Oxford Haemophilia Centre, Plasma Fractionation Laboratory,
Churchill Hospital Oxford OX3 7LJ.

With compliments Sonecy the Abbott 7.3.73

Literature (selected by me)

A useful little handbook on dosage was also provided

GRO-C

Telephone: Oxford 62002 (STD 0865) OR
Oxford 64841 Ext.....

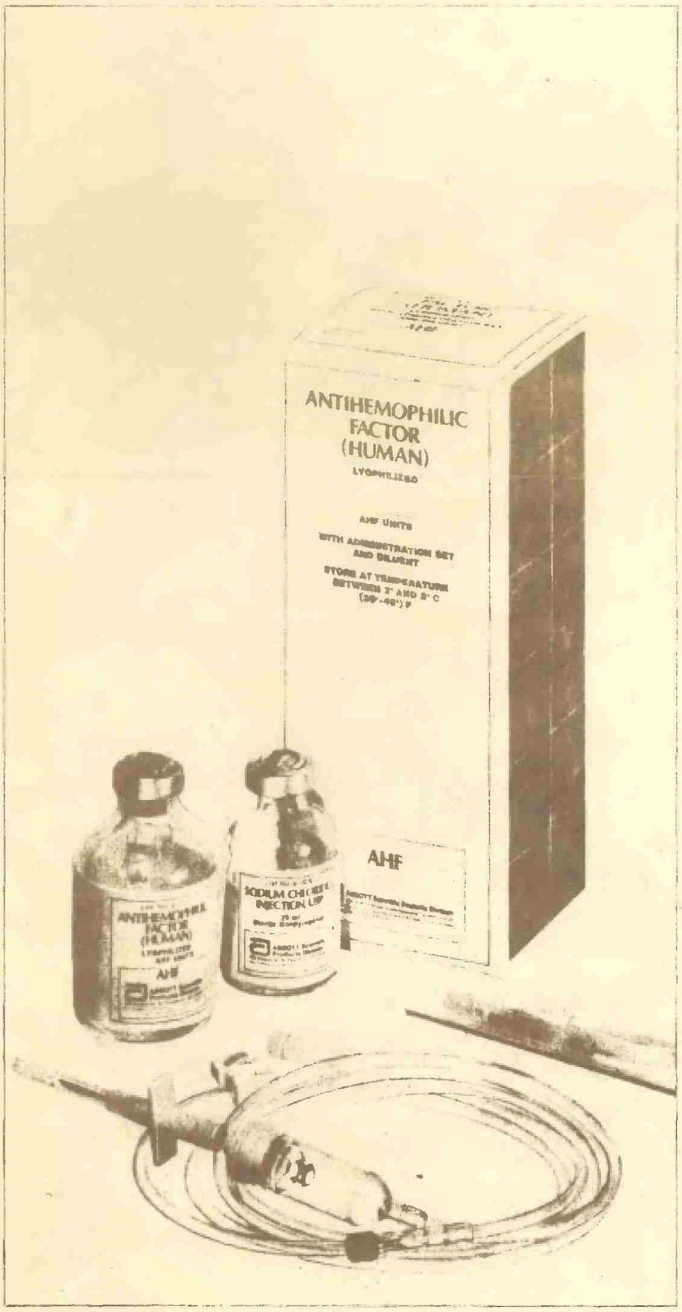
From Dr Rizza
7.3.73.

Antihemophilic Factor (Human)

LYOPHILIZED

AHF

with Diluent and Disposable Administration Set



Description

AHF is a stable dried concentrate (Factor VIII: AHF AHG) to be used in the treatment of Hemophilia A (classical hemophilia). Easily reconstituted, it can be administered without the side effects occasionally associated with the use of plasma. It can reduce the incidence and severity of bleeding episodes. With proper medical supervision and training, even outpatient prophylactic treatment is now available.

Features

Stability

One year when stored in refrigerated conditions (2°-8°C).

Safety

There are no known contraindications (see full disclosure).

Labeled dosage

Each bottle is labeled with the number of Factor VIII units it contains. There are a minimum of 200 AHF units in every bottle.

