GUY DODSON

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Guy Dodson’s scientific reputation is based on his seminal contributions to linking chemistry and biology through analyses of three-dimensional structures elucidated by crystallography. He inspired and supported the development of new methods to determine structure, to relate structure to chemical mechanism and to embed structural insights into the lexicon of biological research. He began his career working with Dorothy Hodgkin, at the University of Oxford, and in later life he set up two very successful structural biology laboratories, at the University of York and then at the National Institute of Medical Research, Mill Hill. He is particularly remembered for his research into improving insulin therapy, based on modifications suggested by structural insights. He showed early recognition of how to build synergy in industrial collaborations that led both to fundamental scientific discoveries and to the development of new medicines and products to benefit society. He is also remembered for the enthusiasm he brought to these studies, for the pleasure he got, and gave, from the successes of others, and his generosity of spirit.

EARLY LIFE IN NEW ZEALAND

Guy’s parents, Francis and Molly, were Londoners. In 1927 his father had romantically chosen to migrate to New Zealand to join an Apiarist Training Program, a decision he claimed was made after glimpsing a floodlit poster in New Zealand House on a rainy evening as he was returning home from his job in a City bank. Molly followed him a year later. Financially, it was not a very wise move—they set up their first apiary in 1929, just as the Great Depression hit New Zealand agriculture. The next years were extremely challenging financially as they struggled to support themselves and their two young daughters, Anne and Deirdre. Francis

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continued to keep bees, however, while also accepting relief work on the roads, and in 1935 he was offered a position as instructor in apiary at Massey College in Palmerston North. This represented security at last, and their better fortune was crowned by the arrival of identical twin sons, Maurice and Guy, in January 1937.

World War II disturbed this idyll—Francis and Molly were devout Christians, and Francis volunteered to serve as a chaplain to the NZ Army. This took him to Auckland, and in 1944 the family followed him. The acute housing shortage meant that they lived with friends or in borrowed accommodation. Their difficulties were exacerbated when Francis was demobilized, without a job, but determined to remain in Auckland. Anne and Deirdre were now at secondary school, but housing two lively little boys was a challenge. In 1946 a partial solution presented itself. An Auckland philanthropist who had migrated from Ulster, James Dilworth, had endowed an ‘institution’ in Auckland to educate ‘orphan sons of Northern Irish fishermen who were prepared to emigrate to New Zealand and be educated in the Anglican faith’. Not surprisingly there were very few takers, so the remit was widened to accept needy orphans born in New Zealand, or sons of clergy or military personnel. The family was both needy and Anglican, so the boys were given a place.

It was a traumatic change for them—from home life to a boarding school environment with 134 boys aged 7–17 years. Most boys left school at 15, and only four were left in their senior year. The subject range included English, history, mathematics and chemistry. Guy was the chemistry lab boy and developed a love for ‘bangs and stinks’.

Both boys enjoyed sport, an important part of the school culture. A valuable part of Guy’s education derived from his position as captain of the First XI cricket team (figure 1). He planned matches in meticulous detail, exploited the strengths of the team and inspired them all with a fierce determination to win. Despite the relatively tiny number of pupils at Dilworth, they won the Auckland schools cricket championship in his final year. Maybe this provided excellent training for organizing a laboratory and taught him the importance of collaboration!

University days

In 1955 Guy and Maurice nervously enrolled at Auckland University. No family member had been to university and they had very little idea of what would be required. Their study choices were limited. They both enrolled to do sciences; Maurice chose mathematics, physics and chemistry, while Guy rather haphazardly chose chemistry and geology since he would have been required to pay a ‘late enrolment fee’ if he had chosen history—a subject he loved all his life. He was excited by the logical structures of physical reactions and by the precision of crystallography, so he subsequently enrolled as a postgraduate student in the chemical crystallography group, led by David Hall and Neil Waters.

The Auckland Chemistry Department had an active organic chemistry group specializing in characterization of native plant natural products. Guy’s PhD project was to solve the structure of a chloro-platinate derivative of an alkaloid extracted from Senecio kirkii, the New Zealand tree daisy. He struggled with the limited access to computation—calculations were either done by hand or sent to laboratories in Australia—but this gave him time to read the literature and learn the basics of crystallography. The structure solution used a method pioneered by Dorothy Hodgkin FRS (Nobel Prize 1964) for solving the first vitamin B12 molecule (Hodgkin et al. 1955). Phases were calculated from a heavy atom, and the light atoms were assigned to peaks.
Guy Dodson

Figure 1. Dilworth School First XI (1954). Guy centre front with cricket bats, Maurice to his left.

in the electron density which were consistent with known chemistry. Guy was thrilled by the B12 series of papers and talked so much about them that his supervisor finally said, ‘For goodness sake, WRITE to the bloody woman and see if she can use you as a postdoc.’ This he did, and by great good fortune it reached Dorothy on the day her colleague Marjorie Harding told her she would be resigning to move to Edinburgh. Dorothy promptly wrote back offering Guy a one-year postdoc, and off he set for Oxford.

**INSULIN: THE SEARCH FOR A STRUCTURE, OXFORD 1962–1969**

This period produced few publications but culminated in the determination of the insulin crystal structure. Many innovative crystallographic techniques were developed, and it is noteworthy that four internationally recognized structural laboratories have since been established by researchers working in Oxford during this period.

