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**Use of Animal Antihæmophilic Globulin in Surgery:
Exarticulation in the Hip in a Haemophiliac**

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Major surgery in haemophiliacs has previously been a perilous undertaking, but the recent introduction of concentrated antihæmophilic globulin (AHG) preparations is an important advance. Preparations of both animal (Macfarlane *et al.* 1954, 1957) and human origin (Kekwick & Wolf 1957, Blombäck & Nilsson 1958) have been used with success in surgery, though there may be important differences in the effect of preparations from different sources.

Experience in this field is necessarily limited, and we therefore report this case in order to point out some of the experiences encountered with animal AHG.

Materials and Methods

AHG preparations were supplied by Messrs. Maw Son & Sons Limited, Aldersgate House Barnet, London, England. Four batches were used, one of bovine and three of pig origin.

AHG levels were measured in one-stage cephalin systems, using hæmophilic plas-

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ma as substrate. The methods are similar to those of Langdell *et al.* (1953) and of Waaler (1959).

References to other methods are given in table I.

Case report

The patient, E. M. N., a 34 year-old man, has suffered from bleeding into the joints, the urinary tract, and the retroperitoneal space since early childhood. Two of his five brothers bled to death as infants.

In 1954 he fractured his left femur, and this failed to heal. He had repeated hæmorrhages around the pseudoarthrosis, and an increasing tumour developed in the area. In January 1959, the situation had become intolerable, and he was admitted to our department.

On admission he showed contractures in ankle, knee and elbow joints with marked muscular atrophy. He was bedridden primarily due to an enormous swelling of the lower part of his left thigh, which had a circumference of 80 cm (fig. 1). His hæmoglobin was 7.7 g per cent and red cell count 4.5 mill. per mm³. The sedimentation rate was 66 mm per hour. The urine contained protein and red cells.

Table I. Results of the laboratory tests on the patient's blood

Tests	Results in the patient	Normal range	Methods
Whole blood clotting time ..	26 min.	2—5 min.	Hjort & Stormorken (1957)
Bleeding time.....	> 30 min.	3—11 min.	Borchgrevink & Waaler (1958)
Platelet count.....	325,000 per mm ³	150—400,000 per mm ³	Nygaard (1933)
Thromboplastin time	16.1 secs.	12—14 secs.	Quick's system with human brain thromboplastin
P and P value	73 %	75—130 %	Owren & Aas (1951)
Cephalin time, firm clot	200 secs.	55—65 secs.	Waalder (1957)
Prothrombin	84 %	75—125 %	Hjort et al. (1955)
Proconvertin (Factor VII) ..	90 %	75—125 %	Owren & Aas (1951)
AHG (Factor VIII)	< 1 %	60—150 %	See methods
Antihæmophilic B factor (Factor IX)	85 %	70—140 %	Stapp (1958)
Clot retraction	8.1 cm	> 7 cm	Voss (1958)
Platelet adhesiveness to glass	24 %	25—60 %	Hellem (1958)
Platelet factor 3.....	Normal		Thromboplastin generation test, Biggs & Douglas (1953)
Fibrinolysis.....	Not increased		Astrup & Müllertz (1952)



Fig. 1. Appearance of the patient's legs in January 1959

Table I gives the results of the laboratory tests of his haemostatic mechanism. There was less than 1 per cent of AHG in his plasma, and mixing experiments with the patient's and normal plasma did not reveal any inhibitor of AHG. The bleeding time had been normal on several previous occasions, but was now markedly prolonged. It could be normalized by cortisone or by transfusions with normal platelet-rich plasma. The prolonged bleeding time was probably due to a platelet defect caused by multiple transfusions (Borch-

