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The evolution of synchrotron radiation and the growth of its importance in crystallography†

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The author’s 2011 British Crystallographic Association Lonsdale Lecture included a tribute to Kathleen Lonsdale followed by detailed perspectives relevant to the title, with reference to the Synchrotron Radiation Source (SRS) and European Synchrotron Radiation Facility (ESRF). Detector initiatives have also been very important as have sample freezing cryomethods. The use of on-resonance anomalous scattering, smaller crystals, ultra-high resolution as well as the ability to handle large unit cells and the start of time-resolved structural studies have allowed a major expansion of capabilities. The reintroduction of the Laue method became a significant node point for separate development, and has also found wide application with neutron sources in biological and chemical crystallography. The UK’s SRS has now been superseded by Diamond, a new synchrotron radiation source with outstanding capabilities. In Hamburg we now have access to the new ultra-low emittance PETRA III, the ultimate storage ring in effect. The ESRF Upgrade is also recently funded and takes us to sub-micrometre and even nanometre-sized X-ray beams. The very new fourth generation of the X-ray laser gives unprecedented brilliance for working with nanocrystals, and perhaps even smaller samples, such as the single molecule, with coherent X-rays, and at femtosecond time resolution.

Keywords: Kathleen Lonsdale; synchrotron radiation; high brightness; neutrons

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1. **Introduction**

This review article is based on the Lonsdale Lecture and Teaching Plenary that was presented by the author under the auspices of the Biological Structures Group of the British Crystallographic Association (BCA) at its Annual Conference held at Keele University in April 2011. This event was chaired by the BCA President, Professor Elspeth Garman. This article is divided into two parts. Part 1 is a short review of the previous Lonsdale Lecturers and also a glimpse of the tributes made to her achievements as well as a short description of her broad interests spanning not only crystallographic science but also her pacifism. Part 2 is my review of synchrotron radiation (SR) and crystallography involving the perspectives that I gained, and their allied topics, at the Synchrotron Radiation Source (SRS) and European Synchrotron Radiation Facility (ESRF), the first dedicated SR X-ray source and the first third generation low-emittance SR source, respectively.
My first preparation before my Lecture was to read Dorothy Hodgkin’s Royal Society Biographical Memoir of Kathleen Lonsdale (1); Dorothy also features in a pivotal position in my account below.

2. Previous Lonsdale Lecturers

The Lonsdale Lecture originated as a special Lecture offered by the BCA to the Annual Meeting of the British Association for the Advancement of Science (BAAS). They were announced in *Acta Crystallographica* (2a) as follows:-

As a result of a suggestion (by Moreton Moore) from the Bragg Lecture Fund committee, the Kathleen Lonsdale Lectures have been established by the British Crystallographic Association to commemorate her achievements. These lectures are intended to educate the public in the science of crystallography and will be given at the annual meetings of the British Association. The first one will be at 2 pm on 27 August 1987 at the British Association meeting in Belfast, Northern Ireland, and will be open to the public. The lecture will be given by Professor David Blow and the title of the lecture is ‘Protein Crystallography Applied to Medicine and Industry’.

From the mid to late 1990s onwards the BCA Council decided to host the Lonsdale Lecture within the BCA Annual Conference. In recent years the Young Crystallographers Group of the BCA was formed, and who started nominating the Lonsdale Lecturer to the Council of the BCA whereby the speaker is ‘a well respected scientist who has a good rapport with students’.

From the BCA website and BCA Newsletters the past Lonsdale Lecture details are:-

* 1987 David Blow (Imperial College) – Belfast BAAS meeting [2a]
* 1988 Michael Hart (Manchester University) – Oxford BAAS meeting Sept 5th entitled *Synchrotron radiation throws light on a microscopic world*
* 1989 Robert Diamond (Laboratory of Molecular Biology, Cambridge) – Sheffield BAAS meeting 12th September 1989 entitled ‘Crystalline Viruses’.
* 1990 Alan MacKay (Birkbeck College) – Swansea BAAS meeting August 22nd entitled *What is a crystal?*
* 1991 Louise Johnson (Oxford University) – Plymouth BAAS meeting August 29th entitled *Designer Drugs*
* 1992 Peter Murray-Rust (Birkbeck College) – Southampton BAAS meeting entitled *Molecules and Disease*
* 1993 Judith Milledge (University College London) – entitled *Diamonds thick and thin* Keele BAAS meeting
* 1997 Andrew Lang (Bristol University) – presented at the Leeds BCA Annual meeting entitled *X-rays and Diamonds*
* 1999 T. Richard Welberry (Australian National University, Canberra, Australia) – presented at the IUCrXVIII held in Glasgow entitled *Diffuse X-ray Scattering*
* 2004 Elspeth Garman (Oxford University) presented at the BCA held in Manchester entitled *Cool crystals: kill or cure?*
* 2006 Mike Glazer (Oxford University) presented at the BCA held in Lancaster entitled *Crystals under the microscope*
* 2007 Bill David (ISIS neutron facility, Rutherford Appleton Laboratory) presented at the BCA held in Canterbury entitled *Combinatorial Studies of Hydrogen Storage Materials.*
3. Biographical sketch of Kathleen Lonsdale and her crystallographic science

Dame Kathleen Lonsdale FRS (Figure 1) was a key figure in British crystallography and science as indicated by a list of a few examples of her accomplishments: President of the IUCr 1966; a key instigator of International Tables; author of numerous crystallography publications and the first female President of the BAAS. She was also a leading pacifist of her time. She trained as a physicist and became a Professor of Chemistry.

Figure 2 shows the front cover of her book ‘Crystals and X-rays’ (3). In the book review by Prof. Martin Buerger (Department of Geology, Massachusetts Institute of Technology, Cambridge, MA, USA) (4) he wrote:

of Investigation. IV, Geometrical Structure Determination. V, Determination of Atomic and Electronic Distribution. VI, Extra-structural Studies. VII, The Importance of the Study of Crystals.... The book is based on a series of public lectures given by the author at University College, London.... For the scientist not versed in X-ray crystallography, perhaps the most important chapter is the comparatively non-technical ‘Historical Introduction’. In this chapter the author not only sketches the history of the development of X-rays and X-ray diffraction, but gives a nicely balanced view of the place of X-rays in modern science. When the evidence is assembled, the debt modern science owes to X-rays and X-ray diffraction is striking indeed. In the reviewer’s opinion, this chapter is beautifully done and should be read by all scientists.... The veteran X-ray crystallographer will probably find that a good deal of the book is a discussion of material quite familiar to him. Yet almost every

Figure 2. The front cover of (my own copy of) her book, ref. (3).
reader will find a smattering of this subject matter which appears in novel and stimulating form.

Figure 3 is one of her famous crystallographic analyses, namely that of hexachlorobenzene (5), which followed her 1929 crystal structure of hexamethylbenzene (6), analyses which showed that the bond distances around the aromatic benzene ring were equal and not alternating short and long distances of single and double bonds. Thus it is a resonance molecular structure. The advantage of the hexachlorobenzene structure is in showing the larger number of (relative scale) contours for the terminal chlorine atoms than the parent carbon atoms. Kathleen Lonsdale is careful to explain in ref. (6) that ‘It must be remembered, however, that these values are measured in arbitrary units and are subject to the addition of an unknown constant. Any attempt at electron counting, for example, is out of the question’.

I now offer examples that illustrate the breadth of her interests and work.

Her obituary in *The Times* (7), in noting that Kathleen Lonsdale was the ‘First woman President of the British Association for the Advancement of Science’, stated that ‘(she) aimed darts at a variety of targets: the sale of arms, the narrowness of many scientists and (the) responsibility of scientists as a whole for the use made of their discoveries.’ In the same role she delivered a lecture at the Leeds meeting of the BAAS on the 4th September 1967 on *Physics and Ageing*.

\[
S(x, z) = \sum \sum F(h0l) \cos 2\pi (hx/a + lz/c)
\]

Figure 3. Kathleen Lonsdale published in 1931 an X-ray analysis of the structure of hexachlorobenzene by the Fourier method (5) illustrated here with her Figure 7 using the formula:–

The unit cell is simple monoclinic prismatic, with \(a = 8.07\), \(b = 3.84\), \(c = 16.61\) Å, \(\beta = 116°52'\) and it contains two molecules of \(C_6Cl_6\). This figure is reproduced with the permission of The Royal Society and HighWire Press and is Figure 7 in ref. (5).
As a pacifist, in her letter to the Minister of Labour and National Services, Whitehall SW1 of 29th May 1942 she wrote (8):

Sir,

...I am absolutely opposed, however, to the principle of universal compulsory registration and conscription for war purposes. As a member of the Society of Friends (Quakers) I believe war to be the wrong method of resisting aggression or any other form of evil... In refusing, therefore, to comply with the regulation or to take advantage of possible exemption on conscientious or other grounds, and in being prepared to take the consequences, I am acting in accordance with what I believe to be my highest duty. I rather wish I did not.

Yours sincerely,
Kathleen Lonsdale (D.Sc London).

She served one month in Holloway Prison in 1943 as a result.

She expressed her pacifist views in detail in her book (9): ‘Is Peace Possible?,’ which I came across in writing up my Lecture in this article. I bought a copy and it is a personally signed one. This signature, like the two letters that I highlight below, gives me a real sense of her presence. The front cover of the book has the headline: A Quaker scientist discusses problems of peace, freedom, and justice in an era of expanding world population and technical development. She researched her topics carefully; she had clearly studied and quotes from the UN Charter as well, for example, of giving a detailed summary of the stages and landmarks in the Israeli–Palestinian conflict, as well as the role of Britain and other countries in that conflict (Chapter 9). The book also contains her strongly held religious beliefs. She sums up her arguments and logic made in the book as follows (p. 127):

...a life of non-violence is essentially one of deep spiritual out-reach to the good in other men and of belief that, even if there is no response, even if we appear to fail, goodness will in the end prevail. Yea, though I walk through the valley of the shadow of death I shall fear no evil, for Thou art with me.

In covering her science I must mention her strong interest in determining the mobility of atoms from crystal structure analyses, and thereby inferring details of reactions in crystals and the crystalline state. In her article with Judith Milledge ‘Analysis of thermal vibrations in crystals: a warning’ (10) the authors are concerned with assumptions regarding thermal ellipsoid determinations from crystal structures and conclude that ‘it is not safe to rely on one determination of a set of b_j deduced from experimental data at one temperature... Finally we would beg crystallographers not to mislead interested research workers in other disciplines...unless and until they repeated their measurements and refinements more than once, independently, and can prove that a claim to such accuracy (4 or 5 apparently significant figures) is justified’. In their acknowledgements they refer to their ‘indebtedness to the referee whose sharp criticisms made us rewrite this paper and, we hope, improve it’. Many years later the IUCr Newsletter published a piece from Prof. Durward Cruickshank entitled ‘Tilting at Windmills’ (11) in which Durward revealed that he was the referee and furthermore a sketch drawn by Kathleen Lonsdale was reproduced; evidently the matter ended in good humour. Furthermore, I would surmise, the general impression left with Kathleen Lonsdale of Durward Cruickshank’s abilities and conscientiousness led to the letters to him when she was the President of the International Union of Crystallography dated 14th June 1966, and subsequently
Kathleen Lonsdale (1903–1971) began her long career in X-ray crystallography under W.H. Bragg in 1922. In 1929 she determined the structure of hexamethylbenzene, the first aromatic compound to be defined by X-ray diffraction, and so proved the planarity of the benzene nucleus. She was a pioneer of space group theory in relation to the structure analysis of crystals and was an indefatigable Editor of International Tables for many years. Among other fields she was an expert on thermal diffuse scattering, divergent beam X-ray photography and synthetic diamonds. At the Moscow Congress in 1966 she became President of the IUCr. Dorothy Hodgkin wrote in her obituary “She was a tough President, who kept her committees working for long hours. Professor Belov, who succeeded her as President, was heard to remark as she dragged him away from a pleasant party at the British Embassy to yet another committee meeting: ‘Kathleen you are a martinet’”.

W.L. Bragg wrote one of his last communications before he died regarding the passing of Kathleen Lonsdale and so I can quote an extract written by him published in *Acta Cryst.* (12):

Others have written about Dame Kathleen Lonsdale’s scientific achievements; I wish to add a tribute to her as a person. She was one of the most thorough, high-principled, and courageous people I have known. We who work in the field of X-ray analysis cannot be too grateful for all she did to help us. Her early collaboration with Astbury in preparing an exhaustive survey of space groups was typical. The set of formulae for structure analysis, and the work on *International Tables* for the Union, were models of accuracy and ordered arrangement. No trouble was too great for her, and it was all done disinterestedly for the general good, much of it behind the scenes and in helping others . . . Her pluck and determination to be of service to others knew no bounds.

In closing this section I wish to quote extracts from one of her devoted colleagues, Dr Judith Milledge, both from her email to me during the preparation of this article and her obituary of Kathleen Lonsdale.

From Judith Milledge’s email to me (13):

You must obviously choose which of her achievements you mention, but being one of the first female FRS’ [Fellows of the Royal Society], the 1st woman professor at University College London, and her contribution to teaching crystallography in the joint MSc with Bernal at Birkbeck, as well as the week-long crystallography practical for 3rd year chemistry students, which was copied by many institutions, might be worth a mention . . . . My article in ‘Out of the shadows’ Edited by Byers & Williams (C.U.P. 2006, pp. 191–201 (14)) also mentions that her diamagnetic anisotropy measurements provided the first direct experimental confirmation of the existence of molecular orbitals . . . . You are correct in assuming that our interchange with Durward (‘tilting at windmills’) ended in good humour.

From Judith Milledge’s Obituary of Kathleen Lonsdale, *Acta Cryst.* (15):

Firstly on Kathleen Lonsdale’s approach: ‘Her exceptional intellect and relentless logic drove her towards practical solutions of problems once she had become involved with them, and her almost infinite capacity for hard work ensured that once a course of action had been determined, progress was steady’.

Secondly, as a complement to the above descriptions of what she did, here is a summary in the obituary on what she was not interested in:- ‘She never took the slightest interest in research on defect controlled crystal growth, refused the offer of good electron diffraction equipment in return for training students to use it, had no interest in the derivation of atomic scattering factors, potential functions or any of the many types of
Figure 4. (a, b) Two letters from Kathleen Lonsdale to Durward Cruickshank when she was President of the International Union of Crystallography.

Notes: These two letters are in the Durward Cruickshank letters archive donated by Durward to the University of Manchester and now properly listed and curated here at our Library, the John Rylands University of Manchester Library (JRULM). These letters are reproduced here with the permission of the JRULM on the understanding that I have the relevant permissions. Thus I have obtained the permission of the IUCr, under whose auspices they were sent since Kathleen Lonsdale was writing as President of the IUCr; from Dr Judith Milledge of University College London, as Scientific Executor for Kathleen Lonsdale; and from the family of Durward Cruickshank namely his son, John Cruickshank, and his daughter Helen Stuckey (née Cruickshank).

