THE SURGICAL TREATMENT OF HAEMOPHILIC BLOOD CYSTS

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The treatment of cystic haematomas in patients with haemophilia and Christmas disease is an unsolved problem, and their occurrence can be a danger to life (Macfarlane, Mallam, Witts, Bidwell, Biggs, Fraenkel, Honey and Taylor 1957). Fraenkel, Taylor and Richards (1959), who reported two examples and reviewed the literature, were able to find only one report of a patient who had survived operation. This patient had a cyst of the thumb, which was amputated (Firor and Woodhall 1936). Abell and Bailey (1960) reported nineteen patients, of whom two survived after operation. One further patient has been reported (Egeberg, Borchgrevink and Hjort 1960) who survived disarticulation of the hip for a cystic haematoma of the thigh. Crock and Boni (1960) suggested that radical surgery as an elective procedure might be delayed too long.

This paper records successful surgical treatment in two cases, and draws attention to the careful haematological management required afterwards. In the first patient the cyst was excised, and in the second patient the limb which contained the cyst was amputated.

MATERIALS

Antihaemophilic globulin concentrate—In both patients animal antihaemophilic globulin was used. The porcine material was supplied by Crookes Laboratories Ltd. and the bovine material by Messrs S. Maw, Son and Son, both materials being prepared by the method of Bidwell (1955). The concentrate is supplied in ampoules, each containing approximately 200 units of antihaemophilic globulin activity (one unit being equivalent to 4 millilitres of human plasma), and is dissolved in physiological saline immediately before use.

It is necessary to assay each dose for antihaemophilic globulin activity before use, because activity may vary from batch to batch and individual ampoules may deteriorate with storage. The values for the plasma equivalents of the doses shown in Figures 2 and 3 were obtained by averaging the results for each particular batch.

Human antihaemophilic globulin used in both patients was prepared by the method of Kekwick and Wolf (1957) and supplied by the Blood Products Research Unit of the Lister Institute.

Administration—The animal antihaemophilic globulin was diluted to a volume of 200 to 400 millilitres according to size of the dose, because concentrated antihaemophilic globulin material gives rise to pain along the course of the vein. All antihaemophilic globulin materials were given by intravenous infusion through a small needle which was removed immediately after each dose. In this way inflammation of veins was avoided, even when the same vein was used repeatedly.

Blood samples before treatment were obtained through the infusion needle and samples after treatment from the opposite arm. The time taken for each dose varied from half an hour to two hours.

Hydrocortisone (100 milligrams as 133 milligrams of sodium hemisuccinate) and chlorpheniramine maleate (Piriton) (10-20 milligrams) were given intravenously with each dose in the hope of preventing or lessening any reaction that the infusion of antihaemophilic globulin material might provoke.

Methods of estimation—Lee and White clotting times (normal range 4-10 minutes), prothrombin consumption index (normal range 0-15 per cent) and platelet count (normal range 150,000-300,000) were all done according to the methods of Biggs and Macfarlane (1957). Antihaemophilic globulin (normal range 50-200 per cent) was assayed by the method of Biggs (1957).

CASE REPORTS

Case 1—A man of thirty-eight had been known to have a bleeding tendency since early childhood. He bruised easily and badly and had never been to school. Episodes of epistaxis and recurrent haemarthroses, particularly of the knees and elbows, had been frequent. Haematemesis and haematuria had also occurred, and the latter had been severe enough to require blood transfusion. One maternal uncle had died from bleeding and two maternal great uncles had also been "bleeders."

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When aged twelve years his left loin and buttock had been run over by a cart wheel with resultant bruising. Three years before admission he developed a swelling in the left loin which gradually increased in size, although it caused him no pain. Three months before admission he consulted his doctor about pain in the left groin and thigh, thought to be due to a small intramuscular extravasation of blood. At the same consultation he mentioned the loin tumour, which by this time was the size of a football. He was admitted to his local hospital where investigations confirmed the diagnosis of haemophilia.

The cyst was aspirated and about four pints of altered blood were removed. The needle track failed to heal, he became pyrexial and the cyst refilled. He was transferred to the Radcliffe Infirmary in December 1959.

