BLEED NOT, MY SON

AN INAUGURAL LECTURE
2010/2011

By

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UNIVERSITY OF IBADAN

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An Inaugural Lecture delivered at the University of Ibadan

on Thursday, 3 March, 2011

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Ibadan University Press
Publishing House
University of Ibadan
Ibadan, Nigeria.

First Published 2011

ISBN: 978 – 978 – 8414 – 47 – 6

Printed by: Ibadan University Printery

The Vice-Chancellor, Deputy Vice-Chancellor (Administration), Deputy Vice-Chancellor (Academic), Registrar, Librarian, Provost of the College of Medicine, Dean of the Faculty of Clinical Sciences, Dean of the Post-graduate School, Deans of other Faculties, and of Students, Distinguished Ladies and Gentlemen.

Introduction

It is with a thankful heart and gladsome mind that I stand before you today to give this Inaugural lecture on behalf of the Faculty of Basic Medical Sciences (FBMS). I am indeed grateful to the Dean FBMS for asking the Department of Haematology to undertake this unique assignment. This would be the third Inaugural Lecture from the Department since it became an autonomous department in 1975. This would suggest that the Sub-specialty of Haematology is a rare field and is only just beginning to attract a younger generation of post-graduate students.

I am therefore grateful to the Vice-Chancellor, the Provost of the College of Medicine, and the entire University Administration for the opportunity to showcase some of the activities of the Department within the 2011 series of Inaugural Lectures.

The first Inaugural Lecture was delivered by Prof. E.M. Essien in 1989 and was titled "May the Blood continue to flow in our Body" The second lecture by Prof. Y.A. Aken'Ova in 2005 was titled "The Streams of Life." The title of my lecture today is "Bleed not, My Son." I intend to discuss the history, aetiology, global prevalence, and also share with you a personal perspective of haemophilia care in Nigeria.

Definition of Haemophilia

Haemophilia is an uncommon inherited sex-linked haemorrhagic disorder characterized by unprovoked bleeding, typically into the joints (haemarthroses), post circumcision bleeding and haematomas (muscle bleeds). It is due either to a deficiency of FVIII (Haemophilia A, Classic Haemophilia) or deficiency of FIX (Hemophilia B, Christmas Disease). The

defective gene is located on the X-Chromosome, hence haemophilia is virtually a disease of males.

Historical Review

Historical reviews (Bulloch and Fildes 1911, Rosner 1969) on bleeding disorders (table 1), recognized that the Jews were the first to describe an inherited bleeding disorder, manifesting only in males, as documented in the Jewish Talmud (rabbinic) writings of 2nd Century AD. At that time, the Jews enacted a law that prevented the 3rd son of a woman from being circumcised, if the two previous sons had bled to death following circumcision. This showed clearly that the Jews recognized the sex linked mode of inheritance: that women carried the gene for this form of bleeding disorder and transmitted it to their sons.

Various names were used to describe the clinical syndrome now called haemophilia. The syndromes include haemorrhaea, idiosyncrasia haemorrhagica, haemophilia, bleeding disease, hereditary haemorrhagic diathesis (Bulloch and Fildes 1911). The term haemophilia ("meaning love of blood") was first used by Hopff in his treatise of 1828.

Surprisingly a disease as remarkable as haemophilia was not described as a distinct entity before the nineteenth century (Bulloch and Fildes 1911). Otto's publication of 1803 on a "haemorrhagic disposition in certain families" was the first to arouse general interest in the bleeder, a term appearing in the literature for the first time.

In 1820, Nasse described the mode of inheritance asserting that haemophilia affected only males and that the disease was transmitted through unaffected females. This was later referred to as Nasse's Law (Bulloch and Fildes 1911). However haemophilia has now been well documented in some women and resembles the disorder seen in affected males in all respects (Wintrobe 1981).

The well-known monograph of Bulloch and Fildes (1911) critically analysed over 200 pedigrees, distinguishing cases of haemophilia from numerous other records of unexplained bleeding, many of which did not bear the stamp of haemophilia. This monograph lacked the clinical evidence for

the obligatory carrier status of haemophiliacs' daughters since at that time few affected males lived to reproductive age (Kerr 1963).

The most characteristic symptom of haemophilia, the involvement of joints, was described in classic detail by Konig in 1890. Haemathrosis had earlier been confused with tuberculosis and this error in diagnosis led to operative interference and death on several occasions (Bulloch and Fildes 1911).

Table 1: History of Haemophilia

S/No.	Date	Event	Author
1.	2nd Century AD	Talmud writings : exclusion from circumcision if 2 older siblings had died post circumcision	Jews
2.	1803	The term "bleeder" was introduced for the first time to describe a "haemorrhagic disposition appearing in certain families	Otto
3.	1820	The mode of inheritance was described: that haemophilia affected only males, and is transmitted through females (i.e. Nasses Law)	Nasse
4.	1828	The term Haemophilia meaning "love of blood" was first used	Hopff
5.	1890	The most characteristic feature of Haemophilia i.e. (haemarthrosis), was described	Konig
6.	1911	Over 200 pedigrees were analysed; haemophilia was distinguished from other unexplained bleeding	Bulloch and Fildes
7.	1963	The obligatory carrier status of daughters of haemophiliacs became known	Kerr
8.	1998	Recent Review of Clinical Management	Christie DA and Tansey EM (editors)

The Royal Disease

Queen Victoria (1813-1901) of Great Britain was believed to be an obligatory carrier of the haemophilic gene. She was considered therefore to be responsible for the spread of

haemophilia through her descendants to the royal families of Europe including Spain, Germany and Russia. The Queen's mother (Victoria, Princess of Soxe – Coburg, 1786- 1861) had expressed her anxiety in a letter to her daughter Vicky, the Queen on the "quality of the blood of the royal family, that there was some little imperfection in the pure Royal descent….."

The appearance of haemophilia in one of Queen Victoria's sons upset and confused her, but she could only protest that the disease did not originate from her side of the family. Prince Leopold, Duke of Albany (the 8th child of Queen Victoria) was the first to show features of haemophilia. Prince Leopold's life was short, having suffered several haemorrhages. In spite of all the protection he received, Prince Leopold, died from intracranial haemorrhage after a minor fall at the age of 32yrs in 1884. Leopold's daughter Alice gave birth to Rupert, another haemophiliac, who also died of intracranial haemorrhage at the age of 21years in 1928.

In the first generation from Queen Victoria, one son was a haemophiliac, there were 3 haemophiliacs in the 2nd generation and 6 in the 3rd generation, all of them died prematurely.

The other 3 sons of Queen Victoria-Edward, Alfred and Arthur were normal and free from haemophilia. The present British Royal family of Queen Elizabeth, descended from King Edward VII, first son of Queen Victoria. Queen Elizabeth and her offsprings are free of haemophilia so far.

Queen Victoria was undoubtedly the most famous haemophilic carrier and her haemophilic off- springs sat on the thrones of Germany, Russia and Spain.