I am keen for readers to see Kathleen Lonsdale’s nice handwriting but to help any reader with legibility if needs be here is a typed version. Dear Durward, The Executive Committee seems at present to have no other nomination for Treasurer and they welcome your willingness to serve. They realize that your own circumstances may change. If you feel that this change, if and when it occurs, obliges you to resign, that will be understood and there is a procedure for dealing with that situation. On the other hand, a change of residence or nationality need not oblige you to resign. It would be a matter for consultation within the framework of the statutes and By-laws; and we can meet that situation when it and if it arises! Yours sincerely, Kathleen Lonsdale.
spectra obtainable from crystals, and made no major contributions to the development of direct methods or other structure-solving techniques.

She remained in essence a crystal physicist, and apart from W.H. Bragg, the most important influence on her scientific outlook was probably Michael Faraday. Working in Faraday’s room at the Royal Institution, she read his notebooks and absorbed his approach to experimentation. She often reminded me that Faraday had discovered all the important laws governing electromagnetic phenomena accessible with the apparatus available to him without recourse to anything other than simple arithmetic. She was herself a great experimentalist, and in her later years became less and less attracted to complicated mathematical formulations of problems which she felt could be tackled directly from first principles; ‘One of us’, she wrote at the end of a paper in 1959 ‘would like here to acknowledge personal indebtedness to the late Sir William Bragg for a training which emphasized that a simple approach to a difficult problem is not necessarily an inaccurate one’.

[Of course on the matter of the power of arithmetic, mentioned above, versus complicated mathematical formalisms in crystallography here I would beg to differ with her to emphasize in my view the power of direct methods and maximum likelihood in phasing and refinement with modern computers and software. She might of course have steered me into a discussion on brute force computing, such as the power of Monte Carlo ray tracing in X-ray optics design, and the understanding of their aberrations. Thus, of course, elegance of the mathematics is not always a guarantee of utility, I would agree].

Thirdly, in summing up, Judith Milledge wrote:

‘Those accustomed to equate religious convictions with unworldliness often had a rude awakening when dealing with Kathleen, who could be a very tough negotiator, and
had always done her homework on the committee papers. ‘It’s lucky one of us is an idealist’ she would remark, while coping expertly with the practical side of some rarefied gathering, because she had an unshakeable conviction that the right course of action in any circumstances was by definition also the most practical one. She also had a great sense of humour and a most perceptive appreciation of the best things in life. She concluded her Inaugural Lecture at University College by explaining that crystallographers were, like Walter de la Mare’s Wizards ‘a flock of crazy prophets who by staring at a crystal can fill it with more wonders than are herrings in the sea’. She did her share.’

In closing this part 1 of my article I wish to conclude with my own tribute to Kathleen Lonsdale and make one final quotation that I found in her book ‘Is peace possible?’ (9). On p. 13 she is describing the hopes of the time after the Second World War, namely for a ‘peace settlement that would end all war. It might take time... Meanwhile my work was fun. I often ran the last few yards to the laboratory. Later on I took my mathematical calculations with me to the nursing-homes where my babies were born; it was exciting to find out new facts’.

I ride my bicycle to the Lab, rather than running, but I also have the joy of being able to be enthusiastically leaping to my computer to undertake my crystallographic calculations that I can now do even on my laptop computer, whether at home or at the Lab. I feel the same as Kathleen Lonsdale about finding out new facts from the power of crystallography as an analytical tool, which appeals to the chemist and molecular biologist in me, as well as the grace and beauty of the foundations of crystallography, and diffraction physics, as a subject discipline, which appeal to the physicist in me.

I feel certain that Kathleen Lonsdale would have greatly appreciated a laptop computer. She would also have appreciated the wonderful capabilities of the current state-of-the-art and evolution of the electron microscope, neutron beams and synchrotron X-radiation as well as the prospects offered by X-ray lasers! Let us now move to part 2 of this article, SR in crystallography.

4. SR in crystallography

This Lonsdale Lecture 2011 describes the evolution and impact of SR X-ray beams in crystallography. A simple list of critical, advantageous, properties of SR X-rays I would give as:

- small focal spots,
- collimated X-ray beams onto the crystal
- tuneable.

And for special applications:

- white beam for time-resolved fast (Laue) data measurements
- defined time structure, e.g. picosecond bunches, for sub-nsec time-resolved studies
- plane polarized.

Clearly a very promising list of X-ray beam properties for a myriad of applications in crystallography!

Synergies in methods developments and applications with neutron crystallography will also be described.
4.1. First experiments and UK planning for SR protein crystallography; a personal perspective

My first experiment with such X-rays was in 1976 at the Daresbury Laboratory, on the Synchrotron Radiation Facility (SRF) on the NINA high energy physics synchrotron run by the UK’s Science Research Council (SRC). The SRF had been set up under the leadership of Professor Ian Munro of Manchester University. My local scientific contact, employed by the SRC, was Dr Joan Bordas. He made early pioneering developments on NINA (e.g. see ref. (16)). Joan is now Director of the Spanish SRS ‘ALBA’, which has been constructed under his leadership in Barcelona.

I had first learnt of synchrotron X-rays in 1975 via a copy of a letter given to me by Prof. Dorothy Hodgkin: Dorothy was Nobel Laureate in Chemistry (awarded 1967). This letter she had received was from Professor Ron Mason to Professor Sam Edwards, Chairman of the SRC (17). Prof. Mason was visiting the Stanford Synchrotron Radiation Laboratory (SSRL) and where he had himself learnt of the first experiments with synchrotron X-rays in protein crystallography led by Prof. Keith Hodgson of Stanford University’s Chemistry Department. This letter was accompanied with a preprint of an article finally published in PNAS in 1976 (18).

The text of this letter is reproduced below with permission of Prof. Mason. NB: SLAC is the Stanford Linear Accelerator Centre.

From Ron Mason, Visiting Professor of Chemistry, College of Chemistry, the University of California, Berkeley, California 94720
July 2 1975
To Professor Sir Samuel Edwards, F.R.S,
Chairman, Science Research Council,
State House, High Holborn,
London WC1, England

Dear Sam:
It is obvious that I cannot keep away from S.R.C matters! But I do have an interesting tale to tell as a result of spending a few hours on Sunday at SLAC and particularly at the synchrotron facility.

There is no need to emphasize the work that is going on in the general area of photoemission from metals, semiconductors and so on. Lots of valence band and core levels are being studied and there is also some nice work on reflection from metals using radiation energies down to 5 eV. Just coming on line is an instrument for measuring the angular dependence of photo-emission, something all of us interested in the field regard as very important indeed. There is also some X-ray absorption edge work going on, looking at transition metal complexes and metalloproteins but I was not impressed.

The main point I want to make, however, is this: you will remember that in our discussions of the S.R.F there was less than an enthusiastic response from crystallographers and I, quite frankly, played down their views for they are not known in general as a forward looking collection of people. Be that as it may, we heard particularly that it had no future in protein crystallography – that radiation damage effects would be impossible and that what was wanted was higher flux conventional fine focus X-ray tubes. It was not clear at the time how this view had been put together but I can now tell you it is nonsense! There has been three months work at SLAC on the proteins, rubredoxin and azurin. With a neat monochromator arrangement – after primary beam splitting, the beam hits a glass plate at grazing incidence (the plate is oriented by stepping motors) and then monochromatized by a single crystal of silicon or quartz. Complete data to 2.5 Å for a single zone is taking 2 hours; complete three-dimensional data are needing 60 hours of conventional precession photography; rubredoxin was still going strongly after 200 hours of exposure to different wavelengths and some very nice results on anomalous dispersion have been obtained. Azurin is going well after 150 hours
exposure – typically an hour’s setting photograph in the laboratory showed nothing, 2 minutes Polaroid photography using synchrotron radiation was enough to show the crystal orientation.

This is all, of course, based on a parasitic 20 mA beam; we should do much better. I think we should plan now and not accept the poor advice we received last Autumn. David Phillips, Uli Arndt and others can see this letter if you felt it appropriate as, of course, should Alick Ashmore (Director of Daresbury Laboratory) and Joan Paton. I am getting some working drawings of the monochromator and the crystallographers can get more details from Dr. Keith Hodgson.

I hope all goes well.

Yours,  
Ron  
Ronald Mason  
Visiting Professor of Chemistry

Dorothy asked me my opinion. I reported to Dorothy that what was described sounded like the sort of direction we need to go in and that I would look into it in detail. It really buoyed me up to be able to talk to Dorothy Hodgkin herself like that! I was a DPhil student under the supervision of Dr Margaret Adams, a member of the Laboratory of Molecular Biophysics and Chemistry Tutor of Somerville College, and we were located in the Department of Psychology, Oxford University in offices proximal to Dorothy’s, as well to as Guy and Eleanor Dodson, as well as John and Sue Cutfield. I was a very lucky DPhil student being in such an environment! I found reference 1 of Phillips et al. (1976) (19): namely the article Rosenbaum, Holmes and Witz 1971 Nature on ‘Use of SR in biological diffraction’ (nearly entirely on muscle fibre samples but with a mention of protein crystals as a possible sample in a summary table) (19). I reported to Dorothy that I found this a most promising development as, in my view, it got round major limitations in laboratory methods in X-ray protein crystallography of the time. It was suggested that I meet with Professor David Phillips, who was the Head of the Laboratory of Molecular Biophysics, based in the Zoology Department of Oxford University. He had interviewed me in the spring of 1974 for a DPhil place in his Laboratory, which was the overall organizational grouping for protein crystallography in Oxford. I had requested to be supervised by Dr Adams on her particular project (X-ray crystallography studies concerning the structure of the enzyme 6-phosphogluconate dehydrogenase (6-PGDH)), which was nicely at the beginning of the crystallographic stage of the project, I felt. Prof. Phillips, in response to my request to visit the SSRL to learn more, after my meeting with Dorothy, suggested instead that I submit a proposal to do the experiment I had in my mind to the SRC NINA SR Laboratory at Daresbury Laboratory. He asked me if Warrington was a problem, compared with Stanford. I said ‘No, Warrington would be fine, I know they have a good rugby league team’, he laughed. The experiment I wished to undertake was to optimize the anomalous scattering at the Pt LIII absorption edge via maximizing the $f''$ value for the 6-PGDH’s $K_2Pt(CN)_4$ heavy atom derivative, which I had found in my first year’s DPhil research. I undertook a 24-h beamtime run at NINA with Dr Joan Bordas in April 1976 shortly before NINA closed. I described this experiment in my DPhil thesis. It was not successful in terms of results but it was important to me for learning about the beamline equipment that I would need to carry the experiment further. This did become possible when I took up an appointment in February 1979 at Keele University 50% jointly with Daresbury Laboratory to develop my ideas (20). This led to the first SRS instruments for
protein crystallography, serving users as well as developing new methods, namely SRS 7.2, 9.6 and 9.5. I became full-time at Daresbury at the cessation of my appointment in 1983. The user support component grew to be too much and I decided to join York University on a Joint Appointment in late 1985. This continued (including a move to Manchester University in January 1989) until mid-1993, when I became increasingly pre-occupied helping to develop ESRF’s macromolecular crystallography plans through the mid 1980s and 1990s.

In 2011 I got further historical insight into the UK position regarding SR protein crystallography when I came across the following document:

‘The Scientific Case for Research with Synchrotron Radiation’ SRC Daresbury Lab DL/SRF/R3 (1975) (21). Within this was the following text:

‘Professor Phillips’ Molecular Enzymology Group at Oxford is also very interested in the possibility of using synchrotron radiation to study transient structural changes in crystalline enzymes. The availability of more intense X-ray beams will also make it possible to extend present day crystallographic structure determinations to molecules with much larger unit cells and to ones which can only be obtained as very small crystals – provided that means can be found to reduce radiation damage. Present studies indicate grounds for cautious optimism in this respect. It seems likely that when the feasibility of carrying out diffraction experiments within very much reduced periods of time become more generally recognised, there will be no shortage of applications in other fields. For reasons which are discussed elsewhere in this report most X-ray diffraction work on biological material is done, and will continue to be done, using wavelengths in the wavelength 1.5 Å region. Thus a synchrotron or storage ring designed to give an output in the wavelength 1.5 Å region would be a very suitable source. Wavelengths longer than this could be used only with a substantial loss of intensity in most specimens. Shorter wavelengths are unlikely to be required’. Obviously my ideas in ref. (20) were partly already covered by David Phillips’s input in 1975: I say ‘partly’ because wavelengths shorter and longer than 1.5 Å it seemed to me were already very clearly going to be important for optimizing anomalous scattering applications in protein crystallography. Also short wavelengths would allow improvements in diffraction data accuracy and longer wavelengths would increase the sample scattering efficiency such as for small crystals.

4.2. The Daresbury SRS and the start of the so-called second generation SR sources

The SRS at Daresbury was the world’s first dedicated SR X-ray source. The details of its genesis were before I became involved in the organizational politics of any such matters. I learnt at second hand that Dr Ian Munro of Manchester University had instigated the NINA SRF Facility and its success meant that the SRS proposal was well received and approved for funding. There is a document of plans for the SRS from ‘The Crystal Optics Panel’ (22). Listed in that Panel, as well as David Phillips himself, is Dr Michael Hart, a key pioneer of SR in crystallography, notably for example for his developments of perfect crystal optics and instrumentation development such as small-angle X-ray scattering and interferometry (see e.g. (23–25)). Professor Hart later became Director of the USA Brookhaven National Laboratory’s National Synchrotron Light Source (NSLS). Professor Munro became SRS Director, and was the person to turn off the SRS for the
last time at a ceremony held at Daresbury in August 2008: Ian’s review of the SRS up to the late 1990s is in ref. (26). I was Director of the SRS in 2002, until I returned to Manchester University in January 2003 to focus more on research than SR source administration.

In ref. (22) the case of ‘Lattice structures’ does feature. Thus for instrumentation the report states:

‘3.5 Lattice Structures and Interferometry

Conventional X-ray sources are adequate for all but the most demanding lattice structure problems. It follows, therefore, that the SRS facility will be used by only those crystallographers who have problems where particular advantage can be gained from a free choice of wavelength with high intensity, low angular divergence, or high degree of polarisation of the primary beam. The monochromated beam will also reduce specimen damage. Apart from a few interested protein crystallographers, potential users are hard to identify. We can assume, however, that future application will include work with small or unstable crystals, and with specimens from which either accurate lattice parameter or structure amplitude measurements are required. Part of the programme will be concerned with the interferometric measurement of X-ray optical constants which are required for structure analysis.

Users of the SRS facility are likely to fall into one of two main categories:

(a) those who require rapid collection of vast amounts of structure amplitude data;
(b) those who make relatively few measurements but require precise control of the experimental conditions.