Guy arrived in January 1962, very uncertain of the laboratory protocols, or of how adequate his training would prove to be. Dorothy was instantly reassuring about formalities—‘we all use first names here, Guy’—but not so reassuring about his training; each person he was
introduced to seemed to have a first-class degree and some special skill. At that time the
laboratory and computing facilities were in Inorganic Chemistry, shared between Professor
‘Tiny’ Powell FRS and Dorothy. The group was international—Oxford research students,
scholarship holders from around the world, eminent crystallographers on sabbatical visits, and
former colleagues of Dorothy who would ‘drop by’ to discuss crystallographic conundrums.
The B12 research was still at the forefront of the laboratory efforts, and those working on
insulin were commonly regarded as hopeless optimists with no prospect of forging a career.
Before leaving New Zealand, Guy had asked to join this team, and although Dorothy offered
him the chance to rethink, he chose to opt for the riskier area of protein crystallography.

His first task was to read the papers outlining the principles of multiple isomorphous
replacement, the method used to obtain the crystal structures of myoglobin (Kendrew et al.
1958) and haemoglobin (Perutz et al. 1960). Different heavy atoms are incorporated into the
crystals, and phase estimates for each protein reflection are calculated using small intensity
differences between the native and derivative crystals. The challenge with insulin was to
obtain any such derivatives, as there were no reactive groups to bind metals, and the low
crystal solvent content made it hard to soak heavy atom compounds into the lattice.

Pure porcine insulin at that time was provided by the Danish pharmaceutical company,
Novo Terapeutisk. Their senior chemist, Jorgen Schlichtkrull, pioneered new crystallization
methods both to purify insulin from the pancreatic extract and also to provide a longer-lasting
treatment for diabetes. His crystals were hexameric, with six protomers, each composed of a
21-residue A-chain and a 30-residue B-chain assembled around two zinc ions that had to lie
on the three-fold axis (Schlichtkrull 1956a). He had also found that a solution with high NaCl
concentration produced a second crystal form with four zinc ions per hexamer (Schlichtkrull
1956b). These two forms are known as 2Zn and 4Zn insulin. As the 2Zn form diffracted better,
it was used for the subsequent structure studies.

The work was totally collaborative, although after 1964 when Dorothy was awarded the
Nobel Prize, Guy took increasing responsibility for the day-to-day organization of the group.
Eleanor McPherson (now Eleanor Dodson, FRS 2003) had joined the lab as a technician three
weeks before Guy’s arrival, and became responsible for much of the computing. Margaret
Adams was a gifted DPhil student working exclusively on insulin; Tom Blundell (later Sir
Thomas Blundell, FRS 1984) joined the team in 1967 after completing a DPhil with Tiny
Powell; Ted Baker also arrived in 1967 from Auckland Chemistry Department, officially to
run the Hilger–Watts 4-circle diffractometer, shared with David Phillips’ group (D. C. Phillips,
FRS 1967, later Baron Phillips of Ellesmere), but soon to be drawn into the insulin research
team; Mamannamana Vijayan joined in 1968 and took responsibility for collecting the best
data possible for insulin crystals and their heavy atom derivatives.

Progress was slow, but that encouraged exploration of new ideas, including those for
exploiting non-crystallographic symmetry, developed by David Blow (FRS 1972) and Michael
Rossmann (FRS 1984) (Rossmann & Blow 1962). They were developing methodology to
describe such symmetry, and insulin was their second test case. Both 2Zn and 4Zn crystals
had two molecules per asymmetric unit; and the analysis suggested that the 2Zn form was
a perfect hexamer, generated by a non-crystallographic two-fold axis that intersected the
crystallographic three-fold, while the 4Zn form had a slightly displaced two-fold axis (Dodson
E. et al. 1966). It was not clear then how to use this information to improve phasing, but
Michael Rossmann was convinced that it could be done, and indeed he went on to solve many
highly symmetric virus structures where the technique provided near-perfect phasing.
There was great interest in using anomalous scattering from heavy atoms to help with phasing—this had been observed from vitamin B12 crystals—and the presence of detectable anomalous scattering in a protein diffraction pattern gave a good indication of heavy atom substitution. To exploit this phenomenon, measurements had to be sufficiently accurate, and Guy became focused on careful data collection as the group developed theory and software to use the information for phasing calculations.

Another important development used a technique suggested by Björn Tilander and Bror Strandberg, who had extracted zinc from carbonic anhydrase crystals using ethylenediaminetetraacetic acid (EDTA) and then replaced it with other metal ions (Tilander et al. 1965). The same method worked for insulin crystals, and both lead and cadmium were introduced into the lattice as heavy atom derivatives. Guy carried out many tedious experiments before establishing the right conditions and finally succeeded in growing three sets of well-diffracting isomorphous crystals (a) with zinc, (b) without any metal, and (c) with lead replacing the zinc atoms. Most of these heavy atom sites lay on the three-fold axis, so did not yield sufficient phase information to solve the structure, but with help from Peter Bailey, a biochemistry graduate student at the time, a mercury benzaldehyde compound was prepared and soaked into the crystal. The diffraction pattern showed only weak substitution, but the anomalous dispersion was measurable, and proved sufficient to generate independent phases used to refine the parameters of the other heavy atoms. Tom Blundell produced a well-substituted uranyl fluoride derivative that gave good anomalous scattering and independent phase estimates for the low-resolution terms, so at last in early 1969 an interpretable low-resolution map was produced; by July a 2.8 Å map was calculated and hand-traced onto transparent sheets. These maps immediately showed a stretch of α-helix.

