One day, I received a knock on my door from a woman working for the Oxford English Dictionary. She informed me that she was responsible for the letter ‘G’. Glycobiology had been chosen, after much discussion and deliberations, to be included in the new addendum to the dictionary, which was to be published in 1992. I subsequently attended a launch of the supplement to the Oxford English Dictionary and was assured by the Vice Chancellor of Oxford University that there was no higher honour for a scientist than to have his name and his word in so eminent a publication as the OED!

From NMR to glycobiology

I was recruited by Professor Rodney Porter, FRS, into the Department of Biochemistry at Oxford in 1969, having come from the group of Sir Rex Richards, FRS, who was one of the pioneers of magnetic resonance in the UK. I initially worked with a number of groups in the department, notably that of Professor Sir George Radda, FRS, as we applied magnetic resonance to a whole variety of biological systems, within the framework of the Oxford Enzyme Group. Other notable collaborations included those with Lord David Phillips, FRS, Dame Louise Johnson, FRS, Professor Bob (R.J.P.) Williams FRS, and Professor Iain Campbell, FRS. One day after a particularly good seminar by one of...
my postdoctoral researchers, who was working on phosphofructokinase, Rodney Porter asked me to come to see him. I expected to be congratulated on the seminar but instead he said that the time had come for me to take on a real structural challenge — that of trying to use magnetic resonance to determine the structure of the combining site of an antibody molecule.

The smallest fragment of the antibody molecule that was known at that time, the Fv, was discovered by David Givol at the Weizmann Institute, Israel. Porter invited him to Oxford to make the Fv fragment of MOPC315, a dinitrophenol-binding antibody. In a team that included Simon Wain-Hobson, Steve Dower, Peter Gettins and Brian Sutton, we determined the structure by using a variety of methods, notably difference magnetic resonance spectroscopy. We assumed that the immunoglobin fold would be conserved and realized that this had the advantage of helping to explain antibody diversity on a common threedimensional framework. Shortly after the paper was published, in a small seminar on this paper to Rodney Porter, Dorothy Hodgkin, Jim Gowans and R.J.P. Williams, Porter suggested that I should move to a bigger challenge. After many discussions, I decided to look for the C1q receptor site on the IgG molecule, since that was very close to Porter’s new interest, which was now switching to the complement pathway. In a team of stars, including Dennis Burton, we identified the location of the C1q receptor site. One of the surfaces of the Fc region of the antibody molecule was a hydrophobic face that was covered by carbohydrates, so it became important to determine the structure of the carbohydrates to see what role, if any, they played in complement activation.

**Glycoforms**

With the help of Tom Rademacher, who arrived as a postdoctoral fellow in my group, we set up the technology that had been developed by Kobata and colleagues in Japan to sequence oligosaccharides. To our amazement, the Asn-conserved site on the heavy chain of the antibody molecule had not one, but over 30 different oligosaccharide structures that could be attached to either heavy chain. Later we termed the glycosylated variants of a protein ‘glycoforms’.

Under Porter’s guidance, I expanded glyciobiology, obtaining funds from Monsanto Company, USA, who were keen to support technology development in the life sciences. Porter reckoned that the sequencing procedures were probably too expensive for a research council here to fund alone, since it involved many techniques (including mass spectroscopy). The contract subsequently signed with Monsanto in 1985 was expanded to provide a basic sequencing facility in the Department of Biochemistry at Oxford. This was also the first industrial contract for Oxford University and was to become a model for academic/industrial relations.

We developed further and refined the techniques that had been pioneered by Kobata so that we were able to sequence smaller and smaller amounts of material. Indeed, today, a full oligosaccharide analysis of a glycoprotein can be obtained from a spot on a gel.

Interestingly, when Fred Sanger came to open the Glycobiology Institute (Figure 1), he understood immediately the technology that we had developed. In fact, he argued that the sequencing itself was simple, but the real challenge with glycoproteins lay in separating the various ‘glycoforms’.

**Biotechnology and glycosylation**

In 1985, my group at Oxford University published a landmark patent on tissue plasminogen activator, a drug that dissolves clots after heart attacks and strokes. This patent, which was largely based on the PhD work of Raj Parekh, taught that the actual glycoforms of a protein were important, rather than only the protein’s amino acid sequence. It was possible to distinguish different glycoforms, and therefore different products, from the same gene when expressed in two different cell lines. In terms of biotechnology, this put glycosylation very much to the forefront.