The experimental needs of the first group are relatively straightforward and typically satisfy the requirements of the protein crystallographer. Experiments performed by the second group are likely to be less routine in nature, and instrumentation specified for these users must be sufficiently flexible to accommodate unidentified demands. Taking into consideration these requirements and the expected use of the SRS facility, it is anticipated that the needs of lattice structure users will be satisfied by two beam line locations and the following equipment:

(i) A low-resolution scanning monochromator covering the range 0.5 to 4 Å and producing a uniform beam of diameter 0.05 to 0.20 mm. The sample should be mounted on a crystal oscillation system similar in concept to that marketed by Enraf-Nonius, but with a large area detector and associated computer readout.
(ii) A high-resolution scanning monochromator covering the widest possible wavelength range, and producing a uniform beam of approximately 1 mm in diameter. The crystal sample should be mounted on a computer-controlled orienting system equipped with beam shaping facilities, a “small” area detector device and associated computer readout.

The Panel recommends that two instruments be provided for work on lattice structures at the SRS, one of each type discussed above’.

For crystallographic computing the report states:

‘Users will also want to analyse their spectra online wherever possible but in some instances e.g. crystallographic work, the large-scale computing facilities that are required would probably have to be provided off-line’.
The other research and technique areas covered by the report were: EXAFS (Extended X-ray Absorption Edge Fine Structure); XPS (X-ray Photoelectron Spectroscopy); X-ray Topography; SAS (Small Angle Scattering); X-ray Absorption Microscopy and Lithography; finally a development programme including radiometry was also identified.

Clearly this was a far-seeing report for the SRS planning, in which one can pick some holes today but these crystal ball gazing exercises are not easy, as I was to wrestle with myself with the European Macromolecular Crystallography Planning Group.

Where did SRS sit in the evolution of SR X-ray sources? Professor Michael Hart drew my attention to Figure 5 (prepared by Dr Gwyn Williams of Jefferson Lab, USA and who kindly has let me use this here). As Michael would describe this, what better way than to show the profound change in X-ray source capability by comparing the SR source X-ray brightness along with computer cpu power, versus calendar year. The SRS emittance placed it in the ‘second Generation’ part of the graph; impressively more than previously but with considerable further optimizations yet to come with the third Generation, such as the ESRF and the fourth Generation, the X-ray laser. A useful summary of the evolution of sources, and particularly projections in the early 2000s decade, is given in ref. (27).

Figure 5. The evolution of SR source brightness vs. calendar year. Figure courtesy of Dr. Gwyn Williams, Deputy Associate Director, FEL/Light Sources, Jefferson La., Newport News, VA 23606 with permission of the author.
4.3. The SR research community gets SR News and then its own Journal of Synchrotron Radiation, the latter published by IUCr

Around the early 1980s I recall a visit by a commercial publisher representative canvassing opinion about launching a community newsletter, SR News. I recall supporting this enthusiastically. It has been published for many years and is very professionally produced and with full representation of the SR facilities and with senior SR scientists as Editors. As well as meeting reports, they carry excellent articles. I have submitted quite a few meeting reports, including two summarizing SR presentations at IUCr Congresses. As Chair of the IUCr Commission on SR, I gathered together performance data for the available SR protein crystallography instruments of the time and SR News accepted it for publication (28). I also, most recently, had my report of the 2009 BAAS Meeting published in SR News in 2010, which has been well received, with a full lifetime look back of the SRS and its science programme as it evolved over the years, as well as a look forward (29).

In the early 1990s, Samar Hasnain put forward the idea to the IUCr to launch a new Journal of Synchrotron Radiation. I was at that time the inaugural Chair of the IUCr’s Commission on SR and was glad to support the idea. I vividly remember what seemed to me a pivotal meeting held at IUCr Chester in March 1992 with the IUCr Treasurer, Prof. Asbjørn Hordvik from Tromsø University, Jim King (IUCr Executive Secretary), Mike Dacombe (IUCr Technical Editor), Samar and myself. I tabled about five of my own SR instrumentation papers, which were in a variety of non-IUCr journals, including Nuclear Instruments and Methods, Journal of Physics E: Scientific Instruments, Review of Scientific Instruments, etc. I was asked by Asbjørn, ‘Why did I not submit such papers to the Journal of Applied Crystallography?’ to which I replied (i) I was constrained by where the SRI Conferences chose to publish their conference proceedings and (ii) I needed to reach a wide instrumentation audience. Some authors still prefer J Appl Cryst over JSR for their SR instrumentation and methods papers. Nevertheless, considering the wide spectrum of SR activity, it was soon recognized widely in the IUCr community that J Appl Cryst was not the best journal for publications in fields only loosely connected with crystallography, such as those arising from the vacuum ultra-violet (VUV) community. Indeed the scope of JSR was set to include such techniques as well as of spectroscopy and microscopy; and in 1993 we gave a report on our business plan at the IUCr Congress in Beijing (30).

The business plan was discussed at a formal meeting of the IUCr Finance Committee on 21–22 March 1992 in Chester, UK with the full attendance being R. Diamond (Convener), A. Authier (President), A.I. Hordvik (General Secretary and Treasurer), C.E. Bugg (Editor-in-Chief), S.G. Fleet (Investment Adviser), A. M. Glazer (for the discussion of JSR), M.H. Dacombe (IUCr Journals Technical Editor), J.N. King (IUCr Executive Secretary) and A. Cawley (Secretary) plus Samar and myself for the item on the discussion of JSR. The business plan was approved by the IUCr Executive Committee under the Presidency of Prof. André Authier in 1993, obviously following support from the IUCr Finance Committee. The Journal was to have three Main Editors: Samar, myself and Prof. Hiromichi Kamitsubo, then Director of Super Photon Ring 8 GeV (SPRing-8) Japan.

The Journal was launched with its first issue in October 1994. Our Editorial (31) stated that:

The IUCr has taken this initiative because the diffraction community has a strong vested interest in synchrotron radiation, and therefore in harnessing the best features of synchrotron radiation instrumentation and methods. We, and the IUCr, believe that the full benefit of this
initiative can only be felt if the *Journal of Synchrotron Radiation* serves the whole of the synchrotron radiation community, across its full spectrum, rather than covering the hard X-ray region alone. This diversity is reflected in the format and scope of the journal and was ensured by conducting the widest possible consultations. Thus, we have approached synchrotron radiation representative organizations and directors of synchrotron radiation facilities, and have made presentations and solicited comments at a wide variety of synchrotron radiation conferences. The Editorial Board reflects this breadth of representation and provides wide-ranging coverage of the interests of the synchrotron radiation community.

The inaugural front cover shows the proliferation of SR sources and thereby the major expansion of this research tool that had already taken place (Figure 6). Estimates of the crystallography usage of the SR X-ray sources we made to be around 50%. The viewpoint of the IUCr Executive Committee with respect to this initiative, and the detailed timeline of events leading to approval for launch, including the balancing of the significant risks and opportunities, as well as some opposition to the new journal, is described in the article by André Authier (32). In my Triennial (1990–1993) Report to the IUCr Executive Committee as Chairman of the Commission on Synchrotron Radiation (33), I reported on this Journal initiative as follows: ‘A proposal for a *Journal of Synchrotron Radiation* has been made to the IUCr. The Commission has had a major input to the deliberations on this. Open discussions were held at a variety of conferences, both national and international, in Europe, the USA and Japan. Representative organizations and the Directors of Synchrotron Radiation Laboratories have also been contacted’. It was indeed a great deal of hard work getting *JSR* approved and launched, as well as the first 5 years of operation when I was one of the Main Editors. In these early years there were regular headaches about thin issues of the Journal (34) and regularly firm questioning by the IUCr Finance Committee, rightly so, which I had to field as IUCr Journals Editor-in-Chief 1996 to 2005.

The evolution of the Journal, and the firm financial commitment of the IUCr, can be judged from our Editorials between 1994 and 2000 (31, 34–36). As we wrote in our Editorial in 1996 (34):

As we enter our third year and write this editorial, we have received the first major review of the *Journal of Synchrotron Radiation* (*JSR*) (37). It is worth repeating some of the points made in this independent review. It says that ‘developments in the application of synchrotron radiation research have benefited enormously from fertilization between otherwise distinct research areas, and there is no doubt that this new journal will play an important part in furthering such interdisciplinary interactions’. The review goes on to say that the ‘speed, together with the quality of the contributions so far and the high standard of production, makes the journal attractive to authors and required reading for workers in what worldwide is still a rapidly expanding field’. We note that the reviewer points out that even though the quality of articles in *JSR* has been high, the issues have remained fairly slim . . . . Our main focus now is to increase the size of the issues without compromising the quality of the papers.

IUCr had given firm financial commitments as we wrote in 1995 (35):

As we enter into our third volume we feel confident that *JSR* is here to stay, as it is essential for the continued growth and stimulus of synchrotron radiation facilities, techniques and applications. But we approach a crucial period. This is the last complimentary issue of *JSR*. Thus, it is essential that we call upon you to ask your libraries and institutions to place subscriptions immediately.

In 1999 we were able to write (36):

With this issue, we celebrate the fifth anniversary of the journal. Since the launch, approximately 850 papers and 3800 pages have appeared. The journal has published the
proceedings of two main synchrotron radiation conferences, SRI’97 (May 1998 issue) and XAFS X (May 1999 issue), where new standards for these proceedings have been set. The journal now features in the top 17% of the Science Citation Index (4800 journals). Its impact factor is greater than that of *Rev. Sci. Instrum.*, *Nucl. Instrum. Methods, J. Phys. A* and *J. Phys. C*, and is approaching that of *Phys. Rev. C* and *Phys. Rev. E*. Thus, the *Journal of Synchrotron Radiation (JSR)* has become clearly established and this it owes to the confidence the community has placed in it from its launch.

In 2011 one can observe, and congratulate the current Main Editors, Gene Ice, Åke Kvick and Toshiaki Ohta, that *JSR* is enjoying regular thick issues and also a pleasing buoyancy of participation of quite a few of the SR facilities with sponsored ‘Facility

Figure 6. The first front cover of the Journal of Synchrotron Radiation. Published by IUCr, with the permission of the IUCr.
The latest obvious major step in the JSR’s evolution has been the addition of the logo on the Journal front covers of ‘including free electron lasers’, recognized by the JSR Editorial in 2001 (38).

5. SR theory and actual magnet sources

The details of the theoretical physics of this phenomenon were originally derived by Prof. Julian Schwinger (39), and a history of the first demonstrations of SR is described in ref. (40). For the purposes of illustration of such matters, I offer the following examples.

The SRS bending magnet shown in Figure 7 is a 1.2 T magnet, which for the SRS, a 2 GeV machine, has an SR universal spectral emission critical wavelength of 4 Å. Thus SRS Station 7.2, fed by SR from such a magnet source provided useful flux for experiments and data collection in protein crystallography from a minimum of ~1.2 Å. The maximum useful wavelength on SRS 7.2 was approximately 2.6 Å. The longer wavelength limit was set by beryllium windows in the beamline, which caused X-ray absorption and a steady reduction of X-ray intensity from ~2.0 Å onwards up to a limit of 3 Å. SRS 7.2’s usual range of wavelengths for data collection spanned monochromatic values between 1.38 Å up to 1.86 Å, and most typically of 1.488 Å for users.

SRS had straight sections which could accommodate insertion device magnets of various types. The ESRF was designed to be mainly an SR source harnessing insertion devices as light sources, rather than the bending magnets. The angular emissions for a single bump wiggler magnet, a multipole wiggler (MPW) and an undulator are shown in Figure 8 along with magnets for each type, as illustrated from SRS and ESRF. The SRS
superconducting wiggler (SCW) type of magnet in Figure 8, of which two were installed in the SRS (in Sections 9 and 16), allowed a much higher magnetic field than the 1.2 T bending magnets. Thus line 9 at 5 T had a critical wavelength of its emission of 0.9 Å. The SCW 16 with 6 T had an emission critical wavelength of 0.75 Å. The electron beam path through an SCW is shown in the schematic top diagram. The natural emission cones of light have opening angles much smaller than the angular deflection through the straight section of the SCW magnet’s field.

The middle diagram and middle photo below it are for a MPW. These magnets have a value of around 2.5 T, with a critical wavelength of emission for the SRS 2 GeV of ~2 Å. The electron beam excursion through this straight section’s magnetic field is not as marked as through the SCW, but the SR cone angle at each peak and trough of the electron beam’s travel do not overlap. The X-ray emission is a simple multiple of the number of poles of a bending magnet of equivalent field: typically 10–20 times increase of emitted X-ray flux is achieved over a 2.5 T (hypothetical) bending magnet. The bottom diagram of Figure 8 shows the undulator case. The weaker magnetic field is chosen so that the emission of the electrons, as they pass through the magnet are deliberately allowed to overlap. Thus there is a constructive interference condition and the polychromatic emission spectrum collapses into a few spectral lines but of duly increased brightness. The brightness increases observed are up to \( N^2 \), where \( N \) is the number of poles in the magnet; so that with \( N \) typically up to 100, gain factors of X-ray brightness are \( 10^4 \), i.e. colossal. The ESRF undulator type is shown: the ESRF at 6 GeV has a high enough machine energy to have undulator emission into the X-ray region. Indeed the ESRF was initially conceived as a 5 GeV machine, which with a 20 mm magnet gap would have an undulator fundamental emission of 1 Å wavelength. In order to provide a fundamental at 0.8 Å for nuclear resonance experiments that began to be proposed, the ESRF machine energy was increased to 6 GeV. An additional requirement for the ESRF undulator interference condition is to have a small electron beam size. Thus, with the high machine energy of 6 GeV, which reduces the SR natural opening angle, the machine emittance is very small (i.e. yielding a high machine brightness).

The ESRF then was conceived with a much improved emittance i.e. smaller than the SRS, as well as a much larger circumference to allow many and long straight sections. Figure 9(a) shows the SR universal curves for the ESRF for each magnet type. (It has two bending magnet types with the magnet fields shown.) The curves for the undulators in Figure 9(a) are the tuning ranges possible by altering the magnet pole pieces gap (20 mm to larger). Figure 9(b) shows an undulator emission for a given ESRF magnet pole-piece gap. This is the ESRF 6 GeV case for an undulator’s X-ray emission for the details given in the inset, i.e. two different cases (at the time of the Foundation Phase Report in 1987 \( (41) \); these have improved considerably since then, notably in terms of spectral brightness). Narrower magnet gaps are possible today (a pioneering example was at the NSLS, see ref. \( (42) \), which reached 3.8 mm gap with 3 mm gap indicated as possible). This is important as it explains why the lower machine energies of Diamond Light Source (DLS), Soleil etc. (3 GeV) still yield useful X-ray emission from a harmonic at 0.98 Å wavelength, the selenium K edge, a popular wavelength amongst macromolecular crystallography (MX) users today.

My earliest experience of the undulator magnet concept in practice was from the visit of a Soviet science delegation to Daresbury in approximately 1984. Not long after this visit an undulator was installed on SRS machine lattice straight section 5. I submitted the colour picture of its visible light emission for the front cover of a special issue of
This emission, being in the visible region of the electromagnetic spectrum, showed nicely the SR emission interference condition, being both wavelength and angular position dependent; thus, the use of a pinhole suitably placed can be a simple means of selecting appropriate portions of the emitted fundamental and harmonic interference peak wavelengths.