It took three heady days to trace the two molecules in the asymmetric unit, before Dorothy, followed by Guy, left for the 1969 International Union of Crystallography (IUCr) triennial meeting at Stony Brook, NY, USA, carrying hastily prepared figures, where Tom Blundell was able to present the first description of the 2Zn insulin molecule (1)* (Vijayan 2002).

**Insulin: analysing the results, Oxford 1970–1976**

Once the structure was more or less solved, the research emphasis shifted towards two new areas: improving the model and reviewing the extensive insulin biochemical and biological literature in the light of the structure. It was known that pro-insulin was produced in the islets of Langerhans in the pancreas, and that in the presence of zinc, it formed hexamers; that the connecting peptide was then cleaved to form the A- and B-chains; and that after entering the bloodstream it disassembled into dimers and monomers. This led to speculative models for receptor interactions with a monomer assumed to be the active form.

Dorothy was determined to optimize the quality of the insulin maps and she pushed the group into first collecting higher-resolution data, then developing refinement techniques. Neil Isaacs (later Joseph Black Professor of Chemistry in Glasgow) joined the laboratory in 1971, and together with John Rollett and Eleanor Dodson, cobbled together a refinement procedure that used X-ray difference maps to suggest corrections to the atom positions, and coupled this information with the imposition of sensible chemical restraints to the model’s geometry, thus

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* Numbers in this form refer to the bibliography at the end of the text.
This was an exciting period for protein crystallography—new techniques were developed and the software to exploit them written in collaboration with the Biophysics group led by Professor David Phillips. Individuals had responsibility for different tasks, but crystallographic routines were organized into libraries wherever possible, and data formats were standardized. This communal effort was formalized into CCP4 later in the 1970s.

Dan Mercola, a biochemist who had done his PhD with the diabetologist, Ed Arquilla, in California joined the laboratory in 1970. He was anxious to see how his predictions of insulin activity squared with the structure. With his guidance, the group embarked on in-depth studies of insulin’s role in endocrinology and biology, and wrote several reviews discussing the structure and biology of insulin (2, 3). By 1972, Ted and Heather Baker, and Vijayan and his wife, Kalyani, also a crystallographer, had left the lab, but Graham Bentley and John and Sue Cutfield (all from Auckland) had joined it.

This is probably the stage when Guy moved from ‘protein crystallographer’ to ‘structural biologist’. Insulin biochemistry was still not fully unravelled, but much was explained by the structure. There is an anecdote of Charles Tanford, a well-known protein biochemist, visiting the laboratory and saying in disgust—’You lot did not even KNOW there was speculation about tyrosine packing on the surface of the molecule, and yet you have answered questions I have spent years investigating.’ Important collaborations began; with Helmut Zahn’s group in Aachen who had synthesized insulin in 1963 (Meienhofer et al. 1963), particularly Axel Wollmer and Dietrich Brandenburg; with Don Steiner, the discoverer of pro-insulin (Steiner & Oyer 1967); and with several pharmaceutical firms producing therapeutic insulins—most notably with the Novo chemists who were anxious to understand their activity and the effect of additives such as protamine on insulin uptake.

The group became increasingly interested in the evolution of insulin. Fred Sanger FRS (Nobel Prize 1958) had determined the first sequence of a protein in 1953, viz. bovine insulin, from samples bought over the counter from Boots (Sanger & Tuppy 1951a,b; Sanger & Thompson 1953a,b). By the 1970s insulins from many other species had been sequenced and assayed, so by comparing these sequences and their relative activity it was possible to speculate about the role of some of the constituent amino acids, a form of rudimentary bioinformatics.

The 2Zn structure showed very small differences between the fold of the two protomers in the crystal asymmetric unit, probably due to the packing within the lattice. Various other crystal forms were known to exist (Harding et al. 1966), and, as these were solved, more light was shed on the puzzle of how the molecule folded and assembled, an example of early molecular dynamics.

Neither Zn-free pig insulin nor hagfish insulin, with 60% sequence identity to pig insulin and reduced activity, formed hexamers; both crystallized as dimers, but the overall fold of each monomer was very similar to that seen in the 2Zn structure.

Significantly different conformations were shown to exist in the hexamers containing four zinks, including very large rearrangements of the N-terminal residues of the B-chain which had moved by 23 Å. Even more surprising was that this shift could be triggered within a crystal without completely destroying it (4, 5). This showed that the molecule was extremely flexible, and that the active form could well differ significantly from the structure, particularly in the C-terminal region in the absence of the stabilizing dimer interactions.
Dorothy was approaching retirement age so her research group had to be wound down. Her legacy is illustrated in the many successful research groups established by her students and postdocs. The Dodsons, always the last to leave, found a new home in the Department of Chemistry at the University of York.

THE YORK STRUCTURAL BIOLOGY LABORATORY (YSBL), 1976–2012

In 1976 Guy was appointed as Lecturer in Chemistry with responsibility for teaching Biochemistry; a somewhat risky move by head of department, Dick Norman (FRS 1977) as Guy had essentially no experience of teaching undergraduates. But he did bring to the department a serious and internationally connected commitment to research. He believed passionately that crystal structures could help reveal fundamental truths about biochemistry and that it was the responsibility of crystallographers in collaboration with biologists to help bring this truth to the fore.

Many projects, often with societal implications, were pursued over the years. Some arose from ongoing collaborations with pharmaceutical companies: insulin with Novo, penicillin acylase with Glaxo, various enzymes with Novo and subsequently Novozymes. With new academic appointments, the laboratory grew to 60–70 members.

