2006 Barry Firkin Orator Professor Ted Tuddenham – The FVXIII Story

Report by Mark Smith, ASTH Council President

Attendees at the Hobart ASM had the opportunity to hear some excellent presentations. This report summarises the Firkin Oration delivered by Professor Ted Tuddenham, who brought to the meeting the benefit of his extensive work in coagulation science.

For 18 years he was the head of the MRC Thrombosis and Haemostasis Research Unit at Imperial College's Hammersmith Hospital campus. Earlier this year he moved from full time basic science research to become the Clinical Director of the Haemophilia Centre at the Royal Free Hospital in London.

Professor Tuddenham gave this year's lecture on the history of factor VIII. He began the story by citing reference to a male bleeding disorder in the rabbinical writings of the second century. Descriptions even as recent as Queen Victoria's family experience with haemophilia do not allow distinction between haemophilia A or B.

Specific protein deficiency was first postulated by Addis in Edinburgh in 1910, and 20 years later Patek and Taylor and later Minot and colleagues in America led attempts to purify factor VIII, referred to as antihemophilic globulin (AHG), found in the euglobulin fraction. As late as 1952 cross correction studies between different patients with X-linked haemophilia differentiated Haemophilia A from the rarer Haemophilia B. This characterisation allowed development of methods for purifying the correcting factor.

In 1960 a committee of the precursor of the ISTH decided on Roman numerals to designate clotting factors and AHG was assigned factor VIII. Judith Pool soon discovered that cryoprecipitation concentrated most of the factor VIII in plasma in a closed bag with simple apparatus in a blood bank, heralding the modern era of haemophilia care.

Professor Tuddenham showed a classic old photo of a young man by his bed at home, his infusion equipment sitting on top of his bedside freezer storing cryoprecipitate for home treatment of a bleed. Low purity cryo saved many lives in the early years of haemophilia treatment.

The plasma fractionation industry developed out of world war II methods for making albumin and other fractions (Cohn fractionation) for use in the theatre of battle. Multiple donor pools in the 1970s produced purer and higher potency factor VIII preparations that could be freeze dried and stored. Excitement over small volume, effective infusion therapy was devastatingly countered by the notorious transmission of HIV and HCV to most haemophiliacs in the developed world. Isolation of factor VIII for biochemical characterisation was hampered by copurification with another factor, first identified by Zimmerman as Factor VIII related antigen in 1976.

With the advent of monoclonal antibodies for protein purification and the development of genetic engineering techniques for in vitro synthesis of such proteins the stage was now set for a race to clone factor VIII and make synthetic factor for treating patients. Tuddenham's group achieved completely pure factor VIII by 1982 and collaborated with Genentech on the cloning in 1984, simultaneously with a similar result from Fass working with Genetics institute. Synthetic factor VIII had become the standard treatment for haemophilia by 1990.

Tuddenham completed the story by making reference to the significant modern day issues in haemophilia management: inhibitory antibody formation causing clinical resistance to FVIII treatment; most of the worlds haemophiliacs in developing economies cannot afford FVIII concentrates of any kind; and finally, the challenge of gene therapy to potentially cure haemophilia.

The only area not presented in depth was the impact of molecular technology in helping to avoid vertical transmittance of haemophilia. A story like this, covering two millennia, delivered by a key character in that compelling saga, was indeed a treat to behold.