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FACTOR VIII CONCENTRATES AND THE TREATMENT OF HAEMOPHILIA

BY

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INTRODUCTION

Haemophilia is the commonest of the hereditary haemorrhagic states and it is caused by the lack from the blood of an essential coagulation factor called factor VIII. Improvements in transfusion and fractionation techniques in recent years have made it possible to separate factor VIII from blood while preserving all other components for use by other patients.

The present communication is an attempt to assess the advantages and disadvantages of various therapeutic materials containing factor-VIII activity and to estimate the total amount likely to be needed in this country each year.

The assessment of the amount of material required involves an estimate of the number of haemophilic patients in the country and of the amount of concentrate that each might reasonably require per annum. At more than half of the 42 Haemophilia Centres in the United Kingdom the Directors feel that the present supply of anti-haemophilic factor is inadequate.

The number of haemophilic patients per 100,000 of the population

The estimates of the number of haemophiliacs per 100,000 of a Caucasian population have varied from 2 to 12.5 (Table I). The figure of 12.5 for the U.S.A. probably includes some mildly affected patients (the criterion for inclusion was the need for anti-haemophilic infusion in a two-year period) whereas other estimates probably include only severely affected patients. Excluding this high figure, estimates for severely affected patients vary from 2 to 6 per 100,000. Naturally the magnitude of the therapeutic problem will depend on the size of the total population. For example, in Denmark, the estimate

made by Sjølin indicates a total of 156 patients in a population of 4 million whereas the estimate for the severely affected patients in the U.S.A. indicates about 12,000 patients in a population of 200 million. For Great Britain the total could be between 1,754 to 3,000 patients. This British estimate is not based on exact data. During the years 1969, 1970, 1971, 1,754 different patients with haemophilia or Christmas disease are known to have attended the Haemophilia Centres from which returns were received. We know that this figure cannot be the total number because some Centres did not make returns and because only a little more than half of the cryoprecipitate made by the Blood Transfusion Service was sent to the Haemophilia Centres in 1971, the rest being supplied to General Hospitals for the care of haemophilic patients. It must be supposed that some patients are being treated at hospitals other than Haemophilia Centres. Thus the lower limit to the number of patients is 1,754 and the upper limit is not known for certain.

The Factor-VIII Preparations at Present Used to Treat Haemophilic Patients

At present the treatment of bleeding in a haemophilic patient consists in giving a calculated dose of an anti-haemophilic factor (factor VIII) preparation as soon as any symptoms of spontaneous bleeding arise and of giving enough material during and following operations to maintain normal haemostasis.

Each of the haemophilic patients treated at Haemophilia Centres during 1971 had on average received material derived from 122 donor units. This figure refers to the total amount of material that the patient received. It does not refer to the number of donors, to whose blood, patients have been exposed through the use of pools of plasma.

Most of this treatment was for "on demand" treatment, (which is given whenever the patient feels that a haemorrhage is occurring), and for major surgery and dental extraction. At many Haemophilia Centres the Directors feel that they could use at least twice as much material as they receive and that the present shortage of materials leads to dangerous selectinn between more or less urgent cases for treatment and the accumulation of patients on long waiting lists for non urgent operations.

The materials available to treat haemophilic patients are listed in Table II. Of these preparations whole blood contains too low a factor-VIII level to be useful in treating patients except where blood replacement is required. The second column of Table II shows that administration of whole blood can only raise the factor-VIII concentration in the recipient to about 5% of average normal.

Plasma is somewhat more effective and is useful for the treatment of spontaneous bleeding when other materials are not available. However plasma, given frequently to haemophilic patients, can lead to the production of antibodies to plasma constituents such as IgA, and to serious and even dangerous reactions. Thus where more purified preparations than plasma are available these are always to be preferred. They are, in any case, essential where high plasma concentrations of factor VIII are required as is the case following dangerous bleeding, for post-operative haemostasis and in certain patients who have factor-VIII antibodies. In fact only about a quarter of the material at present prepared for the treatment of haemophilic patients in the U.K. is in the form of plasma (Table II).

