MEDICINES ACTS 1968 AND 1971

APPLICATION FOR A PRODUCT LICENCE

1. Name of Product:	ANTIHAEMOPHILIC FACTOR (HUMAN) METHOD FOUR-HEAT TREATED HEMOFIL-T
2. Full name and address of proposed licence holder:	TRAVENOL LABORATORIES LTD., CAXTON WAY, THETFORD, NORFOLK, IP24 3SE.
3. Trading style to be shown on licence if different from above:	AS ABOVE
4. Role of proposed licence holder: (please tick in appropriate box(es))	☐ (i) as person responsible for composition of product manufactured in UK, ☑ (ii) in the case of a proprietary medicinal product, as person responsible for placing it on the UK market, ☑ (iii) as person who imports or procures its importation, ☑ (iv) as person who first sells or supplies it as a medicinal product.
5. Activities for which licence is required: (please tick in appropriate box(es))	☑ (i) selling or supplying product in the UK ☑ (ii) procuring the manufacture or assembly of the product for sale or supply in the UK. ☑ (iii) importing or procuring the importation of the product. ☑ (iv) Other (specify) EXPORTING THE PRODUCT
6. Applicants own reference no:	RA.191A
7. Details of earlier applications:	APPLICATION WAS MADE IN MAY 1983 AND SEPTEMBER 1984 TO VARY PL0116/0011 TO INCLUDE A HEAT TREATMENT STEP TO OUR STANDARD FACTOR VIII PRODUCTS. THE ATTACHED ABRIDGED APPLICATION HAS BEEN REQUESTED BY THE DEPARTMENT IN PLACE OF A LICENCE VARIATION.

8. To cover sale and supply of the product manufactured before the grant of the licence: YES/~~NO~~

9. Scientific Evidence:

(i) Chemistry and Pharmacy 142 Pages

(ii) Experimental and Biological Studies 222 Pages

(iii) Clinical Trials 88 Pages

10. Do you give your consent to the disclosure to the British Pharmacopoeia Commission of information given in or in connection with this application or to the pharmaceutical standards applicable to the product or its active ingredient on the understanding that such information will not be used in the compilation of a pharmacopoeia monograph without prior reference to you?

YES/~~NO~~

11. I/We apply for the grant of a product licence to the proposed holder named above in respect of the product(s) to which the Product Particulars in Part 1A refer and in accordance with the other particulars annexed; the said licence to be for a period of five years and subject to the following provisions –

11.1 All the Standard Provisions applicable to product licences under regulations for the time being in force under Section 47 of The Medicines Act 1968.

11.2 The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars as Uses, and shall be sold or supplied in accordance with the said Product Particulars except in so far as may from time to time be approved by the licensing authority.

11.3 The specification of the constituents and of the finished product shall be in accordance with the information contained in or furnished in connection with the application.

11.4 The product is to be manufactured only in accordance with the methods set out in this application or furnished in connection with it.

11.5 No material information has been omitted (within the knowledge of the signatory).

Date 30th November 1984

Signature GRO-C

A.M CAMERON
SENIOR SCIENTIFIC OFFICER

State capacity in which signed

(Official use only)

A 1

Form MLA 201

PRODUCT PARTICULARS - a complete set of pages should be included for each strength of product

Number of Product: (Official use only)

PL

1. Name of Product and Strength: ANTIHAEMOPHILIC FACTOR (HUMAN) METHOD FOUR-HEAT TREATED HEMOFIL-T

(Official use only)

2. Description of Pharmaceutical form (eg tablet, slow-release tablet, capsule etc):

A STERILE LYOPHILISED POWDER WHICH IS RECONSTITUTED WITH WATER FOR INJECTIONS PH.EUR. PRIOR TO INTRAVENOUS ADMINISTRATION.

(Official use only)

(Official use only)

3a. Legal status (place tick in appropriate box(es))

(Official use only)

Prescription	✓	Pharmacy		General Sales	

3b. Method of retail sale or supply: BY PRESCRIPTION THROUGH HOSPITALS, PHARMACIES AND CLINICS

(Official use only)

Text should be completed in block capitals

D 1 (Official use only)

4. Active Constituents:

(Official use only)	Name	Specification Reference	Quantity/Dose Unit or % quantity	Unit
	HUMAN COAGULATION FACTOR VIII (MIN)	EP	225	IU
	DERIVED FROM SOURCE PLASMA HUMAN OR (MIN)	EP	720	IU

1) Please enter constituent as actual substance included in the formulation, eg. as salt not base where applicable.
2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name column and not in the Specification Reference column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column.
3) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.
4) Trailing zeros following the decimal point may be omitted eg 10.02 MG will suffice.
5) Please photocopy page if more space for constituents is required.

(Official use only)

C	1																

5. Recommended clinical indications, and route(s) of administration:

THE USE OF ANTIHAEMOPHILIC FACTOR (HUMAN), HEMOFIL T, IS INDICATED IN HAEMOPHILIA A (CLASSICAL HAEMOPHILIA) FOR THE PREVENTION AND CONTROL OF HAEMORRHAGIC EPISODES.

THE CONCENTRATE CAN BE OF SIGNIFICANT THERAPEUTIC VALUE IN PATIENTS WITH ACQUIRED FACTOR VIII INHIBITORS NOT EXCEEDING 10 BETHESDA UNITS PER ML. HOWEVER, IN SUCH USES THE DOSAGE SHOULD BE CONTROLLED BY FREQUENT LABORATORY DETERMINATIONS OF CIRCULATING FACTOR VIII.

ANTIHAEMOPHILIC FACTOR (HUMAN) IS NOT INDICATED IN VON WILLEBRAND'S DISEASE.

ANTIHAEMOPHILIC FACTOR (HUMAN), HEMOFIL T IS TO BE ADMINISTERED ONLY BY THE INTRAVENOUS ROUTE.

(Official use only)

All entries must be made in full. Cross references, eg. to an accompanying data sheet are not acceptable. If a product is supplied under a generic name for prescription purposes and 1) a data sheet is not required to be held and 2) it is not advertised or supplied direct to the public, then the entry against item 5 should read eg "as in BP" and 6 should read "as directed by a Medical Practitioner". No entry need be made against item 8.

B | 1 | (Official use only)

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

EACH BOTTLE OF ANTIHAEMOPHILIC FACTOR (HUMAN), METHOD FOUR, DRIED HEAT-TREATED, HEMOFIL T, IS LABELLED WITH THE NUMBER OF AHF UNITS WHICH IT CONTAINS, 1 AHF UNIT BEING DEFINED AS THE ACTIVITY PRESENT IN 1 ML OF NORMAL POOLED HUMAN PLASMA LESS THAN 1 HOUR OLD (100% AHF LEVEL).

ABILDGAARD, ET AL REPORTED THAT INFUSION OF 1 UNIT OF AHF PER KG BODY WEIGHT CONSISTENTLY PRODUCES AN INCREASE OF 2% (OF NORMAL), WHILE SHANBROM AND THELIN FOUND THAT 3.8 TO 4.0 UNITS PER KG. PRODUCE AN INCREASE OF 10% (OF NORMAL) IN AHF LEVEL. (THE FORMER AUTHORS WORKED WITH BOYS 8 MONTHS TO 14 YEARS OF AGE, WHILE THE LATTER WORKED PRIMARILY WITH ADULTS). THE FOLLOWING FORMULAE CAN THEREFORE BE USED TO CALCULATE, APPROXIMATELY, THE EXPECTED RESPONSE FROM A GIVEN DOSE OR THE DOSE REQUIRED FOR A GIVEN EFFECT;

I. UNITS REQUIRED = BODY WEIGHT (IN KG) x 0.4 x DESIRED AHF INCREASE (IN % OF NORMAL)

II. EXPECTED AHF INCREASE (IN % OF NORMAL) = $\frac{\text{UNITS ADMINISTERED}}{\text{BODY WEIGHT (IN KG) X 0.4}}$

THE DATA OF ABILDGAARD, ET AL WOULD CALL FOR A FACTOR OF 0.5 INSTEAD OF 0.4 IN THE PRECEDING FORMULAE.

(Official use only)

7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:

HEMOFIL T

HYLAND DIVISION,
TRAVENOL LABORATORIES INC.,
4501 COLORADO,
LOS ANGELES,
CALIFORNIA 90039.

AND/OR

N.V. TRAVENOL LABORATORIES S.A.,
BOULEVARD D'HOURAING,
7860 - LESSINES,
BELGIUM.

WATER FOR INJECTIONS PH. EUR.

PHARMA HAMELN,
3250 HAMELN 1, (ADERDE),
WEST GERMANY.

AND/OR

N.V. TRAVENOL LABORATORIES S.A.,
BOULEVARD D'HOURAING,
7860 - LESSINES,
BELGIUM.

B 1 (Official use only)

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

THE AMOUNT OF AHF THAT A HAEMOPHILIAC REQUIRES FOR NORMAL HAEMOSTASIS VARIES WITH CIRCUMSTANCES AND WITH THE PATIENT. THE AMOUNT OF FACTOR TO BE SUPPLIED WILL DEPEND ON THE DEGREE OF DEFICIENCY AND ON THE AHF LEVEL DESIRED.

KASPER HAS FOUND THAT MINOR HAEMORRHAGIC EPISODES WILL GENERALLY SUBSIDE WITH A SINGLE INFUSION IF A LEVEL OF 30% OR MORE IS ATTAINED. FOR MORE SERIOUS HAEMORRHAGES, A FACTOR VIII LEVEL OF 35 TO 50% OF NORMAL SHOULD BE OBTAINED FOR OPTIMUM CLOT FORMATION. IN SURGERY, KASPER RECOMMENDS THAT THE FIRST DOSE OF FACTOR VIII, TO ACHIEVE A LEVEL OF 80 TO 100%, BE GIVEN AN HOUR BEFORE THE PROCEDURE. A SECOND DOSE OF FACTOR VIII HALF THE SIZE OF THE PRIMING DOSE SHOULD BE GIVEN ABOUT 5 HOURS AFTER THE PRIMING DOSE. IF SEVERAL UNITS OF BLOOD WERE LOST DURING THE OPERATION, A THIRD DOSE OF CONCENTRATE SHOULD BE GIVEN WHEN THE PATIENT REACHES THE RECOVERY ROOM. THE FACTOR VIII LEVEL SHOULD BE MAINTAINED AT A DAILY MINIMUM OF AT LEAST 30% FOR A HEALING PERIOD OF 10 TO 14 DAYS.

EXACT DOSAGE DETERMINATIONS SHOULD BE MADE BASED ON THE MEDICAL JUDGMENT OF THE PHYSICIAN REGARDING CIRCUMSTANCES, CONDITION OF PATIENT, DEGREE OF DEFICIENCY, AND THE DESIRED LEVEL OF FACTOR VIII TO BE ACHIEVED.

(Official use only)

7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:

B | 1 | (Official use only)

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

ANTIHAEMOPHILIC FACTOR (HUMAN) IS TO BE ADMINISTERED ONLY BY THE INTRAVENOUS ROUTE. THE MATERIAL SHOULD BE RECONSTITUTED WITH THE APPROPRIATE VOLUME OF WATER FOR INJECTIONS PH.EUR.

PREPARATIONS OF ANTIHAEMOPHILIC FACTOR (HUMAN), HEMOFIL T CONTAINING 34 OR MORE AHF UNITS PER ML MUST BE ADMINISTERED AT CAREFULLY CONTROLLED RATE: I.E. A MAXIMUM ADMINISTERED RATE OF 2 ML PER MINUTE.

AHF PREPARATIONS CONTAINING LESS THAN 34 AHF UNITS PER ML CAN BE GIVEN RAPIDLY, AT A RATE OF 10 TO 20 ML OVER A 3-MINUTE PERIOD, WITH NO SIGNIFICANT REACTIONS.

AS A PRECAUTIONARY MEASURE, THE PHYSICIAN SHOULD DETERMINE THE PULSE RATE BEFORE AND DURING ADMINISTRATION OF THE AHF CONCENTRATE. SHOULD A SIGNIFICANT INCREASE OF PULSE RATE OCCUR, REDUCE THE RATE OF ADMINISTRATION OR DISCONTINUE.

(Official use only)

7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:

(Official use only)

B 1

8. **Contraindications, Precautions and Warnings:**

CONTRAINDICATIONS

NONE KNOWN.

PRECAUTIONS

THIS ANTIHAEMOPHILIC FACTOR (HUMAN) PREPARATION CONTAINS BLOOD GROUP ISOAGGLUTININS (ANTI-A AND ANTI-B). WHEN LARGE OR FREQUENTLY REPEATED DOSES ARE NEEDED, AS WHEN INHIBITORS ARE PRESENT OR WHEN PRE AND POST-SURGICAL CARE IS INVOLVED, PATIENTS OF BLOOD GROUPS A, B, AND AB SHOULD BE MONITORED FOR SIGNS OF INTRAVASCULAR HAEMOLYSIS AND DECREASING HAEMATOCRIT VALUES. HAEMOLYTIC ANAEMIA, WHEN PRESENT, MAY BE CORRECTED BY THE ADMINISTRATION OF COMPATIBLE GROUP O RED BLOOD CELLS (HUMAN).

IDENTIFICATION OF THE CLOTTING DEFICIENCY AS ONE OF FACTOR VIII IS ESSENTIAL BEFORE THE ADMINISTRATION OF ANTIHAEMOPHILIC FACTOR (HUMAN) IS INITIATED.

SINCE ANTIHAEMOPHILIC FACTOR (HUMAN), METHOD FOUR, HEAT-TREATED, HEMOFIL T, CONTAINS SMALL RESIDUAL AMOUNTS OF FIBRINOGEN WHICH TEND TO CAUSE THE GROUND SURFACE OF GLASS TO STICK, PLASTIC (DISPOSABLE) SYRINGES SHOULD BE USED.

ALLERGIC REACTIONS MAY BE ENCOUNTERED FROM THE USE OF AHF CONCENTRATE PREPARATIONS.

ALTHOUGH DOSAGE CAN BE ESTIMATED BY CALCULATION, IT IS STRONGLY RECOMMENDED THAT WHENEVER POSSIBLE, APPROPRIATE LABORATORY TESTS BE PERFORMED ON THE PATIENT'S PLASMA AT SUITABLE INTERVALS TO ENSURE THAT ADEQUATE AHF LEVELS HAVE BEEN REACHED AND ARE MAINTAINED.

IF THE AHF LEVEL FAILS TO REACH EXPECTED LEVELS OR IF BLEEDING IS NOT CONTROLLED AFTER APPARENTLY ADEQUATE DOSAGE, THE PRESENCE OF INHIBITOR SHOULD BE SUSPECTED. BY APPROPRIATE LABORATORY PROCEDURES, THE PRESENCE OF INHIBITOR CAN BE DEMONSTRATED AND QUANTIFIED IN TERMS OF AHF UNITS NEUTRALISED BY EACH ML OF PLASMA OR BY THE TOTAL ESTIMATED PLASMA VOLUME. AFTER SUFFICIENT DOSAGE TO NEUTRALISE INHIBITOR, ADDITIONAL DOSAGE PRODUCES PREDICTED CLINICAL RESPONSE. IT SHOULD BE NOTED THAT WHEN INHIBITOR IS PRESENT, MEASUREMENT OF LEE-WHITE CLOTTING TIME MAY BE A BETTER INDEX OF ADEQUACY OR DOSAGE THAN MEASUREMENT OF CIRCULATING AHF.

(Official use only)

(Official use only)

B | 1

8. Contraindications, Precautions and Warnings:

WARNINGS

THIS CONCENTRATE IS PREPARED FROM LARGE POOLS OF FRESH HUMAN PLASMA WHICH MAY CONTAIN CAUSATIVE AGENTS OF VIRAL HEPATITIS. HOWEVER, EACH UNIT OF PLASMA USED IN THE MANUFACTURE OF THIS PRODUCT HAS BEEN FOUND TO BE NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN (HBsAg) WHEN TESTED WITH LICENCED THIRD GENERATION REAGENTS. IN ADDITION, THIS PRODUCT HAS BEEN SUBJECTED TO A HEATING PROCEDURE DURING ITS MANUFACTURING PROCESS DESIGNED TO REDUCE THE RISK OF TRANSMISSION OF HEPATITIS. ALTHOUGH THESE TESTING AND HEATING STEPS REDUCE THE RISK OF HEPATITIS TRANSMISSION, THE POSSIBILITY OF SUCH TRANSMISSION SHOULD BE CONSIDERED IN USE OF THE PRODUCT.

(Official use only)

E 1 (Official use only)

9. Other constituents:

(Official use only)	Name	Specification Reference	mod	Quantity/Dose Unit or % quantity	Unit
	HEPARIN, SODIUM	USP	QS		
	SODIUM CITRATE	USP	QS		
	OR	EP			
	GLYCINE	USP	QS		
	OR	BP			
	POLYETHYLENE GLYCOL	NF	QS		
	OR	DAB			
	SODIUM CHLORIDE	USP	QS		
	OR	EP			
	SODIUM HYDROXIDE	NF	QS		
	OR	BP			
	ACETIC ACID	USP	QS		
	OR	BEP			
	WATER FOR INJECTION OR	USP	QS		
	AQUA PURIFICATA	EP			

1) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.

2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name column and not in the Specification Reference column. Where an ingredient has no official monograph please enter HSE in the Specification Reference column.

3) Please complete modifier column marked mod. as follows:
Insert TO if final volume cannot be expressed as a complete quantity.
Insert ND for substances not detectable in the final formulation, eg. solvents.
Insert QS if quantity not fixed, eg. for substances used to adjust pH.

4) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.

5) Trailing zeros following the decimal point may be omitted eg 10.02 MG will suffice.

6) Please photocopy page if more space for constituents is required.

(Official use only)

H 1

10. Description of essential processes in the manufacture:

SOURCE PLASMA (HUMAN) IS THAWED CAREFULLY AND CENTRIFUGED TO REMOVE THE CRYOPRECIPITATE WHICH IS THEN DISSOLVED IN HEPARINISED GLYCINE CITRATED SALINE. INACTIVE PROTEINS ARE PRECIPITATED OUT WITH P.E.G. AND REMOVED BY CENTRIFUGATION. AFTER FURTHER PURIFICATION THE FACTOR VIII RICH PORTION IS DISSOLVED IN CITRATED SALINE SOLUTION AND CLARIFIED BY CENTRIFUGATION AND/OR FILTRATION.

THE PRODUCT IS THEN STERILISED BY FILTRATION THROUGH A 0.22 UM FILTER MIXED AND THEN DISPENSED ASEPTICALLY INTO STERILE GLASS VIALS. STERILE LYOPHILISATION STOPPERS ARE PARTIALLY INSERTED AND THE PRODUCT FROZEN AND THEN FREEZE DRIED. AFTER LYOPHILISATION THE STOPPERS ARE SEATED UNDER VACUUM AND CAPPED.

THE VIALS ARE FURTHER PROCESSED BY HEATING AT 60°C ± 1°C FOR 72 HOURS IN A WATER BATH AND THEN INSPECTED, LABELLED AND PACKAGED.

GLASS VIALS ARE STERILISED BY DRY HEAT AT 200°C FOR A MINIMUM OF 175 MINS, STOPPERS ARE STERILISED BY STEAM AT 121°C FOR A MINIMUM OF 44 MINS, PRIOR TO FILLING.

11. Finished Product Specification:

1. pH - 6.8 to 7.4
2. MOISTURE - MAX. 2%
3. SOLIBILITY - COMPLETE DISSOLUTION WITHIN 600 SECS. AT 20 - 25°C
4. TOTAL PROTEIN - MAX 1.75 MG PROTEIN PER I.U.
5. GLYCINE - MAX. 0.50 M
6. POLYETHYLENE GLYCOL - MAX 1.5 G/L
7. STERILITY - STERILE
8. PYROGENS - NON PYROGENIC
9. TOXICITY - MICE - NO SIGNIFICANT SYMPTOMS
   GUINEA PIGS - NO SIGNIFICANT SYMPTOMS
10. NATURAL ANTI-A OR ANTI-B TITRE - 1:160 MAX.
11. IMMUNE ANTI-A OR ANTI-B TITRE - 1:640 MAX.
12. HEPATITIS B SURFACE ANTIGEN - NON REACTIVE
13. HEPARIN - 1.0 UNIT/ML
14. PROTEIN IDENTITY - HUMAN: POSITIVE
    BOVINE: NEGATIVE
15. POTENCY - 10 ML SIZE: MIN 225 I.U./VIAL
    30 ML SIZE: MIN 720 I.U./VIAL

(Official use only)

G | 1 |

12. Assembler(s):	13. Arrangements for storage:
TRAVENOL LABORATORIES INC., 4501 COLORADO, LOS ANGELES, AND/OR TRAVENOL LABORATORIES S.A., 7860 LESSINES, BELGIUM.	THE FINISHED PRODUCT MAY BE STORED AT THE MANUFACTURING FACILITIES DETAILED ABOVE OR IN LICENCED WHOLESALE PREMISES IN THE U.K. (WHOLESALE DEALERS LICENCE WL0116/0001)
14. Importer:	15. List other countries of registration:
TRAVENOL LABORATORIES LTD., CAXTON WAY, THETFORD, NORFOLK.	WEST GERMANY, U.S.A., CANADA, SPAIN, BELGIUM, SWEDEN, IRELAND - LICENCE TO IMPORT GRANTED IN HOLLAND

16. Site and Arrangements for Quality Control:

QUALITY CONTROL WILL BE CARRIED OUT AT THE PLACE OF MANUFACTURE. THE LICENCE HOLDER WILL BE RESPONSIBLE FOR DECIDING IF A BATCH IS OF ACCEPTABLE QUALITY FOR RELEASE.

17. Type of container(s), pack size(s), shelf life and storage precautions:

	Container Size	Unit	(Official use only)
10 ML AND 30 ML GLASS VIALS OF ANTIHAEMOPHILIC FACTOR (HUMAN) METHOD FOUR, DRIED, HEAT TREATED, HEMOFIL T.	10	ML	
10 ML AND 30 ML GLASS VIALS OF WATER FOR INJECTIONS PH.EUR.	30		
SHELF LIFE IS 24 MONTHS.			
PRODUCT SHOULD BE STORED AT 2-8oC AND MAY BE STORED AT ROOM TEMPERATURE FOR UP TO ONE MONTH WITHIN THE DATING PERIOD.			
FREEZING SHOULD BE AVOIDED TO PREVENT BREAKAGE OF THE DILUENT BOTTLE.			

Note: Please tabulate data in space allowed.
Where applicable enter unit as MG, GM, ML, LT for litre etc.
No entry is required in Unit box for solid dosage forms.
Where coded entry is ambiguous leave as text.

PART IB
Supplementary Details

PART IV
Clinical Studies

TABLE OF CONTENTS

PART 1B - SUPPLEMENTARY DETAILS

1. Product Literature

1.1 Labelling and Package Inserts

The proposed text for the container label is included in Appendix I

The proposed text for the carton is included in Appendix II

The proposed direction sheet is included in Appendix III

1.2 Data Sheets

The proposed text for the data sheet for this product is included in Appendix IV

2. Background

2.1 Application in Other Countries

Hemofil-T is currently licenced for sale in West Germany, U.S.A., Canada, Spain, Sweden, Belgium and Ireland. A licence to import has been granted in Holland.

2.2 Background

HEMOFIL Antihaemophilic Factor (Human) Method Four is currently licenced for sale under PL0116/0011. This licence was first granted on 19th February, 1973 and renewed on 19th February, 1978. Application for the second renewal was submitted on 16th December, 1982, however, the Department requested that the application be resubmitted under the Review/Renewal on Expiry of Existing Licence (MLA.201R) and this was sent on 26th October, 1983.

A variation to our existing licence to include a heat treatment step was submitted on 11th May, 1983. We received notification from the Department (letter dated 14th October, 1983) that the Committee on Safety of Medicines had refused the variation application on the following grounds:

1. Inadequate evidence of safety and efficacy was provided.

2. Justification should be provided for the inclusion and choice of heat treatment

3. The heat treated product was inadequately characterised.

4. In the event of the grant of a variation to the licence, labels and data sheets should be amended to the satisfaction of the Secretariat.

