THE SITUATION AT BPL WHEN I ARRIVED IN APRIL 1977

1. I joined BPL as Director Designate on the 15th April 1977. I should point out, however, (and this will be apparent from many of the minutes of the meetings between April 1977 and September 1978), that Dr. Maycock (who was also the Consultant Advisor to the DOH at the time) kept me very much in the background. He continued to attend Transfusion Directors meetings, etc., as representative of BPL/PFL without me, and although, as I detail later, I was given some specific work to do in planning for the "Stop-Gap" proposals to further up-grade the BPL facilities, it was not until Dr. Maycock's retirement in September 1978 that I found I was able to exert much influence or control over BPL/PFL.

2. When I joined BPL in April 1977, self-sufficiency was still considered as desirable an object as it had been from about the early 1970s for several reasons. First, the World Health Organisation advocated that countries should pursue the objective of self-sufficiency. [**Dr. Lane will speak to Harold Gunson re supporting documentation**]. This gave countries security of supply and the ability to control the standard of the product. From the point of view of England and Wales, another reason why self-sufficiency appeared desirable was the economic one. There was a general belief (although it has to be said there were no hard statistics in support of this) that it was more economic to manufacture Factor VIII through the state owned BPL/PFL than to purchase commercial product on the open market. However, it was a feature of much of the discussion regarding the "pros" and "cons" of self-sufficiency during the 1970's, that neither the DOH nor BPL/PFL could accurately cost production at the BPL/PFL, principally because these undertakings were not organised on an orthodox commercial basis. For example the "cost" of the raw

material was not known. From the point of view of the Regional Health Authorities who were the recipients of Factor VIII concentrate produced by BPL/PFL, the economics were clearly in favour of using "free" issues of Factor VIII produced by BPL/PFL rather than devoting part of their budget to the purchase of commercial Factor VIII. Since BPL/PFL were, however, fractionating FFP produced by Transfusion Centres funded by Regional Health Authorities, there was a cost involved and it is not correct to characterise the NHS concentrates as truly "free". At no stage during the period 1977 to 1985 **[Check whether this should be a later date]** was any system put in place for charging Regional Health Authorities for the product they received from BPL/PFL.

3. Although self-sufficiency was a desirable objective, it was still not seen to be immediately essential in 1977. There remained a number of major obstacles that lay in the path of the pursuit of this objective. First, there was no proper financial co-ordination to implement policies covering the activities of Blood Transfusion Centres who were the source of the FFP, BPL/PFL who fractionated it to produce Factor VIII concentrate, and the Haemophilia Centres at which clinicians responsible for the choice of Factor VIII for the treatment of haemophiliacs were located.

4. The DOH funded the National Health Service and these funds were distributed through the Regional Health Authorities. From their allocations, the Regional Health Authorities had, amongst other things, to fund their Regional Blood Transfusion Centres as well as the Haemophilia Centres located in certain hospitals within their region. DOH policy was that Regional Health Authorities were to all intents and purposes responsible for allocation of budgets, and the DOH would not intervene in the exercise of

their discretion. However, at the same time, BPL and PFL were funded directly by the DOH which closely controlled all but very minor expenditure. Whilst the Regional Health Authorities controlled the Blood Transfusion Centres, the fact was that in 1977, there was no discernable benefit to them, demonstrable in terms of cost savings, flowing from their expenditure at their Transfusion Centres to increase the supply of FFP for fractionation at BPL/PFL. Moreover the Regional Health Authorities had no direct control over the funding of BPL and PFL and with it any expansion in their capacity to fractionate. There was no direct correlation between the FFP Regional Transfusion Centres provided to BPL and the amount of Factor VIII which they received back after fractionation.

5. The practice of the DOH in leaving Regional Health Authorities to determine how they should spend the funds allocated to them through the National Health Service and the distinct reluctance of the DOH to interfere in any way with the Regional Health Authorities autonomy in this regard, created difficulties in striking a balance between increasing the supply of FFP at any given time, requiring funding by the Regional Health Authorities, and increasing the capacity of BPL/PFL to fractionate it, dependant upon the willingness of the DOH to make the necessary finance available if it was to be increased. Only in theory was the possibility of co-ordination ever present.

6. What was "self-sufficiency"? The reality proved difficult to forecast. The problem lay in estimating the future requirements of the increasing haemophiliac population for Factor VIII. Modest increases in the production of Factor VIII concentrate in the early 1970's were concomitant with increasing availability of commercial Factor VIII concentrate provided by

U.S. manufacturers. At the start of the 1970's, cryoprecipitate was used to treat severe haemophiliacs in the vast majority of cases, but by the end of the decade most if not all severe haemophiliacs were using Factor VIII concentrate, which completely eclipsed cryoprecipitate as the treatment of choice. By 1977, as a result of the increased use and convenience of prophylactic treatment, the demand for cryoprecipitate was diminishing. Haemophilia Centre Directors were under pressure from their patients to prescribe Factor VIII concentrate, and what they could not obtain from BPL/PFL via the Regional Transfusion Centres which were supplied with the NHS product, they sought and, in the main, received funds from Health Authorities to purchase from commercial manufacturers. The DOH took the view that it was acceptable to purchase commercial Factor VIII, provided it was paid for out of the Regional budget.

