

AN UNDERSTANDING OF HAEMOPHILIA
FOR ORAL SURGICAL AND DENTAL PRACTICE

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for the Master of Dental Surgery in Oral Surgery.

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PREFACE

The aim of this thesis is to present to the dental profession (general practitioners and specialists) a basic understanding of the haematology and the clinical management of the more common bleeding disorders. The dental literature abounds with articles on the management of the true haemophilic for dental and oral surgical procedures, however, the less well-known bleeding disorders such as Christmas disease and von Willebrand's disease are infrequently reported.

The management of the patient for dental or oral surgical procedures will vary with the type and severity of their bleeding disorder. The aim should be to perform dentistry or oral surgery for the patient, safely and in a manner which will minimise the amount of pain, hospitalisation, emotional stress and bleeding complications.

This thesis has been in effect divided into two main parts, firstly the basic haematology and general management, and secondly the clinical management for dentistry and oral surgery of patients with bleeding disorders.

(ii)

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1.

HAEMOPHILIA

1.1 The Development of the Concept of Haemophilia

In the early part of the 19th century it became apparent that there were certain conditions in which people might bleed uncontrollably from trivial injuries and little could be done to arrest persistent haemorrhage. The condition was referred to by various names - morbus haematicus, haemorrhagic diathesis, idiosynersia haemorrhagica, haematophilia and haemorrhaphilia. Besides haemophilia as we know it, these conditions must have included cases of scurvy, purpura haemorrhagica and bleeding states secondary to other diseases.

In 1803 an American physician, John C. Otto published "An account of an Haemorrhagic disposition existing in certain families" and from this work arose the modern concept of haemophilia. Dr. Otto concluded that there is an inherited tendency for males to bleed and he therefore recognised three of the cardinal features of haemophilia. During the 1820's attention was drawn to the condition in Europe and although the nature of the defect was unknown, its peculiar mode of inheritance through normal females was stressed.

The term "Haemophilia" was used as early as 1828, but did not enter common usage until the 1850's when it became apparent

2.

that the clinical entity had been described in early writings. Alzaharavius, the renowned 11th century Moorish surgeon, observed that in certain villages there were men who suffered uncontrollable haemorrhage when wounded. Many such early observations on haemophilia were of a clinical nature although Meckel (1816) suspected the bleeding was caused by a blood coagulation defect. Liston in 1839 recognised that haemophiliac blood clotted slowly and in 1893 Wright stressed the importance of the abnormally long clotting time. At the beginning of the 20th century haemophilia was regarded as an abnormal tendency in males to bleed, inherited through apparently normal females and associated with a delay in the blood clotting time of those affected. Bulloch and Fildes (1911) selected from the literature those cases which conformed to the above concept of haemophilia. They established haemophilia as a clinical entity but their definition of the complaint is now inadequate. They were unwilling to accept the diagnosis of haemophilia in families in which males had been shown to transmit the disease to their grandsons and they were suspicious of cases with a negative family history. It is now known that all daughters of affected males carry the disease and that 30 per cent of diagnosed cases have no family history.

1.2

The Nature of the Defect

It was noticed by the early investigators that some agent

existed in blood which temporarily improved the patients clotting mechanism. It had also been observed by Meckel (1816) and Liston (1839) that shed blood in cases of haemophilia clotted very slowly and when Wright (1893) devised his method for measuring the blood clotting time, the significance of delayed clotting time in haemophilia soon became a subject of investigation. Although research continued no further progress was made until 1931, when Gonaerts and Gratia published their work. They presented experimental evidence to show that small amounts of normal plasma corrected the slow clotting of haemophiliac blood. In addition they showed that the plasma "factor" was heat labile and exhibited other characteristics of a globulin substance. This idea had been suggested by Addis in 1911 following a number of carefully executed experiments with normal plasma and haemophiliac blood. In 1937 Patek and Taylor repeated the experiments of Addis, and Gonaerts and Gratia and they concluded that normal plasma contains a globulin substance absent from haemophiliac blood.

The first steps toward an hypothesis of human blood coagulation had been taken. With advanced knowledge of coagulation and improved laboratory techniques it gradually became obvious during the early 1940's that haemophilia was not a homogeneous disorder. It had been observed that occasionally blood from a known haemophiliac could correct the clotting defect of another case also thought to have

haemophilia. Later work by Pavlovsky (1947); Schulman and Smith (1952); Pool~~e~~ (1953) supported these observations and developed the theory that two samples of blood which corrected each other were lacking in different clotting factors which could produce the same clinical picture. This became an established fact in 1952 when Aggeler et al reported a case of haemophilia who was found to have a deficiency of a plasma factor and not the anti-haemophilic factor.

In the same year Biggs and her associates (1952) described seven cases in which four exhibited the genetic features of haemophilia. The blood of these patients contained normal amounts of anti-haemophilic globulin but lacked a plasma factor necessary for normal blood clotting. They called the missing factor, Christmas factor, after the surname of the first patient studied by them.

1.3 The Current Status of Haemophilia

In defining the term haemophilia, Kerr (1963, p. 11) draws attention to the two meanings of the term in common use. It may refer to all the congenital disorders of blood coagulation or to the most common condition due to a deficiency of anti-haemophilic globulin (factor VIII). Terms such as haemophilia A (antihaemophiliac globulin deficiency, classic haemophilia),

haemophilia B (plasma thromboplastin component deficiency, Christmas disease) and haemophilia C (plasma thromboplastin antecedent deficiency) appear in the literature, Rosenthal (1959) considered the term "haemophilia" to include at least these three allied bleeding disorders.

Each type of haemophilia is further classified as mild, moderate or severe. Generally haemophilia A is more severe than haemophilia B or C. Von Willebrand's disease (vascular haemophilia or pseudohaemophilia) is another rare inherited disease of variable severity.

In an attempt to clarify the situation, the international committee of research workers in blood coagulation (1959) introduced a system of nomenclature for coagulation (Table 1). Haemophilia and Christmas disease are now defined as sex-linked recessive bleeding disorders due to isolated congenital deficiencies of factor VIII and IX respectively.

Haemophilia is relatively rare, but is the most common of the deficiency states being approximately six times more prevalent than Christmas disease. Von Willebrand's disease, PTA deficiency and Hageman factor deficiency are extremely rare and together form less than 5 per cent of all cases. The incidence of severe congenital blood coagulation disorders in Australia has been estimated at 1 per 10,000 males compared to the highest reported

incidence from Germany and Switzerland of 2 to 5 per 10,000 males.

Without doubt there are many more who are so mildly affected that they have not been detected and so may escape detection unless they undergo major surgery or have a severe accident.

1.4 Inheritance of Haemophilia and Christmas Disease

The abnormal genes for both haemophilia and Christmas disease are sex-linked, being transmitted by asymptomatic females and carried on the X-chromosome. The homozygote male has the fully-expressed condition while the heterozygote "carrier" female may have a partial disorder. If a man with classical haemophilia is married to a normal woman, all their sons will be normal and will not transmit the condition because their only X-chromosomes are from their mother. All the daughters of such a union will be carriers, having one X-chromosome from the mother and another X-chromosome, bearing the abnormal gene, from the father. If a carrier marries a normal man she could contribute either normal X-chromosome or her X-chromosome with the abnormal gene to a son. She could contribute either X-chromosome to a daughter and could therefore have both normal daughters and carrier daughters (Figure 1). There are apparently several abnormal alleles of the X-chromosome factor V111 gene. Different alleles are responsible for different degrees of severity and in a given family with haemophilia, all the affected males have practically the same factor V111 level. Severe

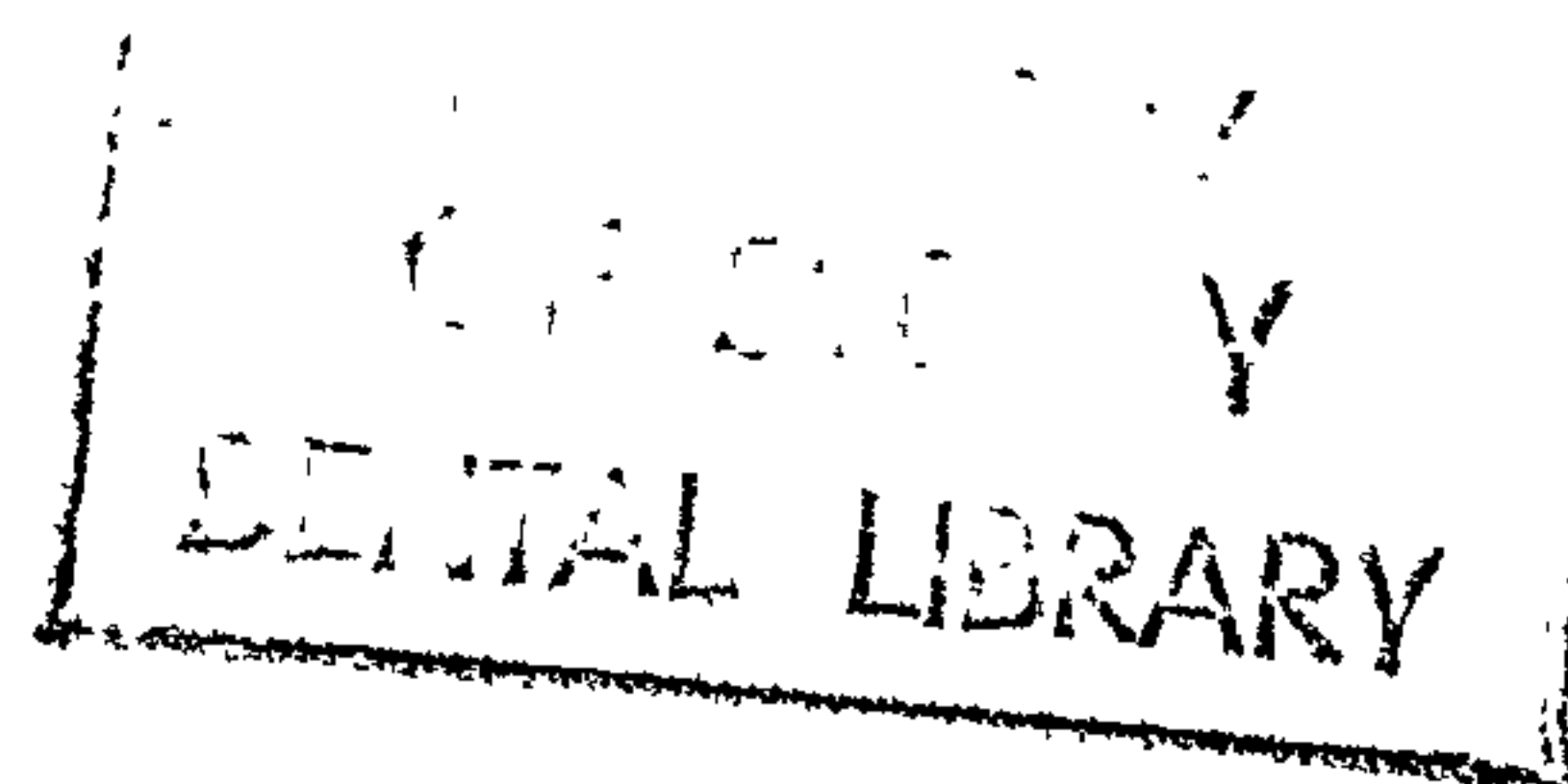


TABLE 1

THE PLASMA CLOTTING FACTORS

Nomenclature:

INTERNATIONALFAMILIAR

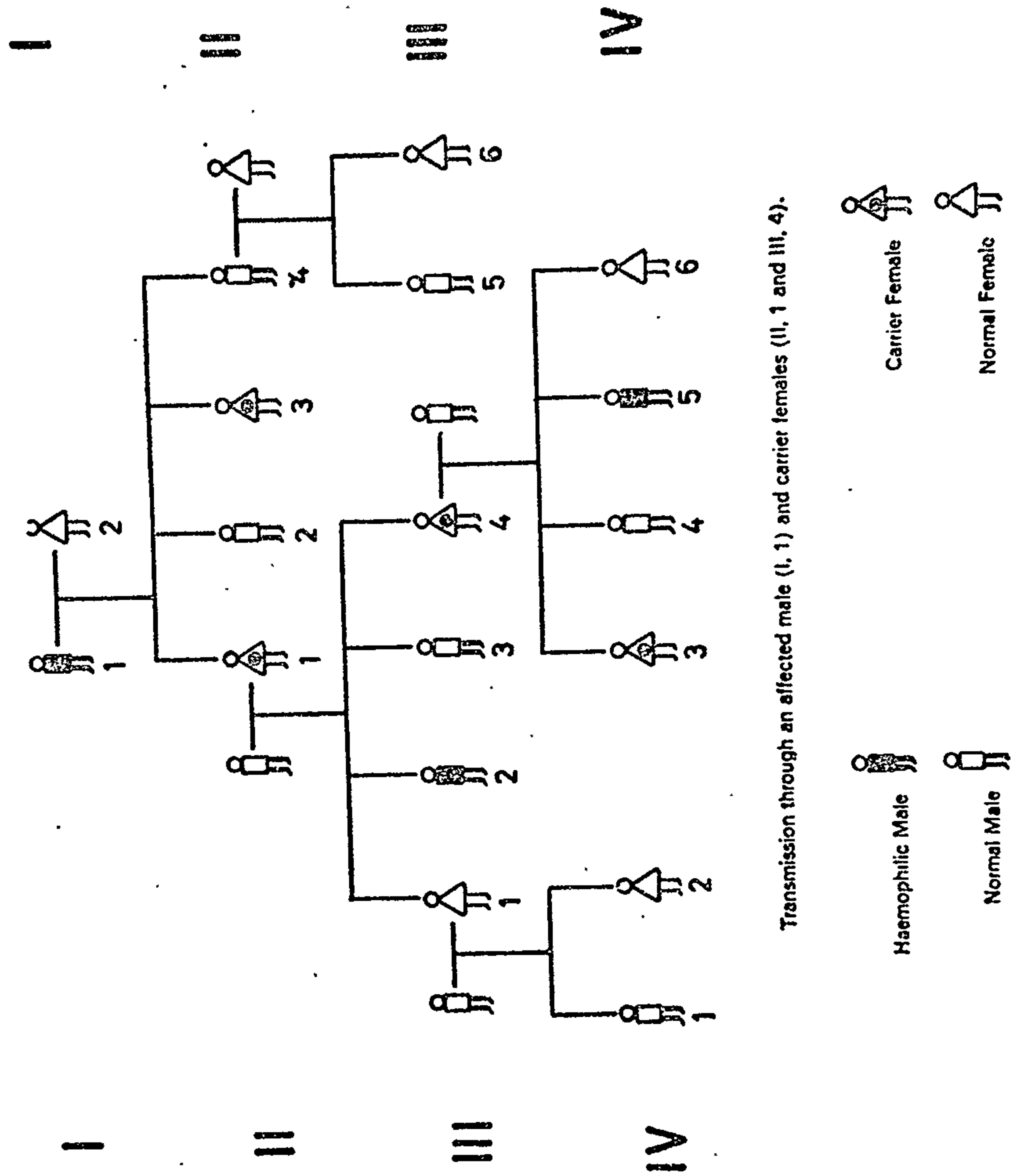
Factor 1	Fibrinogen
Factor 11	Prothrombin
Factor 111	Tissue Thromboplastin
Factor 1V	Calcium
Factor V	Proaccelerin
(No Factor V1)	
Factor V11	Proconvertin
Factor V111	Antihæmophilic Factor or Globulin (AHF, AHG)
Factor 1X	Plasma Thromboplastin Component (PTC) or Christmas Factor
Factor X	Stuart & Prower Factor
Factor X1	Plasma Thromboplastin Antecedent (PTA)
Factor X11	Hageman Factor
Factor X111	Fibrin Stablising Factor

haemophilia is diagnosed where the factor VIII level is found to be less than 2 per cent of normal. Those moderately affected have factor VIII levels from 2 - 5 per cent of normal, while levels from 5 - 30 per cent are regarded as mild.

Females of affected families have in many instances been shown to have abnormal tendencies due to low levels of factor VIII or IX. Laboratory studies by Nilsson et al (1959) and Rapaport et al (1960) have shown significantly lower levels of factor VIII in some mothers and sisters of haemophiliacs. Kasper et al (1969) found the average factor VIII level of a normal woman is 100 per cent with a range of about 45 per cent to 200 per cent. For female carriers of haemophilia A, the average factor VIII level is about 50 per cent with a range of a few percent to well over 100 per cent. Therefore, about half of the carriers have factor VIII levels which are below normal and the rest have levels overlapping the normal range.

