I, Doctor Colin Entwistle, Medical Director of the Oxford Regional Blood Transfusion Service, have the following qualifications:

M.B.Ch.B., F.R.C.Path., M.A.(status) Oxon

I say:

I joined the Oxford Regional Blood Transfusion Service as its Consultant Medical Director in June 1980. The previous Director was Dr. Harold Gunson who is now (January 1990) the National Blood Transfusion Service Director for England and Wales.

Plasma Collection : Oxford BTS Aspects

I have record of a meeting held in 1976 following approval by the RHA for an additional mobile team designed primarily for increased plasma separation for fractionation. This brought the number of mobile teams up to a strength of five (document 5).

In 1977 the Department of Health and Social Security set up a working group "to consider the likely trends in the demand for blood products over the next five to ten years, taking into account the practicalities of supply". The group reported in January 1978. It tried to assess future demand and indicated that considerable further investment would be required in collecting, testing, processing of blood, and premises as well in order to achieve the anticipated demand (document 6). The working party advised that there should be a doubling of factor VIII and a four-fold increase in the availability of albumin in the following five to ten years.

The response of the Oxford Regional Health Authority was that they agreed in 1979 to an extension of the AHG facilities of the Oxford BTS, then sited at the Churchill Hospital, with a view to attempting to keep up with demand for concentrates of AHG (anti-haemophilic globulin) (documents 1 and 2).

In 1980, an important document was produced by the DHSS : RA(80)20 (document 8). This indicated that there would be short-term improvements to the Blood Products Laboratory (BPL) at Elstree, and that in the long term it was intended to replace that facility by a new fractionation plant to be built at some stage in the future.

It was at about that time that the distribution of fractionated blood products from BPL back to Regions was changed such that products would only be supplied pro rata to the amounts of raw plasma sent to Elstree. This policy was designed to encourage increased production of plasma by the Regional Transfusion Centres. Up till then, plasma from Oxford and also from Wessex BTS Centres had been fractionated in the Plasma Fractionation Laboratory (PFL) at Oxford - not a part of the BTS Centre itself. With the introduction of pro rata redistribution of products, fractionation at PFL was integrated more completely with that at BPL. The revised situation was then as indicated in a letter written to me by Dr. R.S. Lane, Director of BPL, on 12th June 1980, seeking my agreement to an arrangement whereby the handling

of plasma from both Oxford and Wessex should be "brought into line with other Regions" (document 11). In addition, each Centre was set an annual target of fresh plasma collection which was to be sent for fractionation, that target for each Regional Centre being based on its catchment donor population.

In October 1980, I reviewed the Oxford BTS plasma collection position since my appointment, and on 23rd October 1980 I produced a paper for the Regional Medical Officer (Dr. E.R. Rue), setting out the possible options for "plasma harvesting" in Oxford. This paper indicated that we were in broad agreement with the principle of targetting plasma collection, but there were several procedures which could be put into effect to achieve those targets; it must be stressed that these procedures were options, any or all of which could be adopted, none being mutually exclusive.

The first was to increase salvage of plasma from whole blood collected, i.e. that the Regional usage of Plasma Reduced Blood (PRB) should be increased from the then figure of about 40% to about 60%, with commensurate decrease in proportion of whole blood used. This meant that there would have to be some change in attitude and practices among clinicians. Each unit of whole blood contains about 200ml of red cells and 300ml of plasma and anticoagulant agent. PRB is in fact only partially plasma reduced, since the remaining red cells need nutrients to keep them alive and therapeutically effective, therefore about 100ml plasma is left with the cells, and only about 200ml plasma from each unit can be retained for fractionation. However in 1986 a system was introduced whereby almost all the plasma from each unit (about 300ml) could be removed for fractionation and replaced by 100ml of an Optimal Additive Solution to preserve red cell function. We did in fact introduce one such commercial solution "SAG-M" slowly at first early in 1986, but now (in 1990) well over half of all units of blood collected in this Region are processed this way, and the use of whole blood has dropped to about 20% overall (the rest being used as PRB or red cells in "SAG-M",

The second method of increasing plasma availability would have been to increase whole blood collection. However we felt that since this would produce residual red cell concentrates which the Region could not use and did not want, it was a very questionable way of collecting plasma, and a way which would be unacceptable to donors and also to the media.

