Sent to members of the Committee on 4.12.69

MEDICAL RESEARCH COUNCIL

Circulation:
Members of Committee

MRC.69/1191
BPL.69/11

Minutes of the 16 meeting of the Managing Committee of the Blood Products Laboratory and Blood Group Reference Laboratory at the Plasma Fractionation Laboratory, Oxford on 28 October, 1969

Present: Professor P.L. Mollison (Chairman), Professor S.S. Cohen, Professor P.G.H. Gell, Mr R.P.S. Hughes, and Dr W. d'A. Maycock, Dr D.K. Gray was also present, as a Deputy for Dr J.G. Thomson. Dr D.G. Berry was in attendance.

A. THE VISIT

In conducting the Committee round the Laboratory, Dr Edith Bidwell made the following points:

1. Research and Development

The chief project at the moment was the development of a new method of preparing Factor IX in which D.E.A.E. was used. At present this method was being used experimentally on batches of 5 litres; the final product was concentrated ten fold.

2. Fractionation Laboratory

Dr Bidwell explained that 68 litres of plasma was processed for Factor VIII in two batches on Monday and Tuesday of each of two successive weeks; in the third week other plasma fractions were separated. Thus an average of about 45 litres of plasma was processed each week. Factor VIII was taken out by cryoprecipitation in the presence of 3% ethanol. Fibrinogen was separated in the presence of 8% ethanol, giving a yield of about 50%. The supernatant contained albumin, and the precipitate contained gamma-globulin and Factor IX. The batch size was limited by the risk of hepatitis and by the hardship for staff of remaining in the cold room long enough for centrifugation to take place. The albumin and gamma-globulin were sent to Elstree for purification. The gamma-globulin was first frozen in the presence of ether, which denatured the contaminating lipoprotein (mainly β-lipoprotein). Dr Bidwell said that their limited bench accommodation restricted the higher purification of Factor VIII.

3. Cold Room

Dr Bidwell said that she had been experimentally extracting Factor IX, using DEAE cellulose, from the supernatant, after the Factor VIII had been cryoprecipitated by centrifugation at about 28,000 g. This preparation of Factor IX had recently been used clinically for the first time.

Dr Bidwell pointed out that two cold rooms were needed at different temperatures. The one that she had at present was kept at sub-zero temperatures, but she needed another one which could be kept at 0 to +4°C.

4. Freeze-drying Room

One corner of this room was walled off to provide the sterile room. The freeze-drying room also contained two spin freezers and one deep freezer, which Dr Bidwell said should be placed elsewhere; the heat generated by these freezers raised the temperature of the room to over 40°C in the summer.

5. Washing-up Room

Dr Bidwell explained that there was no staff room in the whole Haemophilia Centre. The washing-up room was therefore made available to staff (mainly from the PFL), who took their lunch and tea-breaks there.

This room also contained a machine for producing pyrogen-free water, and an autoclave for sterilizing millipore filters and small equipment. Dr Bidwell said that the large equipment was sterilized by the Blood Transfusion Service by informal arrangement. She further noted that, in this small room, the two sinks were used for washing all the small equipment of both the PFL and the Blood Coagulation Research Laboratory of the adjoining Clinical Centre (B.C.R.L.), and that there was thus a high breakage-rate.

6. Outside Storage

Dr Bidwell showed us the alcohol store, and the old store, housed in a nearby hut, of the Churchill Hospital X-ray Department; the latter store was unofficially used by the PFL by courtesy of the B.C.R.L.

7. Dr Bidwell's Office Accommodation

Dr Bidwell's own office is only $11\frac{1}{2} \times 6\frac{1}{2}$ ft., and is also used by her secretary. For interviews and discussions, Dr Bidwell had the unofficial use of a small caravan (parked next to the library of the B.C.R.L.) which had been given to the Churchill Hospital by the Haemophilia Society.

B. DISCUSSION WITH DR BIDWELL

At 3.0 p.m. the members of the visiting party adjourned to the B.C.R.L. library to discuss, first, Dr Bidwell's problems, and, second, a possible plan for the extension of the Laboratory which had been prepared by Dr Bidwell and Mr G.W.R. Dike, and which was demonstrated to the Committee by Dr Maycock and Dr Bidwell.

1. Production of Plasma Fractions

Dr Bidwell, in answer to questions by Professor Mollison, said that all the Factor VIII she produced went to the Oxford Haemophilia Centre; the remainder of the Centre's needs for this fraction was supplied by the Blood Products Laboratory, Elstree. Dr Bidwell said that she made Factor IX not only from plasma processed at Oxford but also from fresh plasma processed

at Elstree. The latter source doubled her output of Factor IX. All the Factor IX that she produced was at present being used by the Oxford Haemophilia Centre, but she had sent some to Birmingham, to Wales, and to Dr K.M. Dormandy. She explained that the Haemophilia Centre might eventually require up to double the amounts of Factors VIII and IX which she was able to produce under her existing circumstances. The storage life of the products was such that in the dry state there was only about 10% loss over six months; she had not had enough surplus products to store so far, so that she could not give a definite figure, but she thought that a life of one year was probable. The Factor VIII was not as stable as the Factor IX.

