A CRC PRESS FREEBOOK

Wide Perspectives In Crystallography And Broad Skills In Science

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Introduction

About this FreeBook

Wide Perspectives In Crystallography And Broad Skills In Science is a FreeBook brought to you by CRC Press - Taylor and Francis Group. It contains a collection of curated content from two of our bestselling books and leading expert. We hope you enjoy it.

"I am glad to support the IUCr's initiative for an Individual Associates category of Membership, alongside the National Membership category that has run from 1948. As soon as it was announced earlier this year (2017) I immediately joined as an IUCr Associate Member myself. To further help launch this initiative I am pleased to offer this booklet comprising selections from my two recent books with CRC Press; *Perspectives in Crystallography* and *Skills for a Scientific Life*. The Contents' headings below make clear from which of each book each section is derived.

Perspectives in Crystallography offers a threefold look into the past, present and long-term development and relevance of crystal structure analysis. It is concerned not only with the state of the field, but with its role in the perpetuation of life on earth. As such, it is a reference of vital interest to a broad range of analytical and practical sciences.

From Skills for a Scientific Life:-

Being, or wanting to become, a scientist requires academic training in the science subjects. To succeed as a research scientist and educator requires specific as well as general skills. ***Skills for a Scientific Life*** provides insight into how to be successful. This career book is intended for potential entrants, early career and mid-career scientists for a wide range of science disciplines.

Overview of the two books together:-

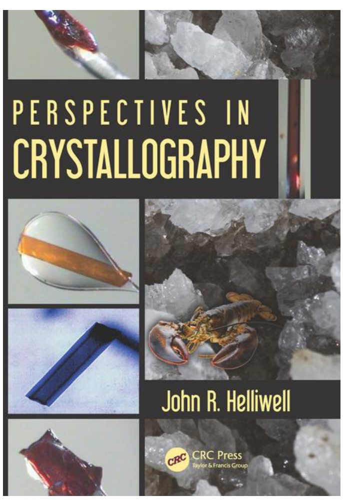
My skills book invites the reader to consider how to best make their own global impacts in science, consider how to change the current organization of science and aim to make a contribution to world peace and to sustainability. The societal impacts that a scientist can realise can be achieved via their lectures and press releases to the Public, and which are both satisfying and needed also by the funding agencies that scientists receive their research grants from. This links with my other recent book, Perspectives in Crystallography, which offers a threefold look into the past, present and future of crystal structure analysis. Crystallography is one of the most multidisciplinary sciences, with roots in fields as varied as mathematics, physics, chemistry, biology, materials science, computation and earth and planetary science. The structural knowledge gained from crystallography has been instrumental in acquiring new levels of understanding in numerous scientific areas. This book resonates with the 2014 United Nations and UNESCO International Year of Crystallography, a celebration of its achievements and importance, undertaken with the International Union of Crystallography (IUCr). Crystallography in both its organisation within IUCr and in its discoveries offers major contributions to sustainability including within the United Nations' Millenium Development Goals." John Helliwell

CRC Press conducted a Question and Answer interview which is also reproduced below from the CRC Press Featured Authors' website **(**Click here to view).

·Please note this Free Book does not include references, endnotes and footnotes. Fully referenced versions of each book can be accessed through crcpress.com .

1

Explaining 'What Is Crystal Structure Analysis?' for a General Audience



1 Explaining 'What is crystal structure analysis?' for a general audience

One of the most challenging situations is to explain crystal structure analysis to a general audience. There are different types of such audiences one can meet, which I now take in turn as to how I approached them including the most general through to quite specialist audiences.

1.1 SCHOOL OF CHEMISTRY, UNIVERSITY OF MANCHESTER OPEN DAYS

These are principally to give the opportunity for people interested in applying to read chemistry as an undergraduate degree the chance to meet staff and see a wide range of 'chemistry in action'. Mostly, the audience would be parents, with their 17-year-old children, who would be deciding to which of the five UK universities they would apply. Figure 1.1a through d show our typical display of molecular models, crystals, computer movie demos and example research or popular magazine articles. Each item on our display would be something about which members of the display team would be both knowledgeable and indeed enthusiastic. Naturally, there would be a fair fraction of research we had undertaken.

From left to right in Figure 1.1a, a side view in Figure 1.1b (with my colleague Dr G. Habash), a close up view in Figure 1.1c (including Dr Madeleine Helliwell and myself) and a more distant view in Figure 1.1d (with Dr Madeleine Helliwell and Dr Peter Skabara):

- The sugar-binding proteins concanavalin A isolated from beans (Jack and the Beanstalk beans fame) and hen egg white lysozyme
- Common salt model
- Calcite model (to explain the planar carbonates and the calcite crystal double image refraction effect as well as each optical image being polarized light demonstrated very readily using a piece of polaroid and a calcite crystal)
- Crystals of calcite, quartz, copper and a silicon wafer
- Molecular models in a mounted case (for ease of rotating each model) of lobster crustacyanin with and without astaxanthin
- A laptop with molecular graphics examples
- Molecular model of the DNA double helix set vertically on a plinth and in a plastic case but easily extractable for people to point with fingers at the base pairs

A poster of the mouse genome given as a pullout of an issue of Nature (on display on the back wall in Figure 1.1c) became a topical context for many people not least when the human genome was eventually first sequenced.

It is also important to look smart in my view. Also my tie would be carefully chosen to illustrate, for example, a regular pattern such as a piece of Escher art work or packing of spheres (the example in this photo of what I am wearing) or crystals.

Additional choices of exhibits would include other molecular models such as: a full molecular model of hen egg white lysozyme with bound hexasaccharide ('Labquip' model type assembled by my student Gail Bradbrook), a Beevers molecular model of a haemoglobin tetramer and a concanavalin A tetramer.

(a)

(b)

FIGURE 1.1 The University of Manchester School of Chemistry Open Days included a crystallography display. (a–d) show different views of such an exhibit; for details and names of staff involved see text.

(*Continued*)

(c)

(d)

FIGURE 1.1 (*continued*) (See colour insert.) The University of Manchester School of Chemistry Open Days included a crystallography display. (a–d) show different views of such an exhibit; for details and names of staff involved see text.

I would always start a discussion with a visitor to our display with either ‘have you seen the double image seen through a calcite crystal?’ or ‘have you seen the DNA double helix?’ These would be unfailing in offering a keen and friendly opener for people who may be quite shy.

1.2 UNIVERSITY OF MANCHESTER LECTURES TO SCHOOLS

There is a considerable outreach effort to bring the best science to schools and of course highlight the quality of the University of Manchester’s science in particular. There are plenty of chances on offer to assist with these. As an example, I reproduce below my abstract for Fleetwood Grammar School near Blackpool (a private school, known in the United Kingdom for historical reasons as a public school).

Abstract: ***The Fascination of Crystals***

Summary
This talk will consider the nature and importance of crystals. Crystals allow the determination of precise molecular structures using X-rays and neutrons, which is vital for molecular structure and function studies. Thus new pharmaceuticals and functional materials can be designed. Crystals can also have specific properties, such as optical, magnetic and electric, which lead to interesting curiosities like the double refraction optical effect in crystals of calcite, based on the structural chemistry of the planar carbonate chemical group, as well as the exceedingly useful doped silicon crystal semiconductors that form the basis of modern computers. Closely allied to the study of crystals in molecular 3D structure determination are the solid state fibres and which for example yielded the DNA double helix 3D structure, the basis of genetic information storage, determined by X-ray fibre diffraction. This needed a clear mathematical theory for *X-ray diffraction from a helix and led to the famous moment when Jim Watson recognised this effect in Rosalind Franklin’s DNA fibre diffraction patterns. These examples will be illustrated with reference to a wide range of molecular models and crystals. The talk will conclude with an overview of the sophisticated technology of modern day synchrotron and neutron beams used these days to probe these states of matter.*

It is worth recalling that in the first module of A Level Chemistry, the syllabus does cover states of matter and students are for example expected to:

** be able to explain the energy changes associated with changes of state;*

** recognise the four types of crystal: ionic, metallic, giant covalent (macromolecular) and molecular;*

** know the structures of the following crystals: sodium chloride, magnesium, diamond, graphite, iodine and ice;*

** be able to relate the physical properties of materials to the type of structure and bonding present.*

Overall then this talk will enrich, and move beyond, the Chemistry A Level curriculum and include undergraduate-level Chemistry concepts and theories through to modern day research and use of crystals. This final overview and summary of the talk seeks then to connect with expectations among the teachers and pupils/students regarding crystallography. In addition the talk will bring out the obvious inter-disciplinarity of crystallography reaching across physics, mathematics, chemistry and biology.

1.3 A MIXED AUDIENCE OF EXPERIENCED SCIENTISTS AS WELL AS ARTS AND HUMANITIES, WELL-EDUCATED PEOPLE

My University of Manchester 150th Anniversary Lecture, advertised as the W L Bragg Lecture, that I presented in 2001 in the University’s Schuster (Physics) Department W L Bragg Lecture theatre was to an audience of experienced scientists in the University and, more widely, to members of the Manchester Literary and Philosophical Society.

This event included a sherry reception beforehand. I prepared a suite of well-labelled exhibits (including those listed in Section 1.1). The captions are reproduced in Appendix 1.A of this chapter.

A similar composition audience of science, arts and humanities as well as business people was present when I delivered a Friday Evening Discourse at The Royal Institution ('the RI') on 'Why do lobsters change colour on cooking?'.

The invitation to me from the Director of the RI, Baroness Susan Greenfield, is quoted in the following.