COMPARISON OF FREEZE DRIED CONCENTRATE AND CRYOPRECIPITATE

At present two types of factor-VIII concentrate are prepared in the United Kingdom, cryoprecipitate and freeze dried concentrate. In 1971, 220,000 donor units of cryoprecipitate and 25,000 donor units of freeze dried material were made (Table II). The preponderance of cryoprecipitate is due to the fact that this preparation can be made at all Transfusion Centres. From a long term point of view cryoprecipitate is not necessarily the best preparation for treatment.

The information required to decide which type of concentrate is to be preferred involves a consideration of:

1. The yield of factor-VIII activity in the different fractionation procedures and the recovery of this activity when the concentrate is administered to patients. A very large loss of activity during fractionation or failure to recover the in vitro activity in the patient would be disadvantageous.
2. The convenience of the material in preparation and in use.
3. The reliability of the material from batch to batch.
4. The complications which might attend treatment with the various preparations.

1. The Yield of Factor-VIII Activity in Cryoprecipitate and Factor-VIII Concentrate made in Oxford

Very large amounts of these concentrates are required to treat haemophilic patients and loss of factor-VIII activity during processing can very greatly affect the cost of production of the material. The ease or difficulty of carrying out the procedure can also affect the cost since such consideration will influence the number of staff and the space required.

Fig 1 shows the yield of factor-VIII activity in cryoprecipitate and freeze-dried concentrate made in Oxford during 1971 and the first three months of 1972. The freeze-dried material was made by a modification of the method of Newman et al (1971). The details of the procedure varied somewhat from one month to the next. The cryoprecipitate was made by pooling the plasma from two donations in a blood bottle, the contents were then frozen and the cryoprecipitate was obtained from the plasma as required. At most Centres cryoprecipitate is presented as the product of single donations in plastic bags.

The overall yield of factor-VIII activity is calculated as follows:-

$$\% \text{ Yield} = \frac{\text{volume of concentrate x activity of concentrate x 100}}{\text{volume of starting plasma x 0.9}}$$

The yields for cryoprecipitate and concentrate are given in Fig 1 (A and B). The mean yield for cryoprecipitate was 36% and that for concentrate was 37%. There is thus no difference between the two procedures from the point of view of average yield of factor-VIII activity. These figures do of course only apply to the procedures used in Oxford.

In addition the in vivo recovery of activity for the two materials was measured over the same period of time. This in vivo recovery is defined as the rise in the patient's plasma factor-VIII level expressed as percent of average normal per unit of factor VIII administered per kg of the patient's body weight. The maximum possible recovery of activity by this method is 2.4 percent. For many years the freeze-dried concentrate

has given a value of about 1.6 percent on average at this Centre. The results for 1971 gave a mean value of 1.6 percent for cryoprecipitate and those for the concentrate give 2.0 percent. These data, taken over the same patients over the same time interval, show that there is no significant difference between the average yield of factor-VIII activity made by the two procedures but that the freeze-dried concentrate activity may have been rather better recovered in the patient.

The fluctuations in values shown in Fig 1 probably have many causes such as changes in factor-VIII assay standards and, as shown by a patient in April and May 1971, some patients may have had unusually good recovery of activity. The yield and in vivo recovery of activity are not assessed independently. The yield of activity is calculated from the assay of doses given to patients. The recovery of activity in the patient also uses the dose assay to calculate the rise in factor VIII per unit of dose per kg of weight. But if for some reason the dose value is wrongly assessed and the concentration in the patient correctly measured (or vice versa) the discrepancy will be seen in the recovery of activity in the patient. For example high yield of activity in the material may be due to improved fractionation procedure but if this yield is associated with a consistently low recovery of activity in the patient, then the adoption of that particular fractionation procedure would have to be delayed for further study.

2. Convenience of Manufacture and Convenience and Safety in Use

Cryoprecipitate is easier to produce than freeze-dried concentrate if small amounts of concentrate are required. On a large scale and widely distributed over Centres with very different facilities the method is less satisfactory. The freeze-dried material requires higher capital expenditure but is probably less expensive in the long run. The way in which the preparation is made available to the doctor can much affect patient safety.