Fig. 1: Queen Victoria and her family (Aronova-Tiuntseva Y and Herreid Freeman C. Hamophilia: "The Royal Disease". *http://www.sciencescases.org/hemo/hemo.asp20.01.11*

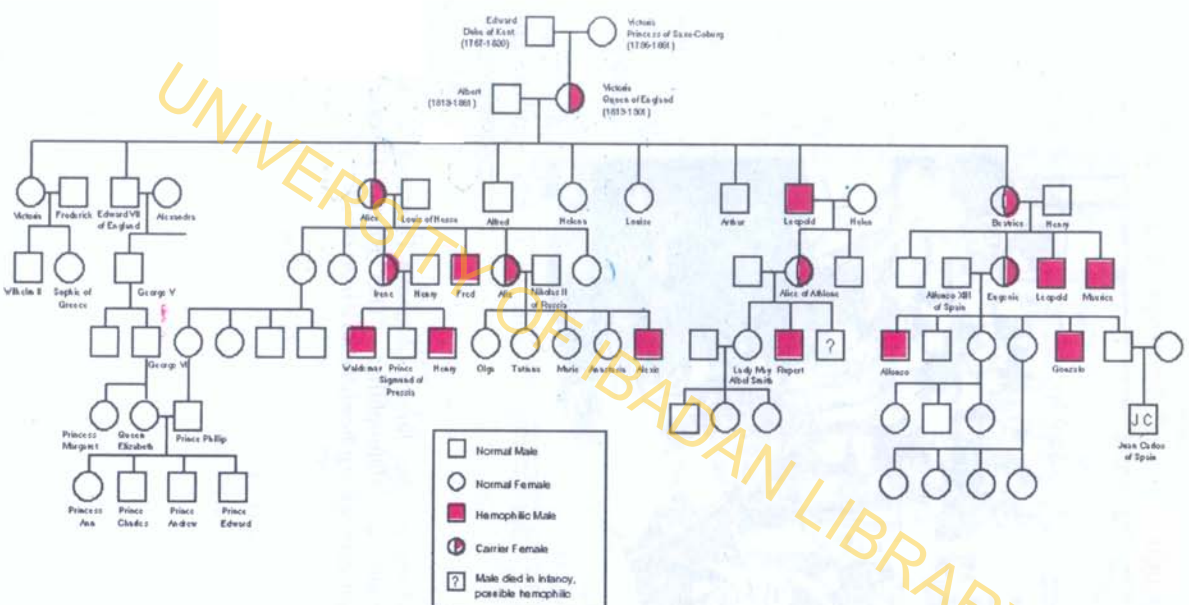


Fig. 2: Pedigree of Queen Victoria

Aronova-Tiuntseva Y and Herreid Freeman C. Hamophilia: "The Royal Disease".

http://www.sciencescases.org/hemo/hemo.asp20.01.11

Descendants of Queen Victoria with Haemophilia

- First generation: Queen Victoria's son
  - Prince Leopold-died at age 30, in 1884
- Second generation: Queen Victoria's grandsons
  - Fred, son of Alice – died at age 3, in 1873
  - Leopold, son of Beatrice –died at age 32, in 1922,
  - Maurice, son of Beatrice – died at age 23, in 1914
- Third generation: Queen Victoria's great grandsons
  - Waldermar, son of Irene – died at age 56, in 1945
  - Henry, son of Irene – died at age 4 – in 1904
  - Alexis, son of Alix – died at age 14, in 1918
  - Rupert, son of Alice of Athlone – died at age 21, in 1928
  - Alfonso, son of Eugenie – died at age 31, in 1938
  - Gonzalo, son of Eugenie – died at age 19, in 1934

The presence of haemophilia in the descendants of Queen Victoria (1819-1901) was one of the factors responsible for encouraging the immense scientific and public Interest in this bleeding disorder (WHO 1977). Two of the Queen's daughters were carriers, transmitting the disorder to three of her grandsons and six of her great-grandsons (Ingram 1976). One of the Queen's great grandsons, Alexis (born in 1904 to Alexandra and Czar Nicholas II of Russia), was presumably the world's most famous haemophiliac.

Alexis NIkolaevich, Heir, Tsesarevich and Grand Duke was born in 1904, the youngest and only son of Emperor Nicholas II of Russia and Alexander (fig. 3). Alexis' was the centre of activity within the family, being the heir to the throne. His education was frequently interrupted by haemorahagic events, though adjudged as intelligent and affectionate. He was prohibited from riding a bicycle and playing too vigorously, and his parents could not assert the expected discipline on him, hence he became lazy and mischievous (Aronova-Tiuntseva et al.).

Alexis was known to tempt fate and would injure himself on purpose. For instance Alexis rode a sledge down the stairs

of the prison in Siberia (where all his family members had been incarcerated) and injured his groins, hence he was confined to the wheelchair for the rest of his life. Alexis' illness was believed to be the main cause of his father's downfall (Ingram 1976). At the age of 14years, he along with his imprisoned parents and sisters, were assassinated in 1918 at the heart of the Russian Revolution. Alexis' remains were found in 2007 in Russia by archaeologists, and in 2008, Russian forensic scientist's confirmed that the remains found were truly those of Alexis and one of his sisters. In 2009, genetic analysis using DNA probes confirmed that Alexis suffered from Haemophilia B (Aronova-Tiuntseva et al.).

Fig. 3: Picture of Alexis

The Aetiology of Haemophilia

In the nineteenth century, haemophilia was thought to be due to vascular abnormality. Wright's publication of 1893 on the determination of the clotting time permitted the discovery of the abnormal coagulation in haemophilia. Quick et al. (1935) noted that his Prothrombin Time test gave normal results in haemophiliacs. He then proposed that the defect in haemophiliacs was the toughness of their platelets, preventing their breakdown and the liberation of their thromboplastin (Quick 1941). However this was later disproved since normal plate-

lets added to haemophilic plasma did not shorten the clotting time (Patek and Stetson 1936).

Patek and Taylor (1937) demonstrated that a small fraction of globulin corrected the clotting time of haemophilic blood. Taylor called this fraction antihaemophilic globulin (AHG). This clotting factor was later named factor VIII by international agreement (Wright 1962).

Factor IX deficiency was distinguished from classical haemophilia by Biggs and her colleagues (Biggs et al. 1952) and the clinical manifestations of factor VIII and IX deficiencies are identical, hence the use of the designations haemophilia A and B respectively.

The expressivity of the genetic defect in haemophilia varies from one family to the other but within a given family the clinical severity is relatively constant (Pitney and Arnold 1959). The occurrence of haemophilia in a female is rare and can be due to (i) extreme inactivation (lyonization) of the normal X-chromosome in a heterozygote female – Lyon's hypothesis (Lyon 1962; Graham, et al. 1975); (ii) genetic homozygosity at the haemophilia locus either as a result of mutation or consanguineous marriages (Kernoff and Rizza 1973); genetic abnormality in a phenotypic female with one X-chromosome bearing the haemophilia gene e.g. Turner's syndrome (Bithel et al. 1970).

Haemostasis

Haemostasis is a complex web of interactions comprising arrest of haemorrhage from the site of vascular injury through the formation of the primary haemostatic (platelet) plug, generation of fibrin-meshwork around the platelet plug by the coagulation cascade (fig. 4), and clot dissolution (fibrinolysis) after tissue healing is complete. Haemostasis comprises of a number of protective, and integrated physiological processes by which blood is kept in the fluid state, haemorrhage is arrested and vascular patency is restored through clot dissolution. The five major components of haemostasis are:

Vascular Endothelium, Platelets, Coagulation factors, Inhibitors of Coagulation, and Fibrinolysis (see fig. 5).

