Journeys in Science: Glycobiology and Other Paths

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Abstract

My scientific journeys began at Oxford nearly 50 years ago. My paths have taken me from magnetic resonance through enzyme systems to antibodies, which led directly to glycobiology. Oxford University's first industrial grant helped the development of the technology for isolating and sequencing oligosaccharides from glycoproteins. This technology was disseminated through a spin-off company, Oxford GlycoSystems, and by the establishment of the Glycobiology Institute. The technology gave rise to the concept of glycoforms, which allow diversification of a protein's properties. Iminosugars, which are glucosidase inhibitors, can interfere with the initial steps of glycan processing on proteins and inhibit three-dimensional folding of glycoproteins. Glucosidase targets for therapy include viral envelope glycoproteins. Clinical trials of an iminosugar as an antiviral for dengue virus are under way. Another iminosugar activity, inhibition of glycolipid synthesis, resulted in a drug for Gaucher disease, which was approved worldwide in 2002. The success of the company and the institute allowed me to undertake several initiatives, in the United Kingdom and abroad, that might help the paths of future generations of scientists.

Contents

NEW BEGINNINGS

Wanderings

The Dweks were expelled from Spain in 1492 as a result of the Inquisition. From there they went to Egypt, one of the few countries that welcomed Jews. Around 1530, they immigrated to Calcutta, India, the center of the silk trade. It is documented that on December 6, 1860, the Dweks became British subjects. As such, they were made to feel unwelcome in India, whose people saw the giving of British nationality as a further way of colonizing India. In 1880, the family moved to Aleppo, Syria, which was one of the most important trading centres for cotton. My grandfather Joe married Aimee Farhi, from one of the most distinguished families of that era. Through this liaison, the Dweks acquired rank, money, and respectability.

My father was one of 10 children. The languages of the family were French and Arabic. The children were educated largely in France and then sent to different countries so that they could trade with each other in cotton. My father was sent to Belgium with his younger brother and was there in 1940 when war broke out. He escaped with my mother, Alice, and my elder brother, Joe, on the last boat to leave Belgium. Within a few years of arriving in England, my father owned several cotton mills in the Lancashire and Yorkshire areas. The family integrated well into UK culture and moved among an Arabic- and French-speaking community of mixed races and religions.

Early Life

I went to boarding school in Cheshire at the age of six and a half. I was accompanied by my brother, Joe, who was 18 months older. The boarding school was a public preparatory school that was tough in many ways, including bullying and anti-Semitism. A year later, I transferred with my brother to Carmel College, a school near Oxford that was founded by and operated under the inspirational leadership of Rabbi Kopul Rosen; it became a notable Jewish public school. It was difficult being the youngest boy in the school, as pupils were not normally admitted until they were at least 9 years old. The rigors of school life and my loneliness led to an intensity in my studies. I also began to realize the dependence of an individual on society and became very idealistic about how society should be conducted.

The headmaster of Carmel College, Romney Coles, was an outstanding and inspirational teacher, the like of whom I have never met since. He loved chemistry—both the practical and theoretical aspects—and kept up to date by reading abstracts from a wide variety of journals. He was rigorous and a great disciplinarian, and thus prepared our minds. He believed in hard work and also put a great deal of emphasis on memory. Carmel College, too, provided a rigorous background in sport, and I rowed very seriously, often training several hours a

day. From both my academic and sporting studies, I learned to apply myself for long periods to difficult tasks, as well as the value of teamwork.

Also at Carmel College, I became fascinated by Hebrew grammar, which remains one of my interests. We were also encouraged to learn large sections of Shakespeare and the Hebrew Bible and other poetry. Those archives in my mind are still a great source of pleasure to me.

University

In 1960, I went to Manchester University to read chemistry and graduated with a first-class degree in 1963. During that year I proposed to my wife, Sandra, who has been my lifelong partner. I stayed at Manchester to complete an MSc and did statistical thermodynamics and quantum theory, as well as a practical project on NMR (nuclear magnetic resonance).

I discovered that Rex Richards was about to become the chair of physical chemistry at Oxford, in succession to Cyril Hinshelwood, and arranged to visit him to discuss joining his research group. I arrived on the same day that it was announced that he was to become the new chair, and we formed a significant bond immediately. So in 1964, having completed my MSc in Manchester, my wife and I moved to Oxford University.

Oxford, 1964

Oxford was and is a dream. It is the "city of dreaming spires" and has the oldest English-speaking university, founded around 1150. The university and colleges have wonderful and inspiring buildings; gardens; collections of books, art, and treasures; and of course musical performances. The world-famous Bodleian Library and the Ashmolean and Natural History Museums are part of the dream. Gargoyles, sundials, and college gardens give the city a magical air. College life creates a unique intellectual atmosphere in which its traditions foster academic excellence and scholarship.

Sandra and I lived within walking distance of the physical chemistry laboratory. Rex Richards's research group was about 40 strong, with everyone involved in different aspects of NMR. Sandra supported my basic scholarship by teaching at nearby Carmel College.

My theoretical background was a distinct advantage in the group, and I joined the team working on nuclear electron double resonance. It was a stimulating time; within a few weeks I had written my first paper.

Postdoctoral Studies as a Physical Chemist

I completed my DPhil in 1966. I had no intention of staying in Oxford or in academic life, even though I continued to rebuff all efforts by my family for me to go into business. However, when Rex persuaded me to stay on as a postdoc, I accepted and realized that the die had been cast. He also asked me to join him in writing an annual review of chemistry on NMR. I took advantage of this golden opportunity to learn many different aspects of NMR.

I enrolled for my DPhil at Lincoln College, which had started the first Middle Common Room for graduates. The international membership and diverse fields of study in the sciences and humanities made Lincoln a wonderful and stimulating environment. I also rowed quite seriously for Lincoln. The picture of nearly 1,000 oarsmen and -women from all over the university taking part in Eights Week "bumps" in the summer, with all the boathouses along the river crammed full of spectators, is still a hugely attractive sight.

Our first child, Juliet, was born in 1965, and we bought a small house in Kennington, about 3 miles from the lab. Rex had asked the university to help arrange our mortgage. Sandra's pregnancy meant that we had lost part of our income, and I accepted a part-time position (Fridays and Sundays) teaching physics and general science at Carmel College. The traveling and the extra work were quite a strain, but that was the price that I was willing to pay for continuing to live in Oxford.

For my postdoctoral studies, I worked on chemical exchange processes using the new "spin echo" techniques. There was nothing like them at Oxford, and I saw them as a link with inorganic chemistry, initially by studying

the exchange rates of the ligands of metal ions. I also started to use paramagnetic ions as relaxation probes, research that brought many collaborations within Oxford, notably Bob (R.J.P.) Williams and his team. Bob had convinced me that studying metal ions in biological systems was important, and we did the first experiments using lanthanides, in particular gadolinium, in enzyme systems. George Radda also started to express a great deal of interest in NMR, and I began some collaborations with his group, using paramagnetic probes to map the various binding sites on phosphorylase b.

The physical chemistry laboratory was a very stimulating place under Rex's leadership, and I was excited about a lot of the research going on. It was a time when discussions about each other's research problems were frequent, usually taking place over coffee and tea each day—something Rex had initiated for the whole department to foster a cross-pollinating and mutually supportive atmosphere. We were expected to know and understand our colleagues' research.

Wonderland, 1966–1973

One day, Rex said that the Dean of Christ Church wanted to see me. The Dean is Head of Christ Church and Dean of the Cathedral, and he was also Regius Professor of Hebrew. I wondered what he wanted. As I walked over to his lodgings in the Deanery, I recalled that Lewis Carroll's *Alice in Wonderland* had been based on the daughter of a previous Dean. I was invited to join the Dean and a few others around a table and was welcomed with the words, "I believe you know something about Hebrew grammar." There was some controversy about some words that his colleagues were translating. I made a number of guesses, thinking it was rather odd. But, after all, it *was* the college of *Alice in Wonderland*! They asked me some questions about my research.

A week later I received an offer, with a salary, of a research lectureship at Christ Church. Its history, buildings, and meadow walks to the river were spectacular. It had the largest collection of portraits outside the Tate Gallery in London, and there were people to tell you all about them. The Dean was exceptionally kind to me and took a great deal of interest in all my activities.

Dining at Christ Church's high table was a marvelous experience. I came across intellectual giants such as Isaiah Berlin, Trevor Roper, and W.H. Auden, as well as many leading politicians and members of the church hierarchy. The latter were always extremely knowledgeable, and we often discussed many aspects of Judaism, religion, and of course the Hebrew Bible. Despite this intense introduction to college life, I still thought it would be difficult to obtain a permanent position at Oxford, so I started studying intellectual property law in the evenings.

I helped with tutorial teaching for the chemistry students at Christ Church and taught thermodynamics. My grounding in thermodynamics at Manchester, with Geoffrey Gee and John Rowlinson, had been inspirational. I determined to build on those studies and provide a new approach in which the teaching would be done using a series of problems each week. I gave out the written answers the following week after I had marked the students' work. Within a short while these tutorials became classes, as word of the "new" way spread among the university. The concept of teaching by solving problems has always been my approach.

The US Army

One day in 1967, I attended a general lecture by an American general on signal transmission. I have read since that at the end of his lecture I apparently told him his approach was wrong. I do not recall the exact incident, but as a result of this brief encounter I was invited to spend some time at the electronics command in Fort Monmouth, New Jersey, where I joined the group of Ed Poindexter. With my wife and our two children (our second child, Robert, was nearly 1 year old) we settled into an apartment in Long Branch, New Jersey, close to the beach, for a long summer in 1968.

The security at the army base was intense, and my wife was never allowed to accompany me there. The research group was large, with

a diverse collection of scientists from many different disciplines. The basis was signal enhancement using some of the techniques I had worked on for my DPhil. It was a marvelous experience, despite my constant run-ins with the bureaucracies of the army, which only seemed to add to my maverick reputation at the base. I also had the opportunity to see how the army expected to work with academic collaborations and their sometimes unrealistic expectations of these "civilian" endeavors. But it was fun. I recall phoning various suppliers of chemicals when my theories did not work out and asking—with the full might of the US Army behind me—for a list of all impurities. It had to be those suspect ingredients rather than my clever theories that were letting me down!

The Dean of Christ Church and many of my Oxford colleagues were clearly worried about my being associated with the US Army. The Dean phoned me to ask how we were getting on and said that he had arranged for us to visit the Roeblings in Bernardsville, New Jersey, who would introduce us to various people. The Roebling family had built the Brooklyn Bridge, and their huge estate had a chapel on it. The Dean occasionally visited them in the summer months. I realized then the enormous power of the Oxford brand—something I was to use in later life to build bridges with Israel and the Palestinians and also to help in Romania after the fall of Ceauşescu.

Israel, 1969

One of the most outstanding groups of NMR spectroscopists had been put together in the 1960s under the leadership of Sol Meiboom in Israel. Zeev Luz was one of his coworkers, and I visited him at the Weizmann Institute in summer 1969 with a grant from the Royal Society. Zeev was a great scholar and had also been involved in chemical exchange methods using spin echo techniques.

However, I saw that the NMR being done there was not keeping pace with the changes to study biological systems that were rapidly advancing elsewhere. The barrier to the biology was significant and difficult for the Weizmann Institute's rigorous physical chemists, but the problems to be solved were exciting.

On my return to the United Kingdom, Rodney Porter, who was the head of the biochemistry department, asked if I would join his department to help introduce the use of NMR. Rex thought this was an excellent idea (it turned out that he and Rod had decided on it while I was away), and after a couple of interviews—for which I prepared by reading every *Scientific American* article published over the previous few years—I was appointed as a demonstrator. I now had two salaries, one from Christ Church and the other from the Department of Biochemistry.

BIOCHEMISTRY, 1969

Rodney Porter, who took over from Hans Krebs as the head of biochemistry, was determined to bring this field into the modern age, and the department expanded greatly under his headship. Rod gave me a lab next door to his office. He stopped in almost every morning to talk to me and discuss various aspects of science. My initial teaching duties involved introducing spectroscopy to third-year biochemists and teaching intermolecular forces and physical biochemistry to first-year students. Keith Dalziel was in charge of most of the physical chemistry, and he taught mainly kinetics.

I introduced mathematics classes for first-year biochemists and started problem classes in biophysical chemistry, using the same formula that I had developed for the chemists, of problems followed by sheets of answers. Within the first 2 years I had acquired a substantial lecturing load, had taken over Keith Dalziel's lectures (and shortened them considerably), and had introduced more physical biochemistry courses for first-year students. Many of these courses' teaching techniques were included in the book I later wrote with Nick Price, *Principles and Problems in Physical Chemistry for Biochemists* (1).

On Boiling an Egg

To teach thermodynamics, I looked for every opportunity to break down the barriers that the

biochemists had in those days. Once I invited a well-known chef to come to the lectures, boil eggs at different temperatures, and then serve them to the students. I wanted to teach the concept of entropy. It was written in the leading physical chemistry textbook that it was virtually impossible to hard-boil an egg at the top of a mountain as high as Pike's Peak, California. The chef boiled the eggs at reduced pressures in the lectures, and everyone saw that it was possible to hard-boil an egg at 91°C, in as little as 10 min. Another scientific myth had exploded, and the students felt that they were part of this myth-busting process and therefore were very excited. I subsequently wrote up this demonstration with Gil Navon, from Israel, who was visiting my lab at the time, and sent it to *Nature*. It was accepted by return of post and appeared shortly thereafter (2). There were nearly 1,000 requests for reprints within a couple of weeks, and it was hailed by the national press as a breakthrough! Rod Porter was not overly impressed: He enjoyed the joke but did not want me to be remembered for frivolous science.

The Oxford Enzyme Group

Oxford science changed as a result of the development of NMR for biology and because of the presence of David Phillips. He and his team from the Royal Institution, who had successfully analyzed the three-dimensional (3D) structure of lysozyme, had arrived in Oxford in 1965 to start the new Laboratory of Molecular Biophysics. The expensive facilities required for interdisciplinary research, such as NMR, X-ray crystallography, and high-speed computation, were also starting to arrive. By 1969, the Oxford Enzyme Group (OEG) was formally created, and it began its regular meetings in October that year. It was funded to stress the importance of collaborative work, supported the development of high-resolution NMR equipment, and had facilities for the preparation of pure enzymes. Rex Richards was the chairman from 1969 to 1983, and David Phillips was his successor. The collaborative element of what Rod Porter described as a consortium was never lost, and at one time or another more than 10 departments had OEG members.

There were also dark times. In the life sciences, egos seemed much more important than I had encountered previously, and the support that I had taken for granted in the physical chemistry department was not there. Biochemistry consisted of several groups doing their own thing. Only Rod Porter provided some glue, with his larger perspective. The idea that the problem was everything and we should all work to solve it had its limitations; too often, group leaders were unwilling to share success with those further down the ladder. There was rivalry between groups and also within the Enzyme Group.

I began a long collaboration with George Radda and his group in which we used paramagnetic probes and spin labels as reporter groups in phosphorylases a and b. At the same time, I was working on fluorinated sugars made by Paul Kent's group in conjunction with Bob Williams and one of his research students, A.V. Xavier. With I.O. Walker and Arthur Peacocke, I studied pyruvate kinase and phosphofructokinase, using techniques involving paramagnetic ions. The most fruitful collaborations involved Iain Campbell, with whom I wrote *Biological Spectroscopy* in 1984 (3). With David Phillips and Louise Johnson, I worked on many structural aspects of substrates binding to lysozyme in solution, and in these studies our joint research student, Stephen Perkins, played a major role.

It was a difficult time, researchwise. Developing methods and learning biochemistry was fine, but I realized that in the life sciences it was more important than ever to focus on a problem and to have a degree of ownership of that problem. Initially, the spin echo techniques and use of proton relaxation enhancement in a number of enzyme systems did help with method development. This period became one of reassessment of what area I wanted to work in. The OEG provided a highly stimulating environment, and it was comfortable to work with so many outstanding stars. I also began to realize that success in science is an unintended side effect of doing science passionately and with

dedication. It usually happens because you have forgotten to think about it.

I remember breaking the news to Rod Porter that, jointly with Gerald Edelman, he had been awarded the Nobel Prize for Medicine in October 1972 for determining the chemical structure of an antibody. I was also in the foyer of the biochemistry department when the telegram arrived, and I took it up to him. We had quite a celebration in the department and afterward.

