WITNESS NAME: Dr Duncan Pepper

PENROSE INQUIRY – TOPIC B3 - VIRAL INACTIVATION OF FACTOR VIII TO 1985

Introduction.

A brief summary of my CV is as follows:

1953-1960 Price's Grammar School, Fareham, Hants.
1960-1963 University College London, B.Sc. (Special) Chemistry, Honours 2(b).
1964-1967 University College Hospital Medical School. Ph.D. (Medicine)
1963-1964 Research Assistant and Lecturer, Department of Physical Biochemistry, South-West Essex Technical College.
1964-1967 Research Assistant, Department of Bacteriology and Virology, University College Hospital Medical School, London.
1967-1969 Research Scientist, Blood Programme, American National Red Cross, Washington, DC.
1969-1974 Senior Research Biochemist, S-E Scotland Regional Blood Transfusion Service, Royal Infirmary, Edinburgh.
1975-1979 Principal Scientific Officer, S-E Scotland Regional Blood Transfusion Service, Royal Infirmary, Edinburgh.
1980-1984 Principal Scientist, SNBTS Headquarters Unit Laboratory, 2, Forrest Road, Edinburgh.
1984-1999 Top Grade Scientist, SNBTS Headquarters Unit Laboratory, later renamed National Science Laboratory.
August 1999 I was offered and accepted early retirement from SNBTS.

Experience:

I first worked on blood as my PhD thesis involved the identification and analysis of the influenza virus inhibitor naturally present in horse serum, this gave me experience of blood fractionation techniques, analytical methods and immunological techniques.

On joining the American National Red Cross, I set up a research group to study the properties of the platelet and its membrane surface glycoproteins. These played a major role in the early stages of blood coagulation. During this time I also became acquainted with the technology of freezing red blood cells and pilot scale plasma fractionation.

On joining the SE Scotland BTS I was asked by Dr Cash to set up frozen blood banking in liquid nitrogen, develop associated processing, testing and supply for patients undergoing renal transplantation. Also at this time I ran a research project to develop functional tests of platelet concentrates, used to treat bleeding episodes. This ultimately lead to the discovery of Beta-thromboglobulin, the development and commercialisation of a radio-immunoassay and the award of a PhD to Steven Moore (Research Assistant). I spent a lot of time working with the senior technical staff in component production, a major task of which was to increase the volume and quality of fresh frozen plasma being shipped from the regional centres to PFC for fractionation. We made considerable progress in achieving both these aims which helped Scotland to be self sufficient in blood products. A major achievement for a small country with a not-for-profit service. Throughout this time I was increasingly aware of the shortcomings of coagulation testing, both from the point of

view of precision and accuracy, and also the critical shortage of severe deficient haemophilic plasma which was dependent on the goodwill of haemophilia patients and their physicians. From conversation with John Watt it became clear that any progress in improving the yield and quality of FV111 would require a major effort to develop artificial haemophilic plasma, radio-immunoassays and chromogenic (ie chemical rather than biological) assays of coagulation factor function. This aspect of work progressed steadily from about 1975 to 1985.

In 1980 Dr Cash invited me to head up and run a new unit called the Headquarters Unit Laboratory, intended to provide expert scientific advice to the National Medical Director. I was head of this unit from March 1980 until January 1990. For personal reasons I relinquished the lead role in 1990 in favour of Dr Prowse but continued to work under him until my early retirement in 1999.

The initial brief was wide, covering any subject that Dr Cash needed scientific advice on. We did not have any service (technical) or clinical responsibilities, but from time to time we had training roles for young technicians/scientific officers and supervision of research students and visiting research workers. A close collaboration was set up on site with a joint MRC unit under Dr Joan Dawes (Head of the MRC Blood Components Assay Laboratory) to develop radio-immunoassays for blood coagulation components, this ran from 1980 to 1988. To support the development of artificial haemophilic plasma we realised the need for an in house panel of monoclonal antibodies to FV111 and von Willebrand factor, this was a major effort extending over several years and resulted in the award of PhD degrees to both Brenda Griffin and Valerie Hornsey (Research Assistants). Throughout this period I was working on a wide range of other topics covering coagulation factors, inhibitors, anticoagulants, fibrinolysis. Techniques involved included affinity chromatography, activation chemistry, assay development, biotechnology, cryobiology, freeze drying, lectin and plant extracts, small animal models, tissue culture, ultrafiltration, ultraviolet irradiation and viral inactivation.