This distribution of clotting factor levels in carriers is currently being interpreted in terms of a theory of X-chromosome inactivation, the Lyon hypothesis. Kerr (1968) provides an excellent summary. The main assumption is that only one of the two chromosomes in each somatic cell of females is genetically active. Inactivation of one X-chromosome occurs during early embryonic life and it is a random matter whether it is the X-chromosome derived from the father or the one from the mother that is inactivated. Subsequently, all

FIGURE 1.



The inheritance of haemophilia and Christmas disease.

descendants of the cell have the same chromosomes active or inactive and so the theory implies that females have two populations of cells differing in the genetical constitution of X-chromosomes.

Factor VIII assays are sometimes performed on plasma of close female relations of a known carrier in an attempt to make a better estimate of the girls chances of being a true carrier. Kasper (1970) makes the point that if a girl has a factor VIII level below normal range, she can be told she is a carrier. If the level is lower than 30 per cent she should be warned of possible excessive bleeding on trauma or surgical operation. The same considerations apply to the inheritance of factor IX deficiency.

Oestrogen and progesterone in combination in sufficient dosage will elevate factor VIII and IX levels in normal women or carriers. Kasper et al (1968) warned that because of this fact, women should not be tested for an estimate of the carrier status while they are pregnant or taking contraceptive hormone.

1.5

Occurrence by New Mutations

A boy with haemophilia is sometimes born into a family in which haemophilia has never been known before. This occurs in about 30 per cent of the diagnosed cases of severe haemophilia and less often in milder forms of the disease.

In some instances, a thorough search of the family tree will

reveal an afflicted relative. If the family tree is negative then the condition may have arisen from a new mutation. Should the mutation take place in an ovum which becomes a boy, haemophilia will be manifested in him. If the mutation takes place in an ovum or sperm which becomes a girl, she will be a carrier and unless she bears a haemophiliac the mutant gene might pass through several generations. Perhaps the most famous mutant carrier was Queen Victoria whose family history was negative for haemophilia.

It was suggested that older parents are likely to have accumulated more mutant genes in their gametes. Dr. Herbert Strauss (1967) has studied this subject in detail and could find no significant difference in the mean ages of the maternal and paternal grandparents at the time of birth of the mothers and fathers of boys with sporadic haemophilia.

2. CLINICAL FEATURES OF HAEMOPHILIA

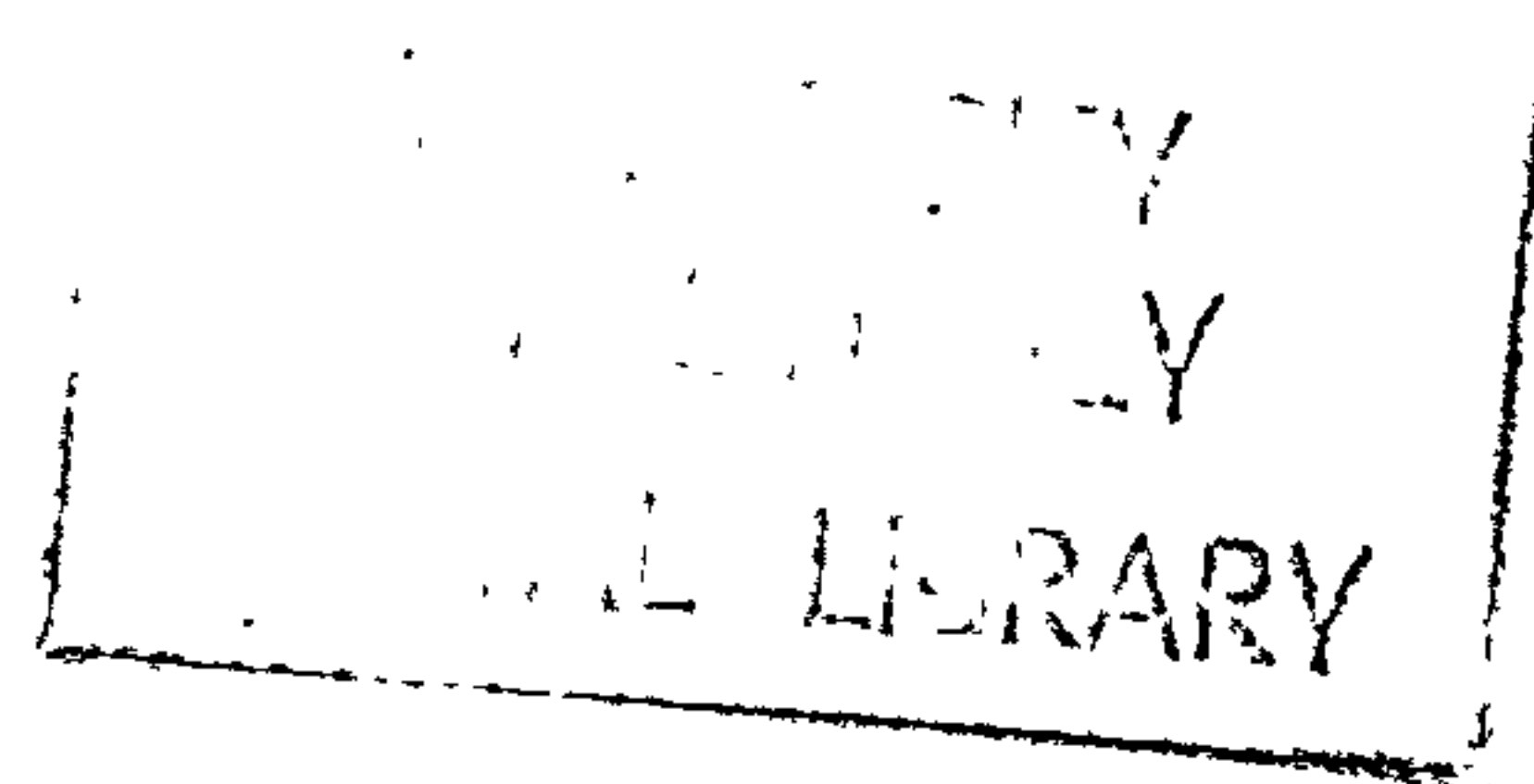
2.1 Normal Haemostasis

When capillaries are injured, they seal themselves by adherence of their endothelial surfaces. When arteries are severed, the pressure of the spurting blood overcomes all mechanisms for haemostasis. In intermediate-sized vessels, the veins and arterioles, haemostasis is achieved by the following mechanism.

Immediately upon injury the vessel contracts and remains so for up to four minutes. The tone of the surrounding tissue, augmented by the mass of blood which has already escaped, creates a back-pressure which tends to limit the flow of blood from the vessel. The platelets adhere to the injured endothelium and to each other; the platelet plug is often sufficient to halt the loss of blood while the vessel is still contracted. In the "still" blood just proximal to the platelet plug in the vessel, plasma clotting factors interact to catalyze the formation of fibrin from fibrinogen, a process requiring a few minutes for completion. The fibrin network, with blood cells enmeshed in it, is a loose jelly, too soft to be an effective plug. The liquid portion, the serum, must be squeezed out to leave a firm, permanent plug, i.e., the clot must retract. In retraction, platelets gather at the

intersections of the fibrin strands, throw out pseudopodia along the strands and draw the strands together to form "knots" at the intersections, thus tightening the network. As the clot retracts, activated clotting factors are squeezed out and begin to stimulate coagulation in the static blood further proximal. This process goes on until the proliferating clot reaches a branch in the vessel where the blood flow is so rapid it carries off the activated clotting factors and dilutes them in the main stream so they are no longer effective. The clot in the injured vessel may be dissolved by natural fibrinolysins after a few days, permitting recanalization, of the vessel (Kasper, 1970).

It can be seen from this mechanism that the bleeding is arrested by a process which has three main components. The first is the contraction of the damaged vessel, the second is the adherence of the platelets to form a plug in which active substances are released, and the third is the blood coagulation process resulting in the production of a fibrin network. The three components of the haemostatic mechanism are closely related and interdependent, failure of any one part of the system may result in faulty haemostasis. Vasoconstriction and platelet adhesion and aggregation may be considered as the primary phase of haemostasis. Fibrin formation and consolidation of the platelet plug may be considered as the secondary phase of haemostasis. Failure of the



primary phase will result in bleeding which continues from the time of injury, as in thrombocytopenia. Failure of the secondary phase is characterised by bleeding which stops initially but recurs some hours or days later, as seen in true haemophilia and Christmas disease.

2.2 Blood Coagulation

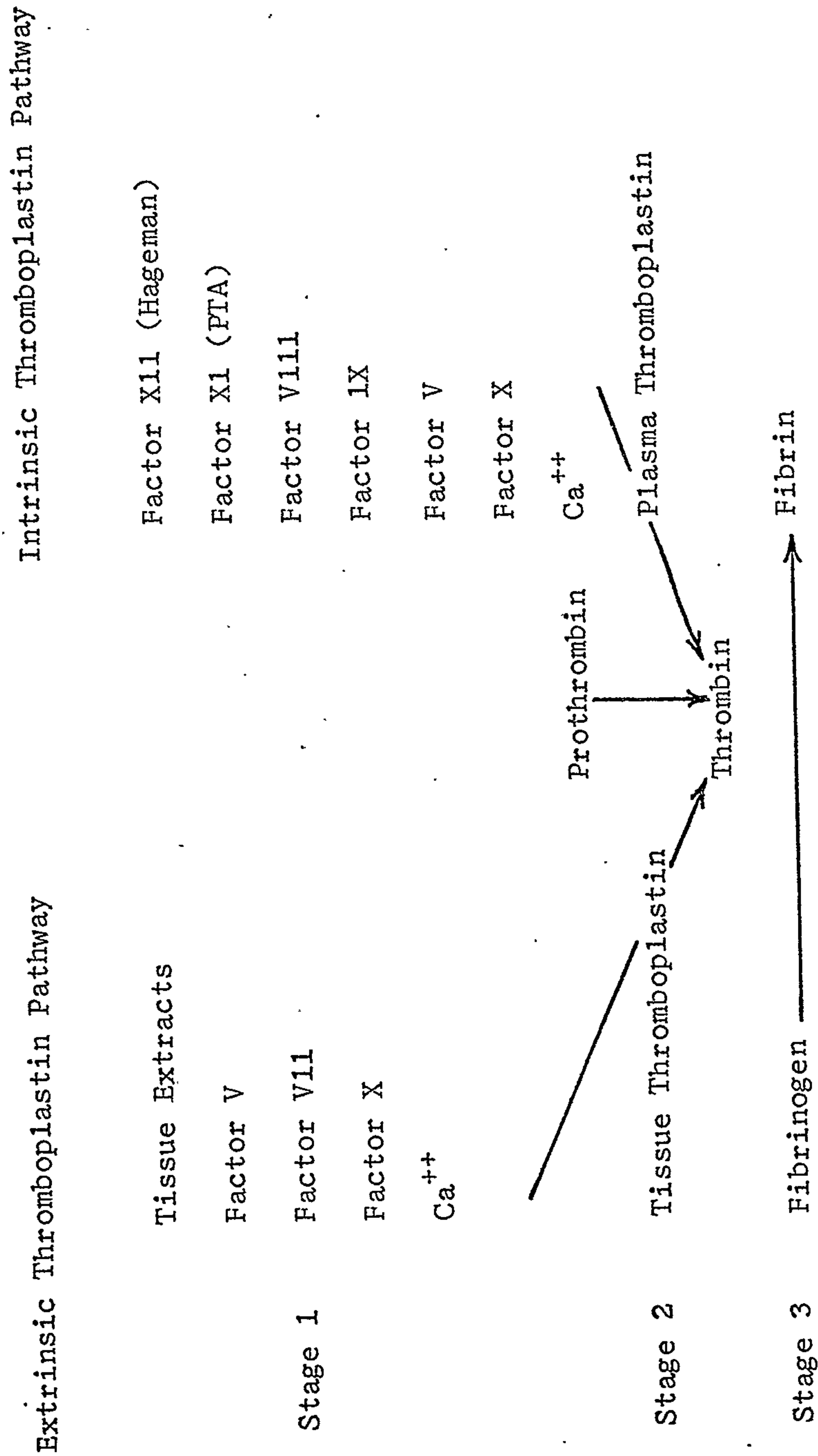
The role of blood coagulation in haemostasis has been recognised for more than a hundred years and for most of this time, has overshadowed the equally important role of the platelets.

The normal clotting of blood is conceived as a dynamic phenomenon extending from the instant blood is in contact with a surface other than vascular endothelium, to the ultimate formation of fibrin (Kerr 1963, p. 14). There is also a naturally occurring antagonistic system involving the inhibitors of intravascular clotting such as the antithrombins or fibrinolysin.

The working hypothesis of normal blood coagulation (Figure 2) was the basis for work published by Macfarlane (1960) and also Biggs and Gaston (1960). However, since none of the clotting factors was characterised as specific chemical species (except for calcium ions), the reactions undergone were related in terms of biological phenomena or hypothetical substances rather than with precise biochemical definition. It was assumed a sequential chain of parallel reactions took place which were divided into three

Figure 2

Working hypothesis of Normal Blood Coagulation^{*}



* After G.B. Kerr 1963

arbitrary phases. The first phase consists of the events initiating clotting and the eventual formation of thromboplastin, which is necessary for the conversion of prothrombin. Two systems are described as leading to the formation of thromboplastin. The intrinsic or intravascular system, involves the interaction of plasma clotting factors with the platelet thromboplastin factor and calcium ions. This can be measured by the thromboplastin generation test as described by Biggs and Douglas (1953). The extrinsic system is described as being initiated by the tissue extracts released by the breach of a blood vessel. In this system a readily available and independent source of thromboplastin is reflected in the one-stage prothrombin time described by Quick (1957).

The second phase of coagulation involves the conversion of prothrombin to thrombin in the presence of tissue thromboplastin and plasma thromboplastin. Biggs and Macfarlane, (1957) named factors V, X and calcium as being necessary for the satisfactory functioning of this stage. Finally, the third phase is the formation of fibrin from fibrinogen in the presence of thrombin.

Research workers in the field continued to try and find out the sequence of reactions involved in the formation of prothrombin activator. In 1964 Macfarlane presented his "cascade" hypothesis which seems at present to fit most of the observed factors. In

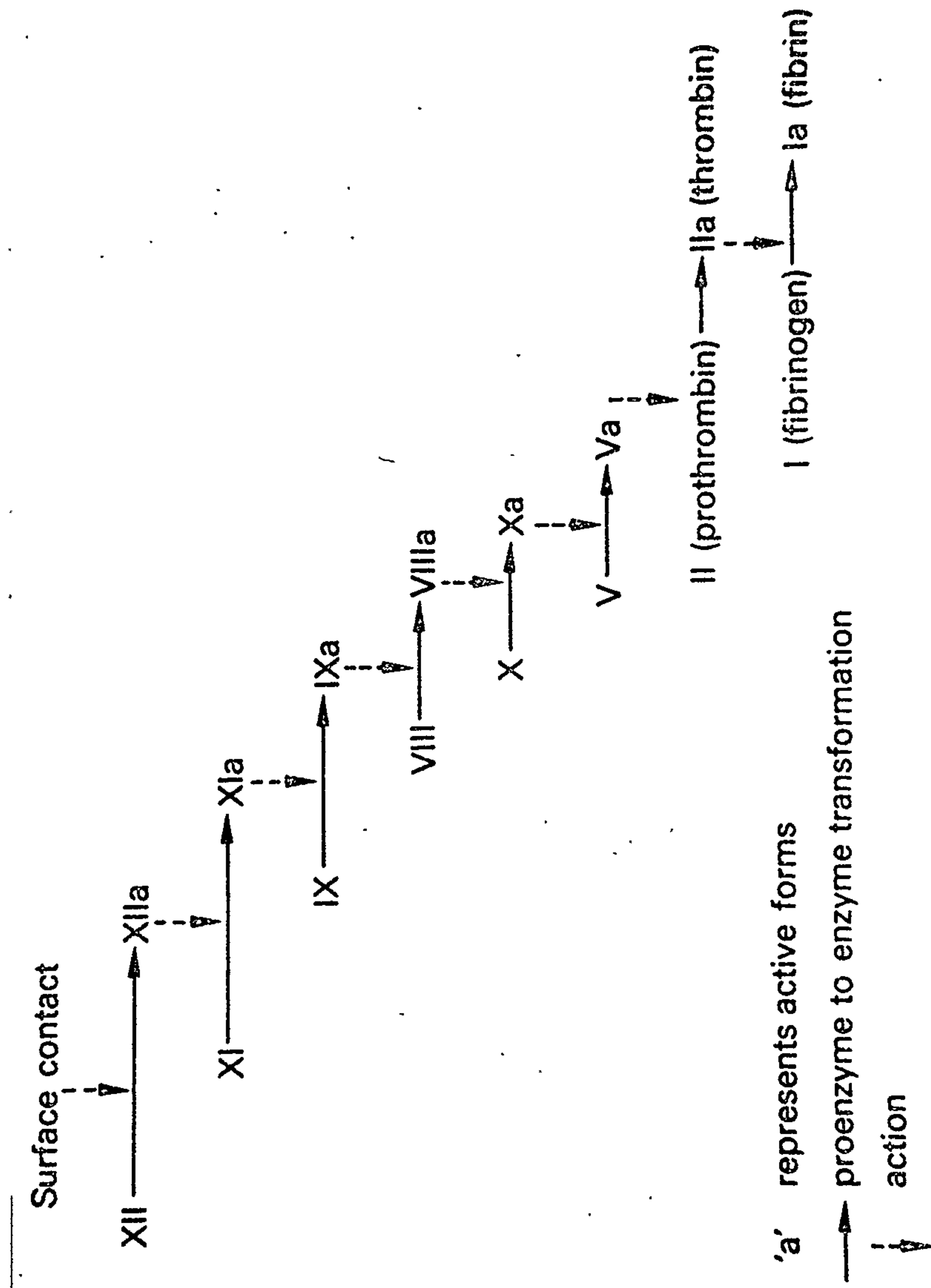
that same year Davie and Ratnoff proposed a similar scheme which they called the "waterfall" sequence and several modifications have been made to both schemes as a result of more recent investigations (Davie et al 1969).