NMR in Biochemistry

To collect my thoughts and to concentrate on scholastic matters, I wrote a series of articles on the use of paramagnetic ions in enzyme systems. I was involved in many high-profile collaborations using these within the Enzyme Group. By 1972, the advances in instrument design, particularly the use of Fourier transform spectroscopy, had greatly improved the sensitivity of NMR spectrometers. People were already talking of using NMR to solve the 3D structures of biologically important molecules, but there were many other applications of NMR in biological systems. I wanted to look at the bigger picture in biochemistry to assess the impact of NMR using a wide variety of techniques. An opportunity presented itself when Arthur Peacocke (who later won the Templeton Prize) asked me to write a monograph on NMR. The result was *Nuclear Magnetic Resonance in Biochemistry: Applications to Enzyme Systems* (4). It was a huge amount of work and took me nearly a year to complete, occupying every spare moment I could find.

One morning in 1973, Porter rushed into my lab holding reviews from *Nature* and *Science* on the book. They were excellent. It had never even occurred to me that the book would be reviewed. The book sold extremely well, and we used the royalties for the school fees of our children, Juliet and Robert, to whom (along with Sandra) the book was dedicated.

The publication of the book resulted in many visitors to my lab and led to numerous invitations to lecture worldwide. A particularly memorable series of lectures was the Lund Lectures, organized by my friend Sture Forsén and his student Dennis Burton. I had encouraged Dennis, when at Oxford, to study for his doctorate in Sture's lab.

In 1973, after what I thought was a particularly excellent departmental seminar by one of my joint postdoctoral students on phosphofructokinase, Porter called me to his office to discuss the seminar. He pointed out that monitoring conformational changes in allosteric enzymes or large proteins using reporter groups might be interesting mechanistically; however, without detailed 3D studies, he did not consider it to be cutting-edge science. What was needed, he said, was a major assault on the antibody molecule!

Extracurricular Activities

A new and more intense chapter in my scientific life was about to begin, which is why, looking back, I was fortunate to have the counterbalancing perspective of extracurricular activities. At Christ Church, apart from my teaching, I was part of the coaching team for rowing. I implemented a strict regime, with training around 6 AM on the river most days. At the college, I initiated special tables in the dining hall for the crews with high-protein diets (much better food!). This encouraged competition for places both at the tables and in the crews.

Christ Church was also a center of learning for theology. There were several clerics who knew classical Hebrew and were always interested in talking about the Hebrew Bible. They were especially fascinated by Judaism, and it was this college, as well as others at Oxford, that had helped many German Jews by offering them an academic home in the 1930s. The roll call of Christ Church Jews included Albert Einstein, who spent time there before going to Princeton.

Actually, Oxford has had a surprisingly long Jewish presence. The earliest Jews arrived from Normandy around 1066, and soon developed a thriving community in the city and surroundings. That community was expelled from Oxford, and England, by a proclamation

of King Edward in 1290. With its many monasteries and study enclaves, Oxford had always been interested in Hebrew in the context of biblical studies. Christian scholars completely dominated Hebrew studies in Oxford during the medieval period, but by the late sixteenth century Jews had returned to Oxford to teach Hebrew. In fact, Hebrew has been taught continuously since the establishment of the Regius Professorship of Hebrew in 1546. Moreover, the Bodleian Library, whose Jewish collections were established in 1600, is the world's richest treasury of manuscripts and books relating to medieval European Jewish civilization. I was able to see many of these books, talk about texts, and study them.

RECOGNITION AND DIVERSITY

The Structure of an Antibody Binding Site

Rod Porter moved me into a new lab with another of his protégés, the late Alan Williams. Alan was brilliant, and although he had not actually published for nearly 3 years, Rod had faith in him. Our lab was described as "the noisiest in the biochemistry department." Science was really fun, and Rod was an inspiring mentor.

I began to write a series of feasibility reports on using NMR to determine the structure of the combining site. In those premonoclonal days, mouse myelomas (usually mineral oil/pristine-induced) were used because they were homogeneous antibodies. The antibody we chose was the dinitrophenyl (DNP)-binding immunoglobulin A mouse myeloma MOPC 315. I usually presented a report to Rod every 6 weeks, and for the most part I concluded that it was unlikely that I would be successful. There were many skeptics in the NMR community, and I was aware of the future career problems should I fail. But the challenge was important and too exciting to resist.

However, to mitigate the difficulties and become familiar with the antibody molecule, I used a series of DNP-spin labels to try to find the dimensions of the binding site. There was also a binding site for lanthanides in the Fc, which I argued was a useful probe for showing that the trigger of the Fc functions following antigen binding was a result of aggregation and not allosteric changes.

One morning in April 1973, during Easter break, I received an excited phone call from Alan. He had gone into the lab to read the journals and had seen that David Givol and his team at the Weizmann Institute in Israel had just prepared an active antibody fragment (Fv) composed of the variable portions of heavy and light chains of MOPC 315, which had a molecular weight of 25,000. This was still too large for NMR studies, but we thought it was exciting and so rang Porter. He mentioned that Givol had worked with him previously. He phoned him and invited him to come to Oxford! His mission was to show us how to make this fragment so that we could initiate structural studies on it. Thus began a 9-year collaboration with Givol and his colleagues at the Weizmann Institute. In 1974, our daughter Deborah was born, and with Sandra and our three children I spent many subsequent summers working at the Weizmann Institute.

When David Givol arrived in Oxford, Rod asked Betty Press and others in his Medical Research Council (MRC) Immunochemistry Unit to help initiate the mice and harvest the myeloma. Rod also recruited Simon Wain-Hobson as my DPhil student to work on the NMR structure. Then we had an amazing piece of luck! Simon found that on adding the DNP hapten to the Fv fragment, and then taking a difference spectrum, he could obtain "an NMR subspectrum of those residues in and around the combining site." The antibody has a rigid structure, so adding a ligand to the binding site simply perturbs the neighboring residues.

We extended this experiment to the use of DNP-spin labels to map out distances of residues around the ligand and the shape and dimensions of the combining site. Two Fab structures from the groups of David Davies and Roberto Poljack had been published; these publications had led to the concept of the immunoglobulin fold, which would be similar in all antibodies. The residues forming the

binding sites that are complementary to the antigen are contributed by hypervariable regions so that replacements of amino acid residues in these segments generate binding sites with new specificities. Such replacements do not disturb the immunoglobulin fold of the variable domains, which remain constant in all antibodies. Thus, on a background of a common 3D structure, a vast number of specificities can be generated.

This research provided a basis for model building using the coordinates of the framework from the X-ray data and the sequence of the Fv fragment of MOPC 315. The hypervariable loops attached to the fold and making up the combining site were built on the basis of structural principles. The initial model was built by Carolyn Mountford, who was an assistant in David Phillips's group and who had a lot of help from Max Perutz's model builder in Cambridge. Carolyn took the model on the plane to the United States for David Davies to inspect it and then flew to the Weizmann Institute for their comments. This caused quite a stir, and Carolyn had VIP treatment on the planes and in immigration. The results of the model building were then refined by a combination of NMR, spin label studies, and chemical modifications. In a team that included Simon Wain-Hobson, Steve Dower, Peter Gettins, Brian Sutton, Stephen Perkins, and David Givol, we wrote a series of papers that were summarized in our *Nature* paper published in 1977 (5).

The binding site was very hydrophobic, and there were large "ring current shifted resonances on the DNP." In another tour de force, Perkins, who was studying for a DPhil with David Phillips, Louise Johnson, and me, recalibrated the conventional NMR ring current tables by using the results from the NMR shift perturbations on sugar ligands bound into six different crystal structural forms of lysozyme. This result provided a further structural tool for analyzing the orientation of the hapten in the binding site.

My research group had become quite large, and I had established collaborations involving different types of antibody binding sites with many colleagues, including Mike Potter at the National Institutes of Health, who many regarded as the father of myelomas. We initiated some research on sugar binding sites that brought me into contact with Elvin Kabat. Like Mike, Elvin was a wonderfully supportive person who shared his knowledge and expertise. That was a real characteristic of nearly all the immunologists I met. I made frequent trips to the National Institutes of Health to attend antibody workshops. I have many happy memories of Mike and his colleagues and of sailing with them and Chris Anfinsen in Chesapeake Bay.

Max Perutz had followed our work and invited me to Cambridge to discuss the structure of the combining site, and we kept in contact. Subsequently, his son Robin was elected to Exeter College, Oxford, to teach inorganic chemistry, and we had a fruitful collaboration studying antibody combining sites by using resonance Raman spectroscopy. The MRC was very supportive of my research on antibodies, and I remember Jim Gowans, who was the secretary of the MRC, coming to Oxford to discuss my research and the requirements for funding. How things have changed today.

On most days Rod Porter had lunch with David Phillips, Henry Harris, Richard Gardener, Walter Bodmer (whom Rod had helped to recruit to the chair of genetics in his department), and Betty Press. I frequently joined them, and it was fascinating to hear them talk about many issues in science. I learned a lot by listening. I was asked by Rod at one of these lunches to apply for the vacant Locke Fellowship at the Royal Society, which could be held in Oxford. It turned out that he, David Phillips, and Bob Williams had decided that this would leave me more time for research and that they would support me. I held this appointment from 1974 to 1976, and I had to go to London for a series of dinners and meetings at the Royal Society. I often went on the train with Dorothy Hodgkin and usually carried her briefcase, as she was suffering from bad arthritis. One of those train rides, a decade later, was to prove transformational for glycobiology.

FROM ANTIGEN ELIMINATION TO GLYCOBIOLOGY

Shortly after the *Nature* paper was published, in a small seminar on this paper to Rod Porter, Dorothy Hodgkin, Jim Gowans, and Bob Williams, Rod suggested that I move to a bigger challenge and think about antibody effector functions. The organization of the antibody molecule into domains allows the recognition of a virtually unlimited range of antigens by the variable part of the structure, while the constant part mediates a number of effector systems that are related to antigen elimination and/or immobilization. The best characterized of these was the classical pathway of complement; the triggering event is the binding of the first component, C1. This macromolecule consists of three subcomponents, C1q, C1r, and C1s. The binding site for the Fc region of the IgG was known to be on the subcomponent C1q, but its exact location was unknown. The structure of C1q had been resolved by Rod and Ken Reid, and it seemed a daunting challenge to try to locate the C1q receptor site on the Fc region of the immunoglobulin G (IgG) molecule. I put together a team to undertake this task.

At lunch one day, Walter Bodmer and Rod Porter suggested that I apply for a newly created lectureship in biochemistry. It was more of an order, really, as I was very happy as the Royal Society Locke Research Fellow and liked the freedom. But after several "talks" by David Phillips, I applied. The lectureship was also to be at Exeter College beginning in October 1976, but Rod also wanted me to teach and build up the biochemistry department at Trinity College, of which he, as the Whitley Chair of Biochemistry, was a fellow.

Women's Lib

Oxford was also changing and considering admitting women. I went to speak at the local state school and found some outstanding young women who had simply never considered going to Oxford. I admitted them and thus became part of that revolution. Oxford biochemistry improved considerably with the admission of women. Exeter was firmly set against women as fellows but did begin to admit them as undergraduates. It was not until 1986, when I introduced the first woman fellow, Jane Mellor, as the Monsanto Senior Research Fellow, that women became part of the governing body.

Political Asylum

Throughout the 1970s, I had kept in touch with Sturé Forsen and Dennis Burton in Lund, continuing to work with them on paramagnetic relaxation enhancement in a variety of biological systems. Dennis had also been in contact with Jiri Novotny in Czechoslovakia, who had written to me saying that he was doing some similar work and asking to collaborate. It was quite a surprise for us all when, after Dennis started a postdoc in my laboratory in 1979 to work on the Fc region of the antibody molecule, Jiri Novotny suddenly appeared, asking for political asylum.

He, his wife, and his baby daughter had been allowed to come to the United Kingdom. They had one small suitcase between them, as they had not wanted to alert the authorities of their plans. Jiri had officially come over to visit David Phillips, who was responsible for having just initiated the first Royal Society exchange scheme with Czechoslovakia. Jiri was the first scientist to come to the United Kingdom. David was quite embarrassed at this turn of events. The Foreign Office made it clear to us that they did not want him to defect to the United Kingdom. They suggested that it would be better done elsewhere, such as in France! Rod Porter, however, was very supportive: He took the attitude that you couldn't always choose when to defect! I took Jiri into my lab; the university arranged accommodation for him, his wife, and his daughter; and we registered him as Jiri Allen (my middle name). I asked him to join the team on the C1q binding site Fc region of the antibody molecule. It must have been difficult for him, but his clear abilities and intellect were apparent to all of us.

In a team of people who would become stars—including, notably, Dennis Burton and

Zeke Emanuel—we proposed the binding site for Clq on the Fc region of the IgG molecule. This location was based on accessibility, sequence-conservation analyses of amino acid residues, chemical modifications, and specific inhibitors. The recognition of C1q on the Fc consisted of a virtually planar array of mostly charged residues involving "surface matching." This finding was dramatically different from the principles of antigen recognition. We published our conclusions in *Nature* in 1980 (6).

Shortly after the paper appeared, Rod arranged with Ed Haber at Harvard for Novotny to be offered a job there doing structural work on antibodies. The problem was how to get him safely into the United States through immigration. We instructed Zeke Emanuel to go with him. If anyone could shout the immigration authorities down with articulate speeches about human rights and common sense, then Zeke could—a talent that has never left him.

Soviet Hungary

In summer 1979, I went with my family—now including our fourth child, Joshua, who was 1 year old—to the Institute of Enzymology of the Hungarian Academy of Science in Budapest. Peter Zavodsky, our host, had spent some time in my lab in Oxford working on hydrogen/deuterium exchange in the Fc. Porter thought it would be a good opportunity for me to report to him on the science in Hungary, as the Royal Society was considering expanding its scientific exchange programs.

We drove to Hungary, taking lots of spare parts for cars that Peter's colleagues wanted. We were given a picturesque house in the artists' village Szentendre, about a 20-min drive from Budapest. Hungary was still under Russian rule, and we soon realized that people had been displaced so that we could have accommodation. We set about finding the owners to compensate them. A very elderly lady who was too old to move remained in the house. My daughter Deborah, aged four at the time, remembered being scared of her. But her abiding memory was that the milk was always sour. We also noticed that there was no litter in the streets because there was little or no packaging of foodstuffs.

With Peter we went all over the country, giving lectures. I set up a collaboration on antibodies and complement with Peter, and several members of my lab went there for a few summers to work. Two of them, Robin Leatherbarrow and Marcella Beale, began a romance there, and in due course they married.

The Sugars on the Antibody Molecule

On returning to Oxford, we completed the paper for *Nature* (6), but I continued to think about the hydrophobic surfaces of the Fc region of the antibody molecule, which were covered by carbohydrates. It became important to determine what role, if any, they played in complement activation, as well as their structures.

One member of the C1q team was Tom Rademacher, a postdoc from Wisconsin, who had remarkable experimental and analytical skills. He started to set up the techniques that Akira Kobata in Japan had pioneered for the release of sugars by using hydrazine. We set up a team with Tom, which included a brilliant, young, and experimentally gifted DPhil student, Raj Parekh, to improve the existing methods, which were labor intensive, very time consuming, and limited in sensitivity to milligram quantities of glycoproteins.

Many of our Oxford colleagues, including Henry Harris and Frederick Dainton (the latter of whom was chairman of the Wolfson Trust), were very supportive and helped me obtain the funds for high-performancy liquid chromatography (HPLC), refractive index and radioactive detector systems, and computers to drive them so as to automate the analytical system as far as possible. We had to collect or make the exoglycosidases needed to sequence the sugars. We used anhydrous hydrazine to release the oligosaccharides from glycoproteins. There were then several processes involving chromatography steps that took, in total, about 14 days before we could even begin to analyze the released tritium-labeled oligosaccharides.

The analysis, which was based on sequential exoglycosidase digestion to remove the sugars, took many more days.

The results for the IgG molecule were amazing! The homogeneity of the Fc would have suggested that there would be one oligosaccharide chain associated with the conserved Asn-297 glycosylation site on each heavy chain of the Fc. However, unexpectedly and excitingly, 32 oligosaccharide structures were found, instead of the expected 1—and the birth of glycobiology was imminent.

GLYCOFORMS: A NEW CONCEPT

The result of the 32 structures associated with the antibody suggested a new concept. A glycoprotein may exist as glycosylated variants, or glycoforms, in which an ensemble of oligosaccharides is associated with each glycosylation site. We were tempted to speculate that such glycoforms could diversify the effector functions of the Fc, and indeed nearly 20 years later this has been shown to be so. In those early days, however, one of the approaches we took to determine the function of oligosaccharides was to find out how they altered in disease states. I also established a unit that would develop a systematic approach to analyzing sugars and develop the necessary technology.