Dr Bidwell explained that the sterilizing stage was the stage which caused her the greatest trouble, because the filter might slow down and have to be replaced, but this was not a problem with Factor IX. She said that, though she hoped to produce a high-potency concentrate of Factor VIII, which could be given by syringe, she did not have enough to divert for this purpose.

2. Plans for Future

(i) Suggested Extensions. Dr Bidwell explained that the research and development laboratory and the fractionation laboratory could be used as originally planned if the former were freed from use as an office and for storage, and the deep freezes were removed from the latter. Likewise, the freeze-drying room was inadequate so long as it housed a deep-freeze and spinner baths. A cold room operating between 0^{o} and $+4^{o}C$ was necessary for handling precipitates, dialysis, and storage. She did not consider it practicable to divide the present cold room into sub-zero and $+ 4^{o}C$ sections, since the resulting rooms would not be large enough for the work to be done within them. She said she had not considered the possibility of a sub-zero store to replace some of the freezing cabinets; such a store would be acceptable.

Dr Bidwell thought that although the proposed extension would probably enable the output of Factor VIII and Factor IX for clinical use to be doubled, its main advantage would be to increase the facilities for research and development.

Dr Bidwell considered a proper staff room necessary for use not only during normal breaks but also when staff had to come into the laboratory during emergencies at week-ends, etc.

Dr Bidwell estimated that some 2,500 sq.ft. additional space was necessary. Dr Maycock stated that the quantity survey of the BPL extension at Elstree had suggested, as a rough estimate, that the PFL extension might cost £12.10.0d. per sq.ft., or £30,000. Dr Gray thought this high; if £5,000 were allowed for the extra cold room, the rest of the extension could easily be built for less than £10 per sq.ft. Thus the total extension should certainly be built for less than £12 per sq.ft.

(ii) Capital Equipment. Dr Bidwell said that she required extra bench space, an extra still, and an extra deep freeze (which would eventually be needed for the increased production that she envisaged). She said that she

would also like a lathe, and she would hope that she could store alcohol barrels in a cold room. She also said that she would like a constant-temperature room for dialysis. Professor Mollison pointed out that, on the research side, more laboratory space might be needed, and thought more benches could be provided.

(iii) Staff. The authorized establishment of the PFL is 2 scientific staff, 8 technicians (including 1 senior technician), 2 maintenance workers, and 1 part-time administrative staff, all of whom (except 1) are appointed to the staff of the Lister Institute. Dr Bidwell, a biochemist, was transferred from the Council to the Lister Institute staff in August 1967. Dr W.H. Ford, a chemist, supervises the fractionation work. Mr Dike is an MRC Technical Officer, with a L.Inst.Biol. diploma, seconded to PFL from the B.C.R.L. He has worked with Dr Bidwell for 15 years and is her research assistant. The remaining staff in post, at present, comprise 5 junior laboratory technicians, 2 laboratory assistants, 2 washers-up, and 1 part-time secretary. One of the junior technicians, Mrs E. Tolley, is taking Part II of the A.R.I.C. examination in 1970 and should be suitable for promotion to senior technician. One other technician is taking H.N.C., and another Part I of the Institute of Science Technology examination.

C. DISCUSSION AFTER DR BIDWELL'S WITHDRAWAL

1. Function of the PFL

Professor Mollison thought the time was opportune for a review of the function of the Laboratory.

(i) Research and Development. Professor Mollison said that the PFL was doing various useful things - for example, finding out whether there was any advantage in carrying out cryoprecipitation in the presence of 3% alcohol. Dr Bidwell was uniquely qualified to do such work, and it was appropriate that she should be supported on a research basis. He feared that the work-load dictated by the needs of routine production was too heavy, and left Dr Bidwell with too little time and energy for research and development. Professor Mollison felt that the emphasis should be on development rather than production. Professor Gell wondered whether it was necessary to attempt to find techniques other than those which were at present used for cryoprecipitation. Professor Mollison pointed out that, as carried out in hospitals, cryoprecipitation was potentially wasteful, and that normally no quality assay was used. Although Dr Bidwell, by using 3% alcohol, might not be able to produce anything better than the average cryoprecipitate, her product would have the great advantage of being standardized by assay. Dr Maycock said that it had been reported from one source in the United States that fractionated Factor VIII and IX concentrates were cheaper to produce than cryoprecipitate, and that Dr Biggs and Professor Macfarlane had previously expressed the view that it would be better to have centrally prepared concentrates than to expand the cryoprecipitate production. This was specially important in view of the new "super-concentrates" which could be given in a syringe.

