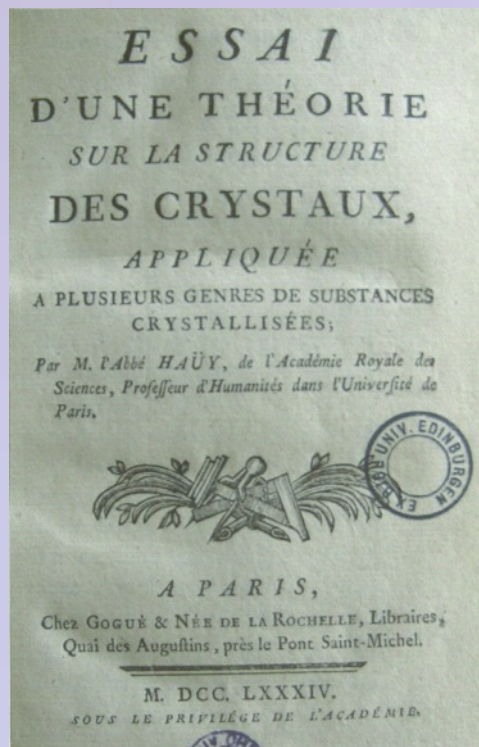


Quartz - <http://www.quartzcrystalsfromarkansas.com/imglib/quartz-crystal-isis-cluster-17bb.jpg>

Steno - <http://www.nndb.com/people/070/000097776/nicolaus-steno-1-sized.jpg>

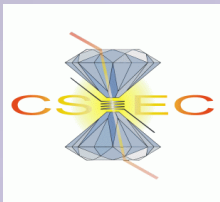


René Just Haüy

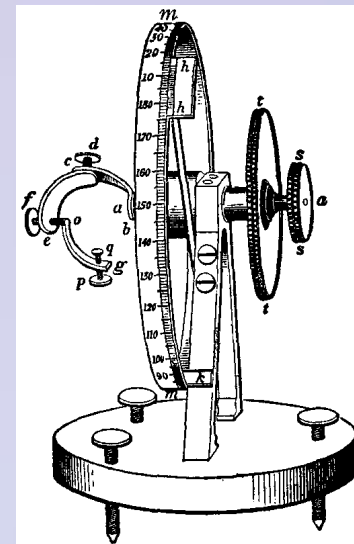
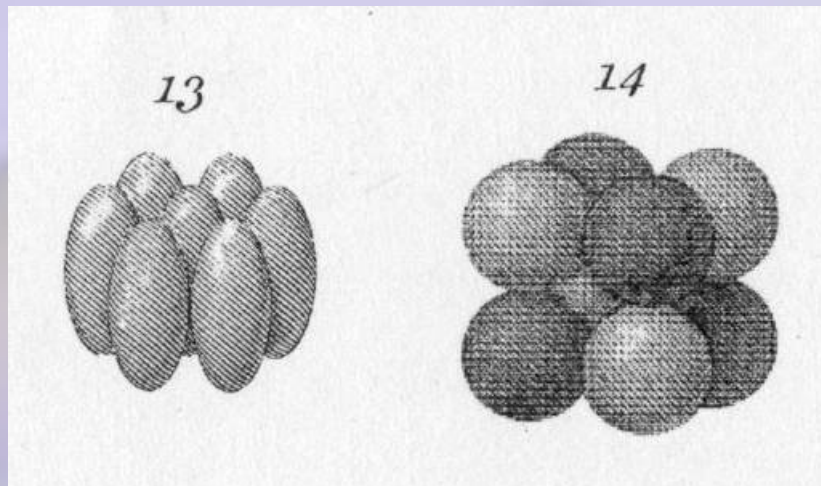
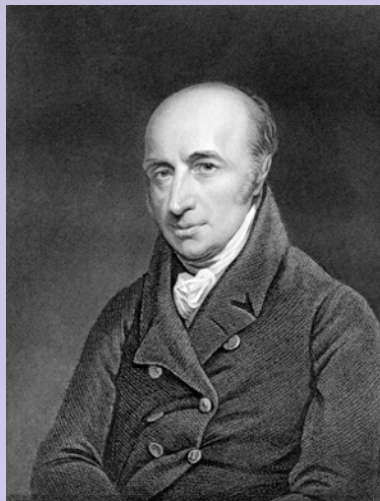


In the late 18th century, the invention of the goniometer allowed some degree of quantification to emerge and Haüy extended the earlier packing ideas using parallelopipeds.

Haüy - <http://xrayweb2.chem.ou.edu/images/Haüy-1.gif>



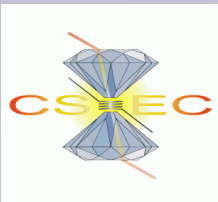
Early Crystallography



William Wollaston (1813) Model of cube based on 4 black balls and 4 white balls but both the same size - in fact boracite.

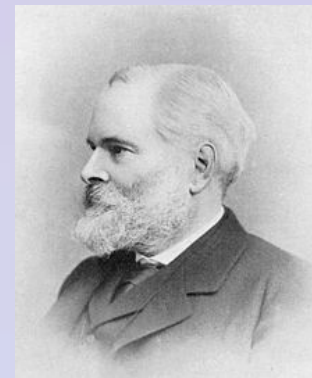
Wollaston (1813) *Phil. Trans. Roy. Soc.* **103**, 51
<http://webmineral.com/specimens/Boracite.jpg>
<http://xrayweb2.chem.ou.edu/>





Predicted Structure, 1883

Several earlier attempts at describing the nature of crystals in general and NaCl in particular had not quite got there. But then ...



Alexander Crum Brown

186 *NATURE* [Dec. 20, 1883]

PROBABLE NATURE OF THE INTERNAL SYMMETRY OF CRYSTALS

SOME studies pursued by the writer as to the nature of molecules have led him to believe that in the atom-groupings which modern chemistry reveals to us the several atoms occupy distinct portions of space and do not lose their individuality. The object of the present paper is to show how far this conclusion is in harmony with, and indeed to some extent explains, the symmetrical forms of crystals, and the argument may therefore in some sort be considered an extension of the argument for a condition of internal symmetry derived from the phenomena of cleavage.

If we are to suppose that crystals are built up of minute masses of different elements symmetrically disposed, it is natural to inquire in the first place what very symmetrical arrangements of points or particles in space are possible.

It would appear that there are but *five*, which will now be described.

If a number of equal cubes are built into a continuous mass (Fig. 1), a system of points occupying the centres and angles of these cubes will furnish an example of one of these symmetrical arrangements. In this system each point is equidistant from the eight nearest points, and if a number of equal-sized spheres be stacked on a base layer arranged so that the sphere centres when joined form a system of equal squares, a side of which bears to the diameter of the spheres the ratio $2 : \sqrt{3}$ (see plan a), the sphere centres in such a stack will also furnish an example of this first kind of symmetry (Fig. 2).

A second kind of symmetry will be presented if one-half the points in the first kind be removed so that we have only those at the cube centres, or only those at the cube angles. In this system each point is equidistant from the six nearest points, and if equal-sized spheres be stacked upon a base layer, arranged so that the sphere centres when joined form a system of equilateral triangles, a side of which bears to the diameter of the spheres the ratio $\sqrt{2} : 1$ (see plan b); and if the layers be so placed that the sphere centres of the fourth layer are over those of the first, those of the fifth over those of the second, and so on, the sphere centres in such a stack will also furnish an example of this second

of the fourth and second; and then the seventh, so that the fifth, sixth, and seventh layers are also in the second kind of symmetry; and so on. The symmetry produced is, like the last, hexagonal in structure and uniaxal.

The writer believes that every one of the various symmetrical forms presented by crystals can be shown to be consistent with the subsistence of an arrangement of the atoms of the crystallising compound in one or other of these five kinds of symmetry at the

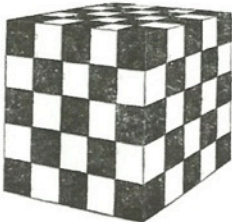
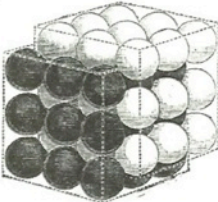
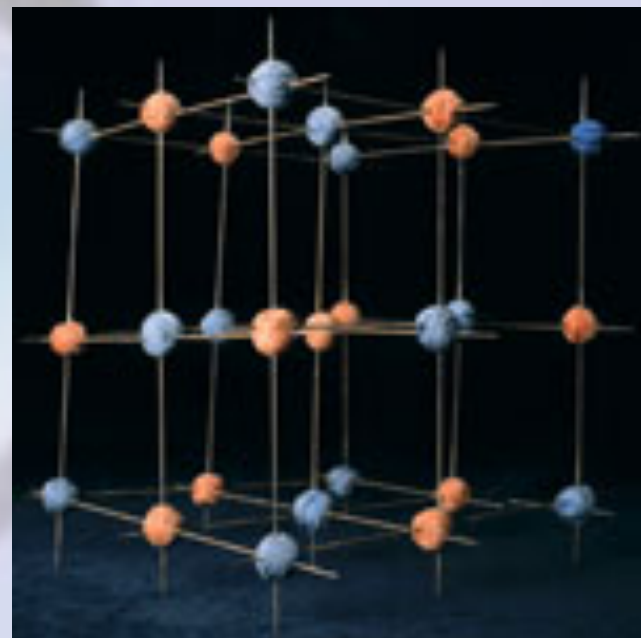
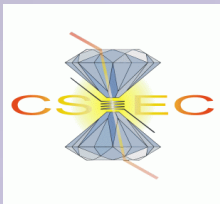


FIG. 1.




William Barlow





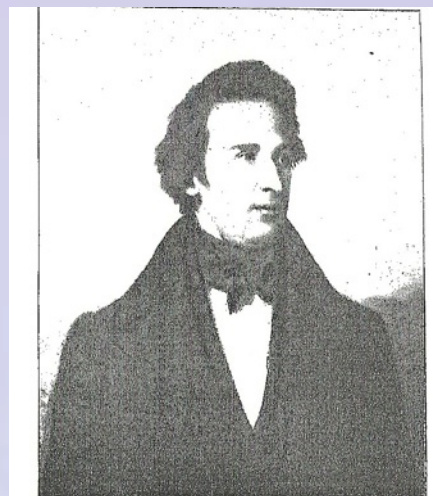
The First Report of a Crystalline Protein



F.L.Hünefeld: Die Chemismus in der thierischen Organisation, Leipzig, 1840. pp160-161.