According to the cascade hypothesis (Figure 3), there is a sequential activation of clotting factors in the process of blood coagulation. Each clotting factor is a proenzyme which can be activated to an enzyme which in turn activates the next proenzyme in the sequence. The clotting reaction is initiated by contact with a foreign surface which activates factor XII (Hageman factor). Activated factor XII then activates factor XI (PTA) and the reaction passes down the line of factors until prothrombin is activated to thrombin. Thrombin is required for the formation of fibrin from fibrinogen. In addition to the factors shown in figure 2, calcium ions in minute amounts and phospholipid are required at various stages for the reaction to proceed normally.

2.3 Diagnosis of Haemorrhagic Disorders

Haemorrhage may occur because blood vessels rupture easily, as in scurvy or allergic purpura. Platelets may fail in several ways; they may be deficient in number, or fail to adhere properly, or fail to release phospholipid, or fail to retract the clot. The cause of platelet failure may be congenital and hereditary

FIGURE 3.



The Cascade Hypothesis.

+ after Macfarlane 1964

(Glanzmann's thrombasthenia, von Willebrand's disease) or acquired (ITP, uraemia, aspirin ingestion).

As previously mentioned, there may be congenital, hereditary, deficiencies of plasma clotting factors. The most common haemophilia is factor VIII deficiency (haemophilia A, almost 80 per cent of cases of haemophilia), the second most common is factor IX deficiency (haemophilia B, almost 20 per cent of cases), and the third most common is factor XI deficiency (haemophilia C, about 1 per cent of cases). Von Willebrand's disease, a combination of factor VIII deficiency and a failure of platelet adhesion, is diagnosed in approximately 1 per cent of cases.

The other plasma clotting factors, fibrinogen, prothrombin, factor V, factor VII, factor X, factor XII and fibrin stabilising factor, may also be deficient as hereditary conditions. They are apparently transmitted on autosomal genes and the homozygotes may have severe deficiencies. Persons with homozygous factor XII deficiency do not haemorrhage, however, patients who are homozygous for the other deficiencies do have a bleeding diathesis. These deficiencies are very rare and will not be discussed further.

Hepatic disease or immaturity, or vitamin K deficiency, or warfarin ingestion may result in the deficiency of several clotting factors. Bleeding may also occur because of the development of an acquired circulating anti-coagulant, for instance in patients with

systemic lupus erythematosus, or in post-partum women. Haemorrhage is occasionally a complication in cancer patients, if the natural fibrinolytic process becomes excessively stimulated. A severe Gram-negative bacteraemia can be followed by a deficiency of some clotting factors.

The accurate diagnosis of coagulation defects requires a careful clinical and laboratory assessment of each patient. In the patient with a clearcut personal and family history of excessive bleeding and bruising, diagnosis is generally easy. The more mildly affected patients may prove more difficult to diagnose and a sound procedure for investigation is mandatory.

2.3.1.

The Clinical History

Although very few specific haemorrhagic disorders can be diagnosed on the clinical history alone, a careful inquiry into the patient's personal and family history of bleeding is perhaps the most important single "screening test" available. Inquiries should be made about bleeding in relatives, previous operations, tooth extractions, mucosal bleeding (nasal etc.) and post-traumatic bleeding. A patient who uses two hands, to show the size of the largest bruise he had following minor trauma, probably has a bleeding disorder (Kasper 1970).

If the patient has had a tonsillectomy, submucosal resection, or perhaps extractions of permanent teeth, without haemorrhage, he

is probably not a bleeder. However, Kasper et al (1968) warn that an affected female may not bleed during these procedures, if taking contraceptive hormone, or in the second to third trimester of pregnancy.

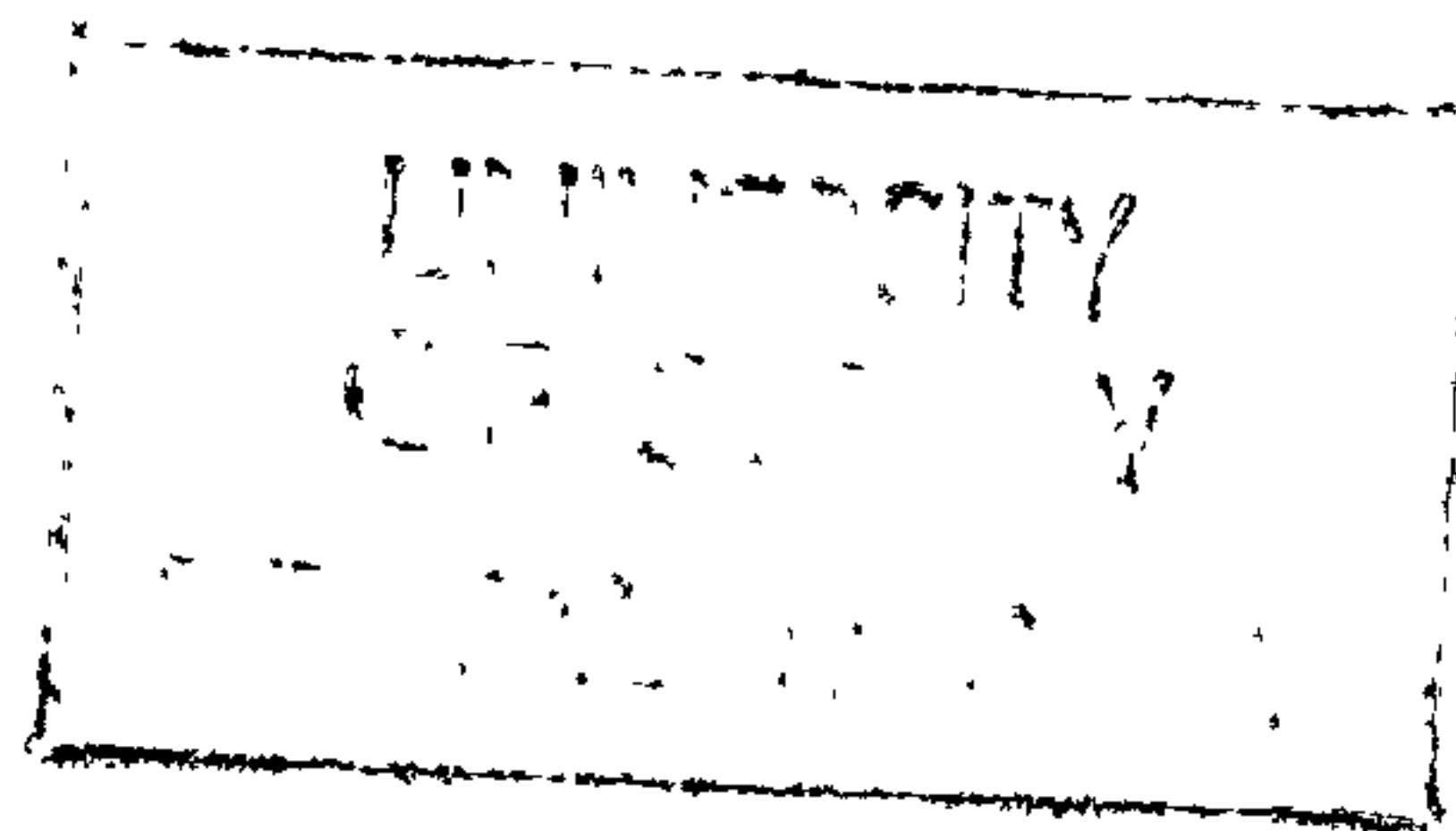
Clearly, the clinician must make careful enquiries from his patient about the haemostatic defect, before ordering laboratory tests and considering the results. The main clinical features distinguishing coagulation defects from platelet and capillary defects, are shown in Table 2.

Severely affected haemophiliacs are now diagnosed as young children, however, their history follows an invariable pattern. If circumcision was performed, bleeding for at least a week is the rule. Severe bruising occurs during infancy and in the year the child learns to walk, painful swollen joints due to acute haemarthrosis usually appear. Haemorrhage from lacerations on the extremities and in the mouth almost always lead to blood transfusions in the pre-school years. It is often difficult to evaluate the history of a mild haemophiliac. The patient may have had only one significant haemorrhage or give a vague history of abnormal bleeding episodes. The childhood may have been free from bleeding abnormality and tonsillectomy or tooth extraction may be regarded as the first common challenge. Kerr (1963, p. 26) is of the opinion that if the patient did not bleed unduly after a tonsillectomy, there is not a significant haemostatic defect. The

TABLE 2

The main clinical features distinguishing coagulation defects from platelet and capillary defects

CLINICAL FEATURE	COAGULATION DEFECT	PLATELET AND CAPILLARY DEFECT
Bleeding from superficial cuts	Usually not excessive	Often profuse
Spontaneous bruises and haematomas	Common and involve the deep tissue	Usually superficial and small
Haemarthrosis	Common in severe cases	Rare
Onset of bleeding	Usually delayed for several hours after injury	Usually immediately following injury
Bleeding symptoms	Bleeding into joints and muscles following injury	Petechiae haemorrhages, ecchymoses, epistaxes, menorrhagia and gastrointestinal bleeding
Effect of applied pressure on the lesion	Bleeding not controlled	Bleeding usually controlled



significance of a post-tonsillectomy haemorrhage may not be appreciated if it responded to local measures and repeated transfusion. The nature of the bleeding is important, as the quantity of blood lost in haemophilia at operation may be unremarkable.

2.3.2

Physical Manifestations

A severe haemophiliac is often pale, and this is sometimes due to anaemia, but more often from being indoors through illness or lack of outside interests.

Haemophilia is present at birth as factor VIII estimations from cord blood, by Baehner and Strauss (1966), have shown. The first manifestations may not occur until the child is 3 or 4 months old and beginning to crawl. At this stage the severely affected boy usually has excessive bruising over bony prominences, or painful swellings deep in the muscles of his buttocks or thighs following mild trauma.

Another common mode of presentation is with prolonged bleeding from tongue, lips or superficial wound. Contrary to lay opinion, bleeding from superficial skin wounds and mucous membrane lesions (other than dento-alveolar) is not excessive and does not constitute a threat to life. Petechiae may be present in conditions where there is an associated vascular defect as in von Willebrand's disease. Occasionally small punctate

bruises resembling petechiae are seen in severe haemophilia.

The most characteristic bleeding in haemophilia and the hall-mark of severe haemophilia, is the spontaneous bleeding into joints. Haemarthroses as previously mentioned usually begin from the age of 12 to 18 months when the child starts to walk and run. An acute haemarthrosis is a hot swollen joint with the distal limb held in a position of maximum comfort, usually flexion. Not only are they extremely painful, but if not treated promptly and effectively they can cause anatomical derangement of the joint, with arthritic changes and limitation of movement and consequent crippling. The knees, ankles, elbows, shoulders, wrists and hips are affected most frequently in that order.

Deep muscle haematomas may occur anywhere in the body and may compress the nerves and blood vessels of a limb. Ischaemia and paralysis with the possibility of permanent crippling may be the end result. (Kerr, (1963, p. 29) describes the severe haemophiliac as usually walking with a limp and showing a variety of muscle and joint changes. Teenagers are particularly susceptible to bleeding into the iliopsoas muscle; the swollen muscle compromises the femoral nerve as both pass under the inguinal ligament.

In mild haemophilia there may be no abnormal superficial physical findings. Patients with strenuous occupations may have haemarthritic lesions of the weight-bearing joints which clinically

resemble those of osteoarthritis.

Intracranial or intraspinal bleeding is uncommon in haemophilia, but when it does occur is usually of serious consequence.

Duthie et al (1972) found that half the cases with intracranial haemorrhage admitted to the Oxford Haemophilia Centre, had a history of some trauma to the head. They also say that this may be the commonest single cause of death in haemophilia, claiming over 1 per cent of severe haemophiliacs each year.

There are other types of haemorrhage in schoolboys and teenagers. The kidneys may bleed, manifesting as haematuria. Ordinary flu or tonsillitis may be complicated by haemorrhage from the inflamed area. Bleeding under the tongue or into the wall of the pharynx is specially dangerous because the mass of blood may press on the trachea and obstruct respiration. A haemorrhage occurring in a vital location, such as the spinal cord or eyeball, may cause severe impairment of function.

Patients with von Willebrand's disease have the same type of bleeding as classical haemophiliacs with similar factor Vlll levels. Patients with 1 per cent or less factor Vlll have haemarthroses and because of the platelet problem, bleed excessively from small superficial cuts to the skin and mucous membrane. Nose bleeds are common and the women often suffer from

extreme menorrhagia.

The physical signs discussed here are a guide to diagnosis and must be considered in conjunction with the severity and nature of the coagulation defect. A full physical examination must be made so as not to overlook conditions with similar physical manifestations like leukaemia, thrombocytopenic purpura, polycythaemia or malignancy.

2.3.3

Laboratory Tests

The system of tests shown in Tables 3a and 3b are representative of those used in most haematology clinics, to investigate patients suspected of having a congenital coagulation defect. A detailed technical description of these tests is given by Biggs (1972) and will not be entered into here.

The bleeding time tests, tourniquet test, whole blood clotting time, prothrombin consumption test, kaolin cephalin clotting time and the one stage prothrombin time are of no individual diagnostic value. In the first instance they may give an indication of the nature of the defect, but additional assays are employed to reach a final diagnosis of the defect and its severity. In addition to these tests of haemostatic and clotting function, haemoglobin estimation, platelet count, white cell count and examination of a blood film are carried out.

A male patient with severe bleeding manifestation and family

TABLE 3a

LABORATORY TESTS USED IN DIAGNOSIS

TEST	LIKELY TO BE ABNORMAL
Whole blood clotting time	Severe deficiencies of factors I, V, VIII, IX, X, XI, XII. The overall coagulation mechanism.
Prothrombin consumption test	Severe deficiencies of factors V, VIII and IX, thrombocytopenia, qualitative platelet defects
Thromboplastin screening test	Intrinsic thromboplastin pathway. Deficiencies of Hageman factor, PTA, factors VIII and IX circulating inhibitor.
Kaolin cephalin clotting time	Moderate and severe deficiencies of factors I, V, VIII, IX, X, XI, and XII
Thromboplastin generation test	Intrinsic thromboplastin pathway. Deficiencies of Hageman factor PTA, V, VIII, IX, and X quantitative and qualitative platelet defects
One-stage prothrombin time	Deficiencies of factors I, II, V, VII and X

TABLE 3b

LABORATORY TESTS USED IN DIAGNOSIS

TEST	LIKELY TO BE ABNORMAL
Factor VIII assay	All grades of factor VIII deficiency
Factor IX assay	All grades of factor IX deficiency
Bleeding time	Thrombocytopenia. Qualitative platelet defects. Capillary defects, von Willebrand's disease. 28.
Tourniquet test	Thrombocytopenia. Qualitative platelet defects, capillary defects
Clot observation	Clot retraction Clot lysis
Blood count	Haemoglobin level. Disorders involving red cells, white cells and platelets

history of excessive bleeding, is likely to be suffering from haemophilia and a factor VIII assay will be done. If, however, the factor VIII level is normal, then factor IX assay is done since Christmas disease is the next most likely diagnosis. Specific assays have also been devised for factor II, V, VII, X and XI and are required for exact diagnosis of their deficiency.