(ii) Routine Production. Professor Cohen asked whether Dr Bidwell could reduce her production to about half, thus enabling her to properly explore the fractionation procedures she was using. However, he agreed with Dr Maycock that much would depend on Dr Bidwell's own views on such a future for her work. Dr Maycock pointed out that the PFL had originally

been planned in principle to provide the Oxford Haemophilia Centre with what it needed. Professor Mollison wondered whether it was, in fact, economic to step up the production of the PFL, and whether it would not be better for Dr Maycock to step up his own production at Elstree instead. Dr Maycock pointed out that the PFL was unique; it was the only fractionation laboratory, as far as he knew, with a specialized knowledge of coagulative factors which was a functional part of a haemophilia centre. There was a great neatness about doing things in this way. Professor Mollison thought that something much more than the extensions which were being proposed would be needed if routine production was expanded as suggested at the PFL.

(iii) Relation of Development and Production. Professor Gell thought that the bigger the PFL became, the less time would there be to devote to research and development, and the more time would the staff be forced to spend on production. He felt that Dr Bidwell needed a biochemist to help her. Professor Mollison said that at present Mr Dike was really wasting his time on such things as the engineering work and the handyman work which he was doing in the Laboratory. Mr Hughes felt that the proposed extension would alter the dual role of the Laboratory to a mainly production role. Dr Maycock said that Dr Bidwell could investigate the methods of fractionation which she was using, only if she had routine production behind her. Dr Johnson, some of whose methods she was investigating and developing, had encountered difficulties because his laboratory had no routine production. Professor Gell accepted Dr Maycock's argument that production must be maintained at not less than the present level (i.e. the processing of about 45 litres of plasma per week), as a background for development and research, but thought that this level should not be increased, since Dr Bidwell did not seem to have the time to investigate even the difference between 3% and 5% alcohol extraction. Professor Mollison wondered whether there were arguments for regular production. Even if there were, Dr Bidwell certainly should not be obliged to meet all the local needs; a local transfusion centre should be able to produce more Factor VIII as cryoprecipitate. She must be able to interrupt her production whenever she wanted if she was to do her development and research work. Professor Cohen supported this assessment. Professor Mollison wondered what would happen if Dr Ford, left, since he was supervising the whole process of production. Dr Maycock pointed out that only 180 donations a week were being processed, and that one could not plan on the assumption of members of the staff leaving. Professor Mollison asked Dr Maycock whether it was essential to keep up the present level of production at the PFL. Dr Maycock in reply said that the PFL at Oxford was the result of some 2 years' negotiation between the MRC, the Ministry of Health, and the Lister Institute and that it had only been running for about 1 year, during which time many quite unexpected difficulties associated with the building had been encountered. He thought the level of routine production should be increased as suggested by Dr Bidwell, but agreed that it could not be said to be essential.

Dr Gray asked about the cost of transferring production to Elstree. It was estimated that about 40 - 50 bottles of AHG concentrate per week were being prepared. This could certainly not be transferred to Elstree before the Elstree extension was complete (about 1972), or to Edinburgh until the new BPL there was built (completion date 1974). The overall plan for providing AHG concentrate and Christmas Factor had included production at Oxford. The extension at the PFL could only double its output, and the only

extra advantage for research would be the freeing of some bench space; the emphasis would be mainly on enlarging output. There were two possibilities, therefore: (1) to enlarge the Laboratory; (2) to decrease the work-load.

2. Need for Extension

Mr Hughes thought that not all the extensions asked for were justified - e.g. the extra working space and washing-up room, and the suggested work-shop. Dr Gray did not agree; he felt that there was inadequate space for washing-up and for freeze-drying. Professor Gell made two points: (1) for different techniques of production you need a fair volume of production in order to draw on the necessary chemical engineering; (2) for the investigation of the molecular basis of coagulation factors Dr Bidwell needed bench space and a junior to help her. Professor Mollison thought that almost all the suggestions for increasing space were justifiable. Mr Hughes asked how urgent the whole question was; with regard to finance, he thought that the £30,000 suggested needed forward provision. He queried the need for providing the whole 2,500 sq.ft. suggested right away, and asked about the timing of the proposed extension in this connection. Finally, he wondered whether the whole Laboratory would need to move when the new teaching hospital was built, but he agreed with Professor Mollison that this would not be for about ten years.

3. Professor Mollison called a close to the discussion, as it was time to return to London, and suggested a meeting of the Managing Committee of the Blood Products Laboratory and Blood Group Reference Laboratory to discuss the whole question with Dr Bidwell herself. He suggested that she should appear at the meeting after preliminary discussion on what questions to ask her, and that these could be discussed, in her absence, after she had answered them. The meeting then ended.