The Royal Institution
of Great Britain

Ri

The Royal Institution of Great Britain
21 Albermarle Street
London W15 4Bs
Switchboard 020 7409 2992
Fax 020 7629 3569
Email ri@ri.ac.uk
Web www.rigb.org
registered charity number 227938

Professor John Helliwell
Department of Chemistry
The University of Manchester
Oxford Road
Manchester M13 9Pl

Friday, 12 September 2003

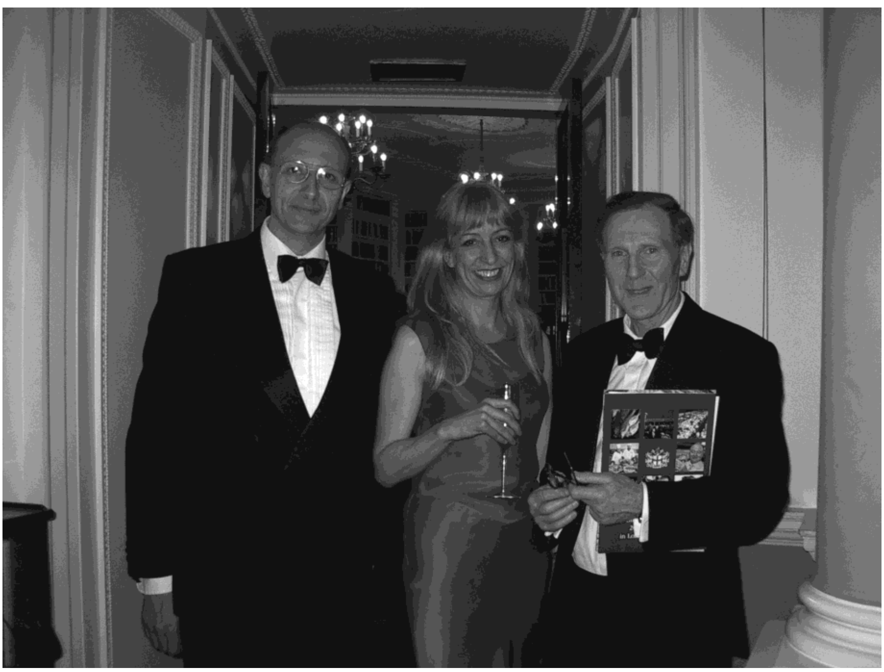
Dear Professor Helliwell

Re: Friday Evening Discourse invitation

I am writing to invite you formally, on behalf of Baroness Susan Greenfield, to give a Friday Evening Discourse at the Royal Institution on 19 March 2004. If you are able and willing to give a Discourse on this date, we would be grateful if you could send us a brief biography of about 60 words, a synopsis of about 150 words and some relevant, colourful images. We will need this by mid-October 2003, and we will use it to advertise your Discourse on our website and in our Spring programme of Events.

As you may know, the Friday Evening Discourses go back to 1826, having been initiated by Michael Faraday, and many famous scientists and others have expounded their work subsequently. The audience is composed of Members and their friends, corporate (industrial) and school subscribers and invited guests —amounting to several hundred people who are interested in science but are, for the most part, not professional scientists. The tradition is that the Discourse should be informal; we like to hear

(a)



(b)

FIGURE 1.2 (See colour insert.) My Royal Institution ('The RI') Friday Evening Discourse April 2004. 'Why does a lobster change colour on cooking?' (a) Here we are assembled in the RI Library (accompanying the drinks were various science exhibits on marine colouration and on crystal structure analysis). (b) With the RI Director Baroness Susan Greenfield and Dr Peter Zagalsky, great expert on marine colouration biochemistry.

the lecturer talking about his/her work rather than reading a prepared address. It is also a tradition that the lecture should last for exactly one hour, and be lavishly illustrated, wherever possible, with demonstrations, experiments, films, slides etc. Our Theatre Manager, Mr Bipin Parmar (bipin@ri.ac.uk), and the lectures staff here would be pleased to give any help you may need in the preparation of lecture demonstrations. Do arrange to speak to Mr Parmar as you start to consider what material you might use.

There is an exhibition in the Library associated with the Discourse arranged by our Exhibitions Organiser, Mrs Irena McCabe (irenam@ri.ac.uk), that illustrates and expands some of the ideas presented in the lecture. The exhibition is open to Members before and after the lecturer, and provides an important adjunct to the evening. Mrs McCabe is happy to advise on the exhibition and, in turn, is helped greatly by suggestions and indeed, if possible, material from the lecturer, so I would encourage you to make contact with her at an early stage.

Friday Evening Discourses will be published on the Royal Institution's web site www.rigb.org. We would be grateful if you could send a copy of the Discourse text to the Events Co-ordinator as soon as possible after giving the Discourse (or beforehand, if this is more convenient). The Discourse will be audio taped, and you are welcome to a copy of this tape if you think it will help you with the preparation of your text. The text may be anything from the summary of say 3000 words to an almost verbatim account, although something between 8000 and 12 000 is preferable.

Baroness Susan Greenfield will host a small dinner party for the lecturer and guest and we hope that you could come to this. If you have any special dietary requirements, we would be grateful if you could let us know in good time. We would also be happy to provide you with accommodation should you like to stay overnight.

Please don't hesitate to contact me if you need any further information.

I look forward to hearing from you.

Yours sincerely
Dr Gail Cardew

Head of Programmes
Fax: 020 7670 2920

E-mail: gail@ri.ac.uk

1.4 COMMUNITY CENTRE LECTURES: E.G. THE WILMSLOW GUILD

The Wilmslow Guild was founded in 1926 and it continues to fulfil its original aims which are: 'To provide a centre in which men and women may find opportunities for the enrichment of life through education, fellowship and co-operative effect for the welfare of the community'.

SCIENCE MATTERS: A NEW SERIES OF SCIENCE LECTURES

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The fourth series of science and technology lectures with brand new lectures which are thought provoking, exciting and entertaining, covering leading edge science and technology. Presented by experienced and enthusiastic lecturers who are mostly new to the Guild, the lectures will be of interest to both scientists and non-scientists alike.

21st September	Physics & Chemistry-more magic than Harry Potter	Dr Andrew G. Thomas
28th September	Making Sense of the Brain	Dr Rochelle Ackerley
5th October	The Gamblers Tale-randomness, chaos and order	Professor David Brooomhead
12th October	The Science of Climate Change: Current State of Knowledge and Challenges for the Future	Professor Hugh Coe
19th October	Wave Energy & the Manchester Botter	Professor Peter K Stansby
2nd November	Fysics of Frisbees ‘n Further Flying Fings	Professor David Abrahams
9th November	The Molecules of Life & the Fascination of Crystals	Professor John Helliwell
16th November	Developments in Computer Science	Dr Adrian Jackson
23rd November	On the Origin of Species by Natural Selection	Dr Robert Callow
30th November	Einstein’s Theory of Relativity	Professor Jeff Forshaw

Mondays 7:30–9:30 p.m. Starting 21st September
Ten meetings

Quoting Keith Wright <keith123wright@tiscali.co.uk>: Dear

John,

Just to say thanks once again for your excellent lecture last night. I was down at The Guild earlier today and many people told me how much they enjoyed it. Your efforts are much appreciated.

John Spawton, the Principal, will also write to you with his thanks and send a cheque covering your fee.

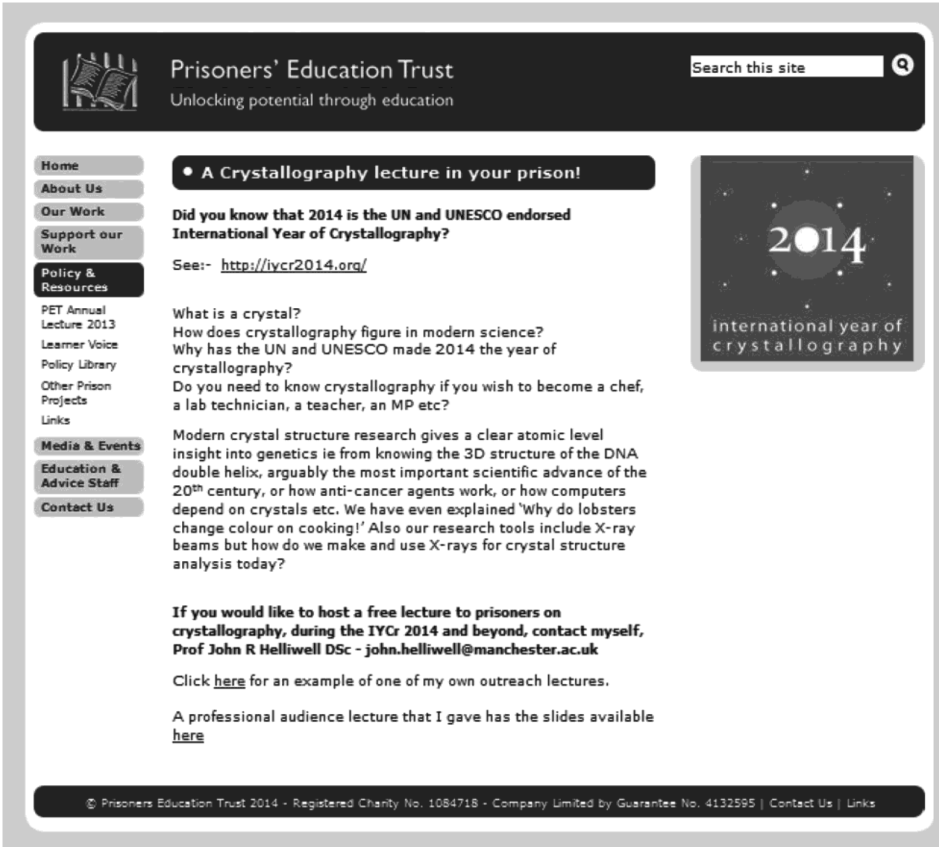
Thanks once again and I hope we can look forward to more presentations of yours at The Guild in the future.

Best Regards

Keith

1.5 INVITATION TO PRISONS VIA THE PRISONERS’ EDUCATIONAL TRUST NEWSLETTER (WITHIN THE IYCr)

Trying to be imaginative, an as yet unfulfilled idea I have had was (is) to take crystallography into prisons as part of my contributions to the IYCr. My idea was that, whilst of course those in prison are there to pay their debt to society and their victims, another aspect has to be reform and self-improvement to turn prisoners of today into the good citizens of tomorrow. My idea to try and do this was prompted when the BBC Radio 4 Today programme had a piece about mentoring of prisoners. I had undertaken a variety of mentoring in the University (Manchester Gold scheme) and within the School of Chemistry as Senior Mentor for New Academics. This was of course no qualification for mentoring of prisoners! But, having undertaken numerous public understanding of science, engineering and technology lectures surely I could achieve some good here. Via the web, I found the Prisoners’ Educational Trust who were helpful to carry my offer via their Newsletter (see the following figure). I have to admit that in my conversations with them, they were sceptical as they focussed on skills training such as prisoners learning car mechanics or being a chef.



Prisoners' Education Trust

Unlocking potential through education

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• A Crystallography lecture in your prison!

Did you know that 2014 is the UN and UNESCO endorsed International Year of Crystallography?

See:- http://iycr2014.org/

What is a crystal?
How does crystallography figure in modern science?
Why has the UN and UNESCO made 2014 the year of crystallography?
Do you need to know crystallography if you wish to become a chef, a lab technician, a teacher, an MP etc?

Modern crystal structure research gives a clear atomic level insight into genetics ie from knowing the 3D structure of the DNA double helix, arguably the most important scientific advance of the 20th century, or how anti-cancer agents work, or how computers depend on crystals etc. We have even explained 'Why do lobsters change colour on cooking!' Also our research tools include X-ray beams but how do we make and use X-rays for crystal structure analysis today?