On further discussion with the Medicines Division it was requested that we submit an abridged licence application to cover the treated product Antihaemophilic Factor (Human) Method Four-Heat Treated HEMOFIL-T.

3. Persons Involved in the Manufacture of the Finished product and its Distribution in the U.K.

3.1 Manufacturer and Assembler

Manufacture, assembly, heat treatment and packaging of Antihaemophilic Factor (Human) Method Four, dried, heat treated HEMOFIL T into the final containers is accomplished in the facilities of:

TRAVENOL LABORATORIES S.A.
B-7860 Lessines, Belgium
a wholly owned subsidiary of Travenol Laboratories, Inc., U.S.A. The product is processed and tested in accordance with requirements established in the Belgian Manufacturing Licence nr 395 ED 402 F 12.

HYLAND THERAPEUTICS DIVISION
TRAVENOL LABORATORIES INC.,
Glendale, California, U.S.A.
The product is processed and tested in accordance with the requirements established by the United States Food and Drug Administration and manufactured under U.S. Licence nr 140.

3.2 Arrangements for storage

The finished products may be stored at the manufacturing facilities detailed above or in licenced wholesale premises in the United Kingdom.

Wholesale dealers licence number WL/0116/001.

3.3 Importer

As licence holder.

3.4 Responsibility for Quality Control

a) Each manufacturer will be responsible for deciding if a batch of product is of acceptable quality for release.

The licence holder will be responsible for release of product within the United Kingdom.

b) Quality Control will be carried out at the place of manufacture.

RA.191

APPENDIX I : PROPOSED TEXT FOR LABEL

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	1	1		KD060-610		

PHYSICAL SPECIFICATIONS

TOTAL COPIES	ITEM: Bottle Label		STOCK
PRODUCT: ANTIHAEMOPHILIC FACTOR (HUMAN), HEAT TREATED - 10 ml			STYLE
PRINTED SIZE	TOLERANCES		
TRIM SIZE		INSPECTION PER CTP NO.	COMMODITY CODE
FOLDED SIZE: SALES		DISPOSITION OF OLD STOCK	
FOLDED SIZE: PACKAGING			
PRINTING		☐ Discard ☐ Use up Use only for _____	

COPY ARTWORK

LOGO
TRAVENOL

ANTIHAEMOPHILIC FACTOR (HUMAN)

Method Four - Heat Treated

10 ml size, dried, sterile

HEMOFIL T

For Intravenous Administration

Reconstitute at room temperature with 10 ml Water for Injections Ph.Eur. Administer promptly (within 3 hours) after reconstitution. Contains max. 1.0 I.U. heparin per ml of reconstituted solution as stabiliser. Do not refrigerate after reconstitution. Do not use if gel forms on reconstitution.

STORE BETWEEN 2° and 8°C

Protect from light.

Warning: The risk of transmitting hepatitis is present.

Read direction sheet and use as directed by physician.

This bottle contains I.U. of AHF activity.

Lot No.:

Exp. Date:

Distributed by TRAVENOL LABORATORIES Ltd.
Thetford, Norfolk, ENGLAND.

PL.0116/
PA.167/7/8

POM

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III. PRODUCTION CONTROL, PURCHASING

HY-1500A

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	1	1		KD060-639		

PHYSICAL SPECIFICATIONS

TOTAL COPIES	ITEM: BOTTLE LABEL		STOCK
PRODUCT: ANTIHAEMOPHILIC FACTOR (HUMAN), HEAT TREATED - 30 ml			
			STYLE
PRINTED SIZE		TOLERANCES	
TRIM SIZE			INSPECTION PER CTP NO. / COMMODITY CODE
FOLDED SIZE: SALES			DISPOSITION OF OLD STOCK
FOLDED SIZE: PACKAGING			
PRINTING			☐ Discard ☐ Use up Use only for _____

COPY / ARTWORK

LOGO
TRAVENOL

ANTIHAEMOPHILIC FACTOR (HUMAN)

30 ml size, dried, sterile

Method Four - Heat Treated

HEMOFIL T

For Intravenous Administration

Reconstitute at room temperature with 30 ml Water for Injections Ph.Eur. Administer promptly (within 3 hours) after reconstitution. Contains max. 1.0 I.U. heparin per ml of reconstituted solution as stabiliser. Do not refrigerate after reconstitution. Do not use if gel forms on reconstitution.

STORE BETWEEN 2° AND 8°C

Protect from light.

Warning: The risk of transmitting hepatitis is present.
Read director sheet and use as directed by physician.

This bottle contains I.U. of AHF activity.

Lot No.:

Expiry Date:

Distributed by TRAVENOL LABORATORIES Ltd.
Thetford, Norfolk, ENGLAND.

PL.0116/
PA.167/7/11

POM

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III, PRODUCTION CONTROL, PURCHASING

HY-1500A

RA.191

APPENDIX II : PROPOSED TEXT FOR CARTON

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	1	2		KD060-610		

PHYSICAL SPECIFICATIONS

TOTAL COPIES	ITEM: CARTON LABEL		STOCK
PRODUCT: ANTIHAEMOPHILIC FACTOR(HUMAN), HEAT TREATED			
			STYLE
PRINTED SIZE		TOLERANCES	
TRIM SIZE			INSPECTION PER CTP NO. / COMMODITY CODE
FOLDED SIZE: SALES			DISPOSITION OF OLD STOCK
FOLDED SIZE: PACKAGING			
PRINTING			☐ Discard ☐ Use up Use only for _____

COPY AR RTWORK

10 ml size, dried

List No. KD060- 610

ANTIHAEMOPHILIC FACTOR (HUMAN)

HEMOFIL T

Method Four

Heat-Treated

STORE THIS PACKAGE BETWEEN 2° AND 8°C or up to 1 month (within dating period) at room temperature, not to receed 25°C. Avoid freezing, which might damage diluent bottle. Protect from light.

Date stored at room temperature:_____

PL0116/ PA167/7/8

POM

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PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III. PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	2	2		KD060-610		

ITEM
PRODUCT

10 ml size, dried List No. KD060-610

ANTIHAEMOPHILIC FACTOR (HUMAN)

HEMOFIL T

Method Four Heat-Treated

This lot contains: International Units of AHF activity per vial

Expiry date:

Contents: One bottle 10 ml dried Antihaemophilic Factor (Human) one bottle 10 ml. Water for Injections Ph.Eur., one double-ended needle, one filter spike, directions for use.

For intravenous administration

Administration: See enclosed direction sheet and use as directed by physician

Stabilised with heparin, not only 1.0 unit (0.010 mg) per ml of reconstituted material. Contains no preservative. Use promptly (within 3 hours) after reconstitution. Do not use if gel forms on reconstitution.

WARNING: Plasma from which this product was derived was found to be nonreactive for hepatitis B surface antigen (HBsAg) when tested with licenced third generation reagents. In addition, the process used in the manufacture of this product includes a heating step designed to minimise the risk of transmission of hepatitis. However, no procedure has been shown to be totally effective in removing hepatitis infectivity from Antihaemophilic Factor (Human).

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PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

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PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	1	2		KD060-639		

PHYSICAL SPECIFICATIONS

TOTAL COPIES	ITEM: CARTON LABEL		STOCK
PRODUCT: ANTIHAEMOPHILIC FACTOR(HUMAN), HEAT TREATED			STYLE
PRINTED SIZE		TOLERANCES	
TRIM SIZE			INSPECTION PER CTP NO. / COMMODITY CODE
FOLDED SIZE: SALES			DISPOSITION OF OLD STOCK
FOLDED SIZE: PACKAGING			
PRINTING			☐ Discard ☐ Use up — Use only for _____

COPY / ARTWORK

30 ml size, dried

List No. KD060-639

ANTIHAEMOPHILIC FACTOR (HUMAN)

HEMOFIL T

Method Four

Heat-Treated

STORE THIS PACKAGE BETWEEN 2° AND 8°C or up to 1 month (within dating period) at room temperature, not to exceed 25°C. Avoid freezing, which might damage diluent bottle. Protect from light.

Date stored at room temperature:_____

PL0116/ PA167/7/11 POM

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PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III. PRODUCTION CONTROL, PURCHASING

HY-1500A

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	2	2		KD060-639		

ITEM
PRODUCT

30 ml size, dried

List No. KD060-639

ANTIHAEMOPHILIC FACTOR (HUMAN)

HEMOFIL T

Method Four

Heat Treated

This lot contains: International Units of AHF activity per vial

Expiry Date:

Contents: One bottle 30 ml dried Antihaemophilic Factor (Human), one bottle 30 ml Water for Injections Ph.Eur., one double-ended needle, one filter spike, directions for use.

For intravenous administration.

Administration: See enclosed direction sheet and use as directed by physician. Stabilised with heparin, not over 1.0 unit (0.010 mg) per ml of reconstituted material. Contains no preservative. Use promptly (within 3 hours) after reconstitution. Do not use if gel forms on reconstitution.

WARNING: Plasma from which this product was derived was found to be nonreactive for hepatitis B surface antigen (HBsAG) when tested with licenced third generation reagents. In addition, the process used in the manufacture of this product includes a heating step designed to minimise the risk of transmission of hepatitis. However, no procedure has been shown to be totally effective in removing hepatitis infectivity from Antihaemophilic Factor (Human).

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PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

RA.191

APPENDIX III : PROPOSED TEXT FOR DIRECTION SHEET

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	i	9		BASIC		

PHYSICAL SPECIFICATIONS

TOTAL COPIES	ITEM DIRECTION INSERT		STOCK
PRODUCT ANTIHAEMOPHILIC FACTOR(HUMAN), HEAT TREATED			STYLE
PRINTED SIZE	TOLERANCES		
TRIM SIZE		INSPECTION PER CTP NO.	COMMODITY CODE
FOLDED SIZE: SALES		DISPOSITION OF OLD STOCK	
FOLDED SIZE: PACKAGING			
PRINTING		☐ Discard ☐ Use up Use only for _____	

COPY . ARTWORK

LOGO
TRAVENOL

ANTIHAEMOPHILIC FACTOR (HUMAN) Method Four, Dried
HEAT-TREATED HEMOFIL T

The potency of each lot of this product is given on the container and package labels. See instructions given under DOSAGE AND ADMINISTRATION and "Rate of Administration" for potency-related administration instructions.

DESCRIPTION

Antihaemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL T, is a sterile, stable, dried preparation of antihaemophilic factor (Factor VIII, AHF, AHG) in concentrated form. It is prepared from fresh-frozen human plasma. The product also contains a trace amount of heparin, 1.0 unit (0.010 mg) or less per ml of reconstituted material, as a stabilising agent. Concentrations of heparin many times greater than this have been shown to have no demonstrable effect after infusion of the volumes encountered in the use of this product.

Antihaemophilic Factor (Human), HEMOFIL T contains high AHF potency with relatively small amounts of fibrinogen and other proteins. Each lot is assayed and labelled for its AHF content expressed as International Units of AHF activity.

Antihaemophilic Factor (Human) is to be administered only by the intravenous route.

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III, PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	2	9				

ITEM

PRODUCT

A change has been made in the manufacture of this product to include a heating step designed to reduce the risk of transmission of hepatitis. No procedure has been shown to be totally effective in removing hepatitis infectivity from Antihaemophilic Factor (Human). (See Section on CLINICAL PHARMACOLOGY).

CLINICAL PHARMACOLOGY

Antihaemophilic factor (AHF) is a protein found in normal plasma which is necessary for clot formation. The administration of Antihaemophilic Factor (Human), HEMOFIL T, provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with haemophilia A (classical haemophilia).

The half-life of AHF administered to haemophiliacs has been variously estimated at 8 to 24 hours.[2-6] In the severe haemophiliac, the half-life of the first dose of AHF in any form appears to be at the lower end of the range, but for subsequent doses it may be safely estimated as at least 12 to 15 hours in the absence of inhibitors and "active bleeding".

An assessment of the efficacy of the heating step employed was performed by administration to chimpanzees of Antihaemophilic Factor (Human) inoculated with 300 and 30,000 infectious units of hepatitis B. While there was no effect of heating on the high dose inoculum, the chimpanzees receiving 300 infectious units did not develop hepatitis B markers until 7½ and 10 months had elapsed, as compared to 4 months for untreated material, which may indicate a reduction in infectivity of the product for hepatitis B. The study also indicated that the heat treatment eliminated an unknown quantity of at least one type of non-A, non-B hepatitis virus present in the administered Antihaemophilic Factor (Human).[7]

In addition to the chimpanzee study described above, the effectiveness of the heating step was also assessed by in vitro viral inactivation studies, using, as a marker, a virus which is not commonly found in plasma. When known quantities of Sindbis virus were added to the product, it was shown that the heat treatment employed was capable of inactivating approximately 3.2 logs of this virus.

INDICATION AND USAGE

The use of Antihaemophilic Factor (Human), HEMOFIL T, is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes.

COPY AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	3	9				

ITEM
PRODUCT

The concentrate can be of significant therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per ml.[8] However, in such uses the dosage should be controlled by frequent laboratory determinations of circulating Factor VIII.

Antihaemophilic Factor (Human) is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

None known.

WARNINGS

This concentrate is prepared from large pools of fresh human plasma which may contain causative agents of viral hepatitis. However, each unit of plasma used in the manufacture of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) when tested with licenced third generation reagents. In addition, this product has been subjected to a heating procedure during its manufacturing process designed to reduce the risk of transmission of hepatitis. Although these testing and heating steps reduce the risk of hepatitis transmission, the possibility of such transmission should be considered in the use of the product.

PRECAUTIONS

General

This Antihaemophilic Factor (Human) preparation contains blood group isoagglutinins (anti-A and anti-B). When large or frequently repeated doses are needed, as when inhibitors are present or when pre- and post-surgical care is involved, patients of blood groups A, B and AB should be monitored for signs of intra-vascular haemolysis and decreasing haematocrit values. Haemolytic anaemia, when present, may be corrected by the administration of compatible Group O Red Blood Cells (Human).

Identification of the clotting deficiency as one of Factor VIII is essential before the administration of Antihaemophilic Factor (Human) is initiated.

Since Antihaemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL T, contains small residual amounts of fibrinogen which tend to cause the ground surface of glass to stick, plastic (disposable) syringes should be used.

COPY AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

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PRINTED PACKAGE MATERIAL SPECIFICATION

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Laboratory Tests

Although dosage can be estimated by the following calculations, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained.

If the AHF level fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralise inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy of dosage than measurement of circulating AHF.

Pregnancy

Animal reproduction studies have not been conducted with Antihaemophilic Factor (Human). It is also not know whether Antihaemophilic Factor (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Antihaemophilic Factor (Human) should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Allergic reactions may be encountered from the use of AHF concentrate preparations.

DOSAGE AND ADMINISTRATION

Each bottle of Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T, is labelled with the number of AHF units which it contains, 1 AHF unit being defined as the activity present in 1 ml of normal pooled human plasma less than 1 hour old (100% AHF level). The stated potency is expressed in International Units of AHF activity and is based upon the use of a standard traceable to the World Health Organisation International Standard for blood coagulation Factor VIII (Human).

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE 5	OF 9	SUPERSEDES	LIST NO.	PART NO.	REV.

ITEM
PRODUCT

Abildgaard, et al[9] reported that infusion of 1 unit of AHF per kg body weight consistently produces an increase of 2% (of normal), while Shanbrom and Thelin[10] found that 3.8 to 4.0 units per kg produce an increase of 10% (of normal) in AHF level. (The former authors worked with boys 8 months to 14 years of age, while the latter worked primarily with adults.) The following formulae can therefore be used to calculate, approximately, the expected response from a given dose or the dose required for a given effect:

I. Units required=

body weight (in kg) x 0.4 x
desired AHF increase (in % of normal)

Example: 70 x 0.4 x 50 = 1,400 units

II. Expected AHF increase (in % of normal) =

$$\frac{\text{units administered}}{\text{body weight (in kg)} \times 0.4}$$

Example: $\frac{1,400}{70 \times 0.4} = 50\%$

The data of Abildgaard, et al would call for a factor of 0.5 instead of 0.4 in the preceding formulae.

The amount of AHF that a haemophiliac requires for normal haemostasis varies with circumstances and with the patient. The amount of factor to be supplied will depend on the degree of deficiency and on the AHF level desired.

Kasper has found that minor haemorrhagic episodes will generally subside with a single infusion if a level of 30% or more is attained. For more serious haemorrhages, a Factor VIII level of 35 to 50% of normal should be obtained for optimum clot formation. In surgery, Kasper recommends that the first dose of Factor VIII, to achieve a level of 80 to 100%, be given an hour before the procedure. A second dose of Factor VIII half the size of the priming dose should be given about 5 hours after the priming dose. If several units of blood wre lost during the operation, a third dose of concentrate should be given when the patient reaches the recovery room. The Factor VIII level should be maintained at a daily minimum of at least 30% for a healing period of 10 to 14 days.[11]

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PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

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ITEM
PRODUCT

The preceding dosage formulae are presented as a reference and a guideline. Other dosage regimens have been proposed such as that of Hilgartner,[12] which outlines dosage according to the various types of bleeding episodes, and Schimpf, et al,[13] which describes continuous maintenance therapy.

Exact dosage determinations should be made based on the medical judgment of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor VIII to be achieved.

Reconstitution: Use Aseptic Technique

1. Bring Antihaemophilic Factor (Human), HEMOFIL T, (dry concentrate) and Water for Injections, Ph.Eur. (diluent) to room temperature.

2. Remove caps from concentrate and diluent bottles to expose central portion of rubber stoppers.

3. Cleanse stoppers with germicidal solution.

4. Remove protective covering from one end of double-ended needle, using care not to touch the exposed end. Insert exposed needle through diluent stopper.

5. Remove protective covering from other end of double-ended needle, using aseptic techniques as above. Invert diluent bottle over the upright concentrate bottle, then rapidly insert free end of the needle through the concentrate bottle stopper at its centre. Vacuum in concentrate bottle will draw in diluent.

6. Disconnect the two bottles by removing needle from concentrate bottle stopper. Shake vigorously for 5 seconds, then agitate or rotate concentrate bottle until all material is dissolved. Be sure that concentrate is completely dissolved; otherwise, active material will be removed by the filter.

NOTE: Do not refrigerate after reconstitution.

Do not use if a gel forms on reconstitution.

Rate of Administration

Preparations of Antihaemophilic Factor (Human), HEMOFIL T, containing 34 or more AHF units per ml must be administered at carefully controlled rates: i.e., a maximum administration rate of 2 ml per minute. Accordingly, the administration of a 30-ml total volume containing 34 or more AHF units per ml must be evenly regulated over a period of 15 or more minutes. AHF preparations containing less than 34 AHF units per ml

COPY AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

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PRINTED PACKAGE MATERIAL SPECIFICATION

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ITEM
PRODUCT

can be given rapidly, at a rate of 10 to 20 ml over a 3-minute period, with no significant reactions.

As a precautionary measure, the physician should determine the pulse rate before and during administation of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue.

Administration: Use Aseptic Technique

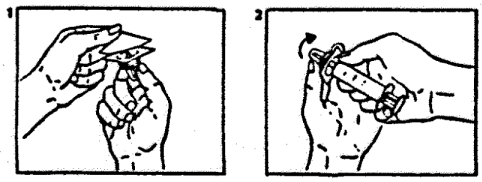
Administration of Antihaemophilic Factor (Human), HEMOFIL T, should begin not more than 3 hours after reconstitution is complete.

The reconstituted material should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

1. After reconstituting the concentrate as described under "Reconstitution", open the filter spike package by peeling back the label of the blister pack. (See Figure 1)

2. Hold the clear plastic blister pack at the rim of the filter spike and aseptically attach the filter spike to an empty plastic syringe. Twist the filter spike onto the syringe to ensure a secure connection. (See Figure 2)



COPY AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

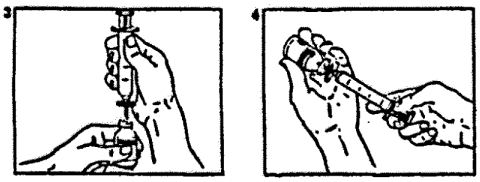
EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	8	9				

ITEM
PRODUCT

3. Draw back the plunger to admit air into the syringe.

4. Place the reconstituted Antihaemophilic Factor (Human), HEMOFIL T, bottle on a flat surface and while holding the bottle firmly to prevent slipping, insert the spike perpendicularly through the centre of the bottle stopper. (See Figure 3)

5. Inject air into bottle and then withdraw the reconstituted material into the syringe. (See Figure 4)



6. Remove and discard the filter spike from the syringe; attach a suitable needle and inject intravenously.

7. NOTE: Discard each filter spike after a single use. If the same patient is to receive more than one bottle of concentrate, the contents of two bottles may be drawn into the same syringe through filter spikes before attaching the vein needle.

HOW SUPPLIED

Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T, is furnished with a suitable volume of Water for Injections Ph.Eur. a double-ended needle, and a filter spike.

The number of International Units of AHF activity, as determined for each lot is stated on the label of each bottle.

STORAGE

Antihaemophilic Factor (Human), Method four, Dried, Heat-Treated, HEMOFIL T, should be stored under ordinary refrigeration (2° to 8°C) Freezing should be avoided as breakage of the diluent bottle might occur.

Antihaemophilic Factor (Human), HEMOFIL T, may be stored for up to 1 month within the dating period at room temperature, not to exceed 25°C.

COPY AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	9	9				

ITEM
PRODUCT

REFERENCES

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DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

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APPENDIX IV : PROPOSED TEXT FOR DATA SHEET

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	1	5		BASIC		

PHYSICAL SPECIFICATIONS

TOTAL COPIES	ITEM DATA SHEET		STOCK
PRODUCT ANTIHAEMOPHILIC FACTOR (HUMAN),HEAT TREATED			
			STYLE
PRINTED SIZE		TOLERANCES	
TRIM SIZE			INSPECTION PER CTP NO. / COMMODITY CODE
FOLDED SIZE — SALES			DISPOSITION OF OLD STOCK
FOLDED SIZE — PACKAGING			
PRINTING			☐ Discard ☐ Use up Use only for

COPY & ARTWORK

DATA SHEET

LOGO
TRAVENOL

ANTIHAEMOPHILIC FACTOR (HUMAN)

Method Four, Dried - Heat Treated

HEMOFIL T

Presentation: Antihaemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL T, is a sterile, Stable, dried preparation of antihaemophilic factor (Factor VIII, AHF, AHG) in concentrated form. It is prepared from fresh-frozen human plasma. The product also contains a trace amount of heparin, 1.0 unit (0.010 mg) or less per ml of reconstituted material, as a stabilising agent.

Antihaemophilic Factor (Human), HEMOFIL T, contains high AHF potency with relatively small amounts of fibrinogen and other proteins. Each lot is assayed and labelled for its AHF content expressed as international Units of AHF activity.

Uses: The use of Antihaemophilic Factor (Human), HEMOFIL T, is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes.

The concentrate can be of significant therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per ml. However, in such uses the dosage should be controlled by frequent laboratory determinations of circulating Factor VIII.

Antihaemophilic Factor (Human) is not indicated in von Willebrand's disease.

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III, PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE 2	OF 5	SUPERSEDES	LIST NO.	PART NO.	REV.

ITEM

PRODUCT

Dosage and Administration: Each bottle of Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T, is labelled with the number of AHF units which it contains, 1 AHF unit being defined as the activity present in 1 ml of normal pooled human plasma less than 1 hour old (100% AHF level).

Abildgaard, et al reported that infusion of 1 unit of AHF per kg body weight consistently produces an increase of 2% (of normal), while Shanbrom and Thelin found that 3.8 to 4.0 units per kg. produce an increase of 10% (of normal) in AHF level. (The former authors worked with boys 8 months to 14 years of age, while the latter worked primarily with adults.) The following formulae can therefore be used to calculate, approximately, the expected response from a given dose or the dose required for a given effect:

I. Units required = Body weight (in kg) x 0.4 x desired AHF increase (in % of normal)

II. Expected AHF increase (in % of normal) =

$$\frac{\text{units administered}}{\text{body weight (in kg)} \times 0.4}$$

The data of Abildgaard, et al would call for a factor of 0.5 instead of 0.4 in the preceding formulae.