Coagulation factors (CF) are glycoproteins produced by the liver, which circulate in plasma in inactive forms called pro-enzymes or as co-factors (FV and FVIII). They have been assigned Roman numerals reflecting the order of their discovery. The pro-enzymes include Factors XII, XI, X, IX, VII, and II. Factors II, VII, IX, and X are Vitamin K dependent. The role of Endothelial Cell (EC) in haemostasis include the following: Endothelial procoagulant activity, TF (tissue factor) release following EC activation by Endotoxin, Il1, TNF, EC-derived inhibitors of activation include TFPI, ATIII, thrombomodulin, heparan sulphate, glycosaminoglycans, EC-derived fibrinolytic factors, tPA, plasminogen activator inhibitor.

The control mechanisms in haemostasis ensure that the haemostatic plug is only formed and maintained where and when necessary. These control mechanisms include: the endothelium, blood flow, inhibitors of coagulation, fibrinolysis, inhibitors of fibrinolysis, feedback mechanisms, and clearance of activated factor inhibitor complexes. Inhibitors of coagulation include the tissue factor pathway inhibitor, natural inhibitor for coagulation (ATIII), heparin co-factor II, α1 anti-trypsin, C1 esterase inhibitor, α2 anti-plasmin, protein C, protein S, and thrombomodulin.

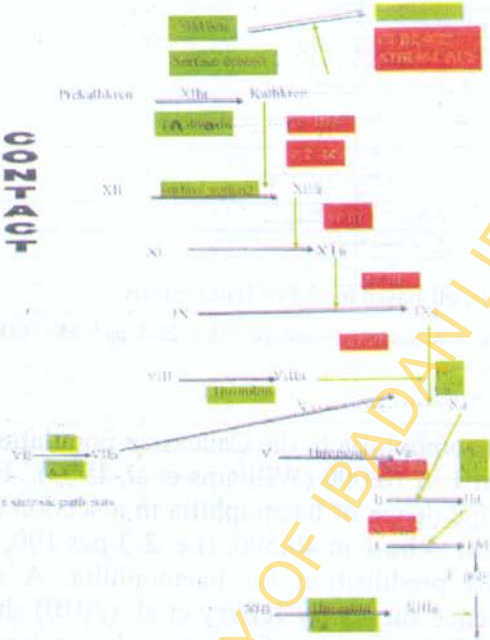


Fig. 4: Coagulation Cascade

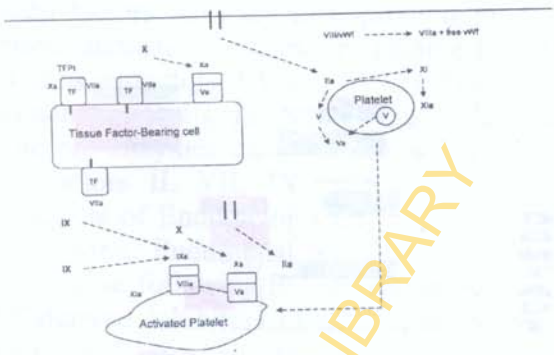


Fig. 5: Cell-based model of Haemostasis

Source: Roberts, HR et al. in Williams Haematology, 7th Ed., 2006. pp 1665 - 1693

Incidence

The incidence of haemophilia in the Caucasian population has been established at 1 in 10,000 (Williams et al. 1983). Essien (1974) found the incidence of haemophilia in a section of the Nigerian population to be 1 in 40,500. (i.e. 2-3 per 100, 000). There is no racial predilection for haemophilia. A recent worldwide prevalence survey by Jeffery et al. (2010) showed variation in the reported cases of haemophilia, noting that these rates were inversely proportional to the economic status of that country (table 2). The high income countries such as Australia, Canada, and United Kingdom, etc, have prevalence rates between 11.1 – 19.1 per 100,000, while countries such as Nigeria, Sudan, Senegal, etc, have rates between 0.05 – 2.0 per 1000,000. Poor resource countries have neither comprehensive haemophlia programmes nor National Registry for haemophiliacs. About 30% of haemophiliacs have mild disease and may not present until they face a major haemostatic challenge.

Table 2: Prevalence of Reported Haemophilia A (per 100,000 males) from 1998 – 2006

Country	Mean	SD	CV (%)
Algeria	4.1	1.1	4
Argentina	8.6	0.6	26
Australia	11.1	1.6	14
Canada	13.2	1.0	8
Egypt	8.7	1.2	13
India	1.1	0.6	52
Iran	9.4	1.2	12
Israel	10.8	0.5	5
Italy	11.7	2.3	20
Japan	5.9	0.5	8
Kenya	2.1	0.5	24
Nigeria	0.05	NA	NA
Russia	7.1	3.2	45
Saudi Arabia	2.0	0.0	3
Senegal	2.0	0.4	19
South Africa	5.5	0.3	5
Spain	8.8	1.3	14
Sudan	1.6	0.2	14
United Kingdom	19.1	2.0	11
Zimbabwe	4.4	0.6	15

SD, standard deviation; CV, coefficient of variation; NA, not available.

Source: Jeffrey S S, Paula H B B, Micheal J S, Irwin W, Mark B. (2010) A study of variation in the reported haemophilia A prevalence around the world. *Haemophilia* **16**: 20-32.

Genetic Mutations in Haemophilia

In haemophilia A, the locus for the defective gene is on the X-chromosome, and is closely linked to those for glucose-6-phosphate dehydrogenase, G-6-PD (Boyer and Graham 1978), colour blindness (Whitaker et al. 1962) and possibly for X-linked hereditary persistence of fetal haemoglobin(Miyoshi et al. 1978), but not to that for the Xg^a blood group (Harrison 1964). The defective genes for haemophilia A and B have no linkeage relationship.

Haemophilia is transmitted from a heterozygous female to half of her sons (fig. 6, generation III). Affected males carry the mutant allele on their single X-chromosome (hemizygous). All the daughters of a haemophiliac will be carriers

(see Appendix 1 for definition) and all his sons will be normal and will not transmit the disease (fig. 6, generation II, and fig. 7).

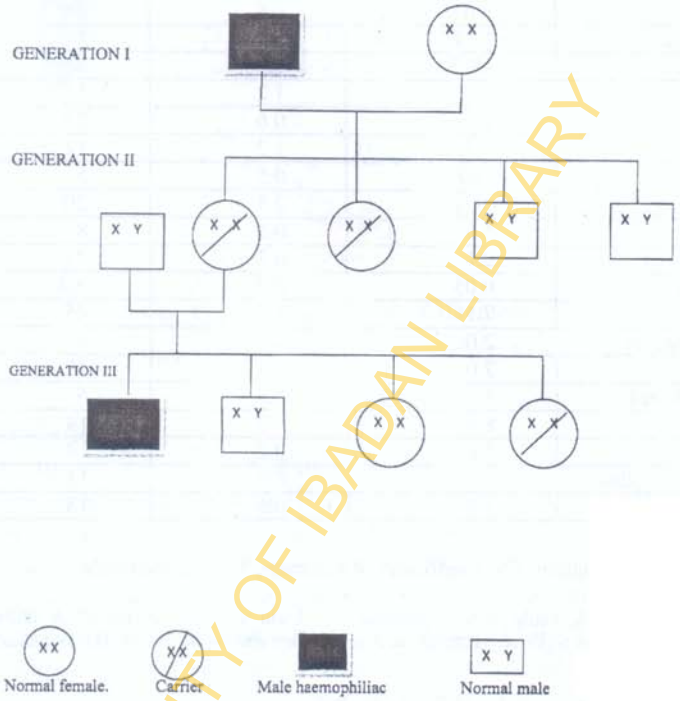


Fig. 6: A hypothetical pedigree to show the inheritance of haemophilia A and B.