J.prakt.Chem. 16, 152; 1839

The blood came from pig (Fig.7) and human (Fig.8).

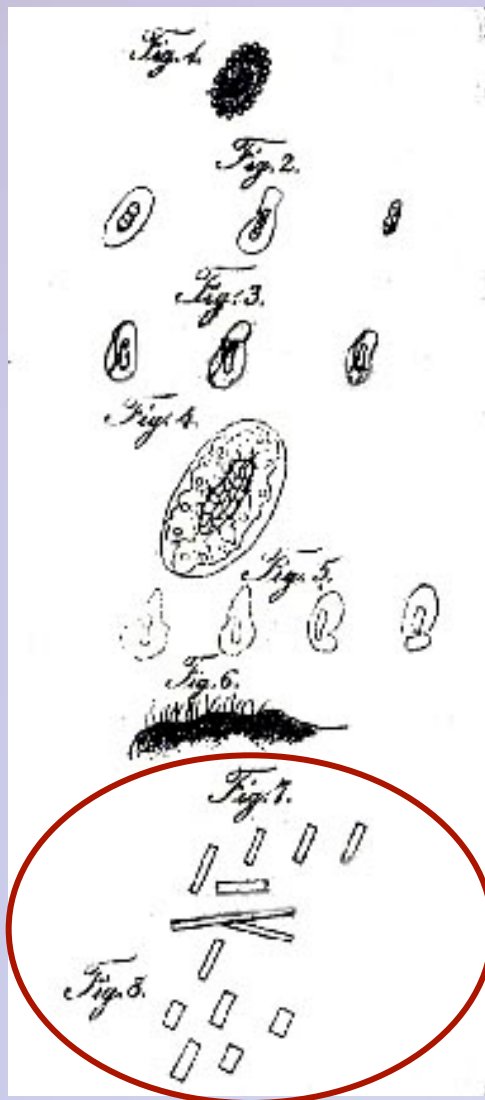


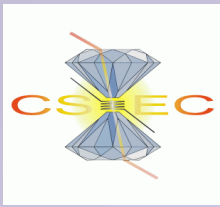
Friedrich Ludwig Hünefeld
Professor der Chemie und Mineralogie 1826—1882.

Many thanks to **Ursula Sauer** and **Andy Hofmann** for finding this text somewhere in Bavaria and for digging out its content.

McPherson's repeat of the Hünefeld's experiment

See McPherson, 1992





The First Published Photograph of a Crystalline Protein?

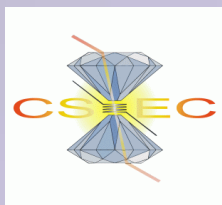


Not a protein but the first published photograph (a contact print) by a Dr Golding Bird using the Fox-Talbot process in 1839.

Sir John Herschel the astronomer coined the term 'photograph' rather than 'photogenic drawing'

The photograph was copied onto a block for printing.

So what about photomicrographs? Or photographs taken down a microscope?



The First Photomicrograph

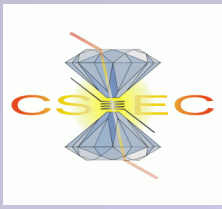
John Benjamin Dancer
1812-1887

In **1840**, he showed the first photomicrograph (actually a Daguerreotype) of a flea, using a gas illuminated microscope and a camera lucida.

(Dancer not the flea!)

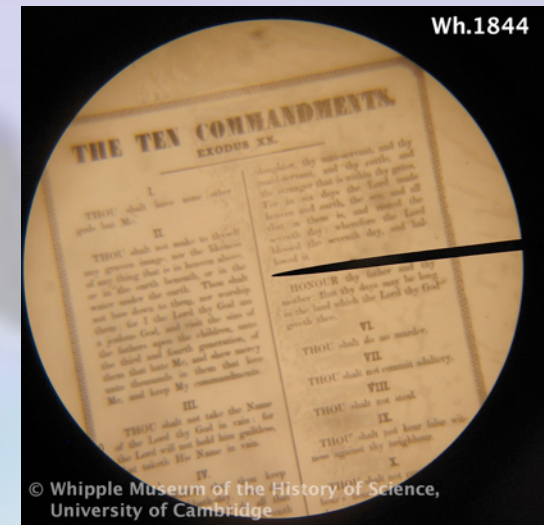


But others also produced photomicrographs even earlier. Rev J B Reade (1836) and W H Fox-Talbot (1839) reported that they had produced them but it is generally agreed that **Donné and Foucault** published the first, including one of uric acid crystals.



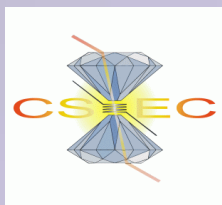
Dancer and the Microphotograph

Dancer's real claim to fame is the microdot, beloved of spies. His slides are still to be found in junk shops apparently.



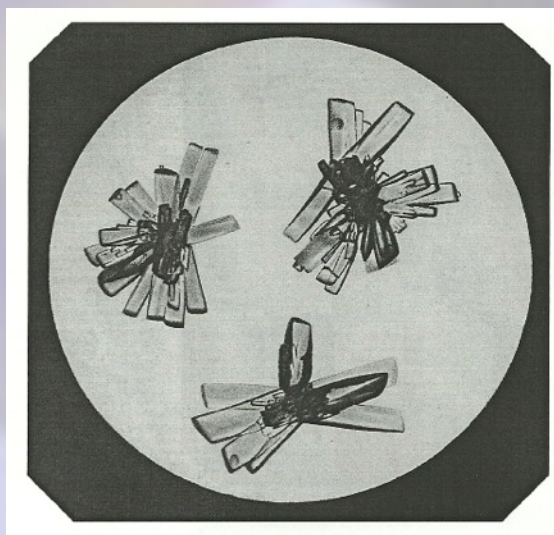
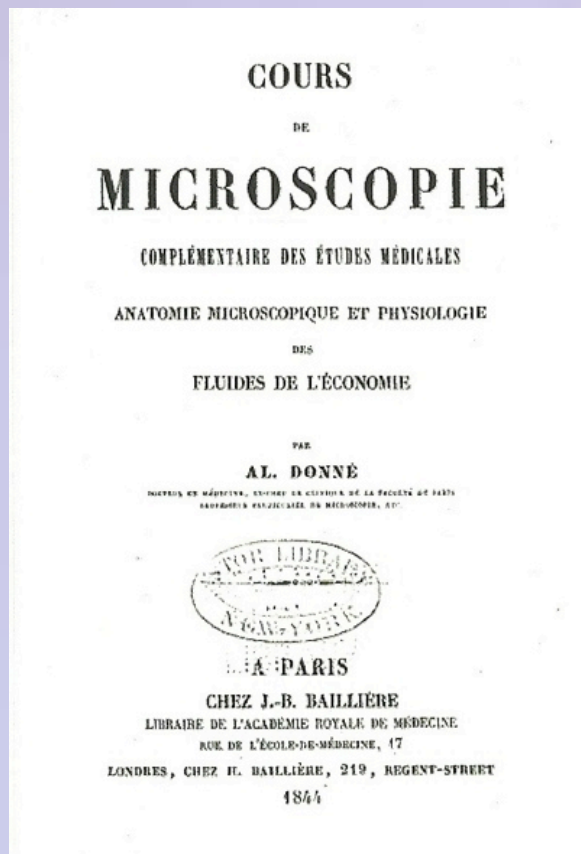
By the 1850s Dancer had developed a method of producing microphotographs containing a full picture occupying only 1/16th of an inch. Microphotographs were made of portraits, monuments, and many popular subject. Microphotography was used to transfer sensitive information in 1870, during the Franco-Prussian war.

<http://www.hps.cam.ac.uk/whipple/explore/microscopes/microphotographs/>

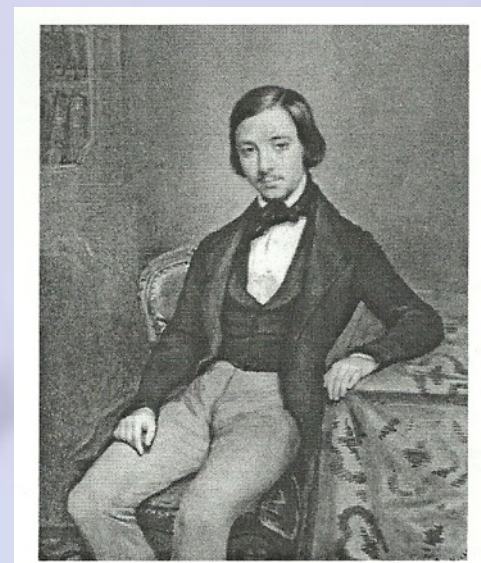


First Protein Crystal Photomicrograph?

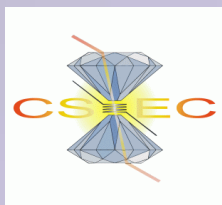
Donné and Foucault published this course on microscopie in 1844 followed in 1845 by an Atlas of photomicrographs made from daguerrotypes



Uric Acid



Foucault in the 1840s



First Protein Crystal Photomicrograph?



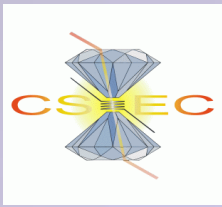
Otto Fünke *Atlas of Physiological Chemistry*, 1852.
Drawings and nothing particularly crystalline!

Weir Mitchell, Blood crystals of the sturgeon.
Proc. Acad. Nat. Sci. Philadelphia, 1859. Drawings!