The amount of AHF that a haemophiliac requires for normal haemostasis varies with circumstances and with the patient. The amount of factor to be supplied will depend on the degree of deficiency and on the AHF level desired.

Kasper has found that minor haemorrhagic episodes will generally subside with a single infusion if a level of 30% or more is attained. For more serious haemorrhages, a Factor VIII level of 35 to 50% if normal should be obtained for optimum clot formation. In surgery, Kasper recommends that the first dose of Factor VIII, to achieve a level of 80 to 100%, be given an hour before the procedure. A second dose of Factor VIII half the size of the priming dose should be given about 5 hours after the priming dose. If several units of blood were lost during the operation, a third dose of concentrate should be given when the patient reaches the recovery room. The Factor VIII level should be maintained at a daily minimum of at least 30% for a healing period of 10 to 14 days.

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PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE 3	OF 5	SUPERSEDES	LIST NO.	PART NO.	REV.

ITEM
PRODUCT

Exact dosage determinations should be made based on the medical judgment of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor VIII to be achieved.

Antihaemophilic Factor (Human) is to be administered only by the intravenous route. The material should be reconstituted with the appropriate volume of Water for Injections Ph.Eur.

Preparations of Antihaemophilic Factor (Human), HEMOFIL T containing 34 or more AHF units per ml must be administered at carefully controlled rate: i.e. a maximum administration rate of 2 ml per minute.

AHF preparations containing less than 34 AHF units per ml can be given rapidly, at a rate of 10 to 20 ml over a 3-minute period, with no significant reactions.

As a precautionary measure, the physician should determine the pulse rate before and during administration of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue.

CONTRAINDICATIONS

None known.

WARNINGS

This concentrate is prepared from large pools of fresh human plasma which may contain causative agents of viral hepatitis. However, each unit of plasma used in the manufacture of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) when tested with licenced third generation reagents. In addition, this product has been subjected to a heating procedure during its manufacturing process designed to reduce the risk of transmission of hepatitis. Although these testing and heating steps reduce the risk of hepatitis transmission, the possibility of such transmission should be considered in use of the product.

PRECAUTIONS

General

This Antihaemophilic Factor (Human) preparation contains blood group

Y AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
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isoagglutinins (anti-A and anti-B). When large or frequently repeated doses are needed, as when inhibitors are present or when pre and post-surgical care is involved, patients of blood groups A, B, and AB should be monitored for signs of intravascular haemolysis and decreasing haematocrit values. Haemolytic anemia, when present, may be corrected by the administration of compatible Group O Red Blood Cells (Human).

Identification of the clotting deficiency as one of Factor VIII is essential before the administration of Antihaemophilic Factor (Human) is initiated.

Since Antihaemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL T, contains small residual amounts of fibrinogen which tend to cause the ground surface of glass to stick, plastic (disposable) syringes should be used.

Laboratory Tests

Although dosage can be estimated by the calculations above, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained.

If the AHF level fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralise inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy or dosage than measurement of circulating AHF.

ADVERSE REACTIONS

Allergic reactions may be encountered from the use of AHF concentrate preparations.

Pharmaceutical Precautions

Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T, should be stored under ordinary refrigeration (2° to 8°C). Freezing should be avoided as breakage of the diluent bottle might occur.

Antihaemophilic Factor (Human), HEMOFIL T may be stored for up to 1 month within the dating period at room temperature, not to exceed 25°C.

PRINTED PACKAGE MATERIAL SPECIFICATION

EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	5	5				

ITEM
PRODUCT

Legal Category

Prescription Only Medicine.

Package Quantities

Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T is furnished with a suitable volume of Water for Injections Ph.Eur. a double-ended needle, and a filter spike.

Unit Size	Average Activity	Code Number
10 ml	250 I.U./Vial	KD060-610
30 ml	750 I.U./Vial	KD060-630
30 ml	1050 I.U./Vial	KD060-639

Further Information

Nil

Product Licence Number

PL0116/

Date of Preparation

July 1984

Travenol Laboratories Ltd.,
Thetford,
Norfolk, ENGLAND.

Telephone Thetford (0842) 4581

Y AND ARTWORK

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
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Section | Page Number

PART IV - STUDIES IN HUMANS

PART IV: STUDIES IN HUMANS RA.191

1. HUMAN PHARMACOLOGICAL STUDIES

Three human pharmacological studies have been performed. These were designed to demonstrate the lack of neoantigenicity and similarity of half life and recovery of Heat-treated AHF when compared with non heat-treated standard AHF.

1.1 Half life and recovery

Haemophilia A is the inherited inability to manufacture the plasma protein known as Factor VIII or Antihaemophilic Factor (AHF). The disorder is inherited as a sex linked recessive characteristic. Patients with haemophilia are therefore males with low levels of AHF in their plasma. Clinically, such patients can be divided into groups who have severe manifestations (AHF <1% of the normal value), moderately severe (AHF = 1-5%), and mild (AHF = 5-20%) (1-2).

In addition to the above correlation between inherited blood level of AHF and severity of disease, it is generally accepted that the level of AHF attained in the patient's plasma following infusion of AHF correlates directly with the efficacy of the administered AHF. (3-5) The clinical studies reported here emphasise the blood levels of AHF achieved following infusion of Antihaemophilic Factor (Human, Method Four, Treated), when compared to the reference material (Antihaemophilic Factor, Human, Method Four, Non-Dextrose). These materials will be referred to subsequently as AHF Treated and AHF Reference respectively.

Two human clinical studies were conducted to demonstrate the safety and efficacy of AHF Treated by evaluating survival and recovery of the AHF.

a) Half-life and Percentage Recovery-Clinical Report from U.S.A.

In the U.S.A. six non-bleeding haemophilia A patients were each infused with both AHF Treated and AHF Reference (as a control). A nominal dosage of 50 AHF units/kg was employed.

A statistical comparison of the results (using the sign test) indicated no significant difference in the average or median half-lives for the two products, AHF Treated and AHF Reference (p=1.0000). The results are given in Table I.

A statistical comparison of the Factor VIII recovery was performed by measuring the Factor VIII levels in the patients blood during the post-infusion period and calculating the maximum Factor VIII activity as a percentage of the normal values. Using the sign test results indicated a nonsignificant difference in the average of median recoveries for the two products (p = 0.2188). The results are given in Table II.

The Clinical Report of the U.S. study is included as Appendix I.

TABLE I

HALF-LIFE

Patient	Half-Life Hours AHF Treated	AHF Reference
JHM	8.3	12.6
JMS	8.5	6.6
ELB	7.0	8.8
GDM	8.1	7.8
RWL	7.2	8.2
CWC	8.3	7.6
Average	7.9	8.6
Median	8.2	8.0

TABLE II

RECOVERY

(Maximum % of Normal Over the Post-Infusion Period)

Patient	Recovery (%) AHF Treated	AHF Reference
JHM	53%	88%
JMS	92%	114%
ELB	75%	81%
GDM	77%	87%
RWL	127%	107%
CWC	60%	80%
Average	80.7%	92.8%
Median	76%	87.5%

b) Half-life and Percentage Recovery - Clinical Report from France

In France six regularly bleeding (>1 bleed per month) Haemophilia A patients were each infused initially with AHF Reference as a control, followed by three injections of AHF Treated for the treatment of spontaneous bleeding as warranted by their clinical condition.

The patients were treated with both materials and were judged on the basis of clinical reponse to have been treated effectively. The effectiveness of treatment was also evaluated by comparing the Factor VIII:c plasma level attained with the AHF Treated concentrate when compared to the plasma level attained with AHF Reference in the same haemophilic individual. The comparison was made in order to allow for individual patient variation. The results of the Factor VIII recovery and half-life are summarised in Table III. The recovery and half-life values show that the AHF Treated and AHF Reference were not distinguishable. No untoward side effects were observed.

The equivalence of Hemofil T concentrate and Hemofil concentrate with regard to recovery and biological half-life support the contention that the two products are therapeutically equivalent.

TABLE III

IN VIVO RECOVERY AND HALF-LIFE OF AHT HTV VERSUS CONTROL

	F.VIII HALF-LIFE, (hours)		IN VIVO F.VIII :c RECOVERY (%)	
PATIENT	AHF REFERENCE Lot 800401AH11	AHF TREATED Lot 2750T001	AHF REFERENCE Lot 800401AH11	AHF TREATED Lot 2750T001
J.P.S.	8.5	8.5	96.7	91
A.F.	8.5	7	(>80)*	83
R.B.	11.5	10.5	102	105
K.K.	10.5	10	102	98
N.K.	11	8.5	100	105
J.P.B.	11	11	94	89
			* no data available after 1 hr.	
mean	10.2	9.3	mean 95.7	95.2
standard deviation	1.3	1.5	standard deviation 8.34	8.99
student test t 1			student test t .12	

In addition, no inhibitors or neoantigens were formed, as evidenced by half-life and percent recovery data summarised below in Table IV for first vs. third injections where no difference is apparent between doses.

These results lend further support to the conclusion that the heat-treatment process has not significantly altered the structure of the Factor VIII.

TABLE IV

IN VIVO RECOVERY AND HALF-LIFE OF AHF-TREATED, FIRST VERSUS THIRD INJECTIONS

	F.VIII Half-Life (hours)		In Vivo F.VIII: c Recovery (%)	
PATIENT	AHF-Treated LOT 2570T001 First Injection	AHF-Treated LOT 2570T001 Third Injection	AHF-Treated LOT 2570T001 First Injection	AHF-Treated LOT 2570T001 Third Injection
2 A.F.	7	7	83	95
4 K.K.	10	8	98	98

The clinical report of the French study is included as Appendix II.

CONCLUSION

AHF Treated has been shown to be therapeutically equivalent to AHF Reference, and was well tolerated. There were no adverse reactions. The dose used was considered appropriate for treating mild bleeding episodes, but higher doses might be necessary for more major bleeding. The contraindications are the same as those for AHF preparations currently in use.

1.2 Neoantigenicity

Assay of Circulating Immune Complexes in Haemophiliac Patients

The six patients treated in the above study (1.1.b) were also used for measurement of circulating immune complexes. Immune complexes were measured before the first and after the third infusion of AHF Treated. The immune complex levels were determined by two tests based on inhibition of latex agglutination using either rheumatoid factor or murine agglutinator.

In conclusion it was confirmed that haemophiliac patients have higher levels of circulating immune complexes than the normal population. However, no significant increase was noted in immune complex levels after three infusions of AHF Treated.

The results are summarised in Table V.

The full report of this study is included as Appendix III.

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TABLE V

LEVELS OF CIRCULATING IMMUNE COMPLEXES

PATIENT	TEST*	TIME OF SAMPLING			
		Before Untreated AHF	10-15 Days After Untreated AHF	10-15 Days After 1st AHF Treated	10-15 Days After 3rd AHF Treated
AF	RF	25	22	24	27
	MAG	340	340	340	370
KK	RF	25	27	25	30
	MAG	275	325	290	280
JPS	RF	38	38	37	45
	MAG	325	350	310	270
RB	RF	42	44	41	47
	MAG	315	360	360	375
JPB	RF	32	30	30	32
	MAG	275	275	300	315
KN	RF	26	26	-	26
	MAG	190	180	-	220

* Tests as follows:

RF - Rheumatoid Factor (in equivalents of heat aggregated IgG (µg/ml)

MAG - Murine Agglutinator (in equivalents of heat aggregated IgG (µg/ml)

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2. CLINICAL TRIALS

A clinical study to assess the degree of reduction of hepatitis risk transmission afforded by heat treatment of Factor VIII is currently ongoing.

A study is being performed on a multicentre basis under CTX0116/0137A and is prospective and non-comparative. Previously untreated ("virgin") haemophiliacs both vaccinated and non-vaccinated against hepatitis B, received AHF-Treated following a first bleed and for each subsequent haemorrhage.

Beginning in December 1982, 34 patients from 10 centres in 5 countries were enrolled into the AHF-Treated studies. However, 12 patients have had to be excluded from the analysis because they did not meet the selection criteria (the majority having been treated with blood or blood products and therefore not "virgin"). Currently 22 patients are being evaluated prospectively, of whom 20 have been followed for enough time (at least 3 months) to provide preliminary data on the safety and efficacy of AHF-Treated.

In summary, 11 of the 20 patients (55%) treated with AHF-Treated developed post transfusion hepatitis (PTH). One patient developed cytomegalovirus infection. However, this was considered to be unrelated to the treatment as the same lot of AHF-Treated was given to another 6 patients without transmitting CMV infection. One patient had elevated transaminases briefly, but this was not interpreted as being due to hepatitis. In 7 patients no symptoms of hepatitis were noted.

Hepatitis in the 11 patients was always of the Non A, Non B type of a moderate severity and anicteric in all but one case. No cases of seroconversion for Hepatitis B have occurred although only 6 of the 20 patients had been vaccinated against hepatitis B. The efficacy and tolerance of AHF-Treated was equal, in all cases, to that recorded for standard AHF.

A copy of the interim report is included as Appendix IV.

3. ADVERSE REACTIONS

The product Hemofil-T (Antihaemophilic Factor (Human) Method Four Heat Treated) has been used widely since early 1983. To date over 4,000 patients have been treated with Hemofil-T (based on sales figures and the annual Factor VIII requirement of a severe Haemophilia A patient). A total of 8 adverse reactions have been reported and these are detailed below.

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The total number of units of AHF-Treated sold in Europe (including West Germany, Spain, Sweden and Belgium) and the U.S.A. is as follows:

HEMOFIL-T USAGE (Millions of I.U.)

Year	U.S.A.	Europe	Total
1983	46.7	41.5	88.2
1984 (7 months)	41.6	60.6	102.2
	88.3	102.1	190.4

The complete number of adverse reaction complaints reported to Travenol Laboratories is as follows:

REPORTS FROM THE U.S.A.

Date	Lot No.	Adverse Reactions
17.7.84	2792X370AA	Hepatitis A
2.5.84	2792X358AB	Non-A, Non-B Hepatitis
20.3.84	2792X371AA	Non-A, Non-B Hepatitis
13.1.84	2792X301AB 2792X331AB	Chest discomfort, hard breathing, rapid heart rate. After steroid administration-hypotension
22.12.83	2792X358AB 2792X371AA	Non-A, Non-B Hepatitis

REPORTS FROM EUROPE

16.8.84	Not Available	Non-A, Non-B Hepatitis
16.4.84	831108AH12A 830207A320A 830308AH11A	Anaphylactic reations occurred in two patients - however, all lots were used in other patients without adverse reactions being reported

In conclusion the reported rate of adverse reactions is low and the reactions noted have been confined to non-A, non-B hepatitis, which is a common condition in haemophilic patients on Factor VIII therapy, one case of hepatitis A (probably not product related) and three anaphylactic reactions. The latter cases involved lots of product used in other patients without complaint and the reaction is probably patient specific.

The adverse reactions reported are characteristic of those found when using coagulation factors prepared from human plasma.

APPENDIX I

APPENDIX I

HALF-LIFE AND PERCENT RECOVERY -

CLINICAL REPORT (DR. BLATT, NORTH CAROLINA, U.S.A.)

Antihemophilic Factor (Human), Method Four,
Heat Treated

Half-life and Percent Recovery
Clinical Report

The following is a summary of the half-life and recovery data for Anti-hemophilic Factor (Human), Method Four, Heat Treated (Hemofil-T) from Dr. Philip Blatt of the University of North Carolina. Six (6) patients were involved, each of whom were infused with both Antihemophilic Factor (Human), Method Four, Heat Treated and identical material nonheated (Hemofil), as a control. A nominal dosage of 50 u/kg was employed. (Actually, the average dosages for the two products were 54.4 u/kg and 47.9 u/kg for Hemofil and Hemofil-T respectively). The detailed analyses are attached.

I. Half-life

	Half-life (hrs.)	
Patient	Hemofil-T	Hemofil
JHM	8.3	12.6*
JMS	8.5	6.6
ELB	7.0	8.8
GDM	8.1	7.8
RWL	7.2	8.2
CWC	8.3	7.6
Average	7.9	8.6
Median	8.2	8.0

*There is reason to suspect this result given the recovery curve and the half-lives for the other infusions.

A statistical comparison of the results (using a nonparametric procedure known as the sign test because of the small sample size and uncertainty surrounding the distribution of half-lives) indicated a nonsignificant difference in the average or median half-lives for the two products ($p = 1.0000$).

II. Recovery (maximum % of normal over the post-infusion period)

	Recovery (%)	
Patient	Hemofil-T	Hemofil
JHM	53%	88%
JMS	92%	114%
ELB	75%	81%
GDM	77%	87%
RWL	127%	107%
CWC	60%	80%
Average	80.7%	92.8%
Median	76%	87.5%

A statistical comparison of the results (again using the sign test) indicated a nonsignificant difference in the average or median recoveries for the two products ($p = 0.2188$).

In summary, there is no evidence to suggest that the two products differ with respect to half-life or recovery. (We should note, though, that the small sample size precludes the possibility of making a much stronger statement about the nonsignificant differences).

dc

Attachments

HEMOFIL®-T TRIAL

JHM
3450 u (50.7 u/kg)
HEMOFIL

For this set of data, 2 periods appear to be evident so we employ a 2-period changeover model.

Estimated change-over point is ~ 1 hr.

(1) Equation for 1st hr:

(x) time (hr)	(y) recovery (%)
.25	88
1	71

$$\frac{y-88}{x-.25} = \frac{71-88}{1-.25} = -22.\bar{6}$$

$$y = 93.7-22.7x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)
1	71
3	61
6	55
9	50
12	36

a = 72.4289
b = -2.8756
r = -.981 (p<.0025)

$$y = 72.4289-2.8756x$$

$$\text{half-life} = \frac{-a}{2b} = 12.6 \text{ hr.}$$

Aside:
Check on change-over point

$$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 1.1 \text{ hr.}$$

(reasonably close to 1 hr.)

JHM
3030 u (44.6 u/kg)
HEMOFIL®-T

For this set of data, there are two periods. However, there appears to be an increase in activity in the first hour, which is an anomaly. For purposes of analysis, a two-period changeover model will be used.

Estimated change-over point ~ 1 hr.

(1) Equation for 1st hr:

(x) time (hr)	(y) recovery (%)
.25	49
1	53

$$\frac{y-49}{x-.25} = \frac{53-49}{1-.25} = 5.3$$

$$y = 47.7 + 5.3x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)
1	53
3	39
6	34
9	21
12	16

a = 52.71066
b = -3.24365
r = -.977 (p<.0025)

$$y = 52.71066 - 3.24365x$$

$$\text{half-life} = \frac{-a}{2b} = 8.1 \text{ hr.} \longrightarrow$$

Aside:
Check on change-over point

$$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 0.6 \text{ hr.}$$

The revised change-over point suggests that perhaps there is only 1 period here and all data should be included (actually the value for 15 minutes is abnormally low, but we have no way of correcting for this).

(3) Equation for 15 minutes and beyond.

$$a = 51.5359$$

$$b = -3.11089$$

$$r = -.979 \ (p<.0025)$$

$$y = 51.5359-3.11089x$$

$$\text{half-life} = \frac{-a}{2b} = 8.3 \text{ hr.}$$

So the half-life has not been altered considerably by the change to a one-phase model.

JMS
4600 u (53.8 u/kg)
HEMOFIL®

For this set of data, the recovery results at 15 minutes and 1 hour do not fit in with the remainder of the points. The slow fall-off period begins with the 3 hour result and the corresponding regression line is estimated from these data. The points at 15 minutes and 1 hour are discarded.

(1) Equation for 3rd hr. and beyond.

(x) time (hr)	(y) recovery (%)
3	48
6	27
9	17
12	8

$a = 57.5$

$b = -4.\overline{3}$

$r = -.977$ $(p<.025)$

$y = 57.5-4.3x$

half-life $= \frac{-a}{2b} = 6.6$ hr.

JMS
4040 u (47.5 u/kg)
HEMOFIL®-T

For this set of data, the two phase model appears to be suitable.

Estimated change-over point = 1 hr.

(1) Equation for 1st hr.

x time (hr)	y recovery (%)
.25	92
1	79

$$\frac{y-92}{x-.25} = \frac{79-92}{1-.25} = -17.\bar{3}$$

$$y = 96.\bar{3}-17.\bar{3}x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)
1	79
3	73
6	63
9	32
12	28

a = 86.86548
b = -5.13959
r = -.968 (p<.005)

$$y = 86.86548-5.13959x$$

$$\text{half-life} = \frac{-a}{2b} = 8.5 \text{ hr.}$$

Aside:
Check on change-over point

$$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 0.78 \text{ hr.}$$

(reasonably close to 1 hr.)

ELB
2300 units (60.2 u/kg)
HEMOFIL®

For this set of data, the two phase model appears to be suitable.

Estimated change-over point = 1 hr.

(1) Equation for 1st hr.

x time (hr)	y recovery (%)
.25	81
1	65

$$\frac{y-81}{x-.25} = \frac{65-81}{1-.25} = -21.\bar{3}$$

$$y = 86.\bar{3}-21.\bar{3}x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)
1	65
3	63
6	45
9	35
12	23

a = 71.15736
b = -4.02538
r = -.991 (p<.0025)

$$y = 71.15736-4.02538x$$

$$\text{half-life} = \frac{-a}{2b} = 8.8 \text{ hr.}$$

Aside:
Check on change-over point

$$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 0.88 \text{ hr.}$$

(reasonably close to 1 hr.)

ELB
2020 units (52.9 u/kg)
HEMOFIL®-T

For this set of data, the two phase model appears to be suitable.

Estimated change-over point = 1 hr.

(1) Equation for 1st hr.

x time (hr)	y recovery (%)
.25	75
1	53

$$\frac{y-75}{x-.25} = \frac{53-75}{1-.25} = -24$$

$$y = 81-24x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)
1	53
3	47
6	38
9	16
12	10

a = 58.82741
b = -4.19797
r = -0.982 (p<.0025)

$$y = 58.82741-4.19797x$$

$$\text{half-life} = \frac{-a}{2b} = 7.0 \text{ hr.}$$

Aside:
Check on change-over point

$$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 1.1 \text{ hr.}$$

(reasonably close to 1 hr.)

GDM
3450 units (55.6 u/kg)
HEMOFIL®

For this set of data, because of the anomalous agreement in results for 15 minutes and 1 hour, only one period is considered (≥ 1 hr). (Note that the value for 12 hr. is probably too high, but it is more difficult to determine a course of action for that point; therefore, it is left alone).

(1) Equation for beyond 1st hr.

x time (hr)	y recovery (%)
1	87
3	60
6	41
9	29
12	28

a = 81.1802
b = -5.19036
r = -0.927 ($p<.025$)

$$y = 81.1802 - 5.19036x$$

$$\text{half-life} = \frac{-a}{2b} = 7.8 \text{ hr.}$$

GDM
3030 units (48.9 u/kg)
HEMOFIL®-T

For this set of data there appears to be only one phase. Therefore, all data are combined for the analysis.

(1) Equation for 15 min. and beyond.

x time (hr)	y recovery (%)
.25	77
1	67
3	48
6	36
9	33
12	22

a = 69.61104

b = -4.30932

r = -0.947 ($p<.0025$)

$$y = 69.61104 - 4.30932x$$

$$\text{half-life} = \frac{-a}{2b} = 8.1 \text{ hr.}$$

RWL
4600 units (52.3 u/kg)
HEMOFIL®

For this set of data, the two phase model appears to be suitable.

Estimated change-over point = 1 hr.

(1) Equation for 1st hr.

x time (hr)	y recovery (%)
.25	107
1	83

$$\frac{y-107}{x-.25} = \frac{83-107}{1-.25} = -32$$

$$y = 115-32x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)
1	83
3	63
6	51
9	32
12	27

a = 82.45178
b = -5.04061
r = -0.975 (p<.0025)

$$y = 82.4517-5.04061x$$

$$\text{half-life} = \frac{-a}{2b} = 8.2 \text{ hr.}$$

Aside:
Check on change-over point

$$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 1.2 \text{ hr.}$$

(reasonably close to 1 hr.)

