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HOUSE MESSAGE

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Armour Pharmaceutical Company Ltd.

To: D. Lewis
M. Cross
K. Dunbar

From: C.R. Bishop

Date: 4th March 1986.

R. B. C.
- 6 MAR 1986

cc: K.W. Fitch
J.D. Michelmore
A. Sheppard
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R.B. Christie
L. Lucas
Master
Day
File

Re: THE HAEMOPHILIA SOCIETY ANNUAL SEMINAR - HEATHLANDS HOTEL BOURNEMOUTH - 28TH FEBRUARY TO 2ND MARCH

For your information, I enclose a copy of the Haemophilia Society Lecture for 1986 delivered by Dr. Lane, Director of the Blood Products Laboratory, and upon which I would like to make one or two comments.

Page 2 - There is the hint that once the NHS become self-sufficient, although Dr. Lane is against it, there could be the possiblity of restrictive legislation against the importation of blood products.

Page 3 - It is confirmed that the Transfusion Service is ahead of its plasma schedule and "they will undoubtely meet future targets". This is the first statement made in print that the Blood Transfusion Service will collect the required 450,000 kg. necessary to produce 100 mill. units of factor VIII. Although some regions we know have set up plasmapheresis units this is yet to extend to all regions but I think the statement should be taken seriously.

Should they produce the 100 mill. units then they can produce 120% of the U.K. Albumin needs, 100% of the Immunoglobulin needs, and 400% of the Factor IX needs.

Of particular significance is the declaration made by the NHS that they will sell excess product on the open commercial market!! (see also copy of article in The Guardian on the 3rd March by Andrew Leitch attached).

Page 4 - They claim a purity for the new 8Y product as being ten times greater than intermediate concentrates.

After nearly a year on clinical trials, the 'inactivation of NANB hepatitis virus seems to be met in all haemophiliacs treated up to this date'. My comment here is that either it is or it isn't and the word 'seems' appears to be non-commital. In the last sentance of paragraph 4, Dr. Lane again expresses doubt when he says "if this process has totally inactivated ..... plasma".

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Page 5 - The statement made by Dr. P. Jones at the AIDS Conference underwent severe critiscm as, of course, it would do since the NHS 8Y product is dry heated, albeit at 80 C for 72 hours, higher than anybody elses.

Dr. Lane also points out that further purification is planned and that already they are self-sufficient in the heat treated factor IX product.

The penultimate paragraph makes a very bold statement - "The products are now the best and capacity, quality and reliability are being underwritten by the most modern pharmaceutical blood products building in the world"!! I doubt whether we as a commercial organisation would be allowed to make such statements.

Page 6 - Dr. Lane foresees that recombinant DNA factor VIII and conventional factor VIII, all be they highly purified products, will run side by side.

In summary, there was considerable scepticism from the Haemophilia Centre Directors present but considerable hope in the future from the haemophiliacs who attended. Many bold promises have again been put in writing but we must now wait and see whether the NHS are able to deliver.

In the meantime, we are working quickly towards the introduction of MONOCLATE with all its expected advantages over even the new super 8Y NHS product.

With regard to the future, a spokesman for the National Executive of the U.K. Haemophilia Society confirmed that they would continue to demand the highest purity and the safest product available, irrespective of source, whether commercial or NHS, and irrespective of price. A realistically price product would also have the total support of the Haemophilia Centre Directors.

If Elstree are going to compete on a "commercial" basis they will have to stand or fall on the quality and safety of their products and will no longer be able to hide behind the shield of "British is best" or "NHS self-sufficiency!"

Please continue your current strategy of promoting purity with a move towards the introduction of MONOCLATE and continue to feed back all information relative to NHS and competitor activities.

GRO-C

pp C.R. Bishop.

