HAEMOPHILIA AND HAEMOPHILIC ARTHROPATHY*

AN HISTORICAL REVIEW AND A CLINICAL STUDY OF 42 CASES

BY

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Haemophilia in man is uncommon, with a prevalence of about 2-3 per 100,000 in Great Britain, but even so, this means there are about 1,500 haemophiliacs in this country. In Northern Europe and North America cases are frequently found, whilst fewer have been reported in the Latin countries (Biggs and Macfarlane, 1957, 1958). In Australia, the incidence is somewhat higher (de Gruchy, 1958). In Asiatics and Negroes of pure breeding, the disease seems to be almost unknown (Nesbitt and Richmond, 1949; Pachman, 1937), cases which have been described almost all having some European ancestry. The only animal in which a similar condition has so far been found is the dog (Hutt, Rickard, and Field, 1948; Graham, Buckwalter, Hartley, and Brinkhous, 1949).

It seems probable that about half those born haemophilic reach adult life and develop joint manifestations, but concentrated preparations of anti-haemophilic globulins (AHG), which are likely to be more widely available in the future, may enable more to live longer. It may be of interest to look at the present problem of joint disease and deformity, and at the methods which aim at preventing it, relating by the way a little of the history of this disease and its arthropathy.

I. HISTORICAL ASPECTS

The word "haemophilia" was introduced into medicine by Hopff (1828), a pupil of J. L. Schönlein, but there are many references in older literature to diseases which could have been haemophilia. In the Babylonian version of the Talmud (a commentary on Jewish life, written in the 5th century A.D.) the story is told of four sisters who lived in Zipporah

in the 2nd century A.D.; the first of them had her child circumcized, and he died; likewise the second and third sisters with their first-born sons; when the fourth sister brought her child along, the Rabbi, Simon ben Gamaliel, ordered that she should not have him circumcized, lest the same fate should befall him (Tractate Yebamoth, fol. 64). A second Talmudic reference (Tractate Shabbath, fol. 134a) describes the experience of the Rabbi Nathan, who, on a visit to a far country, was accosted by a woman "who had circumcized her first son and he had died and her second son and he had died: the third she brought before me. Seeing that he was red, I said to her, wait until his blood is absorbed. So she waited until his blood was absorbed and circumcized him, and he lived . . . On another occasion (a similar history) seeing that he was green I said to her, wait until he is full blooded; she waited and circumcized him, and he lived."

These two rather confusing stories were interpreted by Katzenelson (1884), who considered that in both instances haemophilia was the disease concerned, for he felt it unlikely that two brothers would have died after circumcision otherwise. In the Hebrew, the word "red" had the connotation of "reddish-black", and he considered this to mean that the child showed bruises following a difficult delivery, for as he pointed out, a reddish colour is normal in the skin. "Green", he felt, like the later word "chlorosis", meant the pallor of a severe anaemia, perhaps related to umbilical or internal haemorrhage. It is interesting that in each case, later circumcision did not prove fatal, and that the children were each named after the Rabbi whose advice had been taken!

In the 11th century, Khalif Ibn Abbas, commonly called Albucasis (quoted by Sköld, 1944), described a village where the males suffered from a disease manifested by uncontrollable bleeding from wounds and mucous membranes. In the 14th century,

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a Jewish man was reported to have lost two sons after circumcision, but when his third arrived, this time by a second wife, circumcision was performed without incident. There were a number of similar histories of possible haemophiliacs.

The first reliable account of the disease was given by Dr. John Otto of Philadelphia, who was in his late twenties at that time (Otto, 1803). In between tending victims of a widespread yellow fever epidemic, he prepared for publication (Fig. 1) observations of the descendants of a woman named Smith, who had settled in Plymouth, New Hampshire, and had transmitted to her children a tendency to bleed excessively from wounds. He noted that males only were affected, and that the trait was transmitted through the females of the line. Otto

also mentioned in his paper a Dr. Benjamin Rush, who told him of other cases, one in York, and another in Northampton county, U.S.A., and a Mr. Boardley, who told him of a family in Maryland. It would thus appear that the disease was fairly well known in New England, early in the 19th century.

By 1813 there was quite an extensive literature on bleeding diseases, mainly in the United States and Germany. Dr. John Hay of Reading, Mass., which at that time was a small town near Boston, described in that year the pedigree of the Appleton-Swains, descendants of Oliver Appleton (Hay, 1813). Felt (1834), in his *History of Ipswich, Essex, and Hamilton*, cited this family as one of the curiosities of the district. In his writings, Hay described the disease quite fully, and with much practical experience, as some members of the affected family were his next door neighbours. He appeared quite perturbed about the whole problem, and it was not until the last paragraph of his paper that the reason became apparent:

"My eldest son, Jonathan P. Hay, married a descendant of Mr. Appleton, and has eight children by her: three sons, the youngest about eight years; and has the exact complexion of the bleeders, but has not as yet bled more than common. I am apprehensive that he will exhibit the haemorrhagic disposition."

Subsequent records of the Appleton family (Osler, 1885; Pratt, 1908) do not support Hay's apprehension.

Blagden (1817), Surgeon Extraordinary to the Duke of Kent, published the first reliable English report of the disease. His patient had, as a child, bled for 3 weeks after a dental extraction and had later had a cut on his forehead which bled excessively. The final episode, at the age of 26, was haemorrhage following dental extraction, which continued even after his carotid artery had been ligated.

Bulloch and Fildes (1912) published a comprehensive review of haemophilia with over 900 references, in which early cases of excessive bleeding are fully analysed.