RWL
4040 units (45.9 u/kg)
HEMOFIL®-T

For this set of data, there are two periods. However, there is an anomalous increase in recovery values for the first hour. If we look at the data for 3 hours and beyond, the slow fall-off is evident. Therefore, only those data are considered.

(1) Equation for 3 hr. and beyond.

x time (hr	y recovery (%)
3	64
6	52
9	27
12	15

$a = 82.5$

$b = -5.7\bar{3}$

$r = -0.989$ ($p<.01$)

$$y = 82.5 - 5.7\bar{3}x$$

$$\text{half-life} = \frac{-a}{2b} = 7.2 \text{ hr.}$$

CWC
4600 units (53.8 u/kg)
HEMOFIL®

For this set of data, the rapid initial fall-off is not very noticeable. Therefore, all data are combined for the analysis.

(1) Equation for 15 min. and beyond.

x time (hr)	y recovery (%)
.25	80
1	69
3	49
6	41
9	36
12	15

a = 73.55295
b = -4.84217
r = -0.961 (p<.0025)

$$y = 73.55295 - 4.84217x$$

$$\text{half-life} = \frac{-a}{2b} = 7.6 \text{ hr.}$$

CWC
4040 units (47.5 u/kg)
HEMOFIL®-T

For this set of data, the rapid initial fall-off is not very noticeable. Therefore, all data are considered for the analysis.

(1) Equation for 15 min. and beyond.

x time (hr)	y recovery (%)
.25	60
1	58
3	41
6	30
9	26
12	20

a = 57.15062

b = -3.45292

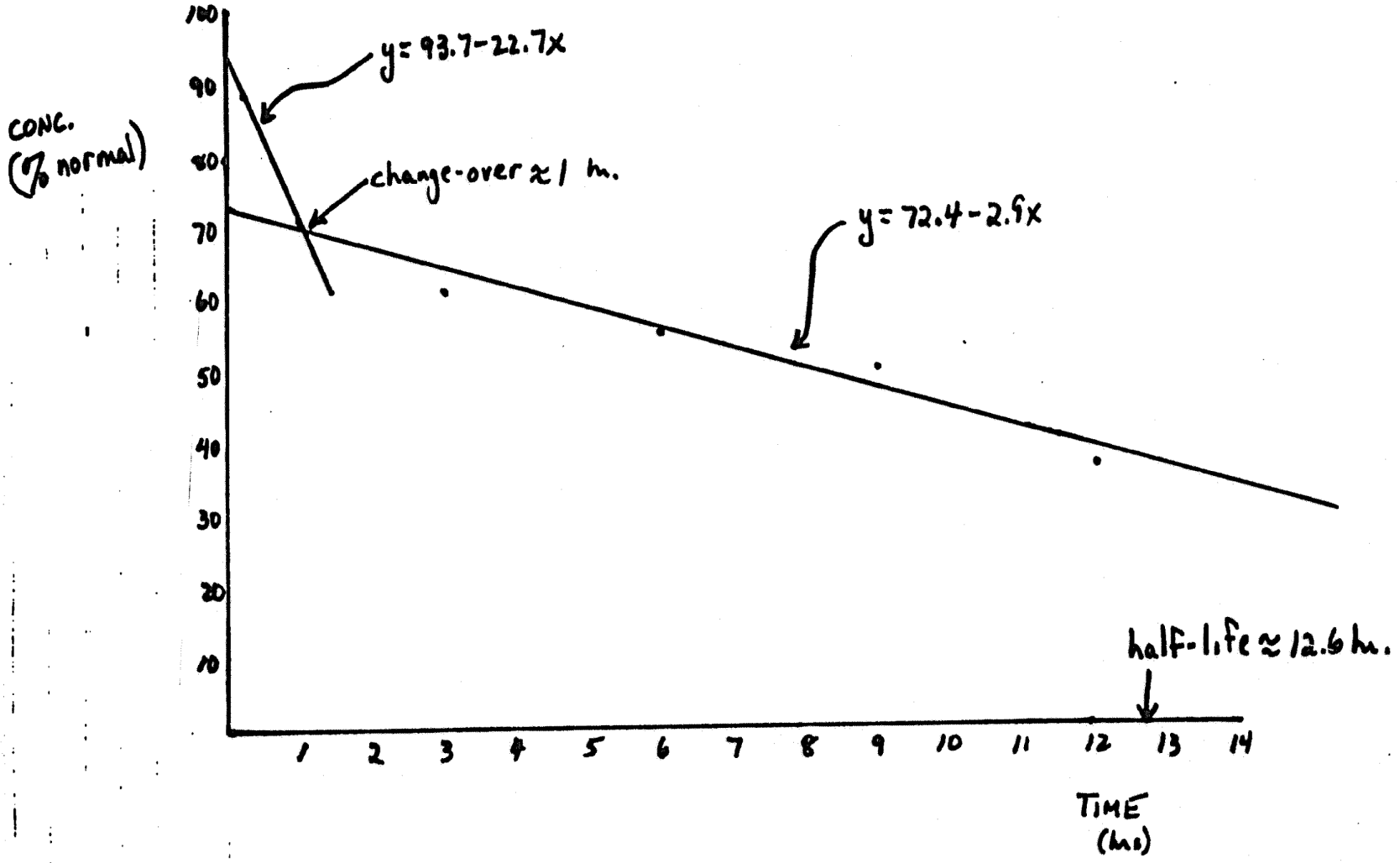
r = -0.955 ($p<.0025$)