**Oxford GlycoSystems**

In October 1988, with the help of Monsanto and Searle (which had just been acquired by Monsanto), the University of Oxford launched its first ever spin-off company in which the University had a shareholding. The idea was to develop further the sugar technology in order to make it available to users all over the world. Oxford GlycoSystems was born as a technology company and succeeded in making several different kinds of instruments to release sugars from proteins and then allow the full oligosaccharide sequence to be obtained. Within a few years, most of the major drug companies in the world had Oxford GlycoSystems’ instruments, as glycosylation became more important in the ‘quality control’ of glycoproteins. It was realized that in
the production process, any slight variation, such as changing oxygen levels or cell culture conditions, could lead to a change in glycosylation pattern.

**Imino sugars as antivirals**

In 1987 the UK AIDS Directed Programme was set up. Twelve scientists met in the rooms of Sidney Brenner, FRS, at King’s College, Cambridge, to plan a strategy to tackle the HIV problem in the UK. It turned out that gp120, on the surface of the virus, was one of the most heavily glycosylated proteins known. The glycosylation, which is host glycosylation in viruses, is effectively a glycan shield. With Max Perutz, FRS, I was delegated to help with the antiviral efforts. Max and I tried to encourage many researchers to send compounds for testing of antiviral activity against HIV. One compound, which initially had been discovered at Kew Gardens and which came from the mulberry tree, was deoxynojirimycin. This was sent to Oxford, where George Fleet’s team modified it, together with a number of other similar compounds that had good antiviral activity. In a joint effort between Oxford and Cambridge and scientists from Kew Gardens, we developed a range of antiviral compounds as part of the MRC AIDS Directed Programme of Research.

**Clinical trials of HIV**

Max Perutz and I then persuaded G.D. Searle in Chicago, with the help of Richard Mahoney, President of Monsanto, USA, to develop some of these compounds for clinical trials. The compound chosen was NB-DNJ (N-butyldideoxyojirimycin; Figure 2) and it was not long before the Monsanto company, advised by G.D. Searle, had lorries going to its ‘Nutrasweet’ factory in Chicago with 100 tonnes of glucose as a starting material for this potential drug. Professor Chi-Huey Wong and colleagues from The Scripps Research Institute then developed a ‘one-pot, three-step synthesis’7, which eventually allowed large quantities to be made much more easily, and G.D. Searle proceeded with the clinical trials in some 80 patients. The imino-sugar era was launched.

**Gaucher disease: an approved drug worldwide**

Although the drug only had mild efficacy in patients, its real problem was that it had a side effect of osmotic diarrhoea. This limited the concentration that could be achieved in serum to make it really effective as an antiviral. At that time, in the Glycobiology Institute, Terry Butters and Fran Platt, working with Gabriel Neises, who was also from G.D. Searle, showed that the glycolipid composition of cells that were treated with the drug NB-DNJ had an altered glycolipid composition. This led to a programme in which the drug was used as a glycolipid inhibitor. It was realized that many of the glycolipid-storage disorders involved accumulating glycolipids and that this inhibition of the first step of glycolipid synthesis would reduce the synthesis of glycolipids, so that there would be less glycolipid storage in patients with glycolipid-storage disorders. Some experiments were done in a macrophage cell line to illustrate the feasibility of using NB-DNJ for this purpose, and because of the clinical trial that had been conducted for HIV, it was possible to go directly to a clinical trial in patients.

Meanwhile, Oxford GlycoSystems refocused as a pharmaceutical company, as Oxford GlycoSciences. The company took a licence from Searle and, with the help of scientists at the Institute, undertook the clinical trials. The compound, which could be taken orally, was approved for worldwide use in Israel, USA and Europe in 2002 for Gaucher disease (Figure 3). The drug has now been used by patients for over 7 years and a number of clinical trials for other glycolipid-storage disorders are also currently underway.

**Glycosylation and hepatitis B and C: glycoprotein folding**

In about 1990, Baruch Blumberg, who had received a Nobel Prize for his work on a vaccine for hepatitis B, joined the Glycobiology Institute, while he was Master at Balliol College, Oxford. Professor Tim Block, from Thomas Jefferson University, PA, came for a sabbatical with Blumberg and myself and we started an antiviral programme in the Institute. Initially, we studied hepatitis B and demonstrated that the secretion of the virus was inhibited in the presence of the drug NB-DNJ.

