children, and to an older age group among children from homes where there is better hygiene and less crowding. The incidence of past infection with each of the three virus types is remarkably uniform, type 3 being a little less common than the others, though not quite so infrequent as Fallon (1956) found in North Wales and in Liverpool.

It is interesting to compare the results of this serological survey carried out in London with two others carried out at the same time, one in the United Kingdom and the other in Morocco. Horstmann (1955) found that amongst Moroccan children in Casablanca the incidence of antibody to all three virus types had reached 80% by the age of 5 years. The rarity of clinical disease, except in those under 2 years of age, was an indication of the widespread dissemination of virus under these conditions. Fallon (1956) carried out an investigation in the rural district of Bettws-y-Coed in North Wales with a population of 780 inhabitants in which no cases of paralysis had been reported since 1912. He found a surprisingly high incidence of antibody to all three virus types in various combinations in children over the age of 4 years. In fact, the incidence of type 1 antibody in Bettws-y-Coed was slightly higher than in Liverpool or in Cairo.

Although the poliomyelitis immune state of any one individual can be learned only from serological tests, the pattern of poliomyelitis infection rates within a community can be drawn from cross-section studies such as the present one. It would suggest that amongst the children from the areas studied it is those under 5 years who would benefit most at the present time from immunization against poliomyelitis, although these findings do not necessarily reflect the immune status throughout the country.

Summary

Sera from 90 London children aged 12 months to 10 years were examined for the presence of antibodies to the three types of poliomyelitis virus.

Tests were carried out for both complement-fixing and neutralizing antibodies, and both methods are described.

As a screening test for antibody, the neutralization method in tissue culture was found to be the more reliable guide to past infection.

In the small group of children studied, subclinical infection began to take place at about the fifth year of life.

The incidence of past infection with each of the three virus types was fairly uniform, type 3 being slightly less common amongst the younger children.

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DENTAL EXTRACTION IN HAEMOPHILIA AND CHRISTMAS DISEASE

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The management of the haemophiliac presents many difficulties, and not least among these is the problem of dental extraction. Haemophilia is a rare disease, the incidence in the population in the West of Scotland being 1 per 30,000–35,000. In contrast to this low incidence is the frequency with which these sufferers require hospital management; amongst the commonest causes of admission is the necessity for tooth extraction. Most haemophiliacs show great reluctance in seeking dental attention. The fear of dental extraction is of course well justified; unfortunately this dread of the dentist prevents the proper care of the teeth by conservative methods, and as a consequence their teeth are commonly neglected. On several occasions we have seen haemophiliacs of about 20 years of age requiring complete clearance of teeth. Many of the teeth are represented merely by shells submerged in the gum margin, and consequently periodontal sepsis is frequent.

It is the object of this communication to report our experiences in the management of dental extractions in patients with haemophilia or the closely allied condition Christmas disease.

Methods

Thirty-two dental operations, involving the removal of 57 teeth, were carried out on 10 patients; nine of these were haemophiliacs, lacking antihaemophilic globulin, and the tenth was a patient with Christmas disease, lacking the Christmas factor (Biggs *et al.*, 1952). The number of dental operations performed on each patient varied from one to seven, depending on how many teeth required extraction. The important features of these dental operations are summarized in Table I. The patients were all admitted to hospital; they were warned that the measures to be adopted were unlikely to prevent haemorrhage completely, but that any consequent bleeding would not be serious in its extent.

Number of Extractions at Each Operation.—The number of teeth extracted at each operation varied from one to four, and may be summarized as follows: at 14 operations, one tooth; at 12 operations, two teeth; at 5 operations three teeth; and at one operation, four teeth extracted. As a consequence of experience it was decided that, in general, only one or two teeth should be extracted at any one operation. When adjacent teeth were carious it was considered justifiable to extract two at one sitting. The extraction of more than two teeth resulted in much troublesome haemorrhage. These observations confirmed the opinion of White and Mallett (1949). The haemorrhage which follows the extraction of large numbers of teeth carries risk to life and is alarming to the patient. It is not practicable to provide maintained haemostatic levels of antihaemophilic globulin over long periods with available sources of supply. The practice of extracting large numbers of teeth after alleged correction of the haemostatic defect by administration of plasma, plasma products, or whole blood should be abandoned. The teeth extracted were all

permanent teeth; deciduous teeth do not present such a great difficulty, there being less trauma involved in the extractions. It is our belief that, unless there be special circumstances, deciduous teeth should be left to shed themselves in the normal manner.

