James Michael Creeth (1924–2010)

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

Michael Creeth died on 15 January 2010 after a short illness at the age of 85. He had a distinguished scientific career and enjoyed a long and full retirement, and, unknown to many, made a significant contribution to one of the greatest scientific discoveries of the last century: it was Mike's experiments as a young PhD student that confirmed the existence of hydrogen bonds between the purine and pyrimidine bases of DNA. This finding, based on measurements of the relative viscosity and streaming birefringence across a range of pHs was published in 1947 – 4 years before the base-pair rules of Chargraff and 6 years before Watson and Crick.

Mike was born in Northampton in 1924 and went to the local Town and County Grammar school. He stayed in the East Midlands to read Chemistry at the then University College Nottingham and commenced a PhD in Physical Chemistry under the supervision of D.O. 'Doj' Jordan and Head of Department, J.M. Gulland. Working on a highly purified DNA sample from calf thymus, 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 using 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 third and definitive part by Creeth, Gulland and Jordan involving a study of the relative viscosity of solutions of this preparation[1], shown to be of a high degree of purity by analytical ultracentrifuge measurements in Sandy Ogston's laboratory at Oxford. For a given concentration, this parameter is a very sensitive function of conformation and conformational 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 concluded to be a highly asymmetric polymeric structure within the range, but collapsed outside it. This behaviour was reproduced using streaming birefringence experiments – also a sensitive function of particle extension.

Creeth and colleagues 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." It later became clear that the data were best understood in terms of hydrogen-bonding between adjacent chains. Indeed his PhD thesis – which also appeared in 1947[2] – makes very interesting reading! In it, Mike proposed a model for the assembly of the DNA molecule, 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 inter-chain hydrogen bonds built up into a very long and elongated molecule leading to a high relative viscosity – and he gave a sketch.

At extremes of pH, the hydrogen bonds are disrupted and the two-chain structure falls apart, leading to a large reduction in relative viscosity and streaming birefringence. Apart from the breaks in the chains – and the absence of a helix – one can see the model isn't too far from what was discovered 6 years later. Few people are aware of this model's existence. The University, proud of Mike's achievements, are now making an electronic copy of his thesis so this work can be more easily appreciated.

Knowledge of the hydrogen bond base-pair links – and the Chargraff rules – proved critical to the double helix discovery and was later acknowledged by Watson and Crick and also by Maurice Wilkins and Rosalind Franklin. The finding was completely missed, however, 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: particularly surprising when Pauling visited Nottingham in May 1948 to give the Sir Jesse Boot Foundation Lecture. One could also speculate 'what might have been' if the Wilkins–Franklin X-ray data showing a double helix had been available in 1947.

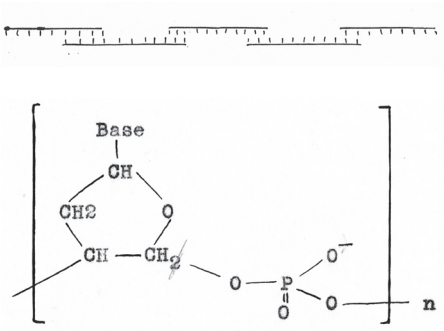

Figure 2. Sketch of a model for DNA from Mike Creeth's PhD thesis of 1947[2] showing two broken chains linked by hydrogen bonds, and an expanded sketch of the sugar–phosphate backbone

At the completion of his PhD, Mike moved to the Courtauld Institute of Biochemistry in London, where the focus of his research switched to the physicochemical characterization of proteins, including a re-evaluation of the molecular mass of insulin and it was there he encountered the Beckman Model E analytical ultracentrifuge – which became one of his principal research tools for the rest of his career. He then embarked on another significant move, to Wisconsin in the USA on a Rockefeller Foundation Fellowship, something of which he was very proud. Wisconsin was then the place to be for an aspiring young physical biochemist – it was intimately linked with the invention of the analytical ultracentrifuge – much of Theodore Svedberg's earlier work was inspired by his own stay there. Mike worked with Lou Gosting on developing diffusion methods as a powerful tool for characterizing the solution properties of proteins. Wisconsin proved highly significant for another reason – it was here he met Pat – then an MS student – who became his wife and whose love and companionship he was to enjoy for the rest of his life.

Towards the end of 1954, Mike accepted a Senior Lectureship at the University of Adelaide where he followed up his Wisconsin ideas on the potential of diffusion analysis as the ultimate criterion of protein homogeneity with respect to size and shape: it was here he introduced his first two graduate students – one of us (DW) and Laurie Nichol – to interacting systems, providing the sound basic training in physicochemical aspects of protein chemistry that proved so valuable in their own subsequent careers. After a brief return to Wisconsin, Mike took up a Readership at the Lister Institute in London in 1960 where the focus of his research switched to the glycoproteins or mucins of the respiratory tract, setting up a dedicated programme with the goal of unscrambling the physicochemical 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 diseases. It was here that he established longstanding friendships with Walter Morgan, Winifred Watkins and Simon Donald. At the same time as all the applied research, Mike continued to combine his interests in the mathematical and experimental basis behind analytical ultracentrifugation, culminating in one of the most widely cited and readable articles in this field – an extensive review with Roger Pain on the accurate determination of molecular masses, which four decades on is still one of the key authoritative texts on the subject[3].

In the late 1970s, the Lister Institute was one of the first major UK research institutes to be closed after increasing financial difficulties. The history was recounted in one of the earliest issues of *The Biochemist*, including an article by Mike himself[4]. Following the sale of the property, part of the proceeds were used to provide the funds for him to continue his work at the University of Bristol – and also paid for a then young postdoc (S.H.) and a PhD student (Brian Cooper). It was there in the Departments of Biochemistry and Medicine that he continued to make significant inroads into our understanding of the conformation and heterogeneity of mucin glycoproteins and their interactions and at the same time developing ultracentrifuge theory necessary to deal with these difficult, heterogeneous and non-ideal systems.

Mike retired in 1984, and he and Pat moved Church Stretton to be near the Shropshire hills were they could pursue their love of walking. He became well known locally as in charge of the footpaths and by-ways, keen crown green bowler and keeper of trees. Last September was the Svedberg 125th Anniversary Symposium in Uppsala and Mike was to give one of the keynote lectures. Unfortunately, because of health issues, he was not able to attend – one of us (S.H.) presented the paper on his behalf, although fortunately he was able to write an article for the special volume[5] .

His scientific colleagues join with Pat, his sons Andrew and Jonathan, daughter Janet and his six grandchildren in mourning the loss of this good man. 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! ■

Figure 3. Pat and Mike

References

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