Much of the laboratory’s success depended on friendship. John Cutfield wrote after Guy’s death:

Looking back we realize how hard and how successfully Guy worked to bring people, projects and funding together. Constant rounds of grant applications, recruiting, mentoring, writing references, writing and reviewing papers, attending countless meetings, conferences, etc. He worked assiduously to support people and we count ourselves lucky to be included in that group.

Starting up, 1976–1981

In 1976 there was some official scepticism about the wisdom of establishing structural research in small laboratories outside the ‘Golden Triangle’. Any such group would require ‘wet’ laboratory space to prepare and crystallize macromolecules, equipment to record diffraction and access to computing hardware and software. For Guy, however, there were some very real advantages in York. There was already a noted Theoretical Crystallographic group in the Department of Physics, led by Professor Michael Woolfson (FRS 1984) and Dr Peter Main who had pioneered developments in Direct Methods to solve small molecules. The Department of Chemistry was supportive, the administrative staff were always willing to help, the skilled workshop technicians rose to the challenge of keeping equipment functional, and the Computing Service provided excellent advice and stretched the university’s, then somewhat limited, computing power to its full extent.

Initially, the work continued to focus on insulin. The department provided funds for a technician, Shirley Tolley, who ran the ‘wet’ lab until 1996. The Science Research Council (SRC) awarded a grant sufficient to transfer Dorothy’s 4-circle diffractometer from Oxford to York, to fund a postdoctoral fellow, Colin Reynolds, and to provide part-time support for Eleanor Dodson to establish computing facilities. Glaxo provided an important windfall; they had requested the insulin model coordinates and ‘paid’ for these by sending Guy a personal cheque for £5000. This provided the first of the very important ‘slush’ funds that
were administered by the university but were available without too many questions asked as needs arose. The ongoing collaborations with Axel Wollmer and Dietrich Brandenburg, with Don Steiner, and with several pharmaceutical firms producing therapeutic insulin, all transferred to York. In 1980 John and Sue Cutfield returned for a sabbatical year and flung themselves into further insulin research. Other sabbatical visitors made important contributions to getting the laboratory up and running, many already friends from Oxford. Neil Isaacs arrived in December 1976, funded by the SRC. He had already programmed Fast Fourier Refinement of insulin (Isaacs & Agarwal 1978) and during his time in York the scope of the program was extended and provided the template for the general structure refinement package soon to be incorporated into the CCP4 suite and used worldwide. Neil was also studying the hormone relaxin, which had 23% sequence identity to insulin with all the cysteine residues conserved. This led to one of the first papers describing homology modelling and helped trigger Guy’s commitment to the value of bioinformatics. As the authors claimed: ‘We have therefore rigorously examined the relaxin conformation by a computer graphics system and found it possible to accommodate the relaxin sequence within the insulin main-chain geometry’ (6). When the crystal structure of relaxin was finally published (Eigenbrot et al. 1991), the match to 2Zn insulin monomer was shown to be extremely close with an RMSD of 0.8 Å for 40 of the 50 Ca atoms.

Neil’s visit was followed in 1977 by Ted and Heather Baker and family who had eight months’ sabbatical leave from Palmerston North, New Zealand. They had solved a protein structure, actinidin (Baker 1977), and Guy had suggested they come to York to refine the coordinates. Eleanor and Ted struggled to generalize the software and were more than delighted when, after three months of bug fixing, the $R$ factor fell 10% at the first cycle (Baker & Dodson E. 1980).

Other visitors joined from the Chinese group at the Institute of Physics in Beijing, who had also solved an insulin structure in 1972. The International Union of Crystallography (IUCr) meeting in Warsaw in 1978 was the first international meeting that Chinese scientists were allowed to attend after the fall of the Gang of Four in 1976, and the group then came on to visit York and compare results. Friendships were established, and collaborations on insulin-related projects meant that many Chinese visitors came to York in the following years. Several were funded by the Royal Society as part of the post-cultural revolution thaw (7, 10, 12).

Serendipity brought several interesting projects to York, including the enzyme barnase (8) and haemoglobin (see below). The laboratory and university provided a welcoming environment, and Guy was known to be an excellent mentor; this led to numerous scientific visitors, young and old, having productive spells in York.

**New projects and funding, 1982 onwards**

In 1982 Dr Rod Hubbard joined the university staff, bringing new computing expertise to the group. Together Guy and Rod raised funds in the following years from SERC Protein Engineering initiatives and, in association with Glaxo, a grant to establish protein expression facilities. They were one of the first in 1988 to gain a SERC ‘Consolidated award’ in which multiple specific awards to a laboratory were amalgamated. Funding from Novo also continued to support insulin research and to develop their industrial enzyme programme.

These extra funds meant that the laboratory expanded rapidly, and by 1990 there were about 40 researchers in the group (figure 2). New academic appointments followed: the organization
ran smoothly; Rod and Guy worked well together, and by a wonderful stroke of luck, in 1988 Caroline Myers saw an advertisement for a laboratory administrator, applied, left the Foreign Office to move north and took over the job. Guy was heard to say later that if only he and Caroline could be left undisturbed until 10 a.m. each day, they could probably run the world!

**New technologies**

By the 1980s, technical changes were revolutionizing structural biology. Guy was quick to embrace these, discussing them in a prescient 1986 review (13). New computational approaches were developing, including graphics systems to visualize molecules and dissect structural features. The emergence of synchrotron radiation brought the advantages of very high X-ray intensity, but probably the most significant development in the field was site-directed mutagenesis, which allowed proteins to be produced in the laboratory and experiments to be tailored to become more tractable and informative.