3. REPLACEMENT THERAPY

3.1 Introduction

Haemophiliac bleeding was dreaded for its persistence in the days before blood transfusions. Even a trivial wound in a vascular area, such as the tongue or lip, could lead to exsanguination and death. Many techniques were tried in an effort to stem the flow, such as tightly suturing the wound and packing under pressure. The bleeding might cease for a time only to recur again later, or continue into the deeper tissue frequently causing death from secondary complications. These local measures often caused necrosis and secondary bleeding. More recently the local applications of adrenaline, thrombin or Russell's Viper Venom have been used with greater success where the lesion was small or the bleeding slow. Sometimes these applications were complimented by non-traumatic, absorbable or non-adhesive dressings.

Although transfusions had been used with mixed success at the beginning of the century, the link between plasma and haemophilia was not appreciated until the 1930's. It was not until 1950, that the therapeutic value of fresh normal plasma in the treatment of haemophilia was generally accepted. Following the discovery of factor IX deficiency, techniques of assaying factor

VIII by Pitney (1965) and factor IX by Bolton and Clarke (1959), hastened the development of factor concentrates. Potent factor concentrates were made from human and animal plasma, dose response and fall-off of factor activity in the patient's blood were measured, thus a rational replacement therapy became possible.

In the early days, replacement therapy was reserved for very severe lesions, early haemarthrosis and haematomas were treated by rest and immobilisation and often at home. The reasons for this were the short supply of materials and the need for an organisation to provide comprehensive care. From 1962 onwards the concept that infusions were only given in a frantic effort to save the lives of dangerously bleeding patients, or to patients having essential surgery, began to change. In 1965 the numbers of infusions began to increase, many more being given for haemorrhages into muscle and joints. Today crippling is not regarded as an inevitable consequence of severe haemophilia.

The emphasis has changed and the aim of treatment, as at the Haematology Unit at Royal Prince Alfred Hospital, Sydney, is to treat bleeding episodes quickly and give effective cover for all surgical cases. Dangerous bleeds are seldom seen and the patients coming for early treatment have no visible lesions and little functional disability.

There is an excellent working relationship between the

Hospital Departments of Dentistry and Haematology, and this is essential for sound oral surgical treatment of patients with haemorrhagic manifestations.

3.2 Therapeutic Materials and Calculation of Dosage

3.2.1 Haemophilia

Factor Vlll is usually given in a concentrated form, either as cryoprecipitate or lyophilized concentrates. The content of factor Vlll in therapeutic materials is described in terms of units. One unit of factor Vlll is the amount of factor Vlll present in one milliliter of fresh, average normal, citrated plasma prepared from blood collected into 3.8 per cent trisodium citrate solution in the proportions of nine parts of blood to one part of trisodium citrate.

To determine the number of factor Vlll units required to achieve a desired plasma factor Vlll level in a given patient, the patients weight in pounds is multiplied by twenty to estimate the plasma volume. The desired increase in plasma factor Vlll percentage is multiplied by the estimated plasma volume to give the number of units required. For example, if a patient weighing 150 pounds has a baseline factor Vlll level of 10 per cent, and the desired therapeutic level is 50 per cent (a desired increase of 40 percentage points or 0.40), then $150 \times 20 \times 0.40 = 1200$ factor Vlll units are required (Glogoff et al., 1972).

The half-disappearance time of factor Vlll from the plasma

is about eight hours. The total therapeutic dose of factor Vlll should be infused in a short period of time so that an optimum clot can form during the period of peak factor level. If the clot is dislodged hours later, after the factor Vlll level has fallen, and further haemorrhage occurs, another dose of factor Vlll is given to achieve another peak of plasma activity. During recovery from a surgical operation, factor Vlll can be infused every eight or twelve hours to maintain a minimum level of about 30 per cent.*

a) Plasma Preparations

Fresh plasma is prepared by centrifugation of fresh blood and separation of the supernatant plasma from the cells within an hour or two of collection of the blood from the donors. Its average factor Vlll activity (content) will be slightly less than 100 per cent of normal owing to dilution by anticoagulant into which the blood was collected. The factor Vlll in fresh plasma, which is deep frozen and thawed, diminishes by 15 to 20 per cent in the process. Fresh frozen plasma at -20 to -40° centigrade, retains its factor Vlll activity with little further deterioration for several months (Duthie et al 1972, p.18).

Fresh-frozen plasma is sometimes sufficient for patients with mild haemophilia. In severe haemophilia, it is not possible to achieve a plasma factor Vlll level above 20 per cent with a volume of whole plasma tolerable to the circulatory system. If

*(Duthie et al, 1972, p.22)

necessary, the patient can undergo plasmaphoresis to make room for more normal plasma. Without plasmaphoresis, a patient with a normal circulatory system can usually tolerate infusion of 250 ml. of plasma per 40 pounds lean body weight.

Whole plasma is also available as lyophilized "anti-haemophilic plasma", prepared from pooled plasma. Plasma contains extraneous protein capable of initiating antigen-antibody reactions, and patients receiving plasma often need antihistamines to prevent allergic reactions.

b) Cryoprecipitate

It has been known for many years that a gelatinous precipitate may be thrown down from plasma which has been frozen and slowly thawed. This "sludge" consists mainly of cold-precipitated fibrinogen. In 1964 Pool and her associates at Stanford University Medical School investigated the material and observed that a considerable proportion of the factor VIII in the plasma was associated with the cryoprecipitate and that this could be reconstituted in more concentrated form to provide a potent preparation of factor VIII. This was an important advance in the treatment of haemophilia since cryoprecipitate could be prepared by relatively unskilled personnel using minimum of equipment.*

On average it is found that about 60 per cent of the factor VIII activity which was originally present in the plasma

*. Duthie et al, 1972, p.18.

can be recovered in the cryoprecipitate, so that starting with 400 ml. of deep frozen plasma containing say 320 units of factor Vlll activity, one can produce cryoprecipitate containing 60 per cent of this, 190 units of factor Vlll. This cryoprecipitate may be redissolved in a small volume (say 15 to 20 ml.) of citrate saline (one part 3.8 per cent trisodium citrate, five parts normal saline) to give a material which is six to eight times more potent than plasma. In many centres cryoprecipitate is made in single donor units in plastic bags; one bag is prepared from one bag of fresh-frozen plasma and varies in factor Vlll content according to the donor's level and the method of processing. The blood is collected in plastic bags and after centrifugation, the plasma is expressed into a satellite bag. This bag is immediately immersed in a quick-freezing bath after which it is transferred to a refrigerator. The plasma thaws slowly overnight at 40°C and the ice crystals remaining in the morning will contain mainly factor Vlll and fibrinogen (Kasper, 1972). The bags are stored frozen at -30°C thawed at $+37^{\circ}\text{C}$ (never higher), and infused promptly. There is less extraneous protein in cryoprecipitate, however, allergic reactions sometimes occur in patients sensitised to plasma. Antihistamines may be given to treat or prevent these reactions. Hepatitis is now an infrequent complication with cryo-therapy because cryoprecipitate is a single donor preparation. It should

be noted that cryoprecipitate does not contain factor IX and is therefore of no value in the treatment of Christmas disease (Duthie et al, 1972).

c) Freeze-Dried Human AHG Concentrates

Concentrates of AHG with fibrinogen are also prepared by precipitation from plasma in the presence of cold ether or alcohol. These preparations are stored as freeze-dried powder and are reconstituted with an appropriate volume of sterile water. The factor VIII activity of this material can be from three to five times that of normal plasma, volume for volume. Freeze-dried pig and beef AHG are also commercially available in some centres, the process being developed when the demand for human AHG far exceeded the supply. These products are antigenic and will cause sensitivity reactions if given for extended periods (Davidson and Macleod, 1971, p. 882).

3.2.2

Christmas Disease

Fresh and fresh-frozen plasma are of some value in the treatment of bleeding in Christmas disease but produce a rise of factor IX activity in the patient's blood only half of that predicted on the basis of dose given and the patient's plasma volume. High quality commercial factor IX is now readily available (Björlin and Nilsson, 1973).

Factor 1X disappears from the plasma in two phases, with an initial rapid half-disappearance time of about 4.6 hours and then a slower half-disappearance time of about 31 hours. Two doses of factor 1X may be needed to sustain an adequate factor 1X level in the plasma during a lengthy surgical operation. In the post-operative period, twice-daily doses of factor 1X similar to the doses of factor VIII used in haemophilia will sustain similar factor levels in the plasma. Fresh-frozen plasma should be used to treat patients with mild Christmas disease.

Lyophilized concentrates containing plasma clotting factors II, VII, IX and X are prepared from pooled plasma by pharmaceutical companies. Factor IX is present in its natural inactivated form and also its activated form in about equal amounts. The factor IX units stated on the label are based on an assay which measures both forms, but only the inactivated form remains circulating in the patient's plasma. To calculate the dose of factor IX required to achieve a desired plasma factor IX level in a patient, the labelled factor IX units should be divided in half (Kasper, 1972).

Factor IX concentrates are stored in the refrigerator and allergic reactions are mild and rare. The risk of transmission of hepatitis to susceptible individuals is high, therefore, concentrates are used primarily for patients who frequently need plasma products. Factor IX concentrates have also been associated

with an increased incidence of thrombophlebitis, especially in post-surgical patients (Kasper, 1972).

3.2.3 Other Factor Deficiencies

Patients with deficiencies of factor 11, V11, or X can be treated with the lyophilized concentrate described above, or with fresh-frozen plasma. Patients deficient in fibrinogen, factor V, factor X1 (PTA), or factor X111 (fibrin stabilising factor) can be treated with fresh-frozen plasma.

3.2.4 Von Willebrand's Disease

The typical patient has a prolonged bleeding time, low platelet adhesiveness and a low factor V111 level, however, some patients have normal factor V111 levels.* For acute haemorrhage in patients with normal factor V111 levels, a dose of one bag of fresh-frozen plasma (average content, 150 AHF units) per 50 pounds body weight, up to a maximum of three bags, will usually stop the bleeding and correct the platelet adhesiveness for a few hours. In patients with low factor V111 levels, cryoprecipitate is given for acute haemorrhages and it may also improve the platelet adhesiveness for a few hours. There is a substance in normal plasma or cryoprecipitate which permits the patient with von Willebrand's disease to make some factor V111 himself, so his factor V111 level will usually remain elevated for a few days

* Westwood et al, 1973

after an infusion. Haemorrhage may recur after the platelet adhesiveness has fallen to baseline levels but while the factor Vlll is still elevated; fresh-frozen plasma can then be given.

For surgery, cryoprecipitate or plasma is given immediately before the operation to assure a plasma factor Vlll level of at least 50 per cent. Thereafter, a bag of plasma may be given every 8 to 24 hours for 10 to 14 days. The frequency of dosage depends on the severity of the patient's disease and the nature of the operation, tonsillectomy or nasal surgery requiring more frequent and prolonged dosages.

3.2.5 Unknown Bleeding Disorder

In an emergency, a patient who is said to have a lifelong bleeding diathesis should be treated with fresh-frozen plasma. If a baseline partial thromboplastin time and prothrombin time are subsequently found to be normal and the plasma does not slow the haemorrhage, qualitative platelet disorder may be suspected and platelet packs (at least eight for an adult) may be tried.*

3.2.6 Epsilon Aminocaproic Acid (EACA) and Tranexamic Acid (TA)

EACA and TA are antifibrinolytic substances and in recent years have been used to increase the stability of the blood clot. They block the activator required for the conversion of plasminogen

*(Kasper, 1972)

to plasmin which acts to break down the fibrin polymers. Plasmin is normally produced in the body, and serves the function of breaking down old clots so that vessels can be recanalised. If the injured vessel is in a strategic location, or the clot is especially large, breakdown may be desirable. For example, if a patient ingesting EACA or TA haemorrhages into the kidney, the clots in his tubules may never break down and he may lose some renal function. However, the failure of a few small capillaries in a tooth extraction socket to recanalise may not matter. For a decade, EACA has been used for dental extractions in haemophiliacs, it has been used in combination with other local measures and together with AHG replacement. Reid et al (1964) and Cooksey et al (1966) carried out dental extractions with EACA and found it was not free from unpleasant side effects. Patients may complain of dizziness, fainting, abdominal discomfort, nausea, nasal stuffiness and headache. There are less side effects with TA.

EACA and TA preserve clots which have managed to form, they do not accelerate or aid the clotting process. It may be useful as an adjunct to intravenous replacement therapy in severe haemophiliacs, or singularly in milder haemophiliacs, to preserve their clots after a surgical procedure until healing is complete. The oral dosage for an adult is about 8 grams a day and may cause mild nausea (Forbes et al, 1972; Travenner, 1972; Walsh et al, 1971).

3.3 Principles of Replacement Therapy

3.3.1 Duration of Treatment

How long the treatment continues depends on how long the site of bleeding or the surgical wound is judged to be in a fragile state. If there are no complications, such as wound infection or haematomas, the replacement therapy should be given regularly for the minimum period of healing and on occasions afterwards, as demanded by special procedures such as physiotherapy, dressings, removal of sutures and so on.

The levels of AHG required for cover of dental extractions has been discussed a great deal in recent years. Haematologists are generally agreed that several daily doses of concentrate are required to raise the patients factor Vlll level to 30 - 40 per cent and this is maintained over a period of 7 to 10 days. The use of TA or EACA may reduce the amount of factor Vlll required.*

Before embarking on any surgical procedure, there must be sufficient therapeutic material in hand to cope with the situation and any possible complications.

3.3.2 Control of Treatment

The patient's plasma is assayed before treatment to determine his basic level of factor Vlll or factor lX, and in the case of a

* (Duthie et al, 1972, p. 22).

severe haemophiliac tests are carried out to ensure he does not have antibodies to factor VIII. The patient's weight is noted, the plasma volume roughly calculated and the amount of plasma, AHG concentrate or Christmas factor concentrate required to obtain adequate cover is calculated.

A sample of the patient's blood is taken into 3.8 per cent trisodium citrate in the proportion of nine parts of blood to one part of citrate, before, and ten minutes after the first dose of therapeutic material is given. These "pre" and "post" samples are assayed to check the actual response obtained from the dose. It is important to obtain a reliable "post" assay as soon as possible after the start of an operation, or even before the operation begins, so as to quickly check the potency of the material used and the patient's response (Duthie et al, 1972 p.23).

Following the operation, pre, post and dose samples may be assayed twice a day for the first few days and once daily thereafter. Daily doses are usually given and assayed in the morning. Samples of plasma obtained before and after evening doses may be stored deep-frozen for assay the following day unless there is a recurrence of bleeding.

3.3.3 Prophylactic Treatment

It is possible to prevent many or most haemorrhages in patients with severe haemophilia by regularly scheduled administration

of plasma products. Patients with weak muscles and deformed joints require higher doses than patients in relatively good physical condition. For patients with Christmas disease, a dose of plasma or concentrate sufficient to raise the plasma factor 1X level to about 15 per cent, given once or twice a week, is usually effective, and is often cheaper than treatment of random haemorrhages (Kasper, 1974). Patients with severe von Willebrand's disease, with factor VIII levels of 1 per cent and less, may be protected with an infusion of one bag of fresh-frozen plasma once or twice a week.

Patients refer to their "good and bad" bleeding cycles, and although clinical experience would substantiate variations, the factor levels do not alter significantly.

3.4 Analgesics in Haemophilia

Haemorrhages may be associated with a great deal of pain, and in the past haemophiliacs have taken large amounts of different analgesics for relief of pain in joints and muscles. Duthie et al (1972, p. 27), place emphasis on the relief of pain by prompt infusion of plasma, cryoprecipitate or AHG. In many instances the pain is relieved in one to two hours and the analgesic effect is not well understood. Patients suffering severe and persistent pain may require hypnotic analgesic drugs such as morphine or pethidine. Mild to moderate pain may be relieved by oral preparations e.g., paracetamol (Panadol), dihydrocodeine (DF 118), mefenamic acid

(Ponstan) and pentazocine (Fortral).

Asprin should not be given to any patient with a bleeding disorder. Not only may it cause local irritation of the stomach with bleeding, but it also decreases platelet aggregation by inhibiting the release of intrinsic platelet ADP (Quick, 1967; O'Brien, 1968). The ingestion of a single tablet by a patient with a platelet defect, may prolong the bleeding time for several days, so it is important to check the proprietary analgesic being prescribed for asprin content.

3.5 Complications in Treatment

3.5.1 Overloading of the Circulation

When high levels of factor Vlll are required, the patients tolerance to large volumes of plasma will be a limiting factor (Kerr, 1963, p. 40). For example, one litre of plasma given twice a day to an adult can increase the factor Vlll level by 30 to 40 per cent. However, three to four days of this therapy will produce signs of circulatory overload with raised venous pressure, pulmonary congestion and progressive oedema of the limbs. These effects can be counteracted to some extent by using diuretics or by temporarily ceasing therapy.