Thirdly, there was the possibility of using large scale plasmapheresis. Manual pheresis was too labour intensive and time consuming for us to consider on any worthwhile scale, but machine-based pheresis using the Haemonetics 50(R) machine was then becoming an established procedure. I discussed the requirements for a workable plasmapheresis sytem in that document. Subsequently, the options in that document were costed, and I was granted limited permission to proceed.

Meanwhile, a DHSS document, dated 18th December 1981 (included in document 16) referred to the report of a working party of the Advisory Committee on the level of plasma supply which should enable England and Wales to become self-sufficient in blood

products by the mid 1980's. On that basis, Oxford BTS was given a final target of 20,300 kilograms, a figure subsequently raised to 22,900 Kgs parri passu with the rising catchment population of this Region. The DHSS wrote to the Regional Administrator of the Oxford Regional Health Authority on 18th December 1981. Although the Regional Medical Officer replied on 5th March 1982 that it was intended to set up limited pheresis facilities towards the end of 1983 to 1984, she indicated that there was no question of that development reaching top priority among the revenue allocations being made about that time (document 16).

By now the project of rebuilding the BPL had begun though this was to take several years to complete. Therefore efforts were made to deal sensibly with the interim situation. A draft report on a meeting of the Regional Transfusion Directors on 28th March 1983 refers to the intention that work would commence on the site of the new factory at the beginning of May 1983, and in the meantime little additional plasma could be fractionated anyway. Nonetheless it was proposed that there should be a continuing drive to increase the amount of plasma produced with a view to stockpiling it at BPL. Figure 1 annexed to the draft minutes and dated 11th April 11983 shows that the aim was to stockpile plasma until a date in 1985. Then when the new factory went into commission the stockpile would be used initially and thus avoid a manufacturing hiatus due to lack of source material. Each Centre was thus given revised annual targets for plasma collection (document 17, and my letter to Dr. Rue, RMO, documents 25 and 26). On the surface, stockpiling plasma seemed at that time to be a sensible idea and the Regions duly embarked with varying degrees of success (Oxford more than most) on the delivery of the additional plasma to Elstree.

Unfortunately this well-intentioned scheme was jeopardised by the identification of HTLV III (now HIV 1) and the later development of screening tests. This meant that none of the stockpiled plasma had been tested at source for HIV 1. The screening tests were in fact introduced a few months before the new factory came into production in 1986. The stockpile was affectionately referred to as the "iceberg". All Centres had to examine the records of all donations sequestered in the iceberg to see whether their corresponding donors had donated blood more recently, had been screened, and had perhaps had proved positive for HIV 1. In Oxford we traced about two thirds of the many thousands of donors concerned and were able to confirm that they had subsequently been bled, tested and were found clear. We understand that the remaining donations, from donors for whom no further information was available, could not be used, and have not been processed.

By 1983, on 28th April, Dr. Gunson sent out a questionnaire enquiring about each Centre's plasma supply for fractionation. It attempted an estimate of future forecast relating to the period 1984 - 1988 (document 18). However, by January 1985, the effects of heat treatment of plasma (to inactivate viruses) on the yield of factor VIII was being appreciated and pro rata redistribution of products had to be temporarily suspended (document 23). Shortly after, on 29th March 1985, and prompted by shortfalls in plasma production nationwide, Mr. Williams of the DHSS (document 24) sought an updated forecast. I replied

that in view of financial limitations I could give no realistic proposals for achieving our final target.