HAEMOPHILIC ARTHROPATHY

The first record of excessive bleeding associated with arthritis, was that of Philip Hoechstetter, of Augsburg, who in 1674 described a case that could well be one of haemophilia. This was of a boy who bled profusely, first at birth from the umbilical cord, and whilst a youth from the nose and subcutaneously, who was also recorded as having haemorrhages into the joints, though details are not given.

Fig. 1.—First page of Dr. J. Otto's article (1803).

Fig. 2.—Frontispiece of Dr. J. Wickham Legg's monograph (1872).

Early references to haemophilic arthropathy are much less numerous than those of exterior bleeding. Little was written about joint manifestations before the end of the 19th century, and most of that came from France and Germany. In the 1860s, Volkmann (quoted by Vegas, 1914) noted that haemophilia and scurvy might be localized in the joints. More recently, Volkmann's ischaemic contracture has been described in haemophilia following haemorrhage into the muscles of the forearm (Groves, 1907; Lord, 1926; Hill and Brooks, 1936; Thomas, 1936; etc.).

J. Wickham Legg, of St. Bartholomew's Hospital, in 1872 wrote a monograph (Fig. 2) in which he described five cases personally seen, with excessive bleeding from minor wounds and after dental extractions, and with spontaneous and easy bruising. Three of these had joint troubles: the first had swelling of the knees intermittently for 6 years before he was seen; the second had pains in the knees, but no swelling; the third had intermittent swelling of the knee from age 4, and by the time he was seen at age 13 it was "out of its natural shape, and caused him to walk lame". The knee

was greatly enlarged on its inner aspect as if the bone ends themselves were enlarged, and the joint seemed to contain fluid. Pain was a feature in all three cases and other joints, hips and ankles, were involved, but not to the same extent.

The best early description of haemophilic arthropathy came from Germany, where König (1892) published a thorough study of eight cases. In two of his cases he operated on the joint, and both patients died of haemorrhage 3 and 10 days later.

EVOLUTION OF TREATMENT

Early methods of treatment of haemophilia are of some interest. Otto, and later Hay, both suggested that a purging dose of sodium sulphate, daily for 3 or 4 days, would stop the bleeding, or, if it did not, to quote the words of both of them "a more frequent repetition is certain to do so". Later authors suggested various procedures, including special diets, purging, and even venesection. Vegas (1914) used subcutaneous injection of rabbit serum with some success. In truth, nothing done was of real value until comparatively recently with the use of fresh blood transfusions at times in massive quantities, and latterly with the use of AHG to stop the bleeding.

ADVANCES IN DIAGNOSIS

Modern methods of diagnosis have shown that a number of factors concerned in the clotting mechanism may be deficient, but in patients with a suggestive clinical picture over 80 per cent. of cases are true haemophiliacs. Christmas disease, the commonest of the other forms of haemophilia, was first described in the U.S.A. by Aggeler, White, Glendening, Page, Leake, and Bates (1952) as "plasma thromboplastin component" deficiency. The name came from that of the first sufferer investigated in Britain, in a joint report from Oxford, Capetown, Plymouth, and the Postgraduate Medical School by Biggs, Douglas, Macfarlane, Dacie, Pitney, Merskey, and O'Brien (1952). Other and rarer types of clotting deficiency have since been recognized. Anti-haemophilic globulin is a labile component of the plasma globulin, and is consumed in the clotting process. Its administration appears to be of greatest value because thereby is supplied the lacking component necessary for clotting in true haemophilia. Because of the lability of AHG, it is essential that blood used for transfusion should be fresh. AHGs have been prepared both from human and animal (beef and pig) plasma, but the large amount of plasma necessary is only one of the difficulties that makes the cost of these very high. The animal types have

the added disadvantage of becoming less effective after about 10 days' administration (Macfarlane, Mallam, Witts, Bidwell, Biggs, Fraenkel, Honey, and Taylor, 1957). Christmas factor is much more stable than AHG and stored blood may be suitable for transfusion, although it seems best to give fresh blood (Brafield and Case, 1956).

FAMOUS SUFFERERS FROM HAEMOPHILIA

In England, haemophilia has been of special interest because of the involvement of the descendants of Queen Victoria (Haldane, 1938; Sköld, 1944; Iltis, 1948). Her son Leopold was a haemophiliac, and the gene was transmitted through two of her daughters, Alice and Beatrice. Among the former's descendants was Czarina Alexandra of Russia, and among the latter's Queen Eugenia of Spain, both of whom had haemophilic sons. Various researches have been made into the House of Saxe-Coburg-Gotha, from which both Queen Victoria and Prince Albert were descended, but no definite earlier case has been found. It thus seems most likely that a genetic mutation occurred in Victoria or her parents.

Probably the most widely known haemophiliac was Czarevitch Alexi, heir-apparent to the throne in Russia at the time of the Revolution, who was great-grandson of Queen Victoria. Fear for his health dominated the life of his mother, Alexandra, and provided the basis for the influence of the "monk" Rasputin, who claimed to be able to stop the bleeding, and who could in fact comfort Alexi even by speaking to him on the telephone (Buchanan, 1954). An American, Cumston (1918), reported on "good authority" that the boy had distension of the knee joints and discolouration of the ligaments, resulting in difficulty in walking, as a legacy of haemophilic haemarthroses. A member of the Czar's household, a sailor, was accustomed to carry Alexi around when he was having trouble (Buchanan 1954). Alexi, a puny boy, twice nearly died of haemorrhage before perishing in the Revolution in 1918.