**Increased computing power, standardized software and the availability of graphics**

In 1976, all the laboratory computing needs were provided by the university’s main-frame, a Dec KL10a, and the structural group exploited these central facilities to the full. In 1980 when Rod Hubbard was still a graduate student doing a PhD with John Garrett on fluorescence studies of membranes (Hubbard & Garratt 1980), he was already moonlighting to write software to plot maps and molecules, spurred on by the need to produce the 2Zn insulin figures used in the *Philosophical Transactions B* paper (15). By 1983 Rod’s academic position was formalized when he was appointed as a ‘New Blood’ lecturer.
Rod and Guy analysed insulin’s many conformational variants, using molecular graphics and dynamics to demonstrate insulin mobility, following the lead of Martin Karplus (ForMemRS 2000, Nobel Prize 2013). Rod’s software was licensed to Polygen (subsequently MSI and then Accelrys) and further developed in York into the suite known as QUANTA to provide a complete set of graphical tools covering all tasks from the tracing of the first map to final refinement and analysis. The whole laboratory benefited from this synergy—the software developers had instant feedback from critical users, and the users had access to excellent software.

*Synchrotron sources for X-ray data collection*

These facilities provided much better experimental data than any laboratory source. The first was set up in 1979 at LURE (Laboratoire pour l’Utilisation du Rayonnement Electromagnétique), France, then in 1981 a second at the Synchrotron Radiation Source at Daresbury, UK; and in 1985 Keith Wilson (now at York) pioneered the development of modern synchrotron data collection at the European Molecular Biology Laboratory outstation in Hamburg.

The first York project to exploit this was haemoglobin, when in 1979 Zygmunt Derewenda collected 2.3 Å data at LURE. In the 1980s, the Daresbury synchrotron was increasingly used, and by 1990 the Hamburg resource was providing the best facilities and allowing collection of atomic-resolution datasets for large molecules.

Guy later became something of a guru on the uses of synchrotron sources, serving on many research committees and advisory boards (14).

*Protein engineering and synthetic proteins*

In 1986 SERC in conjunction with Glaxo gave funds to establish molecular biology facilities at York and to start research on penicillin acylase. Further funding from Novo and Novo-Nordisk provided more appointments and resources. The insulin and penicillin acylase projects provided the training ground, and Tony Wilkinson took responsibility for organizing the new facilities.

**PARTICULAR RESEARCH PROJECTS**

*Insulin*

Insulin provided a lifetime’s project for Guy, and at least one-third of his publications discuss aspects of the research. From 1976 to 1988 Dorothy and Guy continued to refine and analyse the 1.5 Å refined 2Zn insulin maps to tease out structural details, to build the solvent network, and to speculate how these details might influence the folding of the monomer, dimer or hexamer (15) (figure 3). They analysed the hydrogen bonding network in detail, leading to a highly cited review on H-bonding (Baker & Hubbard 1984).

With Cyrus Chothia (FRS 2000) Guy analysed the differences between the four copies of the insulin protomer structures in the 2Zn and 4Zn forms, demonstrating how these could result in long-range modifications (9).

As the decade went on, a major component of this research was linked to the search for better therapeutic insulins, mostly done in collaboration with Novo, and led by Jean Whittingham. The first aim was to establish that modified and genetically engineered insulins
had substantially the same fold. A further objective was to use protein engineering technology, plus chemical insight, to explore rational designs for more effective engineered insulins, including ones used for short- and long-acting treatments for the management of diabetes. This led to the production of clinically applicable monomeric insulins, now the basis of the modern ‘fast-acting’ insulins (26, 28, 29, 35).

Throughout the 2000s Marek Brzozowski and Guy worked with an international team on the development of super-active insulin analogues. Several of these bound to the insulin receptor, and in 2013 the first insulin receptor–insulin complex was reported (37). Most importantly this led to further understanding of how insulin engages with the receptor carboxy-terminal α-chain (αCT) segment, which is itself remodelled on the face of a leucine-rich-repeat domain (L1) upon insulin binding. The insulin B-chain C-terminal β-strand is displaced away from the hormone core, revealing the long-proposed conformational switch of the molecule upon receptor engagement.

**Haemoglobin**

In 1978, the Bakers had visited Łodz in Poland and had met two graduate students, Marek Brzozowski and Zygmunt Derewenda, who were struggling to learn protein crystallography from textbooks. They had grown a new crystal form of haemoglobin under aerobic conditions, using polyethylene glycol as the precipitant. Ted suggested they contact Guy to ask if they could bring their crystals to York to use the equipment there and to gain experience on this apparently rather uninteresting project.
Guy raised £200 from the Royal Society, sufficient to bring Zygmunt to York for two months if he lived with the Dodson family. Data to 3.5 Å were collected in-house, the haemoglobin tetramer positioned by molecular replacement. Although the crystals were grown in air, the haemoglobin in this new crystal form was in the low-affinity T-state but, remarkably, the haems in the α-subunit had a density suggesting that some oxygen was bound. If true, this would be the first example of haemoglobin trapped in an intermediate state and could provide key insights into the allosteric pathway. Guy and Zygmunt travelled to Cambridge to show Max Perutz FRS this exciting result, and a long collaboration ensued.