If you would like to host a free lecture to prisoners on crystallography, during the IYCr 2014 and beyond, contact myself, Prof John R Helliwell DSc - john.helliwell@manchester.ac.uk

Click here for an example of one of my own outreach lectures.

A professional audience lecture that I gave has the slides available here

2014 international year of crystallography

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Did you know that 2014 is the UN- and UNESCO-endorsed International Year of Crystallography?

What is a crystal? How does crystallography figure in modern science? Why has the UN and UNESCO made 2014 the year of crystallography? Do you need to know crystallography if you wish to become a chef, a lab technician, a teacher, an MP, etc.? Modern crystal structure research gives a clear atomic level insight into genetics, that is from knowing the 3D structure of the DNA double helix, arguably the most important scientific advance of the twentieth century, or how anti-cancer agents work, or how computers depend on crystals, or how the future promise of Nanomaterials needs crystallography insights, etc. We have even explained 'Why do lobsters change colour on cooking!' Also our research tools include X-ray beams but how do we make and use X-rays for crystal structure analysis today? If you would like to learn more, during the IYCr 2014 and beyond, contact myself, Professor John R Helliwell DSc, john.helliwell@manchester.ac.uk.

Note: This was a special occasion, the 150th Anniversary of the Victoria University of Manchester, but it will give Prisons a feel for the discipline of crystallography.

1.6 NEWSLETTERS AND SYNCHROTRON FACILITY REPORTS

Example: The ALBA Spanish synchrotron radiation

Photo taken by John R Helliwell in his garden.

The inner life of plants and their responses

Have you ever wondered why plants in an identical pot and under obviously identical weather conditions respond differently? This photo (above) from my own garden in mid-February shows one part of a plant pot that has given up and one part that is still green and obviously alive. Have you ever read the Day of the Triffids by John Wyndham with the giant plants that take over the world? Or have you considered these ideas about life on Mars and beyond in potentially different atmospheres and soils than our own Earth?

● Plant response factors are the biochemical details to address such questions. Recent research published in Cell involves the auxin response. Auxin was originally discovered in research started by Charles Darwin and his son Francis looking at how plant growth responds to the direction of the light illumination (http://en.wikipedia.org/wiki/Auxin#Discovery_of_auxin).

Indole-3-acetic acid is the most abundant and basic auxin in plants. Auxin acts via regulation of genes in the plant. In the study by Boer et al published in Cell [1] they made a truly comprehensive study involving biophysical and biochemical characterisation techniques, including X-ray crystallography data quite recently measured at ALBA on the Xaloc beamline, as well as earlier data measured at ESRF in Grenoble before ALBA came online. From the 3D protein and nucleic acid structures the critical amino acids involved in the gene regulation could be identified. Modern genetics allows specific amino acids to be changed. The modified protein can be isolated and crystallised for further X-ray crystal structure analysis. The mutant G245A (glycine changed to alanine at position 245 in the particular protein polypeptide chain studied) was the one studied at ALBA. Earlier studies involved mutations at several other key places of the protein. These changes were deliberately introduced to disrupt or distort the protein nucleic acid interaction.

Prof John R Helliwell DSc
School of Chemistry, University of Manchester, UK
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With these site specific molecular changes in the genes the 'genetically modified plant' of the Arabidopsis (a small flowering plant related to cabbage and mustard) could be grown. These showed a variety of poor or compact (ie bushy) growing features.

How might this fundamental science make its way to impacting on society at large? Of course, as it did with this writer, it fuelled the imagination from arousing my renewed curiosity of what is happening in my own garden and on to my wilder imagination as to its implications in 'astrobiology'. Genetically modified (GM) crops are the more 'bread and butter' aspects. These are welcomed in some countries e.g. where hunger and famine are common place and controversial in others, notably where the citizens are well fed. How might this research help both community factions? For the hungry in the world such fundamental research will surely assist a more penetrating set of ideas and discoveries as to how to work with plant growers and agriculturalists as well as ultimately farmers. For the GM sceptics such research shows explicitly and clearly how plants respond to their environment via their genes and their biochemical response molecules, in this case auxin. Thus the wish by the sceptics of GM for a greater clarity on the effect of a given genetic mutation within the plant is achieved.

For myself I think the impact of this work is several fold. The team involved in the publication is clearly broad and each team is at the forefront of such modern day research; I am full of admiration. Secondly, as Chairman of the ALBA Beamtime Panel and of the Science Advisory Committee, for me to be able to see over a 4 years period of time the ALBA facility in general and Xaloc in particular move from build to commissioning to regular use is a marvellous thing. The Spanish community in all its range of science and technology skills can be rightly proud of this achievement with ALBA. Thirdly I have learnt a lot more than I did about plant molecular biology. Fourthly, maybe it is time for me to start that novel as a modern successor to the 'Day of the Triffids'!

[1] Boer et al Cell Volume 156, Issue 3, 577-589, 30 January 2014.

If you want to know more about this experiment, go to page 15.

1.A APPENDIX

I prepared an Exhibition to accompany my University of Manchester W L Bragg Lecture of 2001; the captions for the exhibits are given below.

1.A.1 The Difference Between Diffraction and Microscopy Explained

In a visible light microscope, the sample is illuminated and a glass lens combines the transmitted light to produce a magnified image. The microscope resolves detail at the level of cells and larger-scale objects. The resolvable detail cannot be finer than the wavelength/2 of the illuminating light. Visible light has a wavelength of around 500 nm.

Can we have an X-ray microscope to directly resolve details at the atomic level (spacings of 0.1 nm or so)? This would need X-ray lenses equivalent to the lenses in a visible light microscope. These do not exist. So, we must perform the lens function mathematically, that is via the computer. The analysis is known as Fourier series, named after the French mathematician Jean Baptiste Joseph Fourier (1768–1830) who first introduced this mathematical method.

1.A.2 Lysozyme Enzyme X-Ray Crystal Structure

'All atom' model, excluding hydrogens, of this globular protein was determined with X-ray crystallography by D C Phillips and co-workers in the early 1960s at The Royal Institution in London, and where Sir W L Bragg was Director (1953–1966). Lysozyme itself was discovered by Sir Alexander Fleming in 1922. In green is the hexasaccharide substrate, which is a model for the cell wall polysaccharide of a bacterium. This enzyme is found in hen egg white, for example, and serves as an anti-bacterial molecular defence. The aspartic acid residue 52 and glutamic acid residue 35 sit on either side of the bond linking sugar sites 'D' and 'E' (see cotton threads linked to the key bond). The bond is strained and then broken by these enzyme active site residues. Thus, the bacterial cell wall is punctured and bursts. The bacterium and the protein then disassociate and the enzyme is 'reprimed' by the addition of a water derived proton at the glu 35 carboxyl group, ready for the next bacterium. Lysozyme is one of Nature's catalysts. This model was built by Gail Bradbrook.

1.A.3 Concanavalin A Protein Tetramer X-Ray Crystal Structure

'Beevers' type protein model of concanavalin A involving one bead per amino acid residue. This protein is an association of four monomers each of 237 amino acids. The protein binds sugar molecules but is not an enzyme. Instead, it serves as a scaffold, cross-linking protein to sugar to protein, etc., providing vegetable beans with an anti-fungus defence. It is a commonly occurring protein found both in large quantities in jack beans and in different types of beans. The family of proteins is known as the legume lectins. Concanavalin A is the most common member. It is also widely used as a model system for understanding the molecular biophysics and biophysical chemistry of protein ligand interactions and energetics. This protein was first crystallized in 1919 by the Nobel prize winner J B Sumner in Corenll, United States. The X-ray crystal structure was first determined by three groups (two from the United States and one from Israel in the 1970s). Since then, its structure has been extensively studied by the Helliwell lab via synchrotron radiation and neutron protein crystallography as well as by molecular dynamics (Gail Bradbrook), in both saccharide-free and glucose- or mannose-bound forms. Data collection was undertaken either at the Daresbury SRS or the Cornell 'CHESS' Synchrotron (United States), and the neutron facility at the Institut Laue Langevin, Grenoble respectively.

1.A.4 Hydroxymethylbilane Synthase Enzyme X-Ray Crystal Structure in its Active Form

This enzyme is responsible for catalyzing the polymerisation of pyrrole units to form tetrapyrrole, which after release from the enzyme, can cyclize and this serves as the precursor of haem, vitamin B12 or chlorophyll via incorporation of an atom of iron, cobalt or magnesium, respectively. Absence of this enzyme at the genetic level causes the malady known as porphyria (the madness of King George). The enzyme crystal structure in its oxidized form was determined by the laboratory of Sir T L Blundell in Birkbeck College, University of London. This 'Beevers' model (one bead = one amino acid) shows the enzyme in its reduced, that is active form. (The cofactor being the active agent, shown in orange, atom by atom.) This was determined by the Helliwell lab, in collaboration with Dr Alfonse Haedener of the University of Basle, Switzerland, using the Daresbury Synchrotron Radiation Source and the Multi-wavelength Anomalous Dispersion (MAD) technique. In addition, the white extended piece embedded near the cofactor represents the growth of the electron density when an enzyme crystal has been fed substrate and the time-resolved crystal structures have been determined using Laue diffraction (shown here is the '2 hour' electron density); this data collection was done at the European Synchrotron Radiation Facility, Grenoble, France.

1.A.5 'Beevers Lipson Strips'

Before the advent of computers, the calculation of the Fourier Series transforms of the diffraction data to obtain electron density contour maps was undertaken with the help of these boxes of cosine and sine compilations. A calculation of one projection image alone could take many months. Professor Henry Lipson FRS (1910–1991), who had been a co-worker of Sir W L Bragg, was a Head of the UMIST Physics Department, a past Chairman of the Manchester Branch of the Institute of Physics and a past President of the Manchester Literary and Philosophical Society. Dr Arnold Beevers (1908–2001), who was based in Liverpool, joined with Lipson at Manchester in this research and development.