3.5.2 Pyrogenic Reactions

Pyrogens are commonly derived from protein breakdown and may be bacterial in origin. The patient will report a feeling of

coldness, perhaps with a rigor, commonly occurring a little more than an hour after commencement of an infusion. The body temperature commonly elevates to 38° C and occasionally higher, and the patient will complain of headache, which can be severe and persistent, (Davidson and Macleod, 1971, p. 57). The rigor continues from 15 to 30 minutes and is followed by sweating. This reaction is more uncomfortable than dangerous for the patient but may be alarming to the inexperienced observer. The patient should be closely watched and the temperature taken frequently, should it rise to 40° C or above, tepid sponging is employed until the temperature drops to 38.5° C (Duthie et al 1972, p. 24).

3.5.3

Allergic Reactions

Fever, angioneurotic oedema and transient urticaria is frequently associated with plasma therapy, but more severe allergic reactions are rare (Kerr, 1963, p. 40). The urticarial spots or hives commonly appear under the chin and the back of the neck and areas subject to friction or pressure. Tissue oedema is uncommon, but affects eyelids, lips, or pharyngeal and laryngeal mucosa, usually without respiratory embarrassment. Bronchospasm occurs very rarely and the more severe reactions tend to take place early in the transfusion.

A patient who consistently reacts to a given material may

be given a prophylactic dose of antihistamine intravenously such as chlorpheniramine. The more severe reactions may require 1/1000 adrenalin given subcutaneously at a rate of 0.05 ml. per minute for 10 to 15 minutes or intravenous hydrocortisone 100 mg (Duthie et al, 1972, p. 25).

3.5.4

Circulating Antibodies

An occasional patient with severe classical haemophilia and very rarely a patient with severe Christmas disease, will develop an antibody to factor VIII or factor IX respectively. These antibodies are known as inhibitors and those who develop very high-titre inhibitors do so in early life. Lower titre inhibitors may become manifested for the first time in later childhood or adulthood (Kasper, 1970).

Cases reviewed by Hougie in 1969, showed the incidence of factor VIII inhibitors complicating therapy, to vary from 3 to 21 per cent of cases. If a patient with an inhibitor is transfused with plasma or concentrate, the clotting factor molecules will combine with antibody molecules and be inactivated. If the antibody titre is not too high and sufficient plasma is given, all the antibody may be used up to allow the excess clotting factor in the plasma to participate in coagulation. However, patients with high-titre inhibitors tend to produce even more inhibitor when given a dose of plasma

or concentrate (Kasper, 1970).

With few exceptions the inhibitors have been shown to be antibodies of the 7S immunoglobulin (IgG) type. They inactivate factor Vlll in vivo, and on incubation with factor Vlll in vitro (Hougie, 1969).

It seems likely that the stimulus to production of antibody is the transfused factor Vlll, but in individual cases the previous exposure to factor Vlll has varied remarkably with respect to the amount and type of the factor Vlll containing material (Strauss, 1969). Some patients appear to develop only low titres of antibodies to an amount of treatment which in other individuals produces extremely high titres. Duthie et al (1972, p. 26) say the withholding of AHG therapy from patients with antibodies to factor Vlll is followed in many cases, and particularly in those with low titre antibodies, by disappearance of the antibody. If these patients are again exposed to factor Vlll, the antibody frequently reappears in high titre (Strauss and Merler, 1967).

Plasma or concentrate is withheld from patients with antibodies, especially those with high titres. Even very high titres will gradually decline if the patient is not exposed to the antigen. If bleeding occurs, local haemostatic measures are used, such as cold, pressure and oral prednisone. Serious bleeds are usually treated by high doses of concentrate, in an attempt to overcome the antibody for sufficient time to arrest the

haemorrhage. Kasper (1970) refers to plasmaphoresis as a means of eliminating some of the patients antibodies containing plasma, and the experimental use of immunosuppressive drugs.

The presence of factor VIII inhibitors is almost a complete contraindication to elective surgery. While it may be possible to remove a single tooth from such a patient, excessive bleeding is anticipated and regarded as a considerable risk.

3.5.5

Transfusion Hepatitis

All plasma products useful in treating haemophilia can transmit hepatitis. Considering the number of blood donations involved in the manufacture of the various blood products, one would expect the incidence of hepatitis in haemophiliacs to be higher than the general population of blood recipients.

The preparations made from pools of plasma (lyophilized whole plasma, lyophilized concentrate) have a greater risk because at each infusion the recipient receives a sample of plasma from each of a large number of donors, any one of whom might have been infected. Frozen plasma or cryoprecipitate are prepared from a single donation and have a lesser risk of disseminating hepatitis.

Kasper (1972) has observed that most patients with severe haemophilia, who require frequent infusions of plasma products, do not experience clinically obvious hepatitis. Of 208 patients

suffering from haemophilia or Christmas disease treated at the Oxford Haemophilia Centre during 1969, 7 developed jaundice within six months of receiving the material. Each of those patients as a consequence of their transfusions had been exposed to "contact" with 640 blood donors (Duthie et al 1972, p. 26). The incidence of subclinical hepatitis is not known but could be high.

4. DENTISTRY FOR THE HAEMOPHILIAC

Dental health is of major concern for patients with a bleeding defect. Unfortunately these people are inclined to postpone visits to the dentist not only because of the well recognised fear of the dental situation, but also because of the added fear of tissue injury and bleeding. For this latter reason, many dentists are reluctant to provide treatment for these patients in case ill-defined difficulties arise during treatment.

Such hesitation and fears may have been justified in the past, but are unfounded now thanks to the modern techniques and instruments used in the delivery of dental treatment, and the availability of factor concentrates.

Prevention is the key to improved dental health and a better relationship between the haemophiliac and the dental profession. These days most haemophiliacs or their parents receive advice on dental health through their haemophiliac centre. These centres arrange for patients to have specialist dental advice or treatment and when oral surgery is required, provides the basis for a closer working relationship between the haematologist and the oral surgeon and the patient. Most

routine dental treatment can be provided on an out-patient basis, if the dental surgeon understands the nature of the patient's coagulation defect.

4.1 Assessment

4.1.1 Medical and Dental

Before undertaking dental treatment for a patient with a coagulation defect, a thorough medical and dental history should be obtained from the patient. Any information obtained from the patient or his parents concerning his condition should not be accepted as accurate without verification from the haematologist. Lewis (1973) draws attention to the fact that while some mild haemophiliacs demonstrate severe clinical manifestations, the reverse may also occur. Some patients may classify their condition as mild merely because they have experienced few bleeding episodes. The dentist must consult with the patient's haematologist to determine the type and severity of the haemophilia, the patient's previous response to treatment, the availability of products for treatment of the patient and the best location for the performance of the treatment.

4.1.2 Psychological and Social Aspects

The psychological and social problems must not be overlooked in the total dental care of the haemophiliac patient.

Matteson and Gross (1965), subjected 35 haemophiliac children and their parents to a longitudinal psychiatric study in order to evaluate their ways of coping with haemophilia. They found the well adjusted patients and their parents made extensive use of motor activities, emotional expression and psychological defences. The mother's ability to cope with her initial guilt, sadness and fears was important for the haemophiliac's personality development. Hurt (1966) also found this to be the case in his study of the medical and social problems of the haemophiliac.

Browne et al (1960) report that the mother's guilt, the father's ambivalence and the child's conflict about movement are interwoven. They claim the effect upon the family can sometimes be seen in the separation of the mother and the haemophiliac child from the father and the other siblings. They also state that there is a relationship between this situation and the child's bleeding episodes.

Poinsard (1965) considered emotional factors influence the permability of the capillary walls, in addition to the genetic intrinsic blood coagulation defects in haemophilia. Macfarlane and Biggs (1946) demonstrated a direct relationship between emotional factors and an increased fibrinolysis. Later, Ogston et al (1962) in their studies of the influence of anxiety on coagulation, found systemic variations of coagulation related to

different levels of anxiety. They found short anxiety-provoking stimuli increased plasma fibrinolytic activity.

These findings indicate that emotional factors can contribute to the timing of spontaneous bleeding episodes in haemophilia. Some traumatic episodes are also associated with similar emotional factors. Accident-proneness is probably the basis for this in the opinion of Chiono (1973 A).

In the assessment of the haemophiliac patient consideration should be given to the relationship between emotional factors and spontaneous bleeding. Stress and fear are the two factors we must try to control when attending to the dental needs of these patients.

The educational problems of the young haemophiliac must not be overlooked. Their schooling is frequently interrupted by bleeding episodes resulting often in anxiety over falling behind the rest of the class. The dentist, where possible, should give special consideration to timing of appointments for these patients.

4.2 Anaesthesia

4.2.1 Local Anaesthesia

Local anaesthesia has been used extensively in dentistry for more than 50 years. The beneficial effects include; 1) the elimination of pain, 2) the action of an added vasoconstrictor, and 3) the reduction of the reflex flow of saliva into the operative field. However, local anaesthesia for the haemophiliac presents a

problem, in that an avenue for haemorrhage is created by the injection. Therefore the decision to use local anaesthesia on these patients cannot be taken lightly.

There are reports in the literature of extensive and even fatal haemorrhages following the use of local anaesthesia for dental purposes. Archer (1951) reports a case in which bleeding occurred from the pterygoid plexus of veins, pierced during the infiltration injection to anaesthetise a maxillary third molar. In 1954, Archer reported a case in which a bilateral mandibular block was given to a haemophiliac. The patient was admitted to hospital two days post-operatively with swelling of the jaw, floor of the mouth and neck. He rapidly became cyanotic as a result of airway obstruction and subsequently died. Leatherdale (1960) reports 10 cases of respiratory obstruction in haemophiliac patients. He warns against the use of the inferior dental nerve block and the infiltration into the gingiva of the mandible, as both techniques can cause haematomas involving the floor of the mouth and the tongue, with the risk of airway obstruction.

On the other hand many investigators support the use of local anaesthetic for patients with blood coagulation defects. Bumsted et al (1955) report a case where oral surgery was carried out for a haemophiliac using local anaesthesia. They recommend the use of infiltration anaesthesia and the cautious use of the

inferior dental nerve block technique. Cash (1942) and Finkleman (1959) also support the cautious use of local anaesthesia for these patients. Powell (1973) recommends the use of local anaesthetic only when the patient has received replacement therapy, and the deficient factor has been restored to the 50 per cent level.

On the possible complications of injecting local anaesthetic, Webster et al (1968, p. 99) published the results of a three year study. The patients did not receive prior replacement therapy and a comprehensive range of operative treatment was carried out. There were 5 (8 per cent) post-injection haematomas out of 63 inferior dental nerve blocks. None of the 79 superior alveolar infiltrations produced a haematoma.

The control group of 746 bleeders in this study, received operative treatment without local anaesthetic and two post-operative treatment haematomas were observed. On the subject of pain experienced in this group, Webster et al report, that while some patients were able to withstand pain others required Meperidine to raise their pain threshold.

In regrouping these patients according to the severity of their bleeding disorder, Webster (1968, p. 100) found there were more haematomas in the severe groups than the milder groups. He concluded that local anaesthesia can be used for the mild or moderate bleeders without prior replacement therapy. However, he

recommends the use of replacement therapy prior to using local anaesthesia on severe haemophiliacs. Glogoff et al (1972) prefer to use local anaesthetic without a vasoconstrictor because the temporary vasoconstriction instills a false sense of security regarding haemostasis. Plain local anaesthetic allows only a limited working time and I am certain that the temporary anaesthesia obtained would prove totally inadequate for many procedures.

Patients with coagulation defects treated in the Department of Dentistry at Royal Prince Alfred Hospital, are as a rule not given injections of local anaesthetic unless they are having replacement therapy and until recently only infiltration or papillary techniques have been used. However, a small number of patients with milder bleeding disorders are now given inferior dental nerve block injections following replacement therapy. Biggs (1975), reports that patients at the Oxford Haemophilia Centre are allowed to have papillary infiltrations of local anaesthetic for front teeth without replacement therapy.

During a period of one year, two patients with coagulation defects were referred to the Department of Dentistry with haematomas following dental injections without replacement therapy. A 35 years old female with von Willebrand's disease had received an infiltration of local anaesthetic for restorations carried out on her upper right cuspid and bicuspid teeth. The following day she was admitted to Royal Prince Alfred

Hospital with an extensive haematoma of the upper lip and right cheek which had closed the right eye.

4.2.2

General Anaesthesia

The opinions vary widely in the literature on the use of general anaesthesia for patients with haemophilia. However, it is generally agreed that the risk of nasal, pharyngeal or tracheal haemorrhage must be considered extremely dangerous.

Glogoff et al (1972) avoid using general anaesthetic for the haemophiliac oral surgery patient, while McIntyre (1965) is of the opinion that general anaesthesia should be reserved for children and very apprehensive adults. Middleton et al (1965) are in favour of general anaesthesia. They are of the opinion that until some new approach to dental extraction for patients with haemophilia, it is best done as an elective procedure under general anaesthesia with replacement therapy. The anaesthesia was induced with intravenous thiopentone and a muscle relaxant was given. The patient was then intubated orally and anaesthesia was maintained with a nitrous oxide - oxygen mixture. Other advocates of this technique include Wishart et al (1957), Biggs et al (1958) and Leatherdale (1958).

Findlay (1960) in a report on 13 patients in which endotracheal anaesthesia was administered, describes one case in which nasal haemorrhage occurred and stopped spontaneously

after half an hour.

Patients with severe and moderate coagulation disorders admitted to Royal Prince Alfred Hospital for tooth extraction, oral surgery or extensive operative work, are invariably given a general anaesthetic in an operating theatre. The technique described by Middleton et al (1965) is used with Halothane. Although the oral tube restricts access, adjustments may be made to the tube position as required. An endotracheal tube with inflatable cuff is used and a small oropharyngeal pack is placed carefully. Glogoff et al (1972) warn against the use of throat pack, as it may cause blunt trauma to highly vascular tissue, whereas the endotracheal cuff causes pressure in a relatively avascular area. I believe such a pack can be atraumatically placed and is essential to guard against leaving tooth fragments and associated debris in the pharynx.

4.3 Tooth Exfoliation and Eruption

The eruption of the primary dentition usually takes place with minimal oral bleeding. However, the exfoliation of deciduous teeth and the eruption of the permanent dentition is associated with bleeding problems in many haemophiliacs.

As Chiono (1973, B) has observed, tooth exfoliation in haemophiliacs may extend over a long period, with intervals of considerable oozing. These periods are trying for both the child and his parents, and if the oozing continues it may be best to

correct the haemostatic condition and extract the tooth. If this is done, Chiono (1973; B) advocates curettage of all pulp tissue beneath the primary tooth to promote good healing.

Rubin et al (1959) are not in favour of extracting over-retained deciduous teeth unless there are orthodontic reasons, because natural exfoliation is less traumatic. They suggest the oozing may be reduced as the tooth loosens by the application of any of the following: ice, pressure, oxidised cellulose, topical adrenaline or thrombin. On a number of occasions I have controlled intermittent oozing with oxidised cellulose.

A flap of gingival tissue (operculum) over an erupting molar is easily traumatised and in the third molar region the tissue may persist, leading to pericoronitis. A 12 years old boy with severe haemophilia, was admitted to Royal Prince Alfred Hospital with persistent oral bleeding. On examination, the bleeding source was found to be a traumatised flap covering less than half the occlusal surface of an erupting lower second molar tooth. The lingual cusp of the opposing molar was seen to be responsible for the trauma and surgical removal of the tissue was indicated to avoid recurrent bleeding. Cryoprecipitate replacement therapy was initiated, and local anaesthetic infiltrated into the tissue prior to its removal by cautery. The boy was discharged the following day having had no further bleeding.

4.4

Operative Dentistry

There should be no compromise in the standard of care offered to the haemophiliac patient. Every restoration placed for a haemophiliac eliminates a potential extraction. Chiono (1973, C) states: "By patient education and early treatment of caries, theoretically, it is possible for a haemophiliac to have a full compliment of teeth and a minimum of surgical procedures".

A thorough examination with radiographs is essential to enable the most efficient treatment to be formulated. Once the extent and type of restorative work has been determined, consideration must be given to how this work can be carried out for the patient with a minimum of discomfort and a maximum of safety. Where possible, the history of the previous restorative work will be a guide to the patients ability to cope with the treatment required without anaesthesia.

Although there are patients who will cope with the routine operative procedures without anaesthesia, some cannot and will require some means of pain control. Webster et al (1968, P. 100) in a report on 746 operative procedures carried out without anaesthesia, found that some patients required the use of Meperidine to raise the pain threshold. As previously mentioned, the use of both general and local anaesthetics must be considered in

consultation with the patient's haematologist. If anaesthesia is indicated for patients with severe or moderate coagulation disorders, the appropriate replacement therapy will be required.