On examination there was limitation of movement of both knees and both elbows from previous haemarthroses. An enormous fluctuant swelling occupied the left loin and appeared to extend into the anterior abdominal wall. From an aspiration puncture in the centre of the swelling there was a continuous bloodstained serous discharge. Radiographs showed erosion of the ilium, with a large soft-tissue swelling (Fig. 1).

Because of the continuous discharge from the cyst and the likelihood that overwhelming infection would follow, it was considered that only complete surgical excision would be effective despite the very poor prognosis.

Investigations—The haemoglobin was 38 per cent and the platelets numbered 260,000 per cubic millimetre. The clotting time was 36 minutes, prothrombin consumption index 208 per cent and the antihaemophilic globulin blood level 0 per cent. These results were consistent with a diagnosis of severe haemophilia.
Treatment—On the day of admission four pints of fresh blood raised the blood antihaemophilic globulin level to 5 per cent, reduced the clotting time to 4½ minutes and the prothrombin consumption index to 21 per cent. On the next day he was given an initial infusion of porcine antihaemophilic globulin which was accompanied by a reaction, characterised by tightness in the chest and shivering. After this, operation was begun. At operation (Professor P. R. Allison) an elliptical incision was made over the tumour to include the puncture. The cyst was dissected out with relative ease down to the lateral aspect of the wing of the ilium. It was removed together with a wedge of iliac bone and including all the prolongations to the retroperitoneum, anterior abdominal wall, and hip joint. The wound was closed with care to avoid a dead space, and each layer was powdered liberally with penicillin and antihaemophilic globulin.

Progress—Because the response to the initial pre-operative infusion of antihaemophilic globulin was not adequate for a long (eight hours) operation, a second infusion of porcine antihaemophilic globulin was given during operation in addition to six pints of fresh blood. Infusions of porcine antihaemophilic globulin were given once daily afterwards, and no further reaction to the material was noted. On the fifth day after operation the response to the infusion was less and the sample taken after infusion showed a blood antihaemophilic globulin level of only 48 per cent (Fig. 2): a further infusion was given in the evening. On the next day the blood sample before infusion contained for the first time no antihaemophilic
globulin, and, since the sample after infusion only contained 10 per cent of antihaemophilic globulin, bovine antihaemophilic globulin was substituted for the porcine and an evening infusion given. This was associated with tightness of the chest, nausea and vomiting. The following day the patient seemed well, the wound looked healthy and the sutures were removed. By evening, however, the wound had begun to ooze brightly bloodstained fluid and a second infusion of antihaemophilic globulin was given. After this the wound continued to ooze in spite of twice-daily infusions of bovine antihaemophilic globulin. Five more reactions occurred during these infusions and were usually associated with a rigor as well as nausea and vomiting. By the tenth day after operation the platelets were too few to count. The platelet count remained low for the next four days, so the bovine antihaemophilic globulin was stopped,

although a good response was still being obtained, and he was given prednisolone 60 milligrams daily and a daily single infusion of human antihaemophilic globulin. Three days later the bleeding from the wound had ceased and the platelet count was 190,000 per cubic millimetre. Treatment with infusions of antihaemophilic globulin was therefore discontinued eighteen days after operation. By the twentieth day the wound had healed apart from one small sinus which remained near the anterior end of the suture line. Prednisolone was gradually withdrawn.

On the twenty-ninth day after operation, while walking in the ward, the patient fell and developed a considerable haemarthrosis in the left knee, but this settled with pressure bandaging and two daily infusions of one litre of fresh frozen plasma.

FIG. 3
Case 2—Antihaemophilic globulin levels achieved in response to treatment.
A sinograph at this time showed a large cavity in the region of the excised iliac crest. A catheter was put into this to a depth of nine inches, and through this the cavity was irrigated with phenoxytol and continuous suction was applied. On the patient's discharge three months after operation the sinus track was half an inch deep, and it soon closed. The patient later returned to his duties as a clerical officer in the Civil Service, and in December 1960 was leading an active life.

The pathological report on the specimen showed it to be a cystic haematoma like those described by Fraenkel, Taylor and Richards (1959).