II. CLINICAL STUDY

In the present study a systematic examination was made of the joints of patients who had been referred to the Department of Haematology at the Postgraduate Medical School of London for a suspected bleeding diathesis and who were proved to have one of the forms of haemophilia. The 42 cases in this series were those seen personally out of 77 known haemophiliacs living in London and the Home Counties, to whom letters were sent asking them to attend for an examination. Failed follow-up cases

included three who had died, six not traced, fifteen who were traced but did not reply, and eleven who, for various reasons, were unable to come. All cases seen were given a full medical examination. X rays were taken of the involved joints, as well as routine films of the hands, feet, and knees, and in the first 25 seen, of the cervical spine.

Clinical Findings

Of the 42 cases seen, 39 were suffering from true haemophilia (Haemophilia "A"), whilst three had Christmas disease (Haemophilia "B"). Ages ranged from 5 to 69 years and all were males. Only 24 gave a positive family history, which is in accord with most recent series, though proportions vary widely in many (Biggs and Macfarlane, 1958).

In 83 per cent. of cases, the first symptom occurred in the early years of life—haemorrhage after circumcision in the neo-natal period (14 per cent.), prolonged bleeding from a comparatively minor wound under the age of 5 (45 per cent.), and bruising (18 per cent.) being most common. Three cases had curious modes of presentation, one aged 67 with melaena, another aged 44 with post-operative haemorrhage after incision of a perianal abscess, and the third aged 46 with bruising and bleeding after scalene node biopsy. All of these patients had haemophilia of mild degree.

Three patients only presented with their first episodes in a joint; one had a haemarthrosis in the ankle at the age of 18 months, whilst the other two had knees involved when aged 5.

Case 1, a man born in 1932, was admitted to hospital in 1938 with pain and swelling of the right knee, diagnosed as tuberculosis and treated with rest and splinting. Some months later, however, a dental extraction was followed by persistent bleeding, and haemophilia was diagnosed. Subsequently he has had about twelve recurrences of haemarthrosis in both knees, and he now has a little residual deformity. His previous history revealed only an episode of somewhat excessive bleeding from a comparatively minor wound on the foot. An elder brother has subsequently been found to be a haemophiliac.

Of our 42 cases (Table I), fourteen gave no history of episodes involving the joints; of the 28 with such a history, 23 showed abnormal signs of joint involvement on physical examination.

TABLE I
FREQUENCY OF JOINT INVOLVEMENT
IN HAEMOPHILIA

History of episodes involving the joints		28
Residual signs of joint involvement		23
No history or signs of joint involvement		14
Total		42

The knee was the joint most commonly involved (Table II), 25 out of 28 patients with joint manifestations having had the knees affected. Ankles, elbows, and hips were the next most frequent. Most patients had both signs and symptoms of joint disease in each affected joint, but some, as might be expected, had symptoms only in one or more joints. In five cases, however, there were signs of involvement (*e.g.* loss of full range of movement and x-ray changes) in joints about which no history of any joint trouble whatever was obtainable. In all these five patients, other joints were involved both on history and on examination.

TABLE II
PATTERN OF JOINT INVOLVEMENT IN 28 PATIENTS

Joint	Total No. of Patients	Symptoms and Signs	Symptoms Only	Signs Only
Knees	25	20	5	—
Elbows	22	19	3	—
Ankles	22	14	8	—
Hips	19	11	5	3
Wrists	13	7	5	1
Shoulders	10	4	6	—
Fingers	9	4	4	1
Toes	6	2	4	—
Jaw	3	—	3	—
Spine	—	—	—	—

Those who had had numerous episodes of haemarthrosis often found it impossible to remember just how often various joints had in fact been involved. With haemarthroses occurring every month or so, joint pains seem to have become part of their everyday life. One patient, aged 22, made an interesting observation—he had noticed that the pain was more severe when swelling was marked and bruising was not, but that it was less severe and less prolonged when the bruise "came out".

Of the true haemophiliacs, the 24 who first presented after the middle of 1955 have had their plasma AHG level estimated quantitatively by members of the staff of the haematology department. The sixteen patients with a low AHG level (below 2 per cent.) have a high incidence of joint involvement, only one not having had haemarthroses, and twelve having residual signs (Table III); of eight

TABLE III
RELATION OF AHG LEVEL, FAMILY HISTORY, AND JOINT EPISODES IN 24 HAEMOPHILIACS

No. of Cases	AHG (per cent.)	Family History		Acute Joint Episodes		Residual Joint Changes	
		+	—	+	—	+	—
16	2 or Less	9	7	15	1	12	4
8	Over 2	6	2	1	7	1	7

with a AHG level over 2 per cent., only one has had haemarthroses, and he has minimal deformities. A positive family history did not show any relationship with AHG level (Table III).

Management of Acute Haemarthroses

Few acute haemarthroses were seen. The joints, whilst acutely painful, should be rested or splinted in the position of optimal function—thus no pillows should be allowed under the knees, nor should an extreme degree of flexion of the hip be permitted. If the AHG level can be raised by blood or plasma transfusion to that necessary for effective haemostasis, and if the patient is seen early in his course, it is reasonable to aspirate the joint, to relieve pressure and pain. As soon as the pain subsides, physiotherapy and gentle muscle setting exercises should be begun—this will probably be on the second or third day—and early weight-bearing should be the aim. It does seem that early emptying of the joint, cessation of bleeding and early restoration of movement are the greatest factors in maintaining normal function in the long run.