Higher-resolution X-ray data were needed to validate the proposed allosteric events, so Guy organized access to the only functioning synchrotron in Europe at the time, the LURE facility in Paris. Zygmunt returned from Poland in 1979, this time with a European Molecular Biology Organization (EMBO) fellowship. He took the crystals to LURE, collected a complete 2.1 Å data set on film and set off back to York triumphant. Unfortunately, he was apprehended at Dover for trying to enter the UK for the second time on a single-entry visa and was only rescued after the Member of Parliament for York interceded with the Home Office.

York had no facilities for scanning the films, but again the spirit of collaboration that permeated the discipline provided a solution. David Blow’s group at Imperial College had the required equipment, so a phone call earned Zygmunt permission to work the nightshift there, arriving at the laboratory at 8 p.m. and leaving as the cleaners arrived at 8 a.m. Once the measurements had been completed, refinement began in York. The sheer volume of data greatly challenged the local computing resources so Zygmunt was again a night owl, using all available computer memory from midnight till 8 a.m. This was the first haemoglobin refinement to recognize that the T-state haem was domed, not planar, with the Fe lying out of the plane, and the first protein crystal structure done in Poland (11).

The haemoglobin studies continued over the next decade.

Bob Liddington had enrolled for his DPhil in 1981 and worked alongside Zygmunt. He was seconded to the Daresbury synchrotron for six months in 1982 and used every available free shift to collect high-resolution data. In 1988 he reported the structures of three isomorphous T-state crystals: one deoxygenated, one with oxygen bound to the α-haem only, and one with Fe oxidized to Fe(III) with water bound at all four haems (16). After detailed analysis of the small but significant conformational differences between these structures, he could chart the initial triggers of the switch from deoxygenated T to fully oxygenated R state.

By 1988 Guy and Max Perutz felt that these snapshots, together with molecular dynamics calculations, were sufficient to explain the allosteric effects of oxygen binding and release and published their conclusions (17). The results confirmed Perutz’s original allosteric mechanism, but greatly enriched its subtlety.

**ENZYME CHEMISTRY RESEARCH PROJECTS: SELECTED EXAMPLES (1980–2012)**

The specificity and rate enhancement of enzyme reactions have fascinated chemists and biochemists investigating the nature of cellular processes. Guy delighted in the conservation of active site architecture across enzyme reaction contexts, e.g. that the structure of the Asp–His–Ser catalytic triad in trypsin and chymotrypsin matched that of the Glu–His–Ser triad in lipases.
The enzyme penicillin G acylase (penicillin amidohydrolase, EC 3.5.1.11, PGA) is widely distributed among micro-organisms and is used industrially to produce 6-amino-penicillanic acid, the starting material for semi-synthetic penicillins. PGA is encoded as an inactive precursor of 804 residues and activated by cleavage of the peptide bond preceding a catalytic serine, which then becomes the N-terminal residue of the B-chain. As part of the protein engineering initiative, the laboratory had received a grant to study PGA. This was cloned and crystallized, and the structure was finally solved in 1995 (24). The N-terminal serine had no neighbouring residue to act as a base, and the nearest candidate was its own α-amino group. It was quickly recognized that this mechanism existed in other apparently unrelated enzymes, all with a catalytic N-terminal residue, and that these shared an unusual four-layer αββα fold, with the nucleophile and other catalytic groups occupying equivalent sites. This structural super-family was named Ntn (N-terminal nucleophile) hydrolases (25).

Penicillin V acylase (PVA) obtained from Bacillus sphaericus could also be used to produce 6-amino-penicillanic acid. The National Chemical Laboratory and pharmaceutical companies in Pune, India, worked on this protein (Shewale & SivaRaman 1989; Shewale et al. 1990; Sudhakaran et al. 1992). A collaboration was set up, funded largely by the British Council. The PVA structure was published in 1999 (31) and, despite the totally different sequence, the catalytic centre overlapped very closely with that of PGA. Guy was fascinated by the details of the mechanism, and continued to puzzle over the trigger for the autolytic cleavage of these enzymes till his death.

The Novozymes collaboration introduced many exciting projects to the laboratory, which were initiated for commercial reasons but developed into important research fields, and incidentally kick-started several careers.

The hydrolytic enzyme lipase breaks down triacylglycerides into fatty acids and glycerol and has many industrial uses. Its activity is greatly increased at the lipid–water interface. Novo provided purified material, and the structure was reported in 1990 (19), alongside that of the human pancreatic lipase (Winkler et al. 1990). Both show a classic Ser–His–Asp trypsin-like catalytic triad with the active serine buried under a short helical fragment of a long surface loop. However, for activation the insoluble lipid substrate must access this triad. A crystal was obtained with an inhibitor covalently bonded to the active site, and this showed clearly that a 10-residue helical loop ‘lid’ had rotated to expose an extensive non-polar surface, giving the inhibitor access to the triad (20).

Guy was delighted by this example of convergent catalytic chemistry and spent many happy hours searching the Protein Data Bank for other examples. To quote a review co-authored with Alex Wlodawer in which they describe numerous examples of totally different proteins that fold to generate very similar environments for the active site: ‘Review of these enzymes shows that the acid–base–ser/thr pattern of catalytic residues is generally conserved, although the individual acids and bases can vary. The variations in sequence and organization illustrate the adaptability shown by proteins in generating catalytic stereochemistry on different main-chain frameworks.’ (30)

The Novo biochemists had been harvesting α-amylase as a by-product of the insulin extraction process since the 1940s, for use in the paper and textile industry, in household detergents and in the transformation of corn-starch to fructose syrups and biofuels. Novo provided two fungal amylases, and Marek Brzozowski, on study-leave in York at the time, quickly solved the structures (18).
Novo-Nordisk then became interested in more diverse carbohydrate-active enzymes, and one of their first targets was a cellulase, endoglucanase V, used for ‘colour-brightening’ in household detergents. Gideon Davies (FRS 2010) solved this structure (22) and described the details of the enzyme mechanism.