In November 1985, I wrote to Dr. E.R. Rue, RGM, (document 26) and mentioned that we were introducing procedures giving us a longer shelf life for most red cell products. This was the "SAG-M" optimal additive system. Although it enabled greater plasma retrieval per unit, the new system meant that 8% less whole blood needed to be collected. To part-compensate for this, we abandoned our previous policy of not separating plasma from donations from new donors in spite of known higher prevalence of hepatitis B among these as compared to established donors. (Hepatitis screening results would of course be available later to enable retrieval of any units that were suspect before they were sent to BPL). In that same letter I also referred to the need to increase the level of plasmapheresis undertaken.

Response to AIDS

I personally first became aware of AIDS as a medical problem early in 1982. The first AIDS leaflet produced by the DHSS and the Blood Transfusion Services of both England and Wales and of Scotland was made available from August 1983. That leaflet was dealt with by differing methods of distribution in relation to different Regional Transfusion Centres. There was a Regional Transfusion Directors' meeting on 22nd September 1983, and the minutes at paragraph 3 read:

> "MATTERS ARISING FROM THE MINUTES
>
> a. AIDS
>
> Dr. Wagstaff reported that the AIDS leaflets had been issued and Centres had been encouraged to use different methods of distribution. The three methods being used were "(a) posting of leaflets with call up card (b) handing leaflets to donors (c) making leaflets available at sessions for donors to pick up."
> (the Oxford Centre chose option (c) (document 35)

On 16th October 1989 Dr. Gunson, as National Director, asked me for copies of correspondence about this. It can be seen from that correspondence that on 6th July 1983 copies of the final form of the leaflet were sent to all the Regional Directors by the then Chairman, Dr. Wagstaff. His letter of that date indicates that senior staff at the DHSS were then a little perturbed about the low key approach which most of us took and the reasons set out in that letter and in my letter of 14th June 1983 to Dr. Wagstaff in reply demonstrated our thinking at the time, i.e. (document 34).

> "1. Symptoms such as loss of weight, enlarged glands, night sweats etc. were too unspecific and answers to questions about such symptoms would be positively unhelpful.
>
> 2. Even if specific questions were available it is likely that correct answers may not be offered and the truth may be positively concealed.

3. The evidence at that time was the U.K. donors most likely to develop AIDS were homosexuals or drug abusers. Routine questioning of donors in the open forum at a clerking desk to seek information on their personal habits was considered to lead to:

   a) rare disclosure of the truth or
   b) deliberate withholding of information of (c)
   c) a very large number of annoyed/irritated/puzzled/ upset donors

4. A sense of perspective should be maintained seeing the situation in the USA was far worse than in Britain at that time.

5. Too great a fuss about AIDS might mean loss of information on other issues. AIDS should be dealt with like so many other disorders under "any medical doubt".

6. The leaflet being prepared should be made freely available at donor sessions along with other BTS literature" (document 34)

I appreciate that the thinking very quickly changed on this, but I can only stand by my position which was then a response to the situation as it then existed, and as I understood it at that time. On 5th September 1983, I sent a memorandum to all the doctors and other Oxford Region donor session staff dealing with the situation (document 36). The second AIDS leaflet was finally issued from February 1985 (document 38). By that time, the increased public awareness of the expanding AIDS problem and its risks was such that it was accepted that the revised leaflets should be sent by post to each donor called, together with their call-up information, and for those donors who arrived uncalled at sessions the new leaflet should be given by hand. I have an internal memorandum dealing with the steps taken from 1st April 1985 relating to this, and I also issued an undated letter which went out with each of the revised leaflets to all donors (included in documents 39).

Since January 1985 our routine donor registration document NBTS 110 (document 43) was modified to include in red print the words "and the AIDS leaflet". Donors were also encouraged to study the more complete advice sheet with special reference to reading the AIDS leaflet (document 42).