7. Accordingly throughout the 1970's, estimates of Factor VIII use were constantly increasing.There were several reasons for this.

8. First, throughout this period, there was uncertainty (inherent in the nature of the material and the processes in use) as to what was actually being produced at any given time. Plasma is variable in quality and resultant predictions of Factor VIII yield were unreliable.

9. Secondly, in terms of trying to estimate demand, a great deal of treatment during the early 1970's was carried out using cryoprecipitate. There was no real exactitude in estimating how many international units of Factor VIII were to be found in any given bag of cryoprecipitate (indeed the nature of the plasma from which it was derived meant that this could vary quite considerably as explained below). Moreover, there was a tendency

(since no one knew precisely how many units of Factor VIII were in any bag of cryoprecipitate) to over treat a patient suffering a bleed with the consequence that the amount of cryoprecipitate used was not necessarily an exact guide to what patients actually required. Indeed, arguably, it was a wasteful use of plasma for this reason. Further, cryoprecipitate did not lend itself to prophylactic treatment and therefore usage was depressed.

10. Lastly, the fractionation process always involves a compromise between the yield of Factor VIII at the end of the process and the purity of the product. From the point of view of the recipient, the purer the product the smaller the volume of extraneous proteins and contaminants the individual has to inject (in addition the solubility of the product is improved with the consequence that it can be reconstituted for injection more rapidly). Against this, however, a purer product reduces the yield from the source plasma. This was a consideration when, during the period 1982 to 1985, work was carried out on heat treatment of Factors VIII and IX. In particular, to avoid damaging Factor VIII concentrate, it was necessary to increase the purity of the product with consequential loss of the Factor VIII activity in it. Refinements to the process from 1985 onwards have materially improved the yield of the new product 8Y, but production was depressed when 8CRV and HL were heat treated as a prelude to the introduction of 8Y and during the early period 8Y was manufactured.

11. The underlying problem (in retrospect) is that those involved were sometimes thinking of different things when considering self-sufficiency. For Dr. Maycock and some of those in the DOH, self-sufficiency was considered to mean the amount of plasma and concentrate produced from it which was <u>needed</u> to treat haemophiliacs in the way they were treated using

cryoprecipitate. For others (particularly some clinicians) it was the amount wanted by their patients to lead as near normal a life as possible. Estimates arrived at on either basis were, as we now know, wrong.

12. By the time I joined BPL there had been considerable debate about the "target" necessary to achieve self-sufficiency. Although Dr Maycock was actively involved, this debate had largely taken place without the intervention of the DOH. However, notwithstanding the uncertainty as to the "target" for self-sufficiency, BPL and PFL's immediate aim was to achieve Factor VIII concentrate production of 15-16 million iu by mid-1977. (see document no.394).

13. Accordingly, when I arrived at BPL in April 1977, the laboratory was in the midst of efforts to increase its production to this level. Following the DOH decision to earmark an additional £500,000 to increase the supply of plasma, BPL had received some new equipment to enable it to increase production. The effects of this were just becoming apparent when I arrived. However, it was also quite apparent that once the desired level of production was achieved, there would be no room for further expansion at BPL within the existing framework of the plant and buildings.

14. Meanwhile, discussions between the DOH and the Scottish Home and Health Department were taking place with a view towards diverting plasma from south of the border to the PFC at Liberton. It was intended that PFC would fractionate the plasma to provide Factor VIII concentrate which would then return to Regional Transfusion Centres south of the border.(see document no.486). As far as I am aware no action ultimately resulted from these discussions.

15. However, there had been an exchange of products between Oxford and Edinburgh with a view to Edinburgh conducting some quality comparisons on batches of Factors VIII and IX. (see document no.512).

16. Up until 1976, BPL and PFL had been operating under Crown Exemption from the provisions of the Medicines Act. However, in 1976, the Secretary of State had decided that the manufacturing standards in NHS units should be no lower than those in commercial firms. Accordingly, Crown exemption had been waived in 1976 and as a result BPL and PFL had to apply for both manufacturers licences and product licences for the products they produced. This meant that both BPL and PFL would have to be inspected by the Inspectors of the Medicines Division of the DOH. When I arrived in April 1977, these inspections had not yet taken place and indeed did not in fact occur until 1979.