Complete and ready to use

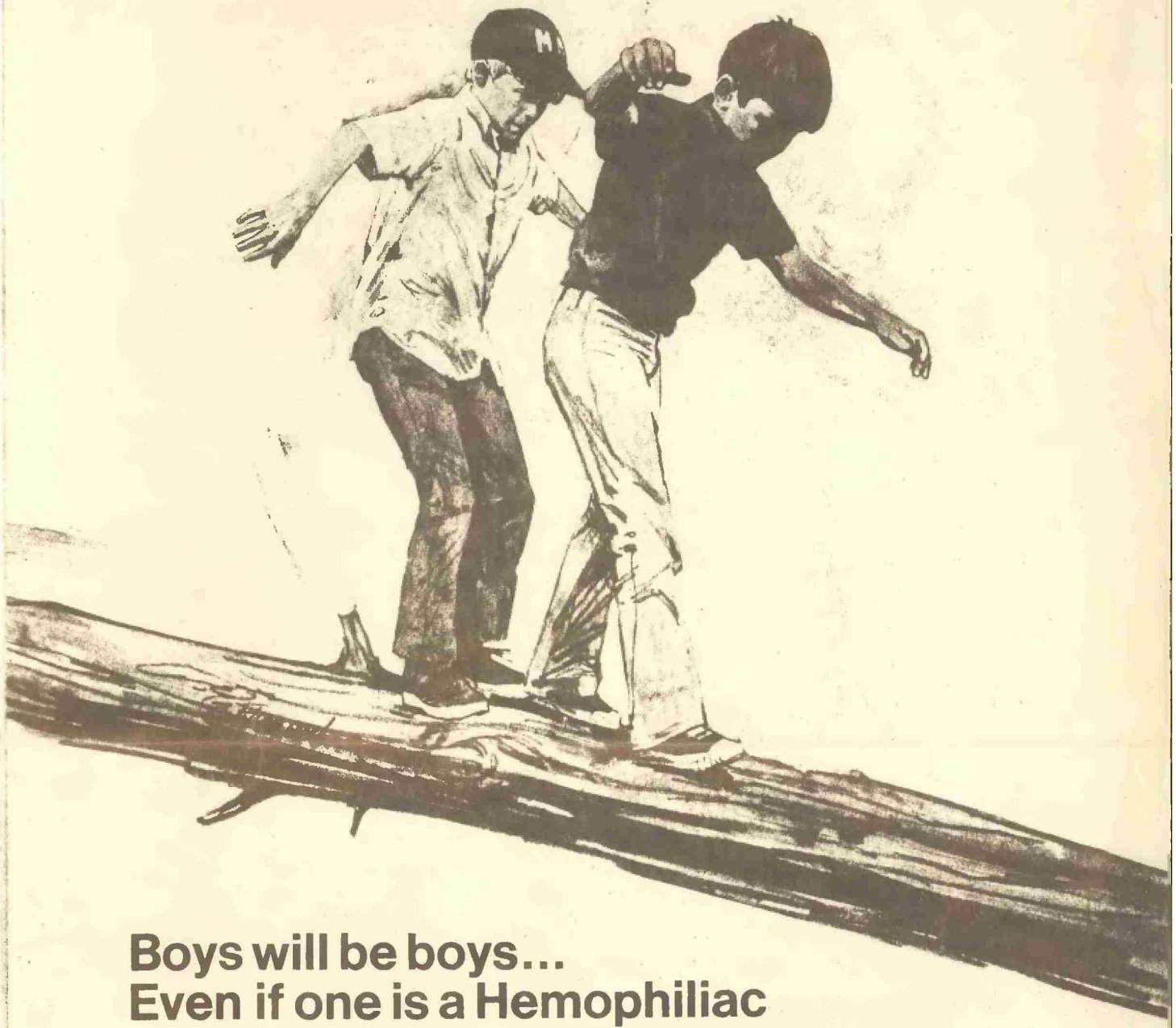
Each package contains all the necessary infusion components for reconstitution and administration.

How Supplied

List No. 6-5151—One each: Vial ANTIHEMOPHILIC FACTOR (HUMAN) AHF Lyophilized, 25 ml vial of Sodium Chloride Injection USP, administration set, 21-G x 1½" IV needle, airway cannula, and double ended reconstitution needle.

Fluid pathway, needle and airway cannula are sterile and non-pyrogenic.