Antibody Glycosylation Changes with Rheumatoid Arthritis: A Diagnostic

Dennis Stanworth, from the Rheumatology Unit at Birmingham University, was a frequent visitor to the lab because he had major interests in and research programs on antibodies. We started a collaboration studying the glycosylation of antibodies from patients with rheumatoid arthritis. In a remarkable tour de force led by Raj Parekh, we evaluated over 1,400 oligosaccharide sequences from antibodies and showed that in rheumatoid arthritis the population of oligosaccharides shifted to oligosaccharides that terminated in *N*-acetylglucosamine (GlcNAc) rather than the normal galactose. We termed these structures G0 (no galactose). There were dramatic and diagnostic differences in the "sugar profiles" from patients with rheumatoid arthritis compared with controls. The shortened G0 structures exposed a "patch" on the Fc that was covered by the normal structures.

The G0 parameter was a useful diagnostic. Pauline Rudd, who joined the group as a technician in charge of all these studies, did so well that she was later promoted to group leader and, in 2005, became a professor in Dublin, leading the Dublin–Oxford Glycobiology Lab. Pauline worked with me for 18 years and was key in helping me organize the Glycobiology Institute after it was built in 1991. That was also a time of change, with its emphasis on immunology, and Pauline helped that effort while continuing to develop oligosaccharide-sequencing procedures.

On rheumatoid arthritis and other closely related diseases, we produced a series of papers with many colleagues, particularly those from the groups of Ivan Roit and David Isenberg in London. We studied around 1,000 patients to verify that the glycosylation diagnostic was disease specific. We also showed that the number of the G0 structures altered with disease severity.

I was discussing these data with Dorothy Hodgkin one day on the train to London. She had severe arthritis and was very interested. She told me that when she had been pregnant her arthritis went into remission but that it returned postpartum or when a miscarriage was imminent. This way she knew of the miscarriage long before the doctors told her of her condition. She mentioned that in 1948, Philip Hench, the discoverer of cortisone, had realized that pregnant women were immune privileged and had looked without success for the "magic ingredient" in their blood and urine. She suggested that we should now study the sugars on the antibodies of women who had arthritis and became pregnant. Our subsequent data showed clearly that when there was remission of disease in pregnancy, the pattern of glycosylation of the antibodies returned to normal but that postpartum it reverted back to abnormal. Therefore,

glycosylation was not random but rather controlled and reproducible in the same physical state.

Monsanto Consultancy

In 1984 one of my colleagues in the physical chemistry laboratory, Graham Richards, who worked on computer-aided molecular design, asked me consult for Monsanto, which was transitioning to a pharmaceutical company. Monsanto was evaluating a drug that interacted with the Fc portion of the antibody molecule. Two days later, after calling numerous contacts, I concluded that the drug was unlikely to work. I phoned my report in, and Monsanto staff responded that the other 16 people that they had asked would not be submitting their report for some time yet. When they did, they were all of the opposite opinion to me. Monsanto thanked me politely, but I told them not to pay me. They would need all their funds to fight the litigation that would happen if they went ahead!

Six months later, Monsanto asked to see me at Oxford. Apparently new data had emerged that supported my opinion, and they wanted to thank me and reward me. On arrival in the lab, Edward Paget and his colleagues asked me what our research was about, and I gave them a three-page summary on oligosaccharide technologies that I had been preparing to take to the five major banks in the United Kingdom to ask for support for our sugar research.

I had struck a chord, as Paget and his colleagues were thinking about the glycosylation of the molecule tissue plasminogen activator (tPA)—a drug that was being developed by both Monsanto and Genentech to dissolve blood clots after heart attacks and strokes. When I showed them the data on rheumatoid arthritis and our ideas for a potential drug based on covering the Fc patch exposed by the G0 sugars, Paget was very excited and asked for an option to fund this research. I asked him for a sum of money as a gesture of trust and donation until I could talk to Porter, who was away for a month. He agreed. Trust was always to be a feature between Monsanto and Oxford University.

Oxford University's First Industrial Grant in 850 Years

Howard Schneidermann was Vice President for Research and Development at Monsanto. He was a distinguished geneticist, a member of the US National Academy of Sciences, and one of the pioneers of genetic engineering. He was also a friend of Porter. Edward Paget reported directly to Howard in 1984. He was helping Monsanto develop a pharmaceutical division. He had an enviable track record, having been James Black's team leader at ICI and at Smith, Kline & French, when Black had invented beta blockers and histamine receptor antagonists.

Howard was in London and had several hours between planes, so he had tea with Rod in his farmhouse in Charlbury. They discussed the possibility of obtaining funds from Monsanto, which was keen to support technology development in the life sciences. Porter reckoned that the sequencing procedures and technology development that I was proposing were probably too expensive for a UK research council to fund alone at that time. I prepared a proposal for Howard with Raj Parekh and Tom Rademacher, and Tom and I flew to Monsanto headquarters in St. Louis, Missouri.

Howard liked the presentation, and after talking to Richard Mahoney, the president of Monsanto, told me that they were going to fund our study. After some negotiations, we agreed on a rolling 5-year grant.

This was the first industrial grant in Oxford University's 850-year history. It was featured on BBC news, and was not without problems. There were people in Oxford who felt that the size of the grant from Monsanto (over £1 million per annum initially) would "overbalance the university." There were questions raised, both in Oxford and elsewhere in the United Kingdom, as to whether it was right to accept industrial money. Monsanto, however, was sensitive to these concerns and did not want to take advantage of Oxford in any way; they even offered to fund lawyers to represent the university against themselves. The final contract became a model for Oxford University

for future interactions with industry. The grant was a "Blue Skies" grant, but interacting with Monsanto taught Oxford the necessity of protecting intellectual property. This was a new area for Oxford University, and we had a lot of help from Monsanto. Indeed, Monsanto always set an example in partnership by looking after the university's interests.

There were many visits from Monsanto personnel to Oxford, and my colleagues at Exeter College were wonderfully supportive. As rector, Lord Crowther-Hunt thought it a marvelous partnership. He had been Minister of Education and Science in Harold Wilson's government and saw this collaboration as an important step forward. David Vaisey was the Bodleian Librarian, and he frequently showed our visitors some of the treasures of the library. I realized then that Oxford's fame owed a great deal to our important collections.

In September 1985, shortly after the grant was initiated, Rod Porter was killed in a car accident. That was a huge loss both scientifically and personally. The enormous support for the Monsanto grant that he had given gave way to constant battles with some members of the administration, who saw the funding as a bank into which they could dip. Those were battles I was not prepared to lose, even though they were time consuming, and I became skillful at protecting the grant for my science.

The award and support for Oxford eventually totaled around US$100 million. These funds included the basic research program, which was to run for more than 13 years, major equipment, a support group from G.D. Searle (see the section titled "Another First for Oxford University: An Industrial Group on Campus," below), a new building (the Glycobiology Institute), the endowment of a Monsanto fellowship at Exeter College, and an endowment for future scientific research at the termination of the agreement.

Commercialization Possibilities of Oligosaccharides

The Monsanto grant attracted a great deal of publicity for Oxford worldwide. Sugars had become interesting. In autumn 1986, I received a visit from three eminent US scientists from Harvard, MIT, and the pharmaceutical company Genzyme. They wanted to purchase oligosaccharides released from proteins using our technology, along with the enzymes used to sequence them. They thought about expanding Genzyme's operations to include this technology. I talked to the officials in the university, and I registered a company named Oxford Oligosaccharides (OO) and considered whether we should sell the reagents.

Another First for Oxford University: An Industrial Group on Campus

In 1985, Monsanto acquired the pharmaceutical company G.D. Searle. The G.D. Searle officers were against commercializing my technology. I therefore agreed to take it no further, as my main interests were to preserve the research contract at Oxford. G.D. Searle was clearly impressed by my agreement and also by my refusal to accept any personal consultancy; they suggested, by way of compensation, to fund and place up to 15 of their scientists in my group to help prepare the technology for commercialization in 1988. These scientists had dual reporting responsibilities to G.D. Searle and to me at the University of Oxford. It was another experiment and another first for Oxford, and it worked because of the excellent quality of the scientists.

The G.D. Searle group was led by Gary Jacobs, who was an exceptional experimentalist and a good manager. He and his team purified and established many of the protocols for isolating and purifying the exoglycosidases that were used in oligosaccharide-sequencing procedures. Their manual, in which all these protocols were compiled, became part of the technology transferred to the spin-off company Oxford GlycoSystems (OGS) when it was eventually formed. Later, this team was heavily involved in the iminosugars program for HIV.

Monsanto appreciated that I agreed to their wishes to postpone starting a company. In another show of support for me and for Oxford, they endowed a Monsanto fellowship at Exeter

College for someone to take over my teaching duties there, leaving me with more time for research. We later elected the president of Monsanto, Richard Mahoney, to an honorary fellowship, and he developed great affection for the college. He was a great anglophile and admirer of Winston Churchill, and he stayed in the rector's lodgings at Exeter on several occasions.

DEVELOPING THE OLIGOSACCHARIDE-SEQUENCING TECHNOLOGY

With the funds from Monsanto, we set about improving the techniques for releasing, labeling, separating, and sequencing oligosaccharides from proteins. We were named the Oxford Oligosaccharide Unit. Tom Rademacher's analytical skills were very important for this research. I also used the NMR and crystallography strengths of Oxford to create a center for oligosaccharide structural analysis. As a result, we formed many collaborations worldwide. We had dozens of applicants who wanted to join the unit. One was Mike Ferguson, who worked out the structures of the first two glycosylphosphatidylinositol (GPI) membrane anchors (with Steve Homans) when at Oxford. This development also convinced me of the need to ensure the technology was disseminated widely.

In 1992, we published a method to sequence oligosaccharide structures in a single step by using an array of enzymes that produced defined fragment patterns that could be analyzed by computer; this method enabled individual oligosaccharides to be sequenced in hours. In 1993, the introduction of fluorescent labeling improved the sensitivity of glycan detection to the femtomole level. This development, together with novel HPLC-based technologies for separating and sequencing, allowed detailed sugar prints from glycoproteins to be obtained. A set of rules was derived that related glycan structure to elution position, permitting structures to be predicted directly from a single HPLC profile. By using a series of multiple enzyme arrays, simultaneous sequencing of oligosaccharide pools could be carried out, eliminating the need to isolate individual glycans.

So, within a decade, it became possible to examine the glycosylation of microgram amounts of proteins. Today, an in-gel release method is routinely used to obtain glycans directly from gels of glycoproteins, and with HPLC columns the technology has become miniaturized.

In 2006, Pauline Rudd and her group left the Glycobiology Institute to set up the Dublin–Oxford Glycobiology Group as part of the National Institute for Biological Research and Training. Part of Pauline's mission was to set up glycosylation analysis and its use in quality control products for the pharmaceutical industry in Ireland. Today, Pauline and her group have transformed the detailed glycan-analysis procedures by developing a sensitive, robust, 96-well plate–based, automated platform for *N*- and *O*-glycan release and labeling. Bioinformatics software and experimental databases enable computer-assisted data interpretation of optimized HPLC glycan separation (the industrial standard for robust, portable, and quantitative glycan analysis). These developments put glycomics on a similar basis to other high-throughput "-omics" technologies.

Furthermore, I considered it important to place oligosaccharides within their biological context. This meant that we would build their structures onto proteins to generate models of the intact glycoproteins. We developed structural databases for structures of sugars and linkages to proteins.

Collaborations Worldwide

From Oxford we facilitated an enormous number of collaborations, notably in the early days with my close colleague and friend Alan Williams. Other important projects include the first structures of GPI anchors with Mike Ferguson; the glycosylation of prions with Stanley Prusiner; and the long-standing collaborations with Ghislain Opdenakker and colleagues at the Rega Institute, University

of Leuven, on a variety of cytokines and gelatinase B, alias matrix metalloproteinase 9. The recent joint collaboration with Ian Wilson and Dennis Burton's groups at the Scripps Research Institute in La Jolla, California has involved glycan immunogens as part of the HIV vaccine program. The collaboration on the glycosylation of tyrosinase with Stefana Petrescu and colleagues at the Institute of Biochemistry in Bucharest, Romania, became an important link to the West for them during the years of regime change after Ceauşescu.

I set up training programs for students from overseas, started joint doctoral programs with several different labs, and encouraged scientific visitors to come to the Glycobiology Institute and learn the technology so they could transfer it back to their host countries. This seemed to me a way to create many excellent scientists who believed in the importance of sugars and were prepared to work in the field, hopefully on important scientific problems. In 2012, we met a milestone of 900 institute publications and more than 100 patents, which involved nearly 2,000 different collaborators worldwide. The technology, while enabling, was always second to the scientific questions.

As part of the training program, we started collaborations with Ben-Gurion University (BGU) in the Negev region of Israel. This university was established in 1969 with a mandate to help the development of that region. It was very much involved in outreach activities to Israel's neighbors. It is my belief that scientific cooperation can bring together researchers and find a common language for the betterment of humanity. I saw the Oxford brand as a means of helping to contribute to BGU's efforts to build bridges to peace through sharing technology and science.

One distinguished visitor to the lab around 1986 was Albert Neuberger, whose pioneering research had shown that oligosaccharides were an intrinsic part of proteins and who, with his colleague Derek Marshall at St. Mary's London, had identified the sequon Asn-*X* Ser/Thr for *N*-linked oligosaccharide attachment. Albert was retiring and wanted to place some of his associates in good labs. I had taught his son, David Neuberger (now UK Supreme Court President), when he was at Christ Church, and I had the feeling that Albert had approved. I agreed to take David Ashford from Albert's lab in London. David started a program on plant lectins in the institute. In plant biochemistry, there was a general feeling that sugars were important! Albert soon became a frequent visitor. He had been Fred Sanger's PhD supervisor, and Fred had been Rod's, so there was a lot of history there. I enjoyed many lively discussions with Albert on diverse topics.

BBC Radio Interview; Glycobiology

Shortly after the publication of our *Nature* paper in which we showed that a change in the glycosylation of the antibody molecule correlated with the occurrence of rheumatoid arthritis (7), I was interviewed on the BBC Radio 4 *Today* program. It became clear that the word oligosaccharide was not user-friendly for the vast majority of the nonscientific public. I coined the word glycobiology to describe the field and, with Tom Rademacher and Raj Parekh, subsequently used it in the *Annual Review of Biochemistry* in 1988 (8). At that time I was appointed professor of glycobiology by Oxford University and encouraged the Oxford University Press to start the journal *Glycobiology*. The word was soon taken up around the world, where it provided a special identity to many people already working in the field. My idea was to emphasize the importance of oligosaccharides in their biological context in the hope that this would reveal their functions.

A Knock on the Door and the *Oxford English Dictionary*

One day, I received a knock on my door from a woman working for the *Oxford English Dictionary* (OED). She informed me that she was responsible for the letter "G." The word glycobiology had been chosen, after many discussions and deliberations, for inclusion in the new addendum to the dictionary, which was to be published in 1992 with a reference to me as having coined the name. I subsequently

attended a launch of the supplement to the OED and was assured by the vice chancellor of Oxford University that there was no higher honor for a scientist than to have his name and his word in so eminent a publication as the OED!

Protein Structure and Tissue Type Influence Glycosylation

Alan Williams was still working on the cell-surface antigen Thy-1. We thought a good test of the oligosaccharide technology would be to determine the oligosaccharide structures at each of its three glycosylation sites, and compare the glycosylation in Thy-1 from rat brain with that from thymus. Again, this was a mammoth task, but the results were very exciting and had important implications. We demonstrated that glycosylation had tissue specificity, superimposed by a significant degree of site specificity. We also determined the set of the individual glycoforms and their amounts. Surprisingly, there were no glycoforms in common between the two tissues, despite the amino acid sequences being identical. This finding implied that although the peptide influences its glycosylation, the expression or exposure to glycosidases and glycosyltransferases mediates the tissue-specific characteristics (glycotype).

Alan and I sent the paper to *Nature*. Within a week a subeditor had returned it with a note to the effect that "there was no function known for Thy-1 and none for sugars, so it couldn't be considered for publication." I didn't mind the prejudice and saw it as a challenge. Fortunately, the *EMBO Journal* liked the paper, and the editor said we could have as much space as we needed to publish all the data (9).