6. The importance of the second and third generation SR sources in bringing about a revolution in crystallography

6.1. SRS Station 7.2; the first protein crystallography instrument on a dedicated SR X-ray source

The SRS was a dedicated X-ray storage ring and, unlike the NINA synchrotron, allowed for dedicated control for SR users from the SRS Machine Control Room of the injection
and beam position and stability, albeit not with source position feedback control immediately. The first station/instrument for protein crystallography at the SRS was on bending magnet 7, ‘SRS 7.2’. This beamline, Number 7, was the first X-ray beamline for SRS and was developed in parallel with beamline 6 for VUV research. X-ray beamlines were separated from the main machine vacuum vessel by a beryllium window, whereas the VUV beamline design had a progressive change in quality of the vacuum, with the machine
Figure 9. (a) The SR spectral curves for the ESRF (at the time of the Foundation Phase Report in 1987; these have improved considerably since then notably in terms of spectral brightness). Reproduced with the permission of ESRF. (b) The ESRF undulator emission for the two conditions shown in the inset (at the time of the Foundation Phase Report in 1987; these have improved considerably since then, notably in terms of spectral brightness). Full line: Gap = 20 mm, Field = 0.5T, K = 2.3. Dotted line: Gap = 32 mm, Field = 0.2T, K = 0.9. With the permission of ESRF.
being held at the best vacuum. A sequence of fast valves was in place on the VUV beamline in the case of a sudden breach of gas into the beamline and thereby the machine. The competition between research communities to secure a place on these first beamlines was significant and so an essential first step I took was to get the backing of the UK protein crystallography (‘PX’) community behind a beamline bid. Thus I called a meeting held at Daresbury of the UK PX research group leaders. Support for the concept of SRS PX 7.2 was secured and I presented the X-ray optical design at the SRS User Meeting of September 1979. I was helped significantly here by the experience of Mr Jeff Worgan of Daresbury Laboratory and indeed we prepared a Technical Memorandum on the monochromator design (44). Initially the idea was to have a point focussed beam from a doubly curved monochromator, but we concluded that the design (45) at Laboratoire pour l’utilization du rayonnement électromagnétique (LURE), Paris and Deutsches Elektronen-Synchrotron (DESY) Hamburg of a triangular shaped, Fankuchen cut perfect Ge (111) monochromator would produce a 10:1 demagnified horizontal source, which was 14 mm for SRS, down to 1.4 mm and thus approaching the expected typical protein crystal sample size of 0.3 mm. A further challenge, besides the very large horizontal source size, in the design for SRS 7.2 was to secure a focussed vertical beam and which could take advantage of a rather nice small SRS vertical source size of 0.3 mm. Dr Richard Tregear, a fibre diffractionist, offered to help by asking Prof. Ken Holmes, ex-Director of the European Molecular Biology Laboratory (EMBL) Outstation Hamburg, for assistance. Prof. Holmes responded with actually letting us have one of his original double 20 cm reflecting quartz mirrors and bender! On detailed consideration however I decided I liked the competing approach pioneered at SSRL of a single-segment platinum-coated fused silica mirror of 60 cm, which is easier for the mirror bender and alignment. This would accept the full vertical divergence of the SRS 7.2, as well as the 4 milliradians (mrad) of horizontal divergence beam allocated to us. China Lake, in the USA supplied the platinum coated mirror. The perfect germanium crystals for the monochromator came from a company in Grenoble at the French Atomic Energy Authority ‘CEA’ called ‘Cristol Tec’ run by Monsieur Guinet, whom Jeff Worgan knew. I ordered these monochromator crystals with a 10° Fankuchen cut and not long afterwards I also ordered the Si (111) Fankuchen cut crystals, but this time with several cut angles to allow for several X-ray wavelength ranges to be harnessed. As part of the acceptance tests for their quality, I took them all to Durham University to work with Prof. Brian Tanner’s research group (including Dr Graham Clark, who later joined the SRS, and Ms Siti Gani, a PhD research student there) to undertake double-crystal diffractometer rocking curve scans, which took a week, and which were fine.

The whole SRS 7.2 mechanical arrangement for the instrument was a big design and build effort that was led by Mr Phil Moore, the mechanical engineer assigned to work with me by the Daresbury Laboratory. There were the various mechanical assemblies and motors controlling all alignment of apparatus, of the mirror bender, of the monochromator rotation stage and the concomitant experimental arm of the instrument, which carried the protein crystallography apparatus (initially an Arndt Wonacott rotation film camera). The mirror bender and the camera alignment table were built to Phil’s design in the Keele University Physics Department Mechanical Workshop. Between 1979 and 1983 I was a Joint Appointee between Keele University Physics and the Science and Engineering Research Council (SERC) Daresbury Laboratory (50%/50%). I also obtained a research grant from SERC to work on the Bacillus Stearothermophilus 6-phosphoglucuronate dehydrogenase, whose crystals were a gift from my DPhil supervisor.
Dr Margaret Adams. This grant included the development of the SRS 7.2 station and funded a post-doc; and thereby I was joined by Dr Trevor Greenhough, a very experienced crystallographer. My first two PhD research students, Mr Paul Carr and Mr Stephen Rule took courses which I gave in the Physics Department. Trevor and I were very interested in the data processing of the oscillation camera films we would measure at SRS 7.2. Trevor, with Paul Carr and help from Daresbury, wrote the software for the SRS 7.2 motors’ control via a controller box designed and built by Daresbury. Trevor also started deriving new formulae for the prediction of the protein crystal reflecting range and partialities important for high quality data estimations and, in the case of virus crystallography, essential as only one diffraction film could be measured per crystal; thus there were many partially recorded reflection intensities which had to be suitably scaled. As I was commissioning the SRS 7.2 instrument, and thereby understanding the basic properties of the SR X-ray beam spectral spread and convergence angles from the X-ray optics scheme I had adopted, it became clear to Trevor and me that a new formalism of the oscillation film camera data processing software for partiality correction was needed. What’s more, these details had not appeared in the literature before. Thus we obtained our first and indeed well-cited articles in *J. Appl. Cryst.* on this topic (46, 47). The SRS 7.2 instrument paper was submitted to a scientific instruments journal and at that time the UK Institute of Physics Journal *J. Phys. E: Sci. Instrum.* was suitable. This paper could also be cited by users of the instrument, since I did not feel that my (automatic) co-authorship of articles published by users was appropriate. This paper (48) also explored and calculated the focus at the crystal or at the detector options; and for these various reasons became very well cited. We also had a paper accepted in *Nature* (49) in a collaboration with Dr Uli Arndt from the MRC Laboratory of Molecular Biology, Cambridge, which involved the overbent setting of the SRS 7.2 monochromator to create a polychromatic profile in each and every diffraction spot. This was demonstrated using a test crystal of a rhenium compound provided by Prof. Judith Howard; this technique later became known as diffraction anomalous fine structure (DAFS).

The properties of the single-bounce monochromator as an X-ray optic fascinated me. So I set about making practical tests of the monochromator in different states of curvature and also examining the spectral behaviour of the horizontal focus. I had pressed Phil Moore to give me a wide rotation range not only for the monochromator but also for the beryllium window in the monochromator vacuum vessel, even allowing me to examine the reflected X-ray beam from the monochromator at \(2\theta = 90\) degrees. The instrument \(2\theta\) arm went up to approximately 60°.

Figure 10 shows a schematic diagram of the range of incident angles across the monochromator crystal surface (from ref. (50)) and which thereby reflected particular wavelengths in the directions shown. The required setting for usual data collection is as shown in Figure 10(c) which minimized the spectral spread of the X-ray beam incident onto the crystal sample. For different wavelengths the focussing distance for this minimum spectral spread setting had to be varied because of the Fankuchen cut angle and so the oscillation camera and its alignment table had to slide along the length of the \(2\theta\) arm. In Figure 10(b) is shown the overbent monochromator condition and where a simple correlation of incident angle with wavelength could be set up onto the crystal and so create the polychromatic profiles mentioned above (49). In Figure 10(d) is shown the curvature condition Figure 10(c), but now illustrating the wavelength correlation across the focal width; thus by placing a narrow slit in the focus and simply translating it across the focal...
full width one could select specific wavelengths and thereby make an edge scan such as from a nickel foil.

For the monochromator $2\theta$ scan through $90^\circ$, mentioned above, I had to set up a simple table to hold an X-ray film cassette and so produced a trace of the monochromator reflected X-ray intensity; at $90^\circ$ of course the trace showed a minimum intensity due to the nearly perfect linear polarization of the synchrotron X-ray beam. The minimum intensity was not zero as there was a residual, small, intensity from the vertical component of the beam polarization. All these details formed part of the Helliwell et al. J. Phys. E paper (48) documenting that the instrument’s X-ray optical properties were well understood.

These details fuelled the various ideas that Trevor and I had about their impact on the oscillation camera data processing, with Trevor undertaking many formulae derivations that feature in our article (47), following on from the preceding article that we published for conventional X-ray sources (46). We also published a more detailed technical paper (51) to accompany the Nature article (49). With our aims being mainly at that time protein crystallography, our efforts to convert the development of ref. (49) into protein structure applications proved too difficult due to the limited detector quantum efficiency (DQE) of film to convert a spot intensity into a measured spectrum with weak intensity variations that would accrue from a dilute metal atom in a protein. This was a pity because to move from a single-wavelength diffraction data set, albeit with the marvellous property of being fully tuneable, to a full spectrum in each and every diffraction spot width, was of course in principle very attractive. Much later, other groups independently rediscovered the approach and named it DAFS and diffraction anomalous near edge structure (DANES) and applied it in inorganic chemistry and materials science crystallography (see e.g. (52, 53)).

The first users of SRS 7.2 of course included all the UK research laboratories undertaking protein crystallography at the time. Prominent in my memory were: Oxford Molecular Biophysics (David Phillips, Louise Johnson, Janos Hajdu); my DPhil supervisor Margaret Adams who provided 6-phosphogluconate dehydrogenase crystals from which to collect data; Birkbeck College (Tom Blundell, Peter Lindley); the York Structural Biology Laboratory (Guy Dodson, Zygmunt Derewenda, Bob Liddington); the
Sheffield Laboratory (Pauline Harrison, David Rice, John Smith); the Imperial College Blackett Laboratory (David Blow, Alan Wonacott); Bristol Biochemistry (Herman Watson, Hilary Muirhead); MRC Laboratory of Molecular Biology, Cambridge (Anne Bloomer, Phil Evans); as well as the nucleic acid crystallographers from Olga Kennard’s Laboratory at the Cambridge Crystallographic Data Centre. An early and prominent methods collaborator was Uli Arndt from the MRC Laboratory of Molecular Biology, Cambridge as mentioned above. We also were becoming noticed internationally: Michael Rossmann arrived promptly from Purdue University with his human rhinovirus crystals; Howard Einspahr (pea lectin) and Steve Ealick (purine nucleoside phosphorylase) from Birmingham Alabama. From Sweden came Carl Branden, Anders Liljas and Ylva Lundquist from Uppsala, and they subsequently established a formal agreement with SRS regarding beam time access that lasted for many years, including leading to SRS 9.5 (see below). Several of these users were first-time users, although others had already visited the LURE and/or EMBL Hamburg instruments for protein crystallography.

Michael Rossmann’s work at SRS 7.2, as well as his work at EMBL Hamburg, led to a protocol for virus crystal data collection which was called ‘the American Method’: ‘shoot first and ask questions later’. This R&D Michael wrote up, with his co-worker John Erickson, in J. Appl. Cryst. (54).

An early policy issue was regarding publications by our users and our expectation regarding our role in the work done, and this was a question raised by our visitors as well. I have no memory of guidance from the SERC management but I was contacted by Dr Roger Fourme from the equivalent protein crystallography facilities at the French LURE synchrotron and by Dr Hans Bartunik from the EMBL in Hamburg. I established a policy at SRS 7.2 where we would publish an instrument paper (i.e. (48)), which general users of SRS 7.2 would be requested to cite, as the place where they had collected their data. Collaborations however could naturally lead to co-publication, and that is what happened.

As well as the basic characterization of the SRS 7.2 monochromator, I also set about exploring the wavelength range capabilities of the instrument. Phil Moore, the mechanical engineer, had worked hard in providing a very versatile instrument 2θ arm, which allowed me to explore short and long wavelengths. I used metal foils and a pair of incident beam and transmitted X-ray beam ionization chambers to measure the X-ray absorption spectra and thereby to locate elemental K edges. Thus the zinc (1.28 Å), copper (1.38 Å), nickel (1.488 Å), cobalt (1.608 Å) iron (1.743 Å) and manganese (1.896 Å) K edges were explored. Diffraction data were most conveniently collected at 1.488 Å wavelength, for which the Guinier condition, monochromator minimum spectral bandpass, was easily established in the mid-range of the allowed focussing distance on the 2θ arm. Away from this wavelength it would become necessary to reduce the horizontal acceptance of the monochromator from the available 4 mrad so as to control the spectral spread values; this was done with the pre-monochromator horizontal slits, which were under motor control. I undertook collaborative experiments with Dr Howard Einspahr on the pea lectin protein at the manganese K edge (55) to locate the manganese and calcium ions in the protein dimer using the optimized Mn anomalous differences. The crystal sample was aligned very carefully so that each rotation photograph had anomalous differences left to right across each film, with a view to minimizing any impact of radiation damage or SRS incident beam decay and fluctuations on the small anomalous intensity differences expected (see Figure 1 of ref. (55)).

A quite speculative set of trials was going to much longer wavelength and I reached 2.6 Å. I think I used a vanadium foil to calibrate the wavelength to 2.269 Å and then made
a simple extra calculated $\theta$ change to set the desired 2.6 Å wavelength. This value I had decided upon because of the simple practical limitations of my various beryllium windows and the air paths I had in the oscillation camera. My first lysozyme crystal mounted in a glass capillary was immediately disappointing. As I developed the exposed X-ray film in the dark room, I realized my mistake of not allowing for the absorption of the glass walls of the capillary and so I simply cut out a piece of Mylar, placed a crystal in the centre along with the usual blob of mother liquor and rolled the Mylar into a cylinder. I inserted a short length of liquid at one end and sealed it up with melted wax. The SRS 7.2 X-ray diffraction pattern now was readily visible. I did not think to publish this at the time but instead, much later, indeed about 15 years later, I was working on a new protein with expected disulphides that would allow me to increase their $f''$ anomalous signal considerably by working at such a wavelength. This we did: (Mr Michele Cianci a research student and Dr Andrzej Olczak, an EC funded post-doc, both with me at Manchester University). The SRS 7.2 was un-mothballed, by our collaborator at the SRS Dr Pierre Rizkallah, which it had become in the early 1990s; and we happily played for many days optimizing the set up for use at 2 Å wavelength. This increased the sulphur $f''$ significantly, but most notably set us nicely to increase the $f''$ for the xenon LI absorption edge (at 2.27 Å). We also had the use of SRS 9.5, which had a CCD, and SRS 9.6 also with a CCD. Thus the crystal structure of apocrustacyanin A1, with crystals grown by Prof. Naomi Chayen, was solved (56). I also wrote a short note featuring the original lysozyme 2.6 Å wavelength diffraction pattern for the new conference series launched by Japanese colleagues: the International Symposium on Diffraction Structural Biology (ISDSB) (57).