ABBOTT Scientific Products Division



Boys will be boys... Even if one is a Hemophiliac

Hemophilia. The constant threat of hemorrhage. Now ABBOTT Scientific Products Division Antihemophilic Factor (Human) AHF offers the hemophiliac the opportunity to lead a more normal life.

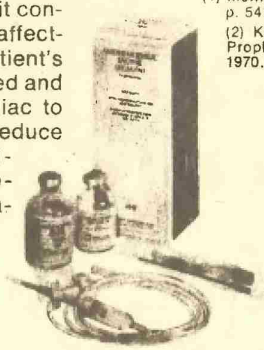
Antihemophilic Factor (Human) Lyophilized is a stable, dried concentrate, easily reconstituted in a diluent and administered without the side effects occasionally associated with plasma.[1] Every bottle is labeled with the number of Factor VIII units it contains. So when the individual patient factors affecting dosage have been established, the patient's average dosage can be accurately calculated and administered; even allowing the hemophiliac to be treated on an out-patient basis.[2] It can reduce the incidence and severity of bleeding episodes, and the pack contains all the components needed — AHF, diluent and administration set — for immediate use.

ABBOTT Scientific Products Division
Abbott Laboratories
820 Mission Street, South Pasadena, California 91030

INDICATIONS: ABBOTT Scientific's Antihemophilic Factor (Human) Lyophilized is a stable, dried concentrate of antihemophilic factor (Factor VIII, AHF, AHG) to be used in the therapy of Hemophilia A (Classical hemophilia). **CAUTION:** This product is prepared from units of human plasma which have been tested and found non-reactive for Hepatitis Associated Antigen. However, it is recognized that presently available methods are not sensitive enough to detect all units of potential infectious plasma and the risk of transmitting hepatitis is still present. **SIDE EFFECTS:** Reactions observed are mild and rare, namely: mild chill, nausea, or stinging in the vein proximal to the transfusion. **CONTRAINDICATIONS:** There are no known contraindications to ABBOTT Scientific's Antihemophilic Factor (Human)

(1) Mollison, P. L.: *Blood Transfusion in Clinical Medicine*, 3rd Edition p. 541, F. A. Davis Co., Philadelphia, 1963.

(2) Kaspar, C. K., Dietrich, S. L. and Rapaport, S. I.: Hemophilia Prophylaxis with Factor VIII Concentrate. Arch. Int. Med., *125*:1004, 1970.



Antihemophilic Factor (Human)
LYOPHILIZED
AHF

ANTIHEMOPHILIC FACTOR (HUMAN)

LYOPHILIZED

AHF

ANTIHEMOPHILIC FACTOR (HUMAN) AHF from ABBOTT Scientific Products Division is a stable dried concentrate of Antihemophilic Factor (Factor VIII, AHF, AHG) to be used in the therapy of Hemophilia A (Classical Hemophilia).

Hemophilia A is a hereditary disorder of blood coagulation associated with a deficiency of antihemophilic factor, a constituent of normal plasma required for blood clotting. Since this abnormality is associated with a rare sex linked recessive mutant gene, the disease occurs almost exclusively in males. Individuals with this disorder tend to bleed profusely following minor trauma usually in their joints, muscles, or internal organs. Surgery on such patients is impossible without temporary correction of their abnormality with specialized transfusions.

Until recently, the medical management of patients with Hemophilia was based on the replacement of the blood component they lack by transfusions of fresh blood, fresh plasma, or fresh frozen plasma.

The usefulness of fresh blood or plasma is limited by the need to administer large volumes of either in order to raise the concentration of antihemophilic factor in the blood to levels required to achieve and maintain hemostasis. The repeated infusions of large volumes of plasma often lead to circulatory difficulties with threatening heart failure as a result of hypoproteinemia. There is also associated kidney dysfunction with albuminuria, edema, and retention of electrolytes.

Because of the limitations of blood and plasma transfusions, many investigators have sought to separate and concentrate antihemophilic globulin (Factor VIII) from plasma in a form suitable for substitution therapy of Hemophilia A patients.

Concentrated antihemophilic globulin of various degrees of purification prepared by methods of Cohn, Wagner and Brinkhous, Blomback, van Creveld, Pavlovsky, Djerassi and others has been used with clinical success.