Biotechnology and Glycosylation

In 1985, G.D. Searle was interested in making and marketing tPA, which dissolves clots after heart attacks and strokes, and was in direct competition with Genentech. Monsanto and G.D. Searle held a meeting of all their opinion leaders in St. Louis to see whether they should continue their program and what commercial freedom to operate they would have. After 2 days, they concluded that the intellectual property was such that they would have little freedom, but none of their arguments took the attached sugars into consideration. The analysis on Thy-1 had indicated that glycoforms were tissue and site specific. Raj Parekh now extended that concept to show that the glycoforms were also cell specific. We analyzed the glycosylation of tPA expressed from the two different cell lines that Genentech and Monsanto were using. Our analysis showed that there were no glycoforms in common. We filed a patent for tPA, which demonstrated that the actual glycoforms of a protein, rather than only the protein's amino acid sequence, were important. It was possible to distinguish different glycoforms and, therefore, different products from the same gene when expressed in two different cell lines. The patent was featured in *Nature* and the *London Times*. In terms of biotechnology, glycosylation was suddenly very important!

These studies also brought us into contact with Ghislain Opdenakker. He had been involved in the first studies of tPA and was an outstanding molecular biologist, clinician, and immunologist. We started a collaboration with him and his institute that has lasted nearly 30 years.

Intellectual Property

The tPA patent was the first of many that we were awarded over the next 20 years. I learned an enormous amount from the gifted and brilliant Monsanto and G.D. Searle lawyers about all aspects of intellectual property and patent law. By 2012, the Glycobiology Institute had a portfolio of more than 100 patents stemming from our research programmes. These patents continue to provide a royalty income that supports DPhil studentships in the different research groups.

The US Food and Drug Administration and Quality Control of Glycosylated Biopharmaceuticals

Basic research had shown that sugar processing was site specific and tissue specific. Data

emerging in the late 1980s demonstrated that the actual sequence of sugars attached to a protein was important. A significant example was erythropoietin (EPO), a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow. EPO can be made in cell culture and used as a drug to treat anemia (low red blood cell count) that is associated with chronic kidney failure in patients who are or will be receiving renal dialysis. The turnover time of EPO is 3 h, but for those glycoforms with missing terminal sialic acid residues, the turnover time can be as short as 3 min. Those glycoforms would be ineffective as a drug. The correct sugars are therefore vital to EPO's action as an effective drug (which, incidentally, has worldwide sales of more than $10 billion).

Furthermore, the glycosylation of drugs grown in cell culture is sensitive to the environment of the cell (such as pH, glucose content, and temperature). Determining the glycosylation is an excellent way of monitoring quality control. I made several visits to the US Food and Drug Administration (FDA) around 1987 and 1988 to make this point and met with a receptive audience. Quality control became a significant part of the business of OGS after it formed.

There were other commercial implications, in that it is possible to collaborate with pharmaceutical companies and choose which cell-culture lines are best for expression of their glycodrugs so as to ensure reproducibility of the product, as well as safety and efficacy. These factors are extremely important in the production of monoclonal antibodies, a $30 billion–a–year industry (and growing). Furthermore, specific glycoforms of the Fc can have dramatic effects on the effector functions of the antibody molecule.

MARGARET THATCHER AND HIV

In the late summer of 1987, David Phillips asked me to drive him and Walter Bodmer to Cambridge. Apparently, Max Perutz had visited the Prime Minister, Margaret Thatcher, and others to stress the urgency of research on HIV. The MRC AIDS Directed Programme of Research was to be set up. Twelve scientists met in the rooms of Sidney Brenner at King's College, Cambridge, to plan a strategy to tackle HIV research in the United Kingdom.

With Max Perutz, I was delegated to help with the antiviral efforts. We set up testing centers, and Max and I tried to encourage researchers to send compounds for testing of antiviral activity against HIV. However, more than half of the molecular mass of gp120, the major envelope glycoprotein sticking out from the viral surface, was carbohydrate, making it one of the most heavily glycosylated known proteins. This glycosylation, which derives from the host cells, is effectively a glycan shield.

Researchers from Kew Gardens discovered deoxynojirimycin (DNJ), an iminosugar isolated from the leaves of the mulberry tree, which we showed had some anti-HIV activity. Max and I arranged to have some DNJ sent to Oxford, where George Fleet's team modified it by attaching side chains. This modification increased the potency of the antiviral properties. In a joint effort between Oxford, Cambridge, and scientists from Kew Gardens, we developed a range of similar antiviral compounds as part of the MRC AIDS Directed Programme of Research. Sadly, the MRC was somewhat bureaucratic, and Max lost patience with their slowness in moving forward with the compounds. He asked me to call the president of Monsanto in St. Louis, Richard Mahoney, with whom I had developed a very good rapport, to see if he could help.

Mahoney was wonderfully supportive and gave instructions for a number of Monsanto and G.D. Searle chemists to help synthesize some of the iminosugars. As the compounds were glucosidase inhibitors, we thought at that time that their mechanism of action was simply to inhibit the removal of glucoses from $GlcNAc_2Man_9Glc_3$, the oligosaccharide precursor for *N*-linked glycosylation of newly synthesized proteins in the endoplasmic reticulum

(ER). This precursor attaches to the sequon Asn-*X*-Ser/Thr-*X* (where *X* is not proline). The description of the glycan processing pathway in the famous review by the Kornfelds in the 1985 *Annual Review of Biochemistry* (10) indicated that the removal of these three glucose residues is necessary for the biosynthetic processing pathway of the oligosaccharides to proceed. However, it was nearly 10 years later that the reason was discovered: The removal of the glucoses was actually involved in the 3D folding process of some glycoproteins. This important finding provided glycobiology with a fundamental concept for understanding some of the roles of *N*-glycosylation in glycoprotein function.

The compound eventually chosen for the clinical trial was *N*-butyldeoxynojirimycin (NB-DNJ). NB-DNJ was made at the G.D. Searle Nutrasweet factory in Chicago. I went there with Max, and we were told that the starting material was 100 t of glucose. Chi-Huey Wong and colleagues from the Scripps Research Institute later suggested a "one-pot, three-step synthesis," which eventually allowed large quantities to be made much more easily. G.D. Searle proceeded with the clinical trials in some 80 patients. The iminosugar era was launched.

LAUNCHING OXFORD GLYCOSYSTEMS

Oxford University's First Direct Spin-Off Company

Meanwhile, the initial plan for business objectives and strategy was being compiled for the university's first direct spin-off company, in which the university had a significant sponsorship. My aim was to establish a world-class company founded on the technology base represented in the Oxford/Monsanto research programs. The initial objectives would be to develop and market products to serve scientists involved in carbohydrate-related research and diagnostics. Therapeutic applications of the technology developed by the program would, however, remain the province of Monsanto and G.D. Searle. The main products would be sugar standards, enzymes, and instrumentation. The business model would also involve contract sequencing by way of validating the technology. Additionally, there would be a contract with Oxford University that would enable the technology to flow from my lab to the company.

Managing the Different Parties

There were still two lines of thought within Monsanto and G.D. Searle. The Monsanto personnel felt that OO should be given a very free range, which they were convinced would create the maximum opportunity to disseminate the technology and encourage others to work in it. In contrast, the G.D. Searle personnel were highly protective of their technology and feared leakage. I had to deal with this constant tension during the formation of the company. However, I also had to deal with Oxford University, which had no experience in scientific start-up companies, as well as ensure there would be no conflicts of interest involving myself, my research, and the company, a very important point in technology transfer that is not always given sufficient consideration. To help in managing all these parties, the university's lawyer dealt with all my legal matters.

Oxford GlycoSystems: The Company

We wrote down the rules of what the company could and could not do. The first rule was: "The Company must do nothing to bring the name of Oxford University into disrepute." The initial investors were Advent Capital and Euro Ventures, two funds managed by Advent Ltd., and Alafi Capital Corporation. Monsanto was a limited partner in each of these funds. The university, Monsanto, the scientists, and the staff were the initial shareholders, and a price was set for the funds to purchase shares. It was the first time that Oxford University had been directly involved as a shareholder in a spin-off company, and I had many meetings with the administration and other personnel to reassure them of the value of this and future similar enterprises.

The company was to be incorporated in the United Kingdom and was expected to have premises in the Oxford area. Members of the board of directors were determined; they included representatives from the university, Monsanto, and the investors. Ernie Jaworski, who was an expert in biotechnology, represented Monsanto's interests and was a great support to Oxford University and my program. Licensing arrangements were to be put in place between Monsanto and G.D. Searle for the intellectual property from my research group, and there was also a technology agreement between Oxford University and the company.

Headhunters were employed to find a suitable CEO. We had to employ scientists who understood the field, and the best choice was clearly my former DPhil student Raj Parekh, who was pursuing postdoctoral research in my group. He initially joined the company for 1 or 2 days a week, but it soon became clear that the company needed him full time to succeed. We changed OO's name to reflect that it was a technology company, and OGS was born on October 14, 1988. Raj became chief scientist.

Although I remained a director of the company, the day-to-day running was firmly in the hands of Dale Pfost, an American who had a successful track record of developing scientific instruments and had excellent entrepreneurial skills. Within a year, the first products, the reagents used in the analysis of sugars, were on the market. OGS was housed temporarily in the start-up premises of Martin Wood (the founder of Oxford Instruments) but soon moved to its own new building in Abingdon. There the team was built up with engineers and scientists, with the idea of making accessible and automating the technology that had come from Oxford University. Indeed, my team had modified the hydrazine conditions to release both *N*- and *O*-linked glycans from glycoproteins. Their results were a crucial contribution to the development of an automated instrument, manufactured and marketed by OGS, which allowed glycans to be released and purified in 8 h compared with the manual method that, at that time, still took 15 days.

There were tensions between the university and OGS, as the university scientists were not involved in the engineering inventions needed to commercialize and miniaturize the technology. There was a lack of understanding as to how a company operated. Then, too, the scientists at OGS were highly focused and did not always seem to appreciate the enthusiasm of the university scientists for constantly trying to improve or change the procedures. I attempted to manage this aspect by appointing a liaison officer from OGS to the university. At times, it was difficult to keep all parties focused on the common mission, with their quite distinct areas. I worked hard to keep the peace between all of them. I must have been reasonably successful, as several members of my research team moved to join OGS.

OGS continued to grow and expand, producing automated machines for the release, separation, and sequencing of oligosaccharides. Nearly every major pharmaceutical company purchased these machines; by 1998, more than 130 of OGS's instruments for preparation, analysis, and sequencing of glycoprotein sugars had been sold worldwide. OGS had also provided a wide range of reagents and kits for glycobiology. Additionally, under Raj Parekh's leadership, OGS's technology development had continued to be imaginative, with the introduction of a world-class automated proteomics platform. The strong technology base of OGS made it one of the first companies to become aware of the opportunity afforded by the Human Genome Project. OGS's proprietary proteomics technology, which analyzed proteins in biological samples, was the perfect adjunct to the human genome. It was becoming clear to OGS that it had all the tools for drug development. To reflect this focus, the company changed its name to Oxford GlycoSciences—still OGS.

The Glycobiology Institute and Visits from Margaret Thatcher

By this time, the collaborations between Oxford University and G.D. Searle had also proven

rewarding for numerous projects, and we had trained several scientists from Monsanto and G.D. Searle in the basic technology. To cement this relationship, Monsanto and G.D. Searle funded the construction of the Glycobiology Institute at Oxford, which was a part of the biochemistry department. The Glycobiology Institute opened in 1991. In recognition that glycobiology had emerged from the immunochemistry program initiated by Rodney Porter, the building housing the institute was named the Rodney Porter Building. G.D. Searle continued its support for the basic research program at the Glycobiology Institute.

Over the next 20 years, the Glycobiology Institute trained more than 100 PhD students and supported 200 postdoctoral workers, as well as hosted several hundred visitors. In addition, there were many external grants. I also encouraged the institute scientists to become involved in teaching biochemistry and immunology, as well as glycobiology, so almost all the members of the institute were involved in teaching at various levels in the university. Even if the field of glycobiology was difficult to appreciate, it was clear that institute was a formidable resource for the biochemistry department.

Margaret Thatcher came to the institute several times over the next 5 years. I was also summoned to Downing Street to see her on two occasions and once had a private meeting with her at Oxford. She told me how much she admired what we were doing—fundamental research in the university funded by industry, and having a spin-off company. She thought it could become a model for British science. She even discussed with me starting a new Glycobiology Institute somewhere else in the United Kingdom. However, I cautioned her against making this a general model. I was aware that it probably sent the wrong message to British science and my colleagues at the university. I think she was offended by my answer.

Gaucher Disease: An Approved Drug Worldwide

The results of the clinical trial for HIV, conducted by G.D. Searle, showed that the iminosugar drug NB-DNJ was mildly effective in patients. There was a problem: It had a side effect of osmotic diarrhea. This drawback limited the concentration that could be achieved in serum to make the drug truly effective as an antiviral.

At that time, Terry Butters and Fran Platt were part of the G.D. Searle group at the Glycobiology Institute. Along with Gabriel Neises, an expert in electron microscopy from G.D. Searle and Monsanto, who had come to Oxford to discuss the project, they noticed that there was an apparent thickening of the cell membranes. There was anxiety about that result as we worried about the effects in vivo. However, it turned out that the staining material was interacting with the drug, resulting in an artifact. Nevertheless, they examined the glycolipid composition of cells that were treated with the drug NB-DNJ and showed that they had an altered glycolipid composition. Fran and Terry proved that the drug was a glycolipid inhibitor. We initiated a program and showed that NB-DNJ inhibits the glucosyl-ceramide transferase, which catalyses the glucose addition to ceramide in the first step of glycolipid synthesis. Personnel from Monsanto and G.D. Searle, who received regular reports on our research and came to Oxford for frequent scientific visits, told me that it was not worth pursuing this line of research and that their employees should stop as it was not mainstream—-instructions that I ignored.

Fran and Terry realized that many of the glycolipid-storage disorders involved accumulating glycolipids. Any inhibition of the first step of glycolipid synthesis would reduce the amount of glycolipids formed so that there would be less to break down. They suggested that this would be a good therapy for Gaucher disease, in which patients have a mutation in the glucocerebrosidase enzyme that breaks glucocerebroside down into glucose and ceramide, with resulting storage of glucocerebroside. We did some experiments in a macrophage cell line to illustrate the feasibility of using NB-DNJ to prevent or reverse storage, with positive results. Importantly, the drug was effective for this

indication at 50-fold-lower concentrations than those used for the HIV trial.

In 1993, G.D. Searle in the United Kingdom was retrenching and reorganizing worldwide. Also, OGS had been formed, so the initial remit of the G.D. Searle group had been fulfilled. I negotiated to keep Terry Butters and Fran Platt so that the program on glycolipid-storage diseases could continue at the Glycobiology Institute.

Meanwhile, OGS refocused as a pharmaceutical company. After much negotiation between Oxford and G.D. Searle, in which I was adamant about wanting to develop the drug, G.D. Searle granted the company a license to develop NB-DNJ for Gaucher disease. However, I had not foreseen the difficulties of convincing OGS to do so. Like many start-up biotechnology companies, OGS wanted a blockbuster drug and did not appreciate the concept of targeting more restricted or "orphan" diseases. Throughout the path to the clinic, there were always problems of commitment to this drug from management at OGS, but—helped by data from the institute—I persevered and was supported by the OGS clinical team, which was first rate and always argued for its continuation. Because of the huge body of data from G.D. Searle on NB-DNJ for the HIV clinical trial, and because the drug had been tested on humans, it was possible to go directly to a clinical trial in Gaucher disease patients with few additional studies to be conducted.

The standard treatment for Gaucher disease was enzyme-replacement therapy, which Genzyme had pioneered. This treatment was expensive, costing between $200,000 and $400,000 per year. Genzyme's marketing seemed very powerful, as there was significant opposition among patient groups to the Oxford drug. Again, I had not counted on that, as I thought that a pill would be preferable to an infusion of enzyme. The pill was sometimes described as being toxic and causing peripheral neuropathy. However, a later study on naïve Gaucher disease patients seemed to indicate that this symptom was associated with this population and not the drug. In a small disease population in which there are no meaningful statistics on naïve patients, it is quite easy to create difficult scenarios to stop new treatments from flourishing.

OGS did team up with Genzyme for a trial in which we initially reduced the storage load with enzyme therapy and then used the iminosugar pill as maintenance therapy. The trial was conducted in Israel but was abruptly cancelled when the clinician in charge said that the pill caused Alzheimer's disease. When asked for the evidence, the reply was that the drug crossed the blood–brain barrier and that there were glycolipids in the brain! The *Wall Street Journal* reported that the trial had been discontinued, and the share price of OGS tumbled dramatically. It took a lot of persuasion from me to ensure that OGS would continue. In 2002, Zavesca®, the NB-DNJ drug, was eventually approved for use in Israel, the United States, and Europe. Interestingly, the drug has now been used by patients for more than 10 years, and no additional serious adverse events have been reported (other than those listed in the original labeling). This fact was instrumental in a reexamination of Zavesca's use as an antiviral agent.

