Jenny Pickworth Glusker's work on the hexacarboxylic acid derivative of vitamin B_{12} in Dorothy Hodgin's laboratory at Oxford revealed the structure of the corrin ring. At the Institute for Cancer Research in Philadelphia where she was first a member of Lindo Patterson's lab and later a principal investigator, she continued her interest in B_{12} structures. Her research focus has included small-molecule compounds related to cancer, the structural aspects of the Krebs cycle and citrates, metal-ion coordination in proteins, the interaction of ligands with metal ions, and the enzymes aconitase and xylose isomerase. She is the recipient of many awards, notably the Fankuchen Award of the ACA and the Garvan Medal of the American Chemical Society. Her many professional contributions include serving as President of the ACA in 1979 and as editor of Acta Crystallographica D *(macromolecules). One of Jenny's major interests is crystallography education; the 3rd edition of the popular textbook* Crystal Structure Analysis: A Primer *by Glusker & Trueblood appeared in 2010. She is the co-author or co-editor of a number of books on crystallography and the history of crystallography.*

As a child I lived in England in the industrial city of Birmingham. Both of my parents were medical doctors and encouraged me in my studies. My mother had wanted to study foreign languages, but she was in high school in the middle of World War I and there was, by then, a great shortage of young men available to go to medical school because so many of them were already at war. So, it was decided to send girls in high school with good grades to medical school. My mother became a medical student at Glasgow University in 1916. The university had been granting medical degrees to women since the 1890s, but was not used to such large numbers of women students in their medical school classes — about half of her graduating class in 1920 was female. She told me that the professors had to change the mnemonics so that they would be more suitable for such mixed classes. By the time that she graduated the war was over, and she went to Dublin, Ireland, and worked there during the social unrest in the early 1920s. Finally she accepted a medical post in Birmingham, England, where she met and, after a few years, married my father. From then on she stayed at home to raise her children — my sister who studied history (not a science, said my father), a brother who became a general practitioner and me. Although she was not allowed by the medical community to compete with other doctors in the area, my mother would substitute for local doctors if they had to be away from their practice for any reason. She was very frustrated that she could not continue with a career that she had put so much energy into. For this reason I decided that I would find a way to continue working, even if I had children. So, in my background, many of my parents' friends were women doctors and it was assumed that I would become one.

But I had other ideas. The school that I went to, a public school in the American sense of the word, was newly built, and had excellent scientific laboratories and a chemistry teacher (Yvonne Way) who inspired me. She had a PhD, but decided that she wanted to teach rather than do research, and it was a joy to go to her classes. I still write to her; she is in her 90s. My interest in chemistry had started when I found a book on incompatible medications among my mother's medical textbooks. It explained the chemical processes that resulted when two pills interact unfavorably for the patient. I then acquired a chemistry set that was stored under my bed and was able to mix chemicals and make wonderfully colored solutions and evil-smelling products. Thank goodness I survived that hobby. However, it made me sure that I wanted to be a chemist.

Chance then played a role in my life. Every day, before classes, the entire school of about 700 students (girls only, in those days high schools were generally not coeducational) met in a large hall. One day, in 1947, the principal announced that she had finally received her full PhD degree from Cambridge University. She explained that, until that date, women students who passed all the requirements for an academic degree did not receive the full recognition that men did. Now the university would finally accept them as members of the university with degrees, as for men. The principal wanted us to celebrate with her. I, however, was puzzled. Why should it matter whether you were a woman or a man if you did the same work? I looked up the situation for Oxford University and found they gave degrees and full university membership to women from 1920 on, so I announced I would try to go to Oxford. But my high school teachers all said that they sent science students to Cambridge and did not know too much about chemistry at Oxford. In addition my parents stepped in and said I should go to medical school (which I could do directly from high school). To deal with these problems I made a pact with my father that if I could get into Oxford University that year I would study chemistry. If not I would go to medical school (and not complain).

Mindful of my aims, I set off for Oxford to take the entrance exams at Somerville College, the most academic of the women's colleges in Oxford University. It was necessary to take a practical chemistry examination in a laboratory, and the test was to identify an unknown material (in the days of hydrogen sulfide which invariably caused a splitting headache). This "unknown material" consisted of beautiful crystals, but, because I had spent many hours helping my father, an amateur photographer, in his dark room, I knew immediately what they were. They were crystals of sodium thiosulfate or "hypo," used in fixing solutions in photography. During this practical entrance examination every chemical I added to the "unknown material" caused sulfur to precipitate. What a mess! The person at Somerville who supervised me during the exam and then interviewed me for college was Dorothy Hodgkin, a crystallographer and future Nobel Prize winner. During my interview with her I explained about the pact with my father. Well, I was accepted by Oxford University. Many years later I asked Dorothy Hodgkin if I got accepted to Oxford because I correctly guessed the identity of the unknown material. She said that was not the case, but that she had noted that I knew how to deal with the sulfur that precipitated every time any new chemical was added.