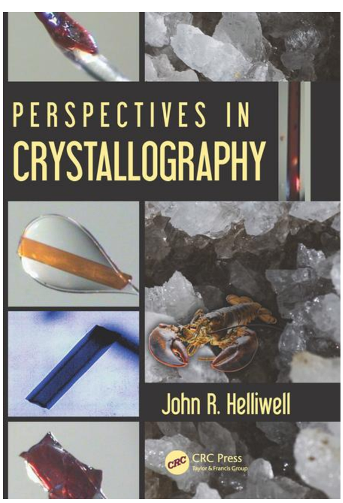
1.A.6 The DNA Double Helix Structure

Through a combination of model building, DNA helical X-ray diffraction patterns and previously available chemical composition data, the structure of the DNA double helix was deduced by James D Watson and Francis Crick at the Cavendish Laboratory, Cambridge. The work was published in *Nature* in 1953. The Director of the Cavendish Laboratory during the period of the work was Sir W L Bragg. The fibre diffraction experimental data were recorded by Rosalind Franklin, in conjunction with Maurice Wilkins at Kings College, University of London.

With the hydrogen bonding complementarity between the nucleotide bases on the inside of each strand, the structure immediately suggested a way that genetic inheritance could be passed from the parents to a child. This scientific result has been described as the greatest single scientific achievement of the twentieth century.

2

Where Is Crystal Structure Analysis Heading in the Future?



Where is crystal structure analysis heading in the future?

If there is a future International Year of Crystallography, and ‘why not?’ since our turn will surely come round again, let’s say at the bicentennial in 2112, what might we see then?

The databases are a reflection of the state of crystal structure analysis and a health metric is the time period over which a doubling of their entries occurs. If we assume a doubling period of 10 years, then in 100 years from now, a theoretical 2^{10} multiplication of entries would promise, if realized, an obviously amazing increase. In terms of the methods of macromolecular de novo crystal structure determination, the last 20 years researchers have veered away from multiple isomorphous replacements through multi-wavelength anomalous dispersion methods of phase determination to, today, molecular replacement being predominant. This trend seems set to continue. I continue to believe however in the vital importance of the use of resonant scattering in phase determination for macromolecules and for precise element identification in chemical crystallography (especially mixed metal sites) and in biological crystallography whether using synchrotron radiation or in the newcomer on the block, the X-ray laser.

In terms of database contents, given the myriad number of proteins, their complexes and their ligands as well as their permutations and combinations that are possible, there apparently will be no limit to the number of new crystal structures. There will only be a limit set by our ingenuity at automation of all the steps of a crystal structure determination. Finally, the number of time-resolved crystallography studies is increasing, and albeit special cases, nevertheless, give a remarkable insight from experiment into the molecular dynamics stimulated by light or other reaction initiators in the crystal. There is a synergy of such experimental and computational molecular dynamics. Indeed as computational simulations stretch now to microsecond time scales, the link of these to help explain the diffuse scattering from a crystal should revive, and hopefully in earnest.

The limitations of needing a crystal are also changing. For the large biological complexes, single particle cryo-electron microscopy is seeing a spurt of development though improved sensitivity electron detectors and the jitter-blurring in the EM images being correctable by adjusting the spatial alignment of recorded timeframes. The X-ray laser has moved through increasingly smaller and smaller samples towards the vision of single molecule diffraction, and which is still a declared objective of those facilities.

In the objective of realizing a biological structure, complete with its hydrogen atoms via neutron protein crystallography, the traditional challenge has been the need for relatively big protein crystals. This need has steadily reduced as initiatives in the methods such as using the white beam of emitted neutrons have helped as well as microbiological protein expression on fully deuterated media have basically doubled the number of significantly scattering atoms (i.e. the effect that deuterium scatters as well as carbon). Assessments of the possible changes to protein structure and/or the ionization properties of deuteration have been examined in a wide range of cases and found hardly ever to occur. (The kinetics of deuterated chemistries is affected obviously as deuterium is heavier than hydrogen.)

Crystallisation methods, which obviously underpin all that we do as crystallographers, have steadily improved too in the last decades. Thus, whilst in the past, protein crystal growth was typically known as a ‘black art’, it has become a scientific and technologically adept area of science.

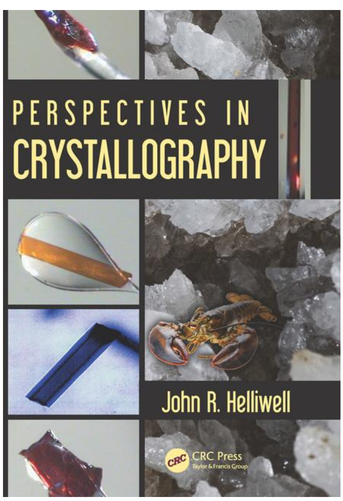
Closely related to crystallography are the complementary methods involving scattering from solutions of macromolecules: Small Angle X-ray and Small Angle Neutron Scattering (SAXS and SANS) methods. Thus, overall details such as the radius and shape of a macromolecule can be determined. Time-resolved studies are most readily done in the solution state, i.e. where large conformational changes are possible. The neutrons case, SANS, can also harness so-called contrast variation by varying the percentage of heavy and light water or by partial deuteration of a complex of protein and nucleic acid.

A further method is used to study the fine details of metalloproteins, namely, X-ray absorption spectroscopy (XAS), i.e. with the X-ray wavelength tuned to the X-ray absorption edge of the inherent metal atom. The XAS signal from the metal is exquisitely sensitive to the immediate neighbouring ligand atoms to the metal atom and also requires relatively small X-ray doses to measure the X-ray spectrum. A modern case is the study by XAS and by X-ray crystallography of the photosynthesis protein ‘PSII’ and its cluster of manganese atoms (the ‘oxygen-evolving complex’) at the heart of its catalytic splitting of water; these two techniques have yielded complementary information.

In a look-back of the last 100 years, it is widely stated that the X-ray fibre diffraction studies of DNA and the subsequent molecular model for the double helix and its explanation of the basis of heredity was the most exciting breakthrough of twentieth century science. Therefore, that scientific discovery and its discoverers (Watson and Crick) surely rival the stature of Isaac Newton and the theory of gravitation. In 2112, what might we as crystallographers have to offer the competition of ‘best discovery’ of the next 100 years? That choice I leave to the reader of this book to contemplate, but I think it safe to assume that we crystallographers will be taking part in that competition. Crystallography has a very bright future.

3

Crystallography and Sustainability



Crystallography and sustainability

8.1 INTRODUCTION

First, what is 'sustainability'? Wikipedia provides a readily available and helpful description.

'In ecology, *sustainability* is how biological systems remain diverse and productive.'

Wikipedia provides further details:

'The world's sustainable development goals are integrated into the eight *Millennium Development Goals (MDGs)* that were established in 2000 following the Millennium Summit of the United Nations. Adopted by the 189 United Nations member states at the time and more than twenty international organizations, these goals were advanced to help achieve the following sustainable development standards by 2015:

1. To eradicate extreme poverty and hunger
2. To achieve universal primary education
3. To promote gender equality and empower women
4. To reduce child mortality
5. To improve maternal health
6. To combat HIV/AIDS, malaria and other diseases
7. To ensure environmental sustainability
8. To develop a global partnership for development

According to the data that member countries represented to the United Nations, Cuba was the only nation in the world in 2006 that met the World Wide Fund for Nature's definition of sustainable development, with an ecological footprint of less than 1.8 ha per capita, 1.5, and a Human Development Index of over 0.8, 0.855.'[†]

Crystallography most obviously is assisting with goal 6. Examples and case studies are cited in Appendix 8.B of this chapter.

Furthermore, crystallography has, since its earliest period when William Henry Bragg had a substantial fraction of his research students being female, had an excellent proportion of its researchers being female relative to other areas of science. These included Kathleen Lonsdale, Dorothy Hodgkin and Sine Larsen as female Presidents of the International Union of Crystallography (1966, 1981–1984 and 2008–2011 respectively), and up to Nobel Prize winner level with Dorothy Hodgkin (Nobel Prize in Chemistry 1964) and Ada Yonath (Nobel Prize in Chemistry 2009). Crystallography research therefore has assisted in goal 3. I have endeavoured to assist in this process via my work as Gender Equality Champion at the School of Chemistry in the University of Manchester via the Athena SWAN framework of the UK Government's Equality Challenge Unit.

† World failing on sustainable development.

Goal 2: Assisting the realization of the goal *To achieve universal primary education*, is less easy perhaps as crystallography is in its details built around the core sciences and mathematics. However, as I have described in Chapter 1, this is not an impediment in finding ways of reaching out to the Public and to school children. ‘Primary education’ however presumably means ‘reading, writing and arithmetic’ basic skills. When I started my enquiries about giving a lecture on crystallography in prisons, I was alerted to the quite often low education skills I might expect in my audience. As I have yet not managed to give a lecture to this audience, my practical knowledge of how to proceed is at the embryonic stage. My ideas include to especially take advantage of the highly visual materials that one has available especially crystals (calcite, quartz and so on) and molecular models.

8.2 RESEARCH EXAMPLES RELEVANT TO SOCIETY

In the lecture that I prepared with Brian McMahon of the International Union of Crystallography in Chester, United Kingdom, for the New Delhi CODATA 2014 Congress and General Assembly (see Figure 8.1 for the conference banner headline), we summarised the topic:

Sustainability of life and molecular crystallography 3D data

We focussed on crystallography’s role in improving health and efficient energy usage which are and can be increasingly at the molecular level based on crystal structure analyses. In health sciences, structure-based drug design is routinely employed; in energy research, hydrogen storage is addressed also using 3D atomic structures. Thus, crystallography has an important role within the topic of the sustainability of Life.

A key part of this process of broad applicability rests on world wide access to the three-dimensional (3D) structures database of biological macromolecules (Protein Data Bank) and the chemical crystallography databases (CCDC, ICDD, COD, Metals). These provide fantastic resources spanning a vast range of the living and material world in atomic detail. The tools of physics (X-rays, neutrons and electrons in diffraction, microscopies and spectroscopies) allow us to determine and study in detail these structures and their atomic interactions. Clear technical understanding of these physical methods provides clarity on how much trust we can place in the correctness of these structures, i.e. their precision and accuracy.

Furthermore, life under ‘normal’ and extreme conditions can be reliably compared: hot springs, high saline and extreme cold examples of protein crystal structures have been determined. It is a natural next step to understand the effects of pollution; a simple example is the binding of nitrates that would come from excessive use of such fertilisers.

Crystallography has a long tradition in community methods development, and in sharing derived and processed data at the databases referred to above. Research journals in this field have long provided links to derived datasets (molecular structures), and in more recent years to processed experimental data (single crystal X-ray structure factors and powder diffraction profiles), and in turn, there have been links from curated datasets in structural databases back to the associated publication.

The journals have *stringent requirements* that articles will only be published with the accompanying data and/or, in the life sciences, Protein Data Bank deposition files (derived coordinates and processed structure factor amplitudes). At the submission stage of an article, information should be provided to convince the referees that the interpretations of the diffraction data and electron-density

FIGURE 8.1 The conference banner for the CODATA conference 2014.