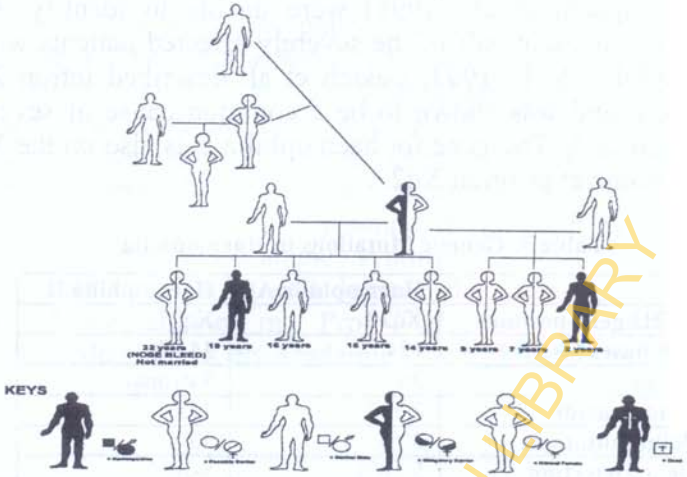


Fig. 7: Pedigree of a Nigerian haemophilia A patient with FVIII level <1% showing obligatory carrier mother in her third marriage and two haemophilic sons in 2nd and 3rd marriages. Note the 22year old daughter with recurrent nose bleed suggestive of an obligatory carrier status. The other daughters showed no bleeding tendencies.

In some families the mutation may be passed through several generations of carrier daughters without the birth of an affected son. This may partly explain why about one-third of haemophiliacs have no family history of bleeding (Wintrobe 1982). Spontaneous mutations, usually in the ovum of the mother may occur, resulting in the birth of a haemophilic child.

Haemophilia is virtually a disease of males. The defective gene for Haemophilia A is located in the long arm of the X – chromosome at position (Xq28) and the gene for Haemophilia B is also on the X- chromosome (Xq28), i.e. the last mega-base of Xq. A variety of nonsense and missense mutations, deletions, frameshifts, duplications, insertions and mRNA splice site mutations have been described (table 3). Gene deletions may be partial or whole. The size of the $FVIII^c$ gene (186kb) has made it difficult to determine all the genetic defects in Haemophilia A (Polakova, Kadosi and Filova

1998). Higuchi et al. (1991) were unable to identify the mutations in about half of the severely affected patients with Haemophilia A. In 1993, Lakich et al. described intron 22 inversion, and was shown to be a common cause of severe haemophilia A. The gene for haemophilia B is also on the X-chromosome at position Xq27.

Table 3: Genetic Mutations in Haemophilia

	Haemophilia A	Haemophilia B
FVIII gene position	Xq28	Xq27
Kilobases (Kb)	184	34 Kb
Exons	26	8 exons
Amono acids	2,332	415
Point mutations	70%	90%
Gene Detection	5-10%	5-10%
Insertions	< 5%	<5%
Intron 22 inversion	20%	<5%

Source: Young NS, Gerson SL and High KA. Clinical Haematology pg 817, Mosby 2006.

The FVIII gene was discovered by Prof. E.G.D. Tuddenham, at the time Co-Director of the Haemophilia Centre, The Royal Free Hospital, London, from 1978-1986 (see table 4). The discovery of the FVIII gene by Prof. Tuddenham in 1985 enabled the in-vitro production of the FVIII molecule by recombinant DNA technology. Recombinant factor VIII (FVIII) became commercially available in 1992.

Prof. Tuddenham was my external examiner in my final professional examination for the award of Fellow of the Nigerian Medical College of Pathologists (FMCPath) in November, 1985. I was the only candidate for that November Postgraduate examination and yet the Nigerian Postgraduate Medical College and the Nigerian Government still funded the cost of bringing the external examiner from UK (for a single candidate). Prof. Tuddenham sat in the examiners chair throughout the 6 hours of my practical examination, just sipping his tea, and occasionally observing how I was handling the instruments and the reagents. He was at the same

time marking my essay papers (papers I and II of 6 hours duration). The other aspects of the examination consisted of 3-hour clinical (long and short cases) and another 2 hours to cover oral exam and defence of my thesis titled "Immunologic Evaluation of Obligatory carriers of Haemophilia and their Haemophiliac Relatives: Relationship of X- Linked Bleeding Disorders to Lymphocyte function and to the Acquired Immune Deficiency syndrome."

At the end of the thesis defence, the examiners called me in and congratulated me. Prof. Tuddenham added that if I ever needed him in my academic career, I should not hesitate to let him know.

Table 4: Haemophilia: History of Laboratory Tests:

Date	Events	Author
1835	Defective blood clotting in haemophilia	Wardrop
1910	Haemophilic blood found to be clotted by addition of thrombin	Addis
1926	vWD was distinguished from Haemophilia	von Willebrand
1935	The Prothrombin time (PT) was found to be normal	Quick
1937	A globin fraction corrected clotting defect of haemophilic blood	Patek and Taylor
1946	The term antihaemophilic globulin (AHG) was coined	Lewis, Taylor et al
1950	Mild haemophiliacs were shown to have normal whole blood clotting time	Merskey
1951	Assay of FVIII was developed	Merkey and Macfarlane, Graham et al.
1960	International Standard for biologic activity of FVIII Nomenclative of clotting factors using Roman Numerals	MRC, UK
1962		Wright et al.
1944	Discovery of FIX deficiency (Christmas Disease) through mixing experiments: there was correction of the defects in Stephen Christmas blood when mixed with haemophilic blood	Parlosky, John Poole; Clarence Merskey

Table 4 contd.

1953	Reduced levels of FVIII were observed in vWD	Larrieu and Soulier
1953	Thromboplastin Generation Test	Macfarlane and Biggs
1971	Assay of FVIII Rag	Ratnoff et al
1979	Antibody to FVIIIc	Tuddenham et al
1985	Amino acid sequencing of FVIII	Tuddenham et al
1985	FVIIIc gene cloning	Tuddenham et al

Von Willebrand's Diseases

In 1926, Erik von Willebrand described a novel bleeding disorder affecting both sexes, termed pseudohaemophilia, with prolonged bleeding time (BT) but normal platelet count and characterized by mucosal bleeding. By 1950, it was observed that the prolonged BT was also associated with low FVIIIC level. In 1970, von Willebrand's factor (vWF) was discovered and the gene for vWF was cloned in the 1980s'.

von Willebrand's Disease is an inherited bleeding disorder, usually autosomal dominant but may be recessive, characterized by a life-long tendency towards frequent episraxis (nose bleed), bleeding into the skin and menorrhagia. Both males and females are affected. Even through vWD is described as a single disease, it is in fact a family of bleeding disorders caused by low or abnormal von Willebrand's Factor (vWF). vWD is the commonest inherited bleeding disorder with a worldwide prevalence of 0.9 – 1.3%. In the USA no fewer than 3% of the population is affected. There is no racial predilection. vWF is a carrier protein for $FVIII^c$. Low level or dysfunctional vWF can lead to a decrease in FVIIIc. In other words, a patient with vWD can have clinical features similar to those of haemophilia (i.e. haemarthrosis etc). Fortunately most patients with vWD have mild disease, and vWF increases with age. Clinical features may be more pronounced in females because of the monthly menstrual flow (table 5). Bleeding may be exacerbated by ingestion of Aspirin and other anti-platelet drugs.