6.2. SRS Station 9.6; the first SCW protein crystallography instrument and electronic area detector initiatives

With SRS 7.2 well underway, with firm user community support, a new opportunity arose to expand the technical specification of what could be made available to SRS PX users with the advent of the SRS superconducting (5 T) wiggler (Figure 8). This wiggler had a critical wavelength of emission of 0.9 Å, and thus opened up this portion of the X-ray range for use. In addition it had a higher intensity than even at the SRS 7.2 favoured wavelengths range such as 1.3 to 2 Å due to the simple fall off of the SRS spectral curve for a bending magnet field of 1.2 T, with its critical wavelength of 4 Å. As I analysed the new station layout and the fact that this wiggler magnet could provide 60 mrad in total angular width of beam, rather than the 28 mrad of the bending magnet, not only could we have 5 mrad for our new protein crystallography instrument (even if we were not able to secure the prized end-of-beamline position), we could still have a ‘straight through beam’ setting for the 2θ arm. This would allow a white beam to pass through to the sample. At this time, 1984, the Cornell High Energy Synchrotron Source (CHESS) group of Keith Moffat published their seminal paper in Science of advocating Laue diffraction for rapid data collection in protein crystallography for time-resolved structural studies in the crystal (58). Not only did this resonate with the vision of David Phillips of harnessing the flow cell of Hal Wyckoff (Yale University; published 1967 (59)), it also became clear later that Louise Johnson and Janos Hajdu with colleagues would become very interested in this option at SRS. Phil Moore was again the mechanical engineer. He and I could build on our design for SRS 7.2 for the 2θ arm, but this time also allow it to be set to this straight through
position. With the computer aided design system drawings it became clear that the film oscillation camera, and soon to be added Enraf Nonius (Fast Area Sensitive Television (FAST)) ‘TV diffractometer’, would collide with the lead shield wall that separated our hutch from the central beamline carrying beam into the outer hall of the SRS. Clearly this was going to be a difficult challenge but Phil could see how keen I was and he checked with the SRS Radiation Safety Group. They concluded that a small piece cut out of the lead shielding at the ‘savage point of interaction’ with the lead shield wall would not be a radiation hazard when we were in the SRS 9.6 hutch.

On the detector provision for SRS 9.6, I wrote up the strategy for electronic area detection (60), heavily influenced by Uli Arndt’s thinking (61), but extending the analysis from 8 keV only so as to span our SRS interests from 0.5 to 3 Å wavelength. I wrote up the SRS 9.6 design and first applications in ref. (62).

A curious feature of the SRS wiggler installation and firing up to 5 T was that the vertical divergence on SRS 7.2 doubled in value. We first noticed this as a simple decrease in the ion chamber current reading of the SRS 7.2 X-ray beam intensity onto the protein crystal sample. Andrew Thompson, who had joined in the SRS protein crystallography effort, and I investigated this in an SRS Outer Hall beamline 7 test hutch where a simple green paper test showed that for the wiggler off the line 7 vertical beam divergence was 2 times smaller than for wiggler on. I reported our evidence to the machine group, Mike Poole, who made their own checks on their SR beam monitor. It was announced that the wiggler would indeed need a slight planarity adjustment as the magnetic field was 0.75 degrees from horizontal. This was duly corrected and we got our beam intensity back on SRS 7.2!

The SRS 9.6 commissioning team by now included as well as Andrew Thompson also Dr Miroslav Papiz who joined me as a Post Doc Research Assistant to commission and implement the FAST TV diffractometer that we purchased from Enraf-Nonius. This effort commenced in 1984. It was a very busy time. The research and development and the expanded user programme (62) on SRS 9.6, broke new ground in various research areas. These included:

- Optimized anomalous scattering at the L absorption elements such as Pt, Au and Hg, i.e. the common heavy-atom derivatizing elements (62, 63).
- Assessing how far small protein crystals might be pushed, in fact as small as 20 μm was tested in a NATO funded collaboration I had with Keith Hodgson and Britt Hedman (64).
- Broad bandpass Laue diffraction tested with pea lectin crystals (a gift from Howard Einspahr from the SRS 7.2 collaboration I referred to earlier) (55), and which led to a whole new software package for evaluating such diffraction patterns (65) in a collaboration with Daresbury colleagues Pella Machin and Mike Elder.
- By use of the pre-monochromator slits being made narrower, an unusual large lattice effect crystalline disorder was resolved in crystals of the enzyme rubisco (66).
- The extensive and pioneering studies of catalysis in the crystal, and including prompt take up of Laue diffraction studies, by Oxford Molecular Biophysics (67, 68).
- Finally, very high profile (reaching even the BBC 9 o’clock news for the FMDV study) was the large unit cells user programme, which included David Stuart with
Porton Down on Foot and Mouth Disease Virus (FMDV) (69), Steve Harrison and Bob Liddington from Harvard University with their SV 40 virus (70) and Ada Yonath for ribosome crystallography (71).

It is important to point out also that the NSLS in Brookhaven USA, generally labelled a second generation SR source, in fact had a superior brightness compared with the SRS (Prof. Michael Hart, personal communication, Figure 11) and allowed pioneering ribosome crystallography studies to move forward (using a CCD device and with improved crystals by that time) (72).

The above SRS 9.6 studies all used photographic film. The Enraf-Nonius FAST TV diffractometer proved a difficult commissioning challenge. Miroslav and I took time in the single bunch low current mode of SRS, as well as portions of the regular multi-bunch SRS operating mode, to undertake tests as well as get familiar with the software that came with the device for the diffraction data image processing. We noticed that the noise floor from image to image varied substantially; this led to a Peltier device cooler being added by the company but this took time to report to the company our findings and accept their technical solution. Since the device did not simply progress into user operation, the SRS senior management started taking a close interest. After all, the device would reduce our substantial photographic film budget: (large quantities of CEA X-ray films were regularly purchased from Sweden as well as dark room supplies of developer and fixer). In addition I had planned this as a major speed up of the ‘measurements to processed data’ pipeline; indeed a contract with Enraf-Nonius for this software described reaching 600 processed reflection intensities a second from the software on a reasonably powerful computer (also controlling the apparatus).

In spite of these commissioning challenges, clearly more than teething troubles, the FAST broke new ground: e.g. working with GLAXO (Dr Alan Wonacott) it was used in

Figure 11. Comparison of the spectral brightness of the SRS and the NSLS (Figure kindly supplied by Prof. Michael Hart with permission).
their drug discovery protein crystallography programme using SRS 9.6 FAST data (73). Secondly a spin-off application was for a small molecule microcrystals research programme funded by SERC to Dr Marjorie Harding, then at Liverpool University, and which employed a Post Doctoral Research Assistant, Dr Pierre Rizkallah. This led eventually to a major new application area for SRS of chemical crystallography and ultimately with dedicated beamline instruments SRS 9.8 and later SRS 16.2. An example crystal structure from the FAST on SRS 9.6 for a very small crystal of piparazine silicate is described in ref. (74); this paper includes a calculation allowing a comparison of the scattering efficiencies of relevant small crystal project challenges of the time. A summary and review of chemical crystallography with SRS, and SR in general, was presented by Dr Marjorie Harding up to 1995 (75) and by Prof. Bill Clegg on the SRS 9.8 and 16.2 utilization years (76).

An overall survey of the timeline of different detectors used at the SRS for protein crystallography is shown in Table 1: this table includes reference to SRS Beamline 14 for protein crystallography led by Dr Colin Nave (77). The overall view of the SRS during this time period up to 1985 is summarized by the SRS Director of the time Dr Jerry Thompson in ref. (78).

6.3. The SRS High Brightness Lattice and SRS 9.5 for rapidly tuneable protein crystallography and point focussed Laue crystallography

In 1985 the SRS Machine Group brought about the ‘High Brightness Lattice’ (HBL) project (79), whereby the addition of new focussing magnets in the electron storage ring gave a reduction of mainly the horizontal source size from 14 mm to ~2 mm, and a slight improvement of the vertical source size, which was already only ~0.4 mm. Thus with no modification of the SRS 7.2 or SRS 9.6 beamline optics, the focal spots improved from 1.4 mm to 0.2 mm or so (FWHM) values. Since the typical protein crystal sample size was 0.3 mm or less, this was obviously a considerable improvement of X-ray beam intensity.

Table 1. A timeline of the detectors provision at the SRS protein crystallography stations. X-ray film was the mainstay of research in the 1980s, noted for the length of time one used to spend running between station and dark room, and the equally onerous task of digitizing the precious diffraction patterns. The FAST area detector drew the users’ attention to the advantages of electronic detectors. Image plates quickly spread around PX facilities across the world, including the SRS, through the 1990s, until CCD detectors became available.

<table>
<thead>
<tr>
<th>Year</th>
<th>Detector</th>
<th>Resolution</th>
<th>Spacing</th>
</tr>
</thead>
<tbody>
<tr>
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<td>83/84/85/86/87/88</td>
<td>0.3 mm</td>
<td>14 mm</td>
</tr>
<tr>
<td>96</td>
<td>97/98</td>
<td>0.2 mm</td>
<td>2 mm</td>
</tr>
<tr>
<td>99</td>
<td>00/01/02</td>
<td>0.1 mm</td>
<td>0.4 mm</td>
</tr>
<tr>
<td>03</td>
<td>04/05/06/07/08</td>
<td>0.05 mm</td>
<td>0.2 mm</td>
</tr>
</tbody>
</table>

Note: Prepared by Dr Pierre Rizkallah and reproduced with permission. The Beamline 14 initiative was led by Dr Colin Nave (77).
intercepted by the sample and data exposure times could reduce accordingly. The rate limiting step was still in effect the film processing in the dark room, which was even more of a bottleneck. The FAST diffractometer software proved to be rather cumbersome since a crystal orientation matrix had to be calculated and adapted if crystal slippage of the crystal in the capillary occurred. This was still in the days before the freezing technique was pioneered for ribosome crystallography by Ada Yonath and Hakon Hope (80). This technique had already been demonstrated by Rossman and Haas much earlier with lactate dehydrogenase (81), and it became more widely adopted and optimized: (see the review and initiatives of Prof. Elspeth Garman (82)). Thus the capillary mounting technique did quite often lead to sample slippage during data collection.

The HBL however created a different and new opportunity, which was to harness a different style of beamline optics from SRS 7.2/9.6, namely a double-crystal monochromator with a toroidal mirror for the point focussing of the beam. Thus this X-ray spectroscopy style monochromator allowed for rapid wavelength tuning for ease of multiple wavelength anomalous scattering measurements around an elemental absorption edge. The water cooled channel cut was provided by Prof. Michael Hart to his own design. There was a spare beamline slot for development on the SRS line 9 wiggler. I obtained funding support from the Swedish Natural Sciences Research Council and who provided a Post-Doctoral Research Assistant, Dr Ron Brammer, who came from Sweden to Daresbury. Ron led the X-ray optical ray tracing details; and this work and results were published in Nuclear Instruments and Methods in 1988 (83). Andrew Thompson was Instrument Scientist for SRS 9.5. This beamline opened up Multiple-wavelength Anomalous Dispersion (MAD) measurements in a routine way from protein or nucleic acid crystals and first results were obtained (84).

6.4. The ESRP and the ESRF planning

In Europe, discussions on an ESRF third generation machine had been going on since the mid to late 1970s (85–89). My first chance to join in such discussions was at the Life Sciences Workshop held in Oxford 25–27 February 1979 (87). I was able to contribute the practical experience of my DPhil project having recorded X-ray oscillation film camera exposures of single crystals on 6-phosphogluconate dehydrogenase on a rotating anode GX6 at the Laboratory of Molecular Biophysics in Oxford University, and then also at the LURE synchrotron Paris. The exposure times were, respectively, 10 h to 2.3 Å diffraction resolution and 24 min to 2 Å resolution. Therefore this extrapolated to 15 s for an equivalent exposure at ESRF. I further commented on the benefits of ESRF for small crystals (90a) as follows:

The effect of reducing the crystal dimensions on increasing the exposure time is large at the national sources but (will be) small on the ESRF where the beam cross-section can be reduced to accommodate the size of the crystal…. In principle then a 0.1 × 0.1 × 0.1 mm³ crystal would take 7 hours to expose on a present day SR source but only 35 seconds on the ESRF…. Theoretically it should be possible to get information in periods of hours from very small crystals, in the region of 10–20 microns per side.

The other sections in the report on protein crystallography at the proposed ESRF, besides the one just referred to, named ‘Amplitude measurements’, were entitled: Anomalous scattering phase measurements, Kinetic experiments on crystals and Practical considerations at the ESRF. Other practical protein crystallography data
highlighted were high resolution data for glycogen phosphorylase b, measured at LURE by Enrico Stura and Keith Wilson, including diffuse scattering (90b). The chemical crystallography applications were referred to in the section entitled ‘Structures with long range three-dimensional order’ with sub-headings: Determination of charge density; Crystal structure determinations (including single-crystal work and powder work); Magnetic materials; and Order in disordered structures. The section ‘Kinetic experiments on crystals’ was suitably cautious ‘since the most primitive measurements have only just begun’ but ‘it may be possible to obtain a diffraction diagram (from a protein crystal) in less than one second’. The use of the Laue method however was not anticipated in this report, neither that the focussed white nor pink beam from an ESRF wiggler-undulator (wundulator) would allow single-bunch exposures from a protein crystal, i.e. with a sub-nanosecond single pulse being sufficient to obtain a protein crystal Laue diffraction pattern (see below).

A report on progress was presented by Buras (91), which included detailed comparisons of the available and planned SR sources’ spectral brightness (Figure 12). Likewise in the USA, Stanford Synchrotron Radiation Lab (SSRL) was hosting New Rings workshops on how to harness the PEP storage ring as an SR Source and which, like PETRA in Hamburg, had the possibility to realize the ultimate storage ring machine design for SR applications.

Spectral brightness was firmly recognized as a particularly important parameter (at that time often referred to as spectral brilliance). The ESRF design was set to outperform any previous or planned source, its closest competitor in the spectral brilliance graphs presented being the NSLS (91), Figure 12.

With Keith Hodgson and Britt Hedman (SSRL), I obtained a NATO-funded collaborative research grant to try and evaluate these new SR X-ray sources: ‘ultra-high-flux-brightness rings’. By using the focussed SRS wiggler white beam for Laue diffraction, the intensity onto the sample was a mimic of the ESRF monochromatic undulator X-ray beam intensities, typically envisaged to be around $10^{14}$ photons/s/mm$^2$ onto the sample. We conducted two main evaluations: one evaluation was ‘could we measure successfully X-ray diffraction from protein microcrystals?’ and the second was ‘what was the chemical nature of X-radiation damage after prolonged dose which would occur as the sample size was made progressively smaller?’ The first evaluation we published in PNAS (64). Since clean diffraction data were obtained from a 20 μm crystal, this immediately meant that finer sample alignment on the diffractometer, which should be 10 times better than sample size, would certainly be needed (that is, 2 μm) and which was much tighter than the typical manufacturer’s diffractometer ‘sphere of confusion’, which was then around 25 μm.