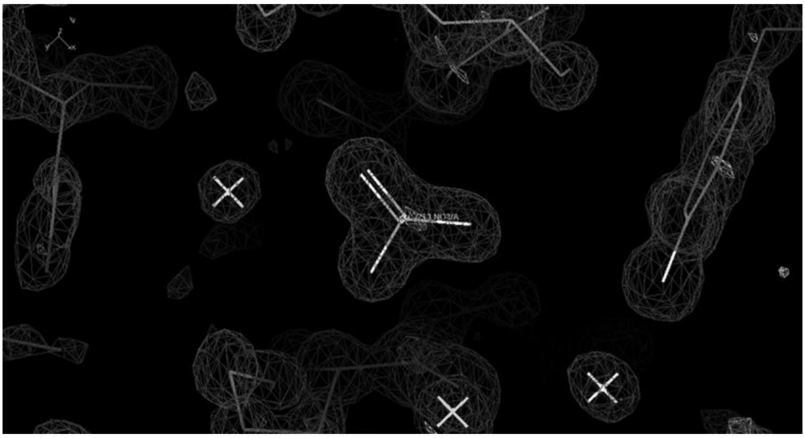


FIGURE 8.2 (See colour insert.) Discrete nitrate ion binding to a protein surface. In this molecular graphics representation, the blue mesh is the electron density derived from the X-ray diffraction from a single crystal of a protein (lysozyme in a triclinic crystal form). The interpretation of this in terms of chemistry then can readily be made: on the left, a nitrate ion and on the right, a tyrosine amino acid.

maps and/or structures are correct, within the resolution of the analysis; in the life sciences, a Protein Data Bank structure validation report is also required on submission. Dataset requirement *recommendations* exist for articles that present experimental small-angle X-ray or neutron scattering data. For these, the deposition of an ASCII file representing the background-corrected scattering profile(s) with errors is recommended. For powder diffraction, articles that present the results of powder diffraction profile fitting or refinement (Rietveld) methods require deposition of the primary diffraction data, i.e. the numerical intensity of each measured point on the profile as a function of scattering angle. For the chemical sciences (which obviously includes many small-molecule ligands of biological macromolecules), the requirements on derived coordinates and processed diffraction data are more stringent, and such data are held for example within the IUCr publication archive. For example, among the IUCr Journals that publish such data, this quote is typical: ‘Supporting information (such as experimental data, additional figures and multimedia content) that may be of use or interest to some readers but does not form part of the article itself will be made available from the IUCr archive. Arrangements have also been made for such information to be deposited, where appropriate, with other relevant databases’. The latest discussions within IUCr are now looking towards archiving of raw data and one of the first examples of such is described in Ref.. T*he Australian synchrotron data archive* ‘*Store.Synchrotron*’ *is an exemplar, whose work includes its support of users with publications having raw datasets, and its ability to manage digital object identifier (DOI) registration. This archive also releases raw diffraction image datasets for public analysis.*

The above description is fairly detailed, but it shows the rigorous efforts made by crystallographers to archive their results along with the metadata being provided as well to describe their data thoroughly. Preservation of data ensures the sustainability of the crystallographic research effort (along with the crystallographic science publications). This is proving an important role within extensive efforts to describe nanomaterials properly, essential for their rigorous safety description. There is a CODATA/VAMAS Joint Working Group on the Description of Nanomaterials from which I quote:

> Nanomaterials are complex, and researchers continue to develop new and innovative materials. Describing nanomaterials is a challenge for all user communities, but a description system is essential to ensure that everyone knows exactly which nanomaterial is being discussed, whether for research, regulatory, commercial, or other purposes.

CODATA and VAMAS, an international pre-standardization organization concerned with materials test methods, have set up a joint working group to help develop a uniform description system for nanomaterials. This international working group includes representatives from virtually every scientific and technical discipline involved in the development and use of nanomaterials, including physics, chemistry, materials science, pharmacology, toxicology, medicine, ecology, environmental science, nutrition, food science, crystallography, engineering, and more. Many international scientific unions actively participate. The IUCr is an active participant. Nanomaterials are one of the most actively pursued areas of modern day materials research.

A major feature of crystallography in the life sciences is the use of synchrotron radiation in macromolecular structure determination (see Appendix 8.B with impact case studies and publication examples).

8.3 CRYSTALLOGRAPHERS AND PEACE

It is striking to me that crystallographers have taken a prominent role trying to ensure Peace. There is surely a crucial role for sustainability of preserving peace; there surely should be a bullet point for World Peace in the United Nations' list quoted at the start of this Chapter!

Kathleen Lonsdale (President of the IUCr 1966) wrote a slim but powerfully argued book entitled *Is Peace Possible?*. She went to jail during the Second World War for her beliefs as a pacifist.

Dorothy Hodgkin was President of Pugwash from 1976 to 1988. The Pugwash Conferences on Science and World Affairs is an international organization that brings together scholars and public figures to work towards reducing the danger of armed conflict and to seek solutions to global security threats. In their *Dialogue Across Divides* they state:

> We have to learn to think in a new way. Pugwash seeks a world free of nuclear weapons and other weapons of mass destruction. We create opportunities for dialogue on the steps needed to achieve that end, focusing on areas where nuclear risks are present. Moving beyond rhetoric, we foster creative discussions on ways to increase the security of all sides in the affected regions. Remember your humanity, and forget the rest.

Linus Pauling won two Nobel Prizes, one for chemistry (1954) and one for Peace (1962). Linus Pauling was a great early practitioner of X-ray crystal structure analysis with a wide variety of his crystal structures featuring in his famous textbook on chemistry *The Nature of the Chemical Bond*. He also wrote *No More War* (1958) and specifically his concerns about the safety level limits set for radiation:

> I believe that the nations of the world that are carrying out the tests of nuclear weapons are sacrificing the lives of hundreds of thousands of people now living and of hundreds of thousands of unborn children, and that this sacrifice is unnecessary.

In the 1980s, I was at a dinner for early career scientists hosted by the then Secretary of State for Education, Kenneth Baker, and I sat next to his Principal Private Secretary Sir David Hancock (1934–2013). I explored the argument on Sir David of removing the Defence budget in favour of spending it instead on more scientific research. He replied to the effect that any such move, whilst impossible for any modern Government to contemplate, would not lead to more spending on scientific research but would be used instead to reduce taxes; sobering thoughts.

8.A APPENDIX: EXAMPLES OF THE SOCIAL AND ECONOMIC IMPACT OF CRYSTALLOGRAPHY: TOWARDS A MORE SUSTAINABLE FUTURE FOR LIFE ON EARTH

RCUK Analysis of the impact of SRS Protein Crystallography in Knowledge Transfer: Protein Crystallography at the Synchrotron Radiation Source (SRS), Daresbury Laboratory (1981–2008; Figures 8.3 and 8.4).

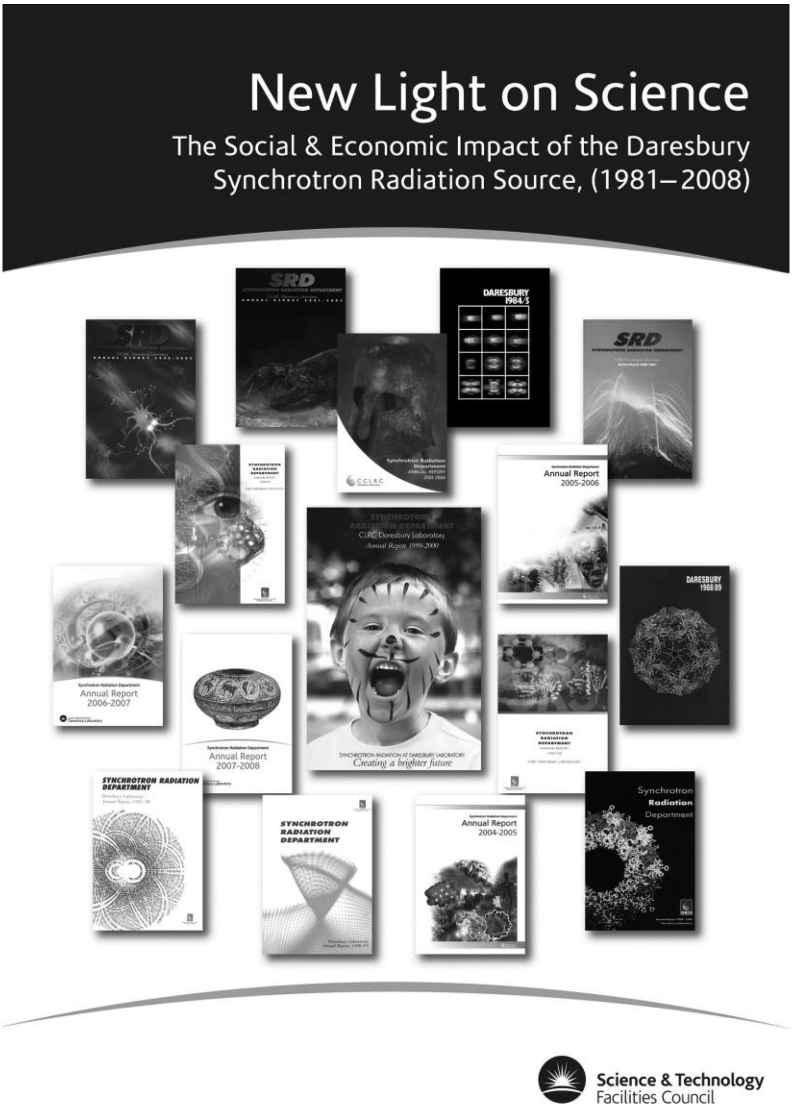
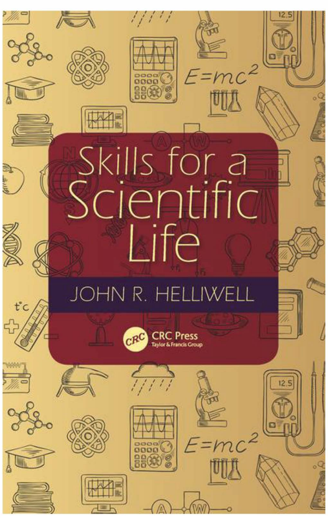


FIGURE 8.3 **(See colour insert.)** The UK's Science and Technology Facilities Council (STFC) undertook an analysis of the social and economic impact of the Daresbury Laboratory Synchrotron Radiation Source, which operated from 1981 to 2008; this figure shows the front cover of the report.