At the same time in the Glycobiology Institute, work was underway by Stefana Petrescu (from the Bucharest Institute of Biochemistry, Romania), using NB-DNJ to inhibit the metalloglycoprotein tyrosinase, which is involved in melanin biosynthesis. This pointed to the involvement of cal-

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**Figure 2** The structure of NB-DNJ.

**Figure 3** Oral drug useful for Gaucher disease which has been in use with patients for 7 years.
nexit in the ER (endoplasmic reticulum) in glycoprotein folding, and this is still a pivotal result for glycobiology; it soon became clear that many viruses also achieved the three-dimensional structure of their surface glycoproteins using the calnexin pathway. We showed that the action of NB-DNJ was as an inhibitor of glucosidase I and 2, and thus could prevent proper folding as it inhibited the interaction with calnexin. Thus a large antiviral programme was begun, using imino sugars to create this misfolding. Today those studies have been expanded to hepatitis B and C, under Nicole Zitzmann at the Glycobiology Institute, and she has a programme to develop a series of morphology inhibitors. Her article in this issue of The Biochemist (pp. 23–26) outlines an important aspect of the future programme. A clinical trial on hepatitis C has already been undertaken by United Therapeutics, USA, and more are planned.

**Structural glycobiology**

The placering of oligosaccharides within their biological context meant that we would take the structures and build them onto the proteins to generate models of the intact glycoprotein. Some of the molecules that Pauline Rudd’s team (together with Mark Wormald and David Harvey) have worked on in the last 10 years are shown. The Institute has developed structural databases for structures of sugars and linkages to proteins. The basis of the determination of all these structures has been advances in technology. It is now possible to sequence one fentomole of an oligosaccharide. The article by Dr Pauline Rudd in this issue of The Biochemist (pp. 18–21) highlights the recent advances and the prospects for the future for a high-throughput biomarker, which would be both prognostic, diagnostic and hopefully able to change with drug treatment.

**Collaborations**

The Glycobiology Institute has facilitated an enormous number of collaborations, notably in the early days with my close colleague and friend, the late Alan Williams (with whom I shared a lab under Porter’s early direction). Other notable work includes the first structures of GPI (glycosylphosphatidylinositol) anchors, with Mike Ferguson, and the glycosylation of proteins, with Stanley Prusiner, and the long standing collaborations with Ghislain Opdenakker and colleagues at the Rega Institute, Leuven. The joint collaboration in recent years with Ian Wilson’s and Dennis Burton’s groups at The Scripps Research Institute has led to the discovery of an unusual structure of a neutralizing antibody, 2G12, against HIV, which recognizes sugar clusters on gp120. This is the basis of the current vaccine programme for HIV at the Institute. At the same time, the concept of misfolding of glycoproteins and the ER-associated degradation has led us, together with Stefana Petrescu in Bucharest, to a programme for a melanoma vaccine in which retention of tyrosine mutants in the ER may lead to enhanced MHC presentation.

Additionally, the Glycobiology Institute has trained nearly 100 PhD students and almost 200 postdoctoral workers, as well as hosting over 80 visitors. We have made a significant contribution to the teaching of glycobiology, in particular through the work of Professor Kurt Drickamer, the discoverer of C-type lectins who spent 10 years in the Institute, and Dr Maureen Taylor, who was here for 15 years, working mainly on the macrophage mannose receptor.

Glycobiology has thus become firmly established as part of mainstream biochemistry. Viruses are major future challenges. Almost every aspect of glycobiology is found in viruses, including recognition, folding, secretion and immune presentation. The need for high-throughput diagnostics for glycosylation as part of a plethora of diagnostic tests remains another future challenge. The two articles from the Glycobiology Institute in this issue of The Biochemist indicate the current developments and future trends.

**References**


Raymond Dwek, FR.S., is Professor and Director of Oxford GlycoSciences. He is currently a Director of United Therapeutics and also of his Innovation, a wholly owned company of Oxford University that was created to exploit its intellectual property. He has received several honours including the 7th Welcomes Trust Award for Research in Biochemistry related to Medicine (1994), the Hepatitis B Foundation Leadership Award, USA (1997), and the Romanian Order of Merit (2000). He is a member of the European Molecular Biology Organization and Fellow of the Royal Society and the Royal Society of Chemistry. He holds honorary doctorates from Katholieke Universiteit, Belgium (1996), Ben Gurion University of the Negev, Israel (2002), The Scripps Research Institute, USA (2004), and the Babes-Bolyai University, Cluj, Romania (2006). Professor Dwek has published three books, 490 articles and 70 patents.

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