Acquired vWD may occur (about 300 cases have been described), and may be due to auto-antibody to vWF, or increased proteolysis of the vWF or associated with

monoclonal gammopathies. vWF protects Factor VIII[c] from proteolytic degradation and localizes factor VIII to the site of vascular injury. vWF also links exposed collagen to platelets and mediates platelets aggregation through its binding to GPIb on activated platelets. Detailed discussion on vWD is beyond the scope of this lecture.

Table 5: Clinical Manifestations of vWD

Signs/Symptoms	Frequency (%)
Epistaxis	60
Bleeding post dental extraction	50
Petechiae/Ecchymotic patches	40
Menorrhagia	35
Gingivial bleed	35
Trauma-induced bleed	35
Post partum haemorrhage	25
Post – operative bleeding	20
GIT Bleed	10

Circumcision and Inherited Bleeding Disorders

Circumcision is believed to have originated in Egypt (fig. 8). This picture (which I obtained in Egypt during the ISH (International Society of Haemotology) conference in the year 2000), depicts the practice of circumcision in Egypt. An adult male in erect position being restrained by strong hands of other male adults, while the prepuce is being cut off. Circumcision is defined as removal of the sleeve of skin and mucosa, the tissue covering the glans (head) of the penis.

Fig. 8: Egyptian Circumcision: Pictorial Representation of art form found in an Egyptian Saqqara (dates to 2400BC)

The word circumcision is derived from two latin words: circum means "around" and caedere, which means "to cut". It is one of the oldest surgical procedures, and it is the world's most controversial surgery.

Most anthropologists disagree on the origins of circumcision, though according to the English Egyptologist, Sir Elliot Smith, it is believed that circumcision originated in Egypt over 15,000 years ago. An art form of circumcision was found in Egypt dating back to 2400BC. It is believed that the Jewish people borrowed the practice of circumcision from the Egyptians, circumcision is also practiced throughout Africa, Near East, by the Australian Aborigines, and by muslims in Southeast Asia. Up till the time of colonization, Europeans knew little about circumcision. Only one in seven males worldwide is circumcised (Kavakli 1997).

In the Holy Bible, several references were made to circumcision both as a physical procedure (Joshua 5 v29) and as a spiritual phenomenon (Phillipians 3 v3). In Genesis (17 v 10) God said to Abraham "You and your descendants must agree to circumcision, every male among you." And in v23,

"On the same day Abraham obeyed God and circumcised his son Ishmael and all the other males in the household, including slaves born in his house and those he had bought."

Abraham was 99 years old when he was circumcised and his son Ishmael was 13 years old. As regards the instrument employed in the Biblical era, the evidence in Joshua 5 v 2-9 says "make some knives out of flint and circumcise the Israelites".

Among the Christians in the Southwest of Nigeria, neonatal circumcision is often practised. In Kenya, circumcision is often practiced at puberty, and the word Kihii is used to describe a big boy that has not yet been circumcised. Life expectancy of haemophiliacs: before 1960 was 11 years, now 50-60 years. From the 1980s, death rate was 0.4 per million, 1978-1981, but increased to 1.2 per million by 1983.

Circumcision and Islam

Islam recommends circumcision at an early age according to a recent review by Anwar M .S. et al.; 'ideally on the 7th day of life but up to 40 days after birth or hereafter until the age of 7years depending upon the health of the infant at that time."

Anwar further stated that "the Qur'an (holy book) states; "It is the basis of inbred nature, a symbol of Islam, an indication of the law of the Lord, and the attainment of the true society."

In Africa, circumcision is often performed to coincide with the naming ceremony of the male child on the 7th day of life or within a few weeks thereafter. Circumcision is widely practised in Nigeria for religious and customary rites (Ajuwon et al. 1995). The age at circumcision in Nigeria varies widely amongst various tribes and religious groups. There are many health reasons why circumcision is advantageous—it reduces the incidence of phimosis, paraphymosis, balanitis, and cancer of the penis. The rates of Sexually Transmitted Diseases (STDs) are also reduced in circumcised individuals. Cancer of the cervix is much less

common in women living in societies where circumcision is routinely practised.

Bleeding is the most common complication, even in healthy boys, with an incidence of between 0.1 and 35%. In infants and young children with unsuspected haemophilia, this complication can be fatal.

Treatment of Haemophilia

The sight of a patient slowly becoming exsanguinated from a trivial injury left a lasting impression on the early observers. Miscellaneous treatments were used in haemophilia (table 6). They include the use of lime, thyroid gland, bone marrow, hydrogen peroxide, splenectomy, oral tissue fibrinogen, bromide extract of white egg, oxalic acid (intravenously), inhalation of oxygen, injection of sodium citrate and female hormone therapy in the belief that feminity prevents the expression of the haemophilic gene (Ingram 1975).

Macfarlane used local application of snake venom based on the fact that Russell's viper venom clotted haemophilic blood very rapidly (Macfarlane and Barnett 1934). In our environment we have anecdotal reports of the use of "*Efinrin*" in attempts to stop the bleeds in the Nigerian haemophiliacs.

Table 6: Haemophilia: History of Treatment

Date	Event	Author
1840	Transfusion of blood from " a stout young woman" to a boy with history of bleeding disorder, who had bled profusely post a surgical procedure	Lane
1931	It was established that human blood transfusion was the only effective treatment for haemophilia	Macfarlane
1934	Russell viper snake venom – RG	Macfarlane
1936	Bromide extract of egg white – Lancet	
1941	Cohn fractionation of plasma	Cohn
1946	Cohn's fractionation commenced	
1950s	Human freeze dried plasma fractions were developed	Kekwick and Wolf , Soulier, Blombo
1954	Ox (bovine) and pig (porcine) freeze – dried plasma were introduced	Bid nev
1955	Intravenous infusion of FVIII 1st prepared	
1957 – 8	Human preparations of FVIII commenced	
1961	1st experiments with concentrates of FVIII	
1965	Cryoprecipitate was discovered	Judith Pool
1966	Peanut flour – Nature	
1968	Lyophilised FVIII concentrate commercially available	
1970's	EACA and Tranexamic acid	
1971	Use of antifibrinolytic drugs, in patients undergoing dental extractions	Welsh
1977	Use of 1 – deamino- 8- Darginne Vasopression (DDAVP) in mild haemophilia and vWD	Mannucci
? 1977	Rise in FVIII after exercise	Rizza
? 1977	Rise in FVIII with adrenaline	Ingram
1985	Viral inactivated factor concentrate	
1992	Recombinant FVIII	
1997	Recombinant FIX	
1998	Gene therapy trials in humans began	

The Use of Transfusion

Harvey's description of the circulation in 1628 stimulated interest in blood transfusion, initially from one animal to the other, then animal to man and finally man to man (Lyon 1984). In 1965, cryoprecipitate became available for routine transfusion to treat haemorrhagic episodes in haemophiliacs in the developed countries. In clinical terminologies, the term cryoprecipitate was soon shortened to "cryo" (Pool and Shannon 1965), a term which can be commonly heard at haemophilia treatment centres before the advent of lyophilized factor concentrates.

The first transfusion used in the treatment of haemophilia was done by Lane in 1840 when he transfused 170ml of fresh whole blood from a female donor to a known bleeder whom Lane had operated upon for a squint. The bleeding stopped after the transfusion and the patient recovered. However blood transfusion in the treatment of haemophilia was not utilized to any significant extent until some decades later when it became the main stay of treatment (Ikhala 1982).