OXFORD GLYCOSYSTEMS: THE BILLION-POUND COMPANY

Late in 1998, OGS was positioned to meet the requirements to be listed on the London Stock Exchange as a pharmaceutical company. One of the two drugs that were required to gain this status was to be for Gaucher disease; this drug had come directly from research at the institute. I had always made it clear that any financial rewards to me were to be given out in research grants or blue-sky grants to the institute. In recognition of this pledge, OGS announced blue-sky grants of £1.5 million to the Glycobiology Institute and a grant of around £0.5 million for my Public Understanding of Science series. In addition, OGS set up a state-of-the-art proteomic facility at the institute. In all, OGS gave several million pounds in grants to Oxford. OGS's close liaison with the university continued, sometimes with difficulties, but the clear

success of the company was apparent to all. By 2001, there were more than 250 employees at OGS, and the stock market value of the company was more than £1 billion.

We had come a long way from 1988, when the seed funding to write the business plan for the company was provided by Advent Capital and Euro Ventures. Once we received the funding, we recruited our first CEO, Dale Pfost, from the United States in September 1988. The initial investment agreement was then completed, and the company was valued at £600,000.

Between 1988 and 1996 we had five rounds of financing and raised around £15 million from many international funds and, importantly, from Oxford University. However, by 1996 it had become clear that the direction of the company was moving toward pharmaceuticals.

We recruited Michael Kranda, who had spent 12 years at Immunex (now Amgen) as its president and chief operating officer, as our CEO. During his tenure, he established the company as the leading proteomics platform–based drug-discovery company. Private financing of around $13 million from the investment company Warburg Pincus in New York, which we obtained when Michael joined OGS, was contingent on the change from a reagents company. By 1998, we had £11 million in cash. The company went public, raising an additional £30 million, and was valued at £150 million.

By 2000, it had become clear that we needed extra funds for our growing pipelines and proteomics developments. With Lehman Brothers, we raised an additional £210 million, the most ever raised in the biotechnology sector, on the London Stock Exchange. Dealing with Lehman Brothers was never easy, and we asked that there be no exchange of information between their branches in the United States and the United Kingdom so we could challenge each division to outdo the other! In the event, the offer was oversubscribed by approximately fourfold. The company was also listed on NASDAQ, with the valuation reaching about £1.6 billion (more than $3 billion dollars at the time).

Monsanto and the University of Oxford sold their shares at a handsome profit. The university passed 15% of its profit back to the biochemistry department after I became its head in 2000. I used these funds for a variety of projects, including planning a new building for the department.

Many people made a lot of money from buying and selling OGS shares, and I received countless calls and letters of thanks. Few understood what the company actually did, though. I also noted that I was referred to as a biotech "guru" by the *London Times* on several occasions. I was even invited to give a seminar at the Bank of England on start-ups and commercialization. Although I was happy to give seminars on OGS, I always emphasized the science in order to promote glycobiology—that, after all, was my real currency.

By May 2000, the proteomics side of the company was flourishing; it interacted with most of the major pharmaceutical companies and was developing technology with several partners. OGS had been granted a major patent covering computer-assisted methods and instruments that were used to image, select, and robotically isolate proteins from biological samples. This approach was considered to be a revolution in the process of identifying disease-associated proteins for use as diagnostics, protein therapeutics, or new drug targets.

In general, drug discovery was proving more difficult than developing the proteomics platform. There were successes. In June 2000, OGS received fast track designation from the FDA for Zavesca for the oral treatment of Gaucher disease. Subsequently, Zavesca was designated an orphan medicinal product by the European Commission, and OGS became one of the first companies to have a drug designated under this status in the European Union (under legislation that had been passed in 1999). By August 2001, we had completed the submission of a new drug application to the FDA. I believe every drug that comes to market needs a champion who is passionate about it, and OGS did not yet have that culture. Whenever there were difficulties with the trials for Gaucher disease, there was often

talk at OGS of abandoning the drug. Michael Kranda, having overseen the company's transition, realized this weakness, I think, and returned to the United States for valid family reasons. This left the CEO position somewhat in limbo. The chairman of the board, Kirk Raab (formerly of Genentech), initiated a search for a CEO. Although one was appointed, it became clear that to succeed as a drug company OGS needed a better pipeline, which they could acquire by acquisition or a merger. My interests, however, were shifting to infectious diseases, and it was clear that the scientists at OGS did not share my enthusiasm.

When in January 2003 I was in India opening a conference, I received a phone call from Raj Parekh informing me that OGS was thinking of merging with Cambridge Antibody Technology (CAT). I was initially opposed to this idea and became even more so after meeting their CEO on my return to the United Kingdom. I wrote to the board of directors that there was no pressure to do this merger because the valuation of the company at which it was being done was just above its cash value, and the company took no account of the proteome technology. However, I was the minority voice, and it was clear that the OGS board was in favor overall. On reflection, I thought that it might be beneficial for the biotechnology industry in Europe to create such a large company with huge resources, but I was still worried about the leadership.

On March 23, 2003, the boards of directors of CAT and OGS announced that they had agreed on the terms of a recommended merger to create a leading European biotechnology company that would combine the key strengths of both organizations. However, Celltech Group PLC, a large UK biotech pharmaceutical company, saw the potential merger between OGS and CAT as a threat to their dominance in the industry, and launched a hostile takeover bid. On March 26, Celltech's board announced the terms of a cash offer for OGS, which OGS accepted because their major shareholders had reversed their positions and indicated that, if it came to a vote, they would be in favor. I think the OGS board members were tired and that there was a lack of leadership. In November 2002, they had even licensed out the Gaucher disease drug to Actelion, a Swiss biopharmaceutical company. The management of OGS then argued with me about payment of the additional licensing fees that I had negotiated for Oxford University with G.D. Searle, in the event of such sublicensing. It was clear that the OGS management was losing the passion needed to succeed.

Importantly, I had met Martine Rothblatt, the CEO of United Therapeutics (UT), with whom we were discussing partnering for the iminosugars program for antivirals, as OGS was not interested in this area. Martine was imaginative, creative, and an inspiring leader, with insightful scientific tastes and understanding. That leadership is what makes the difference in a successful pharmaceutical company. Clearly, UT had it, but I realized that it was now lacking at OGS.

OGS was and still is regarded as a success story. It had developed a drug, had a powerful technology, and was cash rich when it was taken over. Wherever I went in the world, there was a feeling that although most people might not understand glycobiology, we had succeeded in a world that they did understand—finance! My advice on start-ups was continually being sought so that I would reveal the magic ingredient that led to success. I usually replied, "people, passion, patents, and partnerships, but above all leadership." The success of OGS and of the Glycobiology Institute provided the credentials that, together with the brand name of Oxford, opened up a range of opportunities in science, particularly in Romania, Israel, and Ireland, as well as the United Kingdom, where I felt I could help make a difference.

GLYCOBIOLOGY AND VIRUSES

Baruch Blumberg Joins the Institute

In May 1989, Baruch (Barry) Blumberg came to my office and asked if he could join the Glycobiology Institute, which was then under

construction. He had just been appointed the master of Balliol College, Oxford, a post he held until 1994. He was interested in genetic polymorphisms, inherited variants of proteins that he believed might be associated with human diseases. As a follower of Darwin, he thought that all such variants that had persisted in human populations had to be important. He thought that there was a lot in common between his ideas on polymorphisms and my ideas about the diversity and importance of sugars and their evolutionary persistence. He made these remarks in the era in which scientists were still questioning whether there was any real role for sugars.

Barry and I became very close friends, a friendship that lasted until the end of his very full life, in 2011. He was terrific with all the students and took a great interest in the new building but was looking for further challenges. I asked him to join the scientific advisory board of OGS, which enabled him to become familiar with the clinical trials of the iminosugar (NB-DNJ, Zavesca) for Gaucher disease and to find out about early research on this iminosugar as an antiviral in the HIV trial.

As we prepared to move into the new institute, I told Barry that I wanted all the scientists to be involved in experiments. We had frequently discussed his pioneering work on identifying hepatitis B virus (HBV) and developing a vaccine, for which he was awarded the Nobel Prize in Physiology or Medicine in 1976. By chance, in 1992 Tim Block from Thomas Jefferson University, who knew Barry, wanted to come to Oxford for a sabbatical year to study the glycans on the S antigen of HBV. He thought, correctly, that just as in the case of rheumatoid arthritis the glycans would change as the disease progressed, in this case to liver cancer.

Iminosugars as Antivirals Against Hepatitis B Virus

Tim Block was a delightful person, full of energy and with a mission to help sufferers of hepatitis B. He and his wife, Joan, were among the founders of the Hepatitis B Foundation, based in Philadelphia, which is dedicated to finding a cure and improving the quality of life of those affected by hepatitis B worldwide. Tim's presence at Oxford and his subsequent annual visits, combined with his expertise on HBV, allowed us to explore the effects of NB-DNJ on HBV secretion. There is only one conserved glycan site on HBV attached at Asn-4 on the M-envelope glycoprotein, and there is a partially occupied site on each of the other two envelope (glyco)proteins, termed L and S. The effect of the drug was to prevent secretion of the virus.

We assumed that the drug, a glucosidase inhibitor, had prevented the removal of the glucose residues from the 14-sugar oligosaccharide precursor for *N*-linked glycosylation, $GlcNAc_2Man_9Glc_3$, which is attached to newly synthesized proteins in the ER. We determined that an *M*-glycoprotein in the ER was the triglucosylated glycoform. Surprisingly, we found that a considerable fraction of the HBV envelope glycoproteins retained within the cell were not rapidly degraded and aggregated, which we hypothesized was the result of misfolding.

We were amazed, however, that the single conserved sugar site on the virus might be responsible for such a startling antiviral effect. We felt that something much more fundamental, a missing link, was required to explain the effects of the drug. Understanding that link would be key to the later development of the iminosugars as antivirals. Barry was delighted both about the discovery and because he could now claim to be involved in experiments at the institute. The parent compound of this class of iminosugar (DNJ) comes from the leaves of the mulberry tree, and it was perhaps no coincidence that Barry's portrait at Balliol, painted in 1993, shows him under this tree.

Three Glucoses and a Puzzle, and the Mechanism of Action of Iminosugars

One of the early enigmas of glycan processing was why the initial oligosaccharide precursor $GlcNAc_2Man_9Glc_3$ for *N*-linked glycosylation,

which attaches to the sequon Asn-*X*-Ser/Thr-*X* (where *X* is not proline) of newly synthesized proteins in the ER, contains three glucose moieties that are then removed before further glycan processing occurs. We know now that these glucoses can have a role in the 3D folding process of the glycoprotein. Inhibition of the enzymes that remove them, the ER α-glucosidases, is the potential mode of action of iminosugars that are antiviral drugs. Such iminosugars are mimics of monosaccharide residues, with the ring oxygen replaced by a nitrogen atom, and can be regarded as substrate analogs of glucose. In protonated form, they approximate to the transition state in the enzymatic process. The nitrogen atom also provides a further point for chemical modification, giving rise to a spectrum of iminosugars.

Glycoprotein Folding: The Details

By 1995, several groups had shown that folding intermediates of several *N*-linked glycoproteins associated transiently in the ER with the type I membrane protein calnexin. In 1997, in collaboration with John Bergeron from McGill University, we demonstrated that calnexin acts exclusively as a lectin. A primary role for *N*-linked glycosylation in many mammalian systems may have been to retain the glycoprotein in the ER so that it folds correctly.

We can thus add to the fundamental scheme for glycan processing by noting that the terminal glucose residues may have functional significance in terms of 3D folding and the controlled assembly of many newly synthesized glycoproteins. The $GlcNAc_2Man_9Glc_3$ precursor rapidly loses two glucose residues to become $GlcNAc_2Man_9Glc$. This monoglucosylated form then binds to the chaperone glycan binding protein (GBP) calnexin. This binding provides access to a folding pathway; allows the recruitment of the thiol oxidoreductase, ERp57; and assists in the assembly of subunits and oligomerization. From the solution structure of the glucosylated *N*-glycans, we proposed that the glucosidase II that cleaves the final glucose from the glycoprotein would still be bound to the GBP, thus promoting dissociation from it. Inhibitors of the ER α-glucosidases, such as iminosugars, can be used specifically to target glycoproteins that depend on this interaction.

In their role as quality control factors, the GBPs (calnexin and calreticulin) retain unfolded glycoproteins in the ER until they are correctly folded and assembled, an event signaled by the permanent removal of the terminal glucose residue by glucosidase II. The folded glycoprotein, or the assembled multimolecular complex, is then transferred to the Golgi apparatus, where the oligomannose sugars may be further processed. Misfolded or unassembled subunits are reglucosylated by a transferase, which allows them to rebind to calnexin/calreticulin and enter a cyclical pathway until they achieve their correctly folded structure and are released; otherwise, they are targeted for retrograde transport and degradation.

Glycobiology Against Viruses; Antiviral Drug Discovery

A fundamental concept that helped glycobiology develop as a distinct discipline was the finding that glycans attached to a protein play a role in a glycoprotein's correct folding. Of particular relevance is that this finding applies to the envelope glycoproteins of many viruses. Because viruses are subjected to rapid evolutionary pressures, this is strong evidence that glycosylation has important functions. Indeed, the pathogenicity of three major human pathogens, hepatitis C virus (HCV), HBV, and HIV, as well as the two most prevalent acute viruses, influenza and dengue, depend on their glycoproteins.

Mammalian viruses are not known to encode their own carbohydrate-modifying enzymes; they use the host cell glycosylation machinery to modify their envelope proteins. The attached glycans may have many roles, including protein folding and stability, immune presentation, and escape from immune surveillance and infection of target cells. The concept of using drugs that interfere with the initial glycoprotein-folding process in viruses is a novel strategy for

antiviral therapies. These drugs target host enzymes and thus reduce the chances of the emergence of escape mutants, which is the major drawback of most other antiviral strategies.

By 1998, research performed at the Glycobiology Institute had demonstrated that iminosugars were a novel class of antiviral drugs that act as morphogenesis inhibitors. In collaboration with Tim Block and Anand Mehta, who was also from Thomas Jefferson University in Philadelphia (and who had worked for several years with Tim and was completing his DPhil at the institute at that time), we discovered that one of these iminosugar drugs (*N*-nonyl DNJ) was able to reduce HBV to undetectable levels in infected woodchucks at doses that appeared to target the virus specifically, without being detrimental to the animals. This drug also worked well in in vitro studies in bovine viral diarrhea virus (BVDV), which was then the surrogate virus for HCV.

Because it appeared unnecessary to inhibit the glucosidases to any great extent to achieve an antiviral effect in vivo, we speculated that the sensitivity of the virus may be due to a requirement to oligomerize the glycoproteins and assemble the envelope in the ER, where protein folding takes place. A few misfolded envelope glycoproteins may be sufficient to disrupt the proper envelopment process and amplify the effect of the inhibitor on virus assembly, when compared with the effect on host cell proteins, which did not seem to be impaired at antiviral inhibitor concentrations. We proposed that other viruses that acquire their envelopes from intracellular membranes, such as the ER, would be equally sensitive to ER glucosidase inhibition, provided that one or more of their glycoproteins depended on calnexin-mediated folding. The idea of a general antiviral therapy was very appealing.

As a result of this successful animal trial and the potential of these iminosugars as general antiviral agents, a new company, IgX Oxford Hepatitis, was created to support further preclinical research and with a view to conducting clinical trials. Baruch Blumberg was one of the founders, along with Tim Block, and the Hepatitis B Foundation was a beneficiary. There are around 500 million HBV and HCV sufferers worldwide, many of whom will die from liver failure if left untreated, and current therapeutic options are limited and often problematic. The approach of targeting the structural envelope glycoproteins via a host enzyme represented a very different mechanism of action from the other therapies being developed.

Difficult Territory

IgX Oxford Hepatitis, unlike most other biotechnology start-up companies, was structured as a scientific consortium rather than as a company. Oxford University was not a shareholder this time but opted to receive a £350,000 research grant over 2 years toward the preclinical studies that were necessary for approval for the clinical trials. Financial backing came from the US biotechnology company IgX; Monsanto (later Pfizer) licensed to the company its large patent estate of iminosugars (many from the Glycobiology Institute) because of its good relationship with Oxford University.

IgX hoped to become a publicly quoted company and wanted to use some of the proceeds to fund IgX Oxford Hepatitis. It was developing pathogen-specific treatments for infectious diseases of the gastrointestinal tract. Its basic technology was to use polyclonal antibodies derived from hyperimmune egg yolks of hens that had been hyperimmunized with specific and purified antigens. However, its clinical trials failed shortly after we had established this new company. We then changed its name to Synergy and looked to partner the iminosugar platform from Oxford.