$$y = 57.15062 - 3.45292x$$

$$\text{half-life} = \frac{-a}{2b} = 8.3 \text{ hr.}$$

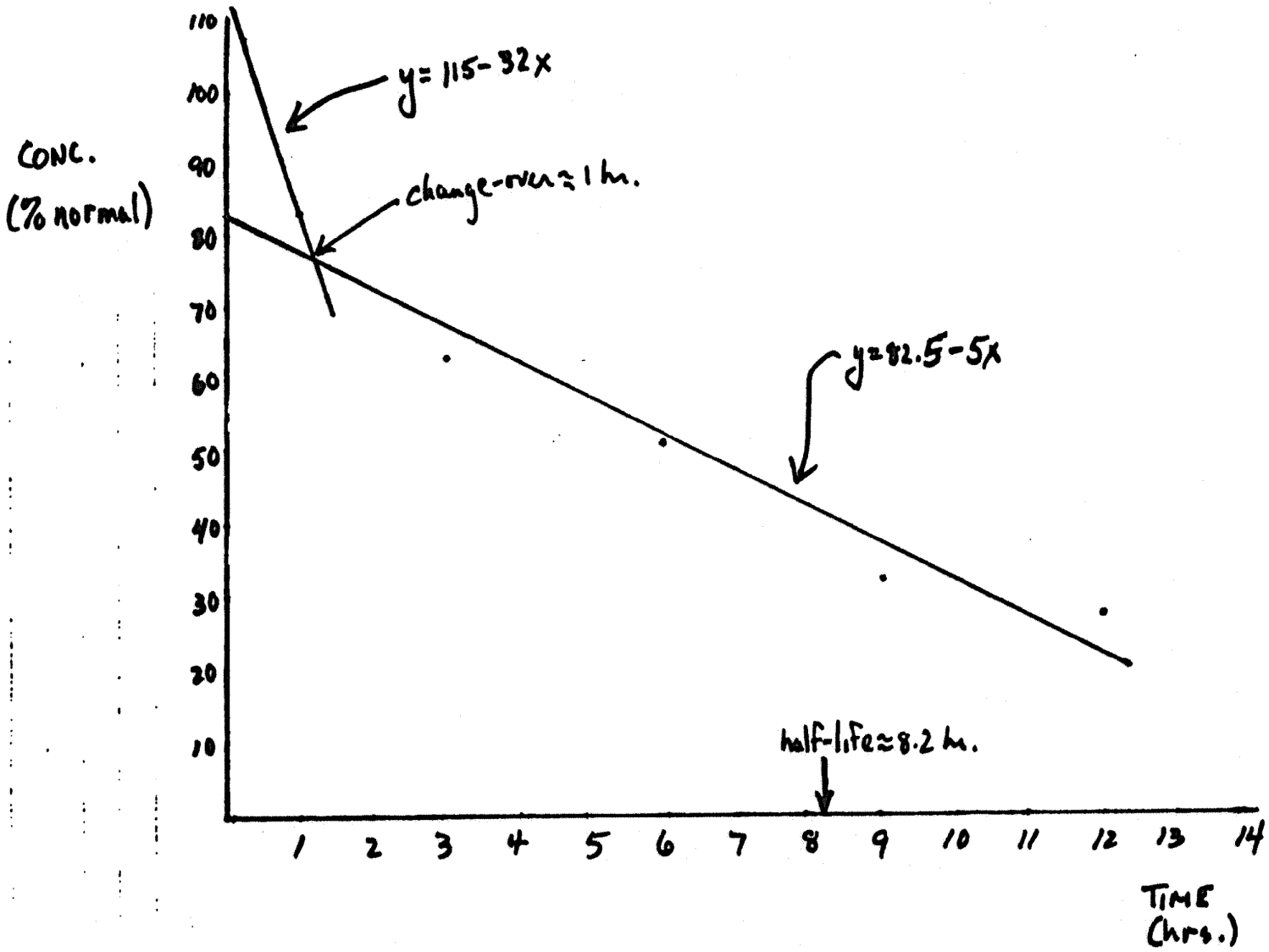
JHM , 3450 units (50.7 u/kg) , Hemofil®

3/30/82



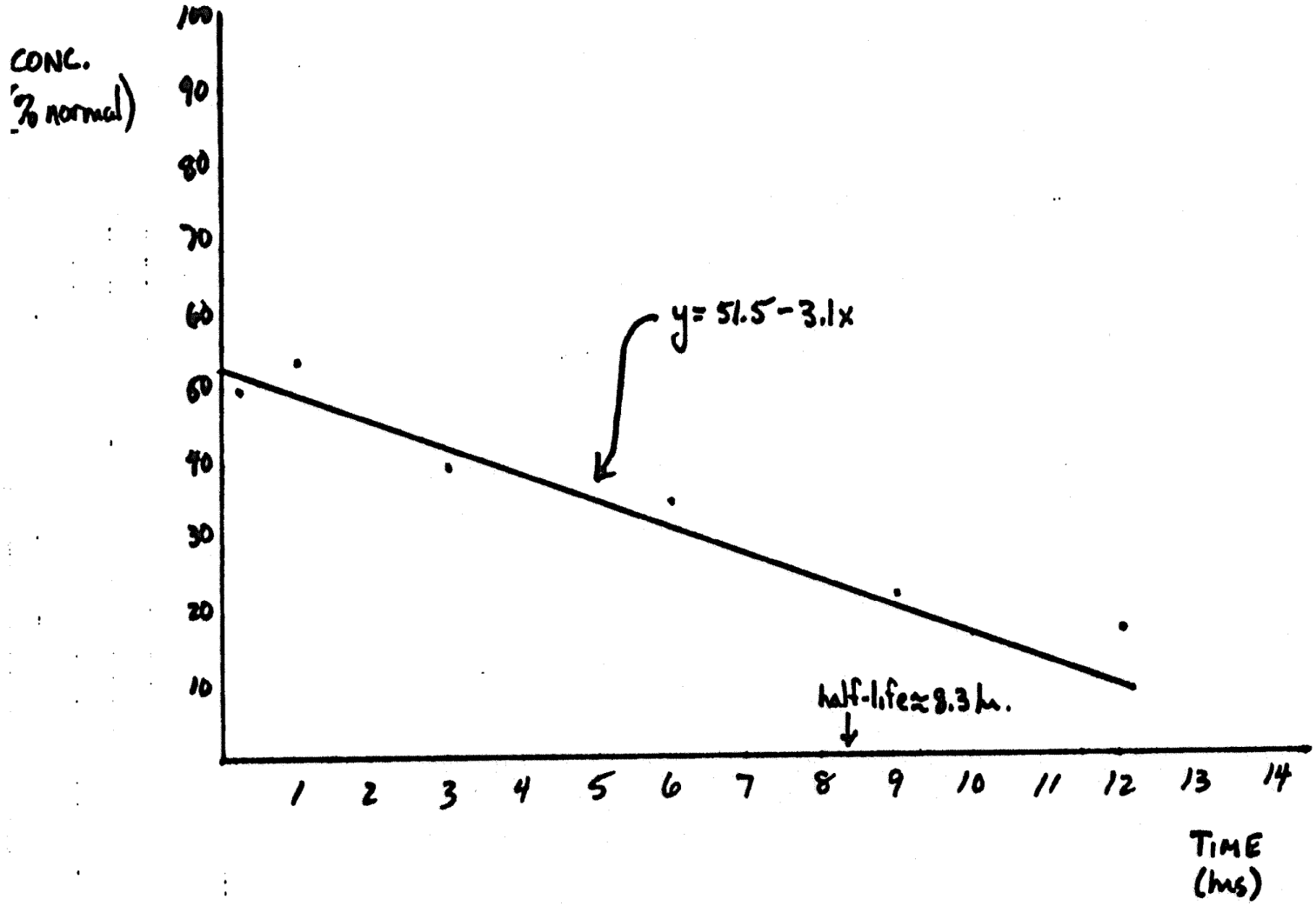
RWL, 4600 units (52.3 u/kg), Hemofil®

4/20/82



JHM, 3030 units (44.6 u/kg), Hemofil®-T

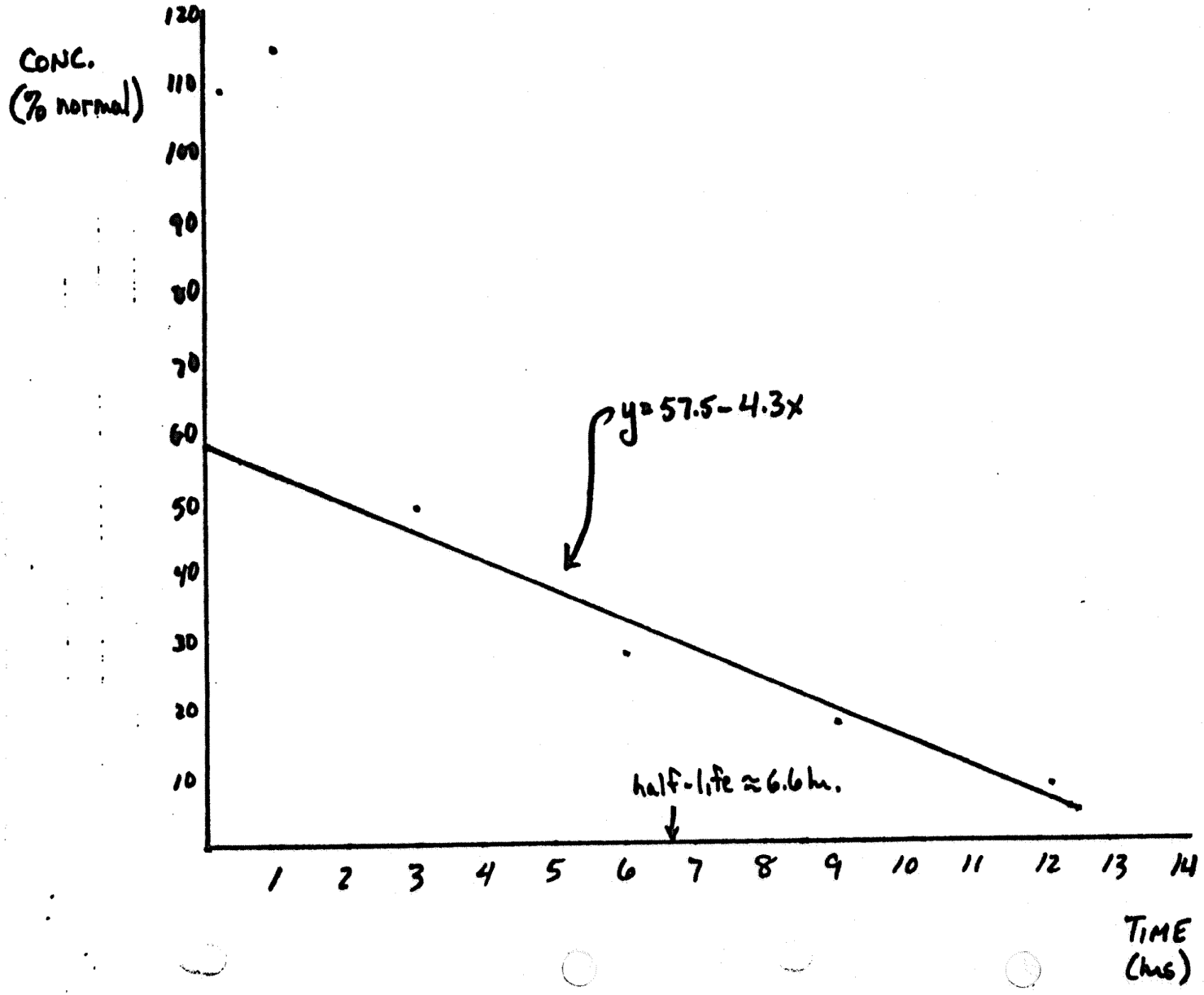
4/20/82



330

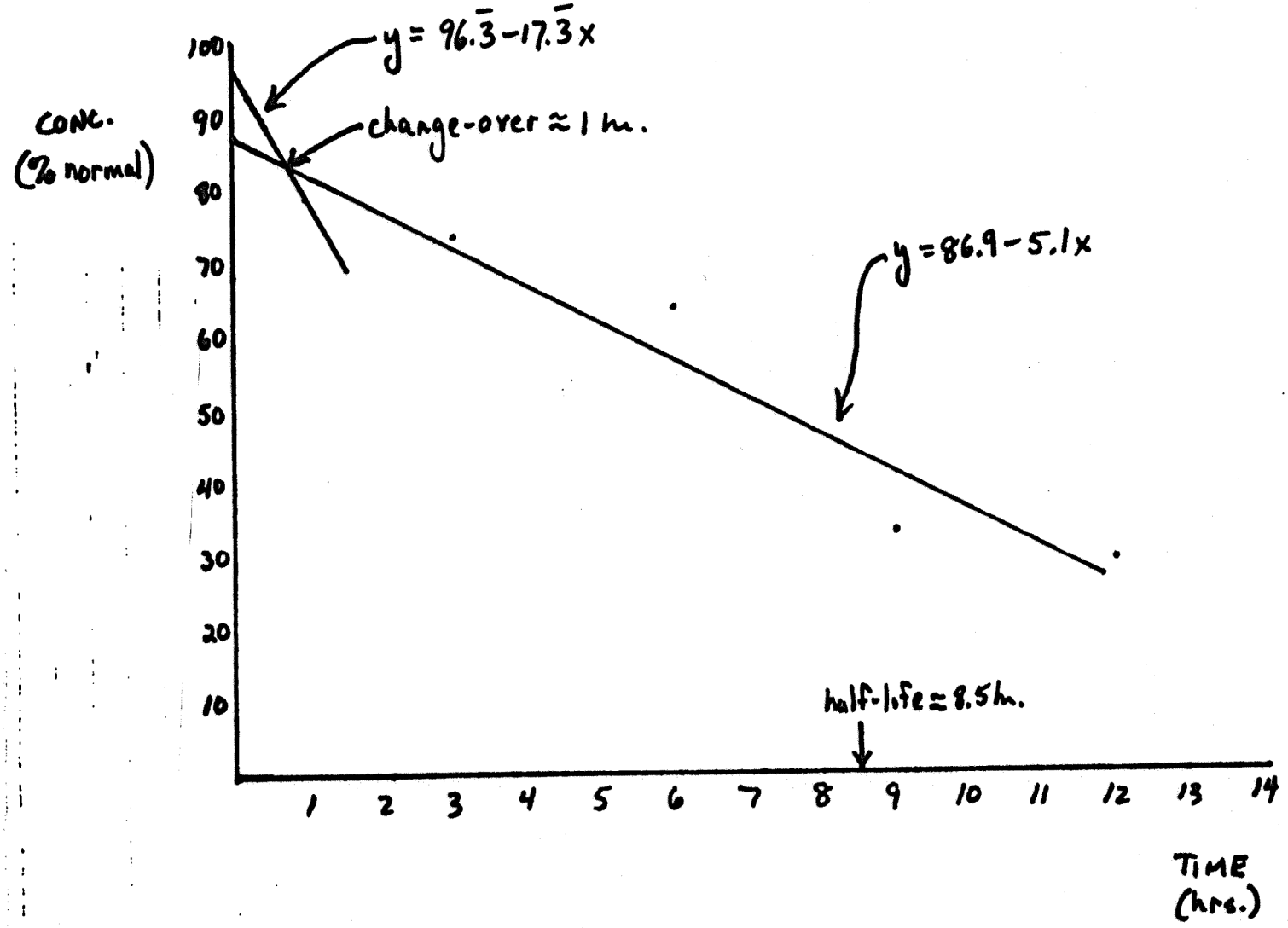
JMS, 4600 units (53.8 u/kg), Hemofil®

3/26/82



JMS, 4040 units (47.5 u/kg), Hemofil®-T

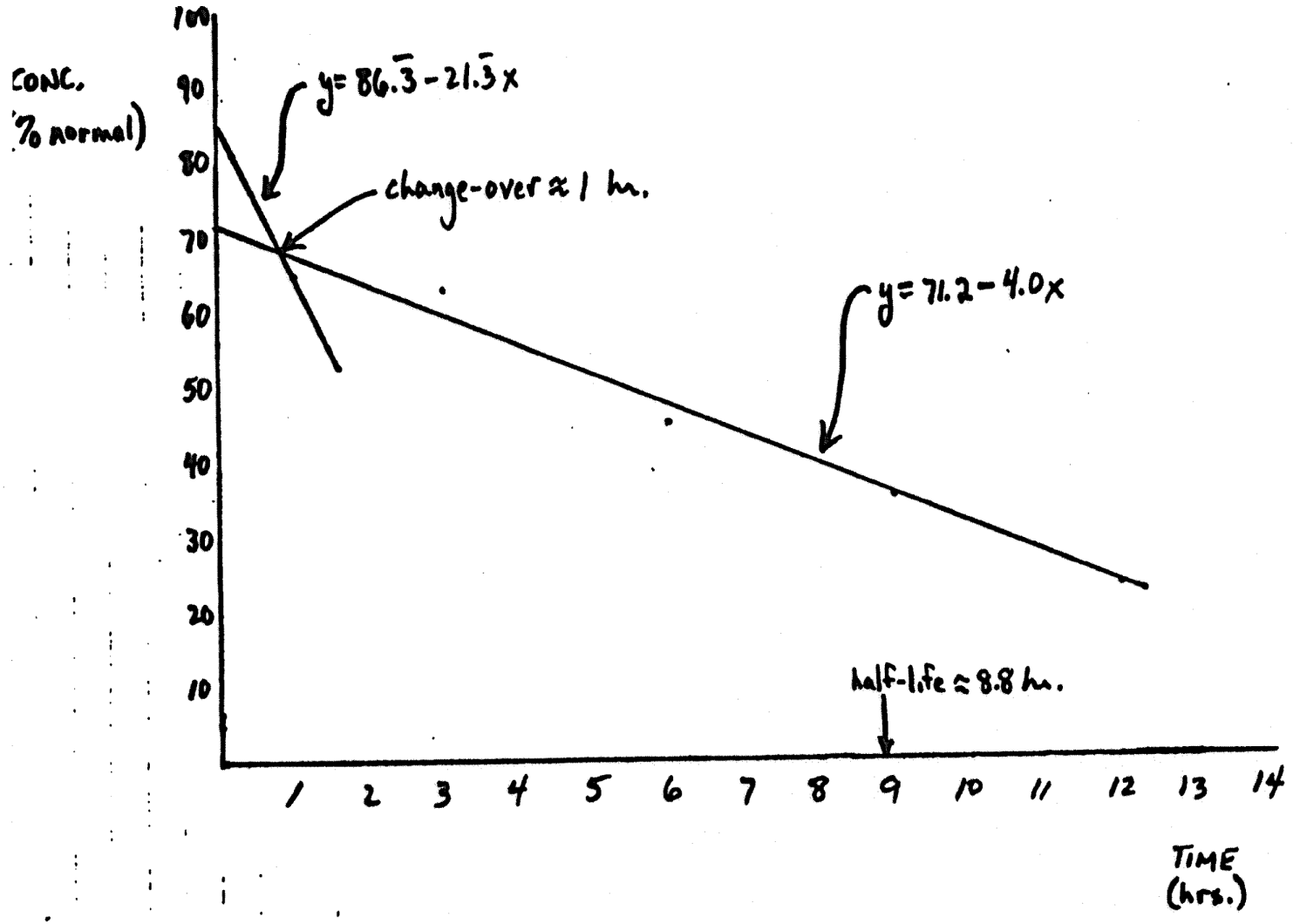
3/16/82



32

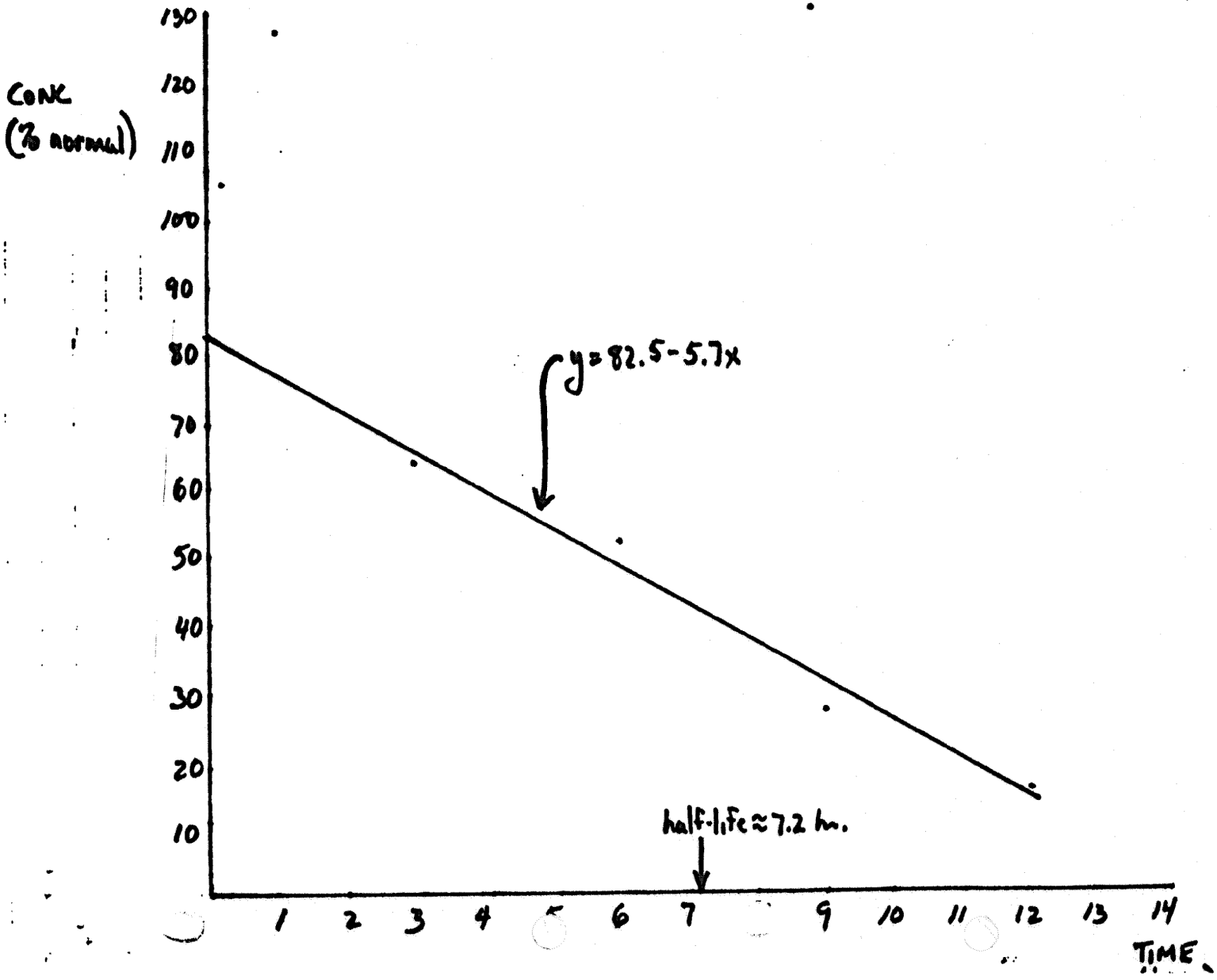
ELB, 2300 units (60.2 u/kg), Hemofil®

4/13/82



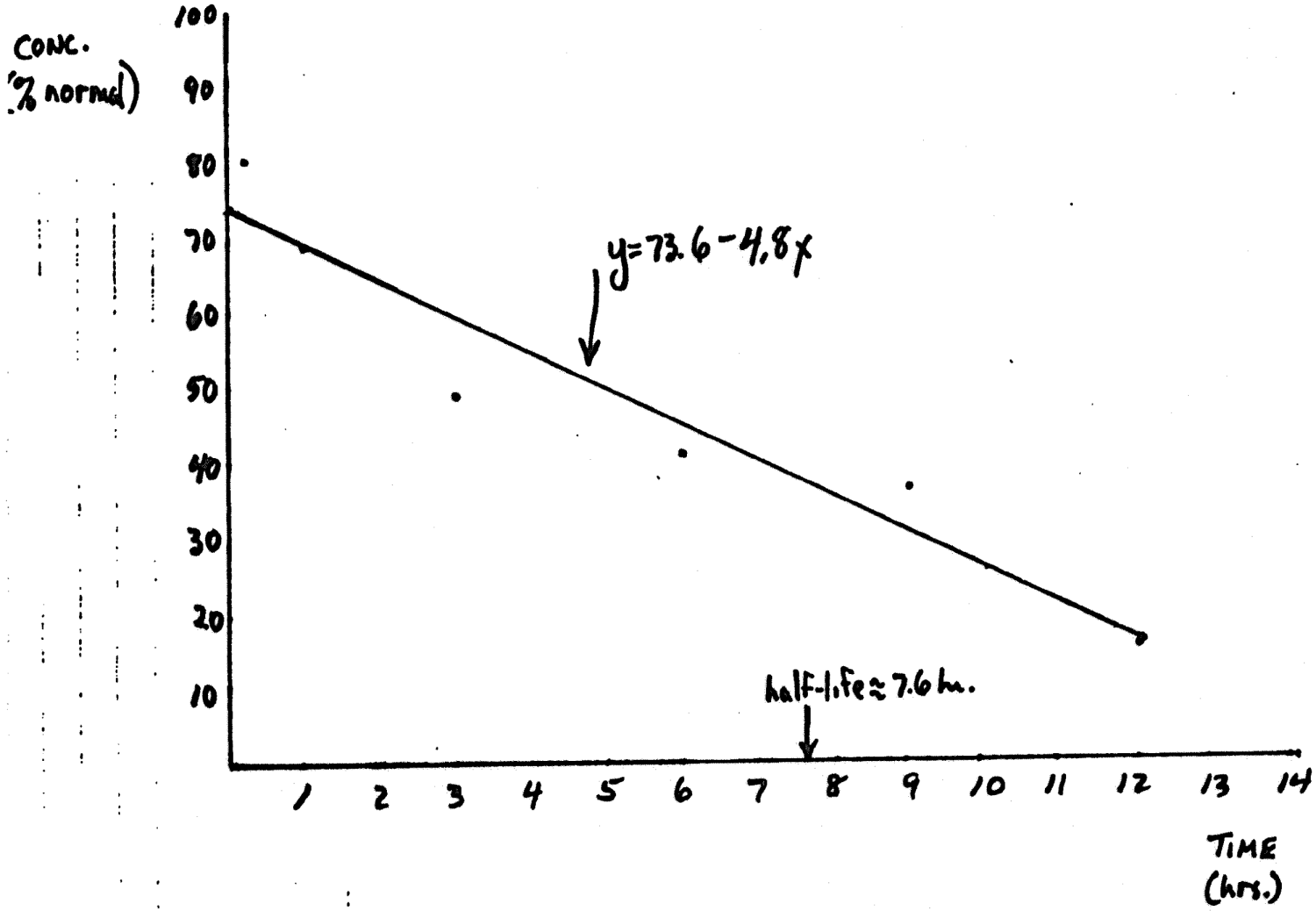
RWL, 4040 units (45.9 u/kg), Hemofil®-T

3/29/82



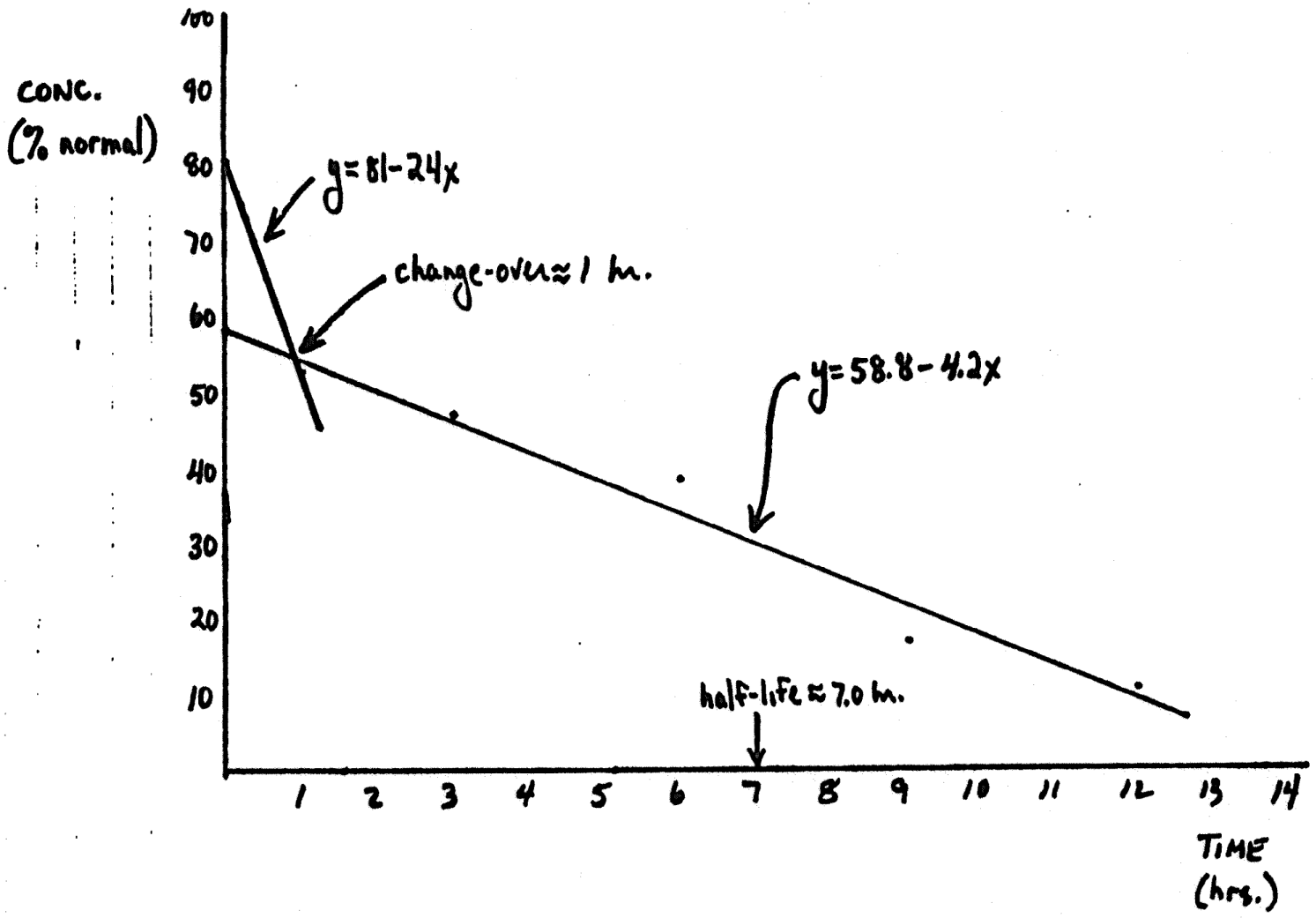
CWC, 4600 units (53.8 u/kg), Hemofil®

3/18/82



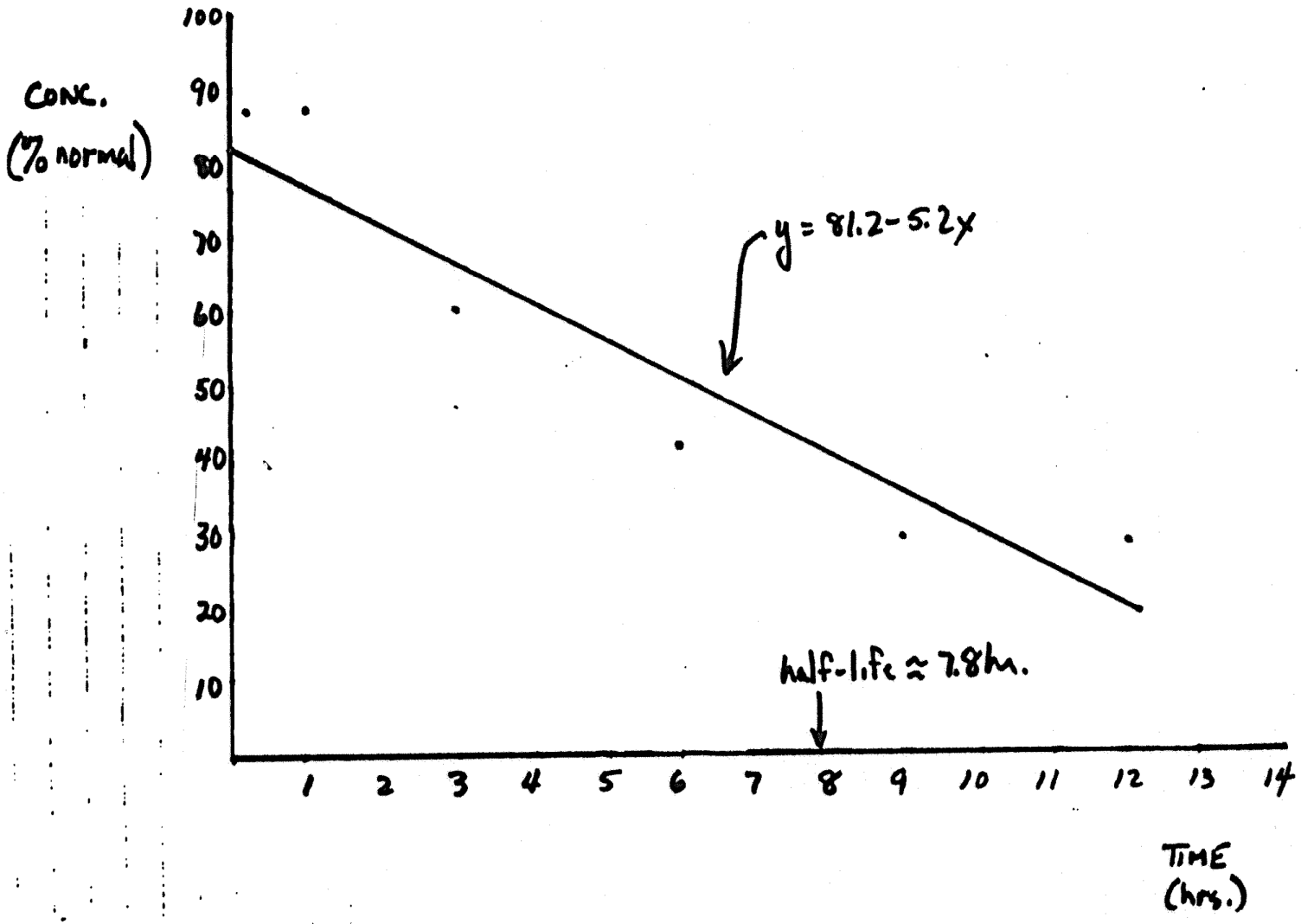
ELB, 2020 units (52.9 u/kg), Hemofil®-T

3/18/82



GDM, 3450 units (55.6 u/kg), Hemofil®

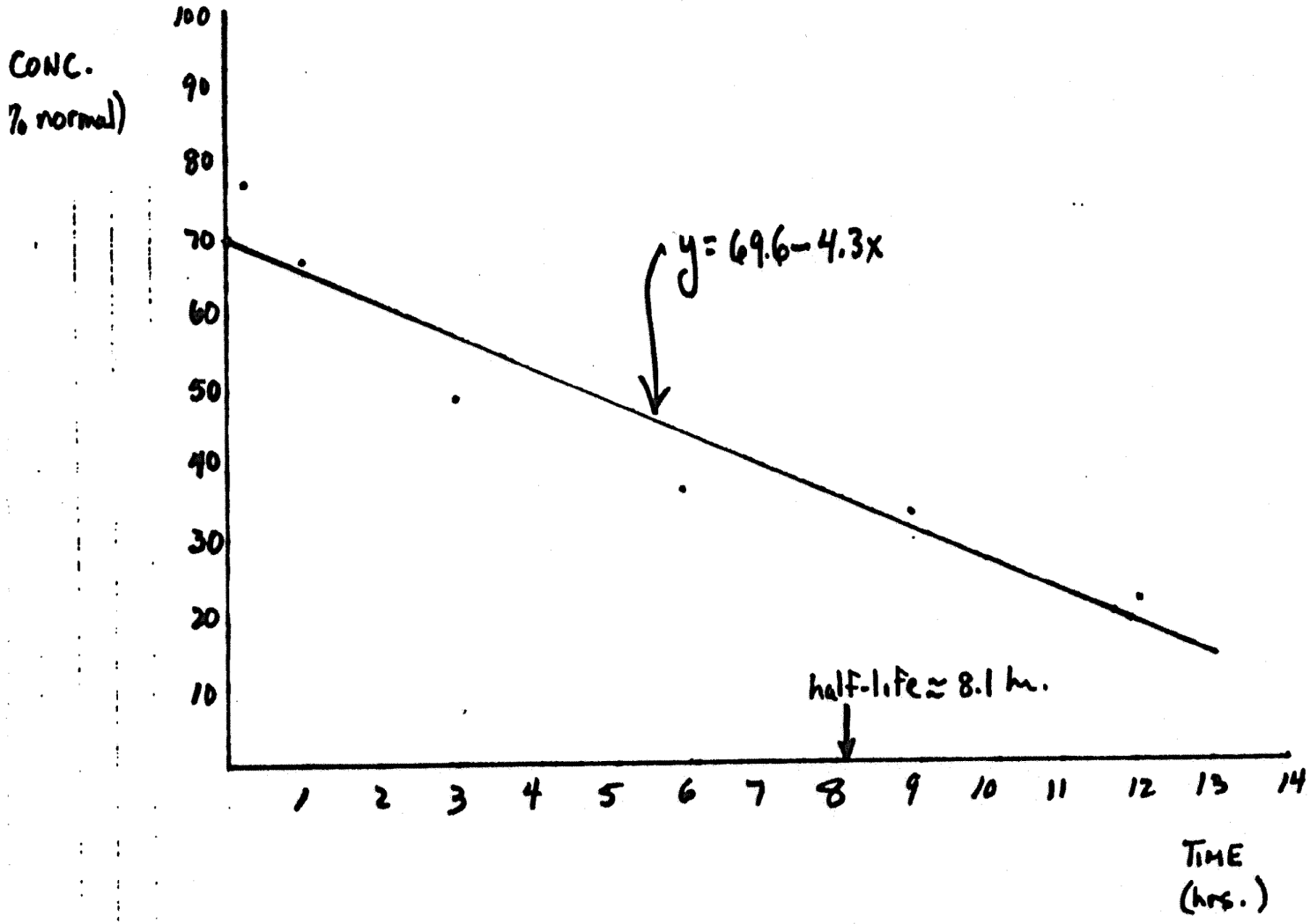
4/20/82



37

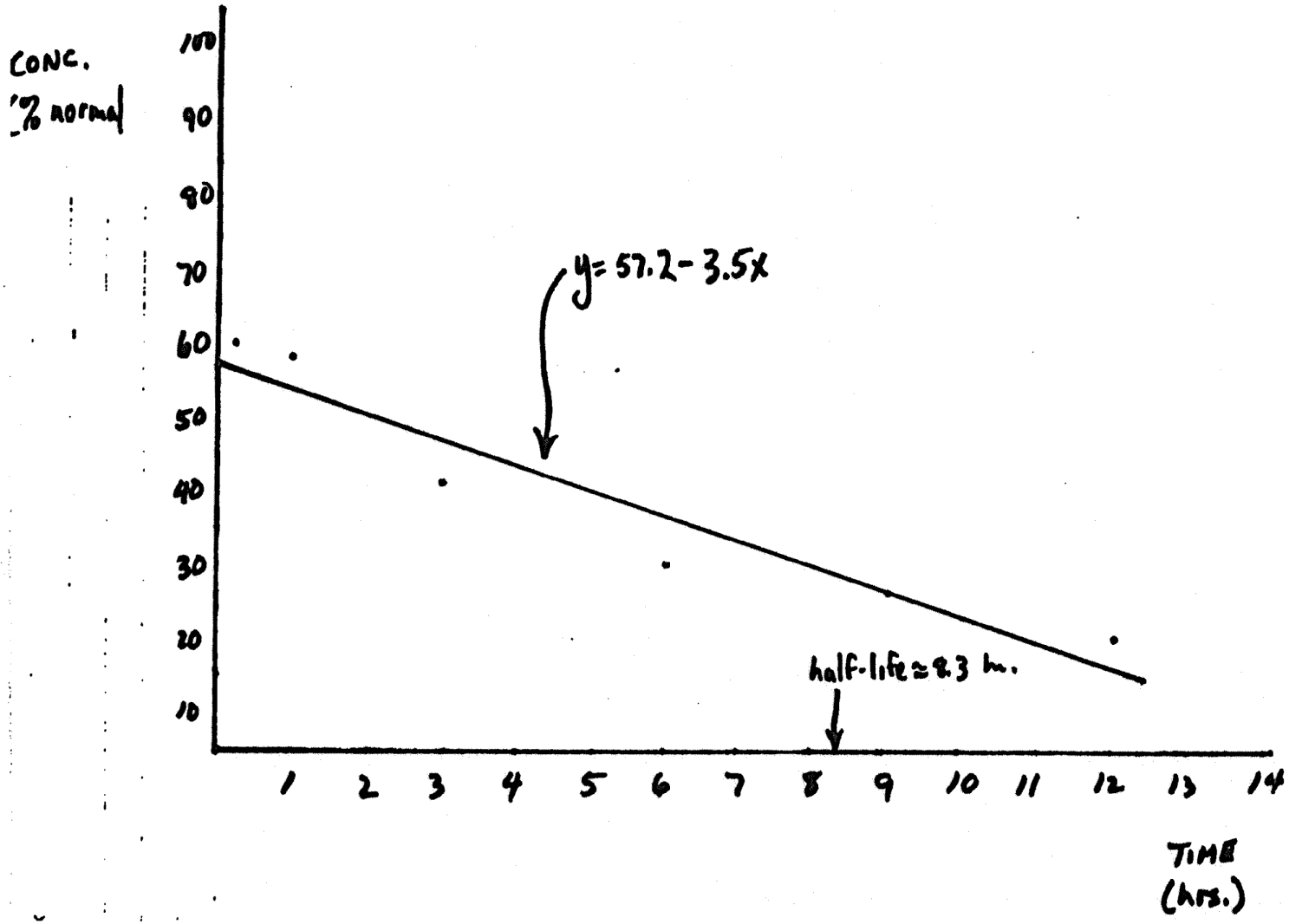
GDM, 3030 units (48.9 u/kg), Hemofil®-T

3/30/82



CWC, 4040 units (47.5 u/kg), Hemofil®-T

4/13/82



APPENDIX II

APPENDIX II

HALF-LIFE AND PERCENT RECOVERY -

CLINICAL REPORT (DR. ALLAIN, PARIS, FRANCE)

TO WHOM IT MAY CONCERN

Summary

A clinical and biological evaluation of Factor VIII concentrate lot n° 800401 AH 11B was done. This lot was divided in two parts. Part 1 (NT) was infused first and part 2 (T) was infused second in each of the 6 patients involved in the study. The clinical tolerance of both parts was excellent and none of the patient suffered any side reaction. The clinical efficacy for 3 hemarthroses and 3 hematomas treated with NT, 4 hemarthroses and 2 hematomas treated with T was satisfactory.