Plasma became available for intravenous infusion following the pioneering work of Strumia in the collection and storage of plasma (Strumia and McGraw 1941). It was observed that early cases of bleeding into joints and muscle responded adequately to plasma infusion. However major trauma needed large volume of plasma which jeopardized the recipient's circulation. In addition, there was the problem of frequent allergic reactions to plasma infusion. This problem was overcome by the use of cryoprecipitate. The noteworthy discovery of cryoprecipitate by Judith Pool followed her observation that on slowly thawing fresh frozen plasma, much of the factor VIII activity remained with the cryoglobulin precipatate (Pool and Hershgold 1964).

Home Therapy

The production of cryoprecipitate by Judith Pool in 1965 made a big difference to the care of haemophiliacs in the developed countries and made home treatment achievable at

that time. Dr Katharine Dormandy (1926–1978) pioneered home therapy by helping patients to raise funds to purchase deep freezers where the cryoprecipitate was kept. In 1977 she was awarded the first gold medal by the Haemophilia Society for her pioneering work in home treatment. In the last 10 years in Ibadan, we have been able to supply limited quantity group compatible cryoprecipitate to our haemophilic patients living outside Ibadan (e.g. Benin, Warri) provided they have a deep freezer at home and a family physician who could infuse this wet concentrate whenever they have a haemorrhagic event.

In home therapy programmes, parents and patients are trained to administer the lyophilized concentrates (which are stable in home refrigerators) at the first sign of bleeding (Rabiner 1970) and such programmes have resulted in improved preservation of joint function (Levine 1974; Hilgartner 1977). A drop of 50% in the mortality rate in three successive decades (1950-1979) has been observed, each corresponding respectively to the increased use of blood transfusion, the use of fresh-frozen plasma and the availability of cryoprecipitate (Ikkala et al. 1982).

Current Treatment of Haemophilia

Hemophiliacs are obligate recipients of blood and blood products because they lack specific clotting factor – FVIII in haemophilia A and FIX in haemophilia B. Preparations of wet or dry coagulation factor concentrate could be from single or multiple pooled blood donors. A substantial proportion of haemophiliacs in USA, UK and some other developed countries became infected with HIV and other viruses such as HBV and HCV. For instance Mr Christmas (whom FIX deficiency was named after) died of HIV and AIDS. Prior to the AIDS epidemic, intracranial bleeding was the leading cause of death in haemophiliacs.

In the USA, between 1987 and 1989, AIDS accounted for 55% of all deaths in haemophiliacs (CDC – Haemophilia Data and Statistics – NCBDDD) (table 7).

Table 7: HIV Seroconversion in Haemophiliacs according to Clinical Severity

Severity	HIV Seroconversion (%)
Severe haemophilia	75
Moderate haemophilia	46
Mild haemophilia	25

The occurrence of AIDS in haemophiliacs played a role in the successful attempts to improve blood safety. Improved safety in blood supply (by excluding high risk donors), and safer manufacturing process for concentrates (such as immunoaffinity chromatography, nanofiltration technique, heat and solvent detergent treatment of the final product) have rendered FVIII concentrates virtually safe (table 8). However, there is no zero-risk in blood transfusion. The best techniques still allow non-lipid-enveloped viruses such as hepatitis A, parvovirus B19 and the prions associated with variant Creutzfeldt-Jacob's Disease (CJD).

Table 9: The Form of Replacement Therapy, Liver Function Tests and Hepatitis B Viral Markers in Patients with Haemophilia A or B

Haemophiliac	Age (yrs)	Clinical severity	Form of replacement therapy	ASAT	γ GTP	HBsAg	HBsAb	HBcAb
1. AK	20	Severe	FVIII concentrate	56↑	14	--	+ve	--
2. AJ	16	Severe	FVIII concentrate	67↑	21	+ve	--	--
3. BD	30	Severe	FVIII concentrate	118↑	88↑	--	+ve	+ve
4. CMi	17	Mild	Cryoppt	22	14	--	--	--
5. CMa	10	Mild	Cryoppt	28	<0.5	--	--	--
6. MV	42	Severe	FVIII conc	50↑	71↑	--	+ve	+ve
7. VMi	20	Moderate	FVIII concentrate	32	42↑	--	+ve	+ve
8. ZS	16	MILD	FVIII concentrate	31	14	--	--	--
9. BB	17	Severe	FIX concentrate	55↑	37↑	--	+ve	+ve
10. HA	3	Mild	FFP	65↑	7	--	--	--
11. HS	11	Mild	FFP	968↑	79↑	--	+ve	+ve
12. JC	8	Mild	FFP	18	9	--	--	+ve
13. JG	5	Mild	None	31	10	--	--	+ve

*average of the two preceding years
**as FIX concentrate
–negative
+ve positive
↑ above the upper limit of normal.

To further reduce the risk of acquiring transfusion-transmissible infections (TTIs) in the haemophilic population following transfusion of blood products, further intense research hastened the development of genetically engineered FVIII and FIX concentrates using Chinese hamster ovary or baby hamster kidney cell lines (tables 9 and 10).

The only major drawback at least for the developing countries like Nigeria, is that these recombinant factor concentrates are very expensive. For instance, 500 iu of recombinant FVIII concentrate may cost as much as N100, 000. In some developed countries, these recombinant concentrates are being used as primary prophylaxis (given 3 times a week) at subsidized rates, and there is evidence that such patients have shown better outcome particularly if treatment is started at an early age. However, some health insurance schemes may not authorize re-imbursement for primary prophylaxis with recombinant factor concentrates (Kessler, 2008). The estimated annual cost of treatment of on-demand treatment for haemorrhagic episodes in a severe haemophiliac is about USD 50,000 (Kessler, 2008), implying that annual cost of primary prophylaxis would be more substantial.

Table 9: Lyophilized FVIIIc Concentrate for Replacement Therapy in Patients with Haemophilia A.

Available products	Examples	Source	Methods of viral inactivation
Products with intermediate purity (FVIII-specific activity 1-10iu/kg)	Humate-P	Plasma	Heat-treatment
	Profilate	Plasma	Solvent-detergent treated
Products with high purity (FVIII-specific activity 50-100iu/kg)	Alphanate	Plasma	Solvent-detergent treated
	Koate HP	Plasma	Solvent-detergent treated
Products with ultra high purity (purified by monoclonal antiboby) FVIII specificity >3,000iu/kg.	Haemophil-M	Plasma purified by monoclonal antibody.	Solvent-detergent treated
	Monoclate-P	Plasma purified by monoclonal antibody.	Pasteurized
Recombinant products	Advate	Recombinant DNA technology	Solvent-detergent treated
	Bioclate	Recombinant DNA technology	Solvent-detergent treated
	Helixate	Recombinant DNA technology	Heat treated
	Kogenate	Baby hamster kidney cells	Solvent-detergent treated
	Recombinatee	Chinese hamster ovary cells	Solvent-detergent and heat-treated
	Re-Facto	Chinese hamster ovary cells	B domain deleted
	Xyntha	Synthetic (non-human, non-mammalian based	Albumin-free purification plus a nanofiltration step.