In 1990 the biochemist Dale Wigley (FRS 2004) was awarded a SERC Advanced Fellowship and chose to come to YSBL from Leicester to master crystallography and study the N-terminal fragment of DNA gyrase B protein with Gideon Davies. This revealed a 20 Å hole through a protein dimer, suggesting that the protein could ‘guide’ the DNA strands during the supercoiling reaction (21).

Fred Antson, a ‘refugee’ from the 1990 partial ‘collapse’ of the renowned Institute of Crystallography in Moscow, came to York in 1992 to work on an insulin project. He did this so successfully that he was left with a completed project and 10 months’ funding, so Guy suggested, ‘Fred, you can now start to investigate whatever you like.’ Paul Gollnick, a collaborator from Fred’s PhD days, was studying Trp RNA-binding attenuation protein (TRAP), and was eager for any structural insight. Helmut Zahn had shown that TRAP regulates transcription of the trp operon in Bacillus subtilis in response to changes in the intracellular concentration of l-tryptophan; and that when activated it bound specifically to a leader region of the RNA transcript containing 11 GAG or UAG triplets (Otridge & Gollnick 1993). Pleasingly, the structure showed that TRAP formed an assembly of 11 subunits related by rotational symmetry in a β-wheel arrangement, with the subunits stabilized through intermolecular β-sheets and with the l-tryptophan bound in clefts between subunits (23). The structure of TRAP bound to RNA has 11 binding pockets for the RNA, forming a belt around TRAP, thus explaining how transcription is arrested (32).

**National Institute of Medical Research (NIMR), Mill Hill, 1993–2003**

In 1993 Guy took a part-time position at NIMR with a brief to establish a structural research group and stimulate structural thinking in the various medically oriented divisions. Mill Hill was a world centre for research into influenza and had divisions in parasitology, tuberculosis and malaria, as well as mathematical biology. Guy had been a member of their 1990 quinquennial review panel and was sure that structural information on a range of these projects would stimulate new thinking.

Organizing the structural group was fairly straightforward—he followed the procedures shown to be successful at York: appoint enthusiastic, imaginative and able young scientists and work alongside them. The environment was ideal as most research teams worked in the same massive cruciform-shaped building, all lectures were on site, and the relative isolation meant that most people shared the canteen and met informally over lunch and coffee. The opportunity for such easy contact with many able and interesting people gave Guy enormous pleasure, and he rapidly formed new friendships and became a welcome collaborator with the biologists and biochemists. The building also housed a beautiful art deco library where he could browse to educate himself in medical aspects of the research and read at random (figure 4). He drew attention in a Mill Hill essay to his amusement at reading about the research council’s ‘new’ vision of promoting multi-discipline research as he knew it already existed in spades at Mill Hill.
Guy was particularly interested in tuberculosis and malaria research, both of which strengthened his connections with Indian science. Dr Balasubramanian Gopal came to NIMR from Bangalore to work on the *Mycobacterium tuberculosis* transcriptional regulation proteins NusA, NusB and NusE, and their role as controls during RNA transcription (33, 34).

Guy’s contribution to the malaria projects is perhaps best outlined in this letter from Mike Blackman—then a group leader at NIMR on the mechanistic basis of host cell invasion by the malaria parasite.

Guy was a source of great encouragement from the first weeks of his time at NIMR. In 1998, he was asked to host a short-term EMBO Fellow, Dr Chrislaine Withers-Martinez. He suggested that she took up a joint position with me, focusing on the structural examination of proteins involved in red blood cell invasion by the malaria parasite *Plasmodium falciparum*. Guy was
an outstanding mentor for her and a wonderful collaborator, always ready with new ideas and proposals to overcome technical hurdles. This included the first suggestion that we should generate codon-optimised synthetic genes to overcome the long-standing problem of expression of the highly A+T-rich malarial coding sequences in heterologous expression systems. (At that time production of synthetic genes was a major technical feat.) In fact, this turned out to be the ideal solution to our problems, leading to the first recombinant expression and eventually the x-ray crystal structural determination of an enzymatically active malarial serine protease.

**Ongoing molecular dynamics studies**

Thinking about biochemical mechanisms had become a passion for Guy. When he ‘retired’ from Mill Hill in 2003, he could often be found in York, creating ever more complex comparisons and images to explore and illustrate these mechanistic and dynamic aspects of protein structure and function. He collaborated with Dr Chandra Verma, an expert on computational protein dynamics who was then based at YSBL. They shared a belief that it was essential to include water structure as well as protein conformation in meaningful molecular dynamic simulations. In a 2006 review (36), they demonstrated that computer simulations at the atomic level could provide realistic modelling of protein and solvent flexibility, and that this could be extended to predict the molecular and atomic motions associated with protein mechanisms.

**Teaching and mentoring, public and international service**

Guy supervised 21 DPhil students at York and engaged with all the other YSBL graduate students and postdocs. He was notorious for his ability to apparently doze through a seminar, then ask relevant and searching questions.

Guy served on many BBSRC and MRC research committees and review boards, and synchrotron boards. He took these responsibilities extremely seriously, was meticulous in his preparation and would pursue arguments with unfailing courtesy and respect for other points of view, but with determination to hold on to what he felt was right.