The chemistry course at Oxford took three years, and if one wanted a classified degree, one did an additional year's

research. I had a marvelous time. Dorothy Hodgkin was my tutor and we spent many hours in one-on-one weekly tutorials. She was an ideal role model with three children and a supportive husband who was at Balliol College. Her home was a haven for many visiting scientists and it was always interesting to visit her there. For my tutorials Dorothy would insist that I read and comment on all the original papers relevant to the subject she had chosen for my essay that week, so I spent much time in the Radcliffe Science Library. The laboratory experiences were good, but some of the buildings seemed antique compared with those that we had at high school. The design for the 100-year-old octagonal inorganic chemistry laboratory (later replaced) came from the Abbot's Kitchen in Glastonbury Abbey and it had a high ceiling with wooden rafters. For my research year I chose to work with Harold W. Thompson, an infrared spectroscopist who was interested in details of molecular structure. Under his tutelage I determined the interatomic distance in deuterium chloride, for comparison with that of hydrogen chloride being studied by another member of the laboratory. Then I worked on some more complicated molecules, methyl halides, but could only measure moments of inertia and not distances between atoms. However I also met my future husband, Donald Glusker, a Rhodes scholar from the University of California, Berkeley, who was working in the same lab on the spectroscopy of charge-transfer complexes.

High-resolution infrared spectroscopy was not, at that time, giving me the information that I wanted. So I started my graduate work in the laboratory of Dorothy Hodgkin, with the aim of learning how to determine molecular structure by x-ray diffraction. Dorothy was already well-known for her structural work on cholesterol while working with J. D. Bernal. She was the first to show that it is possible for protein crystals to give good diffraction patterns, and, particularly, she determined the chemical formula of penicillin by x-ray diffraction studies in the days when structure determination was very difficult. Dorothy's laboratory and workrooms were in the Oxford University Museum of Natural History that had been built with the help of the artist John Ruskin. We had desks in the very room in which, as commemorated by a plaque on the walls, Thomas Henry Huxley defended Darwin's recently published theory of evolution by natural selection against the Right Reverend Samuel Wilberforce, the then Bishop of Oxford. This took place at a meeting of the British Association in 1860. Dorothy's lab was a busy one and she shared it with Herbert ("Tiny") Powell who was famous for his work on clathrate structures. Jack Dunitz, who, in 1948, had determined the crystal structure of a calciferol derivative, at that time the most complex structure determined by x-ray crystallography, was there when I first started research. Jack was working in an elevated area in the lab that contained the microscopes for crystal viewing, but he was about to go to Caltech. David Sayre had recently left the lab, but everyone was excited about his squaring method for solving structures. Most of the other people in the lab were working on the structure of insulin or vitamin B_{12}. Work on this vitamin, the antipernicious anemia factor, and some of its derivatives, had been in progress in Dorothy's lab for a few years, particularly by John H. Robertson, June Broomhead (later Lindsey), Maureen Mackay and Clara Brink (later Shoemaker). John White at Princeton University was working independently on the same structure, and he collaborated with Dorothy on this throughout the years. Dorothy had decided at that time that no one should work on the much larger insulin molecule for a graduate degree because there was no guarantee that good results could be obtained for it at that time.

Shortly after I had started graduate work some deep red crystals arrived in the lab from Cambridge University. They were of a degradation product of vitamin B_{12} for which the 5:6-benzimidazole, D-ribofuranoside, 1-amino-2-propanol, phosphate and cyanide groups of the vitamin had been removed and the amide groups had been converted to carboxylic acid groups. The central part of the molecule, containing a cobalt atom, was still present, and that was the part of the chemical formula that was unknown and that we needed to find. Jack Cannon, an Australian, had been trying for some time to crystallize this degradation product that he had made, and finally, in despair, threw into its solution every liquid organic material he had access to, and went to Europe for a holiday. When he came back there were beautiful crystals, never grown again. So I started to work on them. The molecule was large and spectroscopic studies had shown that, like the vitamin itself, its degradation product contained a ring structure similar to (but not the same as) that found in porphyrins. Both the vitamin and Cannon's degradation product contained cobalt atoms which were useful as heavy atoms. I collected three-dimensional x-ray diffraction data on the B_{12} degradation product (referred to as the hexacarboxylic acid) with a Weissenberg camera and estimated intensities by eye. Dorothy thought that anyone new working on the problem (that was me) should not be given information on what had been guessed so far from crystallographic studies on the vitamin itself. Unlike many x-ray crystallographers, she liked to work in three (rather than two) dimensions. This greatly increased the number of diffraction data to be measured and the time that had to be spent, particularly in calculating electron-density maps. But the results were much clearer.