Cryoprecipitate. The material is usually presented frozen in plastic bags, each bag containing the plasma from 1 donor. In Oxford the amounts from 2 donors are pooled. The volumes which need to be given vary from the product of 4 to 40 blood donations or even more on occasion. Reconstitution involves thawing the contents of the bags, pooling the material in the bags, washing out the bags and adding the washings to the already pooled material. The work involved and the time taken is considerable.

Much of the work in making up the dose material is done by house officers and nurses. The process is open to many abuses. If the material is thawed at too high a temperature activity will be lost. If the bags are not washed out half of the activity may be left inside. Material may easily be infected and the germs may multiply if the material is not used at once. Small alterations in the process of manufacture will affect the yield, none of the material can be assayed before it is used and thus the activity of the dose cannot be known before it is given to the patient. This preparation must be stored in a deep freeze at $-30^{o}C$.

Freeze-Dried Concentrate. This is presented in bottles each containing about 400 units of factor-VIII activity. The value of the particular material is indicated on the bottle. Each bottle is reconstituted by adding 25,50 or 100 ml of distilled water. The amount required for one dose may vary from 1 to 10 bottles depending on the weight of the patient and the reasons for treatment. The dose is given by infusion or syringe depending on the volume to be used.

The material at present available over the whole country is of variable solubility. Insoluble material can add difficulty to use but the best material dissolves well even at room temperature and there is no reason why all the material should not in the end be equally good. Material which has good solubility is very convenient to use, easy to make up and the dose can be determined accurately. This preparation may be stored at 4°C with safety.

3. The Reliability of Material from Batch to Batch

Table III gives the results of a study of the factor-VIII activity of cryoprecipitate in 1971-72 at three Haemophilia Centres. It will be seen that the dose assays do not reflect variation of single donor units of blood since each dose was made up of pools of from 5 to 26 donors. The assayed factor-VIII values of the samples are very variable from one sample to another suggesting variable yield from time to time at one Transfusion Centre. There is also a large mean difference between the Centres. It may be noted that values of less than 75 units per bag of cryoprecipitate

indicates a lower yield of factor VIII from starting material than can be obtained for a freeze-dried product (Fig 1).

The freeze-dried material made in large batches is stable on storage and can be assayed to give a reliable estimate of dose activity.

4. Complications of Treatment

About 1 in 800 donors is a carrier of hepatitis B antigen. The larger the number of donors concerned in the preparation of concentrate the greater the risk of exposing the recipient to material containing hepatitis B antigen. The use of freeze-dried concentrate, which is made of pools of 200 donors (or even higher numbers for commercial material), must carry a higher risk than single donations. But there is the possibility that the development of jaundice may be dose related and that single infected bottles may be more dangerous to the individual patient than pooled material in which the virus is diluted. Despite this the frequency of hepatitis in severely affected patients does not seem to increase significantly with increased use of freeze-dried concentrates. This is shown by a low incidence of jaundice in patients treated in Oxford (who have half of the material given to them as freeze-dried concentrate) and in those treated at other British Centres. The conclusion is also supported by data collected in the United States (Kasper and Kipnis 1972).

An exception to this rule concerns the mildly affected patients to whom very little treatment is given. These patients do seem to have a high incidence of hepatitis if large pool fractions are used. Kasper and Kipnis 1972

showed this as did also the British survey where female carriers of haemophilia treated with concentrate had a high incidence of hepatitis.

Since the majority of patients are in the multi-transfused category the increased risk of exposure to hepatitis would not seem to be an important disadvantage to the use of concentrates from pooled material. Hepatitis is, in any case, a complication which should decrease with universal screening of donors for hepatitis antigen.

The incidence of factor-VIII antibodies does not seem to be related to the type of material used (British Survey).