One of Guy’s great pleasures from his life in science was meeting and working towards a common cause with people from all nations. In the 1960s the Oxford group was made up of New Zealanders, Indians, Chinese, Americans and Australians—at one point Margaret Adams and Dorothy were the only two British citizens.

In time the York laboratory also became very multinational. EU exchanges helped this; the collapse of Russian scientific funding after 1990 brought wonderful colleagues to YSBL; insulin research brought many Chinese visitors; and in the 1990s the British Council funded exchange visits between York and Indian scientists from Pune. Several graduate students spent a year in York to exploit the laboratory resources, then returned home to submit their theses. This exchange was valuable to both sides and led to multiple publications (e.g. (31)). In 2004 Guy was elected a Foreign Member of the Indian National Science Academy.

In 1995 Guy became Chair of the International Union of Crystallography (IUCr) Commission on Biological Molecules and helped establish criteria for the deposition and release of data and coordinates of biological structures, driven by the belief that experimental information should be available to everyone. The Commission, together with Ted Baker, then IUCr President, lobbied all journals to insist that data deposition should be a pre-requisite for publication, and this initiative has helped make the Protein Data Bank (http://www.pdb.org) the outstanding, free and complete biology resource that it is today (27).
Figure 5. A close family: (a) Assorted antipodean and York relatives at Fountains Abbey (Easter 2011); (b) Guy with granddaughters Grace and Amelie at Castle Howard (2010). (Online version in colour.)
Guy was probably one of the longest serving parent school governors in York. In 1976 York still maintained single-sex grammar schools and secondary moderns. Our eldest son went to the local grammar school, and Guy was dragooned into becoming a parent governor. This required him to help oversee the transformation of the school system to mixed comprehensives, something that pleased him but encountered a great deal of local opposition. Again, his tact and ability to present a case with courtesy and determination helped greatly in the transition period. Our youngest son was one of the first cohort of comprehensive pupils so Guy was able to follow the challenges of the transition and to provide support to teachers and pupils.

**Family life**

In 1965 Guy married Dorothy Hodgkin’s research assistant, Eleanor McPherson (the author of this memoir), thus setting a precedent for married couples working together on the insulin project. We have four children, Richard, Philip, Victoria and Thomas. We bought an enormous house in York which could easily accommodate the family and, on many occasions, friends, antipodean relatives and collaborators (figure 5a). This meant that the children grew up as part of the wider laboratory ‘family’. On the whole they seemed happy, or at least resigned to this, although at one point the eldest did complain ‘Why does Zygmunt always want to talk about haemoglobin at dinner?’ Guy’s twin brother, Maurice, was already an academic in the Department of Mathematics at the University of York, and in 1983 Maurice’s wife, Haleh Afshar, took up a position in the Department of Politics. These close family ties could have proved somewhat ‘inbred’, but in fact were always a delight—the children and their cousins are still good friends, and the older generation are still mutually supportive. Our grandchildren are also based in York, and Guy knew (and doted on) three of them, Grace, Amelie and Lucy; he was very important to them, as they were to him (figure 5b).

**Conclusion**

There are three main characteristics of Guy for which he is remembered. The first was his passion for protein structure. He inspired and supported the development of new methods to determine structure, to relate structure to chemical mechanism and to embed structural insights into the lexicon of biological research. The second was his early recognition of how to build synergy in industrial collaborations that led to fundamental scientific discoveries but also the development of new medicines and products to benefit society. Ultimately, Guy’s enduring legacy will be as a mentor and friend. Many scientific careers blossomed through his interest, passion and infectious enthusiasm. Both within science and beyond, Guy’s unbridled warmth, joy and love will be long remembered.

**Honours, degrees and awards**

**Qualifications**

1958 BSc, University of New Zealand
1959 MSc, University of New Zealand
1962 PhD, University of New Zealand
Guy Dodson

Posts

1962–72 Postdoctoral Research Assistant, University of Oxford
1972–76 Research Fellow, Wolfson College, Oxford
1976–80 Lecturer, University of York
1980–85 Reader, University of York
1985– Professor, University of York
1993– Head of Protein Structure Division, National Institute for Medical Research, Mill Hill (joint appointment)
1995 Head of Structural Biology Group (NIMR)

Committees/commitments

MRC College of Excellence Reviewing Committee, BM14 Advisory Board (ESRF)
A director of the Feldberg Foundation for the German/English scientific exchange for experimental medical research

Honours

1977 Lawrence Lecturer, British Diabetic Association
1991 Kratos Medal for Structural Chemistry, Royal Society of Chemistry
1994 Fellow of the Royal Society
1997 EMBO Fellow
2002 Fellow of Academy of Medical Sciences
2003 Honorary Fellow of the Indian Academy of Sciences
2004 Foreign Member of the Indian National Science Academy

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I should like to thank Guy’s many colleagues who have read these memoirs and contributed their own recollections of the research projects they were involved in. Particular thanks are due to Professor Tom Blundell, who reshaped the sections on insulin, and to Professor Ted Baker, who helped with the original draft.

All photographs are courtesy of the Dodson family unless otherwise indicated. The frontispiece photograph is Copyright © John Olive, Chemistry Photographics, University of York.

Author profile

Eleanor Dodson

Professor Eleanor Dodson was a research assistant to Dorothy Hodgkin in Oxford, and worked alongside Guy there. They married in 1965. She was responsible for the computation and active in developing software for macromolecular crystallography. After moving to York she was involved in many of the projects described in the memoir.

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