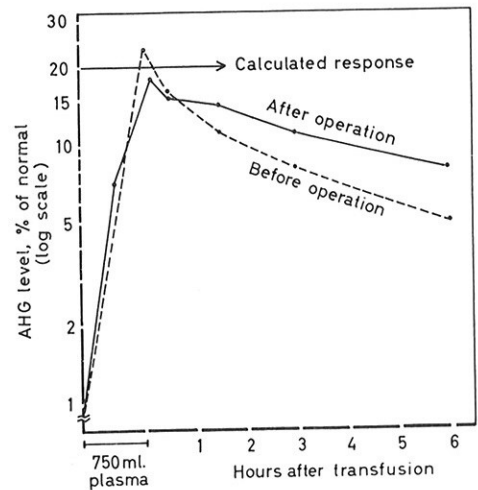


Fig. 2. Disappearance of transfused AHG in the patient. The figure shows the effect on the patient's blood AHG levels of transfusions with 750 ml human plasma, before (2. 2. 1959) and five months after (30. 10. 59) amputation of his leg.

grevink 1959). When transfusions were stopped, the bleeding time became normal and has remained so since.

Table II. *In vitro* and *in vivo* studies of the animal AHG preparations. The *in vivo* AHG level was measured 10 minutes after the infusion was completed, and the response was calculated on the basis of an assumed blood volume of 5,000 ml. The *in vitro* activity and the *in vivo* level were measured in the same test system

Tested	AHG activity per ampoule of different batches: equivalent in ml human plasma			
	Bovine	Pig — 1	Pig — 2	Pig — 3
In vitro	230	186	285	110
In vivo	ca. 90 (75 — 90)	ca. 70 (25 — 85)	ca. 105	ca. 35 (25 — 45)

In order to evaluate the *in vivo* turnover of AHG he was transfused with 750 ml of fresh plasma. The AHG level rose to 23 per cent. (Assuming his plasma volume to be 3,000 ml, the expected rise was calculated to be about 20 per cent.) Fig. 2 shows the rapid disappearance of the infused AHG: the flatter part of the curve indicates a half life ($T/2$) of about 4 hours.

The swelling after some weeks started to necrotize, and his general condition deteriorated rapidly. Finally, the necrotic areas covered more than half the tumour, and an amputation was deemed to be his only chance of survival. Preoperatively, his condition was improved by treatment with cortisone and antibiotics, and an exarticulation in the hip was carried out on the 26th of May (Surgical Department A, Professor Efskind).

AHG concentrates were given immediately before the operation, and this therapy was continued for 16 days with injections every 6—8 hours. Fig. 3 gives the details of the therapy and also the results of relevant laboratory tests during this period. *In vitro* and *in vivo* effects of the 4 batches are given in table II.

There was no excessive bleeding during operation nor for the following 6 days. Then, however, he started to bleed from the wound and had to be transfused daily with 1 litre of fresh blood in addition to the AHG concentrates. A large haematoma formed in the stump, and because of the danger of necrosis, most of the stitches were removed on the 14th day. This was followed by total disruption of the wound and increased bleeding. During the following weeks he was transfused daily with 1—2 litres of fresh blood or corresponding amounts of plasma. Seven weeks

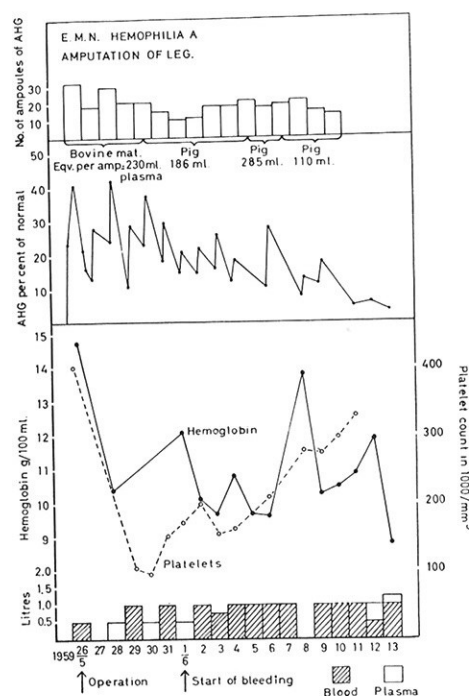


Fig. 3. Treatment with AHG during and after operation. The upper section shows the total daily amounts of AHG, given as 3 divided doses a day (May 28—31 as 4 doses a day). The middle section shows the AHG levels in the patient's blood, measured in a sample taken before one of the daily AHG doses, and in a sample taken 10 minutes after the infusion had been completed. The lower section shows the haemoglobin values, platelet counts and daily transfusions with blood and plasma.