Chronic Joint Changes

Examination of chronically affected joints revealed many interesting changes. It was common to find apparent enlargement of the bone ends, loss of normal range of movement, wasting of muscles acting on the joint in question, and often bizarre deformity. In the knee, the femoral condyles were more prominent than usual, with loss of the final 5°-30° of full extension and backward displacement and often rotation of the tibia. In the elbow too, the articulating bones were enlarged, whilst movements were reduced, especially extension. Deformities in the small joints of the hands were not common, and those seen were minimal.

Radiology

In the knees, many different findings were noted. In severe cases, there was narrowing of the joint space, due to cartilage erosion and loss, and frequently irregularity of the joint surface. An appearance of "squaring off" of the tibial and femoral surfaces was found in many cases and osteophytic lipping was common, though not severe. Severe radiological and clinical changes were not always allied with loss of function as in the following cases:

Case 2, a man aged 30, a telephonist, first bled when aged 3 months after circumcision. He has had numerous episodes involving the joints, "hundreds" in all, but mainly in the right knee and the elbows. The right knee (Fig. 3) was found to have 30° flexion and 30° valgus deformity and marked posterior subluxation of

Fig. 3.—Case 2, right knee. Note loss of joint space, irregular articular surface, and appearance suggesting collapse of lateral tibial condyle. Note large nutrient artery (Middlemiss, 1960).

the tibia. The range of movement is 30°-80°. Despite this the patient is able to walk quite well with a stick, can drive a motor car, and has a sedentary occupation from which he rarely loses time.

Case 3, a man aged 56, a clerk, was first noticed to bruise excessively in the first year of life. He has had "hundreds" of joint episodes involving all the joints of the body, including the temporo-mandibular joint and the small joints of the fingers and toes, but excluding those of the spine. Over recent years he has had fewer haemarthroses and these tend to be of a minor nature. He was found to have a 60° flexion deformity with a range of movement of 60°-85° on the right, and a 30° flexion deformity with range 30°-35° on the left (Fig. 4, opposite).

Despite this he travels to work each day by bus and walks approximately half a mile at each end of his journey. He has not seen a doctor for years.

Osteoporosis was very common in affected knee joints, though a far from universal finding. Gross loss of normal trabecular pattern and coarsening of the remaining trabeculae often gave a cystic appearance in the bone ends. Such changes were not always present, however, and severe residua were at times unaccompanied by osteoporosis or by evidence of past healed porosis, as illustrated in Fig. 5 (opposite, Case 4).

Osteoporosis appeared to have caused collapse of the lateral tibial condyle in some cases, and we feel this, rather than differential lower femoral epi-

Fig. 4.—Case 3, x ray of knees, showing gross narrowing of joint space, irregularity of joint surface, and lipping, with a suggestion of "squaring" of the bone ends. Poor detail on the right is due to a 60° flexion deformity of the knee.

Fig. 5.—Case 4, a linesman aged 25, who had many episodes of haemarthrosis in the right knee, but none in the left. Note 10° flexion deformity on the right; the film shows squaring, narrowing of joint space, and lipping, but no obvious osteoporosis.

physeal overgrowth, to be responsible for such valgus deformities at the knees as were seen in Case 2 above (Fig. 3).

Overgrowth of epiphysis was seen in the distal end of the femur, but only in two juvenile cases, one aged 14 and the other aged 8, and in neither was there any greater increase in one condyle than in the other. In none of the adults was the result of such a differential growth change seen.

Overgrowth of the patella (Escande and Tapie, 1919) is well illustrated in Case 5, a boy aged 8 (Fig. 6, overleaf), in whom there is an increase on the left side, in which he had had eight or ten haemorrhages, when compared with the unaffected right side.

"Squaring" of the lower end of the patella, as stressed by Jordan (1958), was seen in only four of the 25 patients with affected knees. All of these had had their first episodes before puberty, and thus before growth was completed. Irregular calcification of cartilage was seen in the line of growth of the lower femoral epiphysis as it advanced into the articular cartilage in Case 5. Such irregularity can be seen in normal subjects, especially by magnification techniques, but it is of lesser degree (Bywaters, 1959).

Fig. 6.—Case 5, a boy aged 8, had numerous haemarthroses in the left knee, but none in the right. Note increase in size of left patella when compared with the right, and the irregular line of advancing calcification in the femoral condyle on the left when compared with that on the right.

Growth arrest lines, common in normal subjects and in Still's disease, were seen frequently, and were in four instances unusually prominent (as noted by Middlemiss, 1960):

Case 6, a boy aged 12, first bled after circumcision when 8 days old. Since the first joint episode in the right wrist in 1948, he had had many haemarthroses,

involving all the large joints of the body, plus those of the hands and feet. In June, 1958, he developed a haematoma in the lower thigh, which became spontaneously infected, despite surgical drainage the infection spread to involve the bone. In the sequestrum (Fig. 7) the growth arrest lines are especially prominent. The patient, now aged 12, has a chronic discharging sinus, the pus from which is only rarely blood-stained.

Fig. 7.—Case 6, a boy aged 12, with chronic osteomyelitis of femur following an infected haematoma. Note growth arrest lines in sequestrum.

Haemosiderosis of the joint capsule (Alexander and Landwehr, 1948; Doub and Davidson, 1926; Newcomer, 1939; MacDonald and Lozner, 1943; Collins, 1951) was not seen in the *x* rays of any of our cases, though it has been seen in previous cases at this hospital (Bywaters, 1959).