In all cases, the peak of Factor VIII:C plasma level was obtained 60 min. post-infusion. The in-vivo recovery was 99 % of expected with NT and 95,5 % with T. This difference was not significant.

Calculated on 39 pairs of plasma samples collected at corresponding intervals, in the 6 patients, the mean FVIII:C plasma level obtained with NT was 0,269 u/ml and 0,223 u/ml with T. The correlation between these paired values was 0.976 and T levels were 17.1 % inferior to NT levels.

When calculated on samples collected beyond 1 hour post-infusion, the average FVIII:C half-life was 9 hours for NT and 8 h for T. Such results were not significantly different.

In addition, Factor VIII recoveries and half-lives were measured in two patients after the third infusion of the treated material. No change in either parameter was detected when compared to the first infusion of treated concentrate.

Paris, January 21, 1982

GRO-C

dr. Allain M.D.

PATIENTS

1 - GRO-A — 29,5 kg — Hematocrit 36-37 %
Bleeding site : right ankle
Doses 27 - 25 u/kg

2 - GRO-A — 27 kg — Hematocrit 41-39 %
Bleeding site : left elbow
Doses 29 - 27 u/kg

3 - GRO-A — 27,9 kg — Hematocrit 37-35 %
Bleeding site : NT right knee, T. left deltoid
Doses 28 - 26 u/kg

4 - GRO-A — 23,9 kg — Hematocrit 36-37 %
Bleeding site : NT right knee, T left deltoid
Doses 28 - 26 u/kg

5 - GRO-A — 28,5 kg — Hematocrit 36-34 %
Bleeding site : NT chest hematoma, T right elbow
Doses 27.8 - 35.6 u/kg

6 - GRO-A — 25,7 kg — Hematocrit 37-38 %
Bleeding site : NT soft tissue, T. right thigh
Doses 30.8 - 28.5 u/kg

IN VIVO RECOVERIES a = Not treated
b = Treated.
c = "

Factor VIII:C (u)

Patient	Before	15 min	30'	60'	4 h	12 h	24 h	48 h
1 a	- 0.01	0.19	0.265	0.51	0.345	0.195	0.047	0.026
b	- 0.01	0.155	0.29	0.45	0.255	0.135	0.035	0.011
2 a	- 0.01	0.21	0.30		0.43	0.25	0.046	0.02
b	- 0.01	0.175	0.255	0.46	0.25	0.145	0.03	- 0.01
c	- 0.01		0.32	0.535	0.35	0.185	0.061	0.04
3 a	- 0.01	0.195	0.29	0.57	0.46	0.31	0.102	0.042
b	- 0.01	0.15	0.27	0.53	0.37	0.225	0.08	0.03
4 a	- 0.01	0.27	0.355	0.665	0.57	0.305	0.102	0.056
b	- 0.01	0.225	0.315	0.60	0.39	0.25	0.08	0.035
c	- 0.01		0.27	0.615	0.34	0.215	0.096	0.047
a	- 0.01		0.32	0.55	0.37	0.225	0.067	0.037
b	- 0.01		0.28	0.515	0.31	0.19	0.046	
6 a	- 0.01	0.215	0.30	0.575	0.385	0.26	0.063	0.033
b	- 0.01	0.21	0.28	0.51	0.30	0.21	0.06	0.025

(6)

STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT.Nos.

Patient initials GRO-A Birthdate GRO-C 69 (mo d. yr) Weight 125.7

Hemophilia A diagnosed 1.79 (mo d. yr) Patient status X (Bleeding) ____ (Not bleeding)

Last previous AHF 9.22.81 12.21.81 (mo d. yr) Product used ____ (cryo ppt.) CNTS (Commercial conc.brand)

Last blood transfusion 9.22.81 (mo d. yr)

CLINICAL AND LABORATORY DATA

Lot number :

	NT	T	T	T
	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	10-1-81	1-7-82		
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion				
Platelets pre-infusion x 10^3 /mm^3	185/173	216/205		
Fibrinogen pre-infusion				
FSP pre-infusion				
Factor VIII antigen pre-infusion VIII: CAg				
Concentrate injected (UFVIII) dosage U/kg				
Factor VIII activity in vivo U/ml				
pre-infusion	-0.01	-0.01		
post-infusion 15'	0.215	0.21		
30'	0.30	0.29		
60'	0.575	0.51		
4 hrs	0.585	0.50		
12 hrs	0.26	0.21		
24 hrs	0.065	0.06		
48 hrs.	0.035	0.025		
* Plasma volume (ml) = 30 x kg body wt. x (100 - hematocrit) / 100	1295	1274		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theroretical peak of FVIII:c = amt.of FVIII: c injected plasma volume	0.61	0.57		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	94	89		
	**	**		***

* Ref.Allain, J.P.,Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

** 5x1.0ml serum pre infusion for Prof.Masson, store at 20°C

*** 5x1.0ml serum post-4h.infusion + 1 wk.for Masson

Date : 1.13.82 (M D Yr.)

J.P.Allain
Investigator

C.N.T.S.
Hospital

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	Infusion n°1					Infusion n°2					Infusion n°					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 hr	48 hr.	Pre-inf.	30 min	60 Min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	57					58																			
Fibrinogen																									
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	soft tissue		right thigh													
Pain	Before	yes: X	no:	yes:	no: X	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:		
	24hrs.after	yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:		
Bleeding -another site after 24 hours		yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:		
Circumferential measurement if relevant, before treat.		cm		29/34.5/39 cm			cm				cm				cm		
Circumferential measurement if relevant, after 24 hrs.		cm		29/34.5/39 cm			cm				cm				cm		
Other drugs used	no			no													
Other treatment	immobilization			immobilization													

Observations during infusion		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure	before	10	5	11	6						
	After 5'	9	5	10	5						
	end of infusion										

Adverse effects	yes	no	yes	no	yes	no	yes	no	yes	no
chills		X		X						
nausea		X		X						
back pain		X		X						
resp.distress		X		X						
urticaria		X		X						
itching		X		X						
other										

P. Gilmore
Investigator

CNTS
Hospital

Date 1 15 82
m. d y

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Page 2

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STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. 800401 19H 11A

(5)

Patient initials GRO-A Birthdate GRO-C 71 (mo d. yr) Weight 28.5

Hemophilia A diagnosed 73 (mo d. yr) Patient status X Bleeding ____ Not bleeding

Last previous AHF 11.15.81 (mo d. yr) Product used X cryo ppt. ____ Commercial conc.

Last transfusion 11.15.81 (mo d. yr)

CLINICAL AND LABORATORY DATA

	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	12-2-81	12-10-81	1-11-82	1-29-82
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+15'	+15'		
Platelets pre-infusion	171	165		
Fibrinogen pre-infusion	—	—		
FSP pre-infusion				
Factor VIII antigen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg				
Factor VIII activity in vivo U/ml				
pre-infusion	0.011	0.01		
15'	—	—		
30'	0.82	0.78		
60'	0.55	0.515		
4 hrs.	0.57	0.51		
12 hrs.	0.215	0.19		
24 hrs.	0.067	0.046		
48 hrs.	0.057	—		
* Plasma volume (ml) = 80 x kg body wt. x (100 - hematocrit) / 100	1436	1489		
Amt. of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theoretical peak of FVIII:c = amt. of FVIII: c injected/plasma volume	55	49		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	100	105		

* Ref. Allain, J.P., Verroust, F. and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

Date : 1.5.82 (M D Yr)

JP Allain
Investigator

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	Infusion n°1					Infusion n°2					Infusion n°3					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 Hr	48 Hr.	Pre-inf.	30 min	60 Min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	57					54																			
Fibrinogen	–					–																			
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	Right Pectoral		Right elbow		left forearm.		right elbow													
Pain Before	yes X	no	yes X	no	yes X	no	yes	no	yes	no										
Pain 24hrs.after	yes	no X	yes	no X	yes	no X	yes	no	yes	no										
Bleeding -another site after 24 hours	yes	no X	yes	no X	yes	no X	yes	no	yes	no										
Circumferential measurement if relevant, before treat.	cm		cm		cm		cm													
Circumferential measurement if relevant, after 24 hrs.	cm		cm		cm		cm													
Other drugs used																				
Other treatment			immobilisation																	
Observations during infusion	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic										
Blood Pressure before	11	6	10.5	5																
After 5'	11	5	11	5																
end of infusion																				
Adverse effects	yes	no	yes	no	yes	no	yes	no	yes	no										
chills		X		X		X		X												
nausea		X		X		X		X												
back pain		X		X		X		X												
resp.distress		X		X		X		X												
urticaria		X		X		X		X												
itching		X		X		X		X												
other																				

JP Allain
Investigator

CNTS
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Date 1.5.87
m. d y

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46

47

Yo.04.01 FH 11B

STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. _____ (4)

Patient initials GRO-A Birthdate GRO-C 70 (mo d. yr) Weight 23.8

Hemophilia A diagnosed 12 (mo d. yr) Patient status Y (Bleeding) _____ (Not bleeding)

Last previous AHF 9.24.81 (mo d. yr) Product used Y (cryo ppt.) _____ (Commercial conc.bra

Last transfusion 9.24.81 (mo d. yr)

CLINICAL AND LABORATORY DATA

	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	10.5.81	11.12.81	12.9.81	1.15.82
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+ 20'	+ 15'		
Platelets pre-infusion x 10^2	172	161		
Fibrinogen pre-infusion	-	-		
PSP pre-infusion				
Factor VIII antigen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	33.2	30.7		30.7
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01		- 0.01
15'	0.27	0.225		
30'	0.555	0.515		0.27
60'	0.665	0.60		0.615
4 hrs.	0.57	0.39		0.34
12 hrs.	0.305	0.25		0.215
24 hrs.	0.102	0.08		0.096
48 hrs.	0.056	0.035		0.047
* Plasma volume (ml) = 80 x kg body wt. x (100 - hematocrit) / 100	1221	1201		1161
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		730
Theoretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume	64.7	60.7		62.9
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	102	98		98

* Ref.Allain, J.P.,Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

Date : 1.5.82 (M D Yr)

JP Allain
Investigator

C or YS
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	Infusion n°1					Infusion n°2					Infusion n°3					Infusion n°4					Infusion n°5				
	Pre-inf	30 min.	60 min.	24 Hr.	48 Hr.	Pre-inf.	30 min.	60 Min.	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	36					37										35									
Fibrinogen	-					-																			
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	Right Deltoid		right knee		Right elbow		right elbow									
	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no
Pain Before	✓			✓												
Pain 24hrs.after		✓		✓												
Bleeding -another site after 24 hours		✓		✓												
Circumferential measurement if relevant, before treat.		cm	26	cm		cm		cm								
Circumferential measurement if relevant, after 24 hrs.		cm	25	cm		cm		cm								
Other drugs used	-		-													
Other treatment																

Observations during infusion		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure	before	10.5	5	11	6						
	After 5'	11	5	10.5	5						
	end of infusion										

Adverse effects	yes	no	yes	no	yes	no	yes	no	yes	no
chills		✗		✗		✗		✗		
nausea		✗		✗		✗		✗		
back pain		✗		✗		✗		✗		
resp.distress		✗		✗		✗		✗		
urticaria		✗		✗		✗		✗		
itching		✗		✗		✗		✗		
other										

dr Allatu
Investigator

CNTS
Hospital

Date 1.5.87
m. d y

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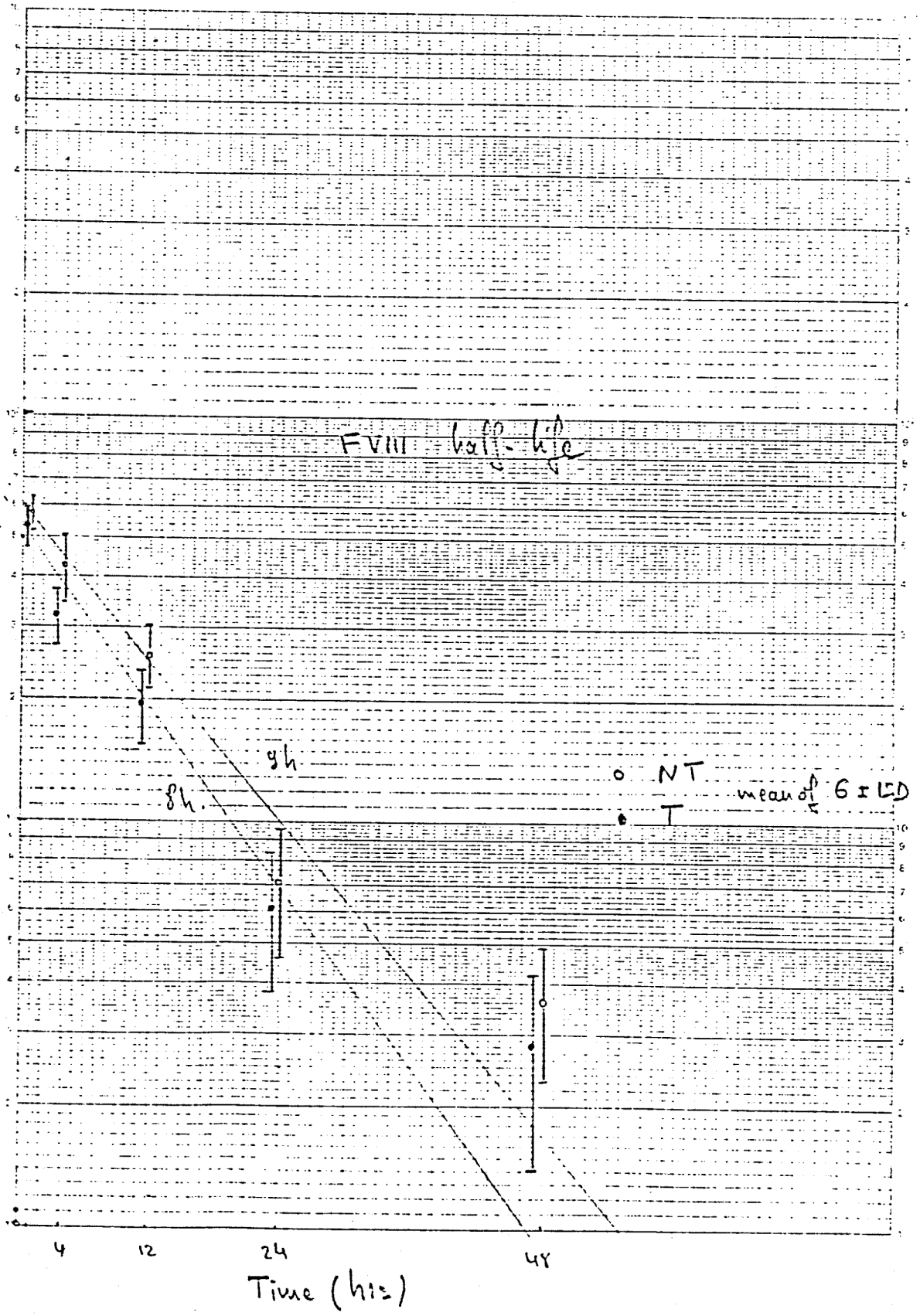
FVIII half-life
1
0.5
0.1
gh.
gh.
NT
mean of 6 x LD
T
4
12
24
48
Time (hrs)
FVIII:C plasma level (u/ml)

STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. _____

Patient initials GRO-A Birthdate GRO-C 71 (mo d. yr) Weight 27.9

Hemophilia A diagnosed 74 (mo d. yr)

Last previous AHF 10.1.81 (mo d. yr)

Last transfusion 10.1.81 (mo d. yr)

Patient status ✓ Bleeding ____ Not bleeding

Product used ✓ cryo ppt. ____ Commercial conc.bra

CLINICAL AND LABORATORY DATA

	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	10.13.81	10.25.81	12.27.81	
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+20'	+15'		
Platelets pre-infusion	261	280		
Fibrinogen pre-infusion	-	-		
FSP pre-infusion				
Factor VIII antigen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	28.5	26		
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01		
15'	0.195	0.15		
30'	0.19	0.27		
60'	0.57	0.53		
4 hrs.	0.46	0.37		
12 hrs.	0.21	0.225		
24 hrs.	0.102	0.08		
48 hrs.	0.042	0.03		
* Plasma volume (ml) = 80 x kg body wt. x (100 - hematocrit) / 100	1406	1451		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theoretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume	56	50.3		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	102	105		

* Ref.Allain, J.P.,Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

Date : 1.5.82 (M D Yr)

JP Allain
Investigator

C.N.T.S.
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	Infusion n°1					Infusion n°2					Infusion n°3					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 Hr	48 Hr.	Pre-inf.	30 min	Min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	4 hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	37					35																			
Fibrinogen	-					-																			
FSP																									

CLINICAL ASSESSMENT

Bleeding Site		Right Knee		left Deltoid		left forearm										
Pain	Before	yes: X	no:	yes: X	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:		
	24hrs.after	yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:		
Bleeding -another site after 24 hours		yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:		
Circumferential measurement if relevant, before treat.		28.5 cm		cm		cm		cm		cm		cm		cm			
Circumferential measurement if relevant, after 24 hrs.		28.5 cm		cm		cm		cm		cm		cm		cm			
Other drugs used																	
Other treatment				immobilisation													
Observations during infusion		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic		
Blood Pressure	before	11	6	10	5												
	After 5'	10.5	6	10	6												
	end of infusion																
Adverse effects		yes	no	yes	no	yes	no	yes	no	yes	no						
	chills		X		X		X										
	nausea		X		X		X										
	back pain		X		X		X										
	resp.distress		X		X		X										
	urticaria		X		X		X										
	itching		X		X		X										
	other																

SP Allain
Investigator

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Hospital

Date 1 5 87
m. d y

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42

STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. _____

Patient initials GRO-A Birthdate GRO-C 79 (mo d. yr) Weight 2.7

Hemophilia A diagnosed 1 1 72 (mo d. yr) Patient status Y (Bleeding) _____ (Not bleeding)

Last previous AHF 9.10.81 (mo d. yr) Product used Y (cryo ppt.) _____ (Commercial conc.)

Last transfusion 9.10.81 (mo d. yr)

CLINICAL AND LABORATORY DATA

	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	9.28.81	10.19.81	11.16.81	12.4.81
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+15'	+10'		
Platelets pre-infusion x 10^3	250	257		
Fibrinogen pre-infusion	3.2	3		
FSP pre-infusion				
Factor VIII anticen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	29.2	27		27
Factor VIII activity in vivo U/ml				
pre-infusion	-0.01	-0.01		-0.01
15'	0.21	0.175		
30'	0.295	0.255		0.32
60'	—	0.46		0.538
4 hrs.	0.43	0.25		0.35
12 hrs.	0.25	0.145		0.185
24 hrs.	0.046	0.03		0.061
48 hrs.	0.02	-0.01		0.04
* Plasma volume (ml) = 80 x kg body wt. x (100 - hematocrit) / 100	1274	1517		1296
Amt. of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		730
Theoretical peak of FVIII:C = amt. of FVIII: c injected/plasma volume	62	55.4		56.3
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	—	83		95

* Ref. Allain, J.P., Verroust, F. and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

Date : 1.5.82 (M D Yr)

JP Allain
Investigator

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Hospital

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	Infusion n°1					Infusion n°2					Infusion n°3					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 Hr	48 Hr.	Pre-inf.	30 min.	60 Min.	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	4 hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	41					39										40									
Fibrinogen g/l	3.2					3.																			
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	left elbow				left elbow								left elbow							
Pain — Before	yes: X	no:	yes: X	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:				
Pain — 24hrs.after	yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:	yes:	no:				
Bleeding -another site after 24 hours	no: X		no: X																	
Circumferential measurement if relevant, before treat.	20.5 cm		20 cm		cm		cm		cm											
Circumferential measurement if relevant, after 24 hrs.	20.5 cm		20 cm		cm		cm		cm											
Other drugs used	—		—																	
Other treatment	immobilisation		immobilisation																	
Observations during infusion	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic				
Blood Pressure — before	11.5	6	10	5																
Blood Pressure — After 5'	10	5	9	5																
Blood Pressure — end of infusion																				
Adverse effects	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no				
chills		X		X						X										
nausea		X		X						X										
back pain		X		X						X										
resp.distress		X		X						X										
urticaria		X		X						X										
itching		X		X						X										
other																				

Dr Allain
Investigator

C.N.T.S.
Hospital

Date 1.5.81
m. d y

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STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. _____

(54) 1

Patient initials GRO-A Birthdate | | | | Weight 29,5
mo d. yr

Hemophilia A diagnosed | | | | Patient status X
mo d. yr Bleeding Not bleeding

Last previous AHF 20,8,81 Product used X
mo d. yr cryo ppt. Commercial conc.br

Last transfusion 10,8,81
mo d. yr

CLINICAL AND LABORATORY DATA

	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	12-10-81	20-10-81	26-11-81	1-25-82
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+15 min	+15 min		
Platelets pre-infusion x 10^3	275	293		
Fibrinogen pre-infusion	2.9	2.8		
FSP pre-infusion				
Factor VIII antigen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	26.9	24.9		
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01		
15'	0.19	0.155		
30'	0.265	0.29		
60'	0.51	0.45		
4 hrs.	0.345	0.255		
12 hrs.	0.195	0.135		
24 hrs.	0.047	0.035		
48 hrs.	0.026	0.011		
* Plasma volume (ml) = 80 x kg body wt. x (100 - hematocrit) / 100	1500	1476		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theoretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume	52.7	49.5		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	90.7	91		

* Ref.Allain, J.P.,Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

Date : 1,5,82
M D Yr

J.P. Allain
Investigator

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	Infusion n°1					Infusion n°2					Infusion n°3					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 Hr	48 Hr.	Pre-inf.	30 min	60 Min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	36					37																			
Fibrinogen	2.9					2.8																			
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	Right ankle		Right ankle		right elbow		right elbow									
Pain Before	yes X	no	yes X	no	yes X	no	yes	no	yes	no	yes	no	yes	no	yes	no
24hrs.after		X		X		X										
Bleeding -another site after 24 hours		X		X		X										
Circumferential measurement if relevant, before treat.	21.5	cm	22.5	cm		cm		cm		cm						
Circumferential measurement if relevant, after 24 hrs.	20.5	cm	21	cm		cm		cm		cm						
Other drugs used	—		—													
Other treatment	—		—													

Observations during infusion												
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure before	10	6	12	8								
After 5'	10	6	12	7								
end of infusion												

Adverse effects												
	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no
chills		X		X		X		Y				
nausea		X		X		X		Y				
back pain		X		X		X		Y				
resp.distress		X		X		X		Y				
urticaria		X		X		X		Y				
itching		X		X		X		Y				
other		X		X								

JP Allain
Investigator

CNTS
Hospital

Date 1, 5, 82
m. d y

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Travenol International Services, Inc. [illegible]

	Infusion n°1					Infusion n°2					Infusion n°3					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 Hr	48 Hr.	Pre-inf.	30 min	60 Min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr
Hematocrit %	37					35																			
Fibrinogen	-					-																			
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	Right Knee		Left Deltoid		Left forearm		Left triceps									
Pain — Before	yes: X	no:	yes: X	no:	yes:	no:	yes:	no:	yes:	no:						
Pain — 24hrs.after	yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:						
Bleeding -another site after 24 hours	yes:	no: X	yes:	no: X	yes:	no:	yes:	no:	yes:	no:						
Circumferential measurement if relevant, before treat.	28.5 cm		cm		cm		cm		cm							
Circumferential measurement if relevant, after 24 hrs.	28.5 cm		cm		cm		cm		cm							
Other drugs used																
Other treatment			immobilisation													
Observations during infusion	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic						
Blood Pressure before	11	6	10	5												
After 5'	10.5	6	10	6												
end of infusion																

Adverse effects	yes	no	yes	no	yes	no	yes	no	yes	no		
chills		X		X		X		X				
nausea		X		X		X		X				
back pain		X		X		X		X				
resp.distress		X		X		X		X				
urticaria		X		X		X		X				
itching		X		X		X		X				
other												

SP Allain
Investigator

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Date 3 5 87
m. d y

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Page 2

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(3)

STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. _____

Patient initials GRO-A Birthdate GRO-C 71 (mo d. yr) Weight 2,7,9

Hemophilia A diagnosed 74 (mo d. yr) Patient status Bleeding / Not bleeding

Last previous AHF 10,1,81 (mo d. yr) Product used cryo ppt. / Commercial conc.br

Last transfusion 10,1,81 (mo d. yr)

CLINICAL AND LABORATORY DATA

	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	10-13-81	10-23-81	12-27-81	2-22-82
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+20'	+15'		
Platelets pre-infusion	261	280		
Fibrinogen pre-infusion	-	-		
FSP pre-infusion				
Factor VIII antigen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	28.3	26		
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01		
15'	0.195	0.15		
30'	0.19	0.27		
60'	0.57	0.53		
4 hrs.	0.46	0.37		
12 hrs.	0.21	0.225		
24 hrs.	0.102	0.07		
48 hrs.	0.042	0.03		
* Plasma volume (ml) = 80 x kg body wt. x (100 - hematocrit) / 100	1406	1451		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theoretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume	56	50.3		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	102	105		

* Ref.Allain, J.P.,Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)

Date : 1,5,82 (M D Yr)

JP Allain
Investigator

C.N.T.S.
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	Infusion n°1					Infusion n°2					Infusion n°					Infusion n°4					Infusion n°5				
	Pre-inf	30 min	60 min	24 Hr	48 Hr.	Pre-inf.	30 min	60 Min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	30 min	60 min	24 hr	48 hr	Pre-inf	min	60 min	24 hr	48 hr
Hematocrit %	37					36																			
Fibrinogen																									
FSP																									

CLINICAL ASSESSMENT

Bleeding Site	soft tissue				right thigh				right ankle				right quadriceps							
Pain	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no
Before	X			X																
24hrs.after		X		X																
Bleeding -another site after 24 hours		X		X																
Circumferential measurement if relevant, before treat.					29/34.5/39 cm								29.5/36/40 cm							
Circumferential measurement if relevant, after 24 hrs.					29/34.5/39 cm								27.5/36/39.5 cm							
Other drugs used	no				no															
Other treatment	immobilisation				immobilisation				immobilisation				immobilisation							
Observations during infusion	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure before	10	5	11	6																
After 5'	9	5	10	5																
end of infusion																				
Adverse effects	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no
chills		X		X		X														
nausea		X		X		X														
back pain		X		X		X														
resp.distress		X		X		X														
urticaria		X		X		X														
itching		X		X		X														
other																				

J P Athanasiou
Investigator

CNTS
Hospital

Date 3, 15, 82
m. d y

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STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT.Nos.