Antibiotic Therapy.—As a result of the teeth being neglected, sepsis at the site of extraction was frequently present. To combat the additional risk of bleeding which might result from socket infection all the patients were given oral antibiotic therapy for five days, starting on the day of operation. Initially, parenteral penicillin was administered, but this resulted in troublesome haematomata at the site of intramuscular injection and was discontinued.

Anaesthesia.—In a small number of the earlier operations of the series anaesthesia was regional by inferior dental injections; the great majority of the operations were undertaken with local or infiltration anaesthesia, and this was eventually adopted as the method of choice. Regional anaesthesia by inferior dental injection carries the risk of haematoma in the neck and of permanent damage to the nerve by haemorrhage. Haemophiliacs not infrequently suffer peripheral nerve damage as a consequence of haemorrhage. Endotracheal intubation during general anaesthesia is potentially dangerous by virtue of the possible development of laryngeal haemorrhage or haematoma.

Acrylic Resin Protective Splint

For each patient a protective dental splint was prepared before the operation and inserted immediately after removal of the teeth. The splint was constructed in the following manner: an impression of the upper and lower teeth was taken with one of the alginate impression materials such as "zelex," and models from this were poured in stone-hard plaster. From the models the tooth or teeth to be extracted were removed and over this area a layer of dental wax was fitted. Another alginate impression was taken from the first model and a second model cast in stone. The models were then set up on an articulator with the aid of a wax bite. Upon the second model a layer of wax was placed, trimmed to the exact requirements of the splint, and then processed in clear acrylic resin.

The reason for the first layer of wax over the tooth socket was to allow sufficient space between the acrylic splint and the socket for insertion of black gutta-percha. From experience it was found that this gutta-percha was tolerated by the soft tissues in the region of the wound much better than the hard acrylic. At the same time there was a close seal. Fig. 1 illustrates a splint with the gutta-percha in position. When significant bleeding occurred there was no hesitation in removing the splint for reapplication of local haemostatic measures; the splint was then reinserted. Where insignificant bleeding occurred the splint was left in position for 10–14 days before removal; at the end of that time there was generally a healed socket when the splint was removed. In a few of the earlier operations, as indicated in Table I, no splint was used.

The purpose of the splint was to protect the soft friable clot in the socket from trauma by food or from disturbance

FIG. 1.—An acrylic resin dental splint with black gutta-percha inserted in the splint opposite the extraction site.

by the tongue; a less important role of the dental splint was to hold haemostatic dressings in position. The splint was not used for the purpose of exerting pressure on the socket. Such pressure may be dangerous in consequence of haemorrhage occurring into tissue; such a haematoma in the neck can be large enough to block the airway. Qvist, Endicott, and Mitchell (1942) report a case of fatal asphyxia following dental extraction in a haemophiliac where the obstruction to the airway was due to massive haemorrhagic infiltration of the floor of the mouth. Pressure on a socket also causes its enlargement and increases the area for potential haemorrhage. It is essential that the splint be made skilfully; a badly fitting splint is worse than no splint at all. The splint must fit accurately on the remaining teeth and remain firmly *in situ*; a loose splint causes disturbance of the poorly formed clot in the socket. It must not cause pressure on the gingival margin at any part, as such trauma will certainly result in an additional site for haemorrhage. The application of the black gutta-percha to the splint at the area of the wound was found to be of great value in preventing injury of the gum by the splint. The splint enables the patient to take a soft pulped diet and he can be ambulatory in the ward. The use of protective splints has also been favourably reported by White and Mallett (1949) and Matheson (1949).

Local Haemostatic Treatment

This consisted of an adsorbable dressing such as "calgitex" or gelatin sponge with bovine thrombin or Russell viper venom.