Table 10: Treatment of FVIII Inhibitors

Product	Dose	Comment
Human FVIII concentrate	Loading dose of 10,000iu then 1000 units/hour.	Subsequent doses depend on FVIII levels desirable for the severity of the haemorrhagic event.
Feiba VH (factor FVIII by-passing activity)	25-100 units/kg every 12 hours	Should not exceed 200units/kg/day.
Autoplex	25-100 units/kg every 12 hours	
Porcine FVIII	50-100 units/kg every 12 hours	Dose is based on inhibitor titre and absence of cross reactivity to the patient's inhibitor
Recombinant FVIIa (rFVIIa)	30 µg/kg every 2-3 hours	

Life Expectancy

A review of 98 British haemophiliacs by Birch in 1937 showed that only six patients survived until adulthood: they either died in childhood or early adolescent. Today the average haemophiliac in the developed countries has the hope that life expectancy will be like that of the normal population. What has made this transformation in quality of life and life expectancy possible are targeted component therapy now in the form of pure recombinant FVIII and FIX concentrate. So long as the haemophiliac does not bleed, he can lead a normal life. Hence the perennial unspoken prayer of the parents of haemophiliacs would be "Bleed not, my son".

Ngugi Wa Thiong'o (1962), the author of *Weep not, child,* and also the author of the *River Between* (1964), *A grain of wheat* (1967), was described by Ime Ikddeh (1985) as a creative writer, who successfully combined creative writing with full-time university courses. My English and Literature teacher at Christ's School, Ado-Ekiti, Prof. Niyi Osundare, a world-acclaimed scholar and social critic, ensured that his students received the best a teacher could ever give. "A book

that furnishes no quotations is no book – it is a play thing" says Thomas Peacock. One of the books and titles that have always fascinated me is 'Weep not, child,' and the poem by Walt Whitman:

> Weep not, child,
> Weep not, my darling,
> With these kisses let me remove your tears,
> The ravening clouds shall not be long victorious,
> They shall not long possess the sky……'

Haemophilia Care: A Personal Perspective

After passing the Part I fellowship examination of the Nigerian Postgraduate Medical College, the Federal Government sponsored me on a one year overseas training Programme for Residents, so as to have opportunities for further professional development, usually at a Teaching Hospital anywhere in the world. I was able to secure a 2-year Research Fellowship position at St. Joseph's Hospital, London Ontario Canada, where the regional haemophilic centre resided. I was a recipient of a federal government scholarship (although nominally) in addition to this fellowship. The choice of Canada was deliberate as my husband was undergoing his Residency training in Neuroanatomy and Neurosurgery at the University of Western Ontario, London.

The Teaching Hospital of the University of Western Ontario (UWO) consisted at that time in 3 hospitals (University Hospital, St Joseph's Hospital and Victoria Hospital). For the two years of my Research fellowship in St Joseph's Hospital, I was directly supervised by Prof Martin J. In wood, who was then the Head of the Department of Haematology and the Regional Director of the South-western Ontario Haemophilia Programme. He also had served in the British army during the 2nd World War, when plasma was first being prepared by the Americans and shipped to Europe to treat wounded soldiers at the war front.

A strict register of all haemophiliacs in the South-western Ontario Regional Haemophilia programme was kept. Detailed information on each haemophiliac including the coagulation factor level, the number of joint bleeds in a year, the units of factor VIII or FIX consumed annually, their pedigree, side effects of therapy etc were kept. I was given access to this data bank which became very useful for my thesis work titled: "Immunologic Evaluation of Obligatory Carriers of Haemophilia and their Haemophilic Relatives: Relationship of X-Linked Bleeding Disorders to Lymphocyte Function and AIDS" fig. 8 and table 11).

A comprehensive haemophilia programme was fully established at St Joseph's Hospital at that time. The haemophiliac was co-managed with orthopaedic surgeons, physiotherapists, nurse practitioners (who would regularly conduct home visits to the haemophiliacs and oversee their home therapy), psychologists and other relevant health professionals.

Annually, all haemophiliacs were invited to the centre for a comprehensive medical review that covered the extent of their flexion deformities, application of joint prosthesis, psychosocial evaluation assay of FVIII or FIX inhibitors, screening for HIV, HBV and HCV. As at 1983, some haemophiliacs had become HIV positive, having been infected through the use of contaminated factor concentrates.

The first HIV and AIDS patient I had the opportunity to meet at the haematology ward in St. Joseph's Hospital in 1983 was a Canadian haemophiliac, a musician by profession, who developed Central Nervous System (CNS) lymphoma. His death within a few weeks of this complication left a lasting impression on me as regards complications of the treatment of haemophilia, particularly immune dysfunction.

My findings of the immunological status of the Canadian haemophiliacs and their haemophilic carrier mothers can be summarized as follows:

Prior to the HIV AIDS epidemic, not much was known about the immune status of the haemophiliac. Even in the absence of an infective agent, blood transfusion on its own does cause immune dysfunction, hence my interest in studying the immunological status of the haemophiliac and their obligatory carrier mothers. It was then decided that my dissertation would be on "Immunologic Evaluation of Obligatory Carriers of Haemophilia and their Haemophilic Relatives: Relationship of X-linked bleeding disorders to lymphocyte function and to the Acquired Immune Deficiency Syndrome" (Shokunbi 1985).

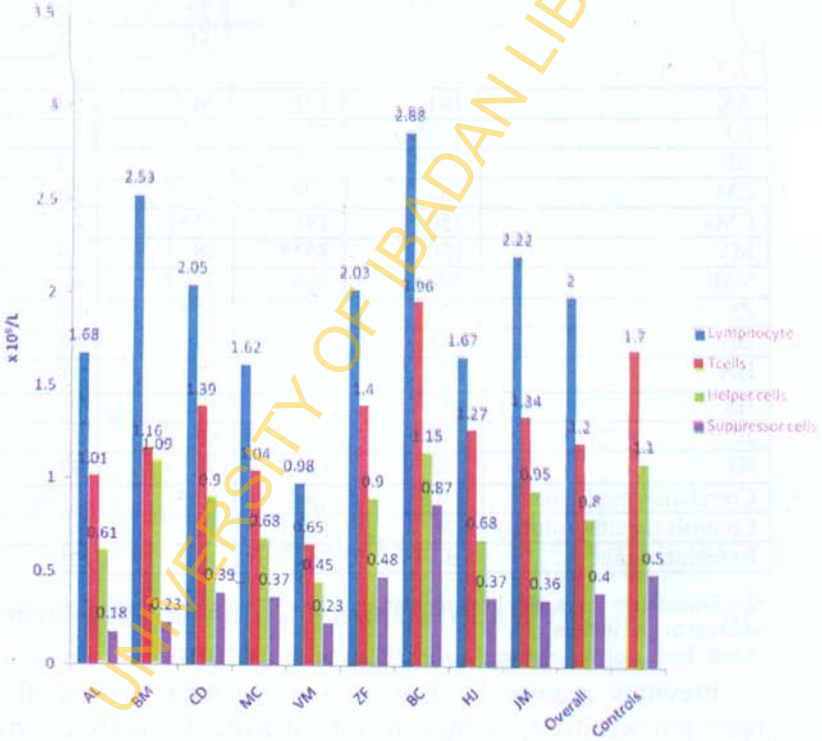


Fig. 8: The Lymphocyte count and T-cell subsets in obligatory carriers and the mean value for female controls

Table 11: Proliferative Response of Lymphocytes of Obligatory Carriers and their Haemophiliac Relatives