**Case 2**—A man of thirty-five had been known to have a bleeding tendency since early childhood. He bruised easily, had bled after a tooth extraction and recurrent haemorrhages and haematuria had been frequent. In 1945 he had developed a haemarthrosis of the left hip which had kept him in bed for some weeks, and during this time he developed considerable wasting of the left calf muscles. Some months later, while walking, he developed pain in the left calf, and that evening the calf became swollen and tender and the skin over it shiny and tense. The haematoma was aspirated but only a small quantity of blood was obtained. The pain continued for three or four weeks and he was on crutches for a long time. He gradually recovered but he was left with a hardness of the calf muscles. There was also shortening of the calf muscles, and since this was a considerable disability, tenotomy of the calcaneal tendon was done in 1954 under the cover of fresh blood and antihaemophilic globulin (Cohn's fraction). There was no bleeding at the time of the operation but he bled for two weeks after it and required blood transfusion.

In 1956 he had a cerebral haemorrhage with aphasia which lasted for six months, and in 1958 he was admitted to the Radcliffe Infirmary with haematuria and a haemoglobin of 29 per cent. He was transfused and the diagnosis of haemophilia was confirmed. In June 1959 a lump appeared over the inner and upper aspect of the left tibia which gradually increased in size. There was no history of injury and the lump was not painful. He was admitted to the Nuffield Orthopaedic Centre in November 1959. Examination revealed a hemispherical mass two and a half inches in diameter on the upper end of the left leg just medial to the tibial tubercle. It was sharply defined, hard in consistency and firmly attached to the underlying tissues. It was thought that this was probably a local haematoma, but malignancy could not be excluded and an exploratory operation was decided upon.

**Operation and progress**—The operation was performed under cover of an infusion of human antihaemophilic globulin. The mass was found to consist of chocolate-coloured solid material and was connected, through the interosseous membrane, with a large cyst in the calf, compression of which released much brownish fluid. Further interference seemed unwarranted; so the wound was closed and a pressure bandage and plaster backslab were applied to immobilise the limb. During the next eight days, six infusions of human antihaemophilic globulin were given. On the eighth day the sutures were removed and the wound appeared to be well healed. A plaster cylinder was applied to immobilise the limb and he was discharged home. The wound reopened, and five weeks after the operation he was admitted to the Radcliffe Infirmary. On examination the wound was gaping and filled with blood clot, the left calf was swollen and tense, and he had a mild pyrexia. A swab of the wound showed pus cells but no organisms. Since the patient was apprehensive of further operation it seemed reasonable to adopt expectant treatment, by immobilisation and antibiotics. Low-grade pyrexia persisted, and a week after his admission the calf was a little larger and there was no evidence of healing. The next day the leg was more inflamed and the patient agreed to operation. Amputation through the knee was decided upon because it would avoid cutting large muscle masses and the risk of subsequent bleeding would be reduced. Immediately before operation an infusion of porcine antihaemophilic globulin was given which raised the blood antihaemophilic globulin level to 36 per cent and reduced the clotting time to normal.
Investigations—The haemoglobin was 78 per cent and the platelets numbered 210,000 per cubic millimetre. The clotting time was 50 minutes, prothrombin consumption index 120 per cent, bleeding time 6 minutes, tourniquet test negative, antihaemophilic globulin blood level 0 per cent and no antihaemophilic globulin inhibitor was detected. These findings were diagnostic of severe haemophilia.

Operation—The leg was amputated through the knee with the flap cut on a bias so as to exclude the sinus. Each tissue layer was liberally dusted with powdered antihaemophilic globulin, and the wound was drained.

Progress after operation—Since the initial response to porcine antihaemophilic globulin was not so good as expected a further infusion was given during the operation and then daily for eleven days. A good response was achieved at first, but less so with the last four infusions (Fig. 3). During this period minimal oozing occurred. The drain was removed on the third day after operation. The wound healed by first intention and all sutures were removed on the tenth day. On the sixteenth day a haematoma formed on the lateral aspect of the suture line. In spite of an infusion of fresh plasma the haematoma increased in size and on the eighteenth day bovine antihaemophilic globulin was begun again and continued for six days. Three of the infusions caused reactions, and after the fifth and sixth infusions the patient developed a petechial rash. Platelets had been reduced to 24,000 per cubic millimetre and 42,000 per cubic millimetre respectively on these days. Further infusions were therefore discontinued. The haematoma became infected with a penicillin-resistant staphylococcus but healed gradually after a course of erythromycin. The patient was discharged home seven weeks after operation with a haemoglobin of 75 per cent. Since his discharge he has been able to get about with a pylon limp and is being fitted with an artificial limb.

