James Michael Creeth, 1924–2010

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Great scientific discoveries are more often than not the culmination of a number of other key findings and insights. In their discovery of the double helical structure for DNA in 1953 J. D. Watson and F. H. C. Crick pointed to the important finding made some six years earlier that the bases in DNA were linked by hydrogen bonds and at such a low concentration that the bonds were likely to be part of the same macromolecule. That earlier discovery was made by a team of scientists at what was then University College Nottingham and central to that finding was a young Ph.D. student, J. Michael Creeth (Figure 1) working under the supervision of D. O. Jordan and J. M. Gulland.

Working on a highly purified DNA sample from calf thymus — its purity checked by the powerful but still fledgling technique of analytical ultracentrifugation — a carefully performed series of measurements clearly showed the hydrogen bond link between the residues, a finding which was reported in the 1947 volume of the *Journal of the Chemical Society* as the final — and key — part of a trilogy of papers. The first, by Gulland, Jordan, and Threlfall considered the extraction and purification, the second by Gulland, Jordan, and Taylor showed by acid titration studies that treatment with acid or alkali led to the liberation of titratable groups at low and high pH — whereas the addition of neutral salts did not. This led to the definitive Creeth et al.[1] study of the relative viscosity of solutions of this preparation. For a given concentration this parameter is a very sensitive function of conformation and conformation change as a function of solvent conditions. High relative viscosities that remained constant between a pH of 5.6 and 10.9 were observed but fell to a much lower value outside these limits. The DNA was in a highly asymmetric polymeric structure within the range which collapsed outside it. This behavior was reproduced using streaming birefringence experiments — also a sensitive function of particle extension. Creeth et al. remarked as follows "The critical pH values are coincident with those at which a liberation of amino and hydroxyl groups has been observed and it is considered that the two phenomena are related and are due to the fission of the hydrogen bonds postulated as linking the purine-pyrimidine hydroxyl groups and some of the amino-groups." In the paper Creeth et al. make the guarded comment that the data "do not show whether bonding of neighboring polynucleotide chains or nucleotides in the same chain is involved" although it later became clear that the data were best understood in terms of H-bonding between adjacent chains (Figure 2).

His Ph.D. thesis — which also appeared in 1947[2] — makes very interesting reading! In it Mike proposed a model for the assembly of the DNA model, with the phosphate-sugar backbone and the sugar linked bases available for pairing. The model has two strands each made up of overlapping short chains linked by interchain hydrogen bonds built up into a very long and elongated molecule leading to a high relative viscosity — and he gave a sketch (Figure 3) which accounts for the hydrogen bonded and highly asymmetric structure and its disruption at high and low pH leading to a large reduction in relative

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Figure 1. J. M. Creeth near the time of the discovery of hydrogen bonds in DNA.