AMOUNTS OF FACTOR-VIII CONCENTRATES REQUIRED TO TREAT HAEMOPHILIACS IN GREAT BRITAIN

On Demand Treatment. Assessment of the amounts of material required cannot be based on the amounts at present given since this is known to be less than optimum at most Centres. Careful observation of the boys at Treloar College gives an average number of bleeds per boy per year of 25 and these 25 bleeds required about 30 doses of material. Each of these doses may be assessed on a more general basis as "the material required to raise the plasma factor VIII to 20%". It is also assumed that an average patient's weight is 50 kg (95 patients were weighed at the Oxford Haemophilia Centre in 1971 and the average weight was 51.6 kg). Under these assumptions the average amount per patient per dose should be:-

$$\frac{20 \times 100 \times 50}{2.4 \times 66} \quad \text{(Biggs \& Macfarlane 1966)}$$

$$= 630 \text{ units}$$

In practice, using the concentrate, patients receive one or two bottles for a dose since it would clearly be very wasteful to be too precise. Since the preparation of concentrate is associated with a loss of about 60% of the factor VIII starting activity the amount of plasma from which units could be derived would be:-

$$630 \times \frac{10}{4}$$

Each donor provides 200-220 ml plasma. Thus each treatment should on average require material from 7-8 donors. This theoretical estimate is unlikely to overstate the case since, as can be seen from Table III, the actual amounts given to each patient often exceed this estimate substantially.

These calculations may be considered according to the distribution of concentrate to various types of patient. Fig 2 shows the distribution of bleeds per year per boy based on data for 45 boys during the spring term of 1971 at Lord Mayor Treloar College. It will be seen that the number of bleeds per boy varies from 0 to 70 with a mean of 25. In general it is a characteristic of those patients who bleed frequently that they continue to bleed frequently but the boys who approximate more closely to the mean may have spells of frequent bleeds interspersed with periods of freedom from trouble. The material that would be required to treat these boys according to the

above calculations is also shown on Fig 2. It will be seen that the boys with above average number of bleeds (5/9th of the total) consume 75 per cent of the material.

From these calculations the total amount of material (donor units) considered desirable to treat these Treloar boys for one year is 9,690. In fact, in 1971, 7,270 donors-worth of material was used for nine months' treatment and over a whole year the total should be about 9,700 donors-worth. Thus the theoretical calculation would seem to be about right for the Treloar School boys who, while at school, are probably treated on the optimum desirable level.

Taken over the Country as a whole the estimated 1,754-3,000 patients would require treatment from:-

7-8 x 1,754-3,000 x 30 donors a year

which is the product of 378,340 to 720,000 donors a year. The lower figure is certainly an underestimate since the number of haemophiliacs exceeds 1,754.

Major Surgery. When considering operations patients who are mildly affected must be included as well as those who are severely affected. An additional 1,000 patients have

been added to make this allowance. It is assumed that each patient has a life-expectancy of 50 years and that each patient will require one major surgical operation in his life. According to these assumptions the number of operations per year would be:-

$$\frac{4000}{50} = 80 \text{ operations}$$

In fact, during 1969, 44 operations were carried out at Haemophilia Centres but many patients still remain on waiting lists. If each operation requires the level of factor VIII to be raised to 100% daily for ten days then the amount of material required for each operation will be:-

$$35 \times 10 = 350 \text{ donors}$$

(35 donor units being the amount required per day)

and for 80 operations

$$350 \times 80 = 28{,}000 \text{ donors/year}$$

Dental Extractions. For dental extractions it is assumed that each patient will require three such operations in his life giving a total of 240 per year as an estimate (in fact 173 patients underwent dental extractions at Haemophilia Centres during 1969). Each operation should require 2,330 units (Walsh et al 1971)[x] or the material from 35 donors. Thus the total material should be:-

$$35 \times 240 \text{ donors/year} = 8{,}400$$

Thus for all types of bleeding (spontaneous, at operation and dentistry and after) the total material required is likely to lie between 400,000 and 750,000 donor units per annum. This estimate includes "on demand" treatment. It implies an allowance of 217 to 250 donor units per severely-affected patient per year. The estimate agrees fairly well with the American survey which suggests that about 2.8 million donor units would be needed in the U.S.A., or about 250 donor units per severely-affected patient. This figure also agrees well with the estimate of Lazerson (1972) that each well-treated patient requires 222 donor units of cryoprecipitate per year and for a Spanish assessment of 181 donor units per patient.