In 1954, Brinkhous noted that partially purified antihemophilic globulin (Factor VIII) was not soluble in cold media and concluded that it was a cryoglobulin.

Pool recently explored the solubility properties of this fraction of human plasma to prepare antihemophilic globulin concentrates for clinical use. The *plastic bag* closed system, developed by Klein and Djerassi, was utilized to extract antihemophilic globulin from plasma simply and efficiently by controlled freezing and thawing. The cryoprecipitate derived from plasma by Pool's technique has higher Factor VIII activity per unit of protein than Cohn's Fraction I. Its use requires the infusion of less protein and fluid than does the administration of fresh or frozen plasma for the treatment of Classical Hemophilia.

ANTIHEMOPHILIC FACTOR (HUMAN) AHF from ABBOTT Scientific Products Division is a highly potent source of antihemophilic factor activity. Since it is a purified cryoglobulin, only relatively small amounts of protein need be given to a patient in order to increase his level of antihemophilic factor. Since this product is of human origin, no danger of species antigenicity is associated with its use. Blood group isoagglutinins are not present in significant amounts. This product is easily reconstituted in the sodium chloride diluent and can be administered rapidly without the side effects occasionally associated with the administration of plasma.

The dry product is stable when stored according to label and can be administered with assurance concerning the dose requirement. The material is highly effective in arresting bleeding due to deficiency of Factor VIII. Whenever needed ANTIHEMOPHILIC FACTOR (HUMAN) AHF can be used to increase the Factor VIII levels of patients to normal or near normal values without overloading their circulatory system.

Dosage

Each bottle of ANTIHEMOPHILIC FACTOR (HUMAN) AHF is labeled with the total units of AHF contained therein. One AHF unit is defined as the activity present in one ml of fresh pooled human plasma.

The dosage of ANTIHEMOPHILIC FACTOR (HUMAN) AHF must be individualized according to the weight of the patient, the severity of the bleeding, the severity of his blood condition, the source of bleeding, inhibitors present (if any), and other factors as determined by the managing physician or surgeon. Laboratory aids, whenever available, should be used to supplement clinical observations for guiding therapy.

Djerassi suggested the following dosage schedule for various clinical conditions based on the experience with substitution therapy in a large pediatric hemophilia service.

1. Joint Hemorrhages

If no aspiration is carried out, 10 units per kilogram body weight is repeated at eight to twelve hours for two to three days. If aspiration is carried out, 10 units per kilogram just prior to the aspiration with repeated similar dose six to eight hours later. An additional infusion of 10 units per kilogram body weight is given the following day if the patient cannot stay off his feet for four to five additional days (one infusion of 10 units per kilogram, once a day is given for three to four days).

2. Muscle Hemorrhages

a. Minor hemorrhages (e.g., contusions of extremities or trunk (non-vital areas)): 10 units per kilogram once a day for two or three days.

b. Massive hemorrhages (in vital areas): Two infusions at 12 hour intervals, first and second day; one infusion a day for two more days (10 units per kilogram for each infusion).

c. Muscle hemorrhages in vicinity of vital organs (neck, throat, subcutaneous, iliopsoas muscle, etc.): 20 units per kilogram followed by 10 units per kilogram every eight hours. Larger doses if not arrested. Maintain schedule for forty-eight hours and continue with half the dose for another forty-eight hours.

3. Overt Bleeding (cut lips, tongue, cheeks, various cuts and wounds)

20 units per kilogram. Continue with 10 units per kilogram every six to eight hours for twenty-four hours, then every twelve hours for three to four days.

4. Massive Wounds

Given until bleeding stops and maintain with 20 units per kilogram every eight hours. Obtain levels and maintain a minimum of 40% AHG level in patient.

5. Surgery

Levels of 40% AHG or more if needed. Thirty to forty units per kilogram of body weight are needed prior to surgery followed by 20 units per kilogram every eight hours after surgery. This should be done with laboratory control, and the dosage should be increased if the AHG level is less than 30% just prior to the next infusion. The post-infusion level should be around 60% AHG. (It has been suggested by McMillan that the AHG level be raised to 30-40% of normal for at least ten days postoperatively.)