The Silver Lining

UT, which was growing as a biotech company, was working on pulmonary arterial hypertension (PAH) but was interested in diversifying into unmet medical needs such as that caused by HCV. The CEO, Martine Rothblatt, came to Oxford to meet with me. It was a wonderful meeting, and I was bowled over by her brilliance

and incisiveness. It was the beginning of a great friendship.

Martine had been responsible for conceiving, persuading, and obtaining global agreements, the first of their kind, that brought mobile satellite communications to the entire world. By 1990, she had solidified her place in history as the inventor of satellite radio, recognizing that national and even international digital radio services could be provided to moving vehicles from a series of broadcast satellites. Similarly, in her role as chair of the Bioethics Committee of the International Bar Association, which represents more than three million lawyers, she was the driving force behind its undertaking to present the United Nations with a draft *Universal Declaration on the Human Genome and Human Rights.*

In 1996, Martine founded UT, a biotechnology company focused on developing therapies to treat patients with PAH, a life-threatening disease that afflicted her youngest daughter. In 1999, UT was listed on NASDAQ, and it has been one of the most successful biotech companies in the past 10 years. I have met most of the key leaders in the biotech and pharmaceutical industries, and few approach Martine's understanding of medical, biotechnological, legal, and ethical issues.

As CEO of UT, Martine took the view that long-term investment was required for the development of the iminosugar compounds, so UT became solely responsible for the research funding at Oxford University and handling the licensing arrangements with Monsanto. UT wanted to deal directly with Oxford, rather than through an intermediary. The records at Oxford University show what "a delight and refreshing experience it was to have UT as a partner." The good experiences of the Monsanto arrangements were, in effect, repeating.

That had not been our experience in dealing with Synergy, and the resulting disentanglement took time and energy. The people involved did not seem to share the same values that we at Oxford had acquired from our limited exposure to the biotech industry. But the silver lining was in meeting and interacting with UT, whose idealistic and helpful approach convinced Oxford again that industrial partnerships could be wonderful. We concentrated, with UT, on developing the antiviral program. The driving force was always the science, which cemented this new partnership and its dynamic management team. UT's appreciation of science and discovery empowered both the university and me.

United Therapeutics at Oxford

In 1999, Nicole Zitzmann was appointed a Dorothy Hodgkin Fellow at the institute; in 2000, she led the UT program on antivirals. Nicole's initial screening of the iminosugars also revealed that the long-chain alkyl derivatives of the iminosugars were likely to be inhibitors of the p7 ion channel in HCV and the surrogate virus BVDV, thus providing another viral target. In those days, HCV-permissive cell lines were not available, and the BVDV-permissive cell line was not always a reliable indicator of HCV activity. And so it proved. In 2003, UT undertook the first clinical trial of one of these long-chain iminosugars, which inhibited p7 in BVDV but was not a glucosidase inhibitor, in patients with HCV. It did not reach the efficacy required, but recent data on the HCV-permissive cell line clearly show that this compound did not significantly prevent secretion of the virus and therefore was not a true test of the oral p7 iminosugar antiviral concept for HCV.

Further redesign of the iminosugar platform and regimes for their treatment followed as a cell-culture system for HCV became available. Nicole and her team then demonstrated in vitro that these iminosugars could be used as maintenance therapy for HCV patients following conventional treatment with interferon and ribavirin, which could then be withdrawn. Indeed, even the drug Zavesca, at concentrations used to treat Gaucher disease patients, could be used in this regime. Unfortunately, although UT encouraged this approach, Actelion—the Swiss pharmaceutical company that was marketing the drug for Gaucher disease—failed to

agree on terms with UT to test this approach in the clinic. The potential use of iminosugars in treatment regimes remains an attractive possibility. Oxford University did not understand Actelion's reluctance, given the huge number of people affected by hepatitis.

With the help of UT, a platform of iminosugars was subsequently developed and shown to have broad antiviral activity. Data in animals suffering from dengue (a painful mosquito-borne tropical fever suffered by millions of patients worldwide each year) and influenza, the two most prevalent acute viruses, led to a 2011 award from the National Institutes of Health to UT, of up to $45 million, to support the Glycobiology Antiviral Program. The overall objective for this program is to develop a safe and orally available broad-spectrum antiviral drug, initially to treat viruses such as dengue and influenza.

In 2008, with Nicole Zitzmann and Stephanie Pollock, we sought to extend the range of concentrations of iminosugars that could be delivered to patients (and limit any side effects from high concentrations in sera). We discovered a new class of liposomes that deliver cargo directly inside cells to either the ER or the cytosol. Liposomal delivery allows the encapsulated cargo (in this case, an iminosugar) to bypass the cellular membranes that act as molecular barriers, thus targeting and amplifying the effects of these drugs by several orders of magnitude. ER-targeting liposomes were especially desirable due to the location of our drug target, the α-glucosidases, which reside inside the ER lumen. Although ER-targeting liposomes [subsequently termed polyunsaturated ER-targeting liposomes (PERLs)] decreased the dose by only a further 1.5-fold, compared with liposomes that deliver cargo to the cytosol, PERLs were serendipitously revealed to be antiviral against HIV, HBV, and HCV in the absence of drugs. Their antiviral activity is apparently due to an ability to lower cellular cholesterol to an even greater degree than statins.

This finding launched a new branch of research within the lab focused on the use of liposomes, and the manipulation of lipid metabolism in general, as a component of the broad-spectrum antiviral strategy. Lipidomic studies also made clear that iminosugars might lead to changes in lipid rafts. The glucosylceramide species resulting from the presence of iminosugars contained fewer saturated fatty acids, which can affect the stability of lipid rafts and are important in several life-cycle steps for some viruses. The disrupting of lipid rafts provides a further mechanism of antiviral activity of iminosugars, particularly because the partial inhibition of the formation of GlcCer is also the basis of the approved iminosugar drug for Gaucher disease. Current research is focusing on developing a new generation of liposomes, as well as a new series of iminosugars linked to natural products, that marry the two main qualities we observed following many years of intense research: drug targeting/delivery and intrinsic antiviral activity. With UT, both approaches are being developed for proof of concept in HCV, HBV, and HIV. The drug-delivery and antiviral strategy should be generally applicable as a broad-spectrum therapy and, therefore, should be able to treat coinfections from different viruses.

The design of the liposomes is nontrivial, and issues relating to targeting, stability, toxicology, and retention of cargo are major stumbling blocks in creating new types of liposomes. However, the iminosugar natural product hybrids may provide an attractive alternative by, for example, using natural products that are known to target the ER and have long lifetimes. To this end, in 2013, a new organic laboratory was opened at the institute, to study and synthesize iminosugar–natural product hybrids. The laboratory was named after Richard Lerner from Scripps, in recognition of his close links with Oxford. The integration of chemistry into biology by Richard, while he was president of Scripps, had made it a world-class center and set the standards for other institutions to meet.

In November 2006, the Unither Antiviral Drug Discovery section of the Glycobiology Institute opened, with Nicole Zitzmann as its director. Martine Rothblatt and other board

members from UT were present, along with dignitaries from the university. The plaque that marked the occasion was inscribed with a quotation from André Gide: "In order to discover new oceans, you first have to lose sight of the shore." The Glycobiology Institute had done just that in moving its interests to the glycobiology of viruses. Barry Blumberg was very pleased.

The UT-sponsored blue-skies research at the Glycobiology Institute is currently funded until 2016, making it the longest-funded industrial partnership in Oxford University's history. In 2011, Nicole became professor of virology and deputy director of the institute. In 2012, the Department of Biochemistry formally named her Baruch Blumberg Professor of Virology, in memory of Barry, who had died in April 2011. Another legacy from Barry was that in 2007 he had persuaded UT to endow a series of Distinguished Lectures in Virology at Oxford. These lectures will continue for the next 32 years, which will help strengthen the focus on viruses at the institute.

OXFORD IN THE NEGEV

The Scholarly Path to Peace

Around 2,400 years ago, Nabatean traders crossed the desert by way of the Spice Route, from the gorges of Petra in Jordan through the Arava and Negev regions of Israel. Today, travelers on the same ancient Nabatean trails would encounter BGU at Be'er Sheva in the Negev. The patriarch Abraham's sojourn in the ancient city of Be'er Sheva is described in the Book of Genesis. This city is the capital of the Negev region, a vast and spectacular desert expanse of an area that covers 60% of the country's land mass but is home to only 8% of its population. Strategically located at the axis point between Egypt, Jordan, and Israel, BGU has been a leader in cooperative research projects. Egyptian/Israeli autonomy talks on the West Bank and Gaza in the late 1970s took place at BGU, as did the exchange of ratifications of the Egyptian/Israeli Peace Treaty under the Camp David Accords. Shortly thereafter, in commemoration of this historic event and on the exact spot where Anwar Sadat, Menachem Begin, and Cyrus Vance once walked, a Gate of Peace was erected, welcoming guests to the campus.

I arrived at BGU in late 1996 as part of an international peer-review team of the research programs at the Institute of Applied BioSciences (IAB), which had been established by a donation from a Swiss banker, Edgar de Picciotto, the chairman and founder of Union Bancaire Privée in Geneva. He had met and been influenced by the charismatic Avishay Braverman, a Stanford-educated World Bank economist. In the 15 years of his tenure as president of BGU, beginning in 1990, Braverman transformed what resembled a small local college into an internationally recognized institution of higher education with more than 20,000 students. His dream—to create what he called "a new Israel in the Negev"—extended this transformation even further; he invested in people, ideas, and technologies that strengthened the weaker sectors of society and helped to build bridges with Israel's neighbors. I saw these challenges and felt that science could also help build these bridges, particularly with the support of Oxford University, which has traditionally been accepted by all peoples in the region as a center of excellence and of neutrality in politics. Oxford would offer technology training and collaboration, using the Glycobiology Institute as its main conduit. In fact, it was David Ben-Gurion, the founder of the state of Israel and its first prime minister, who was deeply inspired by Oxford (where he used to spend time reading and thinking) and wished to create "Oxford in the Negev." BGU was founded on the basis of this vision of its namesake.

In 1996, the institute in Be'er Sheva was based in two "huts." Edgar de Picciotto wanted to help develop the Negev. He saw biotechnology as a way of doing that. He had followed the story of OGS and liked the Oxford brand, which made him trust my judgment. The initial work of the IAB focused on polysaccharides (mainly from algae) and biosensors and

was directed by Professor Shoshana Arad. I felt that the science had to be more ambitious if it was to become world class. I put my ideas to Braverman and Arad and became the presidential advisor on biotechnology, a post I have held ever since, but my duties increased when Rivka Carmi became president in 2006. Of all my many files and records at Oxford, those involving BGU from 1996 until today are by far the largest. The complexities of dealing with the academics at BGU, the Israeli government, and de Picciotto in Geneva have been "never-ending." Each had a different agenda, and I had to find creative ways to satisfy all of them. Aaron Klug was initially involved with BGU because his late son was a faculty member there. He helped the whole science scene immensely with his wisdom, understanding, and patience. With Aaron, we created a scientific advisory board for the IAB; we invited Philip Needleman from the United States to join us. I had met and interacted with Philip when he was chief scientist at Monsanto and G.D. Searle (and, later, Pharmacia) and responsible for their grant to Oxford. His track record of developing Celebrex® for arthritis, while he was at Pharmacia, made his involvement a coup for the young IAB.

At the 2000 World Economic Forum in Davos, Edgar de Picciotto, with Avishay Braverman, met representatives from the Israeli government and offered to help fund a National Institute of Biotechnology in the Negev (NIBN) if there were matching funds. I agreed with Edgar's vision that the NIBN would bridge the gap between basic and applied research and would help establish a scientific infrastructure for the biotech industry in the Negev. With the government's matching funds, the NIBN would incorporate the existing infrastructure of the IAB on the BGU campus. The interdisciplinary nature of the research would utilize biology, chemistry, physics, engineering, and computer sciences.

There were growing pains as the scientific advisory board aimed to create a truly new and focused scientific agenda, while many faculty members wanted the NIBN to support whatever they were doing. We introduced rigorous peer review so that membership of the NIBN was not automatic but rather based on productivity and world-class science, but this was not achieved without difficulties. Membership did bring research support and other privileges, and I felt that there had to be excellence and flexibility in research if the NIBN was to make its mark. In 2001, Aaron Klug, David Walt from Tufts University (an expert on biosensors), and I, along with Israeli scientists Chaim Aviv, Yehudith Birk, and Meir Wilchek and members of BGU, agreed on the "constitution" for the NIBN.

On May 21, 2001, the prime minister of Israel, Ariel Sharon, declared the establishment of the NIBN during BGU's annual board of governors meeting, but the agreement was not formally signed until May 11, 2009. The government always had to confront more "pressing security matters," and the investment was not forthcoming.

It was a roller-coaster ride over the 8 years following the initial declaration, but eventually the sum of $90 million was committed, with equal contributions from the government; BGU; and the Swiss donor, de Picciotto. This sum also included funds for a new extension of the NIBN. The NIBN was the first Israeli autonomous research body, and it operates as a separate and distinct institute, steered by its own scientific advisory committee in which the Israeli government, major donors, and university representatives have equal representation.

The autonomous status of the NIBN as a not-for-profit private company under an independent board of directors entails an organizational structure and staff membership that differ from standard university practice. de Picciotto asked me to be his representative on the board to help steer the NIBN through many of the initial problems and to help establish the scientific programs with the scientific advisory committee and the director.

Israel is a tough environment, and a young university such as BGU does not have the benefit of tradition in solving problems. The NIBN was also developing its own ambitious research agenda. Initially, many staff on the BGU

campus saw the NIBN as "extra space" and as an add-on to existing departments. The controversies that ensued, which I had to help sort out each time, left the NIBN stronger and more focused. When Rivka Carmi, a distinguished geneticist who was dean of the Faculty of Health Sciences, became acting director from 2002 to 2004, she helped put the NIBN on a firm academic footing. Rivka had initiated a program of mapping genes specific to the Bedouin communities, which helped improve their health care and was a wonderful example of outreach. This project expanded and initially was one of the main themes of the NIBN. Since Rivka became university president in 2006, she has been instrumental in solving problems relating to the administrative establishment of the NIBN with all parties, particularly her colleagues at BGU. It is doubtful that it would have happened without her support.

In 2010, in recognition of Rivka's achievements and the nature of BGU's outreach policies, a scholarship was endowed in her name for students from BGU to do a master's degree at Exeter College, Oxford University; women and/or minority candidates received preference. Indeed, BGU's outreach also appealed to Oxford Brookes University, which set up a similar scholarship. I felt that this was a fitting tribute to the new Israel that was emerging in the Negev. Even the UK House of Lords, in July 2011, mentioned and praised these scholarships as a way of helping the peace process.

In July 2006, Varda Shoshan-Barmatz, former chair of the Department of Life Sciences, was appointed director of the NIBN. Her tenacity and enthusiasm were important in keeping the issue on the government agenda until the NIBN was formally constituted in 2009. Her international reputation and work on bioenergetics, coupled with her energy and commitment, gave her the necessary authority to lead the NIBN, which now includes more than 230 staff members, including 26 principal investigators and 150 research students. Many of the young scientists are outstanding and would grace any institution or university lucky enough to have them. Their research today covers a wide range of interests, including cancer therapies, computational biotechnology, human genetic disorders, and novel antibiotics. As of 2013, the NIBN has several spin-off companies. It has made its mark both in the Negev and internationally.

Furthermore, the Bedouin communities have received an immediate benefit in health care. The research programs implemented at the NIBN, in collaboration with the Soroka University Medical Center, gave rise to massive carrier testing and prenatal diagnostic efforts, as well as educational strategies for those Bedouin communities at risk from the genetic problems arising from consanguineous marriages.

Oasis in the Desert

Just 25 miles south of BGU, along the Nabatean Spice Route and on a plateau overlooking the spectacular landscape of Israel's largest desert canyon, the Zin Canyon, is BGU's campus in Sede Boqer. Founded near David Ben-Gurion's home at Kibbutz Sede Boqer, the campus houses the Jacob Blaustein Institutes for Desert Research (BIDR), which include the Zuckerberg Institute for Water Research.

Committed to achieving sustainable desert ecosystems and stemming the spread of desertification, the BIDR are more than an inspiration: They are an ideal laboratory for studying the various ecosystems that converge in the Negev desert. Furthermore, Israel lies at the crossroads of Asia, Africa, and Europe, where three of the Earth's major drylands—the Saharan–Arabian, the Mediterranean, and the Asian steppes—converge. Because dryland ecosystems cover nearly half of the Earth's land surface, the seemingly straightforward mission of making deserts productive and comfortable places to live is a task of stunning significance.