Prophylactic treatment to haemophilic patients would require much more material since this treatment envisages regular administration of factor VIII once or twice a week to the patient regardless of whether or not bleeding has occurred. The estimate of the amount required for such treatment in the U.S.A. is 13 million donor units (Stengle 1972). So for Great Britain an estimate would be about 3 million donor units. Lazerson (1972) estimates 636 donor units per patient for prophylaxis which would give a maximum figure for Great Britain of about 2 million donor units. It is not at present certain that this prophylaxis is desirable for even the most severely affected patients. It is certainly at present impracticable. In the U.S.A. about 4 per cent of patients receive prophylaxis.

Home Treatment should be distinguished from prophylaxis. Home treatment involves the administration of therapeutic material in the home by a relative, by the patient to

himself, or by the General Practitioner. This form of treatment is becoming accepted and should not involve the use of more material than good Hospital care. In fact, the experience of Lazerson (1972) suggests that more material is not used for home care. There is no doubt that the freeze dried concentrate is the best material to use for home care. Were the most severely affected 1,000 patients allocated to home treatment this would require about 250,000 donor units of freeze dried concentrate but this would be instead of, not in addition to, the doses given on demand in hospital.

THE ECONOMICS OF TREATMENT

The cost of treating haemophilic patients is high and mainly results from the treatment of 1,000-1,700 patients who bleed most frequently. (i.e. 5/9 of 1,740-3,000).

It will be related to:-

1. The cost of producing the material.
2. The cost of maintaining Haemophilia Centres.

Neither of these are easy to compute.

It should be pointed out that haemophilic patients who are inadequately treated are not cheaply maintained by the State. These patients may spend a large proportion of their lives in hospital at a cost of £50-100 per week; they become crippled by adolescence and unemployable as adults. The proper treatment is probably no more expensive than that of renal patients requiring dialysis.

CONCLUSIONS

1. Calculations suggest that the amount of material required for optimum treatment of all the haemophilic patients in Great Britain would be derived from 400,000 to 700,000 blood donations a year. The present supply is of the order of 300,000 per year of which most is in the form of cryoprecipitate.
2. Comparisons of cryoprecipitate and freeze-dried concentrate made in Oxford suggest that from the point of view of conservation of the factor-VIII activity of the donor plasma and of recovery of infused activity in the patient the two preparations are equally efficient.
3. The cryoprecipitate is more difficult to make up for administration and much factor-VIII activity may be lost when inexperienced staff handle the material prior to giving the infusion. Moreover the material varies in activity from one Centre to another. There is evidence that the Oxford material may be among the best.
4. The pool size used in the preparation of concentrate does not affect the incidence of factor-VIII antibodies nor of clinical jaundice in multi-transfused patients.
5. For home treatment it is our opinion that only the freeze-dried concentrate is useful in most cases. The gradual introduction of the most severely affected patients who have the most frequent bleeding to home treatment would reduce hospital management of haemophilia by about half (Fig 2). To give this proportion of patients home treatment would involve the use of concentrate from about 250,000 donors a year. The present total supply is of the order of 25,000 a year.

6. We think that a target should be set to provide factor-VIII concentrate from 250,000 donations by 1975 and that, over ten years, an attempt should be made to provide all of the necessary material in this form. By 1975 the magnitude of the problem should be more exactly defined by surveys being made by the Haemophilia Centre Directors.

7. It may be noted that freeze-dried material of good quality is now available commercially. At present patient treatment at many of the Haemophilia Centres in this Country involves a dangerous policy of balancing the needs of one patient against another and of denying patients reconstructive orthopaedic surgery which would greatly improve their lives. We feel it very important that the material made in the U.K., which is second to none in quality, should be substantially increased in amount. Otherwise we feel that material should be bought from commercial sources which now provide material of good quality both from the point of view of factor-VIII activity and from the point of view of screening the donors for Hepatitis Associated Antigen.