The application of local haemostatic agents to the tooth sockets was of very limited value. No surface application of haemostatic agents can be considered highly successful in haemophilic bleeding. To be of value a haemostatic requires to be carried to the site of bleeding by the patient's own circulation. Thrombin, for example, when applied to a socket will produce a surface layer of fibrin from the blood filling a socket, but this does not prevent bleeding occurring from the freely flowing vessels in the base of the wound.

Suturing of the gum is used in the control of haemorrhage following tooth extraction in normal persons. It is, however, contraindicated in haemophilia, as it provides an additional site for bleeding and may encourage haemorrhage into the adjacent tissue spaces rather than externally.

Replacement Therapy

Therapy with blood or blood products was used in an attempt to supply the coagulation components missing in these patients. In the earlier extractions of the series, bank blood was tried, but, later, fresh frozen plasma was used. Fresh frozen plasma was eventually adopted as the routine form of replacement therapy for deficiency of antihæmophilic globulin. In one patient a large amount of the dried plasma fraction (Cohn I) containing antihæmophilic globulin was given. In a few of the later extractions further plasma was administered 48 hours after the initial infusion, the third day being the time of highest incidence of haemorrhage.

In four patients the administration of plasma subsequent to the first occasion caused urticarial reactions. These were treated with a single dose of 100 mg. of oral cortisone and 50 mg. of promethazine hydrochloride. Any further administration of plasma was preceded by cortisone and promethazine hydrochloride one hour before giving the plasma. This appeared to prevent recurrence of the urticaria.

As already stated patients with haemophilia lack antihæmophilic globulin and those with Christmas disease the Christmas factor. The only available therapeutic agents are contained in human plasma or derived therefrom by fractionation.

The life of antihæmophilic globulin in blood stored at 4° C.—that is, in bank blood—is very short; after three to

four days only trace amounts are usually present. If plasma is collected fresh and immediately frozen to -20°C ., at which temperature it is stored, there is very good preservation of the antihæmophilic globulin. This fresh frozen plasma was used in many of the patients included in this investigation (Table I). Apart from the difficulties of preservation of the antihæmophilic globulin there is the problem of the large amounts required in the management of the patients to maintain hæmostatic levels over prolonged periods. The intravenous administration of 2 pints (1,140 ml.) of fresh plasma to a hæmophilic causes a rise in antihæmophilic globulin content from nil to 5-10% of that present in normal plasma. More than half of this has disappeared by 12 hours and only trace amounts are present at 24 hours. The difficulties of the problem can readily be appreciated. Cohn's plasma fraction I, containing antihæmophilic globulin, is available as a lyophil dried preparation in ampoules. In the transfusion services of this

region each ampoule is derived from 75 ml. of plasma. Even with full recovery of antihæmophilic globulin in the ampoules, 10 or more would be needed to give the equivalent of 2 pints (1,140 ml.) of plasma.

In one patient the dried antihæmophilic fraction from 15 pints (8.5 litres) of blood was given as a pre-operative measure, with satisfactory response. It is believed that at the present time the best available therapeutic agent is fresh frozen plasma and that this must be used in large quantities, such as 2 pints (1,140 ml.) at a time (A. S. Douglas, 1956, unpublished observations). Moss (1955) also reports on the value of fresh frozen plasma in the management of bleeding tooth sockets in hæmophilia.

There should be no reliance on bank blood as a source of antihæmophilic globulin unless it has been collected within a few hours of administration. The Christmas factor, on the other hand, is well preserved not only in fresh frozen plasma but also in bank blood.