Lewis (1973) found nitrous oxide analgesia extremely useful in dealing with the apprehensive patient, and particularly during painful restorative procedures. Although this technique is closely associated with local anaesthesia for the non-haemophiliac patient, it will have a place in the future treatment of patients with coagulation disorders.

The normal restorative procedures can be performed for these patients, however, the removal of the enamel and dentine with high speed rotary and manual instruments in an area adjacent to highly vascular soft tissue usually produces some bleeding. In many instances the margins of the restoration have to be carried below the crest of the soft tissue.

For restorative procedures, Lewis (1973), recommends the isolation of an area with rubber dam to minimise the chance of accidental injury. Chiono (1973, B) also advocates the use of rubber dam whenever possible as it protects the patient's tongue and oral tissues. In addition the rubber dam will retract the gingival tissues allowing safe access to the interproximal cavities.

Bleeding from the tongue is very difficult to control in a normal patient, but in a haemophiliac it can be a very serious

problem. Andonian et al (1966), warn that haemorrhages in the lax tissues beneath the tongue may dissect posteriorly to the pharynx. This is potentially dangerous, as airway embarrassment may occur. They stressed that one of the early signs of impending neck bleeding is a haematoma under the tongue. Normal cavity preparation of a proximal surface may disrupt tissue, but if reasonable care is taken this should be minimal. The placement of restorative materials with matrixes and wedges is not a problem, as the slight amount of bleeding caused by these procedures stops relatively quickly (Chiono and Miyamoto, 1968).

Stainless steel crowns for a child can be fitted with a minimum of cervical reduction. Crown preparation for an adult should be modified only to reduce unnecessary trauma during preparation. When impressions are being taken, the tray should be lined with periphery wax to minimise the risk of soft tissue injury (Lewis, 1973).

Gingival proliferation into deep carious lesions can be treated by placement of a dressing of zinc oxide - eugenol to obtain resorption of the tissue (Chiono and Miyamoto, 1968). Tissue of this nature can also be removed by electrosurgery, however, Lewis (1973) warns against the risk of subsequent haemorrhage with this technique.

Endodontic treatment of infected teeth is especially

important to the patient with bleeding disorders, for it may avert the need for subsequent removal of the tooth. If local anaesthesia is required then the haemostatic defect must first be corrected by replacement therapy (Webster et al, 1968, p. 98).

Complete removal of the pulpal tissue can be accomplished without significant haemorrhage and replacement therapy is not usually required. The root canal preparation, sterilisation and filling can be completed without vital soft tissue damage.

Partial pulpotomy can be carried out under the cover of the appropriate replacement therapy, and a successful case is presented by Webster et al (1968, p. 101). Formocresol pulpotomy has been used with great success in primary teeth by Chiono (1973, C), but he does not use it for adults. The technique of indirect pulp capping is particularly suited for haemophiliac patients, in that it can be used without local anaesthetic. Should this procedure fail, the patient may have root canal therapy with replacement therapy at a later date (Chiono, 1973, C and Lewis, 1973).

Care must be taken with the high speed vacuum and saliva ejector to avoid sublingual haematoma. Powell (1973), recommends the use of saliva ejectors with a soft tip.

Plaque control is the most important part of early dental management of these patients. The child is taught proper brushing techniques with the aid of plaque disclosing solutions and the use of fluoride tooth paste. The young patient should experience a prophylaxis and topical fluoride application by the dentist. Advice should be given to the mother regarding the role of nutrition in maintaining good oral health.

Lewis (1973) states: "The parents of many haemophiliacs have told them not to brush their teeth because the gingiva will bleed. Since they feel that coarse foods present a danger to the gingiva, parents may also limit the diet of the haemophiliac to softer foods". When this attitude is expressed by a parent, the dentist should call upon the haematologist to use his influence to establish a sound programme of preventive dentistry.

Routine scaling and polishing usually will not injure healthy gingiva. The occasional persistent oozing can be controlled by packing or replacement therapy. Lewis (1973), Webster and Courtney (1968), recommend the use of the Ultrasonic Scaler, as it results in less bleeding while accomplishing the same degree of cleanliness when compared with hand scaling. Periodontal conditions must receive early care, scaling, curettage and root planing should be carefully performed when necessary (Chiono,

1973, C).

An excellent aid for home hygiene, particularly if periodontal problems exist, is the water irrigating device (Lewis, 1973). Generally, the irrigating device is used in conjunction with, and not in place of the toothbrush (Chiono, 1968).

Prophylactic odontotomy is recommended by Chiono (1973, C). He has found this procedure minimises apprehension and extensive caries. Pit and fissure sealants should be used when teeth erupt, providing they are properly applied and regularly checked.

4.6 Orthodontic Treatment

In the past, orthodontic treatment was not considered practical because of the common need to extract teeth and apply bands; which would cause gingival irritation and bleeding. The extraction of teeth with modern replacement therapy, together with the advent of resins which enable brackets to be cemented to teeth, has changed this situation.

Orthodontic procedures were carried out on two patients by Chiono and Miyamoto (1968). In one patient a lingually displaced upper central incisor was corrected using a palatal plate. Two teeth were moved in a second patient and no bleeding was experienced during these procedures.

4.7

Prosthetics

Very little comment is made on the literature regarding prosthetic treatment for patients with coagulation disorders. There are occasional difficulties encountered in the management of these patients and in the design of their appliance.

Rubin et al (1959) report a case where extractions although necessary, were contraindicated because the patient was refractory to plasma. The retained roots and sharp tooth fragments were reduced to the gingival level and a full denture constructed. Fortunately such cases are rare and the replacement of missing teeth can be readily accomplished for the haemophiliac patient.

Consideration should be given to features of denture design which may inadvertently cause trauma. Clasps on partial dentures must allow safe insertion and removal; teeth should be positioned to avoid cheek or tongue biting.

Before inserting a new prosthetic appliance for a haemophiliac, it should be examined carefully for sharp or otherwise irritating tissue contacts. Although these precautions should apply to all prosthetic patients, a number of patients with bleeding disorders examined by the writer, were wearing potentially traumatic dentures.

5. ORAL SURGICAL MANAGEMENT

5.1 Assessment of the Patient

The medical complications entailed in these disorders are such that oral surgery should not be undertaken, except in consultation with the haematologist acquainted with the patients condition. Any information obtained from the patient or his parents should not be accepted without verification.

The type and severity of the bleeding disorder, the patients previous response to treatment and the availability of products for treatment should be assessed. Consideration is then given to the best location for the planned surgery. Elective procedures, such as the surgical removal of third molar teeth, should be planned with great care.

The psychological factors may be difficult to assess and according to the literature reviewed by Chiono (1973 A) may greatly influence the ultimate success of the treatment plan.

5.2 The Treatment Plan

Following a thorough oral examination with full mouth radiographs and diagnosis, a treatment plan may be formulated. The oral surgeon has the responsibility of planning procedures which are safe for the patient, and that will not inconsiderately

involve lengthy patient care. Although haematologists in large centres will have experienced such problems, many will depend upon the sound judgement of the oral surgeon.

The literature abounds with reports of the dangers of elective procedures, histories of prolonged haemorrhage and a variety of methods for controlling haemorrhage. Chiono (1973, B) lists the following factors which may have caused difficulties during oral surgical procedures:

- 1) The lack of critical assessment of the medical and dental history.
- 2) Insufficient preoperative administration of plasma or factor concentrates.
- 3) Too radical a form of surgery.
- 4) Removal of too many teeth at one time.
- 5) Failure to prepare adequate means to control local haemorrhage.
- 6) Premature dismissal of the patient from hospital.
- 7) Lack of consideration of the psychological problems of the patient.

Björlin and Nilsson (1965), and Findlay (1960), are of the opinion that the extent of the operation must be limited according to the severity of the patient's coagulopathy. Chiono (1973 B) will not extract more than one multirooted tooth at a time. Although

these opinions are soundly based, the decision may be difficult when there are a number of teeth to be extracted under general anaesthesia.

There is a wide variation in opinion in the literature regarding the numbers of teeth which should be extracted at one time. The number ranges from one to as many as thirty two in one operating session. A study involving 120 haemophiliacs by McIntyre (1965) was based on the extraction of 1,036 teeth in 149 operations. The number of extractions varied from one to thirty two teeth at one operation. Linenberg (1961) extracted twenty three teeth from one patient in two consecutive operating sessions, eleven mandibular teeth on the first day and twelve maxillary teeth on the second day. A case report by Ingram and Winstock (1960), describes the extraction of ten teeth and an alveolectomy for dentures. Those opposed to multiple extractions include Landbeck (1961), who recommends that only one tooth be extracted at a time and Rubin et al (1959) who advocate the extraction of only two teeth, which should be adjacent or at least in the same quadrant.

McIntyre (1965) stated, "There is no relationship between the number of teeth extracted, the length of stay in hospital or the grade of haemophilia". Biggs et al (1965) in a report of some forty two haemophiliacs based on medical records, found that the

amount of treatment required to ensure freedom from abnormal bleeding varies a good deal. The extraction of deciduous teeth required less treatment than adult teeth and a single extraction in an adult did not result in abnormal bleeding. They found that in general, the greater the number of teeth extracted, the greater the risk of bleeding.

The difficulty of the planned oral surgical procedure or tooth extraction can be anticipated to some extent from anatomical features and, when available, the past dental history. Difficulties can arise even with the most carefully planned procedure and consideration should be given to the possible complications in each instance.

5.3 Replacement Therapy

It is generally accepted that the most effective way to control haemorrhage in patients with coagulation defects, is by replacement of the defective or missing factor. Local means of haemorrhage control are less effective, but useful; these will be discussed in the following section.

The complex haematology involved in the correction of the various coagulation disorders is beyond the scope of this review.. However, it is necessary for the dental surgeon to have a basic knowledge of the materials used in replacement therapy for the common coagulation dyscrasias.

5.3.1

Haemophilia

The proper level of AHF (Factor VIII) required to maintain haemostasis and promote healing in true haemophilia, has received a great deal of attention. Winstock and Ingram (1961) are of the opinion that the patient's AHG must be at the 20 per cent level for seven days. Glogoff et al (1972) say that the successful management of a haemophiliac is based on the need to maintain the patient's antihaemophilic globulin (AHG) level at a minimum of 20 per cent of normal. Findlay and Nicholl (1960) found that a haemophiliac with a 10 per cent level of AHG should have the level raised to between 20 and 30 per cent. They also noted that in haemophiliacs whose level was above 5 per cent spontaneous bleeding was uncommon, but below 20 per cent the post-traumatic haemorrhage was noticeably long. Wishart et al (1957) and Abildgaard et al (1966) are of the opinion that 20 to 30 per cent of factor VIII is the desired level to create good haemostasis. Pool and Shannon (1965) recommended minimum levels of 10 to 35 per cent of factor VIII be achieved and maintained for twelve days. Walsh et al (1971) gave preoperative concentrate in amounts estimated to raise the deficient factor to 50 per cent average normal.

Replacement therapy with plasma alone may be inadequate during dental surgical procedures on a severe bleeder; plasma

fractions are more effective agents (Webster et al, 1968, p. 103). Cohn's fraction I is a highly concentrated AHF rich fibrinogen, used by Marder et al (1966), and Gamble (1964) for oral surgery. They reported that bleeding usually occurred four to five days after surgery and was controlled by further infusions of concentrated Cohn's fractions. Archer (1951) had used Cohn's fraction I preoperatively, but had found it effective post-operatively on two occasions after extractions. Abildgaard et al (1966) felt the glycine precipitated factor Vlll provided more AHF in less volume than plasma or Cohn's fraction I, and because of its relatively low total protein content, its use is associated with little or no risk of overloading the total plasma volume.

A considerable amount of research has been done in recent years, in the hope of developing more concentrated fractions of factor Vlll.

Factor Vlll concentrates are currently available in the form of Human Antihaemophilic globulin (HAHG), prepared by the method described by Bidwell et al (1971); as plasma cryoprecipitate prepared by the method of Pool and Shannon (1965); or as fresh-frozen plasma.

Hattersley (1966) used the cryoprecipitate on four haemophiliacs. He reported satisfactory results, all patients exhibited a prompt haemostasis. Although the early product

lacked uniformity of assayable factor Vlll, it was undoubtedly a breakthrough for the future treatment.

Glycineprecipitate antihaemophilic fraction is another concentrate, first reported by Webster (1965). It is prepared by a procedure of utilising the amino acid glycine as a precipitating agent and is claimed to have 7 to 10 times the factor Vlll level found in normal plasma. Webster used the concentrate on 6 haemophiliacs and showed that after the first administration, the factor Vlll level was 25 to 49 per cent. Abildgaard et al (1966), in their study using 17 haemophiliacs, concluded that the glycineprecipitate is a stable and potent source of factor Vlll.

Perhaps the biggest advance in recent years, is the availability of high quality commercial factor Vlll (Biggs, 1975). Therapeutic materials are assayed for factor Vlll activity and the results are expressed as per cent average normal plasma. One unit of activity being the amount contained by 1 ml. of average normal plasma as collected for testing in the laboratory (see p. 32).

Within one hour of the extractions or oral surgery, the patient receives a loading dose of factor Vlll concentrate to raise their level to 50 per cent average normal. The dose is calculated according to the formula (Walsh et al, 1971):

Dose in factor Vlll units

= $\frac{\text{weight of patient (kg)} \times (50 - \text{Preinfusion factor Vlll level})}{1.5}$

It is now common practice to immediately follow the infusion of factor concentrates with an initial dose of antifibrinolytic agent. These agents have greatly reduced the post-operative replacement therapy required.

5.3.2 Christmas Disease

The level of factor IX required for haemostasis in the patient with Christmas disease, is considered to be equivalent to the level of factor VIII required for haemostasis in true haemophilia.

Fresh-frozen plasma is useful in the treatment of this disorder, however, the rise in factor IX activity in the patient's blood is half that predicted on the basis of dose given and the patient's plasma volume (see section 3.2.2). The factor IX disappears rapidly from the patient's plasma and twice daily doses equivalent to those of factor VIII in haemophilia may be required.

Bidwell et al (1967) described the preparation of a factor IX concentrate. This preparation was used by Walsh et al (1971) for replacement therapy in patients having dental extractions. Preoperative levels of 50 per cent were achieved by calculating the dose from the following formulae:

$$\begin{aligned} &\text{Dose in factor IX units} \\ &= \frac{\text{Weight of patient (kg)} \times (50 - \text{Preinfusion factor IX level})}{0.5} \end{aligned}$$

Antifibrinolysins are also used in these patients and greatly reduce the quantity of factor 1X required postoperatively.

5.3.3 Plasma Thromboplastin Antecedent Deficiency

The amount of bleeding experienced with deficiency of factor XI is extremely variable and attempts have been made, at correlating the level of the factor in the blood with the degree of bleeding experienced (Phillips et al, 1965). Rapaport et al (1961) suggested that a level of 20 per cent was required for effective haemostasis while Rosenthal (1965) observed patients with levels of 10 to 15 per cent who did not bleed; and others with 50 to 70 per cent who did bleed.

This condition is particularly unpredictable in its behaviour and for this reason the factor should be replaced prior to surgery (Williams, 1972). Fresh-frozen plasma may be used for these patients but difficulties may arise if large volumes of plasma are required. To avoid overloading the circulation, Bennet and Dormandy (1966) suggest the use of exhausted plasma recovered from the preparation of cryoprecipitate.

Williams (1972) recommends the combined use of fresh-frozen plasma and epsilon aminocaproic acid in severe cases, to prevent overloading the circulation.

5.3.4

Von Willebrand's Disease

This is a complex bleeding disorder in which problems remain despite recent advances (Quast and Schoettger, 1974). There appears to be an unknown plasma factor deficient, as well as a low factor Vlll level in severe cases. The prolonged bleeding time tends to indicate capillary defects.

For elective surgical procedures, the use of fresh-frozen plasma pre and postoperatively is the preferred treatment (Quast and Schoettger, 1974). Factor Vlll replacement may be required initially in severe cases but will not correct the bleeding defect alone. In most cases the plasma therapy alone tends to correct the low factor Vlll activity and maintain a high level for some time.

Where large volumes of blood are lost during an operation or as a result of trauma, the use of whole blood is indicated for replacement. A subfraction of Cohn's fraction I of plasma, the so-called fraction I-0, has also been used (Westwood et al, 1973).

Epsilon Aminocaproic acid is also used in the management of these patients.