Jenny in her laboratory at ICR about 1980. The DNA model was built by Ann Geale Diamond (Bob Diamond's wife). Ann grew up in the next street to Jenny in England and they went through the same schools and college. After the model arrived, Jenny learned that Ann had made model when she worked for a model-building company in Cambridge, England.

The computational analysis of the hexacarboxylic acid was started with Patterson projections, and, to the surprise of everyone, they showed the position of the cobalt atom (saving us from the need for a three-dimensional Patterson map and thereby much computing time). One great asset of these crystals, unlike the situation for the complete vitamin crystals, was that the heavy metal, cobalt, did not lie in the unit cell near zero for two of the atomic coordinates (space group $P2_12_12_1$). This helped reduce some ambiguities in heavy-atom electron-density maps. The first map that I calculated and drew, phased only on the cobalt position just found, took six weeks (day and night) to produce (compared with seconds nowadays). The calculations were done in a room in the basement of a building at the corner of South Parks Road in Oxford on a Hollerith adding machine (used for population censuses). This calculator could only add, and we had to fool it to make it subtract numbers. The calculations were essentially those previously done with Beevers-Lipson strips. The IBM cards that were used lay in filled boxes throughout this room; they were painted different colors to show if they represented sine or cosine functions, even or odd, but they swelled when the weather became hot and humid and could not then be used. Often a policeman, bored with his beat, would escort me home in the middle of the night after a long computing session. From this cobalt-phased map John Robertson and I, late one night, found a ring structure around the cobalt. It is now called a corrin ring and consisted, like a porphyrin, of four five-membered heterocyclic rings, but had only three bridging atoms; two of the rings were directly connected.

I obtained my D. Phil. degree with J. Monteath Robertson as the external examiner, and then went to Caltech in Pasadena to work in the laboratory of Robert Corey. There, with Dick Marsh as a mentor, I studied simple peptides for a year as a postdoc. Linus Pauling kept an eye on all of us and greatly increased our interests in protein structure.

Don and I, now married, then looked for two chemistry jobs in one city. There were many companies with anti-nepotism rules, and many thought women with doctorates in chemistry should work in libraries, and then not at all if they had children. I had written to Dorothy Hodgkin for a letter of recommendation. She wrote back a letter which begins "You silly girl," telling me to go and work with Lindo Patterson (of the Patterson function) who was at the Institute for Cancer Research (ICR) in Philadelphia. That is how I came to the ICR laboratory in Philadelphia where I have worked ever since.

I had again come to a wonderful lab. Structure determination in Lindo Patterson's laboratory was then focused on molecules, such as citrates, in the biochemical Krebs cycle. Our crystallographic studies that have been carried out through the years after Lindo died in 1966 continued his studies of substrates and inhibitors of the Krebs cycle enzyme aconitase, which binds ferrous iron and interconverts citrate, isocitrate and *cis*-aconitate. Other work concentrated on the conformations and absolute configurations of biochemical ligands and how they bound metal ions. Our studies of citrates and their derivatives led to a proposal for the three-dimensional mechanism of action of aconitase (the "ferrous-wheel mechanism"). It involved all the stereochemistries (including those of cation binding) and absolute configurations of the structures that we had determined.

Some of the compounds involved in cancer, both chemical carcinogens and antitumor agents, captured our attention. A major class of compounds that we studied were the "ICR compounds." These are acridine derivatives some of which showed antitumor and/or mutagenic activity. ICR compounds were presumed to interact with DNA, intercalating, as does acridine, between the bases of DNA; the side chains of these agents could then provide further action, such as alkylation of DNA. We determined the conformations and extents of overlap of their ring systems in packing in the crystalline state for several of these compounds.

We also tackled chemical carcinogens, starting with polycyclic aromatic hydrocarbons (PAHs) such as benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene (DMBA). Such carcinogenic PAHs are oxidized in the body and the active agent is an alkylating agent such as a diol epoxide. We wanted to see if we could contribute to an understanding of their reactions in the body. Several PAHs become more carcinogenic when they are methylated at certain positions in the chemical formula. Such methylation may make it impossible, for steric reasons, for the substituted PAH molecule to remain totally planar. We wondered whether the twisting that results from this methylation enhances their possibility of interaction in the helical structure of DNA and what the effect was on the charge distribution in the molecule, that is, the ability of a metabolite to act as an alkylating agent, which is believed to be its function in cancer. Crystal structures of several metabolic products of carcinogenic PAHs that we determined included a diol epoxide of 5-methylchrysene, a presumed activated metabolite of a PAH more carcinogenic than chrysene itself. A detailed electron-density study of DMBA with Cheryl Klein and Ed Stevens resulted from high-resolution x-ray data collection and multipole refinement of the structure. Assuming that the action of a carcinogenic PAH involves interaction of a PAH metabolite (presumably formed by an interaction with cytochrome P-450), we synthesized and studied the structures of some adducts of PAHs with nucleoside portions of DNA. We measured the extent to which the PAH ring system lay between the bases of the nucleoside.