TABLE I.—Details of 32 Dental Operations

Case No.	Disease	No. of Teeth Extracted	Details of Teeth Extracted	Anti-biotic	Local Treatment	Anaesthesia	Transfusions		Haemoglobin Values (%)		Days Before Bleeding Ceased	Days Before Sockets Well Healed
							Before	After	Before	Lowest After		
1	Haemophilia	1	6	C	NoS; C+T; Sut.	R	2B	4B	92	80	7	14
		3	6/67	P	NoS; C; Sut.	R+I	—	7B	98	68	6	15
		2	46	P+C	NoS; G+T; Sut.	I	1B	2B	98	90	6	14
2	Haemophilia	1	6	C	NoS	I	1B	3B	90	84	6	16
		1	7	C	NoS	I	1B	5B; 1FFP	90	58	14	23
		4	21 12	—	NoS	I	1FFP	6B; 4FFP	105	68	10	16
		1	6	—	S; G+T	I	—	—	95	89	6	14
3	Haemophilia	1	6	—	S; G+T	I	—	—	100	86	7	12
		1	6	A	S; G+T	I	2FFP	—	105	102	5	10
		3	876	A	S; G+T	I	2FFP	1B; 1FFP	104	62	6	16
		2	12	A	S; G+T	I	2FFP	—	100	99	3	9
4	Haemophilia	1	1	A	S; G+T	I	2FFP	—	103	94	4	10
		3	678	A	S; G+T	I	2FFP	—	96	96	5	10
		2	76	A	S; G+T	I	2FFP	—	100	75	9	13
		2	45	A	S; G+T	I	2FFP	—	75	75	3	11
5	Christmas disease	1	6	A	S; G+T	I	1½FFP	—	74	64	6	13
		1	6	A	S; C+T	I	1½FFP	—	65	62	3	13
		2	6/6	A	S; C+T	I	2FFP	—	76	68	No Bl.	15
		2	75	—*	S; G+T+RVV	I	2FFP	—	105	80	6	13
6	Haemophilia	2	84	—	S; G+T	I	2FFP	—	101	80	6	9
		3	578	—	S; G+T	I	2FFP	—	85	69	6	10
		2	13	—	S; G+T	I	2FFP	2FFP	99	76	6	10
		1	4	A	S; C+T	I	AHG	—	101	99	No Bl.	11
7	Haemophilia	2	67	A	S; C+T	I	2FFP	—	99	95	2	12
		1	6	A	S; C+T	I	2FFP	1½FFP	110	92	11	17
8	Haemophilia	1	6	A	S; C+T	I	1FFP	—	97	97	6	9
		1	6	A	S; C+T	I	1FFP	1FFP	102	88	14	17
9	Haemophilia	2	56	A	S; C+T	I	1½FFP	1FFP	95	93	7	11
		1	6	A	S; C+T	I	1½FFP	1FFP	86	83	No Bl.	12
		2	6/6	A	S; C+T	I	1½FFP	1½FFP	86	54	17	20
10	Haemophilia	3	256	—	NoS	I	—	2FFP	118	84	9	21
		2	6 7	A	S; G+T	I	2FFP	—	92	92	3	12

Antibiotic

C = Chloramphenicol
P = Parenteral penicillin
A = Chlortetracycline
* Oral antibiotics caused vomiting.

Local treatment

S = Splint
NoS = No splint
C = Calgitex
G = Gelatin sponge
T = Thrombin
RVV = Russell viper venom
Sut = Suturing

Anaesthesia

R = Regional
I = Infiltration

Transfusions

Figures express amounts in pints
B = Blood
FFP = Fresh frozen plasma
After = At times from first to eleventh day after extraction
AHG = Antihæmophilic globulin fraction from 15 pints (8.5 litres) of blood

Time in days before bleeding ceased
No Bl. = No bleeding.

Haemorrhage

In Fig. 2 is shown the incidence of haemorrhage, subsequent to the 32 dental operations. Even when the bleeding was minimal in extent, possibly only the staining of saliva over a short period, haemorrhage was recorded as

FIG. 2—Histogram showing the incidence of haemorrhage during the days subsequent to the extraction. Abscissa—time in days after extraction of the teeth. Ordinate—number of dental operations.

having occurred on that particular day. Comparison with the fall in haemoglobin level as recorded in Table I will show that bleeding was often minimal in its extent. Bleeding was rare on the first day but very common on the third day—that is, 48 hours after extraction. There was some bleeding at this time in 23 out of the 32 operations. Haemorrhage was common up to the eighth day after extraction, but unusual after that time. In one patient bleeding stopped only at the seventeenth day. The relative immunity from haemorrhage during the first 36–48 hours following extraction may be explained by the replacement therapy given just before the operation or as a result of the thromboplastic activity of the damaged tissue at the extraction site.