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The Haemophilia Society

THE HAEMOPHILIA SOCIETY LECTURE

1986

DELIVERED BY

DR R S LANE
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DIRECTOR, Blood Products Laboratory,
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The Heathlands Hotel
BOURNEMOUTH

1st March 1986

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SELF-SUFFICIENT MANUFACTURE OF BLOOD PRODUCTS IN ENGLAND AND WALES

Morally, socially and politically, the concept of self-sufficiency in provision of blood and blood products is wholesome and desirable, particularly when fostered by the principle of voluntary donation of blood as in Great Britain. Equally, there are the straightforward sanitary benefits of restricting import and export of blood derivatives, already observed in some countries, firmly legislated for in the vetinary field and becoming more compelling year by year on normal public health grounds. As the Dean of the School of Public Health, University of Michigan pointed out to a select meeting on AIDS at the National Academy of Sciences in Washington, September 1985, the USA has little to be proud of in the way it has made itself host to the virus of AIDS, LAV/HTLV-III and the efficiency with which it has passed to friends and neighbours.

However, self-sufficiency is no static objective. In making this commitment, politicians may initially have underestimated the totallity of its content and now find that simple capacity to manufacture and ability to raise plasma supply are the tip of an iceberg dependent for its presence, stability and life on the greater unseen mass of organised resources such as trained staff, management capability, financial accountancy, research and development, marketing and sales. Some of these resources do not become available as rapidly and predictably as do production buildings and others do not rest easily within the standardised practices of the public sector.

The last decade saw the establishment of clinical management of haemophilia with concentrates of human factor VIII. The effect on the transfusion services was generally underestimated, although formative work on factor VIII concentrates at the laboratories of the Oxford Haemophilia Centre had already established a potential for great progress and success. Underestimation was not limited to the National Blood Transfusion Service, however, since the predictions for future use of factor VIII from the haemophilia services were substantially below reality. Growth in plasma supply was inadequate; financial provision and management planning were decentralised and varied significantly between regions. Fractionation capacity for England and Wales persistently failed to meet demands and the perceptible increase in regulatory pharmaceutical standards was largely unnoticed.

During this period, an attempt to get some centralised management into the National Blood Transfusion Service failed and one outcome was the unco-ordinated approach to meeting centrally originating demands on the Service. Plasma supply to Elstree was on a 'grace and favour' basis which was reflected in quality and quantity - in fact the same basis applies now, although the present high voluntary commitment from transfusion centres has improved quality and quantity within targets. The problems created for the Transfusion Service by the plasma demand for national self-sufficiency are matched by difficulties in meeting the growing requirements for platelets and other services. Once again, the need for a more centrally managed service has become obvious to the Regional Directors who have collectively conveyed their concern to the Department of Health.

The potential uncertainties of obtaining source plasma from whole blood was an important factor in determining that American industry planned their own independent economic plasma supply from paid donors. Thus, in the 1970's the American Blood Resources Association took a commanding lead in blood product manufacture to the extent that much of Europe was able to depend on imported supplies: factor VIII and albumin are prime examples and I would immediately recognise the great benefits in health care which resulted from the American initiative.

At the end of the decade, I took directorship of the Blood Products Laboratory, October 1978 to be precise, and this followed two ye[illegible] experience at the Regional Blood Transfusion Centre at Brentwood, a period of [illegible]ce which has proved to be of considerable subsequent value.

Early discussions with the Department of Health defined the task at Elstree, if not its size and complexity. At that time, a senior civil servant of some perception noted then that the Blood Products Laboratory 'functioned more in the manner of a cottage industry'. In terms of pharmaceutical manufacturing and industrial financial management, he was absolutely right. Nonetheless, things were not all bad; for example, there was a cohesive group of staff of established technical and scientific merit and having great loyalty to the laboratory; there was an intact safety record for all products going back nearly thirty years; finally, except for albumin and factor VIII, all other blood products were produced in amounts able to meet National Health Service needs - NHS patients have never used imported Anti-D immunoglobulin for the prevention of rhesus disease of the newborn.

All the credits have been preserved and extended during the past five years, however, a comfortable historical perception that quality and product safety are assured is not enough. It must be proved and documented in its many parts since it is the wide validation of quality that amounts to assurance. It is here that the greatest changes have taken place involving people, materials, systems design, control procedures and process methodology. The most significant of these, a new production facility, is now in its completion and commissioning phases. Before the potential of the new factory is discussed, it is worth mentioning some of the pre-conditions that have been raised and to consider some attitudes that have been adopted during this transition.