The second evaluation with Keith Hodgson and Britt Hedman built on a suggestion of Prof. Greg Petsko of Brandeis University that a marker of X-ray dose damage to a protein could be the splitting of disulphide bridges. Thus we examined this with monochromatic data measured both at Stanford and at Daresbury and revealed for the first time that this had in fact occurred, with negative density where the two sulphur atoms had been and positive density where they had moved to, i.e. they had moved apart (92).

Dr Roger Fourme, who was leading the LURE, Paris synchrotron protein crystallography programme, and I produced a report for the European Synchrotron Radiation Project (ESRP), based at CERN in Geneva. The ESRP was the precursor stage before the ESRF had been agreed to be funded (and therefore well before the site of the ESRF was decided upon by the partner countries). This report (93) offered projections on the utilization of these totally new, high level, monochromatic undulator intensities.
The report included simulations of beam heating of the sample and a risk management strategy involving a novel crystal sample mount on a copper fibre with a heat conducting glue or grease to attach it.

These sample beam heating calculations were of a simple adiabatic modelling type, introduced by Kam previously (94). Later simulations involving detailed isothermal interactions were modelled (95), and were followed up by actual heating measurements by Snell et al. (96). Again microcrystals were advised to be a territory of user science for SR where there was a risk of adverse beam heating effects. Snell et al. concluded as follows: ‘However, microcrystals require more careful considerations. The integrated intensity of

Figure 12. Spectral distribution of brilliance for the ESRF bending magnet, 24-pole wiggler and several undulators and, for comparison, the brilliance from, bending magnets on ADONE (Frascati), DCI (Orsay), DORIS (Hamburg), NSLS (Brookhaven), Photon Factory (Tsukuba), SPEAR (Stanford), SRS (Daresbury) and the 32-pole wiggler on DORIS and the 54-pole wiggler on SPEAR. The brilliances for the MPWSs are on axis. From ref. (91) Courtesy of Brookhaven National Laboratory.
the diffraction peaks is proportional to the product of flux intercepted by the crystal, crystal thickness and exposure time per frame. If the experimenter chooses to increase the flux on the sample instead of increasing the exposure time to make up for the smaller sample thickness in order to achieve the same intensity of the recorded diffraction peaks, they may steer into dangerous territory. The same caveat applies to radiation damage studies where maximum fluxes are used instead of just maximum flux densities. A flux of \(6 \times 10^{12} \text{photons s}^{-1}\) intercepted by the sample, i.e. four times the ‘typical’ flux used for the extrapolation, would result in a predicted temperature rise of 20 K (24 K for a 0.025 mm-diameter sample). This, indeed, would bring the sample close to the onset of enhanced free-radical mobility with associated consequences for radiation damage.

These pessimistic prognostications for the ESRF applications territory of biological microcrystals were countered by the prudent experimental tests on SRS 9.6 with the focussed white beam that led us to publish Hedman et al. (64). These kept the risks for this area of application at a level that did not impede our proposal for microfocus applications of ESRF including for microcrystals. Of course Hedman et al. (64) had used gramicidin crystals, where gramicidin, although biological, is a rather small protein, indeed some would say only a polypeptide of 3 kDa molecular weight. That said Hedman et al. (64) also included tests with the focussed white beam on normal sized haemoglobin crystals, and which still produced clean Laue diffraction patterns, although suffering radiation damage after several exposures. ESRF did indeed set up a microfocus beamline facility in the first phase of instruments and which were advertised under an ESRF Newsletter article by the Science Director of the time Prof. Andrew Miller (97) that macromolecular microcrystallography could expect 25% of the beamline allocations on it. This application area grew substantially under the excellent leadership of Dr Christian Riekel (98) and ESRF became a global leader in the area for many years, and indeed other facilities were subsequently engaged in ‘catch up’. The Advanced Photon Source at Argonne National Laboratory (APS) was quick to respond with more than one of the ESRF EMBL microdiffractometers (99) being purchased and installed on beamlines, such as NE CAT and GM CAT.

The overall point about the experimental tests, simulations and calculations described above was to prove sufficient to carry the community usage plans forward in conjunction with the ESRF Facility. I came across a most interesting reference in writing up this Lecture. It is by Holton and Frankel (100) who assessed the question of the minimum crystal size for a complete diffraction data set. This study mainly worked within an ideal limit of zero background. Their abstract states that a crystal of lysozyme of 1.2 \(\mu\)m could yield 2 \(\AA\) diffraction data, and if photoelectron escape models are included (101) then even a sample as small as 0.34 \(\mu\)m could be used. Adding that with the current ‘detection limit’ whereby ‘100 photons/\(hkl\) are needed (after data merging of likely symmetry related or multi-measured spots) to attain a signal-to-noise ratio of 2 (means that) a lysozyme crystal will have to be 8.3 microns in diameter for 2 \(\AA\) data, and (for) 3.5 \(\AA\) data for a 10 MDa case would require 43 micron crystals, limiting the usefulness of X-ray beams smaller than this’.

The ESRF Foundation Phase Report (known as The Red Book) (41) comprised \(\sim1000\) pages of machine and beamline descriptions; the undulator spectral emissions, for example, at that time are shown in Figure 9. The Working Group for macromolecular crystallography proposed the provision of at least a bending magnet for MAD use, a MPW for monochromatic and white-beam Laue work, a monochromatic undulator beam for large unit cell and small crystals and, more speculatively, a beamline for providing very
high photon energies to access high atomic number K edges (such as Pt, Au and Hg) for optimized anomalous scattering. This last request was never serviced but a generic high energy beamline was established and some tests ensued much later. A very broad instruments’ provision for macromolecular crystallography now exists at the ESRF with these various sources led by Dr Sean McSweeney.

The first ESRF Science Advisory Committee (SAC) decided to establish generic beamlines emphasizing specific beam properties such as ‘High flux’, ‘white beam’ etc. Whilst it was an expeditious way to serve many research communities, it was a set back to expectations to access substantial portions of beamtime for macromolecular crystallography. Roger Fourme and I complained about this in writing to the ESRF SAC. An outcome of this was that macromolecular crystallography was represented at the second ESRF SAC; Prof. Jens Als Nielsen, Copenhagen Physics Department, was elected as Chair, and I was elected Vice-Chairman. As Vice-Chairman this meant I represented the SAC at the ESRF Machine Advisory Committee (MAC), as the SAC Chair Jens had to attend the ESRF Council.

Thus I had at least four meetings per year in Grenoble, two SAC and two MAC meetings. The MAC was chaired by Dr Jerry Thompson of Daresbury Laboratory, the SRS Director. The number of meetings in Grenoble escalated further as the concrete floor to the ESRF Experimental Hall was laid incorrectly by the contractor (who, much later, had to pay damages costs to the ESRF). The Concrete Working Party met several times, under increasingly vitriolic argument both within the in-house Directors (the Director General and the two ESRF Science Directors) and within the ESRF SAC. By this time Prof. Jen Als Nielsen had joined ESRF and had to vacate the ESRF SAC Chair; as Vice-Chair I assumed the role of Chair. This meant I chaired the joint MAC with SAC meeting which brought the issue to a head with all competing factions and personalities present. It proved to be the most difficult meeting I have ever chaired. Two extreme views were expressed. The Director General Ruprecht Haensel emphasized a civil engineering solution known as ‘shallow grouting’, and which involved squirting liquid grouting compound between cracks in the floor slabs every 12 months; this seemed immediately unsatisfactory as it was meant to be a clean scientific working environment which would be forced to be a ‘building site’ every 12 months. The contrary view championed by Prof. Michael Hart was that the concrete floor should be dug up and taken away by the contractor who should then lay a new floor; this option seemed also unworkable as not least the sheer quantity of concrete to be dug up and lorried away was very large. Prof. Massimo Altarelli, from within the ESRF Management proposed that the civil engineering consultants continued to hunt for a more long lasting solution to the problem. This option which faced the joint MAC/SAC meeting had the danger of looking like procrastination if we took it but in spite of that disadvantage it was the only realistic thing to commend to ESRF Council, who had the ultimate authority over such decisions. As ESRF SAC Chair I attended the next ESRF Council. Prof. Jules Horowitz was in the Chair and was greatly experienced in all manner of large building projects. The civil engineers did indeed by that time offer the ‘deep grouting’ solution to the problem and for which they estimated that the floor would be rendered stable and sufficiently flat for up to 20 years. This was received with great relief by all participants, not least as engineers’ safety factors in any project would likely be such that it could be good up to twice that length of time! Whilst the whole problem was lamentable that it had even occurred in the first place, it was a profoundly satisfying business to be resolved. Of course, most importantly, it was a great thing to be involved with such a supranational pan-European project.
The ESRF put European scientists involved with SR and its applications in a global leadership position. Approximately 2 years later, the USA followed with the 7 GeV APS and not long after the 8 GeV SPRing-8 Japanese project was approved. Innovations were not only the domain of ESRF in SR science and its evolution. The APS introduced the top-up machine operating mode so that beam currents were essentially constant: this had two benefits, firstly, the integrated flux was obviously larger per unit time and, secondly, beamline optics’ stability under a constant thermal load was much better than a decreasing beam current situation. Also the 7 and 8 GeV machine energies allowed a wider tuning range as undulator magnet gaps were varied, in effect giving a continuous sweep of X-ray energies from a single undulator emission fundamental or harmonic.

From the ESRF, APS and SPRing-8 the necessary experience was gained in both the machine and science domains to generate the designs for the new 3 GeV SR national machines such as the UK’s DLS. Using narrower undulator gaps, pioneered at the NSLS (42), the lower machine energy of around 3 GeV still allows undulator emission into the most popular portions of the X-ray region of the emission spectrum.

6.5. ESRF BM14, the first macromolecular crystallography instrument on a third generation SR source

Following the details of the SR source evolution described in the previous section, it is worth mentioning some of the details of the first macromolecular crystallography instrument on a third generation SR source. The ESRF BM14 design was based on the SRS 9.5 design. It was a development led by Andrew Thompson who had joined ESRF from SRS. A weakness of SRS 9.5 was that the vertical divergence angle had to be controlled by vertical slits and which led to a weaker beam intensity than users had come to expect on SRS 9.6 in particular. The ESRF BM14 could instead accommodate a collimating pre-mirror, pioneered at NSLS (102), instead of slits; and thus a gain in intensity of ESRF BM14 over SRS 9.5 of a factor of about twenty was immediately apparent.

At this point, since this lecture was also a Teaching Plenary for the BCA Biological Structures Group, it is appropriate to explain the key facts of phasing in protein crystallography. Using isomorphous or anomalous differences at a single wavelength leads to two possible choices of the phase angle for a reflection, shown in Figure 13 via the two vector triangles which are compatible with the measurements. A third measurement is needed, for example, from a second isomorphous heavy atom derivative, to realize a unique phase value determination (not shown); summarized in (103). If the crystal sample contains a metal atom, then data measured at two wavelengths are adequate with the anomalous difference to yield three measurements and a unique phase determination. Since nearly all proteins contain methionine, which contains sulphur, it is possible to harness selenomethionine, where the selenium has identical chemistry, being in the same chemical group of the periodic table. Thus the rather inaccessible sulphur K edge of 5 Å wavelength is much easier for the selenium K edge of 0.98 Å. The selenomethionine approach as a general phasing vehicle for proteins was the brainchild of Wayne Hendrickson (104). In bringing to the fore SRS 9.5 and ESRF BM 14, along with demonstrating the utility for such measurements of the ESRF Image Intensifier electronic area detector, we collaborated with Dr Alfons Haedener of Basle University who had selenomethionine hydroxy methylbilane synthase crystals. A successful MAD structure
determination on both instruments of this enzyme in its active, i.e. chemically reduced form, resulted (105).

6.6. SR Laue crystallography at SRS and ESRF

The development of the Laue method for quantitative crystal structure analysis was an important new thread to the development of the field of SR crystallography. This development followed the initiative of Moffat and colleagues at CHESS Cornell (58). On seeing this paper I immediately felt it was an exciting development in which we at Daresbury should join. I had already made sure that SRS 9.6 could take a straight through beam into the crystallography camera or FAST diffractometer, as mentioned above. This could be either a white beam or a monochromatic beam from a double-crystal monochromator. I recorded the broad-bandpass Laue diffraction patterns from a pea lectin crystal during single-bunch (i.e. normally a non-user) mode during early 1984. These Laue patterns were of a very high quality of signal-to-noise ratio and immediately looked promising for quantitative analysis. By chance I was looking at the proofs of my Reports on Progress in Physics review article and asked if I might be allowed to show a figure or two of these protein crystal, broad wavelength bandpass, Laue diffraction patterns, which was granted by the IOP Publishers (50). These Laue patterns were of a different kind to those published by Moffat, Szebenyi and Bilderback, who had carefully explained the need for a wavelength bandpass of 0.2 so as to avoid the overlapping orders problem of Laue diffraction.

At Daresbury, colleagues Dr Mike Elder and Dr Pella Machin ran the SERC Microdensitometry Service for digitizing Weissenberg diffraction films and these data were passed back to the crystallographer for crystal structure solution. They were immediately captivated by the high quality in terms of signal to background of the pea lectin Laue

Figure 13. The unique solution for each reflection phase stems from three unique measurements from a minimum of two wavelengths at an absorption edge. Illustrated here are both the reflection and its Friedel mate at $\lambda_1$ and the Friedel mate only at $\lambda_2$. 

diffraction patterns. Mike said he would write a Laue diffraction spot prediction program and asked me for the experimental parameters of the white SRS 9.6 X-ray beam and the pea lectin unit cell and space group details. The beam spectral parameters were $\lambda_{\text{min}} = 0.2 \, \text{Å}$ and $\lambda_{\text{max}} = 2.6 \, \text{Å}$. The short wavelength at that time of the SRS 9.6 instrument was as yet unmodified by the SRS 9.6 reflecting mirror, which was installed later. The long wavelength cut-off was approximate and set by the beryllium window transmission. I told Mike about the ‘overlapping orders’ challenge: see for example Bragg (106), from which I quote:

X-ray analysis started with the Laue photograph. Although this method was developed further by Wyckoff in America (107), with a considerable measure of success, it never came into general use. It is too hard to attach a quantitative significance to the intensity of the spots, which are due to the superposition of diffracted beams of several orders selected from a range of ‘white’ radiation. The (monochromatic) spectrometer proved to be of much greater analytical power because it measured accurately a diffracted beam of monochromatic radiation of definite order, and the first crystal structures were solved by it.

That said, Bragg’s analysis of sodium chloride and related crystals (108) is a tour de force of Laue diffraction photos, recorded by him in Cambridge, and quantitative analysis along with complementary monochromatic measurements, the latter measured with his father W.H. Bragg in Leeds.