Blood Loss.—In an attempt to estimate the blood loss, haemoglobin levels were assayed daily, and the lowest value recorded in the post-operative period was used as an approximate indication of the extent of the haemorrhage. The mean fall in haemoglobin over all the extractions was 7% per tooth removed. As would be expected, the loss of haemoglobin was proportional to the number of teeth removed at each operation (Table II). The numbers

TABLE II

Operation	Mean Fall of Haemoglobin per Operation
One tooth extracted	10%
Two teeth	13%
Three	25%
Four	37%

involved in each group are small, but the figures probably give some indication of the anticipated loss of blood from these extractions.

Blood Transfusion

Matched blood was held for each patient for a period of 10–14 days from the time of extraction. Haemophiliacs are often the recipients of multiple transfusions, and there is the danger of haemolytic transfusion reactions unless sensitive compatibility tests are employed. In case there should be a bleeding emergency, therefore, cross-matched blood was reserved for each patient. Two of the patients were

rhesus-negative and had anti-D antibodies in consequence of previous transfusion.

As haemophilic patients often require transfusion through out their lives there is the consequent risk of development of immune antibodies. With the adoption of the measures described, transfusion after dental extraction was very rarely required. This benefits the patient in so far as the opportunity for development of immune antibodies is reduced.

Duration of In-patient Management

In-patient treatment varied from 9 to 23 days, with an average of 13 days per dental operation. It will be appreciated that where a complete clearance of teeth was required this involved a protracted stay in hospital. It was our policy to carry out a small number of operations, possibly two, on one hospital admission and discharge the patient for subsequent readmission. The morale of these patients is remarkably good, considering the life of chronic invalidism which they have to suffer. Nevertheless it is of benefit to them not to make their stay in hospital too protracted on any one admission.

Discussion

These experiences in dental extraction of haemophilic patients failed to provide a complete answer to the problems of management. We are satisfied, however, that the adoption of the measures described is successful in limiting haemorrhage. Such haemorrhage as occurs will not be severe enough to endanger life.

The first eight observations in the series may be regarded as pilot studies. As a consequence of these the measures finally adopted may be summarized as follows: (a) extraction of not more than two teeth at one time; (b) construction of an acrylic resin protective splint, with gutta-percha lining at the site of extraction; (c) administration of 2 pints (1,140 ml.) of fresh frozen plasma just before the extractions; and (d) oral antibiotic therapy.

During the eight pilot observations a total of 22 pints (12.5 litres) of blood was required for replacement of blood loss due to the extractions. In the subsequent 24 dental operations only 1 pint (570 ml.) of blood was used. It is tempting to assume that this striking difference was due to the measures adopted.

The observations in the last case form an interesting comparison. The first operation was performed without any of the above measures; in particular there was no splint and no previous administration of plasma. Bleeding continued for nine days and the haemoglobin fell by 24%. Two weeks later further extractions were done with the preparation of upper and lower jaw splints and the previous administration of plasma. The only bleeding consisted of some staining of saliva on the third day and there was no fall in the haemoglobin level.

The ideal answer to the problems of management of tooth extraction in these patients is the administration of adequate amounts of antihaemophilic globulin or the Christmas factor over a sufficient period of time. The maintenance of haemostatic levels of these factors over the period of 10–14 days required for the complete healing of the socket is not a practical possibility at the present time.

Summary

The results of 32 dental operations for tooth extraction in patients with haemophilia or Christmas disease are reported. The commonest time for haemorrhage was the third day after extraction, but in one case this was still occurring as late as 17 days after the extractions. It was inadvisable to extract more than two teeth at a time; where possible, two adjacent teeth were removed. An acrylic resin protective dental splint was used to protect the operation site subsequent to extraction. Black gutta-percha was inserted in the splint opposite the extraction site. Replacement therapy consisted of 2 pints

(1,140 ml.) of fresh frozen plasma immediately before extraction and on the occurrence of bleeding, provided this was severe enough. Oral antibiotic therapy was used for five days from the time of extraction.

