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cc. Mr Nodder
Mrs Firth (we spoke)
Miss Edwards
Dr Graveney
Dr Sibellas

Dr Harris

(173)

BRITISH PLASMA-DERIVED VACCINE AGAINST HEPATITIS B

In view of the questions which have been raised about the underlying technology for the development of a British plasma-derived vaccine against hepatitis B (particularly the efficacy of the underlying technique, and the problems and timing of the transfer of the technology from the London School of Hygiene and Tropical Medicine to the PHLS Centre for Applied Microbiology and Research), together with the concern generated by the possible risk of the transmission of AIDS by blood products of the sort, we spoke about the need to review the continued financial involvement of the Department. As a first step, it seems advisable to look again at the work at the London School, while at the same time inviting the Director of the PHLS to let us have a report of the problems experienced by the CAMR in the transfer of the technology, with an appreciation of the future of the project from the point of view of the PHLS. Because of Ministers earlier expectations of this project, expressed at the time when we were considering the introduction of the US vaccine, it is clear that we shall have to update them on the matter and seek their agreement to the proposed scientific review.

The background to the present situation is detailed in the attached draft submission from you to Mr Patten, intended to be copied to other Private Offices. I think the draft is self-explanatory, so the only comment I will add here is about the identification of the individuals who might take part in the proposed scientific review.

Dr Joe Smith is an 'obvious' for such a review, bearing in the mind the personality of Professor Zuckerman. However, we doubt if Dr Smith will have the time to undertake the detailed work of the review himself, hence the suggestion that we use Dr Geoffrey Schild in that role. If Ministers agree, the liaison between Joe and Geoffrey will be greatly facilitated by their respective roles at the National Institute for Biological Standards & Control.

Unfortunately, identifying a second individual for the detailed work of the review has been a little more difficult. We considered Dr Tedder or one of his team at the Middlesex Hospital, but they are already involved in the project as advisers to the North London Blood Transfusion Service. When I discussed the matter in confidence with Sir Robert Williams (as Chairman of our Hepatitis Advisory Committee), we came to the conclusion that Dr Tom Flewett might be suitable (he has the strength of character to stand up if necessary to Professor Zuckerman, as well as the necessary virological expertise), but when we came to draft the submission I realised that Tom had been one of the original referees of the work - which you may feel rules him out now. (Dr Craske, who is Chairman of the PHLS Working Party on Hepatitis has the expertise too, but I hesitate about putting him up against Professor Zuckerman, quite apart from the fact that Dr Craske was one of the original referees as well.) I can think

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of no other experts in the hepatitis B field with the weight for this assignment, so in the draft submission I have inserted Dr Flewett's name in square brackets, adding the name of Dr Andrews (again in square brackets), as I thought you might wish him to be considered. I am sure we only need two for the detailed work, so I leave you to decide whose name should go forward with that of Geoffrey Schild.

Meanwhile, in the light of our last discussion on this, I have written to Michael Whitehead inviting him to comment on the problems experienced in the transfer of the technology to the CAMR and to offer his appreciation for the future.

Dictated by ..... but despatched in his absence to avoid delay.

DR IAN T FIELD
Med.IMCD
AFH C716
Ext. GRO-C

31 August 1983

Mrs Walden

cc. Mr Godber
Mr Alcock
Mr Joyce
Mr Nodder
Dr Field
Mrs Firth
Dr Walford
Miss Edwards
Dr Graveney
Dr Sibellas

BRITISH PLASMA-DERIVED VACCINE AGAINST HEPATITIS B

The Issue

1. For some years the DHSS has been making a contribution - £167,000 to date - towards the development of a plasma-derived vaccine against hepatitis B, based on a micelling technique elaborated by Professor Ari Zuckerman at the London School of Hygiene and Tropical Medicine. Doubts have been raised now about the project, triggered by difficulties with the inactivation processes necessary to render any such vaccine non-infective from free virus and by recent concern over the possibility of transmission of AIDS (Acquired Immune Deficiency Syndrome) via the human plasma from which the vaccine is derived. We need to consider whether to continue DHSS involvement either with this project specifically, or with any other use of Professor Zuckerman's micelling technique.