About this time I became anxious that we should if possible obtain information from the Special Clinics as to any of new donors who may also be clients there (document 21). There was a certain amount of correspondence at the time about this and it is also referred to in the minutes of the Regional Transfusion Directors' meeting of 23rd January 1985, item 8 (document 22). However that idea was thwarted because of the Venereal Disease Regulations which effectively prevented the Special Clinics from disclosing any information (unless of course with the clients' consent)

Testing

By early 1985 I understand a commercial HTLV III (HIV 1) screening test by Abbott was being introduced in the United States of America. However, experience with that first test kit was not happy in that it gave up to about 10% false positive results. The UK BTS Directors felt so strongly that it should not be used in this country that we wrote a letter to the Lancet, a copy of which is annexed to the letter from Dr. (now Prof.) John Cash to me dated 22nd February 1985 (document 48). Other manufacturers soon also produced test kits and it was agreed that the Public Health Laboratory Service Central Reference Laboratory at Colindale would undertake a critical appraisal of all kits available, whether licenced at that time or not. That evaluation was conducted in the spring/summer of 1985. Ultimately three kits were recommended as suitable for use in BTS Centres; we in Oxford adopted the one most widely used (Wellcome). The DHSS agreed to introduce donor screening in all Transfusion Centres as from a common date: 14th October 1985. It was strongly felt, I believe quite rightly, that introduction of screening should have been co-ordinated to start on the same date, and that it would have been totally wrong for it to have begun piecemeal in different areas.

Since screening began, we in Oxford have experienced only two positive results; one in the early months of screening, the second in the last few months. Both were in donors who had given blood more than once previously.

At the Regional Transfusion Directors' meeting of 10th July 1985, (document 53) it was indicated that should there be a positive donation (confirmed positive, not just screen positive) that donation should be destroyed. Also, it was agreed that BTS medical staff should take the responsibility for initiating the delicate task of counselling the donor concerned. To this end, I myself, as well as an Associate Specialist colleague, Dr. Mary O'Sullivan, attended an AIDS counselling course at St. Mary's Hospital, Praed Street, Paddington in September 1985 (document 54).

With regard to the AIDS screening tests used, it is totally impractical for us at a Transfusion Centre to use routine tests on all donors for the presence of the HIV virus particles themselves in sera. Whatever tests we have to use must be capable of yielding reliable answers preferably within about a couple of hours, so that suitably "cleared" donations will be available for issue almost immediately. The only tests for HIV which can reasonably do this in these circumstances are those for the HIV antibody in the donor(s) plasma, a measure of the infected persons bodily response. Should a donor become HIV infected, the corresponding antibody does not develop and become detectable until after a timelag which varies from a few weeks to perhaps several months. The risk of a donor giving blood during such a timelag or "window" of infection has been calculated to be in the order of about 1 in a million, that risk being less in the Uk than some other countries who accept donations more than twice a year from the average donor. Consequently, if a donor were to

become infected there is a good chance of there being only one previous possibly virus-containing plasma donation which would be most probably still held in quarantine anyway before being pooled and fractionated.

The situation could potentially be slightly different in respect to donations given by pheresis, in view of the much greater frequency of donation, and also in view of the rapidly expanding role of pheresis in meeting plasma demand.

Pheresis as a principle has been known for several decades, but it has only become a really practicable and potentially cost-effective possibility within the last ten years with the evolution of machine-based systems and disposable, sterile harnesses. The current Code of Practice for pheresis in the Uk allows for the procedure to be repeated if so required at not less than two-weekly intervals. In Oxford, most of our approximately 400 pheresis panel donors arrange to come monthly. Although this frequency of donation could be a possible problem if a donor were to become infected, safeguards are provided by our knowing the donors concerned very well, by undertaking rather more rigorous health checks on them before embarking on pheresis and at regular intervals thereafter, by routinely screening every donation, and by keeping their donations in quarantine, frozen both at the Centre prior to shipping to BPL, and for several months at BPL before fractionation. Although we have no proof for our impression, we believe that pheresis donations may possible if anything, constitute a lesser risk from HIV "window" infection of plasma for fractionation than conventional donations.

GRO-C

C.C. Entwistle

4th January 1990