Mike Elder looked for that multiplicity effect and displayed a histogram of how many predicted pea lectin Laue spots were singlets, doublets, triplets, etc. Of special interest for him was the particular type of computer workstation for which he would write the program. This was a PERQ computer which had been bought in a bulk buy by SERC as a special initiative of high performance (at the time) distributed computing workstations. It also had a high quality display screen, albeit black and white, well suited to displaying the predicted Laue spot patterns, comprising up to about 10,000 reflections, for the particular crystal and beamline parameters. This program was very promptly written in a few days by Mike Elder. It immediately showed that the predominant population of spots, by a long way, were singlets. Further analysis proved that the low-resolution diffraction reflections were nearly always members of Laue spots that were multiplets. The initial difficulty in extracting the intensities of Laue spots containing several ‘Bragg reflections’ led to our test crystal structure analyses initially being based around the population of Laue diffraction spots that were singlets. These singlet Laue spot intensities still needed wavelength normalization to bring them all onto a common intensity scale (109). Another Daresbury computer programmer, John Campbell, focussed on this development and wrote a computer program called ‘LAUENORM’ (described in (65)).

The pea lectin Laue diffraction patterns were duly processed and the details of this and the software were published in ref. (65). The theoretical properties of the multiplicity distribution were studied in detail as well by Durward Crucikshank, Keith Moffat and myself (110, 111).

The Oxford University team was also quick to see the potential of this synchrotron Laue method development for application to time-resolved crystallography studies of their phosphorylase enzyme, thus extending their results in EMBO Journal (67) on ‘Catalysis in the crystal: synchrotron radiation studies with glycogen phosphorylase b’ and publishing a study: Hajdu et al. (68). Clearly these results and developments affirmed the excitement of Laue diffraction identified by Moffat et al. (58).

We also undertook a wide range of validation experiments to establish both the credentials of the Laue method and our own, that is, the ‘Daresbury Laue software..."
package’. In my Lecture I illustrated this major R&D program with a validation evaluation on an amylase enzyme crystal, kindly provided by Zygmunt Derewenda (112). This study included deconvoluted doublet spots into two reflection intensity components, which yielded clearly the mercury atom site from the difference Fourier map. Furthermore, at the time, there were critical remarks about the difficulty of including a focusing mirror, in terms of focussed beam instabilities at the sample. I remarked ‘Figure 3 (112) provides the “acid test” for data quality with a mirror and shows difference Fourier maps for Laue and monochromatic data. Figure 4 (112) used phases derived from Laue Hg amylase data; the three sections indicate that the anomalous differences are very significant when measured in Laue geometry with a mirror’. These results I presented in a lecture at the International Synchrotron Radiation Instrumentation Conference in Tsukuba, Japan (1988) and published in *Reviews of Scientific Instruments* in the Conference Proceedings (112).

The ESRF ‘white beam’ beamline ID09 aimed to serve various research communities, such as time-resolved Laue diffraction and high pressure experiments. Dr Michael Wulff was the Beamline Leader for ESRF ID09. He came to SRS Daresbury in the early 1990s to see SRS 9.5 for himself and how we had achieved a point focussed Laue beam using a toroidal reflecting mirror. Andy Thompson was the SRS 9.5 Instrument Scientist and we measured example Laue patterns. The mechanical engineer for this station was Neville Harris.

Michael, with ESRF ID09, brought about such intense point-focussed white beams, initially broad bandpass from an MPW but eventually preferring narrow bandpass from a tapered undulator, that a single bunch of electrons in the ESRF ring produced a measurable Laue diffraction pattern from a protein crystal. The notion of taking such a single bunch had been advanced by Prof. Keith Moffat and by which the time resolution for studying structural changes in a crystal became the time width of the electron bunch, namely 100 picoseconds or so. In the case of a stroboscopically cooperating crystal sample/molecular system, then enough of these pulses could be accumulated to achieve reasonable measuring statistics per time point, after a given light-driven stimulus. In my Lecture I showed a molecular movie, the study by the Moffat team with Michael Wulff on carbon monoxy myoglobin, in which a light-stimulated carbon monoxide molecule is driven off the haem group; and where it wanders is studied in successive time-lapsed movie frames (113). The clock at bottom left of the movie ticks away throughout until a time has elapsed of 3.16 μs.

As we concluded the Daresbury Laue software development, and all the associated analyses procedures, for photographic films, new detector opportunities arose. ESRF ID 09 had an image intensifier TV detector developed by J.P. Moy of the ESRF Detector Group (114). This was both more sensitive to X-rays, over a wide wavelength range, than film and its ease of read-out made a dramatic improvement to both the ease of conducting such experiments but also increased substantially the number of Laue diffraction exposures per protein crystal. On moving to the University of Manchester as Professor of Structural Chemistry I was able to combine my interest in methods developments at the synchrotron for crystallography with my own structural studies research programme. One such study was with Dr Alfonse Haedner of Basle University on the enzyme hydroxymethylbilane synthase. Thus a mutant of the enzyme proved viable for Laue diffraction, with the highly X-ray sensitive Moy detector, and we could measure a large number of Laue patterns leading to high quality electron density maps (115). We also measured a sequence of time-resolved electron density maps (115) as the enzyme crystal
was fed substrate via a flow cell (59), the device first shown to me by David Phillips at my DPhil interview in 1974!

### 6.7. Synergies of Synchrotron and Neutron Laue macromolecular crystallography: initiatives at the Institut Laue Langevin

In the early 1990s I was contacted by Drs Clive Wilkinson of the Grenoble Outstation of the EMBL and Mogens Lehman of the Institut Laue Langevin (ILL) about the possibility of the ILL introducing the neutron Laue method for biological and chemical crystallography with neutrons. The idea was that neutron fluxes were low compared with X-ray fluxes and by harnessing a wide spectrum of emitted neutron wavelengths this would open up a range of new and more challenging projects for crystal structure analysis. Thus, in biological crystallography, protonation states (as deuterium) of ionizable amino acids such as histidine, aspartic acid and glutamic acid, as well as more detailed information on the orientation of water (D₂O) molecules, could be determined on molecules which had been previously out of reach of monochromatic neutron beams, such as higher molecular weight proteins and/or smaller crystals. For chemical crystallography, the interest was usually the determination of the anisotropic vibrations of hydrogen atoms, but again many studies were out of reach of neutron monochromatic methods due largely, in this case, to too small a crystal being available (since the molecular weights were by definition relatively small already). Clive and Mogens had kept a watch of the progress with the synchrotron X-radiation Laue method for quantitative crystal structure analysis and also noted that the Daresbury Laue software (65) could be readily adapted to processing neutron Laue diffraction data. They proposed then a cold neutron source at the ILL reactor experimental hall for macromolecular (largely protein) crystallography with a mean wavelength $\lambda \approx 3.5 \text{ Å}$, so as to benefit from the crystal sample scattering efficiency increasing as a function of $\lambda^2$ and from a cylindrical image plate diffractometer, which would be called LADI (Laue Diffractometer). Secondly, for chemical crystallography, a hot source neutron beam, providing shorter wavelength neutron wavelengths, would allow the naturally higher diffraction resolution needs for data collection to be satisfied. This instrument would be called Very Intense Vertical Axis Laue Diffractometer (VIVALDI). Each apparatus involved a cylindrical neutron-sensitive image plate fully surrounding the crystal. The Daresbury Laue software coordinate prediction algorithm (for a flat detector) needed amendment (for the cylindrical detector), as did the polarization correction formula (116). A critical feature was the provision of neutron-sensitive image plate materials by Dr Nobuo Niimura from the Japanese Atomic Energy Research Institute (JAERI) in Tokai, Japan, which was a most helpful and collaborative gesture that was greatly appreciated here in Europe.

Japan took a special initiative in this area of neutron macromolecular crystallography within a major funded project known as an Organized Research Combination System (ORCS) grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan to Dr Niimura and Dr Mizuno (Agriculture Research Institute, Tsukuba). Within this project many scientists were involved, including many who took part in several international workshops hosted in Japan. Along with Prof. Eric Westhof from France, I was involved on the ORCS Advisory Committee over the period from 2000 to 2005. Thus I was able to repay our gratitude, on behalf of Europe and myself, and give our thanks to
Dr Niimura and Japan for the gift of the neutron sensitive imaging plates referred to above.

Clive and I wrote up a jointly authored book chapter for the HERCULES Course students book and which outlined the ideas briefly summarized above (117).

By a happy coincidence, at the same time as Clive Wilkinson and Mogens Lehmann contacted me for collaboration in the matter of the synergistic possibilities between synchrotron X-ray and neutron Laue diffraction and software for data processing, I was rummaging around the crystallization laboratory in the School of Chemistry, University of Manchester and saw a large measuring cylinder with a dialysis bag. This had been set up by my PhD student Dr Susanne Weisgerber. This dialysis bag contained several very large (~ 5 x 2 x 1 mm³) crystals of one of our structural chemistry/biology projects of the time, the plant lectin concanavalin A. This opened up our own user programme on LADI-I.

Initially our objective was to solve a neutron protein crystal structure including the bound water structure for concanavalin A, especially the waters bound in the saccharide binding site which are displaced on sugar binding. Of course our 0.94 Å X-ray crystal structure of concanavalin A had revealed, via bond length analyses, protonation states of various Asp and Glu amino acid side-chains and even, to our surprise approximately 10 bound waters where the hydrogens were visible in the final difference Fourier electron density map. We labelled this X-ray crystal structure, via the title of our article, ‘The structure of concanavalin A and its bound solvent determined with small-molecule accuracy at 0.94 Å resolution’ (118). In effect then the contribution that a neutron protein crystal structure could make did rather focus on the saccharide site bound water structure. Could we see their hydrogens too? – which were obviously too mobile to be delivering their X-ray scattering signal to a high enough diffraction resolution. Initially I assumed that this meant that the hydrogens had to diffract to 0.94 Å to see them in X-ray derived electron density maps. In fact, commented on by several neutron specialists, the rapid fall-off of the hydrogens’ X-ray scattering factor means that their main signal is at a lower resolution relative to the other atoms. Thus the role of 0.94 Å X-ray resolution is in resolving the (slightly) heavier atom with an appropriately small atomic radius of electron density; and that way the heavier atom does not submerge the detail latent in the hydrogen electron density.

In our first neutron concanavalin A LADI-I experiment, we tried to effect our hydrogen to deuterium exchange, of the H₂Os and the protein’s exchangeable hydrogens/protons using a sealed jar with two pots; one pot with a crystal in mother liquor and another with D₂O, heavy water, in it. This was left sealed for at least a week before crystal mounting and taking to Grenoble by Dr George Habash, a Post-Doc working with me for many years, for measurements on LADI-I. The crystal diffracted well but to our surprise there was basically no bound water visible in the nuclear density map presumably because of poor H₂O to D₂O exchange and the cancellation of the two hydrogens’ signal, being negative (2 x ~0.374) and of approximately the correct magnitude as that of oxygen (0.58); and the example of a protonated Asp, based on the X-ray crystal structure, was that there was some density where the hydrogen was, but it was still a hydrogen, i.e. with negative nuclear density. The manganese site showed clear, albeit not strong, negative nuclear density, as to be expected for the neutron scattering signature of manganese. This study we published as a companion paper to Deacon et al. (118), i.e. Habash et al. (119). However it was clear this study needed repeating but with a better method of H/D exchange. So, with our collaborator Dr Joseph Kalb Gilboa from The Weizmann Institute, who used repeated dialysis against heavy-water based mother liquor of another large crystal of

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concanavalin A, over a period of 4 months, more LADI-I neutron Laue diffraction data were recorded. This time the diffraction was better, to 2.4 Å resolution versus 2.7 Å in the previous case. Now the bound waters were available for detailed study in the nuclear density maps (120).

Next, we sought to see more clearly the saccharide binding site bound waters via a cryo-version of (120), which had been made at room temperature. This was taken forward, led by Dean Myles of the Institut Laue Langevin, with our joint research student Matthew Blakeley, working with concanavalin A and a few other proteins. This R&D established cryo-freezing conditions even with such big crystals, indeed the biggest, to our knowledge, attempted to be frozen. LADI-I had a 15K cryo-pad cooling-type device and so after plunge freezing, a crystal was transferred to LADI-I, where it was held at 15 K. There was a considerable increase of the number of bound waters discernible (121) versus the room temperature neutron study (120), which in turn was an improvement versus the X-ray cryo-structure (118). The saccharide site bound waters’ nuclear density was improved to define their orientation in a network. It is also interesting to emphasize the strategic importance of this for neutron macromolecular crystallography in general, i.e. with respect to freeze trapping of reaction intermediates that could be inducible in a crystal sample.

There was also a push to raise the molecular weight ceiling of such neutron crystallography techniques. Thereby we undertook a neutron Laue diffraction experiment on a complex of concanavalin A with methyl α-D-glucopyranoside extensively soaked in D₂O (space group I213, a = 167.8 Å), which resulted in 3.5 Å diffraction data. In our longstanding programme of structural studies of crystalline saccharide complexes of concanavalin A, the unit cell of the cubic I213 complex of concanavalin A with methyl α-D-glucopyranoside was one of the largest. With its cell edge of 167.8 Å and its asymmetric unit of molecular weight 50 kDa, it represented a nice challenge for the then current neutron diffraction technology. The size of the crystal used in the experiment, although large (4 × 3 × 2 mm³), was not the largest ever produced for this complex! The degree of spatial overlapping of diffraction spots observed in the Laue experiment, however, suggested that use of larger crystals would be a disadvantage. On the basis of these observations, several technical improvements for macromolecular neutron crystallography were suggested (122). These were incorporated, along with others, in the LADI-III apparatus and which subsequently came online at the Institut Laue Langevin reactor replacing LADI-I.

Subsequently, led by a new PhD student, Stu Fisher, we analysed the freely available protonation prediction tools regarding their efficacy (123) and assessed the risks of deuteration altering a molecular structure (124).

A major review and summary of the field of neutron macromolecular crystallography has been published by Dr Matthew Blakeley (125). This includes a comparison of the effectiveness of Laue methods in neutron macromolecular crystallography, which shows how the limits of high molecular weight and of small sample, as well as the speed of measurement, has been significantly improved with the neutron Laue method. The reduced background noise that inevitably comes from using the broader spectral bandpass has so far had only a marginal effect on worsening the diffraction resolution limit achieved. The total elapsed time to make a data set measurement has also reduced significantly, as the evolution of apparatus exploiting technical developments has occurred (Figure 14). Briefly, the sequence of apparatus developments at the Institut Laue Langevin had been as follows. The LADI apparatus was an EMBL development. It became known as LADI-I, i.e. first version, as VIVALDI for chemical crystallography was in effect...
LADI-II. Later the LADI-III replaced LADI-I with improved features, which were that the readout head was on the inner surface of the image plate, yielding an improved DQE (16% for LADI-I and 46% for LADI-III) and was therefore close to a factor of 3 times more sensitive (126). The radius was also somewhat larger thus allowing a larger crystal and subsequent spot-to-spot spatial resolution to be better. Also, for a given crystal sample size, the unit cell diffraction order-to-order resolution could be improved.