This led to a general interest in intermolecular interactions since structural studies reveal not only what a molecule looks like, but also how it interacts with other molecules (generally in a crystal of the same kind). Our investigations of these were greatly helped when Peter Murray-Rust came to our lab on a sabbatical. We investigated the three-dimensional geometry of the manner by which oxygen and nitrogen atoms in molecules bind to atoms in other molecules. We represented the results of our analyses in probability plots (looking like electron-density maps). Such analyses required the use of crystallographic databases, such as the Cambridge Crystallographic Data Base in England and the Protein Data Bank in the USA. We then examined, in a similar manner, several other types of intermolecular interactions, including the locations of metal ions around carboxylate ions and near heterocyclic ring systems. Each relevant published crystal structure was examined in

Jenny in her laboratory at ICR in 2011

detail to ensure that we knew the coordination number of the metal ion and its geometry; results of such investigations were provided to the appropriate database staff. Results were then used in theoretical density functional calculations in order to obtain the energies of various states. Of particular interest to date were the surroundings of divalent Mg, Mn, Ca, Zn, and Pb (which has an interesting lone pair of electrons), and trivalent aluminum. We were able to show how different Zn^{2+} and Mg^{2+} are when they bind ligands such as water. The binding capacities of metal ions in various ionization states and coordination numbers were represented in triangular plots with oxygen, nitrogen and sulfur at the three corners of the triangle. They showed where the metal ion lay with respect to these three most likely binding atoms in proteins. These plots serve as useful signatures of each metal ion in each of its possible valence states. For example, Mg^{2+} binds the oxygen atoms of six water molecules in an octahedral arrangement, whereas Zn^{2+} can have a coordination number of 4, 5 or 6 and will bind nitrogen or sulphur as well as oxygen. Theoretical studies showed that divalent and trivalent cations will bind water molecules with their hydrogen atoms pointing away from the positive charge of the metal ion. Monovalent cations do not have the full extent of this power, while quadrivalent cations may tend to initiate a chemical reaction between water and the metal ion. This suggests why so many enzymes utilize divalent metal ions to bind their substrates and, often, to aid in the catalytic mechanism.

The enzyme structure that we have been studying through the years is D-xylose isomerase which converts D-xylose to D-xylulose and D-glucose to D-fructose. It is used industrially for the conversion of glucose to fructose to obtain high-fructose corn syrup for soft drinks and so is also referred to as "glucose isomerase." The mechanism of action of D-xylose isomerase involves binding of the sugar substrate, opening of the sugar ring system, isomerization of the sugar and possibly cyclization, and then ejection of the sugar from the active site. Time-of-flight neutron diffraction studies of this enzyme (in collaboration with Gerry Bunick and Paul Langan at Los Alamos National Laboratory) showed the ionization states of the various side chains. In one structure a deprotonated water (that is, a hydroxyl group) is located near the site of sugar isomer- ization, suggesting how a hydrogen atom might be transferred from one carbon of the substrate to its neighbor. By varying the metal ions and ligand it was found to be possible to view various stages of the catalytic mechanism. So, if by chance one can obtain large enough crystals, the combination of neutron and high-resolution x-ray studies will contribute greatly to the elucidation of an enzyme mechanism.

I have greatly enjoyed my career as a crystallographer and a member of the ACA and thank all of you for the honors and tasks that have been bestowed on me through the years. I also thank the many people in my laboratory at Fox Chase, Philadelphia, who have helped make all of this possible. I have been interested in the teaching of crystallography and served as Chairman of the Teaching Commission of IUCr for several years and organized schools in Egypt, Thailand, the Chinese University of Hong Kong, Tianjin (China), Madras (India) and recently spoke at a crystallographic meeting in Turkey. Ken Trueblood and I wrote a text on x-ray diffraction of crystals and it was expanded in a later text with Miriam Rossi and Mitch Lewis. Finally, I still teach in the ACA Summer School for Small Molecules run, through summer 2011, by Charles Lake and Bryan Craven.

Jenny Glusker