For each unit of ANTIHEMOPHILIC FACTOR (HUMAN) AHF administered per kilogram of body weight a two per cent rise in Factor VIII activity was observed by Abildgaard, et al. Djerassi states that the dosage of ABBOTT Scientific's ANTIHEMOPHILIC FACTOR (HUMAN) AHF can be used interchangeably with glycine precipitated AHF. This linear dose-response relationship may be shown by the formula:

$$\text{Expected AHF increase (in percent of "normal")} = \frac{2.0 \times \text{units administered}}{\text{body weight (in kg.)}}$$

The clinical effect on the patient is the most important factor in the evaluation of adequacy of therapy. It may thus be necessary to administer more ANTIHEMOPHILIC FACTOR (HUMAN) AHF than would be estimated in order to obtain the desired result. The dosage requirements of AHF when inhibitors are present are extremely variable, and the dosage can only be determined by the clinical response. Occasionally, low increments of AHF in patients with AHF inhibitors may suffice to produce satisfactory clinical responses.

Side Effects

Reactions observed are mild and rare, namely: mild chill, nausea, or stinging in the vein proximal to the transfusion.

Contraindications

There are no known contraindications to ANTIHEMOPHILIC FACTOR (HUMAN) AHF.

Reconstitution and Administration

1. Warm sodium chloride diluent and concentrate bottles to room temperature (but not above 37°C).
2. Remove aluminum band and dust cap from the diluent bottle.
3. Swab the exposed rubber surface with alcohol. (Do not leave any excess cleaning agent in indentation on stopper.)
4. Remove all covering from one end of a double ended needle. Insert this exposed end of the needle through the depression in center of the stopper in the bottle of diluent.
5. Remove aluminum band and dust cap from the concentrate bottle.
6. Swab the exposed rubber surface with alcohol.
7. Remove plastic cap from the upper end of the double-ended needle now seated in the stopper of the diluent bottle. Hold concentrate bottle in one hand, invert the bottle of diluent in the other hand, and push the exposed end of the needle through the depression in the center of the stopper, making certain that the diluent is always above the bottle of concentrate. There should be enough vacuum in the bottle to draw in all the diluent.
8. Disconnect the two bottles by removing needle from concentrate bottle stopper. Then gently agitate or rotate concentrate bottle until all concentrate is dissolved. (Do not shake vigorously.) Reconstitution requires fifteen to twenty minutes.
9. Remove cover from airway needle and insert airway needle into concentrate bottle stopper.
10. Close clamp on administration set.
11. Remove cover from stopper – puncture needle of set (near drip chamber) and insert needle into concentrate bottle stopper. Suspend bottle in inverted position.
12. Squeeze and release drip chamber once to allow it to partially fill with liquid.
13. Remove needle adapter cover and insert adapter into hub of administration needle.
14. Open control clamp and fill set with liquid from bottle. Close clamp and insert administration needle into vein.
15. Discard administration equipment after use.

How Supplied: List No. 6-5151

One each: Vial ANTIHEMOPHILIC FACTOR (HUMAN) AHF Lyophilized, 25 ml vial of Sodium Chloride Injection USP, administration set, 21-G x 1½" IV needle, airway cannula, and double ended reconstitution needle.

Fluid pathway, needle, airway cannula and reconstitution needle are sterile and non-pyrogenic.

Storage

ANTIHEMOPHILIC FACTOR (HUMAN) AHF should be stored at temperatures between 2°C and 8°C (36°F to 46°F).

Caution: Federal (USA) law prohibits dispensing without a prescription.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or other licensed practitioner.

Single dose container for intravenous administration.

Discard unused contents.

Discard administration equipment after single use.

This product is prepared from units of human plasma which have been tested and found non-reactive for Hepatitis Associated Antigen. However, it is recognized that presently available methods are not sensitive enough to detect all units of potential infectious plasma and the risk of transmitting hepatitis is still present.

Bibliography available on request

ABBOTT Scientific Products Division
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Comments

PAPER 1 "generous"?

PAPER 2

p 2 line 9 Figures would have to be increased by 33% !

Last para

Increased use of all concentrates would be an alternative way of achieving production of more fresh plasma & may be more economical than plasmapheresis.

12.3.73

GRO-C