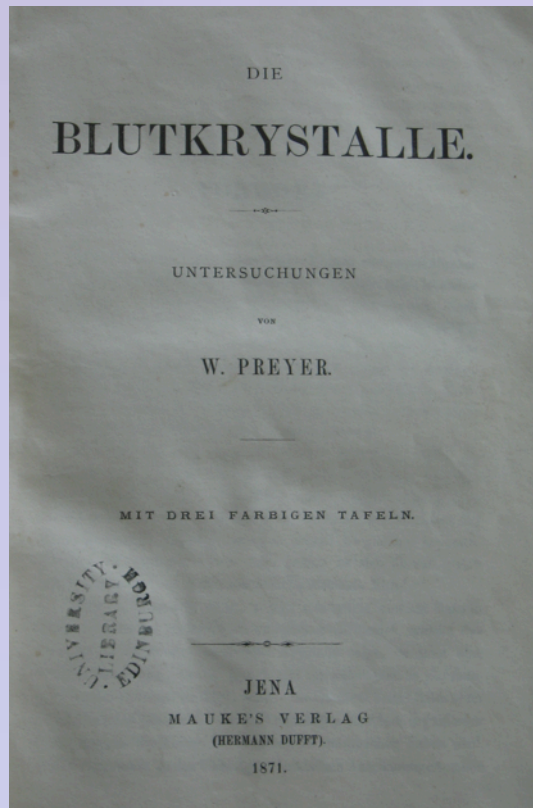
Albert Moitessier *La Photographie appliquee aux
Recherches Micro-graphiques*, 1866. Uric acid!

Wenham, and Shadbolt in the UK around
the 1860's, Bertsch and Nadet in France
and Mayer in Frankfurt were also interested
scientific applications of photography.





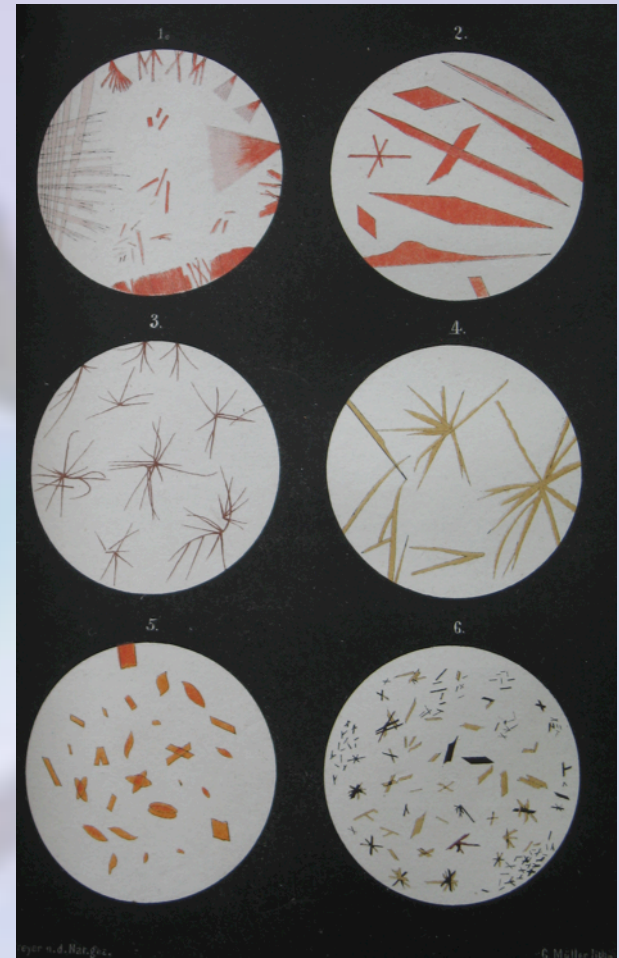
First Protein Crystal Photomicrograph?

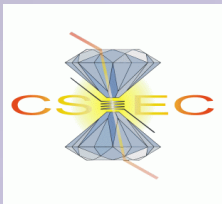


Photomicrographs of Hb (Blutroth) from a variety of species were taken and published by Preyer in 1871.

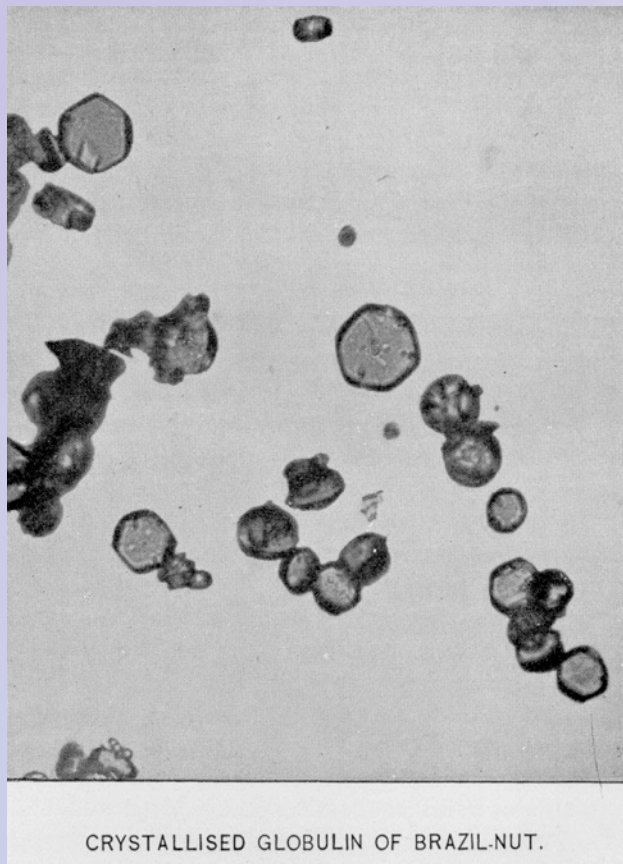
Top left - dog

Top right - baboon





First Protein Crystal Photomicrograph?

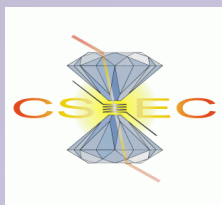


CRYSTALLISED GLOBULIN OF BRAZIL-NUT.

Excelsin

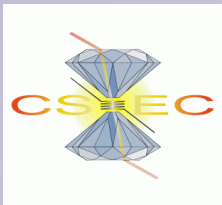
It looks like the first publication in a journal of a protein crystal photomicrograph was of excelsin, first crystallised by Maschke in 1858. *Bot.Z.* 13, 882, although observed in vivo by Hartig, 1855.

T.B.Osborne, 1892. *Am.Chem.J.* 14, 662



Crystallisation Methods

Method	First Report (not necessarily X-ray crystals!)
Salting Out (Batch)	Miller, <i>Elem.Chem.</i> 3 , 332; 1857 (OED)
PEG	Polson <i>et al.</i> , <i>Biochim.Biophys.Acta</i> 82 , 463; 1964
Many early protein crystallisations were done on the mL scale!	
Salting In	Wright, <i>J.Chem.Soc.</i> 1926 , 1203; 1926 (OED)
Salting in generally requires dialysis, since most proteins are insoluble in distilled water (<i>globulins</i> in the old nomenclature, unlike <i>albumins</i> which are soluble)	
Dialysis	Graham <i>Phil.Trans. Roy.Soc.</i> 151 , 186; 1861 (OED)
Alcohol	Drechsel, E. <i>J.prakt.Chem.</i> 19 , 331; 1879
Small scale	Zeppezauer, M. <i>Arch.Biochem.Biophys.</i> 126 , 564; 1968
Vapour Diffusion	Abraham & Robinson <i>Nature</i> 140 , 24; 1937
Reference made by Davies and Segal,	<i>Meth.Enzymol.</i> 22 , 266; 1971
Hanging Drop	Wlodawer & Hodgson <i>et al. PNAS.</i> 72 , 398; 1975?
Sitting Drop	Hampel <i>et al. Science</i> 162 , 1384; 1968



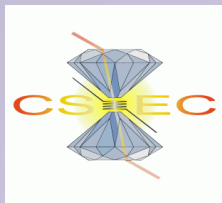
Other Crystallisation Methods

Method	First Report (not necessarily X-ray crystals!)
Free Interface Diffusion	King <i>et al.</i> , <i>Acta Cryst.</i> 9 , 460; 1956 Salemme, <i>Arch.Biochem.Biophys.</i> 151 , 533; 1972
Salt Extraction	Zahn & Stahl <i>Hoppe-Seylers Z.phys.Chem.</i> 293 ,1; 1953 Jakoby, <i>Anal.Biochem.</i> 26 , 295; 1968
Gel growth	Marriage 1891 - PbI_2 in fruit jelly, jam Liesegang <i>Naturwiss.Wochenschrift.</i> 11 , 353;1896 Robert & Lefauchaux <i>J.Cryst.Growth</i> 90 , 358; 1988
Microgravity	Littke & John <i>Science</i> 225 , 203; 1984
Excess gravity	Karpukhina <i>et al.</i> <i>Kristallografiya</i> 20 , 680; 1975



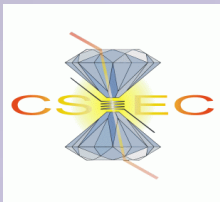
Some Notable Firsts

Protein	First Crystals	Comment
Haemoglobin	Hünefeld, 1839 Funke, 1851	First protein First deliberate crystals
Myoglobin	Theorell, 1924	First protein structure
Urease	Sumner, 1926	First enzyme
Insulin	Abel <i>et al.</i> , 1927	First hormone
Pepsin	Northrop, 1930	First globular protein X-ray picture
TMV	Stanley, 1935	First virus & first structure
Lysozyme	Abraham & Robinson, 1937	First enzyme structure
TBSV	Bawden & Pirie, 1938	First spherical virus structure
DL-Rubredoxin	Lovenberg & Williams, 1969	First protein racemate crystallised



We have now looked at crystals, how they can be built from basic building blocks or unit cells leading to predictions of simple crystal structures, and how protein crystals in particular can be prepared.

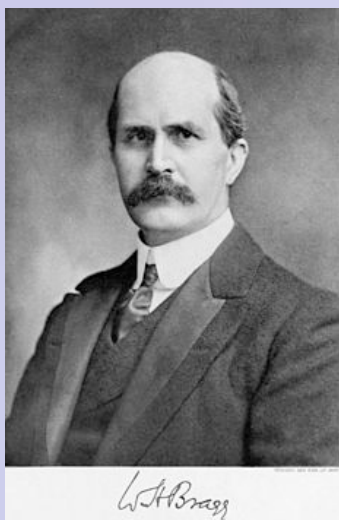
But what does the molecular structure look like?



the Light Dawns!



In 1895, Roentgen discovered X-rays, the first photograph being of his wife's hand. By 1896, there was a medical X-ray department in Glasgow Royal Infirmary.

