MEDICAL RESEARCH COUNCIL

Circulation:
Members of the Working Party

HAHG.64/2

WORKING PARTY ON HUMAN ANTI-HAEMOPHILIC GLOBULIN

SUPPLIES OF HUMAN ANTI-HAEMOPHILIC GLOBULIN

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1. Several estimates of the amount of HAHG needed annually for the care of the haemophiliac population have been published.

(a) Macfarlane et al. Lancet 1954,1,1316. HAHG from a panel of 500,000 donors would be necessary for maintenance therapy, assuming a haemophiliac population of 500.

(b) Kekwick and Wolf. Lancet 1957,1,647. Assuming that a single crisis in a haemophiliac might on the average be countered by HAHG from 2 litres of plasma, that each haemophiliac suffered one crisis annually, and that there are about 2,000 haemophiliacs, HAHG from 14,000 donations annually would be needed.

(c) Maycock et al. Brit. J. Haemat. 1963,1,215. In a series of 69 haemophiliacs of all ages observed over 5 years, the average number of episodes per patient per year treated with HAHG was slightly less than one and the average amount of HAHG given per episode represented 20-25 bottles of blood. On the assumption that there are about 2,000 haemophiliacs and that each might need treatment once a year, HAHG from 40,000 to 50,000 donations would be required.

2. In the Oxford cases 1962-1963 the average consumption of HAHG, plasma and blood per episode in terms of bottles of blood was:-

	HAHG	PLASMA	BLOOD	T O T A L
Dental extractions (43 episodes (40 in severe, 3 in mild haemophiliacs)).	63	13	1.5	77.5
Reasons other than dental extractions (33 episodes).	22			
Combined average	42			

(MRC.64/283)

/The amount

The amount used for patients other than dental patients was slightly biased by short supply, so that the average consumption of HAHG from 22 bottles of blood is somewhat less than would otherwise have been given. On the other hand the series of dental cases may have contained an unusually high proportion of "difficult" cases; if so the average consumption of HAHG from 63 bottles of blood may be unduly high. However, if the combined average of HAHG from 42 bottles of blood is taken and the assumptions in 1(a) and 1(b) are made, HAHG from about 84,000 donations will be needed annually, as well as fresh plasma and blood.

3. Amounts of HAHG needed for treating all haemophiliacs.

The following assumptions, on which an estimate might be based, are put forward for discussion:-

(a) That the three proposed regional centres for treating major episodes will, between them, treat annually 400 haemophiliacs (i.e. 1/5 of the assumed 2,000 haemophiliacs) and that the average consumption per patient will be of the order of HAHG from 42 bottles of blood.

(b) That the proposed centres for treating minor episodes will, between them, treat annually 800 haemophiliacs (i.e. 2/5 of the assumed population) and that the average consumption per patient will be of the order of HAHG from 20-25 bottles of blood.

(c) That the remaining 2/5ths will not need treatment in any one year.

If these assumptions were considered reasonable, the amount of blood needed annually for preparing HAHG would then be about:-

$$400 \times 42 = 16{,}800$$
$$800 \times 22 = 17{,}600$$
$$34{,}400 \text{ say, } 35{,}000 \text{ bottles}$$

It is obvious that increased supplies of HAHG should be available before centres are organised. Although the above estimate may not take proper account of the role of animal HAHG and fresh frozen plasma and may therefore be wide of the mark, it has been used in the subsequent sections.

4. Type of HAHG to be provided.

Hitherto experience of HAHG in U.K. has been almost exclusively confined to HAHG prepared by ether fractionation and, for this reason, it might be preferable to continue to use this material. If arrangements for preparing HAHG on a larger scale are to be made, the Working Party may like to express an opinion on the type or types of material that should be provided. The choice will be influenced by the need to salvage the remaining supernatant for further fractionation (see below).

5. Possible Ways of Supplying HAHG for Proposed Treatment Centres.

(a) General. However HAHG is provided it is essential that wastage be kept to a minimum, that is to say:

/(i) Red cells,

(i) Red cells, should as far as possible, be used for transfusion. Wastage of red cells from the large number of donations, likely to be needed, should not be countenanced. In fact, greater use of concentrated red cells would enable part of the plasma to be obtained from "current" donations.

(ii) The supernatant remaining after precipitation of HAHG should be fractionated. The 35,000 donations mentioned above would also yield, for example, about 30 kg. γ-globulin and about 180 kg. albumin (i.e. about 7,200 x 25g bottles), assuming 250 ml. plasma containing 5·2g. per cent protein from each donation.

(b) Method of Collecting Blood. Large scale preparation of HAHG would be difficult, if not impossible, if the plasma had to be fractionated within 18 hrs. of collecting the blood. Arrangement of fractionation would be greatly simplified if the fractionation programme were independent of the time of blood collection. This freedom could be achieved if blood were collected in plastic equipment of 'Fenwal' type, which would permit aseptic separation of red cells and plasma, and immediate rapid freezing (e.g. -79°C) of the bags of plasma, which could then be stored at -25°C until thawed before fractionation. Frozen bags could be transported in containers chilled with solid carbon dioxide.

A pilot trial on these lines is being conducted by American Red Cross, and it is understood that the Drs. Blombäck have recommended adoption of this method in Australia for collecting and transporting plasma to Commonwealth Serum Laboratories where HAHG is to be made.

If this method were to be used in U.K. a pilot trial would be desirable. Pertinent information, e.g. concerning rate of freezing and thawing, and volume of anticoagulant, has probably been collected at Oxford during recent investigations on the preparation of fresh frozen plasma.