The greatest challenge is to protect the limited water resources essential to provide quality drinking water for all the residents of the region. It has been said that water is the oil of the twenty-first century and that more than a billion people worldwide do not have access to clean water.

I brought Dan Koshland (from Berkeley) to see the research being done at the BIDR. He immediately wanted to do something about it. His legacy to the university was to be spent on projects at Sede Boqer that may help the entire region. He instructed me to help oversee the science. He was keen to improve water resources of marginal quality and support research into the sources of salinity in groundwater in the Gaza Strip. The management of other transboundary water resources, such as the coastal and mountainous aquifers shared by Israel and its neighbors, was another area in which he wanted to see results.

He supported BGU and Israel in general in their search for more efficient methods of water desalination that would greatly increase the availability of clean water in the region, without further depleting the existing water sources. Dan hoped that sharing water resources would significantly reduce the tension between Israel and its neighbors and be another bridge for peace, a vision and hope I share.

Science on the Diplomatic List

Meeting Matthew Gould, who was appointed UK Ambassador to Israel in September 2010, added another dimension to my scientific work with Israel. On receiving an honorary doctorate at BGU, he expressed his belief that "[e]verything we do is an expression of our values, and it is through our actions that we give voice to those values. Like our belief in science as a potential force for good, above politics, beyond nation, that can unite and heal."

This statement resonated very strongly with my views, which helped build strong scientific relationships between Britain and Israel. Under the guidance of the ambassador, a council of 19 leading scientists from the United Kingdom and Israel formed the UK/Israel Life Sciences Council. It was officially launched in 2010 by the UK Foreign Secretary, William Hague. The ambassador was the chair, I was the cochair for the UK, and President Rivka Carmi from BGU was the cochair for Israel.

The UK/Israel Life Sciences Council focused on regenerative medicine technology, building on the excellent base in both countries. It was to administer a 5-year multimillion-pound program with three main aims: (*a*) to develop advanced regenerative medicine therapies, including both their discovery and translation; (*b*) to establish a leading partnership between the two countries in regenerative medicine; and (*c*) most importantly, to deepen and widen UK/Israel academic collaboration. The UK Foreign Secretary also noted that science was one of the cornerstones of the relationships between Britain and Israel.

The best-known example of regenerative medicine is the use of stem cells to grow tissues and even organs, although there are other aspects of technology (as well as molecular medicine and other areas), including medical devices, that can help stimulate cell replacement. The program is managed by the Britain–Israel Research Academic Exchange (BIRAX), which is run by the British Council. The BIRAX was part of an innovative program, launched by the prime ministers of the United Kingdom and Israel in 2008, to develop a scientific collaboration between the two countries.

The first BIRAX conference was held in 2011 at BGU, where dozens of scientists from both countries discussed possible areas for cooperation. This initiative was very high profile. Miracles were accomplished in fundraising, and at the end of 2012 the first seven collaborative projects between the two countries were announced. The quality and breadth of the projects were stunning.

The 2013 Diplomatic Service and Overseas New Year's Honours List, which is administered by the UK Foreign and Commonwealth Office, recommends awards for British citizens. I was awarded the CBE (Commander of the Most Excellent Order of the British Empire) for furthering UK/Israel scientific collaborations. The press release included the statement that

> Professor Dwek has been a major force in furthering UK/Israel scientific collaboration for over a decade. A key element of his work is

promoting peace through science. He has made significant medical advances, invested enormous time and effort in sharing the UK's science excellence with the international community, all of which has brought many benefits for the UK and Oxford University.

I felt that this recognition was an important and helpful step forward and that it showed the importance that the United Kingdom placed on the value of science in this relationship, perhaps setting new agendas for diplomacy.

MAKING A DIFFERENCE AT HOME AND ABROAD

On my seventieth birthday, I received a book containing contributions from numerous colleagues in different parts of my life in science. This gift prompted me to add some of my memories from them.

On Being Head of the Department, 2000–2006

By 2000, the Department of Biochemistry—more accurately, the Department of Cellular and Molecular Biochemistry—had become the largest in the Western world. When I became the head, the department had more than 600 researchers and staff. There were also 380 undergraduates on the 4-year MBiochem course. The head of department is formally responsible for all teaching and research. The department consisted of six separate independent subunits, spread throughout six buildings. These subunits were organized into three divisions to encompass all the research interests: molecular cell biology, molecular genetics, and structure. The department had expanded a great deal during the previous decade, but its profile at the university had slipped somewhat, and its research income had not increased in several years. I took it as part of my mission to raise the department's profile and introduce new management and scientific structures.

I had no intention of letting up on my science. The head of department's job would be an extra one. I would remain director of the Glycobiology Institute. I needed support to do so and appointed some additional associate heads of department. Furthermore, in a novel move for Oxford, I promoted the senior administrator, Denis O'Driscoll, to be an associate head responsible for finance. To make changes rapidly on research priorities and teaching, I needed accurate and reliable financial data on both. Nevertheless, it took a lot of convincing of the university authorities to ratify this position. It was another example of nonscientists not appreciating the enormous burdens on productive scientists. There is an absolute need to support scientists to allow them to continue to be creative rather than become immersed in administration. Oxford University came round with good grace.

I met regularly with all staff, particularly the junior staff, mainly on an individual basis; I listened to them, and learned from them, so I could encourage them to suggest ways in which their research could be more productive and better funded. The grant income of the department went up by at least 20% every year during my headship. I think that helped set the scene for the 2008 Research Assessment Exercise, in which 75% of research activity within the department was rated world-class quality in terms of significance, rigor, and originality. This result made it the highest-rated life sciences department of all the universities within the United Kingdom.

Oxford University Consulting, Ltd.

In 2000, the university asked me to help establish and become chair of a new company, Oxford University Consulting, Ltd. The company was wholly owned by ISIS Innovation (the university intellectual property company) and promoted consulting services for members of the university from all disciplines. Academic consulting is a great way to start a university–industry collaborative relationship and is one of the best ways universities deliver impact. At the end of its second year, the company had an income of more than £1 million. I suggested

that, having established it as a going concern, it should be subsumed into ISIS as one of its divisions. I had encouraged members of the department to register as a means of creating more funding opportunities for their research and also raising their profiles. In the very first year, we had more than 40 new academic consultants from the department.

Communication

Communication is very important, especially in a large department. To create a sense of cohesion, I placed point-of-information screens in every building so that I could communicate with the entire department, keeping them informed of all activities, committee meetings, and events that were happening worldwide. I started a monthly e-newsletter that highlighted research, international events, and the history of the department; it also had a section for personal issues, such as advertisements (I knew those, at least, would be read). I wrote editorials each month.

I set up a distinguished external review panel, whose members included Paul Nurse, Richard Lerner, Alex Jefferies, John Walker, Ron Laskey, Tom Blundell, Richard Sykes, Mike Waterfield, Charles Weissman, and Baruch Blumberg, together with industrialists such as Martin Wood. They provided valuable advice and a mechanism for members of the department to raise any criticism of the way I ran the department.

Toward Medicine

It was my view that the future of the department and of biochemistry in general lay more toward medicine. An opportunity to move in this direction came after a visit from the vice chancellor and registrar of the university, who asked me if I would also take over the running of the Life Sciences Division, of which the Department of Biochemistry was a member. They thought that I could fit it into my schedule, even on a part-time basis. In declining the offer, I said that an alternative model was to move all the departments from that division into others, as I was thinking of asking to move the Department of Biochemistry into the university's Medical Sciences Division, the largest of the four academic divisions, which ranked third in the world for biomedicine. I consulted with my departmental colleagues, and there was a lot of support for this idea, particularly because the Medical Sciences Division was financially strong enough to support our plans for future expansion. My own research on viruses had already formed initial links with the medical department. In 2006, Kim Nasmyth was recruited as Whitley Chair; he took over the headship of the department from me. He was a world-renowned scientist on chromosome biology with implications for cancer therapy. I felt he would create strong links between the biochemistry and medical departments.

It is interesting to reflect on the changes in the science fields of the Whitley Chairs in Oxford's Department of Biochemistry during my time there. These changes reflect many of the changes and advances in biochemistry. Hans Krebs (1954–1967) worked on cell metabolism and, of course, is widely known for the Krebs cycle; Rodney Porter (1967–1985) was an immunochemist and is known for the discovery of the structure of antibodies; Edwin Southern (1985–2006), a geneticist, is known for the Southern blot and the discovery of DNA microarrays; and Kim Nasmyth (2006–present) works on chromosome biology and discovered cohesin, a complex involved in chromosome segregation during cell division.

Empowerment

Much modernization was needed in the running of science and in the biochemistry department. We had 250 DPhil students at that time, and I realized that we had to set up a proper graduate structure. I spent significant amounts of the OGS funds given to the Glycobiology Institute to set up the first courses in graduate transferable skills. I appointed a director of graduate studies (who had been a research scientist), a secretary, and staff to run the

office. Further support for the graduate students came from the establishment of senior departmental teaching associates (SDTAs) from the postdoctoral students in the department (there were approximately 230 at that time). I had this position recognized as middle management and chose 20 of the most talented postdocs from the department to be part of this trial scheme. With the SDTAs, we wrote the manuals and decided what courses were necessary for transferable skills. Using some of the royalty money from my institute, I set up a fund to run the graduate staff and finally made it an integral part of the department's infrastructure. I also wrote a charter for the DPhil students that defined their rights so that they would also feel empowered.

The DPhil program was very international, and I worked with other countries to bring students to Oxford because I thought it was important for the United Kingdom to have the best possible students doing research there. I also believed in the politics of debt, in which the training element that they took back to their own countries would lead to an acknowledgment of their debt to the United Kingdom and to Oxford.

One scientifically important program for graduates was with the Scripps Research Institute in La Jolla, California. There, the exciting leadership of Richard Lerner, who had become a very good friend, had shown how chemistry and biology could unite to solve important medical and biochemical problems. I wanted Oxford to benefit from this research. Richard came to Oxford and met the vice chancellor, and they agreed in principle to a joint graduate scheme. It still took nearly 1 year of negotiations within Oxford to change the regulations; thereafter, Oxford and Scripps announced their joint doctoral-level graduate program at both institutions. It was named the Skaggs Oxford Scholarship, after the supermarket and drugstore magnate L.S. Skaggs and his wife, Aline. This was the first time in its 950-year history that Oxford University had offered a degree jointly with another institution of higher learning, and the agreement became a prototype for any other institutions wishing to follow this path. The course took 5 years, and at the end the students earned both a PhD and a DPhil.

I fought very hard to obtain university recognition for postdoctoral researchers (many of them had no college associations) and wrote a charter for them to help in their career development. For 5 years previously, I had advised postdoctoral students on career development. I set up a postdoctoral research committee, empowered it with a budget to run seminars and socials, and gave them a major slot in the seminar program each term. I held dinners for them, to which senior staff were invited, to help them interact with each other and feel an integral part of the department.

There were several committees in the department, and their agenda and attendees were highlighted on the point-of-information screens so that each member of the department could approach them. I introduced induction days to explain the facilities, staff, responsibilities, research, and duties of the department (surprisingly, these had never existed anywhere at Oxford) for all new members of staff at all levels. There were special induction days for DPhil students—indeed, I made them into 1-week courses in which some transferable skills were taught. Overall, I wanted to empower people in the department to encourage initiative and personal responsibility. I also wanted to promote more women at all levels and paid for several places in local crèches so they could benefit from child care.

A New Building

I soon realized that we needed a new building to create better facilities to attract people from all over the world and to work in emerging areas of biochemistry. The Biochemistry Tower, built by a Rockefeller endowment to Hans Krebs, was a blot on the picturesque Oxford landscape and no longer fit for purpose.

A new building had to provide world-class research facilities and state-of-the-art core facilities, and there had to be a new ethos for interdisciplinary work. A space where people

could meet and interact was clearly very important. The whole plan of the new building was to be open so as to encourage interaction at every possible area. At the same time, research groups needed space to focus on their cutting-edge work in state-of-the-art laboratories.

Clearly, the Department of Biochemistry was financially the strongest member of the Life Sciences Division. When from time to time additional funds became available from the university, I had a policy to try to support all the other departments in the division. However, when approximately £16 million in government funds became available to the university for the repair of infrastructure, my colleagues in the Life Sciences Division agreed unanimously that our department had a good case for a new building.

I commissioned a plan of the science area. I noted that there had not been a proper plan since that conceived in 1934, which was supposed to be temporary. Indeed, there had been no permanent plans since 1850, when the Museum of Natural History was built to house all of Oxford science. In 1860, the famous Wilberforce–Huxley debate took place there. The defeat of the church allowed science to blossom and the different disciplines to move out from the museum, but there was no coherent plan.

There was, unexpectedly, a second round of government infrastructure funding, and with the planning and acceptance of a new building came further support from the university. I approached the Wolfson Trust and various other charities for additional funding. I also persuaded the university to contribute a further £10 million, on the grounds that I was releasing high-quality space that the university could now use for other expansions.

I asked Jonathan Hodgkin and David Sherratt to oversee the designs for the new building and the eventual movement there of the staff from the other buildings. The Glycobiology Institute was to continue as a separate entity. The job description of the associate head for finance changed, as he was now employed full time in dealing with the problems and contractors for the new building. Kim Nasmyth had been appointed and had not yet taken over the department, but all the designs had been cleared with him and altered where necessary.

The cost of the new building was around £50 million. The project was helped by substantial sums from the university's sales of its shares in the three spin-off companies from the department: OGS, Oxford Gene Technology (founded by Ed Southern), and Oxford Biomedica (founded by Alan and the late Susan Kingsman). In going through the records, I noted that there were still funds left over from the original Rockefeller gift to Krebs in 1965. Additional funds came from the glycobiology endowment. The funding for the building was completed when Kim Nasmyth obtained a grant of £6 million from the Wellcome Trust.

By the end of 2008, the new 12,000-m^2 biochemistry building, designed by Hawkins\Brown, was complete. The project had taken 18 months and 600,000 hours—without any accidents. It was a distinctive facility with glass facades and colored glass fins. Inside was a large open atrium with breakout spaces and specially commissioned artwork. The themes of the building were transparency and collaboration.

To get the plans for building passed by the city council, we had to agree to knock down the old Biochemistry Tower. When that is eventually done, it will be a contribution to restoring the skyline of Oxford back to that described in Matthew Arnold's 1866 poem "Thyrsis": "the city of dreaming spires."

Romania: Courage in Science Inspires Us All

Biochemistry suffered in Romania under Nicolae Ceauşescu (1974–1989) from lack of financial support and a complete blockade of scientific contacts with Western universities. Cecilia Motas, a highly cultured and courageous biochemist, challenged the rules and attempted to promote international collaboration. After the collapse of the communist

regime, Cecilia immediately took action to revive biochemistry in Romania by reestablishing an institute, of which she was director, under the auspices of the Romanian Academy.

I met Cecilia at a conference at Göteborg in 1992. She asked me to help her train her young scientists. I was moved by her example and dedication. In January 1993, Stefana and Andrei Petrescu, both postdoctoral students, came to Oxford in the first step of a lasting collaboration between Oxford's Institute of Glycobiology and Bucharest's Institute of Biochemistry. This partnership was enthusiastically supported by both the Royal Society and the Wellcome Trust, which saw the importance of trying to rebuild and promote Romanian science. This was a difficult transition in Romania for science, and the collaboration was very important. My colleagues in Oxford helped in the training of many Romanian biochemistry students.

In 1997, I was officially invited by the Romanian Academy to lead the first international scientific evaluation of the Institute of Biochemistry in Bucharest; I was invited again in 2000 and paid several visits in between. I have remained an advisor to the institute ever since. There are approximately 60 people there, all of whom are extremely talented experimentalists. My recommendations, aided by my access to the presidents and vice presidents of the Romanian Academy, led to restructuring and changes in scientific directions, which were accepted willingly. In 2000, the President of Romania, Emil Constantinescu, awarded me the National Order for Merit with the degree of Commander, which raised the profile of our scientific collaboration. The Oxford brand and the success of the Glycobiology Institute of OGS were helpful factors. As the collaboration with Oxford increased, the impact on the scientific efficiency of the Institute of Biochemistry became reflected in the quality and quantity of scientific results and publications. In 1997, Stefana became director of the institute. In 2008, it became a Center of Excellence in Protein Science and was ranked best in the Romanian national evaluation of science.