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TABLE I

The Incidence of Haemophilia in Various Populations

Country	Author	Estimate per 100,000 of population
Denmark	Andreassen (1943)	2
	Sjølin (1959)	4
Sweden	Ramgren (1962)	4
Spain	Villar et al (1971)	2.3
U.S.A.	Stengle (1972) (all cases)	12.5
Chile	Larrain et al (1972)	3.5
Great Britain	Biggs (1972)	3-5

TABLE II

Therapeutic Materials for the Treatment of Haemophilia

Material	Factor-VIII Activity u/ml	Possible post infusion level of plasma factor VIII (% Normal)	Approx. donor units at present made (per annum)
Whole Blood	0.3	4-6	-
Plasma	0.6	15-20	44,000
Cryoprecipitate	3-5	100+	220,000
Freeze Dried Concentrate	3-5	100+	25,000

TABLE III (part 1)

Factor VIII Values of Cryoprecipitate

Units/bag

Sample**	Centre 1		Centre 2*		Centre 3	
	No. Cryo. per dose	Units/bag	No. Cryo. per dose	Units/bag	No. Cryo. per dose	Units/bag
1	10	100	5	66	8	43
2	8	120	7	15	8	45
3	8	100	5	39	17	80
4	8	130	5	60	10	80
5	16	87	7	51	20	31
6	16	112	10	12	20	44
7	12	80	5	48	15	70
8	10	98	8	62	10	35
9	12	92	7	63	10	58
10	26	74	10	35	8	77
11	14	49	10	26	8	41
12	20	48	10	40	8	45
13	12	66	10	62	8	40
14	18	50	5	19	10	49
15	12	47	10	64	6	53
16	20	37	10	60	6	69
17	8	88	10	101	6	60
18	14	89	7	29	10	69
19	6	46	7	40	8	61
20	12	43	10	32	5	60
21	12	95	8	45	–	–
22	12	100	10	51	–	–
Mean	13	79.5	8	46	10	55.0
Range		37–130		12–101		31–80

*Paediatric Hospital

**The samples tested at the different Centres were different but the results of each Centre were based on the same assessment of the factor VIII unit.

TABLE III (part 2)

Sample	Centre 4**		Centre 5 1971		Centre 5 1972	
	No. Cryo. per dose	Units/bag	No. Cryo. per dose	Units/bag	No. Cryo. per dose	Units/bag
1	11	48	10	81	6	24
2	10	39	9	94	8	79
3	14	51	8	27	9	44
4	14	62	10	27	8	34
5	10	60	9	69	8	28
6	10	83	8	39	10	55
7	6	34	9	65	8	68
8	8	61	8	85	10	69
9	12	44	10	54	7	32
10	12	50	8	49	8	51
11	10	69	8	83	9	76
12	11	47	7	97	9	25
13	10	40	10	75	10	36
14	12	63	8	79	10	40
15	6	51			6	57
16	14	50			9	47
17					10	29
18					8	22
19					8	38
20					8	42
21					10	56
22					8	37
23					9	34
24					10	27
25					8	28
26					8	27
27					8	60
28					8	45
29					10	24
30					8	48
31					7	70
32					9	66
33					10	72
34					8	88
35					8	59
36					10	66
37					10	27
38					8	56
39					10	38
40					6	99
Mean	10.6	53.2	8.8	65.8	10.3	48.0
Range		34-83		27-94		22-99

**Each bag was assessed separately.

LEGENDS TO FIGURES

Fig. 1A and B. The yield of factor-VIII activity in different batches of material made throughout 1971 and during the first three months of 1972.

A. Freeze dried factor VIII.

B. Cryoprecipitate.

Fig. 1C and D. The recovery of factor-VIII activity in the plasma of severely affected haemophilic patients expressed as percentage rise in factor VIII per unit of dose activity per kg of patient's weight.

C. Using freeze dried factor VIII.

D. Using cryoprecipitate.

Fig. 2. The number of bleeds per year for 45 boys severely affected with haemophilia (open columns). The amount of therapeutic material used for the same boys per year expressed as the number of equivalent single blood donations (cross hatched columns).