This method also seems to have practical advantages for preparing fresh frozen plasma for transfusion.

(c) Collection of Extra Blood Required. The use of plastic bags as described above, so that plasma and cells could be separated aseptically and the plasma frozen immediately after collection, would permit R.T.Cs to participate in providing blood for HAHG irrespective of their distance from the fractionation laboratory and the "load" could thus be spread widely, if necessary to all R.T.Cs.

R.T.Cs taking part might require

(1) additional (high speed) refrigerated centrifuges, equipment for rapid freezing and subzero storage of plasma and suitable transport containers.

(2) Additional staff and vehicles for blood collection.

(d) Fractionation Laboratories: It has to be decided whether all HAHG should be made centrally, or whether the task should be divided between B.P.L. and a small number of selected laboratories or between B.P.L. and a large number of peripheral laboratories including pathology laboratories.

/(i) Central

(i) Central Preparation. Agreement in principle has recently been given to expansion of B.P.L. to prepare more gamma globulin. Plans to enlarge the existing cold laboratory were made 2 years ago with the purpose of expanding HAHG preparation, but when it became clear that greater volumes of time-expired plasma would have to be fractionated, action on these plans was postponed while re-organization of the laboratory as a whole was considered. It is now proposed to erect a new laboratory for fractionating time-expired plasma by the ethanol method. The existing cold laboratory will then be freed for preparing HAHG and other special fractions and could still be enlarged were that necessary.

Its present size, equipment and ancillary facilities, e.g. sterile rooms and -25°C storage are adequate to prepare HAHG from 35,000 bottles/year. This could be done by fractionating 2 x 90 litre pools weekly (48 week year). It would however probably be preferable to retain the present pool size (30L) because of the risk of transmitting serum hepatitis. In the Working Party Trial serum hepatitis has not been reported among 41 patients so far investigated: one patient developed hepatitis 20 days after transfusion: in the pre-trial series of 69 patients treated on 202 occasions, 3 probable cases of serum hepatitis were observed, one of whom received only HAHG. If ether were used the supernatants would be further fractionated in this laboratory into crude globulin and albumin fractions which would then be transferred to the proposed new laboratory. If ethanol were used the supernatant would be transferred without further fractionation, thus leaving more room in the existing laboratory for other purposes. Drying facilities for 180 bottles/week would also be available.

The advantages of this plan are:

(1) The amount of assay work would be minimized.

(2) Transport of bulk supernatant (110 per cent of plasma vol., which would have to be kept at -3° to 0°C during transport) would be avoided.

(3) Accommodation, equipment and ancillary equipment already exist. Some attention to accommodation might be necessary. A disadvantage of this plan is that preparation would be concentrated in one place and might therefore be considered less secure.

(ii) Preparation at B.P.L. and a few peripheral Laboratories. Such a scheme might envisage preparing HAHG, at least at first, at only a small number of peripheral laboratories in addition to B.P.L. Under such a scheme B.P.L. should probably continue to supply Oxford and the East Anglian and Metropolitan Regional Board areas, from all save one of which blood for HAHG is now received.

The peripheral laboratories should be close to the proposed major treatment centres and could therefore be sited at R.T.C. Manchester or Liverpool and at R.T.C. Sheffield or Leeds. Under a decentralized scheme the peripheral laboratories would have to use a method of fractionation yielding a supernatant suitable for further fractionation at B.P.L.

/Each laboratory

Each laboratory would require all or some of the following:

Subzero storage
Cold laboratory (+4°C) and fractionation equipment.
Drying plant.
High speed refrigerated centrifuges.
Additional laboratory staff (possibly).

Advantages:

(1) An additional interesting activity could be undertaken by R.T.Cs.

(2) Supply of HAHG would be divided and thus more secure.

Disadvantages:

(1) Transport of supernatant to B.P.L. for further fractionation.

(2) Cost of accommodation, equipment and staff.

(iii) Preparation at B.P.L. and Many Peripheral Laboratories. Holman and Wolf (Lancet 1963,2,4) proposed preparing HAHG in hospital pathology laboratories. Such a scheme has certain disadvantages, e.g. multiplicity of equipment, difficulty of quality control. A weighty objection is the waste of the potential gamma globulin and albumin which would almost certainly occur and leads to the conclusion that either (i) or (ii) above is preferable.

(iv) The plasma from 35,000 bottles of blood could be fractionated, using either of the first two schemes above. The central scheme would possibly cost less, but could not be put into operation until the proposed new fractionation laboratory for time-expired plasma had been built.

6. Summary

(a) Problems involved in preparing larger quantities of HAHG, assuming that 35,000 blood donations annually may be needed for this, are briefly described.

(b) Certain decisions, on which the Working Party may like to comment, should be made before a scheme for providing extra HAHG is organised.

(i) Method or methods of fractionation.

(ii) Method of collecting blood and separating plasma; use of separated red cells for transfusion. ? Pilot trial.

(iii) Central fractionation laboratory or central and a few peripheral fractionation laboratories

(iv) widely decentralized fractionation.

At present all R.T.Cs are preparing plans for the next 10-15 years, and it would be convenient if they could include in these plans provision for their part in an HAHG programme

/(c) Additional

(c) Additional expenditure will be necessary:-

(i) At all R.T.Cs collecting blood for HAHG (blood collecting equipment (possibly)), laboratory equipment, staff and transport).

(ii) At, say, 2 R.T.Cs if HAHG is prepared locally (laboratory equipment and, possibly, accommodation, staff).

(iii) At B.P.L. (possible alterations to accommodation).

February, 1964.