In twelve of the eighteen patients in whom the elbows were *x*-rayed, there was enlargement of the head of the radius in the affected joint. This is well seen in Cases 7 and 8. Case 7 (Fig. 8) had had numerous episodes in the right elbow but none in the left, and Case 8 (Fig. 9, overleaf) had had six haemarthroses on the right side and none on the left.

Other changes seen commonly in the elbow joints were loss of joint space and lipping, the latter usually of comparatively minor degree.

In the ankles, flattening of the upper articular surface of the talus was seen in advanced cases, along with marked lipping. The lower end of the tibia was at times enlarged, as seen in the ankle of

Case 9, a man who had had many episodes in this joint (Fig. 10, overleaf). Case 10, a young man aged 19, had an ankylosed talo-tibial joint (Fig. 11, overleaf), but this was the only ankylosed joint, either fibrous or bony, found in our whole series of 155 affected joints. Erosion of the joint surfaces was found quite frequently in the ankles.

In the hands, osteoporosis was seen commonly, even when there was neither history nor signs of local joint involvement. Two curious changes were seen. Fig. 12 (overleaf) shows the carpus of Case 11, a man aged 49, who has no history of joint episodes nor of any injury to the wrist and in whom, on clinical examination, the wrist joints are perfectly normal. Such cystic changes have been found in two other cases with similar negative histories and with clinically normal wrists.

Cases 12 and 13 (aged 21 and 14), the former without a history of episodes in the right wrist but with some limitation of movement and the latter without

Fig. 8.—Case 7, a man aged 44, had severe haemophilic arthropathy, but the left elbow and left hip were never involved. The right elbow has a 45° flexion deformity and can only be bent to a right-angle; pronation and supination are half normal. The left elbow normal. Note narrowing of joint space on the right and marked enlargement of the right radial head.

Fig. 9.—Case 8, a man aged 25, had six haemarthroses in the right elbow but none in the left. Note enlargement of right radial head.

any wrist involvement, showed a curious radiographic picture at the distal end of one ulna (Fig. 13A, B, overleaf). Such changes are probably due to disturbance of epiphyseal growth by haemorrhage involving the epiphysis. Records of a similar change in a haemophiliac have not been found, though Newcomer (1939) described, without illustration, a case in which at the left wrist "the ulna is shortened; it does not articulate with the wrist".

No haemophilic pseudo-tumours (Firor and Woodhall, 1936; Ghormley and Clegg, 1948) were seen in the series.

An interesting change was seen in the hip of Case 14, a 25-year-old haemophiliac, an intelligent man who was certain that he had had no trouble in his hip joint (Fig. 14, overleaf). Examination revealed marked loss of rotation and abduction. In contrast to this painless involvement, recurrent painful haemorrhages into a joint which showed no residual changes have been seen from time to time, as in the case of a man aged 22 with Christmas disease, who had had recurrent episodes of bleeding into all the major joints without clinical or radiological change.

Clinical Pathology

The erythrocyte sedimentation rate (Westergren) was tested in 31 cases and was below 10 mm./hr in 29; in two with histories of recent upper respiratory tract infections, however, it was above 40 mm./hr. The differential agglutination test (D.A.T.) was performed (Table IV) to see if repeated episodes of inflammatory joint involvement could lead to the presence of the rheumatoid factor in the blood. The test was positive in only one patient, a boy aged 14 with Christmas disease, who showed a titre of 1 : 256. There was no family history nor clinical evidence of rheumatoid arthritis. His latex fixation test was also positive, as was that of one other man aged 44 with severe joint deformities.

TABLE IV
SEROLOGICAL TESTS IN 32 CASES OF HAEMOPHILIA

Test	No. of Patients Tested	Result	
		Positive	Negative
Differential Agglutination ..	32	1 (1 : 256)	31
Latex Fixation	28	2	26

Fig. 10.—Case 9, a solicitor aged 41, had many haemarthroses in the left ankle as a child, usually following minor sprains. Note widening of lower end of tibia in its AP diameter, loss of joint space, sclerosis in articulating bones, and cystic appearance in lower end of tibia.

Schooling and Occupation

Those with more than minor degrees of joint involvement in childhood all had difficulty in attending school. Most missed at least 2 years, but subjectively all felt they were able to keep up with their class fellows when able to attend. In view of likely disability in later life, it is most desirable that such patients be admitted to hospitals where schooling facilities on the wards are available. Of the six boys in our series in the school age range, three are attending ordinary schools (though two of these, who have haemarthroses, miss a great deal), whilst two of the other three can only potter about at home and one is in an institution for chronic illnesses.

Only five out of the 35 adults are unable to work. 22 have sedentary jobs, mostly clerical, but eight are doing various kinds of manual work. Case 15, a man aged 34, with no evidence of joint disease is a prison warder. He practises judo in his spare time but plans to give this up as his wife objects to the frequent bruises. His AHG level is 7.5 per cent.