after operation the bleeding stopped, his recovery from then on was uneventful, and some weeks later he was out of bed using crutches.

Pathological examination showed destruction of the lower end of the femur, the upper end of the tibia and of the patella. There was no evidence of sarcoma.

Discussion

Before operation the patient represented a diagnostic problem: could such an enormous swelling be caused by bleeding alone, or had a sarcoma developed? The marked destruction of bone, the rapid growth of the swelling, and the extensive necrosis tended to support the possibility of sarcoma. Nevertheless, the tumour was not malignant.

The level of AHG which is necessary for haemostasis during such an operation is not known, and it probably depends on the type of operation. Our patient started to bleed on the 6th postoperative day, when his AHG level was between 15 and 21 per cent, while there was no abnormal bleeding during operation when the AHG level was about 40 per cent. This is in agreement with the statement of Macfarlane *et al.* (1957) that an AHG level of 30 per cent is necessary to maintain haemostasis in such patients.

The turnover of human AHG in our patient was more rapid before (T/2 about 4 hours) than after the operation (T/2 6—7 hours), see fig. 2. This confirms the suggestion of Brinkhous *et al.* (1956) that bleeding and necrosis increase the turnover rate.

Biggs (1957) reports that animal AHG has the same turnover time as human AHG, and our results agree with her observations. The calculations of the postoperative turnover of AHG gave for the bovine preparation a T/2 of 6 hours

(range of 6 determinations: 5—8 1/2 hours), and for the pig preparations a T/2 of 7 1/2 hours (range of 6 determinations: 6—9 hours).

We consistently found that the measured *in vivo* response to the animal preparations was only about one third of the peak value which was calculated on the basis of *in vitro* assays of the preparations (see table II), while the response to human plasma agreed closely with the calculated peak value (see fig. 2). Fraenkel & Honey (1955) and Sharp & Bidwell (1957) also failed to reach the expected peak levels with animal preparations. These results may indicate that part of the *in vitro* activity of the animal preparations is unspecific and thus may not reflect true AHG activity. This may be a serious drawback to such preparations compared with preparations from human origin, since Blombäck (1959) reports expected AHG levels after infusion of human preparations.

Macfarlane *et al.* (1957) reported that some of their patients developed a partial resistance to the animal AHG after a few days of treatment. In our patient we could demonstrate a decreasing effect only of the first batch of pig AHG. Calculated from the peak values following the injections of this batch, one ampoule gave an average effect equivalent to 85 ml human plasma for the first two days of treatment; for the two last days this average value had dropped down to an equivalent of 40 ml human plasma. We do not know the explanation of this phenomenon.

A progressive thrombocytopenia developed during treatment with the bovine preparation, probably due to platelet agglutinins (Sharp & Bidwell 1957, Macfarlane *et al.* 1957). The platelet count became normal when we changed to pig material, which is reported not to con-

tain platelet agglutinins (Sharp & Bidwell 1957). Apart from the thrombocytopenia we did not observe serious antigenic effects of the concentrates.

Summary

Exarticulation in the hip joint was performed in a haemophiliac with an enormous swelling of the thigh. The patient was given animal AHG preparations and survived the operation, but he bled seriously for several weeks.

Apart from a thrombocytopenia when using bovine material the preparations had no serious side effects. The turnover time of infused preparations did not differ from that of human AHG. However, the *in vivo* response was considerably lower than the expected value. This may be explained by unspecific activity in the animal preparations.

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