Macromol. Biosci. **2010**, *10*, 696–699

DOI: 10.1002/mabi.201000073

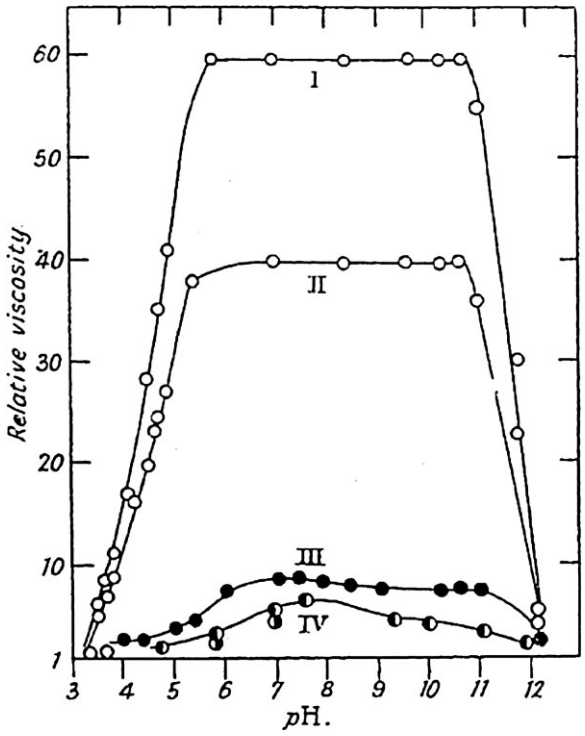

Figure 2. Plot of relative viscosity versus pH of various preparations of calf thymus DNA. III and IV had been treated with strong acid/strong alkali, respectively. Reprinted, with permission of the Royal Society of Chemistry from ref.[1]. A similar figure appears as Graph 3_9 in ref.[2].

viscosity and streaming birefringence. Apart from the breaks in the chains — and the absence of a helix — one can see the model is not too far from what was discovered six years later. One could speculate what Mike and the Nottingham team might have achieved if the X-ray diffraction data of Maurice Wilkins, Rosalind Franklin, and Raymond Gosling had then been available. Few people are aware of this model's existence.

Although acknowledged by Watson and Crick, and also Wilkins and Franklin, the finding of hydrogen bonded base pairs was completely missed by Pauling and Corey who shortly before the double helical model was discovered, published their erroneous model of a triple helical structure with the bases on the outside of the molecule. In a further slight irony of fate, after completing his Ph.D. he applied to the University of Cambridge for a research fellowship — he was not offered this but instead the chance to do another Ph.D. there — which he politely declined.

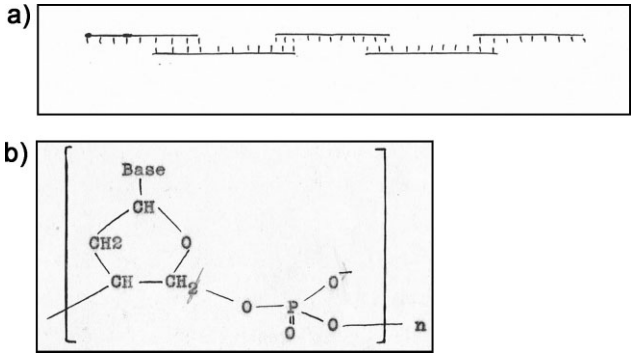

Figure 3. a) Sketch of a model for DNA from Mike Creeth's Ph.D. thesis of 1947[2] showing two broken chains linked by hydrogen bonds, and b) an expanded sketch of the sugar-phosphate backbone.

London, Wisconsin, and Adelaide

At the completion of his Ph.D. Creeth moved to the Courtauld Institute of Biochemistry at the Middlesex Hospital Medical School in London, where the focus of his research switched to the physicochemical characterization of proteins, including a re-evaluation of the molecular weight of insulin.[3] Working with Dr. Peter Charlwood, it was here he obtained his first experience of the newly available Model E ultracentrifuge. After helping to clear up an important discrepancy with the temperature measurement system — he then embarked on another key stage in his career — Wisconsin in the USA. Wisconsin was intimately linked with the invention of the analytical ultracentrifuge — much of T. Svedberg's earlier work was inspired by his own stay there. Creeth joined when Dr. J. D. "Jack" Williams was head of Physical Chemistry and was appointed as a research fellow in the laboratory of L. J. Gosting working on the use of the Rayleigh interference optical system for characterizing diffusion. A highlight of those investigations was the development of a sensitive analysis for the detection of minor deviation from Gaussian behavior in a diffusing boundary[4] and culminated much later in what Mike regarded as one of his most satisfying pieces of work — his paper describing the interplay in a sedimentation velocity experiment of a multi-component system between the boundary speading effects of diffusion and the self-sharpening effects caused by the faster moving

components being slowed by the presence of the slower ones.[5]