Serendipity

At Oxford in 1993, Stefana added the iminosugar NB-DNJ to black melanoma cells that then turned white. She reasoned that the synthesis of melanin was inhibited in the treated cells. The biosynthesis of melanin is initiated by the catalytic oxidation of tyrosine to the amino acid L-DOPA by tyrosinase. Stefana assayed that enzyme's activity on a gel, using DOPA as a substrate, and found it to be inactive. Tyrosinase is a glycoprotein, and Stefana showed that its glycosylation was modified in the presence of NB-DNJ. Its folding was accelerated, but into a nonnative conformation, so the enzyme was inactive and not retained in the ER as expected. However, it trafficked to the melanosomes but was unable to acquire the copper ions necessary for activity. Tyrosinase became an important model system in which we resolved many of the details of glycoprotein folding involving the calnexin/calreticulin system and the effects of glucosidase inhibitors. This joint collaboration was helped significantly when Norica Nichita-Branza, a PhD student and brilliant experimentalist from Bucharest, came to Oxford in 1997. At almost the same time, Nicole Zitzmann joined the Glycobiology Institute as a postdoctoral fellow. They soon joined forces and laid the foundations for the antiviral program that was to become their main interest. In 2011, both became deputy directors of their respective institutes at Oxford and in Romania.

SCIENCE AND POLITICS

The Library of Congress

In October 2005, the Librarian of Congress, James Billington, invited me to spend some time at the Kluge Center at the Library of Congress as the Chair of Technology and Society. Although scholars in these positions utilize resources of the library, they may also speak to a range of concerns within Congress. Indeed, part of the role of the chair was "to stimulate through informal conversations and meetings, members of Congress, their support staffs and

the broader public policy community." Interacting with politicians and policy makers in Washington was a great opportunity. The Library of Congress is very centrally located; adjacent to the capitol; and within walking distance of the major federal museums, including many associated with the Smithsonian Institution. Furthermore, the collections at the Library of Congress are remarkable. It is an exciting place.

I agreed to go there during my sabbatical year in 2007, when I stepped down as head of the department. My departure also gave my successor, Kim Nasmyth, a chance to run the department and establish his own priorities and ideas without my being around.

I held this position between February and June 2007. My work involved technology related to water in the Middle East, HIV, hepatitis, and intellectual property. I had many meetings at the Kluge Center and gave talks to the staff of the Congressional Research Service and other members of the library. I was really pleased to see science so high on the national agenda and had many talks with members of Congress who were genuinely interested in science. I convened two conferences for them, which were broadcast on the Internet; one was on HIV and hepatitis and the other on commercializing university research. I also produced, with the help of the Science and Technology Business Division, an article on water in the Middle East ["The Other Green Line and the Sweetest Tomato in the World" (11)] and one on military history ["George Washington and the First Mass Military Inoculation" (12)]. I think many of the staff were bewildered by the intensity and diversity of interests and profile that I wanted to bring to this position. I had the feeling that I was rocking the boat because I saw new ways of doing things and motivating the Congressional Research Service staff. The director of the scholarly programs wrote to me that my "energy and critical eye had left the position charged [sic] for the better."

My wife, Sandra, and I had a wonderful time socially, attending multiple functions and meeting and talking to many politicians and distinguished people. Of particular note was Vaclav Havel, who was also a Kluge chair and who held a program on dissidents and freedom that featured political dissidents from around the world. John Hope Franklin, another Kluge Chair, gave a lecture titled "Where Do We Go from Here?" that called on Americans to live up to democratic ideals. In contrast, James Baker III and Henry Kissinger gave lectures on the might of the United States with much triumphalism. There were also poetry and music presentations. As a bonus, Barry Blumberg was then nearby in Philadelphia, where he was the president of the American Philosophical Society (APS). Martine Rothblatt, the CEO of UT, was also frequently in DC; she helped me in many ways to keep active in my parallel lives involving Oxford, Romania, and Israel.

The seminar titled "Commercializing University Research" was cosponsored with Oxford University and the APS. I wanted the library to reach out to other sponsors so that the resources of the library could be further exploited in this way. Commercialization was becoming an important issue for many members of Congress. I hoped to convince people that it was possible to commercialize a university's academic results without threatening its mission. The choice of the APS as a cosponsor for this endeavor was particularly important, given that the ideas of Benjamin Franklin (a founder of the APS) led to the concept of patents being included in the US Constitution. In my opinion, a university's role in commercialization has to be based on a clear policy definition of the ownership of intellectual property rights and the allocation of university resources to encourage and support researchers in protecting and commercializing inventions. I think this was the view that prevailed. Later, this view was adopted at the Scripps Research Institute in La Jolla, where I spent the remainder of my sabbatical year.

While at the Kluge Center, I discussed my position with Dan Koshland. He asked me to visit the Marian Koshland Museum and report to him on how it was doing. Sandra and I made two visits there. We reported that the museum

was indeed excellent, with great exhibits on global warming, DNA, and infectious diseases. Indeed, the museum exhibits seemed to reach out in ways that were very typical of Dan's beliefs, namely that science should be made accessible to everyone and that scientists have a duty to the public to explain how science influences daily life. I saw Dan briefly at the National Academy of Sciences in April, where I was attending a meeting of the APS. Dan was pleased that I had been to the museum and told me how much he appreciated it. That was the last time we spoke, for he died that July, a week before Sandra and I had been due to visit him and his wife, Yvonne. I gave an address at the memorial service to celebrate Dan's life at the University of California, Berkeley, in September.

The Institute of Biology, United Kingdom

As a holder of the Kluge chair with access to politicians, I realized how important learned societies are in giving governments advice. The National Academy of Sciences spoke essentially for much of science in the United States. It was influential and authoritative. The Royal Society plays a similar role in the United Kingdom. However, many academics enjoy being members of organizations that are often discipline based. Part of the attraction is meeting with others from the discipline, sharing the state of knowledge, attending conferences, and hopefully having an influence on government policy on the education of the next generation of academics and professionals. But the disciplines in science are blurring, and it is important to have as wide and as general a membership as possible. Richard Gardener asked me if I would succeed him as president of the Institute of Biology (IoB) from 2008 to 2010. The IoB is a professional body for UK biologists that held a royal charter and had about 12,000 members. For many years, the IoB had considered merging with the UK Biosciences Federation (BSF), an umbrella organization that promoted the advancement of biosciences. It included many industrial members and the major learned societies in biology. A merged society would provide a single voice for biology, with potentially more than 100,000 members, that could speak to government and influence public policy. I think Richard hoped that I would be able to help catalyze this merger.

Picture a group of trustees of the IoB, prone to spending time after council meetings declaring the need for change, becoming progressively frustrated with the ongoing situation, but along with others, hoping it would happen sometime in the future. Indeed, the institute seemed to have fought for years to remain on the periphery, safe in the royal charter, but scared of bothering members with the idea of change. My view was that change was not only desirable but necessary. I supported young people and members of the council to empower them to embrace change. The council responded magnificently, and we mounted road shows throughout the United Kingdom to explain to our membership why we wanted to have one voice for biology. I urged on the council electronically, at all hours of the day and night, from wherever I was in the world. I heard later that my colleagues had a fear of not receiving an almost instant reply from me, lest they had gone down the wrong road! But we made it, and in 2010 the Society of Biology was formed, through collaboration and trust with the BSF, as an inclusive organization. Dame Nancy Rothwell became its first president. (She is currently president and vice chancellor of Manchester University.) It was a great experience to see the depth of talent in biology in the United Kingdom, from schoolchildren to eminent Fellows of the Royal Society. The Biology Olympiad was one of the jewels in our crown, and UK schoolchildren have been medal winners for the past 10 years.

Science in the Sun

I spent the remainder of 2007, my sabbatical year, at the Scripps Research Institute in La Jolla, California, at Richard Lerner's laboratory. Richard was a long-time friend. I admired his work and the way he had built

Scripps. Under his inspirational leadership, it had become a flagship for chemistry and biology. His brilliant scientific taste enabled him to recruit the very best scientists to the faculty as he built the institute. His medical degree and flair for chemistry are a wonderful combination, and I learned a lot from watching how he tackled scientific problems. His energy and enthusiasm were contagious and an invigorating experience for all around him. Also, he recognized the value of translational research so that it became part of the culture of Scripps in a way that made my colleagues at Oxford envious.

His authority came from his science. Having been under the influence of Rod Porter, and later Elvin Kabat, I saw Richard as the major figure in immunochemistry. He has been part of virtually every major advance in the field in the past 25 years and, remarkably, a pioneer in most. His discovery of combinatorial antibody libraries revolutionized immunochemistry. It allows construction of immunological repertoires that are many orders of magnitude larger than those of nature. Moreover, libraries such as phage, yeast, and *Escherichia coli* surfaces, unlike their natural counterparts, are not restricted by the constraints of self tolerance, which is especially important because most of the therapeutic antibodies in the clinic are antibodies to self. Without doubt, antibody libraries have profound implications for human health.

It was always fun being around Richard. He has a great sense of humor and a love and passion for science that encouraged his students and colleagues to try the quick-and-dirty experiment to see if it was worth continuing. The year 2007 was the beginning of regular visits to Scripps, where I became an institute professor, and where we spent nearly 3 months each subsequent year. We renewed many friendships with faculty members and discussed new areas of research, and I learned a great deal there. Richard's frequent visits to Oxford resulted in strong links throughout the university. The visits to Scripps were a source of renewal for me, to which of course the climate also contributed much.

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I doubt that my journeys would have been possible at all without my lifelong partner, Sandra. The many journeys that I have made have sometimes been difficult for my children, Juliet, Robert, Deborah, and Joshua, in terms of my availability. I hope this record of some of my journeys will help them understand. During the course of writing this article, my son-in-law Peter (Juliet's husband) was diagnosed with gliobastoma multiforme, grade 4. The immense support and advice that we have all received from my many friends around the world are a testament to the great fellowship of science.

The work described here would not have been possible without my outstanding colleagues and students, mainly at Oxford. Each generation of students brings a sense of expectancy and excitement and provides the inspiration to keep going. I have always found the breadth and depth of knowledge required to be a good scientist challenging, but I have been blessed by meeting many outstanding scientists who have contributed immensely to my appreciation of science and helped me to understand it. Above all, the stimulating and exciting intellectual environment that is Oxford University has given me enormous strength and enthusiasm.

LITERATURE CITED

1. Price NC, Dwek RA, Ratcliffe G, Wormald MR. 1974. *Principles and Problems in Physical Chemistry for Biochemists*. Oxford, UK: Oxford Univ. Press. 3rd ed.
2. Dwek RA, Navon G. 1972. On boiling an egg. *Nature* 240:491
3. Campbell ID, Dwek RA. *Biological Spectroscopy*. London: Benjamin Cummings
4. Dwek RA. 1973. *Nuclear Magnetic Resonance in Biochemistry: Applications to Enzyme Systems*. London: Clarendon
5. Dwek RA, Wain-Hobson S, Dower SK, Gettins P, Sutton B, et al. 1977. Structure of an antibody combining site by magnetic resonance. *Nature* 266:31–37
6. Burton DR, Boyd J, Brampton AD, Easterbrook-Smith SB, Emanuel EJ, et al. 1980. The C1q receptor site on immunoglobulin G. *Nature* 288:338–44
7. Parekh RB, Dwek RA, Sutton BJ, Fernandes DL, Leung A, et al. 1985. Association of rheumatoid arthritis and primary osteoarthritis with changes in the glycosylation pattern of total serum IgG. *Nature* 316:452–57
8. Rademacher TW, Parekh RB, Dwek RA. 1988. Glycobiology. *Annu. Rev. Biochem.* 57:785–838
9. Parekh RB, Tse AGC, Dwek RA, Williams AF, Rademacher TW. 1987. Tissue-specific *N*-glycosylation, site-specific oligosaccharide patterns and lentil lectin recognition of rat Thy-1. *EMBO J.* 6:1233–44
10. Kornfeld R, Kornfeld S. 1985. Assembly of asparagine-linked oligosaccharides. *Annu. Rev. Biochem.* 54:631–64
11. Dwek RA. 2007. *The Other Green Line and the Sweetest Tomato in the World*. Washington, DC: Sci. Technol. Bus. Div., Kluge Cent., Libr. Congr. **http://www.loc.gov/rr/scitech/greenline.html**
12. Dwek RA. 2007. *George Washington and the First Mass Military Inoculation*. Washington, DC: Sci. Technol. Bus. Div., Kluge Cent., Libr. Congr. **http://www.loc.gov/rr/scitech/GW&smallpoxinoculation.html**

RELATED RESOURCES

The Oxford Glycobiology Institute has more than 900 publications and 100 patents listed on its website: **http://www.bioch.ox.ac.uk/glycob/**. The publications from my early career, from 1966 until 1983, as a physical chemist, a biochemist, and a member of the OEG, along with papers on antibodies, are also on the website under the section "Institute Director—Early Publications."

1. Dwek RA, Richards RE. 1967. Nuclear magnetic resonance. *Annu. Rev. Phys. Chem.* 18:99–124
2. Platt FM, Neises GR, Dwek RA, Butters TD. 1994. *N*-Butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. *J. Biol. Chem.* 269:8362–65
3. Malhotra R, Wormald MR, Rudd PM, Fischer PB, Dwek RA, Sim RB. 1995. Glycosylation changes of IgG associated with rheumatoid arthritis can activate complement via the mannose-binding protein. *Nat. Med.* 1:237–43
4. Dwek RA. 1996. Glycobiology: towards understanding the function of sugars. *Chem. Rev.* 96:683–720
5. Rudd PM, Dwek RA. 1997. Glycosylation: heterogeneity and the 3D structure of proteins. *Crit. Rev. Biochem. Mol. Biol.* 32:1–100
6. Rudd PM, Guille GR, Kuster B, Harvey DJ, Opdenakker G, Dwek RA. 1997. Oligosaccharide sequencing technology. *Nature* 388:205–7
7. Mehta A, Lu X, Block TM, Blumberg BS, Dwek RA. 1997. Hepatitis B virus (HBV) envelope glycoproteins vary drastically in their sensitivity to glycan processing: evidence that alteration of a single *N*-linked glycosylation site can regulate HBV secretion. *Proc. Natl. Acad. Sci. USA* 94:1822–27
8. Platt FM, Neises GR, Reinkensmeier G, Townsend MJ, Perry VH, et al. 1997. Prevention of lysosomal storage in Tay–Sachs mice treated with *N*-butyldeoxynojirimycin. *Science* 276:428–37

9. Block TM, Lu X, Mehta AS, Blumberg BS, Tennant B, et al. 1998. Treatment of chronic hepadnavirus infection in a woodchuck animal model with an inhibitor of protein folding and trafficking. *Nat. Med.* 4:610–14
10. Petrescu SM, Branza-Nichita N, Negroiu G, Petrescu AJ, Dwek RA. 2000. Tyrosinase and glycoprotein folding: roles of chaperones that recognize glycans. *Biochemistry* 39:5229–37
11. Rudd PM, Elliott T, Cresswell P, Wilson I, Dwek RA. 2001. Glycosylation and the immune system. *Science* 291:2370–76
12. Dwek RA, Butters TD, Platt FM, Zitzmann N. 2002. Targeting glycosylation as a therapeutic approach. *Nat. Rev.* 1:65–75
13. Arnold JN, Wormald MR, Sim RB, Rudd PM, Dwek RA. 2007. The impact of glycosylation on the biological function and structure of human immunogloulins. *Annu. Rev. Immunol.* 25:21–50
14. Scanlan CN, Offer J, Zitzmann N, Dwek RA. 2007. Exploiting the defensive sugars of HIV-1 for drug and vaccine design. *Nature* 446:1038–45
15. Dwek RA. 2008. Oxford University's first spin-off company: Oxford GlycoSystems. *Biochemist* 30:4–7
16. Royle L, Campbell MP, Radcliffe CM, White DM, Harvey DJ, et al. 2008. HPLC-based analysis of serum *N*-glycans on a 96-well plate platform with dedicated database software. *Anal. Biochem.* 376:1–12
17. Pollock S, Dwek RA, Burton DR, Zitzman N. 2008. *N*-Butyldeoxynojirimycin is a broadly effective anti-HIV therapy significantly enhanced by targeted liposome delivery. *AIDS* 22:1961–69
18. Mackeen MM, Almond A, Deschamps M, Cumpstey I, Fairbanks AJ, et al. 2009. The conformational properties of the Glc_3Man unit suggest conformational biasing within the chaperone-assisted glycoprotein folding pathway. *J. Mol. Biol.* 387:335–47
19. Pollock S, Branza-Nichita N, Böhmer A, Radulescu C, Dwek RA, Zitzmann N. 2010. Polyunsaturated liposomes are antiviral against hepatitis B and C viruses and HIV by decreasing cholesterol levels in infected cells. *Proc. Natl. Acad. Sci. USA* 107:17176–81