Pathological examination of the haematoma showed histological appearances similar to those described by Fraenkel et al. (1959).

DISCUSSION

When a patient with haemophilia or Christmas disease develops a cystic haematoma, treatment presents a considerable problem. These cysts, which because of their nature have sometimes been called haemophilic pseudo-tumours, have extensive ramifications and may erode through bone or other structures, as occurred in the first patient. They do not have a true capsule and thus cannot easily be removed. They develop slowly, however, and patients may survive for long periods.

Silber and Christensen (1959) advised treatment aimed at correcting the coagulation defect. Their patient with "plasma thromboplastin component" deficiency (Christmas disease) had a cyst very like that of our first patient; this was drained and a chronic sinus developed. These authors treated their patient for a period of six months with daily infusions of 750 millilitres of fresh plasma, together with intermittent whole blood transfusions to control the anaemia. During this time the tumour decreased in size to about one-third, and radiographic reconstitution of the ilium occurred. The patient eventually died from staphylococcal septicaemia.

Fraenkel (1957) pointed out that small haematomata may disappear rapidly in the haemophilic patient. Crock and Boni (1960) confirmed this observation in three of their patients and commented that even a large haematoma may be absorbed if appropriate measures to stop the bleeding are undertaken promptly. This form of treatment may be successful in the prevention of the development of a blood cyst or even in resolving a small cyst, but when the cyst is large its limitations are obvious.

Müller (1942) favoured irradiation, which he believed decreased the size of the tumour. Other authors are not so convinced, and no patient treated by irradiation has been followed for longer than six months.

Expectant treatment is not without risk. Hall (1961, Case 1) reported the death of a patient whose cyst ruptured into the sigmoid colon. Abell and Bailey (1960) reviewed the literature and
recorded nineteen cases with twelve deaths. Only three deaths resulted directly from the cyst; the remainder were due to added surgical interference. These authors did not include the two cases reported by Fraenkel et al. (1959) nor that recorded by Egeberg et al. (1960). Crock and Boni (1960, Case 4) also reported a case which conforms with many of those cited in the literature.

Thus, out of twenty-four cases recorded in the literature fifteen died. The mortality may be even higher than this because, of the nine survivors, four were followed for less than one month and two for only six months.

Minor surgical procedures such as aspiration, drainage or biopsy are not adequate and may lead to chronic sinus formation with infection of the cyst and fatal septicaemia, as in Silber and Christensen's case. Even if aspiration is successful it is only a temporary measure because the cyst will fill up again, as in our first patient. Since these cysts are loculated complete aspiration is impossible.

Radical surgical removal of a cyst under cover of animal antihaemophilic globulin may become necessary for three reasons: 1) minor surgical interference has been unsuccessfully attempted; 2) the diagnosis is in doubt and biopsy is necessary to exclude a malignant condition; or 3) the cyst has become large enough to be an intolerable inconvenience to the patient or because the site constitutes a danger to life.

In both our patients surgery was necessary for the first reason, though initially the second reason had applied to the second patient and the third reason could have been applicable to the first patient.

In the second patient the initial operation was a diagnostic one. When the cyst was discovered it might have been safer to proceed to amputation, or to attempt removal of the cyst. It was considered, however, that removal of the cyst would leave the patient with a useless leg and that amputation might not be necessary if the biopsy incision healed. A cyst in this site did not, at this stage, constitute a danger to life. It was hoped that the haemostatic cover of the human antihaemophilic globulin together with immobilisation of the limb would be sufficient to heal the operative incision. Longer immobilisation would have been preferable but even so the wound might have broken down and become infected. The final decision to amputate the leg was easily made because this operation is no more difficult than any other operation in a haemophiliac.