5.4

Antifibrinolytic Therapy

Haemostasis following tooth extraction and oral surgery, depends upon the blood coagulation system and also its antagonist,

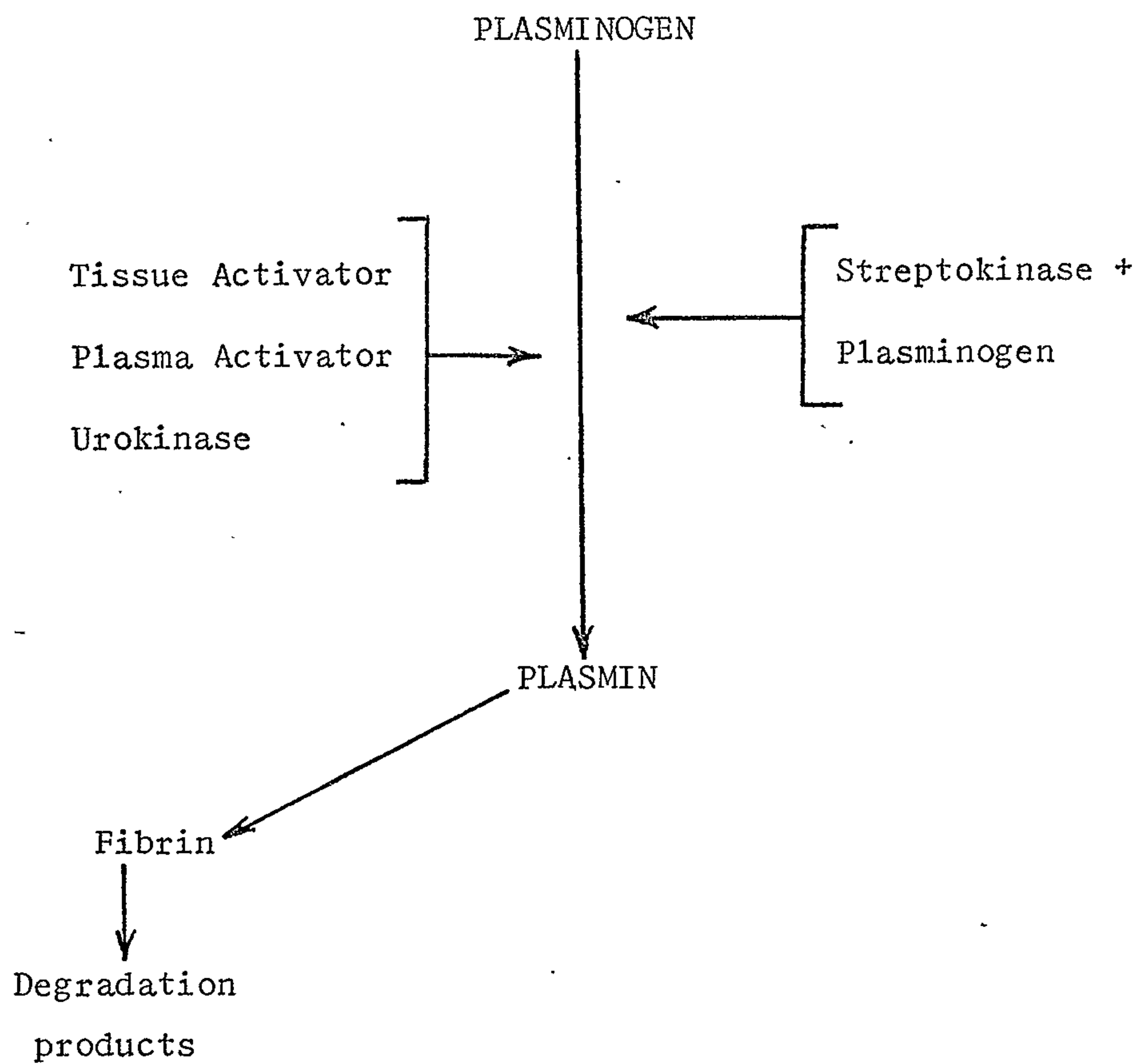
the fibrinolytic system. The coagulation defect can be corrected initially by replacing the deficient factor, but this may be expensive and potentially dangerous for the patient.

It is now possible to inhibit the fibrinolytic enzyme system so that low circulating levels of the deficient clotting factor are enhanced. The fibrinolytic enzyme system (figure 4) consists of four principal components:

- 1) Plasminogen - which is widely distributed throughout the body, and when activated is converted to:
 - 11) Plasmin - whose action is to lyse pre-formed fibrin.
 - 111) Activators - such as in tissue, plasma, Urokinase, Streptokinase.
- 1V) Inhibitors - such as antiplasmins.

Okamoto and Okamoto, working in Japan, began the search for a chemical with antiplasmin activity in 1948. In 1957 they discovered a synthetic amino acid, epsilon amino caproic acid or E.A.C.A., which has an antifibrinolytic effect. Aminocaproic acid ($\text{NH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{COOH}$) is a synthetic monoaminocarboxylic acid closely related to lysine ($\text{NH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}(\text{NH}_2) \text{COOH}$). It lacks the alpha amino group present in lysine; otherwise the molecular structure of both substances is similar.

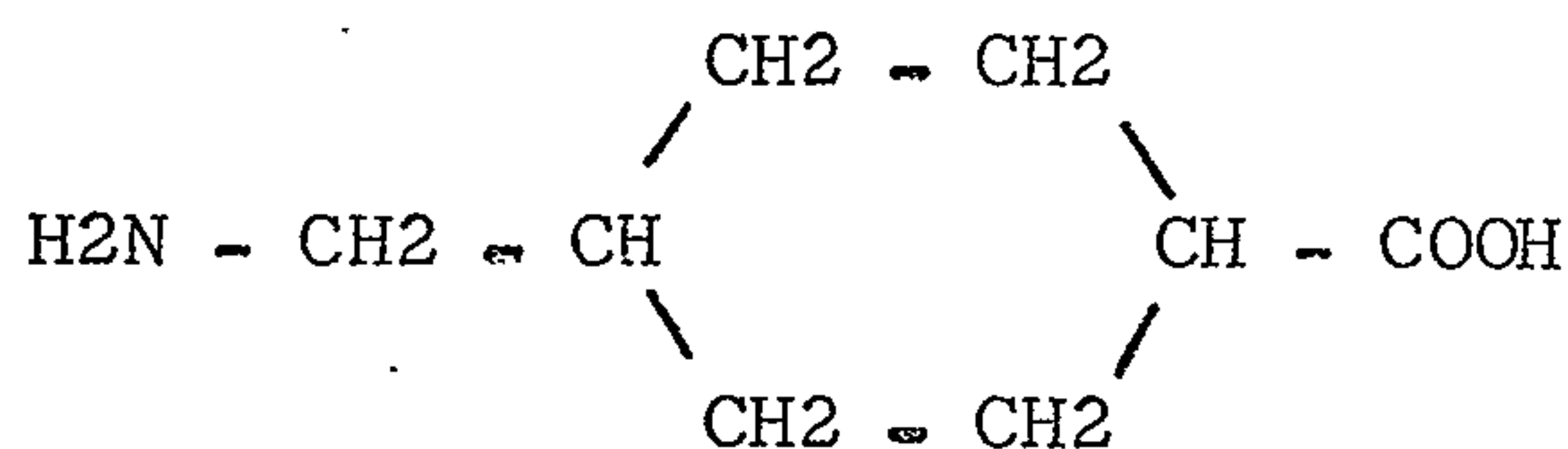
FIGURE 4.



THE FIBRINOLYTIC ENZYME SYSTEM

In 1962, Okamoto and Okamoto developed a further synthetic amino acid, para amino methyl cyclohexane carboxylic acid, or A.M.C.A. This had a more potent antifibrinolytic effect than E.A.C.A., but without having its toxic properties.

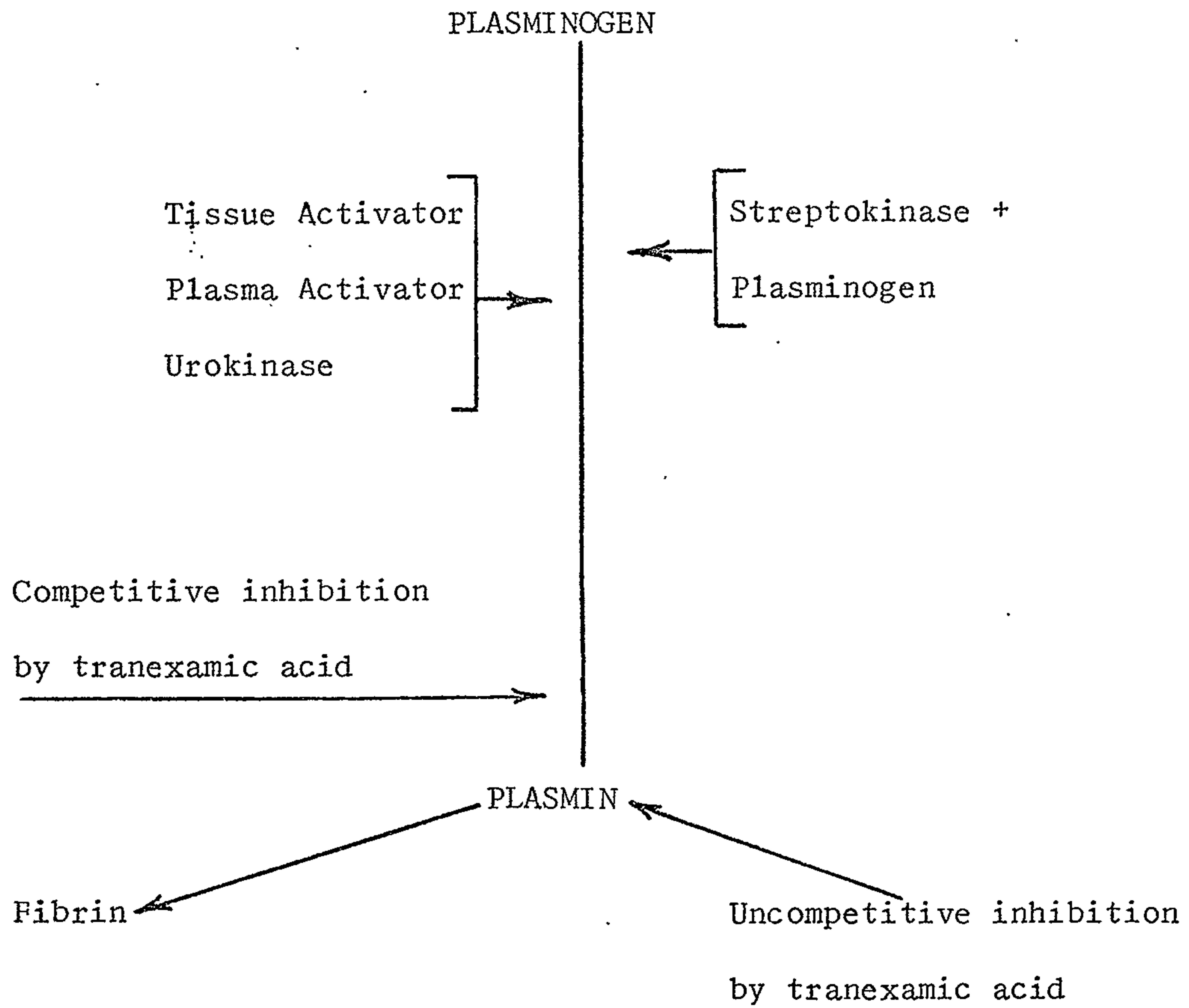
Okamoto (1964) and Melander et al (1964) working independently discovered that A.M.C.A., existed in two isomeric forms, one being 200 times more active than the other. The active trans-stereo isomer was called tranexamic acid (T.A.):



Tranexamic acid inhibits the fibrinolytic enzyme system at two points (Melander et al 1964). It depresses plasminogen activation, by competition, at serum concentrations that are readily achieved by oral administration of the drug. Epsilon amino caproic acid and tranexamic acid act at the same point in the fibrinolytic enzyme system (figure 5).

Melander et al (1964) found that the favourable effect on haemostasis by E.A.C.A. and T.A., seen clinically, was due to inhibition of the fibrinolytic activity locally in the tissues. This suggests that it is the tissue level of T.A. and E.A.C.A, that is important in haemostasis, rather than the

FIGURE 5.



THE ANTIFIBRINOLYTIC MECHANISM

plasma levels (Pell, 1973).

Tranexamic acid is emerging as potentially the more effective and safer drug to use. Dubber et al (1964) found the effect of TA to last longer than EACA and Anderson et al (1965) found TA to be seven times more potent than EACA. Melander (1964) found that similar post operative haemostatic results are obtained when either a dose of 20 mg per kg body weight of TA is given 6 hourly, or 100 mg per kg body weight of EACA is given 4 hourly. The dose of EACA for a 70 kg patient in 24 hours would therefore be 42 g, and for the same patient the dose of TA would be only 5.6 g.

Large doses of such drugs will almost inevitably produce side effects. Walsh (1971) found that the side effects that occurred most frequently in patients given EACA was diarrhoea, but most patients complain of many other symptoms which are attributed to the drug. These include postural dizziness, fainting, abdominal discomfort, loose stool, nausea, nasal stuffiness, vomiting, headache, tingling of the fingers and muscular stiffness. Side effects are less frequent with TA.

All inhibitors of fibrinolysis when used in patients with haemorrhagic disorders have the potential danger of precipitating obstruction of the renal tract with unlysable clots (McNicol et al., 1961); Gobbi, 1967; Van Itterbeek et al; 1968). These drugs should never be given to a patient who has,

or has recently had haematuria (Biggs, 1975).

In a clinical assessment carried out by Pell (1973), the results show that dental patients with bleeding disorders taking antifibrinolytic agents were more easily managed than patients who had not had these drugs. It would appear that tranexamic acid is superior to epsilon amino caproic acid because it is less toxic, more potent weight for weight and has a longer half life, thus necessitating less frequent administrations of the drug. Forbes et al (1972) are of the opinion that the reduction of plasma requirements by the use of tranexamic acid will reduce the incidence of antihaemophilic globulin inhibitors and serum hepatitis as well as reducing blood loss.

The regime adopted for patients with coagulation defects depends on the level of circulating endogenous clotting factors in the blood. Pell (1973) suggests the following routine. Twenty-four hours pre-operatively, the patient receives 20 mg/kg body weight of tranexamic acid orally every 6 hours. If he has less than 5 per cent factor VIII or IX present, then he will receive sufficient cryoprecipitate or factor IX concentrate pre-operatively to raise the level of clotting factor to 45 per cent of normal. If he has more than 5 per cent present, this intravenous supplement is omitted. At the time of anaesthetic induction, 1 g tranexamic acid is given intravenously and postoperatively the patient will

again receive 20 mg per kg body weight of tranexamic acid orally, every 6 hours for 10 days.

5.5

Hypnosis

The folk law concerning the ability of Rasputin to stop the bleeding in the Russian Czarevitch, by hypnosis, was probably unfounded (Brinkhous, 1957, p. 260).

Forbes et al, (1972) are of the opinion that the bleeding from a post-extraction tooth socket probably represents an imbalance between defective fibrin formation, due to the abnormality in the intrinsic thromboplastin system, and the normal removal of deposited fibrin by fibrinolytic enzymes. These enzymes are produced by plasminogen activators locally and in the saliva. Forbes et al., observed that in their patients there was a fall in the euglobulin lysis times, indicating increased levels of circulating plasminogen activator. This has been recorded by several authors in people under stress (Macfarlane, 1937; Biggs et al., 1947).

Lucas et al., (1962) carried out extractions for haemophiliac patients using hypnotic suggestion and protective splints, together with critical packing of sockets. They state that haemostasis cannot be brought about by hypnosis alone, however, capillary haemorrhage and salivary secretion may be affected. The emotionally tranquil patients were reported to

have less bleeding and some did not require anaesthesia for tooth extractions.

Anxiety does appear to affect bleeding in haemophilic patients and while hypnosis can reduce anxiety, it does not appear to be the answer to the problem of haemostasis (Biggs, 1975).

6. CONSIDERATIONS DURING ORAL SURGERY

6.1 EXODONTIA

There is little comment in the literature regarding the implications for the haemophiliac of the conventional techniques in exodontia. Although the same basic principles and care apply for these patients, particular care must be taken during the procedure, not to traumatise tissues unnecessarily.

Where the use of a straight elevator is indicated to loosen teeth prior to extraction, there is a risk of lacerating the papillary tissues and increasing the bleeding points. The beaks of extraction forceps must be positioned carefully around the crown of the tooth to avoid soft tissue damage during the extraction movements. Middleton et al (1965), used a sharp periosteal elevator to divide the gingival attachment from the neck of the tooth prior to its extraction. The tearing of the lingual alveolar tissues, particularly in the molar region, may cause bleeding which is difficult to control.