FIGURE I

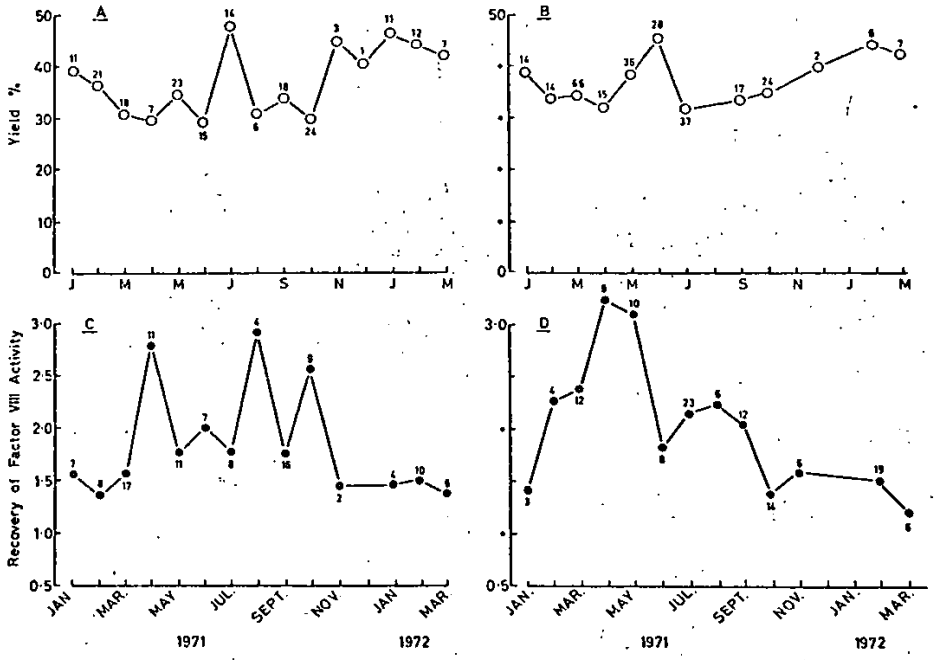
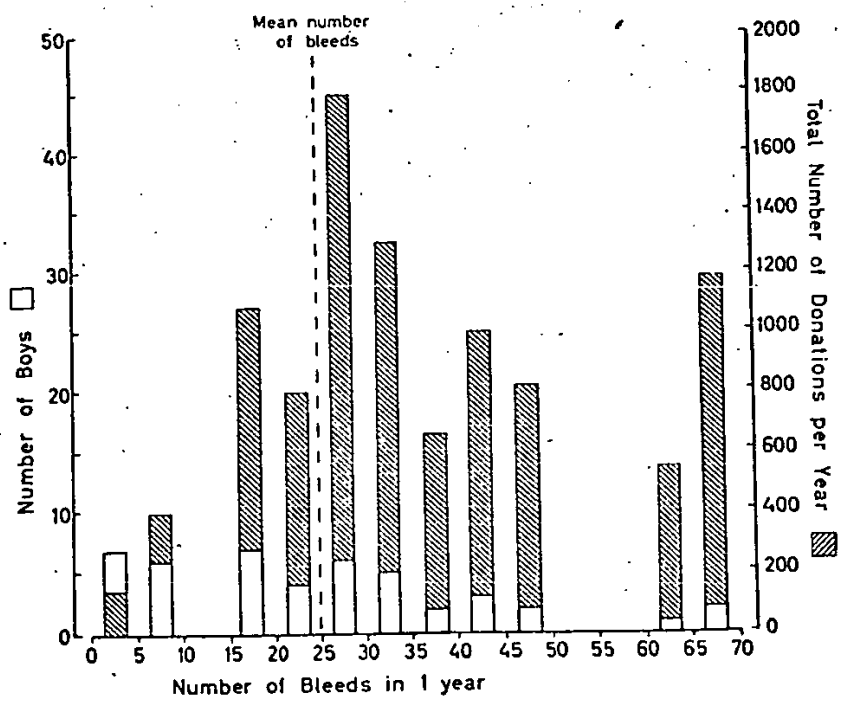


FIGURE II



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