Recommendation

2. As a first step, it is recommended that Ministers agree to the commissioning of a independent and confidential scientific review of the hepatitis B vaccine work at the London School, with a view to assessing the efficacy of the technique elaborated by Professor Zuckerman. It is envisaged that the review could be undertaken by two leading scientists under the oversight of the

Director of the National Institute of Biological Standards and Control.

The Background

3. Scientific: The basis of any hepatitis B vaccine is the surface antigen of the hepatitis B virus, which is contained in the outer coat of the virus itself. If injected into the human body, this antigen stimulates the production of antibodies by the recipient, which in turn provides immunity from the disease. In plasma-derived vaccines the antigen is obtained from the blood of chronic carriers, a small proportion of whom may still have active hepatitis B virus in the blood. Because of the risk that the extraction of antigen from carrier plasma may include some free active hepatitis B virus as well, it is essential that the production process should include operations to inactivate any free virus to obviate any risk to vaccine recipients. The Merck Sharpe & Dohme (MSD) vaccine from the United States, licensed for the United Kingdom in 1982 and now in use here, employes three such inactivation operations.

4. The MSD vaccine from the US consists of surface antigen purified from the plasma of carriers and inactivated. The British project to which this submission refers, is a variant of the other process, in that it is attempting the isolation by fractionation methods (separating constituents elements using their different physical characteristics) of purified antigenic polypeptide components of surface antigen from carrier plasma, and their possible synthesis in the test-tube. As this process also starts with the blood of chronic carriers, effective inactivation operations are equally vital if the ultimate product is to be licensed for human use.

5. Historical: In February 1971, the London School of Hygiene and Tropical Medicine sought financial support from the DHSS for diagnostic, reference and development activities concerning testing for hepatitis A and B which Dr (now Professor) Ari Zuckerman was already providing as a help to the Blood Transfusion Service and various National Health Service hospitals. Extra finances were needed and the Department's then Research Division started to fund this work on a two yearly basis. This continued from 1 April 1971 to 30 April 1981 by which time a total £1370,000 had been provided.

6. By June 1979, when the administration of the project was brought more closely under the control of the Office of the Chief Scientist, the work comprised research, service and development components; the principal, although not exclusive, component being research on hepatitis B vaccines. In August 1980, Professor Zuckerman was told that extension of funding beyond March 1981 would have to be subject to formal scientific assessment of any further proposals. He responded by suggesting: (i) continuation of "the development of a British hepatitis B polypeptide micele vaccine" (and the exploration of other sources of surface antigen); and, (ii) continuation of the "work improving reference and service functions to the Blood Transfusion Service and the NHS".

7. The Professor's proposals were submitted to three referees: Sir Robert Williams (the Director of the Public Health Laboratory Service, and previously Professor of Microbiology at St Mary's Hospital Medical School), Dr T Flewett (Consultant Virologist in Birmingham), and Dr J Craske (Consultant Virologist in South Manchester). In the light of their observations, it was agreed to provide a contribution to the funds necessary for this work, commencing on

on 1 May 1981 for five years. To date, the total spent on this second phase is £130,000.

8. During the next twelve to eighteen months arrangements were made to transfer the techniques elaborated at the London School to the Public Health Laboratory Service, Centre for Applied Microbiology and Research, which would then pursue further development of the vaccine to the point where it would be ready for commercial exploitation. DHSS files do not show specifically how the transfer from the London School to the Centre was negotiated, but it appears probable that the two parties were brought together through the good offices of Sir Robert Williams. Meanwhile, the British Technology Group had become interested, and were contributing to the funding of the technology transfer. By May 1982 the Group was talking of withdrawing its financial support, but was persuaded to continue for the time being, albeit on a reduced ad hoc basis.