At the outset, once it was determined that the Blood Products Laboratory should be rebuilt at Elstree, other stipulations were made. First, there should be a commercially orientated management board which materialised in 1982 as a Special Health Authority, the Central Blood Laboratories Authority. Second, the terms of reference for production should allow full use to be made of raw materials, human and non-human, for a wide range of products to be made including therapeutic, technical and diagnostic, along with freedom to exploit the scientific intellectual resource. Third, terms and conditions of employment should enable effective recruitment and retention of staff in the face of competition from the pharmaceutical industry.

Clearly some distinct differences from the National Health sector were drawn, but then a principal difference lies within the Blood Products Laboratory's aim of self-sufficiency which is to save substantial sums of taxpayers' money currently used on importation of expensive blood products, serologicals and diagnostics. To the Health Service, BPL is revenue-sparing - a worthwhile difference indeed.

It is essential, therefore, to examine some of the content of self-sufficiency and attitudes it engenders. Making enough for the UK is inviting other large commercial operators to effectively withdraw from lucrative markets they have hitherto enjoyed. It is not anticipated that this will happen readily unless importation is legislated against (as in some countries), and I would not wish to develop self-sufficiency against a background of restrictive legislation, since this apparent protection may give justification to financial restriction and resultant mediocrity.

Self-sufficiency quite clearly embodies the notion of a monopoly but of my own conviction I believe that clinicians should use blood products made by Blood Products Laboratory if they are as good as imported alternatives and represent an economic advantage to the Health Service. I do not, therefore, wish to be contentious about matters like clinical freedom and its running partner medical audit - there are in any case many in the wings waiting their time. I do also recognise in a monopoly system that the matters of reliability of production and distribution assume a paramount role. There is reason here to lose patience with those who seek to lower national expectations of Blood Products Laboratory on this score, since our record of production and supply is excellent - even in the most compromised production facilities.

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Herein lies the main challenge of self-sufficiency: to maintain product standards using industry's yardstick - literally we are in direct competition at every level to some degree.

For those who think that plasma supply is the main challenge, I would say this: the National Blood Transfusion Service, in spite of decentralised management, maintains a vital central philosophy. Thus, in the past, the service has always delivered the goods - not 'only just' - usually with style; the latest example being implementation of AIDS antibody screening. Thus, contrary to all that has been said, the Transfusion Service is ahead of its plasma schedule and, although I would not minimise the problems ahead, will undoubtedly meet future targets. Like a vintage thriller, we may all be kept on the edge of our seats to the last, but we shall all go home contented and say, 'we knew how it would end'.

No - not plasma - the key to the main challenge lies in matching today's production with research and tomorrow's development. Self-sufficiency is only as long as today's research. Thus, the new production facility is necessarily underwritten in the future by paralleled Research and Development and pilot-process resources in operation today. If the Department of Health and Press are here today, it is the need to pass this message that I would make use of this opportunity. The scientific intellectual stable in this country remains second to none despite the many runners that bolt. It is true in the field of blood products, protein separation technology, hybridoma development and recombinant genetics, and I perceive great opportunities if the scientific and politcal wills can be squared.

The new factory will be completed and commissioned this year. The building is to a high pharmaceutical standard and, in use, will be the best of its kind in the world. The quality of the building and its environment will, in complement to the existing experience of staff and assurance of methods, give reason to have the highest expectation of the finished products.

Future capacity has been designed to process 500,000 kgs of plasma to full product completion. Of this plasma, 450,000 kg will be fractionated from freshly frozen material. This is the starting target to product 100 million international units of factor VIII per annum which, in line with current plans, will all be in the form of high purity concentrate. The residual volume of plasma for fractionation will be in the form of hyperimmune plasma and time-expired recovered plasma. It is not generally realised that the plasma volume needed to produce 100 million units of factor VIII can also produce 120% of NHS albumin need, 200% of NHS immunoglobulin need and 400% of NHS factor IX needs. Any further growth in NHS factor VIII needs that cannot be met by improvements in process yield, merely accentuate this imbalance. Up to the present, the waste (that is the product potential in excess of NHS requirements) has been incinerated. Until 1978, this was policy; between 1978 and now, handling of excess has been limited by capacity. In the future, the excess will be made and sold as the most expedient way in which full economic realisation of manufacture of NHS blood products can be achieved. Sale of the excess blood products has no problem of reconciliation with the voluntary unpaid motivation of blood donors when it is understood that the alternative is nonutilisation and loss. There is still some reasonable anxiety that unpaid voluntary donors will find any charge made for blood products offensive and might withdraw their goodwill. If this were to happen, it would represent a failure of communication on the part of the Service: it is in sensitive areas such as this that the news media can be of assistance or, conversely, can mislead to the detriment of the Service as a whole. Haemophiliacs need to appreciate this since their needs create the excess above NHS demand in all other products.