Towards the end of 1954 Mike Creeth accepted a Senior Lectureship at the University of Adelaide as part of a drive by his former Ph.D. supervisor D. O. Jordan (who had become Head a year earlier) to establish physical chemistry in a Chemistry Department where little attention had been paid previously to this area of the discipline. The acquisition of a Spinco Model H electrophoresis/diffusion apparatus afforded Creeth the opportunity to follow-up his Wisconsin ideas on the possible use of diffusion analysis as the ultimate criterion of protein homogeneity with respect to size and shape. However a diffusion study of the A_1 component of ovalbumin under isoelectric conditions yielded concentration distributions that deviated from Gaussian shape in a manner symptomatic of the presence of a fast impurity — a finding traced to a flow interaction whereby the diffusion of protein induced a concomitant movement of solvent components.[6] Although negative in the context of diffusion analysis as a sensitive criterion of protein homogeneity, those studies introduced the two participating graduate students (L. W. Nichol and D. J. Winzor) to interacting systems — a field to which both have since contributed substantially. Their success attests to the sound basic training in physicochemical aspects of protein chemistry that they received from Mike during his four years in Adelaide.

The Lister Institute

After a brief return to the University of Wisconsin Creeth moved to London in January 1960 to take up a Readership at the Lister Institute of Preventive Medicine, where R. A. Kekwick had a well-established center for ultracentrifugal research. His return to England heralded a shift in research focus from the physicochemical characterization of essentially pure macromolecular systems to those at the other end of the homogeneity spectrum — the glycoproteins or "mucopolysaccharides" for which there is no unique molecular mass because of extreme heterogeneity with respect to chain length of the saccharide component. This became the main thrust of his research interests for the remainder of his career, with a particular focus on the glycoproteins or mucins of the respiratory tract, with a dedicated program trying to unscramble the physico-chemical secrets underpinning the characteristic viscoelastic and protective properties of these challenging substances — and what happens when things go wrong, as in the case of cystic fibrosis, chronic bronchitis, and other respiratory disease. With Ph.D. student C. G. Knight he established, using a novel combination of the concentration dependence of the sedimentation coefficient with the intrinsic viscosity[7] that the blood group specific glycoproteins adopted an overall spheroidal conformation,[8] an observation confirmed later by thermodynamic non-ideality and electron microscopy measurements. More modest levels of glycosylation may have influenced the denaturation and renaturation of molecules like ovalbumin, investigated by Mike with his Ph.D. student John Holt.[9] With M. Denborough[10] he developed ways of using isopycnic density gradient ultracentrifugation in caesium salts for obtaining glycoproteins at a very high degree of purity and this work continued with K. Bhaskar[11] who later went on to continue this work at Harvard. At the same time as all this applied research Mike continued to pursue his interests in the mathematical and experimental basis behind analytical ultracentrifugation, culminating in one of the most widely cited and readable ultracentrifugation articles — an extensive review with R. H. Pain on the accurate determination of molecular weights which four decades on is still one of the key authorative texts on the subject.[12]

Bristol — Mucus and All Things Sticky

In the late 1970's the Lister Institute was one of the first major UK research institutes to be closed after increasing financial difficulties. From the sale of the property part of the proceeds was used to provide the funds for Mike to continue his work at the University of Bristol — and also paid for a then young postdoc (SEH) and a Ph.D. student (Brian Cooper). It was there in the Departments of Biochemistry and Medicine he continued to make significant inroads into our understanding of the conformation and heterogeneity of mucin glycoproteins and their interactions,[13–15] and at the same time developing ultracentrifuge theory necessary to deal with these difficult, heterogeneous, and non-ideal systems.[16,17]

Like his supervisors "Doj" Jordan and J. M. Gulland, Mike Creeth was a true gentlemen and meticulous towards his science, an approach which was passed down to all those privileged to have been trained by him. So we say goodbye Mike, and we forgive you for making us wear those silk gloves before handling Model E rotors!

Received: February 16, 2010; Published online: June 22, 2010; DOI: 10.1002/mabi.201000073

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