Although I had no formal role or responsibilities within PFC, I did sit on the committees set up jointly with them by Dr Cash, the minutes of these meetings I believe render a full and accurate report of our thoughts, understandings and actions at that time. From time to time I did informally provide scientific advice to individuals within PFC which may not appear in minutes. I recall working on improved methods of moisture analysis in freeze dried products using infra-red spectroscopy and Karl-Fischer automated titration, in both these cases I sourced the equipment and developed the methodology. Another project involved improving the sensitivity of the assays for residual levels of solvent / detergent used in inactivating enveloped viruses.

During the course of my scientific career I have published some 185 scientific papers, posters, presentations and several patents. I have also attended numerous international and national scientific congresses as a representative of SNBTS. I believe that between approximately 1975 and 1990 the SNBTS had a high reputation internationally as a result of its innovative research, development and service delivery. This was achieved by good working relations amongst staff, high morale and outstanding leadership, all the more remarkable given the modest size of the organisation, capitalisation and compared to multinational commercial competitors with multi-million budgets.

In responding to the enquiry I should point out that since my early retirement in 1999 I have not sought nor had any access to SNBTS documents, my responses are thus largely based on memory. In responding to the specific points raised in the Schedule I have only commented on those points which I have any knowledge, most of the points

raised are outwith my knowledge and so I have not felt able to comment on them, as they relate to management or production issues which I was not involved in.

Snapshots and Landmarks

Parag 6 "The report of the first meeting (see para 11.56) does not describe any work in progress on the viral inactivation of FVIII---"

In fact in the minutes of the FVIII study group (SNF.001.3813) page 6 Mrs B Griffin (Graduate Research Assistant) from the HQ unit laboratory presented preliminary results on experiments using gamma-irradiation to inactivate viruses.

In my opinion it was not clear at that time (1982) that heating (either dry or wet) was likely to be successful with FVIII. The reason for this was that many decades of experience had shown that coagulation factors generally, and factor VIII in particular, were exquisitely sensitive to damage and inactivation by environmental factors. Temperature in particular was a major influence, so it was routine to store FVIII containing material frozen at below -20'C and preferably at -40'C. To be successful a heating process would need to not only inactivate the virus but also not damage the sensitive biological activity of the FVIII molecule. This was a very tall order, and given the extreme sensitivity of FVIII to thermal damage, it seemed highly improbable if not impossible that heating would work. Thus it was prudent to consider all possibilities including gamma irradiation, ultraviolet light, detergents, chemical inactivation and physical removal. Also at that time successful inactivation could only be demonstrated by using animal models or use in previously untreated patients. Tissue culture was not (and is still not) available for hepatitis B or C and HIV had not been isolated. Surrogate (model) viruses were not then considered accurate alternatives by the regulatory licensing authorities. Recombinant DNA technology was also not available nor PCR. Animal models had been tried by US and German workers but these had ethical, regulatory, cost and technical problems; subsequently chimpanzee results were shown not to predict infectivity in humans. Procuring high titre virus preparations of hepatitis C (of sufficient volume to spike into test processes) was also problematic. There was also a shortage of severe haemophilic plasma for assaying FVIII biologic activity. Considerable work was undertaken to prepare artificial depleted plasma substrate and this was really only successful after monoclonal antibodies had been isolated. Until the advent of chromogenic substrate commercial kits (ca 1985) this was the only feasible way to monitor the yield of FVIII clotting activity after viral inactivation.

All the above tended to slow the rate of innovation in viral inactivation of FVIII.

Parag 7

I wrote this report as head of the HQ Unit Laboratory, set up by Dr Cash to provide him with expert scientific advice. The actual experiments on wet heating (pasteurisation) referred to were carried out at PFC by Dr Alex McLeod, so my knowledge of them was second hand. At this time I can not add further to what I wrote in that report.

Parag 8

A general point is that SNBTS could not copy directly any commercial process that was patented, so the value of the Behringwerke patent is that it shows that FVIII can in principle be heat treated if suitably protected and that secondly it is necessary to move to a higher purity product to avoid insolubility problems. PFC would need to develop new patentable technology of its own to solve these two problems.

I do not have anything to add to any of the other paragraphs, but if there are any further questions, I will be happy to answer where I can.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed ..... Dated 25th February 2011