The new factory has been designed in a way that will p[illegible]t flexible use in the future. Accordingly, it will be possible to segregate downstr[illegible] processing of human and non-human sourced products. The design is intentional, since the primary functional parameter for the Blood Products Laboratory is the development of separation technology for biomolecules. It is immaterial whether the biomolecules emanate from human plasma, hybridomas or cloned cell lines. Equally, it is believed that the downstream separation of proteins and their pharmaceutical presentation as finished products will always constitute the main basis for judgement of safety and efficacy of a product for therapeutic administration.

In the new Blood Products Laboratory, a full range of therapeutic blood products will be produced. For today, factors VIII and IX are of obvious importance and I will not enlarge on others. Some years ago, it was already clear that non-A non-B hepatitis was an unacceptable risk associated with factor VIII administration. For reasons which remain unclear, this disorder manifests in haemophiliacs in an indolent or aggressive manner which is not characteristic of the infection in the general population. Patients receiving factor VIII or IX concentrates from large plasma pools stood a high risk of contracting this disorder after the first or second injection. The risk of infection, although not the severity of the disease, was similar in plasma products originating from paid and unpaid plasma donors.

A meeting with the research and production staff resulted in an instruction to accelerate work on methods to inactivate viruses in plasma, intermediate and final products. For each product line, the presenting problems differed: however, with factor VIII it was realised that the intermediate concentrate was less amenable to treatment than would be a purer fraction. Many of the undesirable characteristics of intermediate concentrates, from the point of view of the user and clinician, provided a dual reason to refine the factor VIII product.

A much purer factor VIII was prepared in 1984 which was found to have remarkable in vitro stability to heat in the absence of conventional stabilisers which confer their benefits on protein and virus alike. The new factor VIII, described as 8Y, differs substantially from earlier intermediate concentrates. The potency is increased since the purity is at least ten times greater with the resultant loss of protein contaminants. This added purity has permitted reduction in volume and has increased solubility of the product. The reduced protein content is considered to be a factor of considerable importance because of the desirability of minimising the effect of repeated injections of unnecessary protein material into haemophiliacs. For these reasons, the product appears to be extremely well tolerated in those patients who have so far received it. Factor 8Y went rapidly through scaleup processing and was admitted to clinical trial nearly one year ago. This factor VIII could be heated to 80°C for 72 hours with minimal loss of biological activity. This degree of dry heat is considerably greater than any applied to other dried concentrates currently available for use. In vivo, the product has efficacy and normal survival - it works - but the main purpose - the inactivation of non-A non-B hepatitis virus - seems to be met in all haemophiliacs treated up to this date. If this process has totally inactivated the hepatitis viruses in factor VIII, this is progress above all other methods.

The AIDS virus, LAV/HTLV-III, and the problems caused by transmission in blood and blood products, was superimposed on the research and development programme just outlined. While the thermostability of LAV has not been totally defined at today's date, it is seen as highly unlikely that a product incapable of transmitting non-A non-B hepatitis through heattreatment will transmit LAV.