4

How Do You Know You Are Suited to be a Scientist



The following is excerpted from *Skills for a Scientific Life* *by John R. Helliwell* © 2016 Taylor & Francis Group. All rights reserved.

To purchase a copy, click here.

Section I

Introduction: How Do You Know You Are Suited to Be a Scientist

You may be a scientist already engaged in research, development and discovery. You may be a person considering starting science as a career. You may be at school deciding between science subjects versus arts and humanities subjects. This book will describe for you what science is like, including the successes, as well as the challenges, and yes, some trials and tribulations. In your wider reading about science as a career, you will encounter books that describe how the skills that you will learn are transferable skills, and that no doubt is true. But I will not be describing how you would get along as a scientist-with-skills become banker or accountant or computer employee or detective. As a scientist, you will naturally wish to see your discoveries put to good use, and for other discoveries, you will have no conception as to their application, as they may well be too fundamental and basic science to be applied yet. Your work as a scientist in all its forms will be important, if you are good at selecting what to work on. You know, or simply sense, that your own skills are not to be neglected. You may also be sceptical that the softer skills beyond your laboratory bench are relevant; nevertheless, take a look; you may well be surprised. At some point, I will need to state a caveat and may as well do it here at the start; my book is a guide and cannot offer you rules or recipes.

The thought 'how do you know you are suited to be a scientist' could well arise at two stages of your scientific career:

1. You are thinking of becoming a scientist, which can occur when you choose an undergraduate BSc degree course (or BA, as my alma mater, York University, would describe my degree in physics) or an even bigger step,

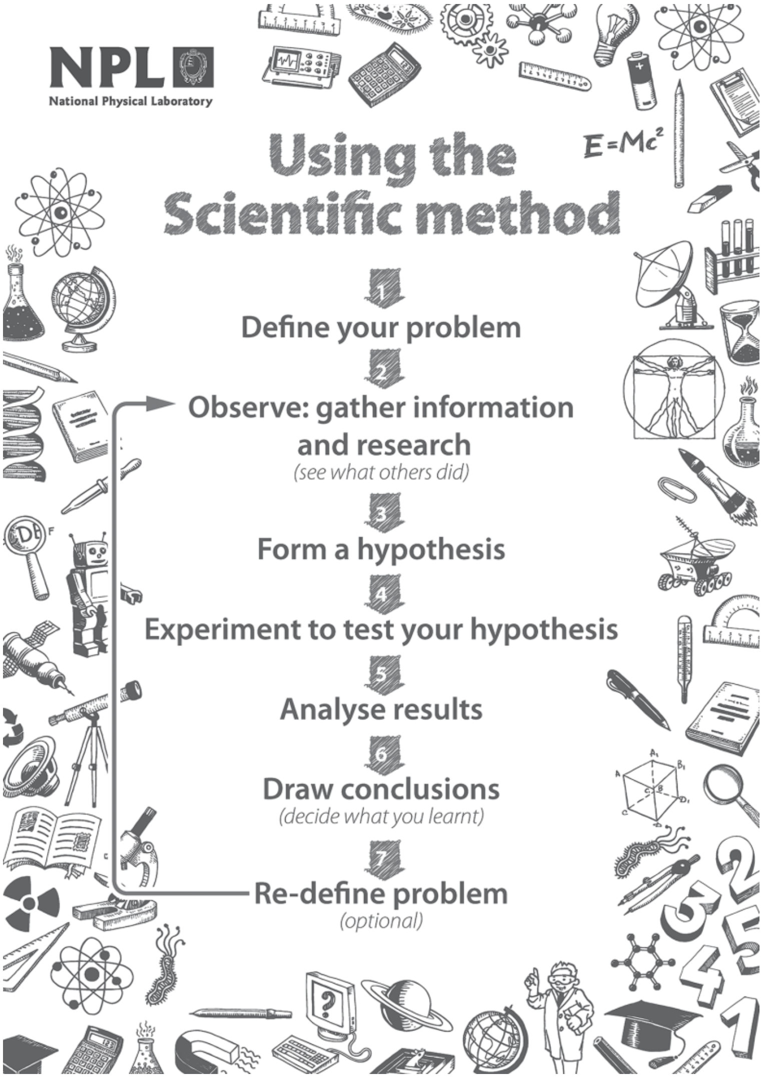
whether to undertake a PhD (or DPhil, as my alma mater, Oxford University, would have it).

2. You have doubts; this can be of the ‘I am not sure I am cut out for this’, which may arise during stressful challenges, especially if you or your laboratory make a mistake, or more likely if you are frustrated by a career ceiling, that is, when you cannot secure promotion especially if you have tried several times.

Suffice to say, are you naturally curious? Or a better way of putting it, are you curious about nature? If you are then, yes, you are suited to becoming a scientist. This is a fundamental point! You then need to assess your evidence of being good at science or mathematics.

In school, in England, I faced the usual specialisation decisions at age 15 and then at age 18. At 15 years old, one has to decide between arts and humanities subjects versus science and mathematics subjects. But I straddled both! My slightly better subjects were history, geography and mathematics. A crucially timed parents evening, which I attended with my parents, led to a crucial decision; the careers adviser, who was especially on duty for the parents evening, advised us that there was a much better chance of a job in chemistry. We discussed this back home, and so I chose chemistry, mathematics and physics. My general studies were fortunately not abandoned, as the school policy was to also have pupils undertake a general studies curriculum, although I quickly found that a better way of learning this subject was to read a quality Sunday newspaper each week. The career adviser not only was commenting on the buoyancy of the British chemicals industry, which therefore provided good job opportunities, but also had a gleam in his eye that I might receive my school senior chemistry prize when I was 17 years old, which I did. At that age pupils then have to choose a university degree subject, and I chose physics, this time fascinated by the role of mathematics in its formulations and interpretations of the natural world. The University of York awarded me a first class honours degree in physics in 1974. My doctorate was in molecular biophysics, and the laboratory of my supervisor was based in the psychology/zoology building of Oxford University. Subsequently, I did hold faculty positions in the physics departments at Keele University and later back at York University, totalling seven years. But guess what, in 1989, I was promoted to a professorship, in chemistry, and served in that role until my (semi-)retirement in 2012. I suppose I can rationalise that I steadily worked against the forces of specialisation during the whole of my scientific life. How did I continue my strong interests in history and in geography you wonder? For history, I enjoy reading political autobiographies, and for geography, I enjoy travelling, which has included much of the whole globe. Academic training is necessary for a career in science, but it is not sufficient for you to know if you will really follow a career of scientific research and discovery. One of the crucial options for deciding that comes with the first job after the doctorate, namely the postdoctoral post. Not least, it will be your first salaried position, and your success in it will determine if you embark on a scientific research life’s work.

A unifying aspect for any stage of our science interests and development, from school days through to retirement, is to reflect on what the scientific method is. The National Physical Laboratory based at Teddington, United Kingdom, has an explanatory card describing the scientific method, which I reproduce with their permission. They also have an extensive, helpful website on a wide range of scientific topics, for those coming to this book from any background and who are curious about this activity called *science*.



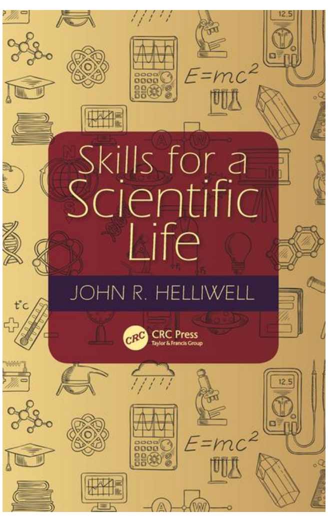
(Courtesy of the NPL.)

Figure: The National Physical Laboratory (NPL) based at Teddington, United Kingdom, has this lovely card explaining the scientific method. Notice of course the beautiful iconic scientific images decorating the words.

Overall, we can join the wonderful process of science and discovery. If we hone our skills to the best possible, we contribute as fully as we can to a scientific life.

5

How to Retain Your Own Peace of Mind: The Ethical Aspects



How to Retain Your Own Peace of Mind *The Ethical Aspects*

Integrity without knowledge is weak and useless, and knowledge without integrity is dangerous and dreadful.

Samuel Johnson
The History of Rasselas, Prince of Abyssinia (now Ethiopia)

I have something that I call my Golden Rule. It goes something like this: Do unto others twenty-five percent better than you expect them to do unto you. … The twenty-five percent is for error.

Linus Pauling
His reply to an audience question about his ethical system, following his lecture circa 1961 at Monterey Peninsula College, California

There are two aspects to ethics in science I wish to deal with. Firstly, there are the ethical implications of (some) scientific discoveries. Secondly, there are the ethics of how we respect other scientists.

Perhaps the most well-known example of scientists wrestling with the ethical aspects of a discovery is the physics behind the critical mass of uranium needed to sustain a chain reaction and thereby a nuclear explosion. The counterpoint to this new science implication was the knowledge that this was also a new source of con- trolled production of our energy supplies. On the perils of Germany developing the first atomic bomb, Einstein signed a letter drafted by Szilard to the then president of the United States, Franklin D. Roosevelt, on 2 August 1939, commending that research be undertaken to enable this to be achieved first by the Allies, rather than the Nazis. Einstein later expressed regret that he had signed the letter. In response to the Einstein–Szilard letter to him, President Roosevelt established an advisory committee, and whose recommendations developed into the Manhattan project to develop such a weapon led by J. Robert Oppenheimer (1904–1967) who was

> an American theoretical physicist and professor of physics at the University of California, Berkeley. As the wartime head of the Los Alamos Laboratory, Oppenheimer is among those who are called the 'father of the atomic bomb' for their role in the Manhattan Project, the World War II project that developed the first nuclear weapons that ended the war with the atomic bombings of Hiroshima and Nagasaki. The first atomic bomb was detonated on July 16, 1945, in the Trinity test in New Mexico; Oppenheimer remarked later that it brought to mind words from the Bhagavad Gita: 'Now I am become Death, the destroyer of worlds'.

After the war Oppenheimer became chairman of the influential General Advisory Committee of the newly created United States Atomic Energy Commission, and used that position to lobby for international control of nuclear power to avert nuclear proliferation and a nuclear arms race with the Soviet Union.

In a totally different field of science, genome editing, Professor Jennifer Doudna recently wrote about the ethical dimensions of her gene editing science and the potential it has, for example, for editing of human embryo genes, including her ethical concerns (quoted with the permission of Professor Doudna and from Macmillan Publishers Ltd):

> I am excited about the potential for genome engineering to have a positive impact on human life, and on our basic understanding of biological systems. Colleagues continue to e-mail me regularly about their work using CRISPR–Cas9 in different organisms – whether they are trying to create pest-resistant lettuce, fungal strains that have reduced pathogenicity or all sorts of human cell modifications that could one day eliminate diseases such as muscular dystrophy, cystic fibrosis or sickle-cell anaemia.