(6)

Patient initials GRO-A Birthdate GRO-C 69
mo d. yr

Weight 25.7

Hemophilia A diagnosed 1 1 70
mo d. yr

Patient status X Bleeding ____ Not bleeding

Last previous AHF 9.22.81 12.21.81
mo d. yr

Product used X cryo ppt. CNTS Commercial conc.brand

Last blood transfusion 9.22.81
mo d. yr

CLINICAL AND LABORATORY DATA

Lot number :

	NT	T	T	T
	INFUSION NUMBER			
	1	2	3	4
Date of Bleed	10-1-81	1-7-82	1-26-82	2-15-82
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion				
Platelets pre-infusion x 10^3 /mm^3	175/175	215/205		
Fibrinogen pre-infusion				
FSP pre-infusion				
Factor VIII antigen pre-infusion VIII: CAg				
Concentrate injected (UFVIII) dosage U/kg				
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01		
post-infusion 15'	0.215	0.21		
30'	0.30	0.29		
60'	0.575	0.51		
4 hrs	0.585	0.30		
12 hrs	0.26	0.21		
24 hrs	0.063	0.06		
48 hrs.	0.035	0.025		
* Plasma volume (ml) = 30 x kg body wt. x (100 - hematocrit) / 100	1295	1274		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theroretical peak of FVIII:c = amt.of FVIII: c injected plasma volume	0.61	0.57		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	94	89		
* Ref.Allain, J.P.,Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)				
	**	**		***

** 5x1.0ml serum pre infusion for Prof.Masson, store at 20°C

*** 5x1.0ml serum post-4h.infusion + 1 wk.for Masson

Date : 1.13.82
M D Yr.

J.P. Allain
Investigator

C.N.T.S.
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APPENDIX III

APPENDIX III

ASSAY OF CIRCULATING IMMUNE COMPLEXES IN HAEMOPHILIAC PATIENTS (PROF. MASSON, BRUSSELS, BELGIUM

The assay of circulating immune complexes in hemophilic patients

Samples

Two groups of serum samples were analyzed separately. The first one comprised 12 samples from 3 patients and, the second, 11 samples from 3 other patients.

Assay

The immune complex levels were determined by two tests based on inhibition of latex agglutination, using either rheumatoid factor (RF) or the so-called murine agglutinator (MAG) as agglutinating agents of the IgG-coated particles. The agglutination was measured in the PACIA system (Particle Counting ImmunoAssay) as described by Cambiaso et al. (J. Immunol. Methods, 23: 29, 1978 and 26: 3, 1979). The instrument is counting the residual non agglutinated particles of which the number is expressed in peak heights (see enclosed copies of the recorder sheet).

Results

The results (Table 1) are given in equivalents of heat-aggregated IgG (see standard curves on recorder sheet). The above normal limit established on healthy blood donors is 35 µg/ml for RF and 350 µg/ml for MAG. ~~As~~ shown in Fig. 1 the results tended to be higher in the hemophilic patients than in blood donors ($P < 0.001$ for RF and MAG) but only two patients, de S, JP and BR, had significant and constant abnormally high values (Table 1). The levels of immune complexes were slightly higher in the samples collected from some patients after repeated perfusion of treated Factor VIII (Table 1). However, the differences were not statistically significant in the Kruskal-Wallis rank test. The increase of immune complexes detectable by both RF and MAG tests was observed only in two patients FA and BR. The lack of correlation between the RF and MAG results (Fig. 2) can be explained by the differences of specificity of the two agglutinators regarding the size of the complexes and their antibody content.

Conclusion

We confirm the tendency of hemophilic patients to have higher levels of circulating immune complexes. No significant increase was noted after three perfusions of the new preparation of Factor VIII.

March 1982

Prof. P.C. MASSON

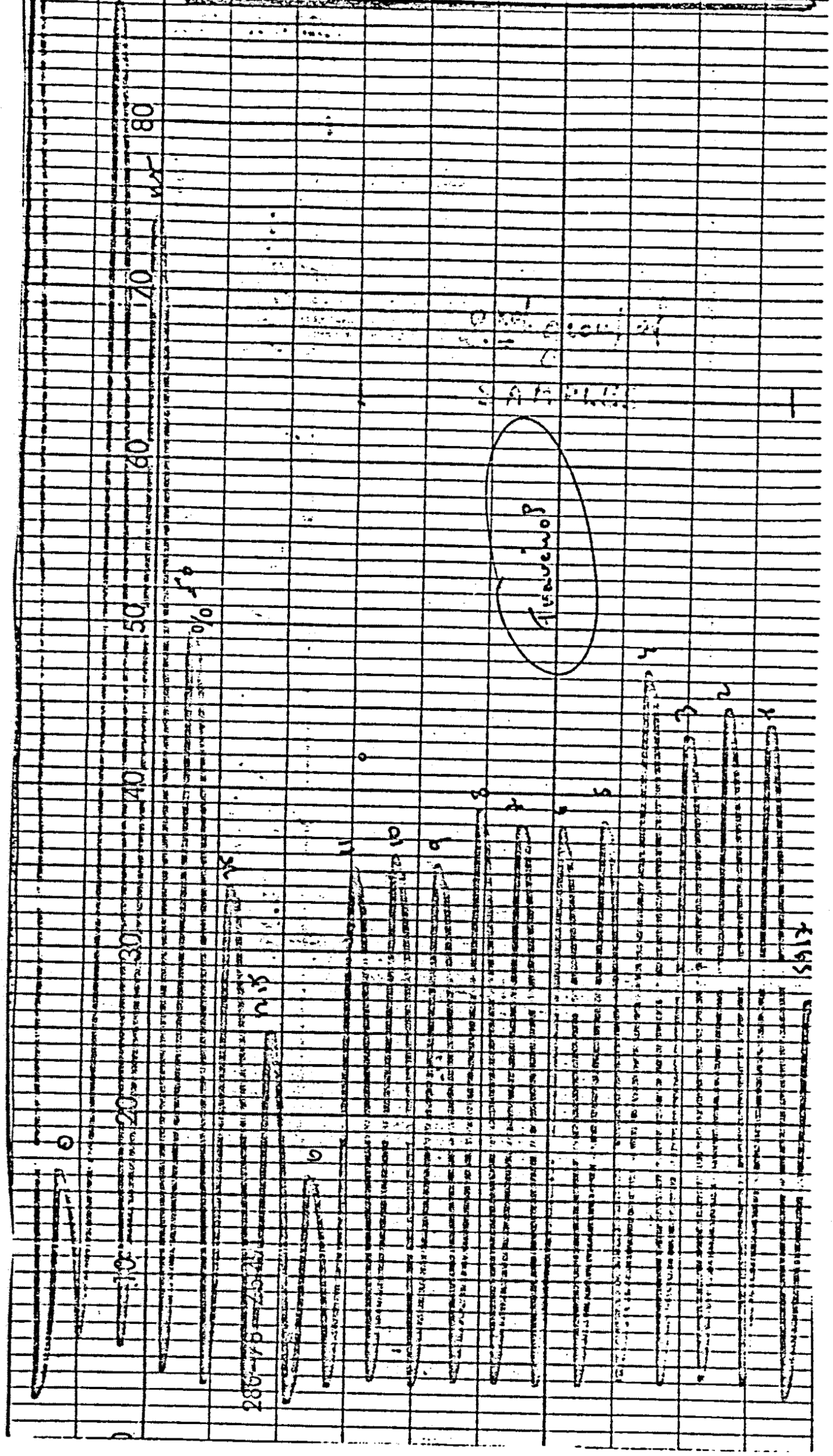
Table 1. Levels of circulating immune complexes

Patients	Tests	Time of sampling			
		Before untreated FVIII	10-15 days after untreated FVIII	10-15 days after 1st treated FVIII	10-15 days after 3rd treated FVIII
GRO-A		(5) Sept 28,1981	(6) Oct 12, 1981	(7) Oct 29, 1981	(8) Dec 22, 1981
	RF	25	22	24	27
	MAG	340	340	340	370
GRO-A		(9) Oct 5,1981	(10) Oct 17, 1981	(11) Nov 23, 1981	(12) Jan 29, 1982
	RF	25	27	25	30
	MAG	275	325	290	280
GRO-A		(1) Oct 12,1981	(2) Oct 20, 1981	(3) Oct 30, 1981	(4) Feb 2, 1982
	RF	38	38	37	45
	MAG	325	350	310	270
GRO-A		(1) Oct 13, 1981	(2) Oct 23,1981	(3) Nov 1, 1981	(4) March 4,198
	RF	42	44	41	47
	MAG	315	360	360	375
GRO-A		(5) Oct ?, 1981	(6) Oct 12,1981	(7) Jan 26,1981	(8) Feb 25, 198
	RF	32	30	30	32
	MAG	275	275	300	315
GRO-A		(9) Dec 2, 1981	(10) Dec 10, 1981		(11) Feb 15, 198
	RF	26	26		26
	MAG	190	180		220

(n) = code of samples on the recorder sheets
RF = inhibition of rheumatoid factor
MAG = inhibition of murine agglutinator
Results are given in equivalents of heat-aggregated IgG (µg/ml)
Upper normal limits for RF = 35 µg/ml
for MAG = 350 µg/ml
Within-assay precision for RF : CV = 3.4 %
for MAG : CV = 6.6 %

INHIBITION OF THROMBIN AGGLUTINATION BY

INHIBITION OF RHEUMATOID FACTOR



EQUIVALENTS OF HEAT-AGGREGATED J_1G

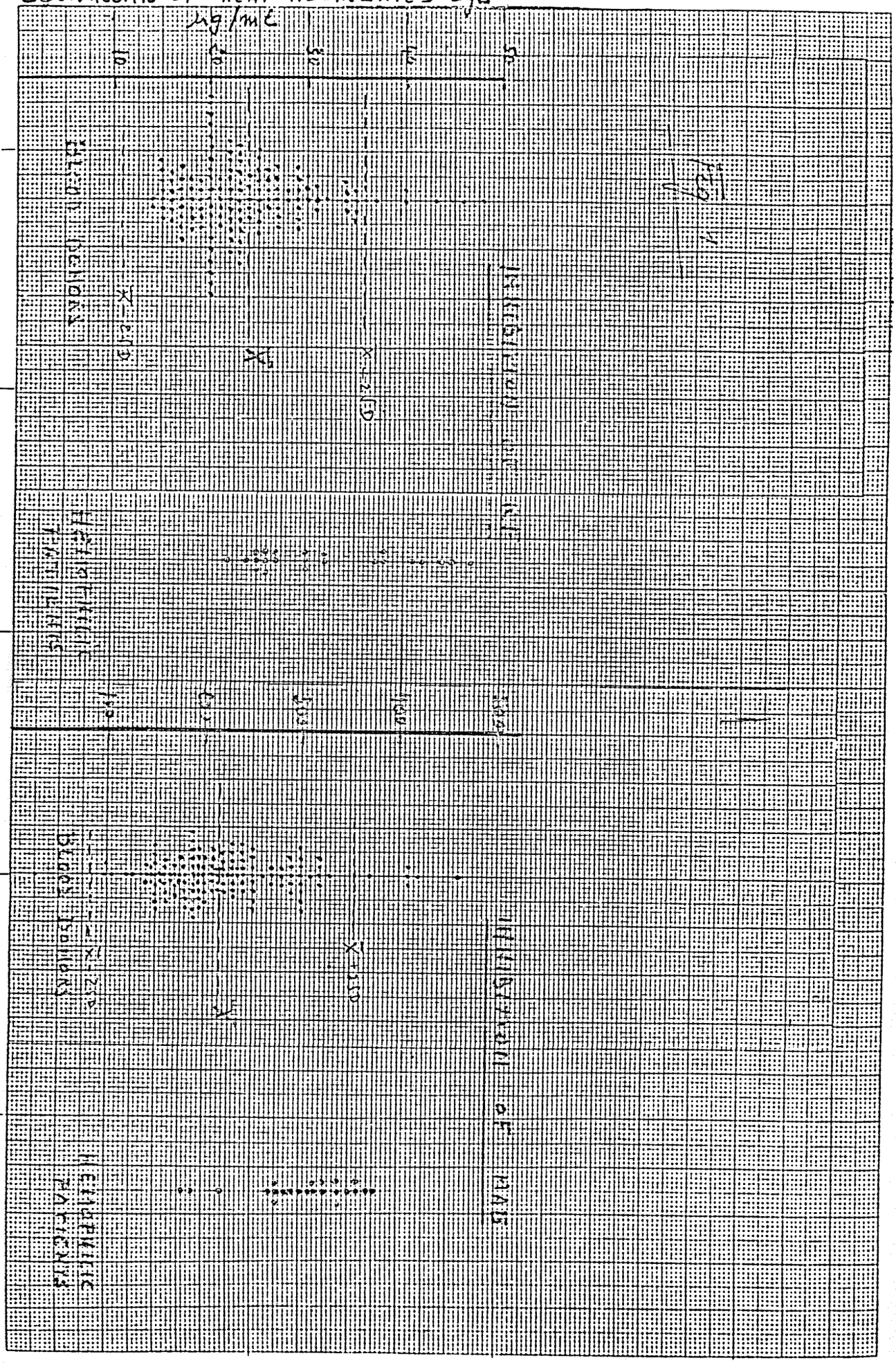
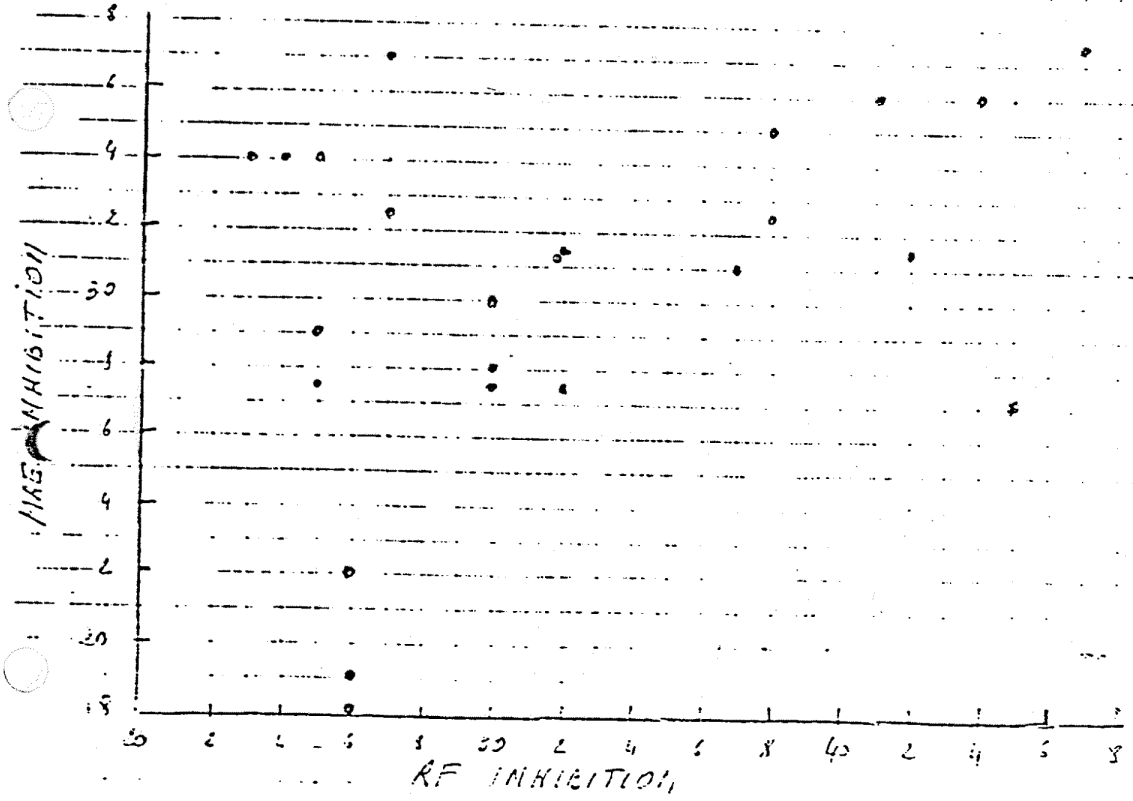


Fig 2



APPENDIX IV

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APPENDIX IV

AN ATTEMPT TO REDUCE THE RISK OF HEPATITIS WITH HEAT TREATED FACTOR VIII CONCENTRATE - INTERIM REPORT

(DR. COLOMBO AND PROF. MANNUCCI, MILAN, ITALY)

AN ATTEMPT TO REDUCE THE RISK OF HEPATITIS WITH HEATED FACTOR VIII CONCENTRATE INTERIM REPORT

Presented by : M. COLOMBO - P.M. MANNUCCI

2nd International Workshop on Prevention in Hemophilia, Paris, February, 23-24, 1984

This is a report of the preliminary results of an ongoing multicentre clinical study of the use of a heat-treated F.VIII concentrate, Hemofil-T. The main objective of this study was to assess the attack rate of hepatitis in hemophilia A patients during administration of Hemofil-T. Additional questions were the type and severity of the hepatitis and its relationship to lots and doses of F.VIII concentrate (Fig. 1).

Centres from 5 countries took part in this study (Fig 2).
After 1 year enrolment (Dec. 82 - Dec. 83), patients were to be prospectively followed up for 12 months. Patients included in the study were hemophilia A patients of any age who had never been exposed to blood or any blood products (so-called virgin patients), with normal transaminase levels and no markers of hepatitis B infection except for those vaccinated against hepatitis B. Both patients on prophylaxis or on on-demand treatment, were included (Fig 3). The events monitored were post-transfusion hepatitis (PTH) and/or seroconversion to known hepatitis viruses, namely hepatitis B, hepatitis A, cytomegalovirus, herpes and Epstein-Barr virus. PTH was defined according to internationally accepted criteria, i.e. as a rise in ALT values to more than 2.5 times the upper limit of the normal range on at least 2 consecutive occasions, 7 to 21 days apart, between 14 and 180 days after transfusion.

NANB hepatitis was diagnosed by standardised exclusion criteria. Questions to the patients about drugs and alcohol assumption were relevant for this diagnosis (Fig 4). Patients were to be followed up for a maximum period of one year, with serial clinical and laboratory assessments (Fig. 5). From December 82 to December 83, 34 patients were enrolled into the study. However, 12 had to be excluded from the analysis because they did not meet the selection criteria listed previously. The majority of them were non-virgin.

Therefore, 22 patients are now being prospectively evaluated. So far, 14 patients have been followed for enough time (at least 3 months - median 6 months) to provide preliminary data about the safety and efficacy of Hemofil-T administration (Fig. 6). Of these 14 patients, 9 developed NANB PTH, 1 had laboratory signs of CMV hepatitis and 4 were still hepatitis free after 5 to 13 months of follow-up.

Interestingly, none of the patients developed serum markers for HBV infection (Fig. 7). The incubation period for NANB PTH ranged from 4 to 12 weeks (median 6). However, this information refers only to the 6 patients who received the treatment in the very first days of enrolment.

PTH was mild to moderate in all but one case, who developed jaundice. In fact, the median ALT peak was 8 times greater than normal; biliburin never exceeded 1.8 mg/ml in the 9 anicteric cases (Fig. 8). Figure 9 summarises the follow-up of all patients given Hemofil-T. Hepatitis is represented by the solid bars. An interesting finding was the lack of any relationship between frequency of treatment and PTH.

The case of CMV infection is shown as a broken bar. This patient was a three month old baby with transient, mild liver damage associated with a rise in anti-CMV IgM antibodies from 1:8 to 1:32. However, since the same lot of Hemofil-T was infused into another 6 patients without transmitting CMV infection, we believe this case of CMV hepatitis was not related to the treatment. Intrafamilial contacts were likely to be responsible for this case of CMV hepatitis (Fig. 10).

Among the cases with NANB hepatitis, patient No. 1 from Dr. Carnelli had a monophasic pattern of ALT abnormalities. ALT was moderately elevated and returned to normal within 12 weeks (Fig. 11). Another patient from Milan had a biphasic pattern of ALT abnormalities (Fig. 12): the first peak occurring 12 weeks after the onset of the study, the second peak 19 weeks later. Since the majority of the infusions overlapped with the incubation periods for NANB hepatitis, it is unclear whether the biphasic

pattern of ALT elevation is due to two distinct episodes of hepatitis or to reactivation cycles of the same infective agent.

Patients received a median total of 3,000 units of Hemofil-T, having been exposed to therapy a median of 5.5 times (Fig. 13). So far, we have found no relationship between PTH attacks and dosage of F.VIII concentrate (Fig. 14). The same was true for lots of Hemofil-T and PTH. However, it must be emphasised that only three lots of Hemofil-T have been assessed so far (Fig. 15).