Discussion

Most previous writers on haemophilic arthropathy have reported small numbers of cases personally seen (Klason, 1921; Key, 1932; Buus, 1935), though larger series of haemophiliacs, some of whom had arthropathy, have been recorded. Thomas (1936) described 98 haemophiliacs, of whom 77 gave a history of joint symptoms and sixty had permanent deformities. Birch (1937) described 98 patients, of whom 83 gave a history of joint symptoms and 66 had residual deformities. Davidson, Epstein, Miller, and Taylor (1949), on the other hand, noted that 38 out of forty cases had chronic joint changes, though their series was not apparently selected because of arthropathy. More recently, Rodnan, Lewis, Warren, and Brower (1957) have fully investigated 53 bleeders (44 with true haemophilia and nine with Christmas disease), of whom 47 had had haemarthroses and 42 had objective changes in the joints. Jordan (1958) has dealt exhaustively in an excellent monograph with over 100 cases of haemophilic arthropathy, many of whom were

Fig. 11—Case 10, a man aged 19, with severe generalized haemophilic arthropathy. Note plantar flexion deformity of foot due to ischaemic contracture in calf muscles, flattening of upper articular surface of talus, and bony ankylosis of ankle joint.

treated by orthopaedic measures to improve function.

The low follow-up rate, in which only 42 of the 77 haemophiliacs sought were seen, is of interest. A few of our patients, usually the older ones, were very loath to attend hospital, stating that the little that was done for them in hospital while they were young had been of more harm than value. These people now avoid hospitals whenever they can, and such an attitude among others may have accounted for some of the cases which were not followed up.

Fig. 12.—Case 11, a clerk aged 49, with no history of haemarthroses, nor of any bone or joint injury to the hands or wrists, which are clinically normal. Note "cysts" in carpus.

Others were unwilling to take time off work to attend, because they normally lost too much time when their disease was "active".

Some patients with recurrent joint episodes found that the same joint or group of joints was always involved. Thus one patient had many episodes in the right knee and elbow and none elsewhere, whilst another had one ankle and both elbows involved repeatedly but no other haemarthroses.

The pathogenesis of chronic joint changes is not known. Repeated haemarthroses, *e.g.* in patients with haemangiomata, do not produce such joint changes as are seen in haemophilia, nor were similar changes produced experimentally by Key (1929) who injected the joints of dogs repeatedly with citrated blood. It seems to us, as to Key (1932) and to Rodnan and others (1957), that subchondral and intra-osseous haemorrhage in the bone ends, either primary or as an extension from a haemarthrosis in an already damaged joint, may cause ischaemic lesions of articulating bone, with secondary osteoarthrosis—a sequence similar to that of Caisson disease.

Fig. 13(A).—Case 12, a man aged 21, has no history of episodes in the right wrist, but movement is slightly diminished (60° — 0° — 60°) in comparison with that in the left wrist (75° — 0° — 75°).

Fig. 13(B).—Case 13, a boy aged 14, has no history or signs of wrist disease.

Both show obliquity of the ulnar epiphyses in the right wrist and widening of the lower ulnar shaft.

Fig. 14.—Case 14, a civil servant aged 25, had no history of haemarthroses in the hips, though other joints had been affected. Note flattening and shortening of femoral head, with cystic appearance underlying cartilage. The joint space is well preserved.

If such is the case, the best way to prevent irreversible damage would be to stop the bleeding and decompress the joint—moreover, this should be viewed as a medical emergency.

Enlargement of the radial head would seem to be the most characteristic and possibly diagnostic feature of haemophilic arthropathy. Similar changes have been described, but only rarely (De Palma and Cotler, 1956; Middlemiss, 1960). It is interesting to note that the original description and radiological demonstration of this change was given by Shaw from Bristol in 1897, only 2 years after Roentgen

reported the discovery of x rays. Enlargement of the radial head is seen in one of the radiographs reproduced by Buus (1935), though the author does not comment upon it. Our findings of minimal changes in the hands conflict with those of Hart (1955), who considers that haemarthroses in such joints are especially liable to result in destructive changes.

Summary

The historical aspects of haemophilia and haemophilic arthropathy are reviewed.

In 42 cases of haemophilia, 28 gave a history of haemarthroses, whilst 23 had permanent joint deformities of varying grades of severity. In one case, joint disease had been initially attributed to tuberculosis.

In this series, an anti-haemophilic globulin level of 2 per cent. or below was associated with joint manifestations in fifteen, and with residual joint deformity in twelve, of sixteen cases; when the level was above 2 per cent., joint manifestations and minimal residual deformity were seen in only one of eight cases.

Recurrent haemarthroses may be associated with clinically and radiologically normal joints whilst, conversely, changes may be found in joints in which the patient can give no history of past episodes.

The most characteristic radiological change of haemophilic arthropathy was an enlargement of the head of the radius, which was seen in two-thirds of those with involved elbows. Some patients with severe residua of multiple episodes of haemarthrosis

were able to lead quite normal lives despite their deformities.