17. As from 1st December 1976, NHS Factor VIII concentrate had been delivered to the Regional Blood Transfusion Centres in an amount proportional to the number of patients treated at the Haemophilia Centres of that region in 1974. It was intended that NHS concentrate should be given as a matter of priority to patients allergic to cryoprecipitate and to those who were already on home treatment with NHS concentrate. (See minutes of the meeting of Directors of Haemophilia/Associated Haemophilia Centres and Blood Transfusion Centres held on 15th December 1976 - document no. 450). **[Up until that point, I think it is fair to say that distribution was somewhat ad hoc. The documentation from the early 1970's reveals correspondence from clinicians on behalf of individual patients seeking supplies direct from BPL, and there seemed to be no established and formalised procedure adopted with**

regard to the distribution of concentrates, particularly one which encouraged Blood Transfusion Centres to increase their supplies of FFP to BPL.]

18. During the latter part of 1976 I was actively involved as a member of the Regional Transfusion Directors' Working Party to consider "the quality of cryoprecipitate prepared at RTC's and relevant factors" having been invited to join this Working Party by Dr Maycock in July 1976. (see document no.322). It might be thought (with some justification) that cryoprecipitate, which was by this stage quite obviously not the patients' choice of treatment, was rapidly diminishing in importance. This was certainly the case but in fact the principal purpose of the Working Party was to obtain a more accurate idea of the number of international units which the usage of cryoprecipitate actually represented. The result of this exercise was never going to be particularly accurate, but it would provide more reliable data for use in estimating current and future usage and planning production to meet this.

19. The first draft report of the Working Party on Cryoprecipitate was produced in November 1976, and the report concluded that further work was necessary, but identified the significant difference in Factor VIII levels in cryoprecipitate produced at different Transfusion Centres. The overall range of mean values was from 56.6 iu to 113.5 iu per dose of cryoprecipitate.

20. The risk of hepatitis and in particular, hepatitis B had for some time been known to be associated with the use of Factor VIII concentrates and for that matter, cryoprecipitate. However, it was in about 1977, that the existence of another type of hepatitis, initially described as non-B hepatitis but later described as NANB was confirmed.

21. Dr. Craske of the PHLS was responsible for many of the studies in the U.K into the incidence of the various forms of hepatitis arising from treatment with Factor VIII concentrates. Dr Craske's initial study was a retrospective study of the incidence of hepatitis after the infusion of the U.S. Commercial Factor VIII concentrate "Hemofil" produced by Hyland. This study followed an outbreak of jaundice associated with the use of commercial Factor VIII concentrate at the Bournemouth Haemophilia Centre between April and June 1974, which had been reported by Dr Craske in an article published in the Lancet on 2nd August 1975 (see document no.277). Although Dr Craske's survey did not extend to include results obtained from patients treated with, inter alia, NHS Factor VIII concentrate, this early work supported what I believe was in fact the case i.e. that US commercial concentrate was more likely to be infected with hepatitis B having regard to the fact that the plasma from which it was manufactured was obtained from paid donors. The social status of these donors was such that they were more at risk of contracting Hepatitis B than volunteer donors although even in the UK there was a higher incidence of virus carriers in the main metropolitan areas. A non-reactive result with the most sensitive hepatitis B test will not exclude all infectious plasma. Therefore, an intrinsically higher incidence of hepatitis B carrier donors in the total donor population places an added risk of infection into large plasma pools.

22. By 1977, Dr Craske's initial study had been completed and he was proposing, inter alia, a wider study of the incidence of hepatitis arising from treatment with concentrates. Dr Craske's idea was to compare Hemofil, Kryobulin, Scottish and NHS Factor VIII as regards the incidence of hepatitis after infusion with these various concentrates. He had obtained the provisional consent of the Newcastle, Manchester and Alton Haemophilia

Centres to participate in the study of selected batches of the Elstree product.

23. Dr Maycock was in favour of Dr Craske's proposal to study the incidence of hepatitis associated with the use of BPL's Factor VIII concentrate, and had participated in the drafting of the protocol for the study. Dr. Craske sent the final version of the protocol to Dr Maycock on 7th April 1977 (see document no 522).

24. When I arrived at BPL in April 1977 there had been correspondence between Dr Maycock and Dr Rizza regarding the formation of Haemophilia Centre Directors' Working Parties and in particular, the formation of a Hepatitis Working Party. Dr Maycock was not enthusiastic over the idea of such a Working Party (see his letter to Dr Rizza dated 28th February 1977 - document no.509).

25. By the time I arrived at BPL, BPL were using a third generation RIA test for HBsAg. However, [some] Regional Transfusion Centres still used the second generation RPH test. The RPH test used at Regional Transfusion Centres was less sensitive than the RIA test used at BPL. There was no test available for NANB hepatitis, as the virus had not been clinically identified.

26. As a result of the increased sensitivity of the tests used at BPL and Regional Transfusion Centres for HBsAg from 1975 onwards, and the development of antibodies in patients exposed to the virus, hepatitis B infection in haemophiliacs was increasingly being brought under control by the time I joined BPL.