It is appropriate here to note that the heat treatment programme for factor VIII, which was scheduled to become available in April 1985, did commence on time and the transition to distribution of heat-treated factor 8Y was completed by the end of the summer. It is of interest that heat-treated intermediate factor 8CRV from the Plasma Fractionation Laboratory at Oxford was available for clinical trial one year earlier [illegible]act before the danger of LAV transmission had worked its influence in the system. T[illegible]early heat-treated material was prepared to demonstrate the efficacy of heat

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for the inactivation of non-A non-B hepatitis virus: however, in these clinical trials there was still a marked preference for selected small plasma pool-derived intermediate concentrates since there was legitimate concern at that time that heat treatment might have untoward effects on the protein content of the factor VIII. These niceties were rapidly overturned once it was appreciated that LAV could be transmitted in blood products. In the wake of the recent AIDS meeting in Newcastle, it should be said that unspecified statements about the efficacy of heat treatment on the inactivation of virus, particularly LAV, are harmful only to recipients of the products needed for their wellbeing. To assess heat treatment requires that the exact parameters of the process are stated in relation to the product in question. Generalisations are of no practical value and unnecessarily fuel concern.

After one year in use, factor 8Y continues to meet the challenge and recognition of the research input is acknowledged. The yield of this new high purity product does not impose upon national self-sufficiency plasma targets, set before AIDS complicated blood transfusion practices in the UK. Factor 8Y is not an end-point: other downstream technologies are now defined which can improve the purity of factor VIII from human plasma and which are applicable to factor VIII separation from non-plasma source materials.

The heat treatment of factor VIII has been applied to factor IX essentially to inactivate the virus origins of non-A non-B hepatitis. Heat-treated factor IX was considered to carry a potential risk from heat-induced thrombogenicity. Concern about the effect of heat on activation of the product delayed clinical trial, so that studies in animals could be completed. The animal studies showed that alterations in the process had succeeded in controlling thrombogenicity and, as a result, clinical trials were initiated in the autumn of 1985. These trials have continued without complication and National Health Service heat-treated factor IX is now available for use in amounts equivalent to that used in preceding years.

Moving to a conclusion, it is appropriate to summarise in the following way: the Department of Health, through the Central Blood Laboratories Authority, has substantially invested in a new factory to enable the Blood Transfusion Service to meet the blood products requirements of the National Health Service in the foreseeable future. Providing that the ancilliary requirements of research and development, marketing and collaboration with other industries are given full provision, then an optimistic expectation is justifiable.

The total programme of self-sufficiency is one which should engender considerable national support since, in most cases, the need is perceived. However, the transition from being inadequate to adequate is not easy and the sensitivities of the various groups whose collective interests make up self-sufficiency need to be reconciled. Past lack of some NHS products, notably factor VIII, and the intermediate purity and limited solubility of this product have for some years been the whipping stick of the Haemophilia Society in their entirely justifiable endeavours to increase support for their organisation. The effect has been to lower the expectations of patients and clinicians alike to the possibility of adequate achievement from within the Health Service. The position is now changing and a decade of untoward experience must be overturned. The products are now the best, and capacity, quality and reliability are being underwritten by the most modern pharmaceutical blood products building in the world. These changes need to be effectively communicated throughout the Haemophilia Services who can now turn their attention to other areas of haemophilia management that continue to require support, in particular, the maintenance of effective Research and Development. I believe the Haemophilia Society has already responded.

This leaves me with my own response. In a final word to the press who have reported widely on the continued importation of paid donor blood, may I say that the UK has

never imported blood. In America, as here, blood donation is voluntary and unpaid - only plasma from paid plasmapheresis donors forms the basic resource from which imported factor VIII originates. I'm sure that American blood donors would find this collective identity objectionable as would donors in this country.

At a different level, I should state my view that proper conventional management of haemophilia with factor VIII, using existing materials and applying current approaches to safe manufacture, does not impose an unusual financial burden on national health care resources. If, because availability of safe factor VIII improves, utilisation increases well above current estimates, then the economics of plasma as source material become tested. There is plenty of incentive to retain the economic balance through improving the process yield of factor VIII, but it is in this uncharted area where I expect factor VIII from recombinant-DNA sources to augment conventional supplies.

My commitment is to make human plasma a safe economic source material for manufacture of a range of therapeutic protein fractions. For many reasons, biotechnology will not resolve all the fractionator's problems simultaneously or, I suspect, cheaply. In the meantime, high quality plasma from human blood will remain available and in the foreseeable future its potential should not be neglected.

R. S. LANE,

1 March 1986.

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