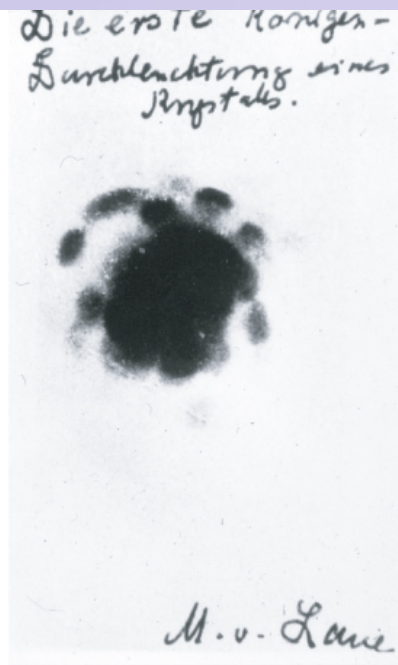


Soon after W H Bragg started experiments on the nature of X-rays that led to his developing an X-ray spectroscope which of course allowed father and son to measure intensities.

<http://en.wikipedia.org/wiki/X-ray>
http://en.wikipedia.org/wiki/William_Henry_Bragg



Laue's Experiment 102 Years Ago



Copper Sulphate

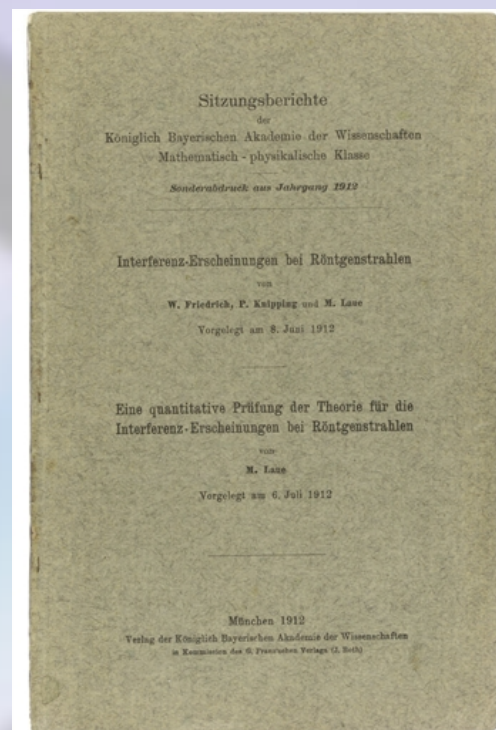
www.wiley-vch.e-bookshelf.de

Friedrich, W., Knipping, P. and von Laue, M. (1912) *Interferenz-Erscheinungen bei Röntgenstrahlen*, *Sitzungsberichte der Kgl. Bayer. Akad. der Wiss*, 303--322

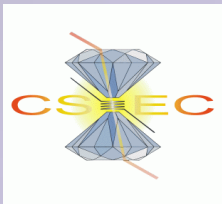
$$a. (s_h - s_o) = h \lambda$$

$$b. (s_h - s_o) = k \lambda$$

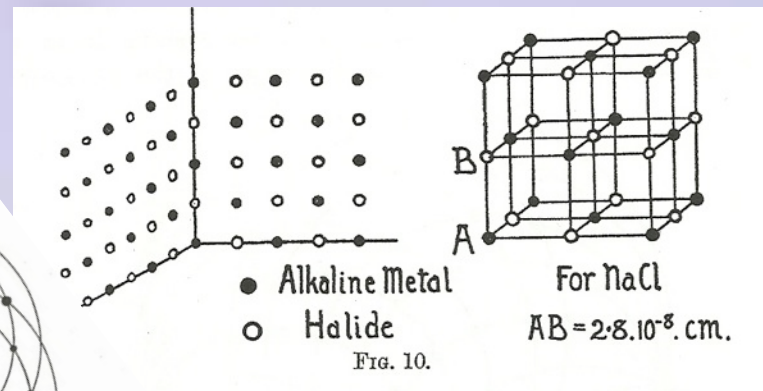
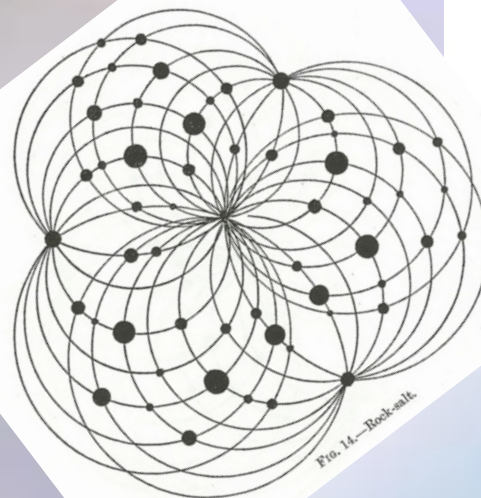
$$c. (s_h - s_o) = l \lambda$$



<http://www.christies.com/lotfinderimages/d50673/d5067359x.jpg>
(Sold for ~£8000 in 2008!)



Bragg's Interpretation 101 Years Ago

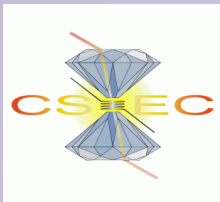


$$n \cdot \lambda = 2 \cdot d \cdot \sin \theta$$

W.L.Bragg (1913) *The Diffraction of Short Electromagnetic Waves by a Crystal*. Proceedings of the Cambridge Philosophical Society. **17**, 43.

W.L.Bragg (1913) *The Structure of Some Crystals as Indicated by Their Diffraction of X-rays*. Proc.Roy.Soc. **A89**, 248.





The First X-ray Data on a Biological Material



Sept., 1913.]

TRANSMISSION OF X-RAYS ETC.

131

This torsionmeter has been patented in Japan and Germany, and the patent application filed in Great Britain and other countries.

Transmission of X-Rays through Fibrous, Lamellar and Granular Substances.

BY

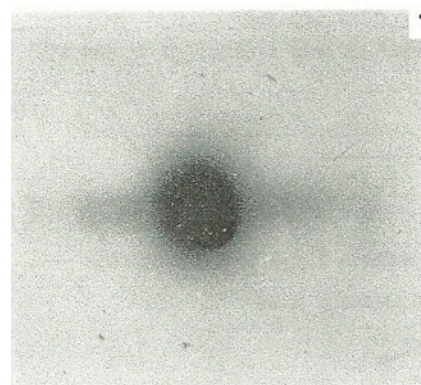
S. NISHIKAWA AND S. ONO.

[READ SEPT. 20, 1903.]

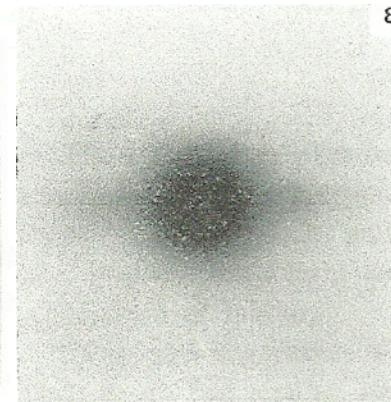
The interference phenomenon of the X-rays recently discovered by Laue, Friedrich and Knipping (¹) has been one of the most favourite subjects of investigation, and many researches which have hitherto been made, throw a fresh light on the nature of the radiation itself and on the structure of matter.

At a kind suggestion of Professor Terada, we have made some experiments on the similar line with several fibrous substances. At the same time, some experiments with lamellar and granular substances were also made. A brief account of the results obtained will be here given.

Tôkyô Sû. But. Kw. K., Ser. 2, Vol. 7, Pl. VII.



Asa (Cannabis sativa)

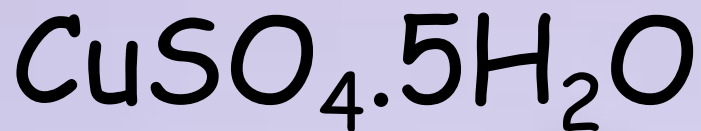
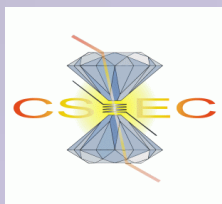


Bamboo (Phyllostachys mitis)

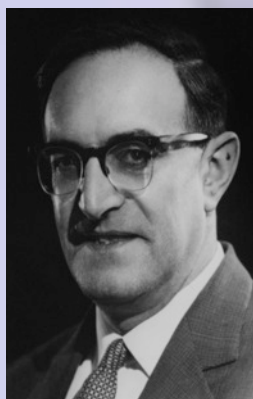
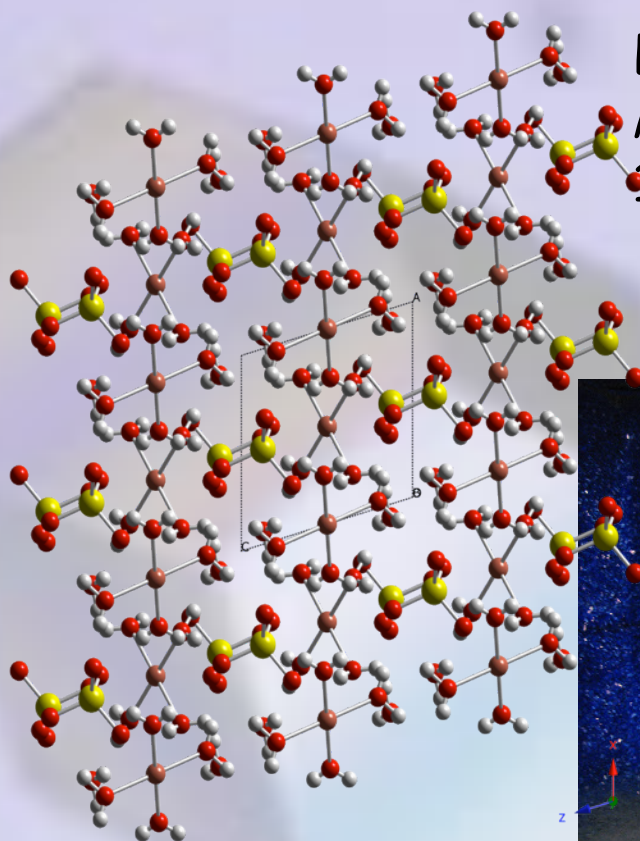
Cannabis

Bamboo

1913



Beevers, C.A. & Lipson H.
Proc. Roy. Soc. A **146**, 570;
1934



www-outreach.phy.cam.ac.uk
<http://commons.wikimedia.org/wiki/File:Copper%28II%29-sulfate-pentahydrate-b-axis-xtal-2007-CM-3D-balls.png>
www.reddit.com

Seizure by Roger Hiorns, 2008
www.xtl.ox.ac.uk



Pepsin - the First Protein Crystal to be X-Rayed



CRYSTALLINE PEPSIN

I. ISOLATION AND TESTS OF PURITY

By JOHN H. NORTHROP

(From the Laboratories of The Rockefeller Institute for Medical Research,
Princeton, N. J.)