In summary, 64% of the patients treated with Hemofil-T developed PTH. Hepatitis was invariably of the NANB type, anicteric in all but one instance, and of moderate degree (Fig. 16). The lack of a control population makes it impossible for us to compare the attack rate of Hemofil-T-related PTH with that related to administration of regular factor VIII concentrates. However, reports in the literature indicate that NANB hepatitis in patients who were first exposed to the regular concentrates may be more frequent and severe than that reported here. Obviously, it is too early to define the risk of chronicity in patients with Hemofil-T-related hepatitis.

The other facet of the same investigation is to know whether exposure of Hemofil-T will vaccinate the patients against a more severe form of PTH. None of the patients in our study developed serum markers for HBV. This might reflect more accurate selection of the plasma donors, but further follow-up of these patients is required to rule out the occurrence of delayed HBV infection with prolonged incubation.

Finally, all the investigators reported that the efficacy and tolerance of this product were equal to those recorded for the regular concentrates (Fig. 17).

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Addendum to the Interim Report

The status of the study as at 26th July, 1874 is as follows:

20 virgin patients have been followed for at least 3 months the majority for more than 6 months although some will not complete a full year of follow-up. We now have 174 patient-months of clinical and laboratory data for assessment.

None of the 20 virgin patients now receives prophylaxis; 15 are receiving on-demand therapy while the other 5 received short treatments for surgery or dentistry.

Of these 20 patients, 13 have shown elevated ALT levels (>100 IU/l) but only 11 meet Dr. Colombo's criteria for post-transfusion hepatitis, giving an incidence of non-A, non-B hepatitis of 55%. This compares favourably with the 64% calculated from the last assessment in February. The other two cases of elevated transaminases were due to CMV infection and an isolated peak not interpreted as hepatitis.

It should be noted that no clinical signs or symptoms of hepatitis have been seen with the exception of one patient who developed post-surgical jaundice. No case of seroconversion for hepatitis B has occurred although only 6 of the 20 patients were vaccinated against hepatitis B.

HEMOFIL T
EUROPEAN CLINICALS
OBJECTIVES

- **OVERALL : ASSESS THE ATTACK RATE OF HEPATITIS**
- **SUBSIDIARY QUESTIONS :**
  - **Severity ?**
  - **Chronicity ?**
  - **Type of Hepatitis ?**
  - **Lot relationship ?**
  - **Dose relationship ?**
  - **Tolerance ?**
  - **Efficacy ?**

FIGURE 1.

HEMOFIL T CLINICALS
DESIGN

MULTICENTER STUDY

☐ Italy	■ Carnelli
	■ Mannucci
☐ Germany	■ Schimpf
	■ Klose
☐ U.K.	■ Savidge
	■ Aronstam
☐ France	■ Pommereuil
	■ Gazengel
	■ Larrieu
☐ Luxembourg	■ Dicato

PROSPECTIVE : Follow-up 12 months
NO CONTROL
ENROLLMENT : December 82 - December 83

FIGURE 2.73

INCLUSION CRITERIA

- ☐ Hemophilia A patients
- ☐ Normal liver enzymes
- ☐ Virgin (★)
- ☐ Vaccinated / Non vaccinated against Hepatitis B
- ☐ Any age
- ☐ Any bleed, surgery, prophylaxis

(★)Non virgin also enrolled but data showed retrospectively to be scientifically hard to interpret.

FIGURE 3.

DIAGNOSIS OF NANB HEPATITIS BY EXCLUSION OF

- KNOWN HEPATOTOXIC DRUGS AND ALCOHOL
- HEPATOTROPIC VIRUSES
  - Hepatitis B
  - Hepatitis A
  - Epstein Barr
  - Cytomegalo
  - Herpes

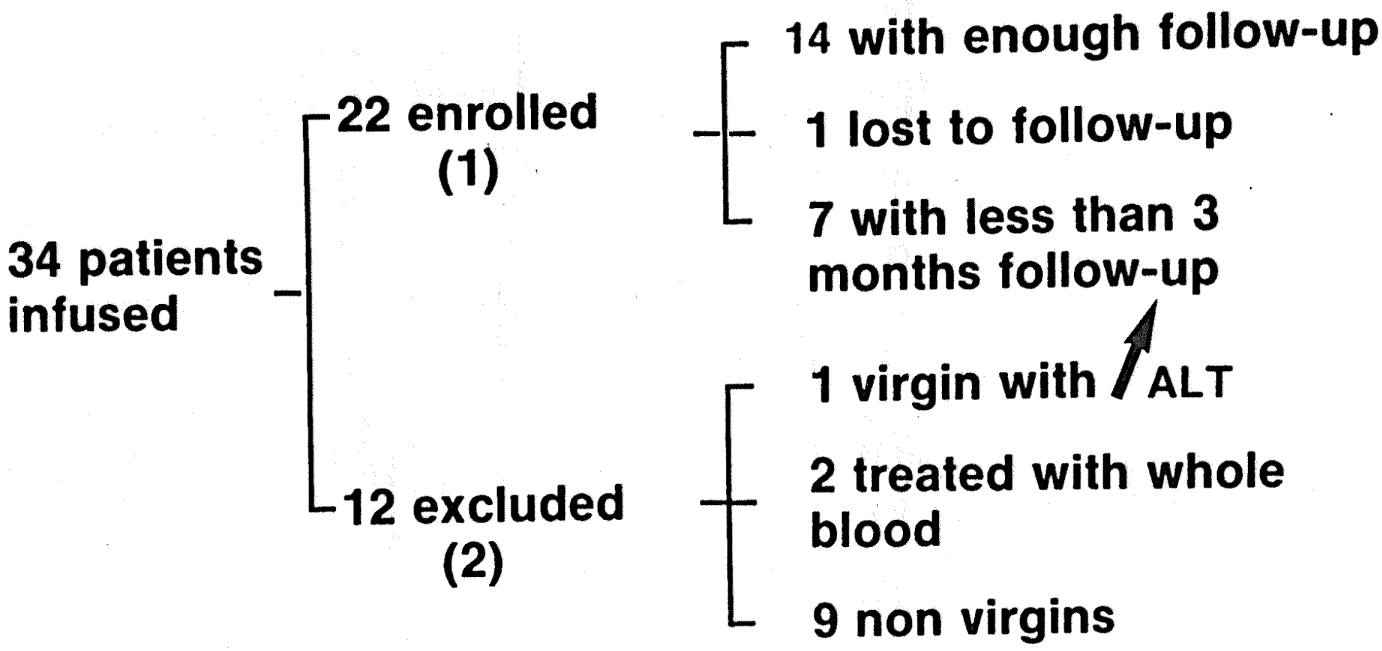
FIGURE 4.

TIMING OF LABORATORY AND CLINICAL ASSESSMENT

ZERO TIME	=	1st assessment 1st infusion of Hemofil T
1ST MONTH	=	Every two weeks
2-6 MONTHS	=	Every three weeks
7-12 MONTHS	=	Monthly

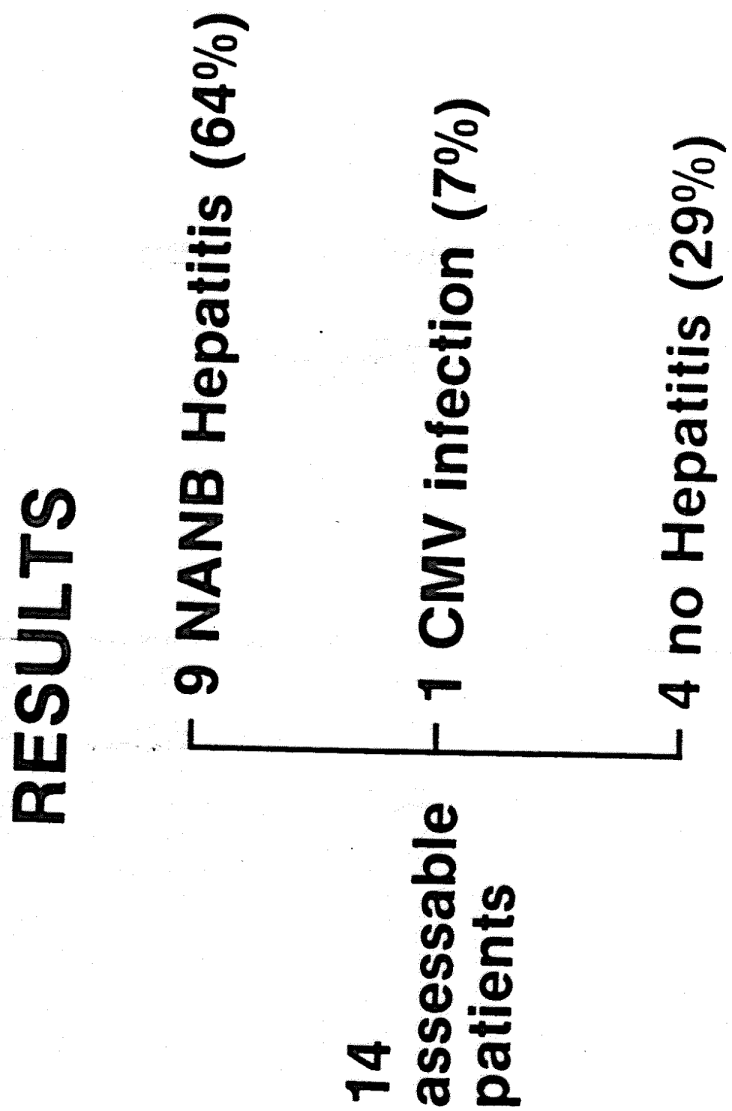
FIGURE 5.

ENROLLMENT STATUS AS OF FEBRUARY 1984



(1) Three lots infused
(2) Four lots infused

FIGURE 6.


RESULTS
14 assessable patients
9 NANB Hepatitis (64%)
1 CMV infection (7%)
4 no Hepatitis (29%)

CLINICAL AND LABORATORY FEATURES OF NANB HEPATITIS

NUMBER OF PATIENTS		9
CLINICAL SYMPTOMS AT ONSET OF ALT		1
	Range	Median
AGE (YEARS)	0.2 - 58	2.5
INCUBATION (WEEKS)(★)	4 - 12(★)	6
ALT LEVELS (x NORMAL)	4 - 91	8
BILIRUBIN (PEAK)(mg/dl)	0.44 - 10.70	1.11

(★) Only 6 patients are assessable

FIGURE 8.

HEMOFIL T STUDY
POST-TRANSFUSION HEPATITIS
IN VIRGIN PATIENTS
(DATA AVAILABLE AT 26.1.84)

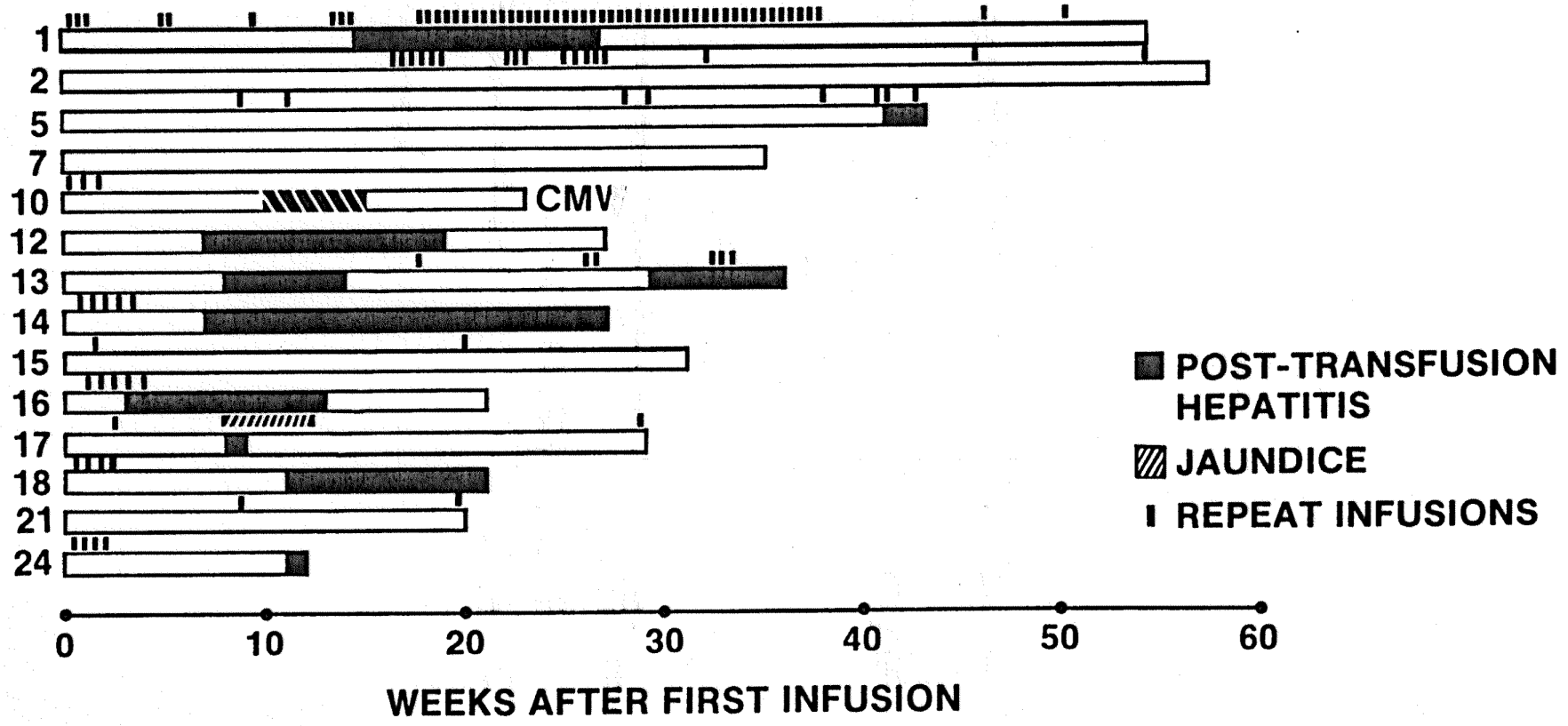


FIGURE 9.

THE C.M.V. CASE

- Six other patients receiving same lot did not show seroconversion
- Low titers

FIGURE 10.

HEMOFIL T STUDY

PT I ML C 2 YEARS VIRGIN 10 KG ON DEMAND
TOTAL DOSE = 20,100 UNITS
NORMAL LAB VALUES : ALT 40 AST 37 BILIRUBIN < 1

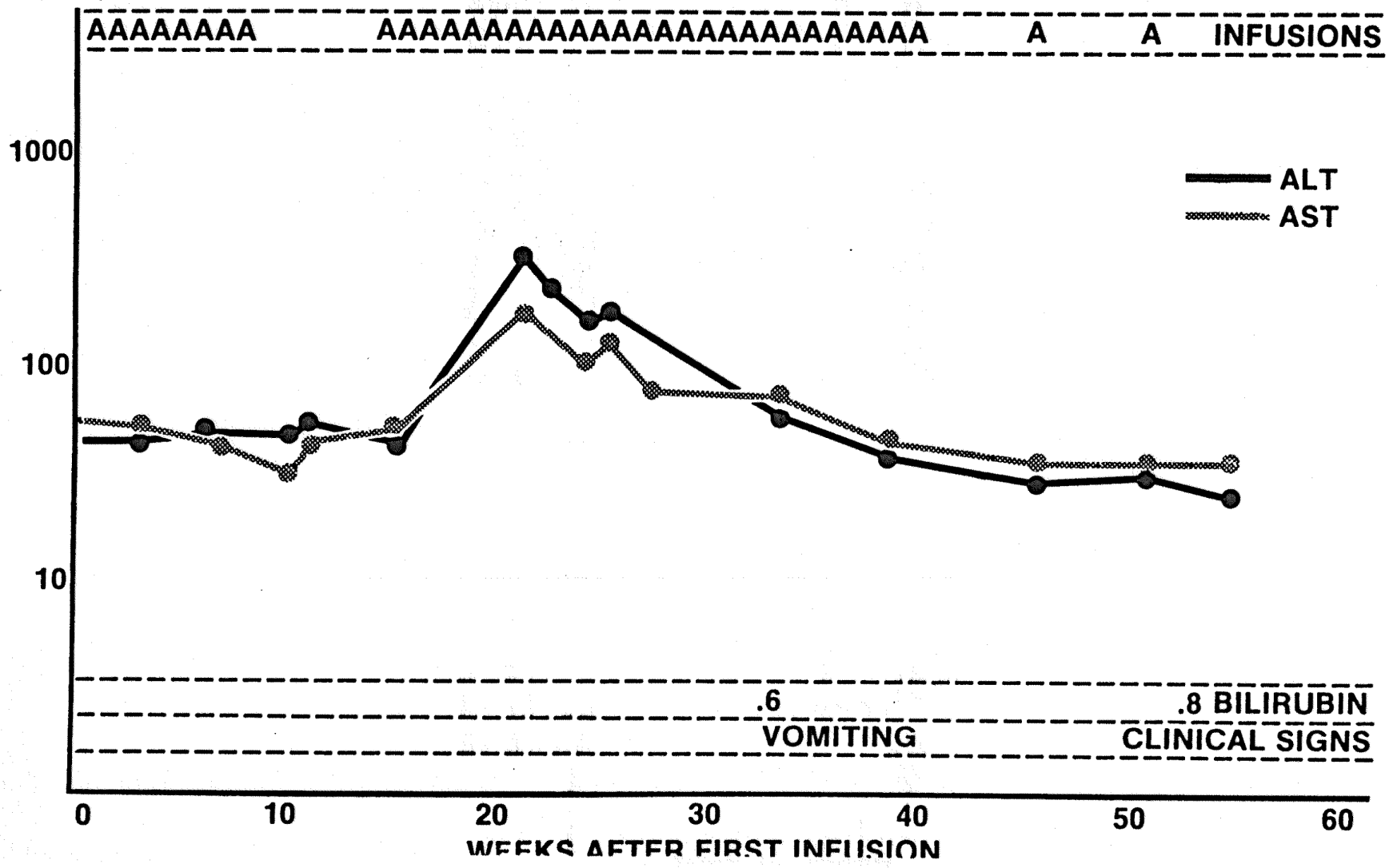


FIGURE 11.

HEMOFIL T STUDY

PT 13 MP C II YEARS VIRGIN 34 KG ON DEMAND
TOTAL DOSE = 5,100 UNITS
NORMAL LAB VALUES : ALT 40 AST 37 VACCINATED AT WEEK 3

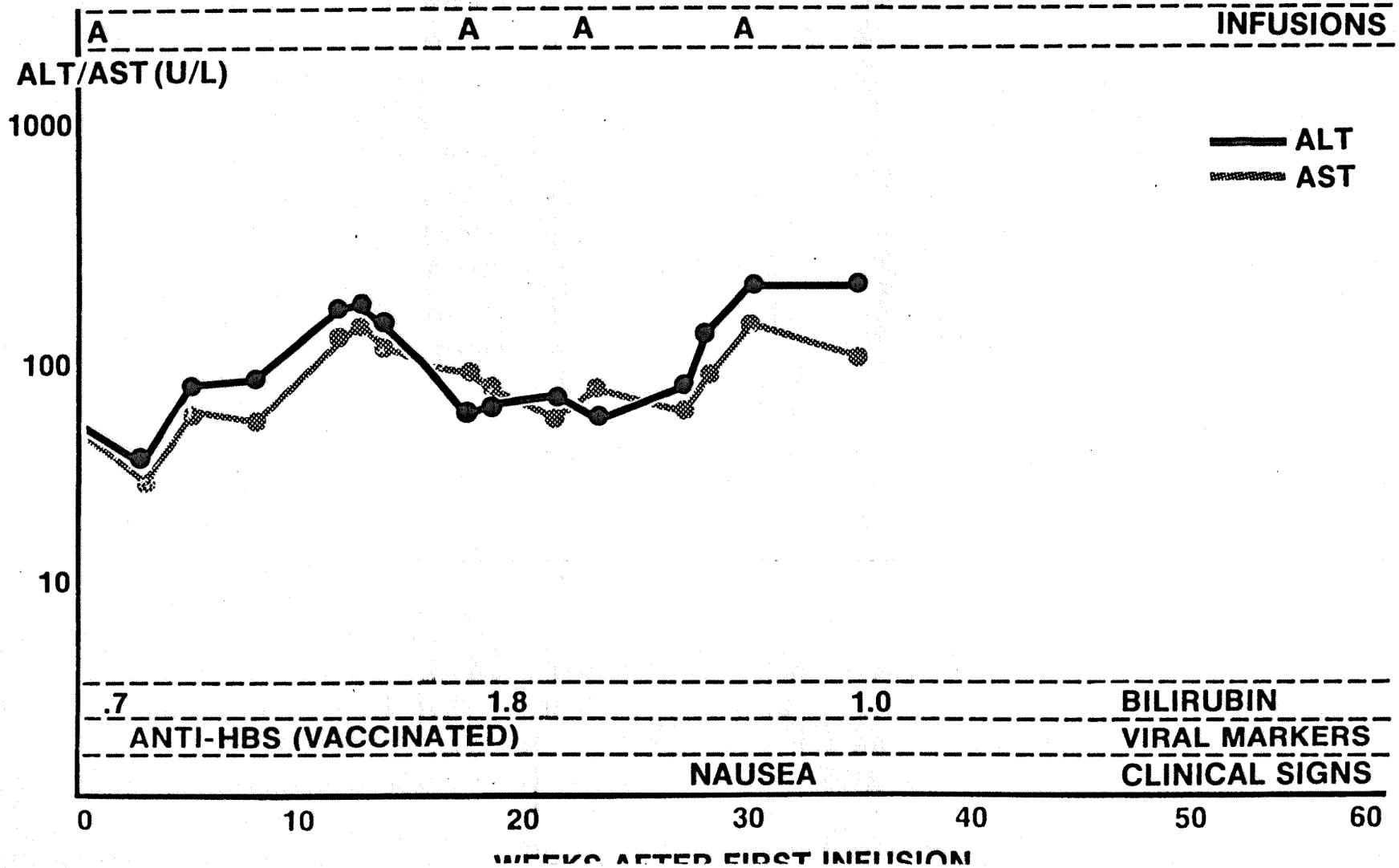


FIGURE 12.8.3

SHPL0000283_005_0130

HEMOFIL T
INFUSION DATA FOR 14 VIRGIN PATIENTS

PATIENT Nº	WEIGHT (kg)	TOTAL DOSE (U)	Nº EXPOSURES	U/KG x EXPOSURES
1	10	20,100	67	2,100
2	11	8,750	21	795
5	6	3,000	11	500
7	90	2,600	1	29
10	10	3,000	4	300
12	50	1,650	1	33
13	34	5,100	5	150
14	80	22,000	11	275
15	12	1,260	3	105
16	82	19,980	17	244
17	9	2,130	3	236
18	70	44,680	10	638
21	10	1,900	5	190
24	12	1,800	6	150
MEDIAN	12	3,000	5.5	240
RANGE	6-90	1,200-44,680	1-67	29-2,100

FIGURE 13.

HEMOFIL T
HEPATITIS VS. DOSE IN 14 VIRGIN PATIENTS

Disease status / Dose (U/kg x days)	Hepatitis	No Hepatitis	CMV	Total
Low <240	4	3	-	7
High >240	5	1	1	7
Total	9	4	1	14

FIGURE 14.

LOTS AND POST TRANSFUSION HEPATITIS (P.T.H.)

LOT NUMBER	P.T.H.
820628A	5/7 (★)
820817A	4/6
821123A	0/1

(★) CMV case excluded

FIGURE 15.

SUMMARY OF FINDINGS

- PTH

Attack rate	64 per cent
Type	NANB
Severity	1/9 cases
Lot relationship	Absent
Dose relationship	Absent

- ZERO HEPATITIS B (★)

(★) 3/22 patients were vaccinated

CONCLUDING REMARKS
HEMOFIL T CLINICALS

ATTACK RATE REDUCTION	= LIKELY, BUT NOT ASSESSABLE
SEVERITY REDUCTION	= LIKELY
HEPATITIS B	= NONE , SO FAR
TOLERANCE	= EXCELLENT
EFFICACY	= EXCELLENT