In the first patient the position was different, and the only hope of saving the patient's life was by attempted removal of the cyst. This was done successfully and as far as could be ascertained, completely. The danger of haemorrhage into the large cavity left after excision of the cyst was obvious, and for this reason the wound was dusted with a mixture of penicillin and antihaemophilic globulin as each layer was closed. In this way it was hoped that any oozing might be curtailed. The successful use of human antihaemophilic globulin as a paste to promote local healing in a haemophiliac with a circulating anticoagulant has been reported (Hall 1961, Case 3). It seems probable that the local use of antihaemophilic globulin may have played a part in assisting healing of tissues in both these patients, for virtually no bleeding occurred in the early part of the post-operative period.

In both our patients the treatment after operation followed lines which had been successful in previous operations (Macfarlane et al. 1957; Handley, Painter and Hall 1961). Daily or twice daily infusions of antihaemophilic globulin were given and the dose was adjusted according to the response obtained. The measured in vivo response to animal preparations bears little relation to that calculated on the basis of in vitro assays (Fraenkel and Honey 1955, Sharp and Bidwell 1957, Egeberg et al. 1960). The response varies from patient to patient and may be reduced by the presence of necrosis and bleeding. This may be the reason for the initial poor response in these patients. Both patients had to be given booster doses during the operation, but after removal of the cysts good responses were obtained. In the first patient the poor response to the initial dose made us give a double dose, equivalent to 12 litres of
plasma, on the second day and this produced a blood antihaemophilic globulin level of 400 per cent. In both patients it was attempted to keep the blood antihaemophilic globulin level in the normal range for at least part of each day or at any rate above the arbitrary level of 40 per cent suggested by Macfarlane et al. (1957) (Figs. 2 and 3).

In both patients porcine and bovine preparations were used, the porcine material being used first in each case. The first patient had an anaphylactic type of reaction to the initial dose and, although he had a good response, but no reaction on the following days, by the fifth day after operation the response had begun to decrease and bovine material was then given. For some reason this patient’s platelets fell while porcine antihaemophilic globulin was given. This fall was aggravated by the administration of the bovine material, which contains platelet agglutinins (Macfarlane, Biggs and Bidwell 1954). Twice-daily infusions were given because the samples taken before treatment suggested that the antihaemophilic globulin level was falling off rapidly in spite of a good initial response. This may be in accordance with the suggestion of Brinkhous, Penick, Langdell, Wagner and Graham (1956) that bleeding increases the turnover rate, for bleeding was now taking place. Undoubtedly the twice-daily infusions of the bovine material aggravated the thrombocytopenia, and it is possible that much, if not all, of the bleeding that took place may have resulted directly from the thrombocytopenia. Bleeding stopped when the platelet deficiency was corrected by giving steroids and replacing the bovine antihaemophilic globulin by human antihaemophilic globulin.

The thrombocytopenia produced by bovine antihaemophilic globulin is a disadvantage and may even curtail its use, as in the case of the second patient, but extremely good blood antihaemophilic globulin levels may be obtained with this material, and a decreased response does not seem to develop so quickly as when the porcine material is used. Usually when the bovine material is given once a day, as is the normal procedure, the platelet depression is only temporary and the count has returned to normal levels by the time the next dose is due. The possible development of thrombocytopenia should not be allowed to detract from the value of the bovine material, because it is more important in these patients to maintain a high antihaemophilic globulin blood level. Nevertheless, this possibility should be borne in mind and it may be wiser to start by using the porcine material when carrying out any major surgical operation.

Since both these materials contain animal protein there is a theoretical risk of anaphylaxis if they are used again in the same patient. It would naturally have been preferable in these patients to have used only one type of animal material and kept the other in reserve for possible future use. This was not possible, and the fact that both these patients have received both types of material does not necessarily preclude their use on a future occasion should the need arise. Great care in their use will however be necessary.

SUMMARY

1. The treatment of two haemophilic patients with cystic haematoma by radical surgical excision is described.
2. Details are given of their management after operation with the successful use of animal and human antihaemophilic globulin to control bleeding.
3. The literature of cystic haematoma in haemophilia is briefly reviewed and the seriousness of this condition stressed.

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REFERENCES