Professor Doudna also champions the need for scientists to engage with outreach to the public on the ethical consequences of their work (quoted with the permission of Professor Doudna and from Macmillan Publishers Ltd):

> But I also think that today's scientists could be better prepared to think about and shape the societal, ethical and ecological consequences of their work. Providing biology students with some training about how to discuss science with non-scientists – an education that I have never formally been given – could be transformative. At the very least, it would make future researchers feel better equipped for the task. Knowing how to craft a compelling 'elevator pitch' to describe a study's aims or how to gauge the motives of reporters and ensure that they convey accurate information in a news story could prove enormously valuable at some unexpected point in every researcher's life.

I was glad to meet Jennifer Doudna and enjoy dinner with her at the Argonne National Laboratory Guest House Restaurant in around 2005 when she had joined the Advanced Photon Source Science Advisory Committee.

Not many scientists confront so vividly such dramatic implications of their research as the two examples I have described above. However, for us all to study such examples as case studies is important. Also, as Professor Doudna champions, it is vital for us as scientists to be well prepared to face ethical questions, and how to do this should surely be a mandatory part of the skills training we receive. One thing is for sure, the discussions of the implications of scientific research discoveries will not be for us to define on our own, such discussions must include all constituents of society and, at the least, the society's elected representatives. Conversely, these elected representatives must include scientists in such debates to provide firm contact with the scientific facts. I also think that the scientists should be there on an equal footing, with voting rights, just the same as the politicians. This latter point is not necessarily accepted by politicians! Most famously, Winston Churchill remarked, 'Scientists should be on tap but not on top'.

On the second aspect of ethics, namely of how we respect other scientists, a source book of ideas that are quite fundamental about people, good and bad, is by Erich Fromm, philosopher and psychologist, *Man for Himself: A Psychology of Ethics* (1947). A few quotations from his book indicate the good that can come from being, well, good:

> Man's main task in life is to give birth to himself, to become what he potentially is. The most important product of his effort is his own personality.

Then Fromm takes the well-known saying 'Whatever you do to others, you also do to yourself'. And inverts it to

> *Do not do to others what you would not have them do to you.*

On good behaviour to others, he makes the insightful remark:

> No healthy person can help admiring, and being affected by, manifestations of decency, love and courage, for these are the forces on which his (one's) own life rests.

Fromm explains in detail the obverse case:

> (there are people) with an exploitative personality. . . . They use and exploit anybody and anything from whom or from which they can squeeze something. And furthermore that such people want to use and exploit people, they 'love' those who, explicitly or implicitly, are promising objects of exploitation, and get 'fed up' with persons whom they have squeezed out.

Fromm deals with the nurture versus nature aspects of the types of people mentioned earlier by separating temperament, namely what is in our genes, from character, namely what we make of ourselves. He also emphasises that people are in general a blend of good and bad, rather than extremes.

In the end, Fromm observes that 'the decision of what man makes of himself is man's'. Finally, Fromm cites the famous quotation of Plato which addresses the place of individuals within their external environment, namely society itself:

> Until philosophers are kings, or the kings and princes of this world have the spirit and power of philosophy, and political greatness and wisdom meet in one, and those commoner natures who pursue either to the exclusion of the other are compelled to stand aside, cities will never have rest from their evils, no, nor the human race, as I believe – and then only will this our State have a possibility of life and behold the light of day.

The psychology analyses of people by Fromm that I have described above are quite general. Let's now move on to specifically discuss the category of scientists. In 2007, the UK government's chief scientific advisor, Professor Sir David King, laid out a universal code of ethics for scientific researchers across the globe. The UK government has apparently adopted them, although it is not clear quite what that means in practice!

David King's seven principles of the universal code of ethics, intended to guide scientists' actions, are as follows:

1. Act with skill and care in all scientific work. Maintain up to date skills and assist their development in others.
2. Take steps to prevent corrupt practices and professional misconduct. Declare conflicts of interest.
3. Be alert to the ways in which research derives from and affects the work of other people, and respect the rights and reputations of others.
4. Ensure that your work is lawful and justified.
5. Minimise and justify any adverse effect your work may have on people, animals and the natural environment.
6. Seek to discuss the issues that science raises for society. Listen to the aspirations and concerns of others.
7. Do not knowingly mislead, or allow others to be misled, about scientific matters. Present and review scientific evidence, theory or interpretation honestly and accurately.

The details mentioned earlier involving people with whom you work with or meet clearly relate to other chapters in this book such as Chapter 6 (How to Set Up, Lead and Care for Your Research Team), Chapter 13 (How to Coexist with Competitors) and Chapter 15 (How, and When, to Effect Collaborations). However, so much of what you yourself do, and how you conduct yourself, relates to this chapter!

The code of principles covers good practice. Let us also consider the obverse and ask what, formally, research malpractice is. As an elected representative of the Faculty of Science and Engineering to the Senate of the University of Manchester, I took part in the discussion, the amendments and the final approval of the university's policy on research malpractice. This important document had as core elements the definition of misconduct in research, the categories of poor research practice and the categories of research misconduct. The policy of the university covered many types of research both in detail and overall. While I have not been involved in experiments on animals or humans, the points relating to such experiments looked to me reasonable, as they were also to the medical academics on the university. One area that particularly caught my eye, since I have a heavy reliance in my crystallographic research on experimental raw data, processed data and final derived data, was the category of research misconduct relating to data namely 'Mismanagement or inadequate preservation of data and/or primary materials'. While crystallographers, particle physicists, astronomers, climate change specialists and genome sequence researchers, for example, are well known for their efforts to preserve, and ensure access to their data, I was aware of less good practice more generally, but that is certainly changing. In the United Kingdom, this is, for example, through the fine efforts of the Digital Curation Centre and internationally through the International Council for Science's CODATA and the Research Data Alliance. Locally, the University of Manchester now ensures preservation of data and publications by its researchers, via its eScholar* web tool administered by the university library.

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* eScholar at the University of Manchester is being updated to the new system PURE.

One of the very specific areas to which ethics applies involves publications. Very generally, as Wikipedia states, publication ethics is ‘the set of principles that guide the writing and publishing process for all professional publications’. Most obviously, it should be ensured that a publication is not plagiarised in whole or in part. This covers not only plagiarism of another’s work but also self-plagiarism, namely the reuse of text, figures, tables or your data in more than one of your publications. The area of publication ethics is, however, more multifaceted than plagiarism, and cases can be quite complex. An organisation called the COPE exists, which provides ‘a forum for editors and publishers of peer reviewed journals to discuss all aspects of publication ethics. It also advises editors on how to handle cases of research and publication misconduct’. A resource that COPE provides is a whole suite of cases; at the time of writing, there were 531 cases listed! COPE also assists the readers of their case studies in providing a case taxonomy. At the time of writing, this comprises 18 main classification categories and 100 keywords. These categories, slightly expanded by me for clarity and or inclusiveness of relevant topics, are as follows:

> Authorship; Conflicts of interest; Consent for publication; Contributorship; Copyright disputes/breaches; Correction of the literature; Data; Editorial independence; Funding/ sponsorship; Impact Factor manipulation and metrics; Books, social media and legal issues; Misconduct/questionable behaviour by the author(s), by a journal, by an editor, by a publisher, by an institution or by a reviewer; Mistakes; Peer review and/or editorial decisions; Plagiarism; Questionable or unethical research; Redundant/duplicate publication or multiple submissions; Responding to whistle blowers.

As an example of the perspectives of a publisher, the International Union of Crystallography, for which I served nine years as Editor-in-Chief, its ethical publishing policy is described in Reference 9. Within this policy is the practical tool that can be deployed by a publisher to help publishers screen articles for plagiarism.

As a second publisher perspective, I mention Taylor & Francis, as I have served for 10 years as a main editor of one of their journals, *Crystallography Reviews*, and for the last 3 years, as the sole main editor. Their publication ethics policy is described in Reference 11. They also offer an infographic for authors and a useful checklist, which I reproduce below, also with Taylor & Francis’ permission:

“Ready to submit your paper? Your ethics checklist Before you submit,
make sure:

i. You’ve read the journal’s instructions for authors, and checked and followed any instructions regarding data sets, ethics approval, or statements.
ii. All authors have been named on the paper, and the online submission form.
iii. All material has been referenced in the text clearly and thoroughly.
iv. Data have been carefully checked and any supplemental data required by the journal included.
v. Any relevant interests have been declared to the journal.
vi. You’ve obtained (written) permission to reuse any figures, tables, and data sets.
vii. You’ve only submitted the paper to one journal at a time.
viii. You’ve notified all the co-authors that the paper has been submitted.”