9. From the phase of technology transfer onwards, the financing of the work has been problematical, with financial requests being submitted to the DHSS by the London School, the Centre for Applied Microbiology and Research and by the North London Blood Transfusion Service - which undertook to identify the necessary chronic carriers of the surface antigen, to bleed them periodically for supply to the project, however, the Office of the Chief Scientist has resisted requests for funds, other than those committed to the original research at the London School.

10. Present Situation: In June 1982, in considering the importation of the US vaccine which is priced at £72 per individual course - expensive enough to warrant Departmental guidance on the

high risk groups to which it might be offered - the Minister for Health stressed that our positive policy must be to press on to produce a British product at a more realistic price. This has guided officials in their discussions with those working on the product, and with the British Technology Group.

11. However, in recent weeks it has become increasingly clear that the inactivation operations (explained earlier), which had not been perfected fully before starting the transfer of the technology from the London School to the Centre for Applied Microbiology & Research, was giving more trouble than had been anticipated. It is estimated now that the perfection of these operations may take at least a further year.

12. Meanwhile, the transfer of the technology to the Centre from the London School has not proceeded as well as was expected. Not only is it taking more time than had been anticipated originally for this phase, but the Centre in its own work has not been able yet to replicate the encouraging results on the efficacy of the vaccine in animal tests that had been achieved originally by the London School. These several difficulties taken together have raised questions, firstly about the technique itself, and secondly about the timing of the transfer of the technology: was it undertaken too soon?

13. On the commercial side, the British Technology Group recently has informed the researchers and the DHSS that it can find no British company, nor any foreign company with a UK base, wishing to embark on the commercial exploitation of a plasma-derived vaccine. This is due to concern which has arisen about the possible transmission

of AIDS (Acquired Immune Deficiency Syndrome) in plasma-derived products, in circumstances where the blood donors likely to be the most productive sources of hepatitis B surface antigen happen often to be individuals at risk of developing AIDS. (Of the thirteen chronic carriers who are providing plasma for this product through the North London Blood Transfusion Centre, ten are known to be homosexuals, and thought to be in the AIDS 'at risk' group.) This concern could not have been foreseen in the earlier stages of the present project, because the origins, causes and natural history of AIDS has emerged only recently. The commercial firms have indicated that they would prefer to await the development of a non-plasma-derived product, that is one produced by genetic engineering.

14. Very recent reports have revealed that a team of microbiologists in the Netherlands have developed a hepatitis B vaccine using advanced genetic engineering techniques developed by Professor Kenneth Murray of the Molecular Biology Department at the University of Edinburgh. The reports suggest that this vaccine is likely to be available commercially in 1985, and could possibly be cheaper than any of the existing commercially available plasma-derived vaccines. (France and the Netherlands have their own plasma-derived vaccines not licensed for use in the UK, in addition to the MSD vaccine from the USA.) It is impossible to say how accurate are these estimates of availability and relative cost for the Dutch genetically engineered product.

15. Another aspect of the story, is that Professor Melinck of Houston, Texas is adapting Professor Zuckerman's technique and attempting to produce his own version of the British variant, with financial support from MSD itself. The Swedes also appear to be working on an adaptation of the technique.

16. Although there is no commercial interest in the British project at present, if it can be carried to the point of clinical trial of the vaccine - which could only follow confirmation of the earlier optimistic animal trial results and perfection of the necessary inactivation operations - it is possible that British commercial interest might then be stimulated. Alternatively, the Centre for Applied Microbiology & Research might be persuaded to manufacture a limited quantity of a British plasma-derived vaccine for use in this country. Unfortunately, on the information available at present it is impossible to estimate the likely unit cost of a product in either of these circumstances.