(Accepted for publication, May 9, 1930)

Northrop, J.H. (1930) *J. Gen. Physiol.* **13**, 739-766.



John Howard Northrop
(1891-1987),
Nobel Prize 1946

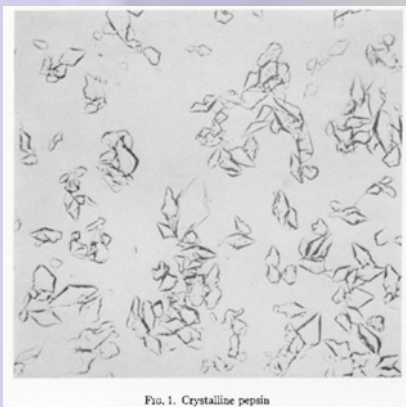


FIG. 1. Crystalline pepsin

X-Ray Photographs of Crystalline Pepsin

It was clearly necessary to avoid alteration of the crystals, and this was effected by drawing them with their mother liquor and without exposure to air into thin capillary tubes of Lindemann glass. The first photograph taken in this way showed that we were dealing with an unaltered crystal.

J. D. BERNAL.
D. CROWFOOT.

Department of Mineralogy and Petrology,
Cambridge.
May 17.

¹ G. L. Clark and K. E. Korrigan (*Phys. Rev.*, (ii), **40**, 639 ; 1932) describe long spacings found from crystalline insulin, but no details have been published.

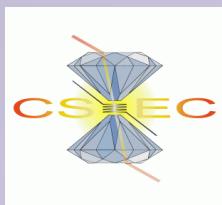
² J. H. Northrop, *J. Gen. Physiol.*, **13**, 739 ; 1930.



Dorothy Crowfoot
Hodgkin (1910-1994),
Nobel Prize 1964



John Desmond Bernal
(1901-1971)



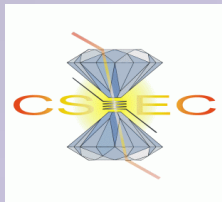
A '30s View of Enzymes

"The conception that crystallised pepsin is pure and that the enzyme is a protein, requires further proof, as it has been shown to be a compound body."

E. Waldschmidt-Leitz *Ann.Rev.Biochem.* **1**, 69; 1932

"Peptide chains in the ordinary sense may exist only in the more highly condensed or fibrous proteins, while the molecules of the primary soluble proteins may have their constituent parts grouped more symmetrically about a prosthetic nucleus."

J.D.Bernal & D.Crowfoot *Nature* **133**, 794; 1934



Myoglobin - the First Protein Structure

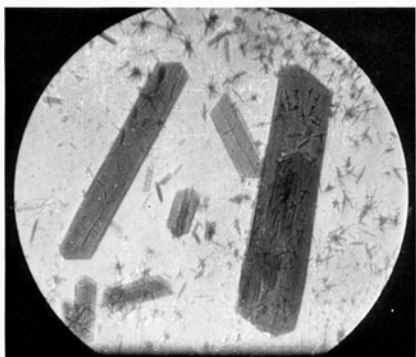
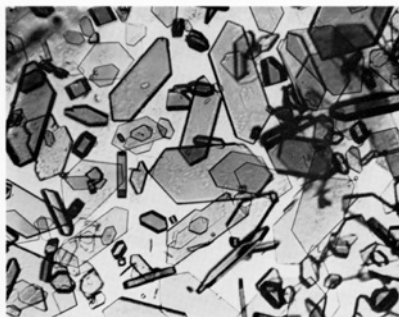


FIGURE 2. Crystals of horse met-myoglobin (magn. $\times 15$ approx.). (By courtesy of M. W. Rees.)

Although Theorell grew crystals of horse met-Mb in 1932, crystals of whale Mb were first obtained in Cambridge by Keilin and Schmid *Nature* **162**, 496; 1948.



(a)



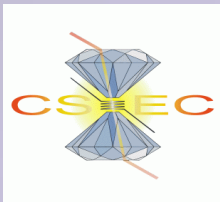
(b)

FIGURE 1. Crystals of sperm whale myoglobin (a) type A (magn. $\times 15$); (b) type B (magn. $\times 15$).

Perhaps the first paper to discuss the X-ray crystallography of the same protein from several different species was Kendrew *et al.* in *Nature* **174**, 946; 1954



Sperm whale Mb



Lysozyme - the First Enzyme Structure



Crystallisation of Lysozyme

The material made according to the method of Roberts seems to possess a high degree of homogeneity and it may be

crystallised by one operation from solution in N/20 acetic acid and concentration over aqueous potassium hydroxide in a vacuum desiccator. The crystal (Fig. 1, photomicrograph by

Mr H. M. Powell) appear to be dodecahedra, and Miss D. Crowfoot has kindly undertaken their crystallographic examination.

Crystalline lysozyme is about as active as the Roberts specimen in bringing about lysis of *Micrococcus lysodeikticus*, but comparisons by the method used are not capable of great accuracy.

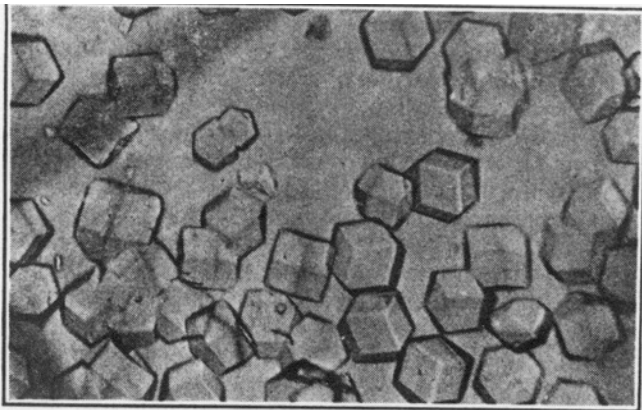


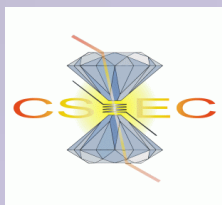
Fig. 1.

E.P. Abraham & R. Robinson
Nature 140, 24 (1937)



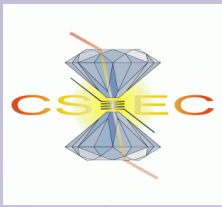
Gareth Mair, Colin Blake, Louise Johnson, Tony North, David Phillips, Raghupathy Sarma

C. C. F. Blake *et al.*, *Nature* 206, 757 (1965)



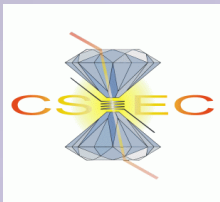
Some Notable Firsts

Protein	First Crystals	Structure (<3Å resolution)	Time/yr
Haemoglobin	Hünefeld, 1839	Perutz <i>et al.</i> , <i>Nature</i> 219 29; 1968	129
Excelsin (Ber e2)	Maschke 1858	Guo <i>et al.</i> , <i>Acta Cryst</i> F63 , 976; 2007	(149)
Ovalbumin	Hofmeister, 1888?	Stein <i>et al.</i> , <i>J.Mol.Biol.</i> 221 , 941; 1991	>103
Myoglobin	Theorell, 1924	Kendrew <i>et al.</i> , <i>Nature</i> 185 , 422; 1960	36
Urease	Sumner, 1926	Jabri <i>et al.</i> , <i>Science</i> 268 , 998; 1995	69
Insulin	Abel <i>et al.</i> , 1927	Adams <i>et al.</i> , <i>Nature</i> 224 , 491; 1991	64
Pepsin	Northrop, 1930	Andreeva <i>et al.</i> , <i>J.B.C.</i> 259 , 11353; 1984	54
TMV	Stanley, 1935	Namba <i>et al.</i> , <i>J.Mol.Biol.</i> 208 , 307; 1989	54
Lysozyme	Abraham & Robinson, 1937	Blake <i>et al.</i> , <i>Nature</i> 206 , 757; 1965	28
TBSV	Bawden & Pirie, 1938	Harrison <i>et al.</i> <i>Nature</i> 276 , 368; 1978	40
DL-Rubredoxin	Lovenberg & Williams, 1969	Zawadzke & Berg. <i>JACS</i> 114 , 4002; 1992	23

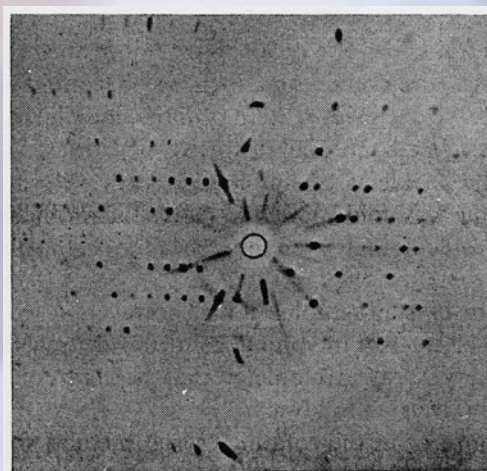
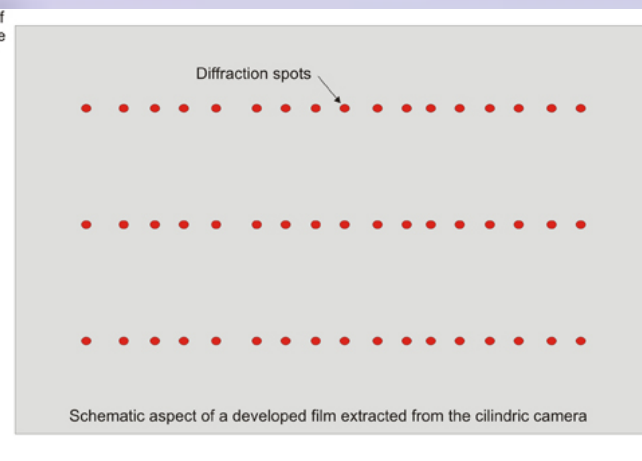
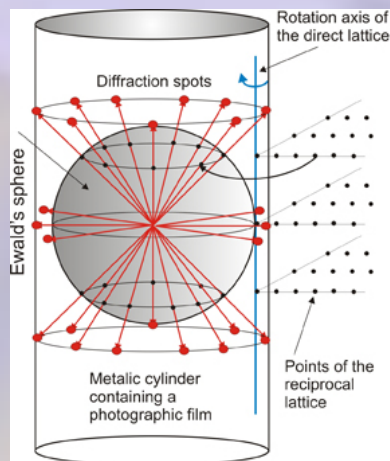


X-Ray Data Collection

- Laue used a photographic method
- The Braggs used a spectrometer
- From the 1930s to the 1980s photography was the main method for proteins
- From the 1980s onwards PSDs have become routine



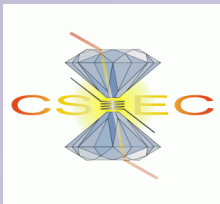
X-Ray Spectrometer



Rotation about a vertical **aligned** axis will produce 'layer lines' like those shown.