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CHRISTMAS DISEASE IN A WOMAN

BY

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In the majority of affected families the inheritance of Christmas disease is of the same sex-linked recessive pattern as true haemophilia, resulting in the transmission of the disease to males by apparently healthy females. In a small number of instances, however, heterozygous females have been found to be mildly affected, suggesting that the Christmas disease gene may be less completely recessive than that responsible for haemophilia. The case is presented here of a young woman with Christmas disease of the same order of severity as her affected male relatives.

Case History

A single woman aged 22 was investigated because of a history of prolonged bleeding following tooth extractions. She had had teeth extracted on several occasions since the age of 6, and each time had bled from the tooth socket intermittently for 7 to 14 days. It had always proved possible to control the bleeding eventually by plugging, and she had never had a blood transfusion. No abnormal bleeding occurred at the spontaneous shedding of the primary dentitions. Two teeth have been extracted since the diagnosis of Christmas disease was made, and on this occasion bleeding was successfully controlled by packing the tooth sockets with an absorbable dressing soaked in thrombin. With this treatment bleeding stopped within 24 hours, but started again three days after the extraction, necessitating repacking, which resulted in permanent haemostasis.

The patient has had no other haemorrhagic symptoms. She has never had any other operations or serious injuries, and does not bruise excessively from minor traumata. Superficial cuts soon stop bleeding, and menstruation is normal. She has never had haemarthroses, epistaxes, purpura, or haematuria. At the age of 17 she swallowed a small open safety-pin without ill-effect.

Family History.—The patient's family tree is shown in the diagram. Her paternal great-grandparents, I 1 and I 2, are said to have been first cousins. Her father, III 3, suffered from prolonged and excessive bleeding after tooth extraction

on several occasions, but had no other haemorrhagic symptoms. He had never had any other operations or serious injuries. He was accepted for military service and was killed at Anzio in 1944. One of his mother's five brothers (II 10), now deceased, is known to have bled excessively after tooth extraction, but another (II 11) has never had any haemorrhagic symptoms. It has unfortunately proved impossible to trace the remaining members of the patient's paternal grandmother's family. There is no history of abnormal bleeding in any other known relatives of either sex on the patient's father's side, nor in any member of her mother's family.

Laboratory Investigations.—The results of tests of the patient's haemostatic mechanism are shown in Table I. It will be seen that these were all within normal limits.

A thromboplastin generation test was performed by the method of Biggs and Douglas (1953), using a suspension of normal platelets with various combinations of serum and $\text{Al}(\text{OH})_3$ -adsorbed plasma. All sera were obtained from blood shaken with glass beads until coagulation occurred, and then incubated at 37° C. for two hours. The sera were

TABLE I.—Results of Routine Laboratory Tests on Patient's Blood

Test	Patient	Normal Control Range
Whole-blood clotting-time (Lee and White) (minutes) ..	7½–10	5–10
One-stage prothrombin time (Quick) (seconds) ..	17.3	17.2–18.6
Proconvertin (Owren) (%) ..	80	70–120
Prothrombin consumption index (Merskey) (%) ..	18	Less than 40
Bleeding-time (Ivy) (minutes) ..	3	3–7
Platelet count (per c.mm.) ..	353,000	200,000–500,000

TABLE II.—Results of a Thromboplastin Generation Test. The Same Normal Platelet Suspension and $\text{M}/40 \text{ CaCl}_2$ were Used Throughout

$\text{Al}(\text{OH})_3$ -adsorbed Plasma (1/5)	Serum (1/10)	Shortest Second Stage Clotting-time (sec.)	Final Thromboplastin Concentration (%)
Normal	Normal	10	100
"	Patient	13½	65
Patient	Normal	10	100
Normal	{ 50% Patient 50% Normal }	9½	108
Haemophilic 10% Normal	Normal	25	17
90% Haemophilic	"	14	52
10% Patient	"	11	83
90% Haemophilic	"		
Normal	Christmas disease	23½	19
"	{ 10% Normal 90% Christmas disease }	12½	65
"	{ 10% Patient 90% Christmas disease }	21	24