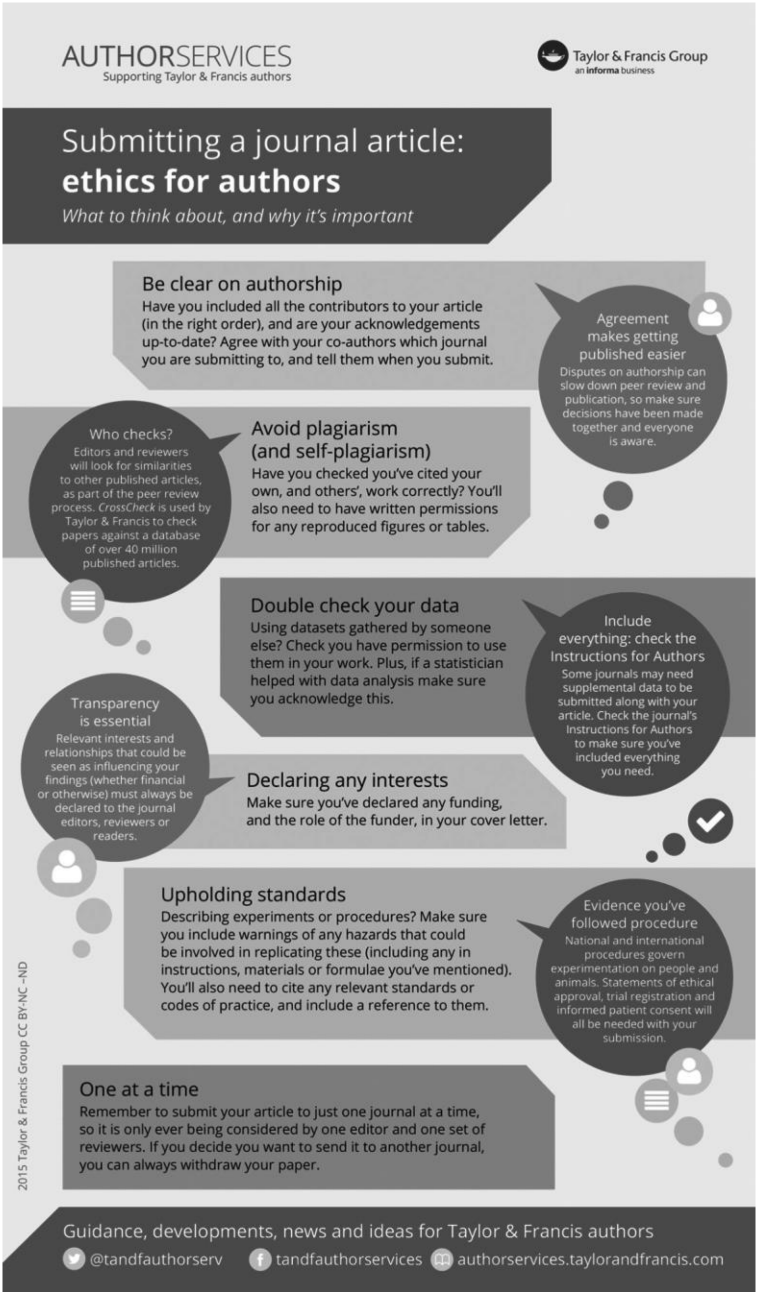


FIGURE 31.1 Taylor & Francis's ethics for authors' guidance before submission of an article. (Reproduced with the permission of Taylor & Francis.)

One aspect that editors, referees and journals are not so successful at monitoring is the comprehensiveness of the citations of relevant references in a research article. Authors, if queried, usually in my experience respond well to suggestions in referees' reports to cite new references and/or state why the suggested new references are not relevant. But this is a haphazard business in my view, and citation tools could surely be harnessed to assist the editor and the referees to ensure a better coverage of relevant literature. As an objective measure of the problem, I will mention the journal citation half-life metric. The cited half-life is the number of publication years accounting for half of the citations received. Formally, this is portrayed as 'an indicator of the turnover rate for a body of work on a subject', and partly, this is no doubt true, but I think it also reflects the memory span of the authors, the referees and the editors and thereby what goes into the article reference lists!

While publications or publication practices that are unethical get exposed sooner or later, a different area of our scientific life is that of research grant proposals, which involves much less transparent procedures. By this I mean that the proposal is unlikely to be openly published, although increasingly a summary of what has been funded is now often available. Here a proposal that is turned down for good reasons, or the quite usual modern situation, 'insufficient funds albeit of international quality', is vulnerable to malpractice. What do I mean by this? A funding agency must turn to experts for referee reports, and in turn, experts may well be, sooner or later, competitors. I have had a situation where it did seem a remarkable coincidence to me to witness a publication on the very area that I had previously proposed coming from a lab where it seemed, in retrospect, that the lab would also have likely been a referee of my proposal. As Fromm observed, there are exploitative people out there. Nobel Prize Winner Bill Lipscomb in the *New York Times*, quoted by Henry Bauer, stated that '(I) no longer put my most original ideas in my research proposals, which are read by many referees and officials. I hold back anything that another investigator might hop on and carry out. When I was starting out, people respected each other's research more than they do today, and there was less stealing of ideas'. Sobering thoughts! But would Bill Lipscomb's approach work today? Lipscomb had a Nobel Prize then, had all the prestige in the world, could write a research grant on basically anything and get funded (and remember that those were the days of 30–40% research grant success rates anyway versus today of around 10–15%). So his model would simply not work in today's research world. With research grant success rates at 10% as a principal investigator (PI), one has to place the best foot forward and reveal one's ideas and plans every time if you want your lab to be funded. I recently attended a lecture by someone whose research in chemistry had strayed into an area, he said, where it was well known as being done by 'an ocean of sharks'! Afterwards, I asked the lecturer what skills or tactics he had deployed in handling the ocean of sharks to which he had referred?! He said he had been lucky as it was not a research grant proposal, rather an unfunded off shoot of another work in his lab. In the publication, his emphasis was to avoid the main keywords that would have suggested to a journal editor to approach one of the sharks. The sharks were thereby avoided!

Overall, probably the way to deal with 'sharks' is to have enough ideas, and enough active research, so that if you get bitten, you can still swim.

In summary, the descriptions mentioned earlier give the necessary guidelines, and indeed laws of the land, for a scientific researcher from my perspective at a leading research university and of two publishers of science that I know well. In addition, my remarks provide a wider context, including my quoting the point of view of a psychologist, Erich Fromm, with an emphasis on how it can go wrong in part or in whole! In any field of scientific research, there will be some degree of problems of fabricated data and results as evidenced by withdrawal of publication by a journal, such cases being often without the authors' consent, and who seemingly have just disappeared! Fortunately, such cases in any field and across the whole of science are very rare. But let us now ask what success would look like in a truly ethical scientific landscape. For this, we must of necessity look to highly regarded individuals. I leave it to you the reader to identify those individuals who in your impression in your field of research behave ethically. As measures, you can check, for example:

1. Do they cite their own lab members carefully in their talks?
2. Do their publications cite the relevant scientific literature, which you will know well the more so as your career progresses and your experience deepens?
3. Do their publications include the relevant data to substantiate their words?

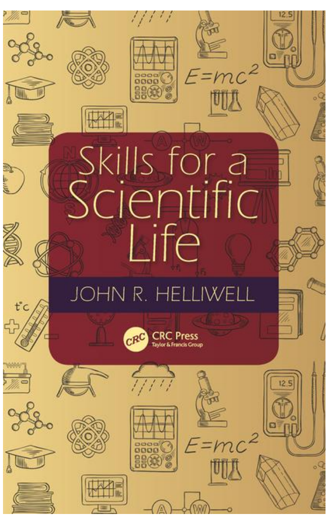
No person is an island, and it is on this simple but important foundation that our ethics in my opinion basically rests. You must therefore develop your feeling and sensitivity to others, while respecting of course your own dreams and visions for your science. You should also not be afraid to assert your views if someone treats you unethically, but if so, you will need to proceed with tact and with clarity of your evidence in your mind.

Organisations and indeed even possibly your employer may act unethically. Receipt of funds from dubious individuals or companies seeking special treatment at your institution are the most obvious cases to voice your opposition about. But internally to an organisation, there are, to me, some strange behaviours that can manifest: For instance, how would you view the writing of documents by staff for their line manager, whose name alone then appears on that document? I view the matter with dissatisfaction. Secondly, how would you view a facility or a research proposal from one laboratory, which is approved, but then for other reasons, for example, regional geography, is forced to be undertaken elsewhere? In the end, you will have to be true to yourself, and those that depend on you, to decide how to proceed on such matters, which can be exceedingly awkward in practice, although clear in the principles.

A book that presents real life case studies of ethical violations in the history of science, whilst providing a firm basis for discussing them, is by D'Angelo. As your own overall guide, I commend that you trust your conscience and by which means you should be able to retain your own peace of mind in your work and your life.

6

How Would You Change the Organisation of Global Science If You Were in Charge for One Day



How Would You Change the Organisation of Global Science If You Were in Charge for One Day

This is your chance to make a wish for improving the world's science! I would pick the following wishes:

1. I propose an open access publications fund for unfunded research.

This would be relevant to those grant proposals that the world's funding agencies judged were fundable in principle, for example, with grades that were outstanding or internationally excellent, but left unfunded because an agency sadly had no more research funds available. In my experience as principal investigator (PI), I try and find some way to take the research forward, for example, in some restricted form financially and in a longer time than proposed. Finally, at the time of publication, the original funding agency could be recontacted by the PI, and the funding agency would be invited to pay the open access fees of the publication from a special fund that would be set aside for the purpose. My point being that open access for one's publications is great, but to do that, you need the monies to pay for it, and for unfunded research, that is likely to be problematic. While the funding agencies contemplate that, then we can use those preprint servers that can provide free open access publishing with a digital object identifier (DOI). Such preprint servers are not a traditional journal with the usual peer review but provide a home for a real, citable open access paper.

2. I propose that all submitted science research articles be accompanied with their data.

The quality of the research publications, and the database deposits that should accompany a published article, would thereby improve, as the referees of course would have access to the data as well as the words of the article; this would be obligatory because the publication would then de facto be words and data. Moreover, the reader of the article, and thereby the potential user of the data accompanying the article, would not have to take the word of the authors for it; the reader/user could repeat the calculations for themselves. The motto of every journal should be 'Do not just take the authors' word for it'. In the past, there has been a possible argument of mitigation that the primary experimental data sets were too large to archive, and only the processed data and the final derived data from that processed data could be archived. With the marvellous improvement of computer disc storage capacities and centralised data stores, even commercially available, the need to delete/lose/not keep the raw data for a given experiment is now very often not necessary. Moreover, the registration of a data set with its own DOI, and clear guidance for citation of data sets through the leadership of the ICSU's CODATA, means that a data set is as much an important piece of knowledge as a publication's words. Also, repeat analyses with a data set may well be with improved software algorithms compared to the software used at the original date of the analysis and the publication, and so our scientific culture should encourage, indeed require, all submitted science research articles be accompanied with their data.

3. I propose that all scientists to give some of their time towards world peace and sustainability.

I wish for all scientists to take part in tackling world peace and sustainability. There are many ways for you to make a contribution. In my own research field, two prominent, capacity-building cooperative projects include the Middle East Synchrotron and the proposed African Synchrotron Light Source. These new facili- ties illustrate the importance of a sufficiently peaceful world and environment for research, pure and applied, for the benefit of all humankind. In sustaining a peaceful world, prominent scientists from the last century, such as Lawrence Bragg, Kathleen Lonsdale, Linus Pauling, Dorothy Hodgkin and many others, made enormous contributions to world peace, both within unavoidable war and against avoidable wars. The United Nations and the United Nations Educational, Scientific and Cultural Organization International Science Years, most recently, the International Year of Crystallography and the International Year of Light, with their numerous activities, successfully brought scientific results to society at large and other research com- munities. The peaceful movement of scientists to labs for training and research collaboration should be encouraged. ICSU's free circulation of scientists statute must also be adhered to. These are examples of sustaining our contributions to research and societal challenges. I offer my own review and thoughts for my own research field of crystallography and sustainability in Reference 1. There are therefore many activities that you can take part in as a scientist to help with global sustainability and world peace.

So what would you wish to change in the organisation of global science?