Note the goniometer on the Bragg instrument

<http://londonhistorians.wordpress.com/2011/12/08/the-appliance-of-science-the-royal-institution/>
<http://weissenberg.bsr.org.uk/1/Weissenbergs%20Influence%20on%20Crystallography.htm>

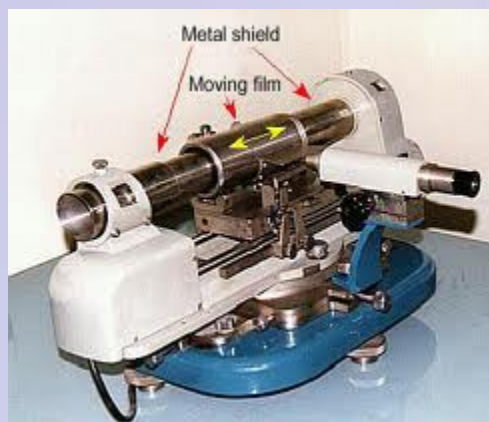
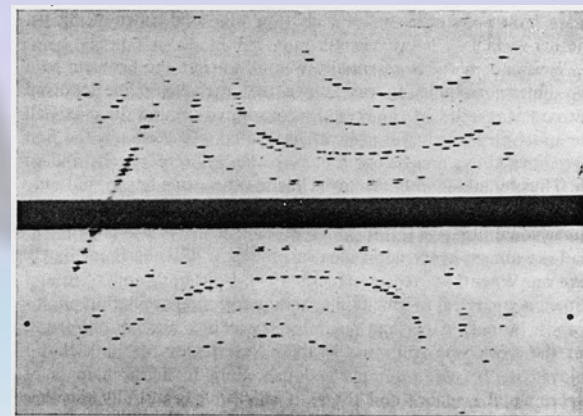
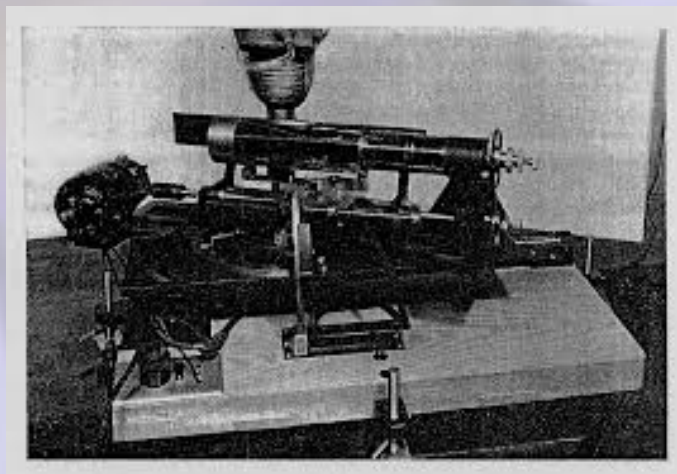


The Weissenberg Camera



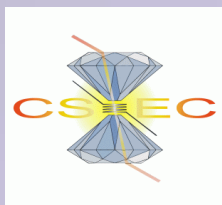
M. Weissenberg

Rotation about a vertical axis coupled with a translation of the film will produce a reciprocal lattice zone, *provided a suitable screen intercepts the unwanted diffraction.*



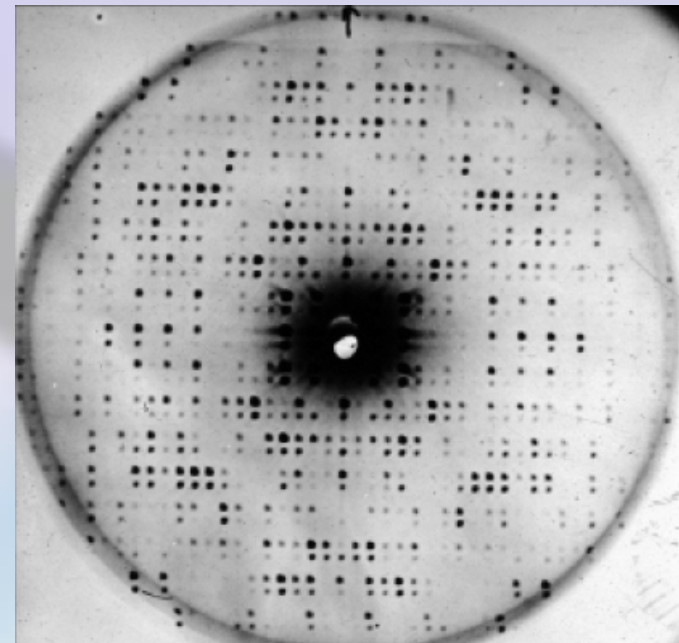
Interpretation is not straightforward but the technique was implemented on an image-plate system at the Photon Factory in Japan (*J.Appl.Cryst.* **4**,136; 1997).

<http://weissenberg.bsr.org.uk/1/Weissenbergs%20Influence%20on%20Crystallography.htm/>

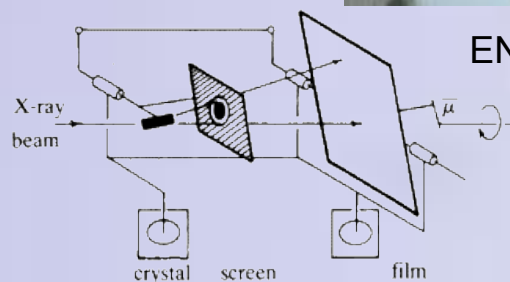


The Precession Camera

The precession method gives an undistorted picture of a reciprocal lattice plane

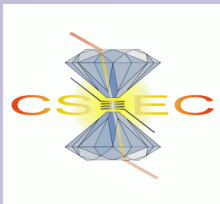


ENRAF-Nonius camera c.1970



Crystal orientation essential and also inefficient.

Buerger, M. J. (1944): The Photography of the Reciprocal Lattice: ASXRED Monograph Number 1.
American Society for X-ray and Electron Diffraction, Cambridge, Mass



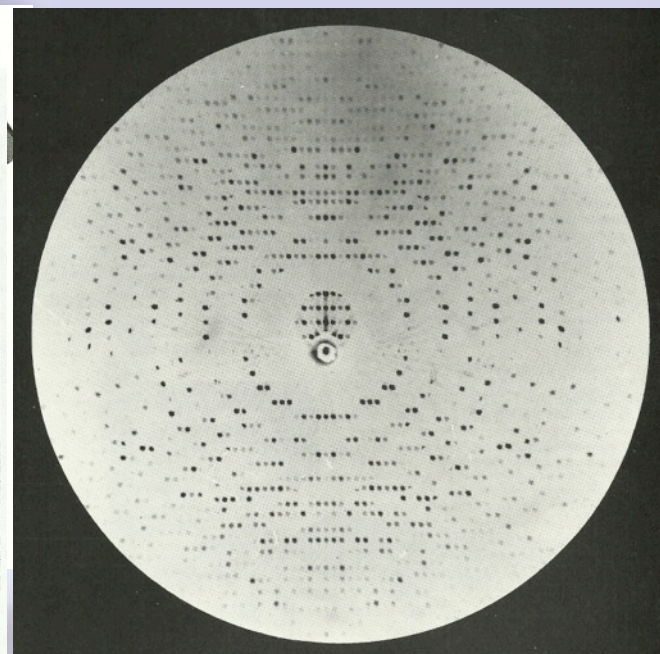
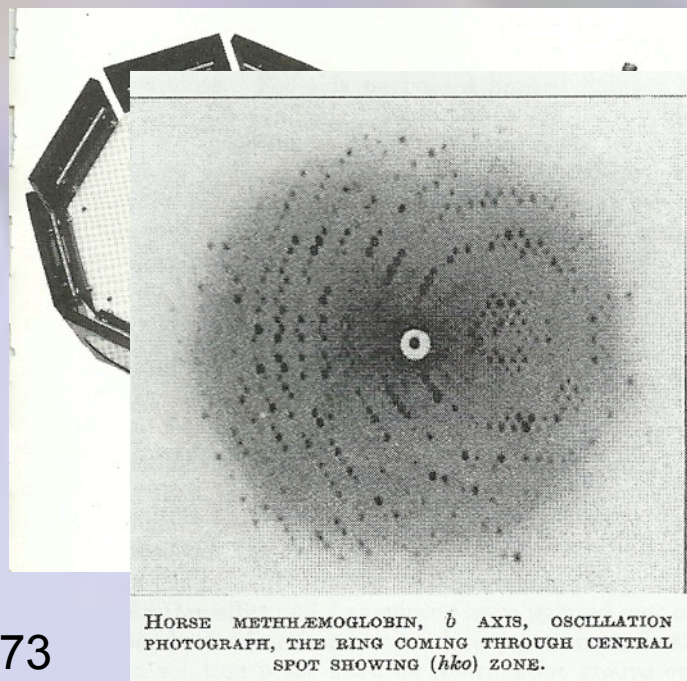
The Rotation Camera

It became clear in the early 1970s that efficient data collection was the key to protein structure determination. Interestingly, we went back to the simple rotation method! Initially, the software required some knowledge of the crystal orientation but that was soon replaced by essentially the method that is used today – shoot first and ask questions later.