In the spirit of the teaching aspect of the Lonsdale Lecture some basics of neutron scattering are as follows. The neutron scattering factors of each element show quite different trends compared with the X-ray scattering factors. For neutrons, the scattering cross section magnitude shows relatively very small variations and with some quite remarkable characteristics such as, deuterium scatters basically the same as carbon. Thus for neutron macromolecular crystallography, even with modest resolution, neutron diffraction data such as 2.5 Å or better, the full hydrogenation (as deuterium) details can be discerned. The perhaps more famous application of neutrons in biology is of course the contrast variation method where, by suitable adjustment of D$_2$O versus H$_2$O relative

Figure 14. Three-dimensional scatter plot of the asymmetric unit-cell volume vs. crystal volume vs. data collection time for the various neutron structures solved so far. The new instruments are able to collect data from larger asymmetric unit cells, from smaller crystal volumes and with shorter data collection times. The original necessity to have crystal volumes of several mm$^3$ is no longer the case with data now being collected from perdeuterated protein crystals close to 0.1mm$^3$. (Includes unpublished results from LADI-III.). From ref. (125) with permission of the author and Informa UK.
percentages can lead to contrasting in or out a protein or a nucleic acid in a multi-
macromolecular complex. Alternatively the specific labelling with deuterium of molecules
in a complex can alter their scattering signature and thus allow their placement to be
determined. A third, yet to be applied in earnest application, is the spin polarization
property of neutrons with potential application in biology. Heinrich Stuhrmann has made
pioneering contributions in this area (127).

7. The impacts of the SRS and ESRF in macromolecular crystallography
An objective measure of impact in the macromolecular crystallography field is via the SR
facility and specific beamline statistics recorded at the website http://biosync.rcsb.org/.
Table 2 summarizes the SRS beamlines’ performance in contributing to these structure
depositions. Also included is BM14, detailed in this review, the first third generation SR
source MX beamline. The data presented here were compiled in October 2011 (see http://
biosync.rcsb.org/) and are likely to be reasonably complete, since the SRS closed
operations in August 2008. The SRS has delivered 1471 structures (2.9%) of the total of
51077 macromolecular crystal structures determined using radiation from synchrotrons
around the world, as of October 2011; in turn the 51077 structures are 74.2% of all the
X-ray crystallography depositions. The ESRF third-generation source, in comparison,
integrated over about half as many years, but about three times more beamlines, has
delivered 7745 (15.2%) of the world’s synchrotron depositions of structures, i.e. at a rate
therefore per beamline of about three times greater than the second-generation SRS, but
also with generally much more complex (larger molecular weight) structures than at SRS.

In more general terms, of impact assessments, two recent review articles on
macromolecular crystallography at SR sources have appeared, one surveying the current
status and future developments (128) and the other describing a personal view of the
impact of SR on macromolecular crystallography (129). My own overviews can be found
in (130) and (131), presented at a researcher level and at a teaching level respectively, both
recently updated in second edition volumes.

<table>
<thead>
<tr>
<th>Synchrotron Beamline</th>
<th>Total number of structures in the PDB</th>
</tr>
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<tbody>
<tr>
<td>SRS7.2</td>
<td>135</td>
</tr>
<tr>
<td>SRS9.6</td>
<td>538</td>
</tr>
<tr>
<td>SRS9.5</td>
<td>146</td>
</tr>
<tr>
<td>SRS14.1</td>
<td>235</td>
</tr>
<tr>
<td>SRS14.2</td>
<td>223</td>
</tr>
<tr>
<td>SRS10.1</td>
<td>181</td>
</tr>
<tr>
<td>SRS_Unknown</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>1471</td>
</tr>
<tr>
<td>ESRF_BM14</td>
<td>802</td>
</tr>
</tbody>
</table>
In this account of the evolution of SR and crystallography, an appropriate perspective is that of one of the authors of the 1971 *Nature* muscle diffraction paper (19) from which I quote (132):

The most important application (of synchrotron radiation) for biology later proved to be protein crystallography. Early tests of protein diffraction on the DESY source (Harmsen, Leberman & Schulz, 1976) (133) showed improvements compared with conventional sources but the gains were limited. The flux was about ten times better than with a conventional source. At this stage one had failed to appreciate that the parallel collimation of the beam was giving an unusually good signal-to-noise ratio. This was the property of synchrotron radiation which ultimately made it the source of choice for all kinds of protein crystal data collection. At about the same time studies on the Stanford storage ring SPEAR (Phillips, Wlodawer, Shevitz & Hodgson, 1976) (18) showed gains for crystal diffraction even with a non-focusing monochromator which indicated that (tailored) storage ring sources were going to be of considerable importance in protein crystallography. These authors made use of the ability to ‘tune’ the wavelength across an absorption edge to demonstrate the potentialities of synchrotron radiation in exploiting the effects of anomalous dispersion…. Protein crystallographers, whose numbers of course vastly exceeded the muscle community, began to appreciate the high speed and convenience of data collection at the storage ring sources, and soon began to realize that their data were better too, since radiation-induced damage had less time to fully manifest itself. Also, it became possible to work with much smaller crystals, especially as the advantages of rapidly freezing them (before data collection) became apparent. It was ironic that the muscle experiments, which to a considerable extent had driven the technology needed for the use of synchrotron radiation, became almost a victim of their own success, for it became increasingly difficult, though not impossible, to obtain beam time because of the pressure from other users!

8. Other relevant topics

I need to add that I obviously had to be selective with the contents of my Lecture, and also to a degree with this publication. This has meant that some favourites were missing in the Lecture through pressure of time. Thus, I did not have time to highlight other favourite user challenges which featured in the evolutionary changes of user expectations. One such on SRS 7.2 was the 80% solvent content purine nucleoside phosphorylase project (134) which helped to contribute to the launch of BioCryst Pharmaceuticals (http://www.biocryst.com/) and brought SRS a mention in *Scientific American* (135). Methods development included a collaboration between Daresbury Laboratory and Rutherford Laboratory for a Multi-Wire Proportional Chamber (MWPC), built at Rutherford (136), for SAXS and Small Angle Diffraction; this may even have been one of the first involvements that Rutherford Laboratory ever had with SR. The 1 mm anode wire pitch for the 20 cm active area diameter was a cutting-edge aspect of the design for this MWPC. This whole arm of the evolutionary tree of instrument development at SR sources of MWPCs for X-ray diffraction and crystallography is a significant one and has been reviewed by Prof. Rob Lewis (137) and Prof. Roger Fourme (138).

I also had no time to discuss the methods and instrumentation lines of research involving the potential and R&D work done so far on harnessing high photon energies in crystallography (ultra-short wavelengths in the range 0.3 Å) (139) and with its potential for charge density studies. This latter field is a growing discipline in structural chemistry but has not yet taken off really with SR, presumably because of its exacting demands on SR source stability. This domain and the use of high photon energies have also been discussed
by Coppens (140) and by Hart (141). A beamline in the final phase of SRS, was beamline 10, for structural genomics (a project led by Prof. Samar Hasnain) (142). Also there is protein powder diffraction at ESRF ID31 for which we have started to make a contribution (143), as one frontier in the protein crystallography field as it moves to individual, ever smaller, crystals even below 1 \( \mu \)m (144), as well as polycrystallography (several single crystals in the X-ray beam at once (145)) and bulk protein powder diffraction (reviewed in (146)).

Nor have I covered adequately the applications of resonant scattering in chemical crystallography, another favourite theme in our laboratory in Manchester, led by Dr Madeleine Helliwell, showing also the synergies between biological and chemical crystallography methods developments (147,148).

Nor did I have time to highlight the important work of the Daresbury Analytical Research and Technical Services (DARTS) (see ref. (149) for a recent summary); nor the economic and social impact of the Daresbury SRS as a whole (150). These aspects are of course important, not least with the increasingly wide, albeit still controversial, recognition now of the importance of the ‘impact’ of the science that we undertake. From the outset of the SRS, I recall explaining the potential impact of these SRS instrumentation developments, for example at the conference in Nordwijk in the Netherlands on Medical Applications of Synchrotron Radiation (151).

The visits to various excellent overseas SR facilities by myself or by members of my group or close colleagues have also not been mapped out due to lack of time in the Lecture, but which involved methods and facility development, besides SRS or ESRF, such as for reciprocal-space mapping at the NSLS (152), resonant scattering crystallography at NSLS and ELETTRA (153,154). Visits as a user to APS IMCA CAT, APS SBC CAT, SOLEIL, DORIS and PETRA III have also not been described.

At IUCr Madrid (2011) I reported on a current study (N. Chayen, L. Govada, J. R. Helliwell and S. Tanley to be published) involving experiments using a micro-beam (about 10\( \mu \)m diameter) scanned across an \( \alpha \)-crustacyanin crystal at the DLS macromolecular crystallography microfocus facility (144), which we have undertaken to search for the best ordered portion.

In terms of patents I could not find in my patent searches any patent attributed to Kathleen Lonsdale. My efforts at securing patents have led to one (the 3D ‘toast-rack’ Laue diffraction film or image plates arrangement (155)) and contributed to one other, but neither have made it big, and so patents remain a future priority objective for my research.

The fascination I have with the foundations of crystallography includes symmetry and all the manifest deviations from perfect symmetry that can occur in Nature, and that we study or find work-arounds for crystal structure analysis (156, 157). There are also the crystals themselves and crystal growth phenomena and their monitoring and evaluation.

After my Lecture there was one question, from Dr Sax Mason of the Institut Laue Langevin in Grenoble (158): ‘With all this improved SR source brightness that we are still witnessing with improved sources is it leading to a higher rate of deposition in the PDB (Protein Data Bank)?’. I replied: ‘Yes and no; there are increases but a user can now be more selective in choosing whichever sample to proceed to data collection with, helped also by widespread availability of robotics for automatic sample changing at beamlines’. In addition I could have said that projects are getting more ambitious, such as time-resolved experiments and larger complexes (e.g. viruses) and the ribosome projects. Indeed
a careful, systematic, analysis of SR versus laboratory source X-ray data determined macromolecular crystal structures deposited in the PDB has been made emphasizing, among a variety of conclusions, the larger molecular weight on average of the SR based studies (159). However there are also, increasingly, complications with X-radiation damage, even with cryo-cooled crystals (160), and several volumes of *Journal of Synchrotron Radiation* have been devoted to the publications arising from several Workshops led by Prof. Elspeth Garman, Dr Colin Nave and Dr Sean McSweeney (161).

9. **Research directions for the future**

It is invidious to pick out particular directions but I select some personal favourites in this simple list below.

- New SR sources: PETRA III, recently on-line, is currently the most brilliant, i.e. the ‘ultimate’, storage ring.
- New SR sources: NSLSII, MAX IV and ALBA all will offer their users marvellous levels of specifications as SR sources.
- Our own national UK DLS is a ‘cutting edge’ source and suite of instruments and also with a vibrant research and development programme. Figure 15 shows the beamline layout for DLS I19 the chemical crystallography beamline, by way of illustration of a modern state-of-the-art beamline for crystallography.
- ESRF has a new upgrade programme for nanofocus beams; UK has a 10% share in ESRF. APS and SPRing-8 also are embarking on major upgrade programmes.
- Structural biology will show a continued expansion into studying large complexes combined with small angle X-ray scattering (SAXS) and electron microscopy (EM); our own example in this area is with the multi-macromolecular complex crustacyanin (162).
- Structural chemistry will I believe show a continued expansion into time-resolved crystallography (163, 164).
• The X-ray lasers user programme will strive towards reaching the goal of single-molecule diffraction.
• New and upgraded neutron sources in Europe, USA and Japan will benefit crystallography, reaching full hydrogenation details completed for mechanistic and functional studies, as well as molecular recognition studies.

The initiatives in SR biological diffraction at DESY (19) and in SR protein crystallography at Stanford SSRL (18), allowed scientists like myself to join in the excitement and help bring about the profound changes in technical and scientific capabilities that SR has brought to the field of macromolecular crystallography, and indeed all of crystallography.

Notes on contributor

This photo of the author in the SRS 7.2 experimental hutch was taken by Stuart Eyres, Daresbury Laboratory in 2002 and is reproduced with the permission of STFC Daresbury Laboratory. J.R. Helliwell is, since 1989, Professor of Structural Chemistry of the University of Manchester. John Helliwell worked at Daresbury Laboratory’s SRS from 1979 to 1993, whilst also a Joint Appointee with the Universities of Keele, York and Manchester, and full time as a scientific civil servant (1983–1985), and earlier on the NINA synchrotron (1976). He was Director of SR Science full-time at CCLRC based at Daresbury Laboratory in 2002. In 2002, he was awarded the Banerjee Centennial Silver Medal of the Indian Association for the Cultivation of Science in Calcutta, India; his Banerjee Centennial Lecture was published (165). He was part-time Science Adviser to the Daresbury Analytical and Technical Research Services ‘DARTS’, then STFC CLIK, from 2003 to 2009. He has served on the ESRF Science Advisory Committee as Vice-Chairman and then Chairman, on the ESRF MAC, and on the Council of the ESRF; as Chairman of the UK SRS Panel for Protein Crystallography; as Chairman of the Cornell University Macromolecular Crystallography at CHESS (MACCHESS) Advisory Committee; as a Member of the Elettra Sincrotrone Trieste Review Committee; as a Reviewer of the EMBL Outstation in Hamburg and on the Science Advisory Committee of the Advanced Photon Source. He was the founding Chairman of the International Union of Crystallography’s Commission on Synchrotron Radiation. He was one of the founding Editors of the Journal of Synchrotron Radiation, an Editor of the OUP Book Series on SR and Editor-in-Chief of Acta Crystallographica from 1996 to 2005. He served as President of the European Crystallographic Association from 2006 to 2009. He is currently serving on the Advisory Committee for the Australian Research Council Centre for Coherent X-ray Science and is Chairman of the Spanish Synchrotron Source ‘ALBA’ Science Advisory Committee.
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[158] Sax Mason question to John R Helliwell at the end of the Lonsdale Lecture.


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Summary of abbreviations used

APS – Advanced Photon Source at Argonne National Laboratory
CCLRC – Council for the Central Laboratory of the Research Councils
CHESS – Cornell High Energy Synchrotron Source
DAFS – diffraction anomalous fine structure
DESY – Deutsches Elektronen-Synchrotron
DLS – Diamond Light Source
EMBL – European Molecular Biology Laboratory
ESRF – European Synchrotron Radiation Facility
ESRP – European Synchrotron Radiation Project
HBL – High Brightness Lattice
LURE – Laboratoire pour l’utilisation du rayonnement électromagnétique
MacCHESS – Macromolecular Crystallography at CHESS
MAD – Multiple-wavelength Anomalous Dispersion
NSLS – National Synchrotron Light Source at Brookhaven
SERC – Science and Engineering Research Council
SLAC – Stanford Linear Accelerator Centre
SPRING-8 – Super Photon Ring 8 GeV
SRS – Synchrotron Radiation Source
SR – Synchrotron radiation
SSRL – Stanford Synchrotron Radiation Laboratory
STFC – Science and Technology Facilities Council