The extraction of multi-rooted teeth tends to present greater management problems for the haemophiliac patient. As previously mentioned, there is considerable variations of opinion

in the literature regarding the number of these teeth that should be extracted in one sitting. During the extraction of the maxillary molars, the buccal plate of the alveolar process may fracture. If the fragment is attached to the roots, the soft tissues should be separated from it to prevent tearing. A similar situation can arise with the mandibular anteriors, particularly following the injudicious use of an elevator to loosen the teeth.

Fractured roots should, if possible, be removed by an intra-socket approach. If necessary bone should be removed through the socket, to facilitate the removal of the fragment with the appropriate instrument. The raising of a soft tissue flap increases the management problems, however, they can be modified to allow access with minimal incising. Class III (three sides) flaps should be avoided in favour of the class II (two sides) flap or envelope flap. The buccal extension of the flaps must not involve the sulcus or reflected mucosa, as serious recurrent bleeding may result. When suturing the wound, the soft tissues must be replaced accurately and with minimal tension (Glogoff et al., 1972).

The alveolar socket should be curetted to remove any granulation tissue (Webster et al., 1968, p. 104) and sharp bone should be smoothed by rongeur forceps and a bone file. The exposed bone should be carefully examined for bleeding points, which

may be controlled by bone wax or burnishing.

6.2

Oral Surgery

The development of commercial factor concentrates in recent years has removed many of the barriers to oral surgery practice in haemophilia and the associated coagulation defects. Approximately ten years ago reports of elective oral surgical procedures began to appear frequently in the literature.

In 1965, Biggs et al., presented two case histories involving third molar surgery for severely affected haemophiliacs. Both patients experienced excessive blood loss despite fairly high factor VIII levels and they concluded that the extraction of third molar teeth is particularly dangerous for these patients. Björlin and Nilsson (1965) carried out the removal of cysts, granulomas and roots on their patients by conventional oral surgical methods. An extensive cystic lesion in the mandible of a haemophiliac was enucleated by Webster et al (1968, p. 105). No bleeding was observed during or after the removal of this lesion. The more recent literature is essentially concerned with the technical aspects of replacement and adjunct therapy, while the case reports cover a variety of oral surgical procedures involving the teeth and their supporting structures. It is also apparent that the elective soft tissue procedures in the oral cavity, such as the excision of fraenum, vestibuloplasty and other preparatory prosthetic operations are contraindicated except in exceptional

circumstances. This is not surprising considering the added risks involved and relatively short supply of commercial factor concentrates, particularly in Australia.

Sound surgical principles must be followed strictly.

The preoperative reduction of infection and aseptic preparation of the surgical field constitute a good foundation. Techniques which minimise trauma to neighbouring structures are based on an adequate surgical exposure, maintenance of blood supply and surgical haemostasis (Glogoff et al., 1972). Bleeding in the oral cavity presents unique problems. Primary haemostasis is gained by observing basic surgical principles. Haemostasis is usually not difficult to maintain following the extraction of one tooth. In multiple extractions and oral surgical procedures, the operative site is extensive and tissue trauma is widespread; hence more bleeding is to be expected. During all surgical procedures, osseous fragments and granulation tissue must be removed to prevent sequestration and continued infection. During the osteoplasty, numerous arterioles may bleed profusely; this may be controlled by crushing the bone over the area or using bone wax to seal the osseous canals. Pressure is beneficial in obtaining primary haemostasis and as previously described, there are a number of ways to achieve this. The use of any effective haemostatic aid may be beneficial in treating the

bleeder, but systemic replacement therapy is indispensable.

Secondary haemorrhage frequently occurs approximately 24 hours after the surgical procedure. The reasons for this are poorly understood, however, the disturbance of the fibrin clot is perhaps the most common cause. When this occurs the splints or packs or sutures covering the area should be removed, and a search for the bleeding point carried out. Webster et al., (1968) advocate the use of local anaesthesia or concentrated solutions of epinephrine to assist in the control of secondary haemorrhage. They advise against the use of chemical cauterising agents and electrosurgical units, since they cause more tissue necrosis and possible haemorrhage subsequently.

A soft diet for approximately ten days following oral surgery will help prevent the disturbance of soft tissue wounds. Adjunctive therapy such as Aminocaproic acid and tranexamic acid prevent fibrin lysis and therefore greatly stabilise the fibrin clot.

6.3 Local Haemostatic Measures

6.3.1 Protective Splints

The splint was one of the earliest means of arresting haemorrhage and according to the earlier literature, the function was to provide a pressure dressing on the soft tissues. Lucas et al.,

(1962) states that the primary purpose of the splint is to protect the surgical region from saliva, food retention, from the tongue and other muscle movements; each of which can disturb the natural haemostatic plug or packing from the socket. They observed that excessive pressure from a splint will cause extravasted blood to penetrate to the deeper tissues. Glogoff et al., (1972) say the splints chief function should be the protection and maintenance of the clot.

Many materials have been used in the construction of protective splints. Dalitsch (1934) constructed splints from Vulcanite; Acrylic was used by Archer (1950); Gilbert and Oldfield (1959); Biggs et al., (1965); Lucas et al., (1962); Middleton et al., (1965) and Glogoff et al., (1972). Impression compound splints were used by Nichols and Baldrige, (1954); Rubin et al., (1959) and Ingram and Winstock (1960). Orr and Douglas (1957) advocated the removal of splints for regular cleansing and this opinion is shared by most workers. Dalitsch (1934) was in favour of ligating the splints into position in the dentulous patients.

Protective splints have been lined by a variety of materials such as Bovine thrombin and Bacitracin (Le Guerre and Kutscher, 1961); and gutta-percha (Middleton et al., 1965). George (1961) recommended the use of an elastic splint of soft denture lining material, claiming that the rigid splint leads to

trauma. This opinion has been expressed by other workers and Glogoff et al., (1972) recommended the use of the precision vacuum adapter (Vacuform), a technique which is primarily used for the fabrication of soft mouth guards. I have used this type of material with limited success; patients report they are uncomfortably bulky.

The possibility of causing trauma with protective splints has concerned many workers in recent years. Archer (1951) reported that splints could impinge on soft tissues or displace the fibrin clot after the first post-operative day. Sherry (1958) and Hayward (1965) also were of the opinion that the splint was of limited value after one to two days as it would greatly traumatise the wound. McIntyre et al., (1959) reported cases of traumatic abrasion and haematoma formation caused by splints.

The displacement of the protective splints is frequently a problem and a number of recommendations have been made. A modified Barton bandage was used by Archer (1950), and McIntyre (1965) used a head harness and an elastic bandage. Rubin et al., (1959) used a head harness in conjunction with either a crepe bandage, a latex rubber band, Pauls tubes or Martins bandage. When teeth were present, Dalitsch (1934) ligated the splint in position.

The more recent advances in replacement therapy have largely eliminated the need for protective splints. They are

no longer used at the Oxford Haemophilia Centre (Biggs, 1975). Despite these advances, there are cases where bleeding cannot be adequately controlled by other methods. Such a case is presented by Quast and Schoetgger (1974), and I am sure that most investigators have experienced the situation where protective splints must be used.

6.3.2.

Suturing

Suturing is the classic method used to control haemorrhage and promote healing. Until the advent of modern replacement therapy, suturing was considered dangerous for patients with coagulation defects (McIntyre, 1965, Findlay, 1960, Dalitsch, 1934). These workers considered the danger lay in the additional bleeding points created by the suture needle.

The majority of investigators surveyed in the literature used sutures in conjunction with other measures to control haemorrhage. In many procedures sutures are unquestionably necessary and Nathan et al., (1964) found this to be the case in the removal of a large cyst from the mandible of a severe haemophiliac. Fleuchaus (1954) removed bone from the socket to allow the close approximation of the surrounding soft tissues. However, Ingram and Winstock (1960) say that tight suturing is contraindicated because if bleeding occurs it is best drained into the mouth rather than into deeper tissues.

Matheson (1949) warns against the use of sutures because they must be tied tightly to be effective, remain in position for a long time and tend to "cut out" creating further bleeding. Sutures cause enough irritation to keep the wound oozing according to Lewis (1973), and may create a separate problem on removal. McIntyre et al., (1959) state that a haematoma may develop causing respiratory obstruction. Ingram and Winstock (1960) and Endicott et al., (1942) also refer to this danger, and Cazal (1959) is of the opinion that sutures should be avoided wherever possible.

There is some comment in the literature regarding the type of suture material and the length of time they should remain in place. Middleton et al., (1965) used an atraumatic silk suture when sutures were required. Glogoff et al., (1972) and Westwood et al., (1973) also prefer 3-0 braided silk on an atraumatic needle for their patients. Silk is considered to be less irritating over long periods by many investigators in this field, and Whissel et al., (1965) allowed silk sutures to remain in place for 10 days. It has been my experience, that once a suture becomes loose it is no longer useful and should be removed to prevent wound irritation.

To eliminate the need to remove the sutures at a later date, some operators prefer absorbable suture materials. Marco

(1972) reports a case where 3-0 plain gut sutures were used and the haemostatic measures failed. The development of the synthetic polyglycolic acid absorbable suture material (Dexon),⁺ has solved some of the suturing problems. This material does not resorb quickly and will remain in place for approximately 10 days.

6.3.3 Socket Packs and Topical Thrombin

The use of packs within sockets as a local measure has been reported by a large number of investigators. These packs are used either alone or in conjunction with other medicaments. Opinions regarding the function of these packs varies considerably.

Lucas et al., (1962) packed the sockets with oxidised, regenerated cellulose (Surgicel).⁺⁺ This is a haemostatic, absorbable material in gauze-strip form. It is reported to be completely absorbed from the socket in a period of time ranging from 7 to 15 days. The affinity of this material for blood is such, that a clot will form within the framework of the material, acting as a mechanical plug.

Lucas et al., (1962) state that, the sealing of the capillary points of bleeding is the main purpose of their

⁺ Cyanamid of Great Britain Ltd., London, England

⁺⁺ Ethicon Ltd.

socket packing technique. Findlay and Nicholl (1960) are of the opinion that packing obliterates the "dead space" of the socket and has some initial value, as it applies pressure to the vessel walls. However, since the sockets are conical, the clot tends to dislodge the pack orally.

Dalitsch (1934) warns against packing sockets with gauze as it does not check the haemorrhage but directs it into deeper tissue. Macfarlane (1948, p. 366) advises against the use of socket packs, since it may produce further bleeding. Kaplan et al., (1960, p. 492), make the point that pressure packing of the extraction socket may be extremely uncomfortable and difficult to keep in position; they may also interfere with healing. They also state that socket packings saturated with haemostatic drugs or surgical cement mixes, may produce further irritation to bone and soft tissues which may lead to necrosis. Gamble (1964), is of the opinion that packing the socket does not prevent post-operative haemorrhage.

In his case report, Cash (1942) used a combination of a gauze pack moistened with adrenalin, snake venom, and tincture of ferric perchloride. Tomey (1941) used a cone shaped cotton pellet moistened with a solution of equal parts of tannic acid, powdered anaesthetic and liquified ferric perchloride.

For many years the resorbable haemostatic agents such as

Oxycel, Gelfoam have been employed. The combination of a gelfoam and thrombin has been used by many investigators including, Archer and Zubrow (1950), Rubin et al., (1959), Finkelman (1959), Glogoff et al., (1972) and Westwood et al., (1973). Others advocate the use of Surgicel or Oxycel with thrombin (Nichols and Baldrige, 1954). Reid et al (1964) used either Surgicel or Oxycel soaked in a solution of 0.5 per cent sodium bicarbonate containing 1,000 units of bovine thrombin per ml.

McIntyre (1959), in a clinical trial with 58 patients used no packs and concluded that there is no advantage to be gained by using thrombin solution in sockets. In view of the modern replacement and adjunctive (antifibrinolytic) therapy, there certainly appears to be little to be gained by routinely packing tooth sockets with the materials mentioned above. There is also a need for further investigation into the effectiveness of the antifibrinolytic agents in the presence of socket packs.

SUMMARY

The literature dealing with the common coagulation defects has been investigated and the development of the current concepts of haemophilia and its management reviewed.

The need to protect the haemophiliac from serious bleeding episodes has been responsible for the outstanding modern techniques of replacement therapy. The dental requirements of these patients have concerned many investigators in the medical and dental fields, and considerable progress has been made by the dental surgeon in understanding the haemophiliac and his problems. It has been shown that the fears and apprehension on both sides cannot now be justified, and that the majority of dental and oral surgical procedures can be carried out without danger.

It has been shown that a comprehensive programme of dental care will minimise the necessity for extractions and such programmes have been established in many of the haemophiliac centres. There is now greater assistance for the patient with the financial burdens, the time lost from school or work and the emotional and psychological problems.

The oral surgeon is usually called on to treat patients who have a well-documented history of a coagulation defect. It

is apparent from the literature that careful treatment planning and consultation with the Patient's haematologist, enables the best surgical results to be obtained. The concept and evaluation of current techniques in management and treatment have been discussed. The techniques for replacement and antifibrinolytic therapy have been reviewed, together with the possible adverse effects. Local treatment including anaesthetics, splints and haemostatic agents have been described.

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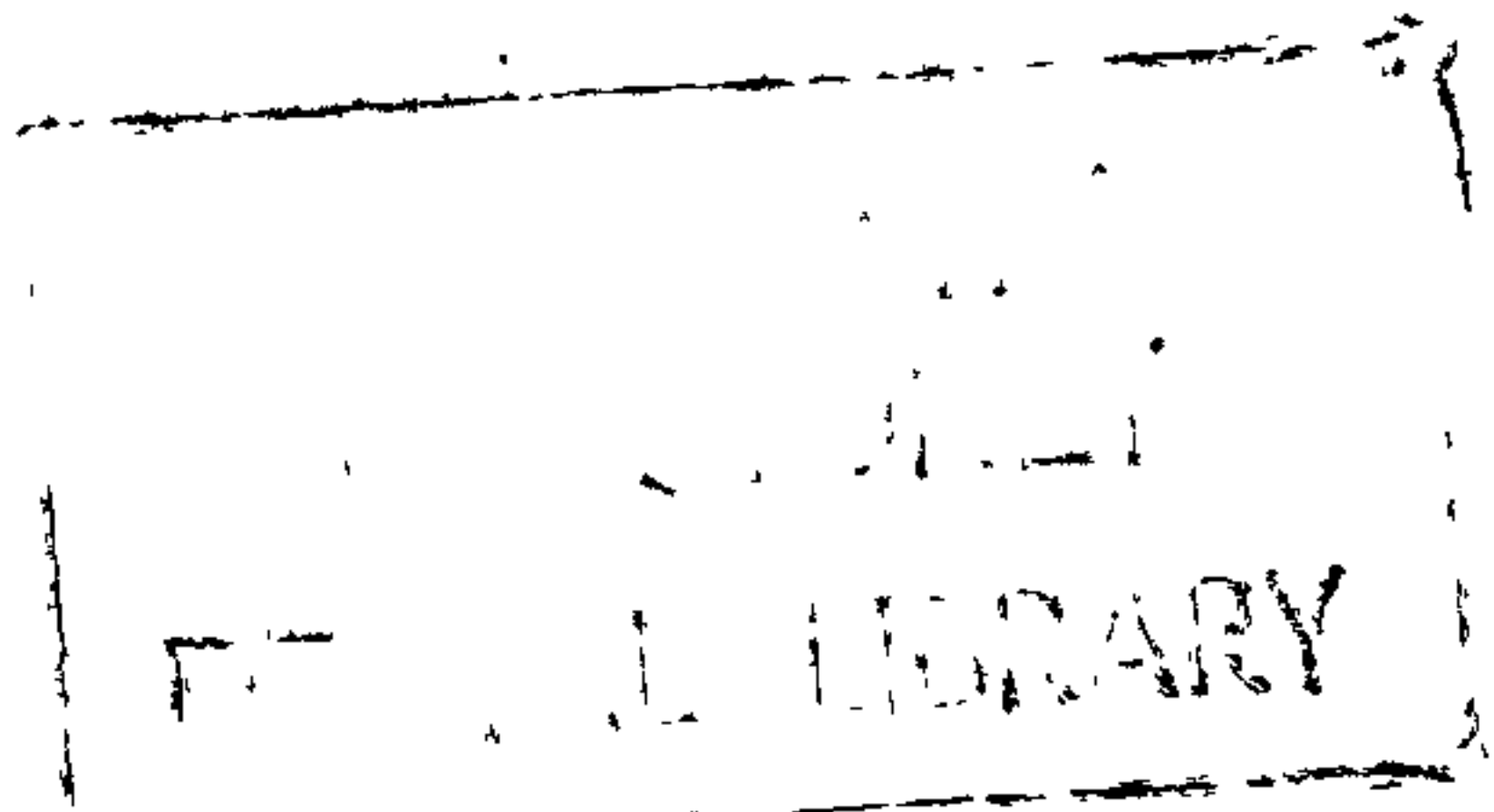
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