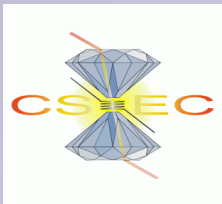


Uli Arndt

J. Appl. Cryst. **6**, 457; 1973

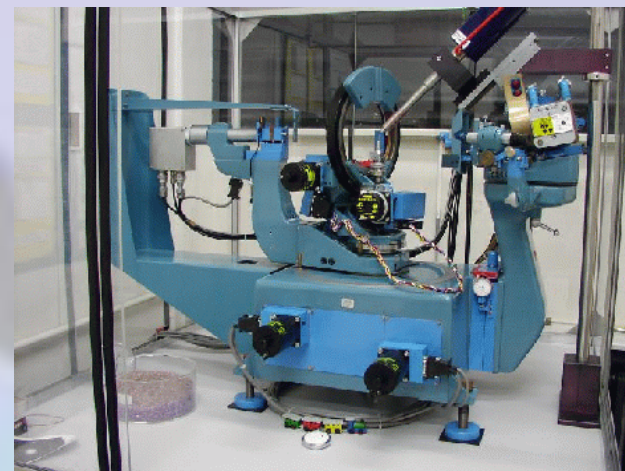
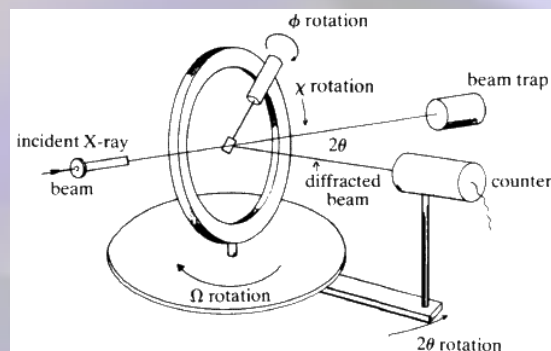
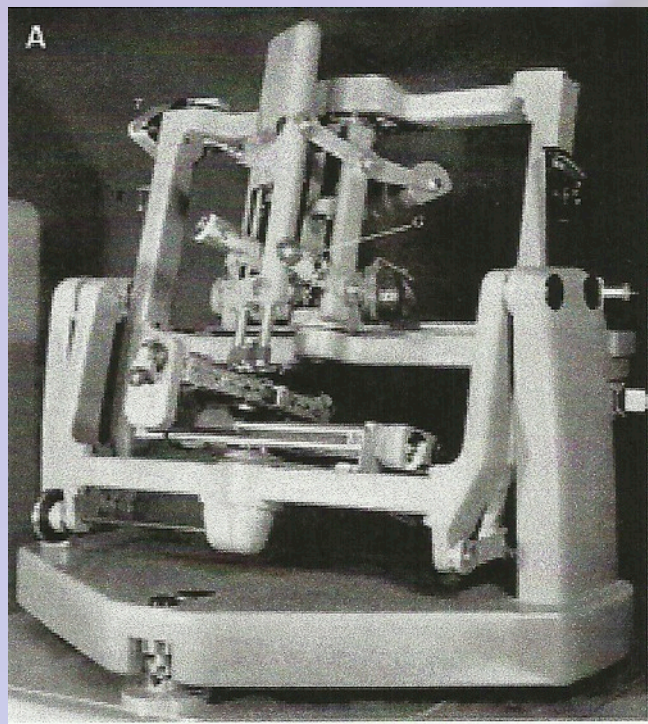


Bernal, *Nature* **143**, 663; 1939



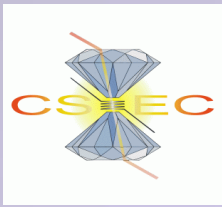
Counter Techniques

Counter techniques generally require moving the crystal and the counter in order to intercept all possible diffracted X-rays, as the Braggs did in 1913. This has been achieved in a variety of ways.

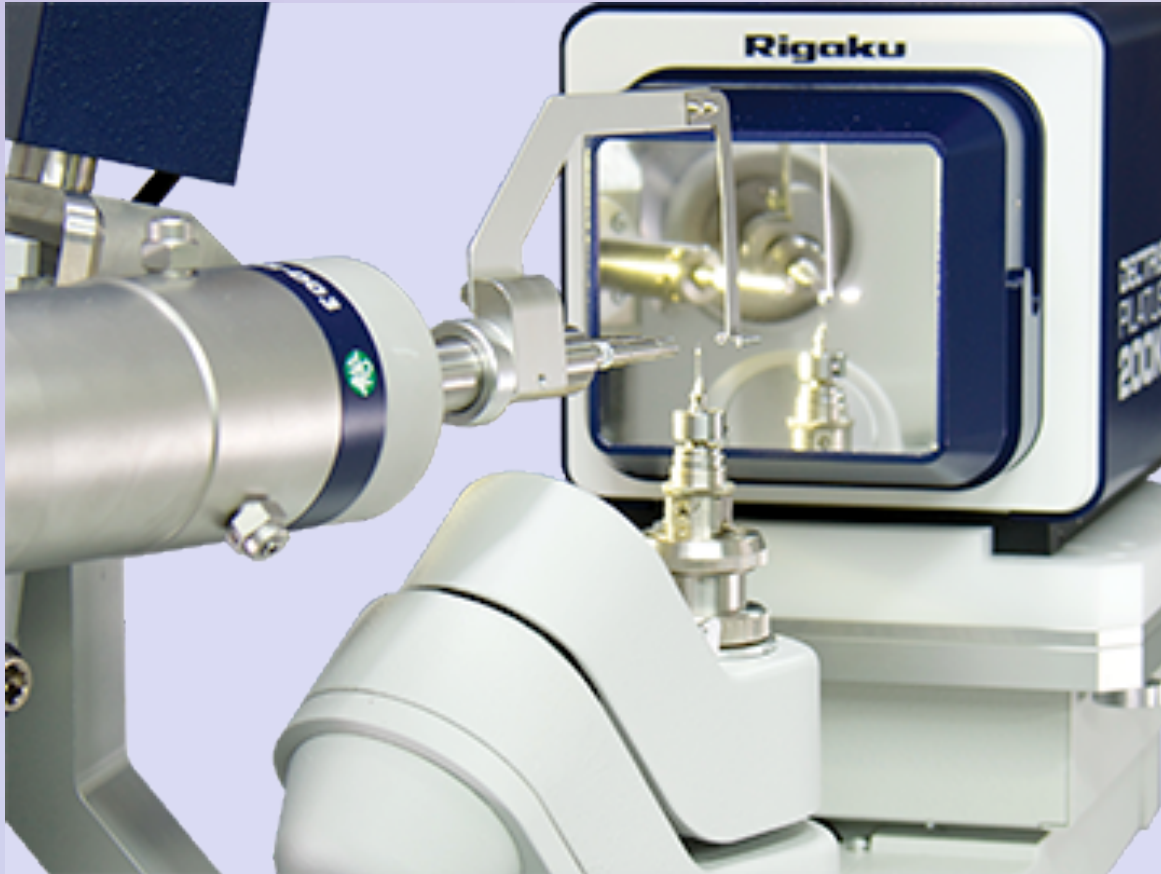


An Eulerian cradle allows positioning by ϕ, χ, ω and the detector by 2θ .
 κ geometry mimics this giving more access space

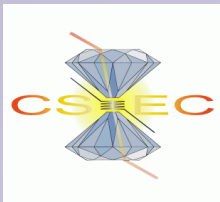
Arndt & Phillips, Acta Cryst. 14,807; 1961. <http://www.beta-sheet.org/page29/page47/index.html>
<http://www.juergenkopf.de/hilger2.gif>



Counter Techniques



Modern instruments have an area detector in place of the single counter on 2θ



Position Sensitive Detectors



Film is of course one such device, but it requires subsequent digitisation.

Early protein structures (Mb, Hb, chymotrypsin) used a scanning microdensitometer to do this digitisation from precession photographs so indexing was straightforward.

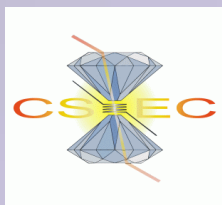
Later, digitisation still required a densitometer but the films were rotation photographs.

Image plates replaced film in the 1990s and are still in use today.



The Optronix film scanner (1973)

<http://www.chilton-computing.org.uk/acl/literature/acl/p004.htm>



Position Sensitive Detectors



The first multiwire PSD appeared around 1975 with a TV-type detector, the Nonius FAST in the early 1980s.



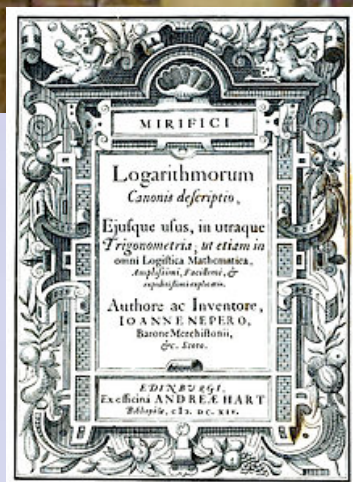
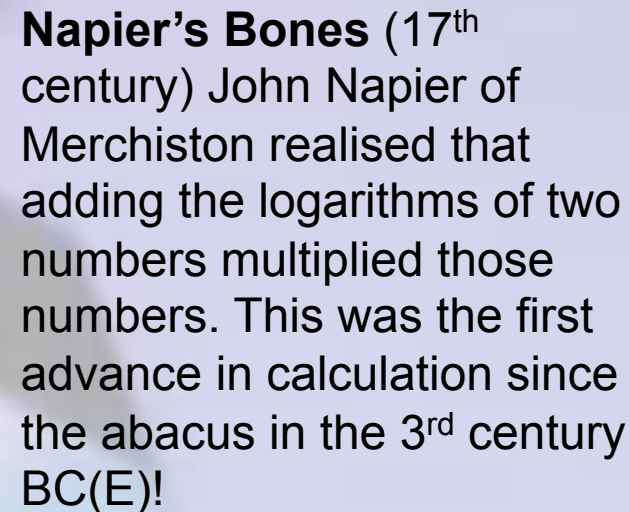
Xuong Nguyen-Huu
J.Appl.Cryst. 7:319; 1974.