17. In any event, the technique elaborated by Professor Zuckerman might have other practical applications if the current problems could be overcome. The question is: given the complicated background, should the DHSS continue to provide funds for the development of the technique, either as the basis of a British plasma-derived hepatitis B vaccine or for some other practical application? If so, what limitations should the DHSS apply to the provision of funds? At present, meaningful answers to these questions are impossible in the absence of up-to-date scientific assessments of the efficacy of the technique underlying the product, together with more information about the problems surrounding the transfer of the technology to the Centre from the London School. To cover the first need, Ministers are invited to commission an independent scientific review of the work at the London School, to be overseen by Dr J W G Smith, Director of the National Institute for Biological Standards & Control (NIBSC) and Chairman of the MRC/Health Departments/PHLS Committee on the Development of Vaccines & Immunisation Procedures. (Although it is thought unlikely that Dr Smith will be able to spare the time necessary to undertake the detail of the review itself, it is hoped he will agree

to oversee this important and delicate exercise, for which his scientific background and standing are impeccable.)

18. It is proposed that the detailed work on the review be entrusted to Dr G C Schild, Director of the Viral Products Division at NIBSC and Chairman of the Hepatitis Vaccines Sub-Committee, together with [Dr T H Flewett, Consultant Virologist at the Regional Virus Laboratory, Birmingham] or [Dr R D Andrews, lately a Senior Medical Officer dealing with immunisation products in the Medicines Division of the DHSS]. (Pending approval by Ministers of the proposed review, no approach no approach has been made yet to any of those nominated for participation.)

19. In the meantime, the Director of the Public Health Laboratory Service has been asked to report in confidence on the problems experienced by the Centre for Applied Microbiology & Research in the transfer of the technology from the London School, and to offer his own appreciation of the future for the project from his Services' point of view.

Date

DR E L HARRIS
Deputy Chief Medical Officer

(B)

CONFIDENTIAL

DRAFT

Dr T D Davies

Dear Dr Davies

HEPATITIS B SUB-UNIT VACCINE: TECHNOLOGY TRANSFER TO CAMR

For some time the Department has been concerned about the wisdom of continuing to encourage work at CAMR directed towards the production of a British plasma derived micelled hepatitis B vaccine. The customer Divisions within the Department which have a direct interest in such work have now had the opportunity to take advice on the subject from a group of advisers representing wide British interests in this matter. The advice to the Department was that it should no longer be involved in the development and production of a plasma derived hepatitis B vaccine for routine use and that no further encouragement or finances should be directed to this end including the specialized collection of plasma at NLBTC and the collaborative transfer of technology between LSHTM and CAMR.

The Department is aware that development over the last ten years or so of the micelle technology has indeed been "money well spent", and that micelling is likely to have a valuable and widespread application to a number of vaccine products in the future. The view was that the work at CAMR had been "overtaken by events". In particular mention was made of (i) the unwillingness of British manufacturers to be involved with a plasma derived product (especially due to the emergence of AIDS) and (ii) that simultaneously developments have occurred in recombinant DNA technology enabling the hepatitis B surface antigen to be expressed in yeast and other cells. Therefore, having made a realistic forecast of the time

necessary to complete the remaining research, development and safety testing of a plasma derived micelled vaccine at CAMR, it was clear that in the same period a clinically acceptable and more desirable yeast derived recombinant DNA vaccine could well become available.

In the light of the advice given to the Department specifically concerning your specialized collection of plasma, OCS now wishes to make clear the following points:-

1. For the Department's purposes there is no need to continue with the specialized plasma collection. The special donor panel and sub-panels could well be kept intact although not necessarily active - you will know best about this.

2. The current stocks of plasma and products should be stored in a secure place (almost certainly not a blood transfusion centre) and preferably CAMR - Professor Melling will advise on this.

3. The Department has no objection, in principle, to your approaching other research workers (e.g. those working on AIDS) to offer your specialist material. It was recognised however that, after sterilization, the plasmapheresis unit could be returned to routine work at NLBTS.

I am sure that this decision will not come as a complete surprise to you and I hope it will be helpful for you to have this explanation of the Department's position.

Yours sincerely

MICHAEL J GRAVENEY
Senior Medical Officer
Office of Chief Scientist