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REFERENCES

- Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B., and Bates, G. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, 79, 692.
- Alexander, B., and Landwehr, G. (1948). *J. clin. Invest.*, 27, 98.
- Biggs, R., Douglas, A. S., Macfarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R. (1952). *Brit. med. J.*, 2, 1378.
- and Macfarlane, R. G. (1957). "Human Blood Coagulation and its Disorders", 2nd ed., p. 245. Blackwell Scientific Publications, Oxford.
- (1958). *Brit. J. Haemat.*, 4, 1.
- Birch, C. la F. (1937). "Haemophilia, Clinical and Genetic Aspects". *Univ. Illinois Bull.*, 34, No. 55.
- Blagden, R. (1817). *Med.-chir. Trans. (Lond.)*, 8, 224.
- Brafield, A. J., and Case, J. (1956). *Lancet*, 2, 867.
- Buchanan, A. M. (1954). "Queen Victoria's Relations." Cassell, London.
- Bulloch, W., and Fildes, P. (1912). "Treasury of Human Inheritance", ed. K. Pearson, vol. 1, p. 169. Dulau, London.
- Buus, C. E. P. (1935). *Acta radiol. (Stockh.)*, 16, 503.
- Bywaters, E. G. L. (1959). Personal communication.
- Collins, D. H. (1951). *J. Bone Jt Surg.*, 33B, 43c.
- Cumston, C. G. (1918). *N.Y. med. J.*, 107, 76.
- Davidson, C. S., Epstein, R. D., Miller, G. F., and Taylor, F. H. L. (1949). *Blood*, 4, 97.
- de Gruchy, G. C. (1958). "Clinical Haematology in Medical Practice", p. 532. Blackwell Scientific Publications, Oxford.
- De Palma, A. F., and Cotler, J. M. (1956). *A.M.A. Arch. Surg.*, 72, 247.
- Doub, H. P., and Davidson, E. C. (1926). *Radiology*, 6, 217.
- Escande, F., and Tapie, J. (1919). *J. Radiol. Electrol.*, 3, 298.
- Felt, J. B. (1834). "History of Ipswich, Essex, and Hamilton" (Printed by Folsom) Cambridge, Mass., cited in *Boston med. surg. J.* (1851), 45, 85.
- Firor, W. M., and Woodhall, B. (1936). *Bull. Johns Hopk. Hosp.*, 59, 237.
- Ghormley, R. K., and Clegg, R. S. (1948). *J. Bone Jt Surg.*, 30A, 589.
- Graham, J. B., Buckwalter, J. A., Hartley, L. J., and Brinkhaus, K. M. (1949). *J. exp. Med.*, 90, 97.
- Groves, E. W. Hey (1907). *Brit. med. J.*, 1, 611.
- Haldane, J. B. S. (1938). *Mod. Quart.*, 1, 129.
- Hart, F. Dudley (1955). *Postgrad. med. J.*, 31, 627.
- Hay, J. (1813). *New Engl. J. Med. Surg.*, 2, 221.
- Hill, R. L., and Brooks, B. (1936). *Ann. Surg.*, 103, 444.
- Hoechstetter, P. (1674). "P. Hoechstetteri Rararum Observationum medicinalium decades sex. ante hac editae, etc.", p. 170. Francofurti et Lipsiae. (Quoted by Bulloch and Fildes, 1912, p. 197.)
- Hopff, F. (1828). "Ueber die Haemophilie oder die erbliche Anlage zu tödtlichen Blutungen" Inaug.-Diss. Würzburg. (Quoted by Bulloch and Fildes, 1912, p. 308.)
- Hutt, F. B., Rickard, C. G., and Field, R. A. (1948). *J. Hered.*, 39, 3.
- Ilitis, H. (1948). *Ibid.*, 39, 113.
- Jordan, H. H. (1958). "Hemophilic Arthropathies." Thomas, Springfield, Ill.
- Katzenelson, J. L. (1884). "Yevreiskaya Obozrenie" (Translated in *Hebrew med. J.* (1958), 1, 178.)
- Key, J. A. (1929). *J. Bone Jt Surg.*, 11, 705.
- (1932). *Ann. Surg.*, 95, 198.
- Klason, T. (1921). *Acta radiol. (Stockh.)*, 1, 26.
- König, F. (1892). "Sammlung klinischer Vorträge", ed. R. von Volkmann, p. 233, n.s. No. 36 (Chirurgie No. 11).
- Legg, J. Wickham (1872). "A Treatise on Haemophilia." Lewis, London.
- Lord, J. P. (1926). *J. Amer. med. Ass.*, 87, 406.
- McDonald, E. J., and Lozner, E. L. (1943). *Amer. J. Roentgenol.*, 49, 405.
- Macfarlane, R. G., Mallam, P. C., Witts, L. J., Bidwell, E., Biggs, R., Fraenkel, G. J., Honey, G. E., and Taylor, K. B. (1957). *Lancet*, 2, 251.
- Middlemiss, J. H. (1960). *Clin. Radiol.*, 11, 40.
- Nesbitt, R. D., and Richmond, J. B. (1949). *J. Pediatr.*, 34, 315.
- Newcomer, N. B. (1939). *Radiology*, 32, 573.
- Osler, W. (1885). "Haemophilia", in "A Practical System of Medicine", ed. W. Pepper, vol. 3, p. 931. Sampson Low, Marston, Searle, and Rivington, London.
- Otto, J. C. (1803). *Med. Reposit. (N.Y.)*, 6, 1.
- Pachman, D. J. (1937). *J. Pediatr.*, 10, 809.
- Pratt, J. H. (1908). "A System of Medicine", ed. W. Osler and T. McCrae, vol. 4, p. 717. Oxford Medical Publications, London.
- Rodnan, G. P., Lewis, J. H., Warren, J. E., and Brower, T. D. (1957). *Bull. rheum. Dis.*, 8, 137.
- Shaw, J. E. (1897). *Bristol med.-chir. J.*, 15, 240.
- Sköld, E. (1944). "On Haemophilia in Sweden and its Treatment by Blood Transfusion", *Acta med. scand.*, Suppl. 150.
- Thomas, H. B. (1936). *J. Bone Jt Surg.*, 18, 140.
- Vegas, M. H. (1914). *N.Y. med. J.*, 100, 549.

DISCUSSION

DR. J. SHARP (*Manchester*): I should like to ask about the cause of pathological cystic changes in the wrists.