Subsequent development of charge-coupled devices (CCD) detectors bring us in to the 21st century.

ADSC founded by one of the Xuong team, Hamlin.



[illegible]



Computing Methods for X-ray Crystallography

76	80	3	12	35	54	68	75	75	68	54	35	12	35	54	68	75	(244)
77	80												35	54	69	76	(246)
78	80												35	55	69	77	(248)
79	80												36	56	70	78	(252)
80	80												36	57	71	79	(256)
81	80	3	13	37	57	72	80	80	72	57	37	13	37	57	72	80	(259)
400	80	3	63	182	2												(1279)
500	80	3	78	227	3												(1599)
600	80	3															(1918)
700	80	3															(2237)
800	80	3															(2557)
900	80	3															(2877)

This is one of the 366 tables from which FOURIER STRIPS were cut. $\text{Acos}2\pi hx$ or $\text{Bsin}2\pi hx$ is tabulated for various values of A or B and h, and for x in 120ths. Over 500 sets were sold between 1948 and 1970.

C. A. Beevers *H. Lipson*

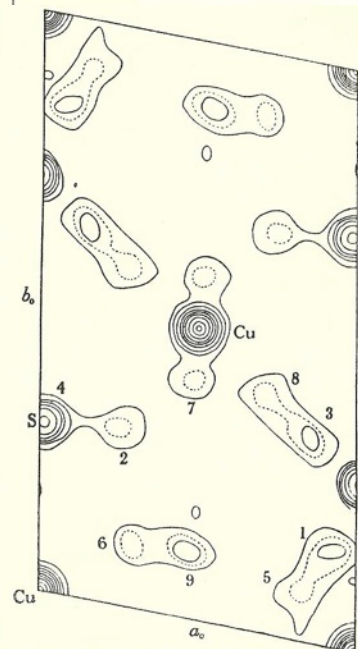
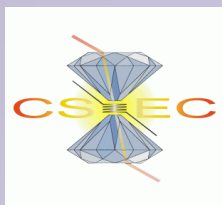


FIG. 207. $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$: (001) electron-density projection. The small peak near the water molecule 9 is a 'ghost' related to the peak 5 (Beevers and Lipson, 1934)

Remember CuSO_4 ?!

Beevers-Lipson strips (1934) allowed rapid summation of $\pm|F|.\cos 2\pi hx$ or $\pm|F|.\sin 2\pi hx$ for $x = 0/60$ to $15/60$ ths

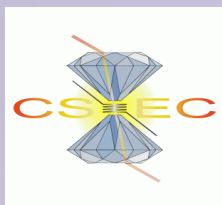




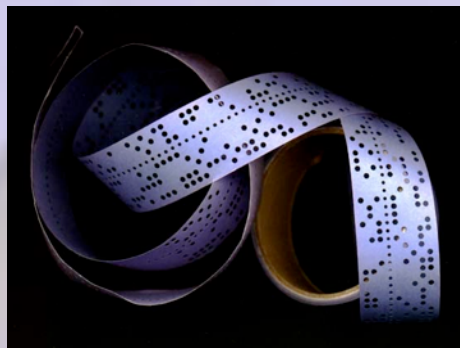
Computing Methods for X-ray Crystallography



EDSAC
~1k RAM. 2D Fourier
of 400 terms at 2000
points = 90 minutes
– Kendrew realised
computers could
make a difference.



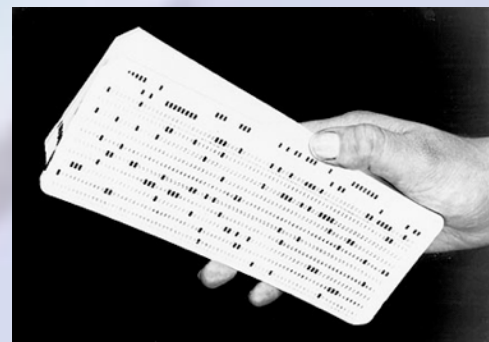
Data Input (1950s-1970s)

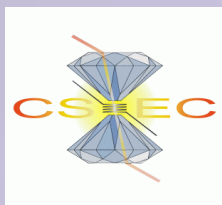


Card punches, card decks and huge metal trays replaced paper tape in the 1970s. Although the idea derived from Jacquard who automated the silk loom in about 1800, the idea was used by Hollerith to handle business data.

IBM 029 Card Punch

<http://en.wikipedia.org/wiki/Keypunch>





Computing Methods for X-ray Crystallography



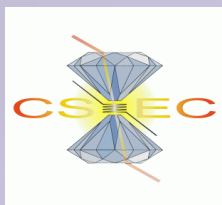
PDP-8 (1965) 4k of 12bit memory, 1.5 μ s cycle time, tape storage, later floppy discs as external storage. Used mostly as an instrument controller.



PDP-11 (1970) 16k 16bit memory, 1.2 μ s cycle time, separate floating point processor, 2.5Mbyte cartridge disc, tape-deck. Could perform serious calculations if slowly.



VAX 11-750 (1980) 32bit memory, 320ns cycle time, 2Mbyte memory. Workhorse for many PX labs in the 1980s and 1990s.



Computing Methods for X-ray Crystallography



IBM 360 (1964) A 32-bit mainframe machine. By the late 1960s these had memories of about 1Mbyte and could perform about 16Mips.

<http://www.nbcnews.com/tech/gadgets/5-reasons-love-mad-mens-new-star-ibm-360-n101716>
<http://www.cs.man.ac.uk/CCS/res/res49.htm>

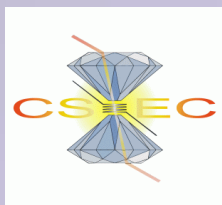


English
Electric
KDF9

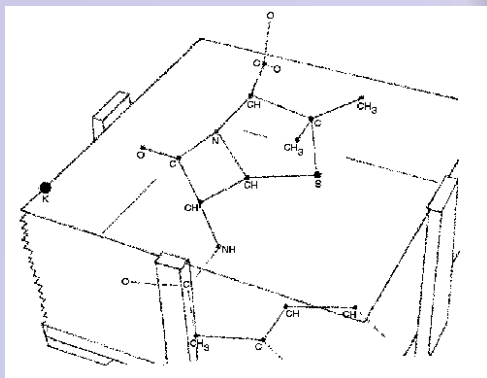
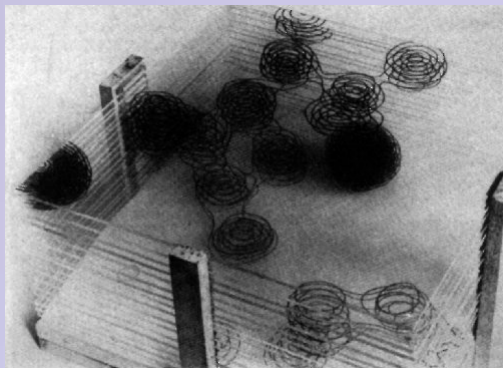


ICL 4-70
(1967)

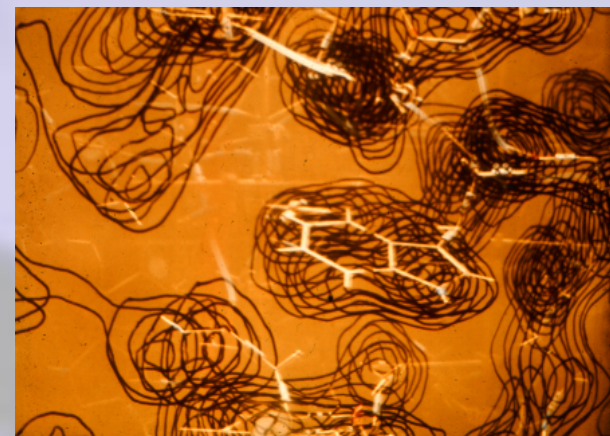
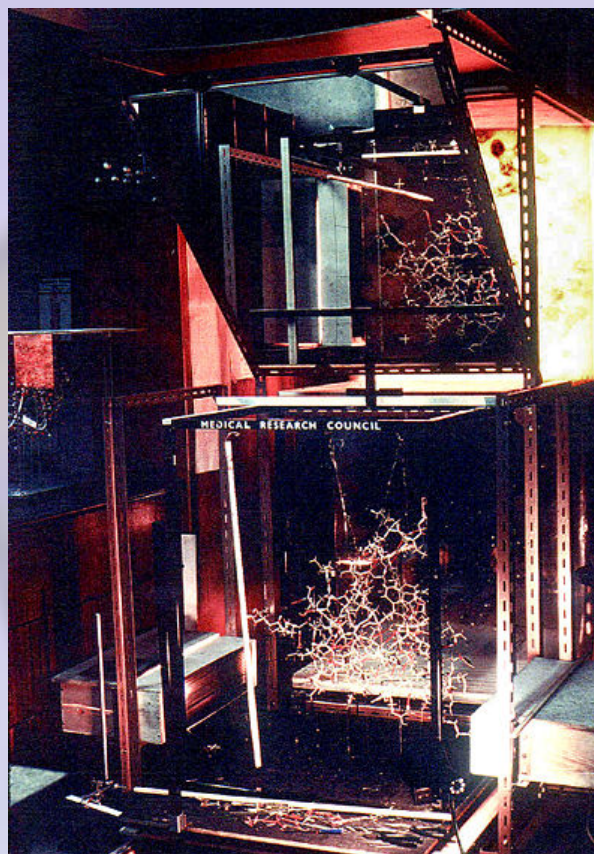
<http://www.flickr.com>



Electron Density Maps

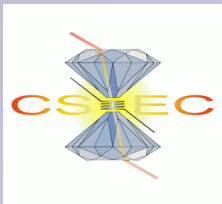


Benzylpenicillin



The Richards' Optical Comparator aka Fred's Folly (1968) allowed superposition of the reflection of a model on the electron density map. After building, coordinates were measured with difficulty and a plumb-line.

http://www.proteopedia.org/wiki/index.php/Frederic_M._Richards
<http://www.portlandpress.com/pp/books/online/tiepac/session6/ch2.htm>



Acknowledgements

In addition to credit already given, David Stammers, Andy Hoffman

Various librarians in the Scottish National Library and Edinburgh University

And you for listening!