PROF. E. G. L. BYWATERS (*London*): I should like to make a comment on the changes seen and described as causing ulcerative lesions opposite each other, usually in the knee. It seems to me that this might be a type of osteochondritis dissecans, due to trauma, with bleeding separating out the bit of bone-cartilage at that particular area of the joint, but we have no evidence for this. I wonder whether anyone has seen this before and has pathological data on the process?

DR. J. J. R. DUTHIE (*Edinburgh*): Why should blood in a joint lead to destructive arthritis?

PROF. S. J. HARTFALL (*Leeds*): I should like to congratulate the speaker on a fascinating review of this subject, well presented.

DR. DUDLEY HART (*London*): Were there any spinal complications of any sort?

DR. J. BALL (*Manchester*): From the work of Prof. Collins one would imagine that haemophilia was not associated with a true arthritis. In the single haemophilic joint I have examined, there had been repeated bleeding into the joint, but there was no synovial hypertrophy or inflammation. Whatever the mechanism of the bony changes it may not be closely related to haemarthrosis. I was struck by the resemblance of the picture of the hip to osteochondritis dissecans; perhaps the changes here are related to haemorrhage beneath the articular cartilage in childhood.

DR. J. FORESTIER (*Aix-les-Bains*): I noticed in the wrists and head of the femur, what looks like an osteonecrosis. Is this a usual mechanism of the joint involvement in haemophilia?

PROF. J. H. KELLGREN (*Manchester*): After the haemarthrosis has subsided and after the blood has been removed, there might not be any sign of inflammation. From a study many years ago, there was no doubt that blood produced a brisk cellular reaction during the period of absorption of the blood into the joint, leaving haemosiderin behind. There is also a systemic reaction due to absorption of blood. You see this with bleeding anywhere in the body. One would have to examine the tissues at the time of the bleeding or shortly after it, when blood is being absorbed, to see this.

DR. DIXON: In answer to Dr. Sharp's question about the cause of cystic changes in the wrists, we do not know, we can only make the observation. In reply to Dr. Duthie's question why a large effusion of blood should cause destructive arthritis, again we do not know. We

assume as many people do, that blood may cause tension inside the bone end and the process may be a question of alteration of the nutrition of the subchondral bone. There may be a vicious circle mechanism, once the bony cortex has been breached further bleeding will cause much more damage by seeping under the cartilage.

We did not see any spinal involvement, only the normal age changes in the older cases.

In reply to Dr. Ball, by inflammatory episodes, we mean the presence of clinical inflammation, with limitation of movement, swelling, heat, and tenderness. We did not see redness.

PROF. E. G. L. BYWATERS (*London*): When we examined joints from a patient with haemochromatosis, we saw a good deal of iron pigmentation in the synovial membrane, but the cartilage was clear. It was in fact a normal joint; but these haemophilic joints do not look normal at all. There must be some inflammation resulting from the repeated stretching and the effusions which occur, quite apart from the deposition of the iron pigments in the membrane.

Hémophilie et arthropathie hémophilique

RÉSUMÉ

On passe en revue l'histoire de l'hémophilie et de l'arthropathie hémophilique.

Sur 42 cas d'hémophilie, 28 présentèrent des antécédents personnels d'hémarthrose et 23 d'entre eux eurent des difformités articulaires permanentes plus ou moins sévères. Dans un cas la maladie articulaire avait été attribuée initialement à la tuberculose.

Dans cette série, un taux de globuline anti-hémophilique de 2 pour cent ou moins fut associé à des manifestations articulaires dans 15 cas et à une difformité articulaire résiduelle dans 12 cas sur 16; lorsque ce taux fut au dessus de 2 pour cent, des manifestations articulaires et des difformités résiduelles minimales ne furent observées que dans 8 cas.

Des épisodes récurrents d'hémarthrose peuvent

s'associer à des articulations cliniquement et radiologiquement normales et d'autre part il peut y avoir des altérations pathologiques dans des articulations sans antécédents d'hémarthrose.

L'altération radiologique la plus caractéristique de l'arthropathie hémophilique fut une augmentation de la tête du radius; cette altération fut présente dans deux tiers des cas où le coude se trouvait affecté. Certains malades ayant des séquelles graves après des multiples épisodes d'hémarthrose furent capable de mener une vie normale malgré leurs difformités.

Hemofilia y artropatía hemofílica

SUMARIO

Se revisa la historia de la hemofilia y artropatía hemofílica.

Entre 42 casos de hemofilia, 28 presentaron historia de hemartrosis, en 23 de los cuales existieron deformidades articulares definitivas de grado variable. En un caso la enfermedad articular había sido atribuida inicialmente a tuberculosis.

En 15 casos con presencia de manifestaciones articulares y en 12 entre 16 casos de deformidad articular residual el nivel de globulina antihemofílica era del 2 por ciento o inferior, mientras que en los enfermos con un nivel de hemoglobulina antihemofílica superior al 2 por ciento, manifestaciones articulares y deformidades residuales mínimas aparecieron solamente en uno de cada ocho casos.

Episodios recurrentes de hemartrosis pueden asociarse con articulaciones clínica y radiológicamente normales, mientras que, por el contrario, pueden aparecer cambios patológicos en articulaciones sin historia de episodio anterior.

La alteración radiológica más característica de la artropatía hemofílica encontrada fue un agrandamiento de la cabeza del radio, alteración presente en dos tercios de los casos en los que estaba afectada la articulación del codo. Algunos enfermos con acusadas alteraciones articulares, consecutivas a múltiples episodios de hemartrosis, eran capaces de llevar una vida bastante normal a pesar de sus deformidades.