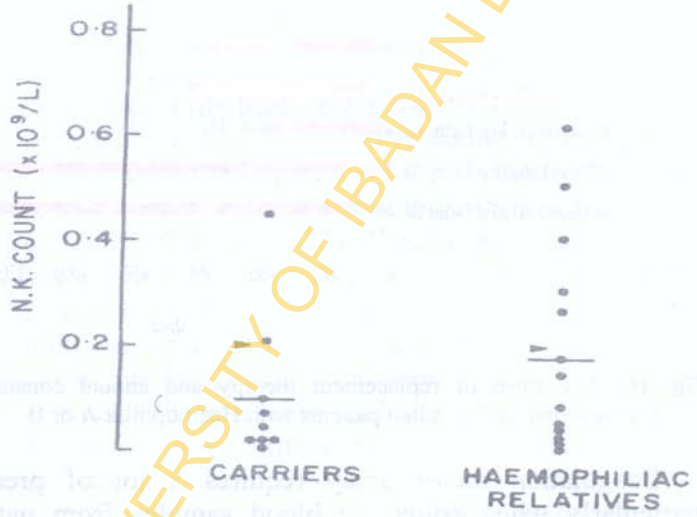
CARRIERS	PHA	Con A	PWM	MLR
	SI	SI	SI	SI
AL	42**	42*	26	14
BM	89**	38*	45	29
CD	94*	79*	47	49
MC	112*	90*	48	37
VM	268	119	91	--
ZF	240	164	100	86
BC	160	138	39	25
HJ	117*	87*	32	45
JM	187	120	51	40
HAEMOPHILIACS				
AK	191	156	34	53
AJ	106*	75*	151	69
BD	39**	30*	50	13*
CMi	263	209	40	88
CMa	250	191	135	--
MV	150	85**	58	34
VMi	292	216	71	--
ZS	155	152	17*	20
BB	88*	62*	57	40
HA	79*	69*	36	18
HS	82*	70*	18	21
JC	194	161	65	28
JG	162	123	32	39
Correlation coefficient	0.33	0.44	0.05	-0.16
Controls (healthy adults)	136	118	48	--
Reference value	≥33	≥13	≥8	≥4

SI = Stimulation index, * = low stimulation index, ** = had low absolute counts in addition to low indices

Previous reports by Broval and Schaeter showed that radiation sensitivity of human Natural Killer Cells (NK cells) was controlled by X-linked co-dominant genes and therefore proposed that X-linked factors are involved in the control of NK cells activity. In order to determine whether the haemo-

philic gene has any control on the NK cells, we studied NK cell counts in obligatory carriers of haemophilia.

The pattern of NK count in obligatory carriers and age and sex matched controls is shown in figure 9. We observed significantly lower NK cells ($p = 0.001$) compared to the values in the control group (Shokunbi 1985). The implications of these findings are not known. Suffice it to say that NK cells are very important in susceptibility to cancer growth and control of infection. We also observed low helper (CD4) cell count in the obligatory carriers compared to the normal control group ($p = 0.05$) but no significant difference in the T-suppressor (CD8) counts.



► **Mean NK count in female and male controls (0.2×10^9 /L)**

Fig. 9: Natural killer (NK) cells count in obligatory carriers and their haemophiliac relatives

Figure 10 shows the dose of FVIIIc concentrate infused annually for the treatment of bleeding episodes (ie. on-demand therapy) in the adult Canadian patients with severe haemophilia A or B ranging from 477 – 1298 iu/kg/yaear compared with a dose of 0 – 48 iu/kg/year for a patient with

mild haemophilia. This implies that a patient with a mild bleeding disorder would be expected to have a much better quality of life and a near normal lifespan.

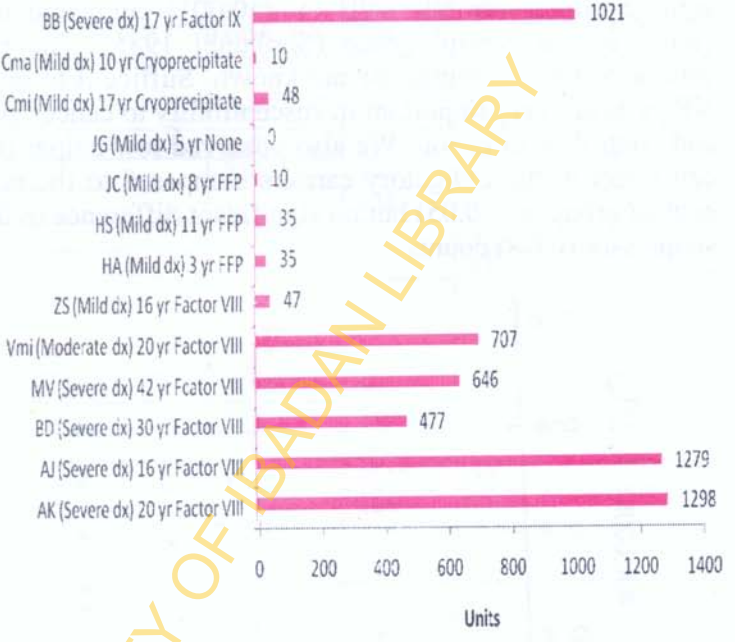


Fig. 10: The form of replacement therapy and annual consumption units/kg/year in Canadian patients with Haemophilia A or B

Coagulation factor assay requires a lot of precision particularly when collecting blood samples from patients. Native blood is withdrawn and mixed with 3.2% Sodium Citrate anticoagulant in a standard ratio of 9:1. In our coagulation laboratory at St. Josephs Hospital, we observed that some evacuated sample tubes overshot or did not draw enough blood leading to spurious blood: citrate ratio. This would certainly lead to erroneous coagulation factor assay result with serious implications in genetic counselling and management of the patients with inherited bleeding disorders. We then set out to determine vacuum action of the evacuated

tubes. We observed variability in the amount of blood drawn by the evacuated tubes (Shokunbi, Harris and Thompson 1989). A formula for calculating the volume of the blood required when the haematocrit of the patient is greater than 60% (0.60) was subsequently derived, particularly when coagulation factor assays are to be performed (Shokunbi, O'Keefe and Schaus 1985).

Where the patients haematocrit is >0.60,
The volume of blood required = $\frac{1.8}{1 - \text{haematocrit}}$
This is the mls of blood to be added to 0.5ml 3.2% sodium citrate.

This work on evacuated tubes was one of the publications considered for an award by the Editorial Board of the Canadian Journal of Medical Technology in 1985.

On my return to Nigeria and after taking up an appointment as a lecturer in the Department of Haematology in 1988, I observed that majority of the haemophiliacs in the South-west were referred to the UCH, Ibadan, as a result of the expert care provided over the years by Prof. E. M. Essien and my other teachers (Prof. GJF Esan, Prof. Aba Sagoe, Prof. CKO Williams and Prof. O. Oluboyede). We are still receiving patients from a large catchment area of Nigeria. We have had patients from as far as Kaduna, Kano, Enugu, Warri, Abuja, etc, and they sometimes make distress calls, even in the night, to our team members, who would usually encourage them to travel to UCH as soon as possible for transfusion of cryoprecipitate (for $FVIII^c$ deficiency) or FFP (for FIX deficiency). Whenever cryoprecipitate was not available, we resorted to the use of group compatible FFP for FVIII deficient patients.

In order to assess the contribution of UCH to Haemophilia care in Nigeria, we assessed retrospectively the treatment records of our patients from 1965- 2000 (a 35-year period).

Circumcision in Haemophiliacs: The Nigerian Experience

We reviewed the case records of 71 Nigerian patients with inherited bleeding disorders (62 had haemophilia A, 5 had haemophilia B, and 4 had vWD) seen over a 35-year period (1961-1994). All the haemophiliacs were males and were all circumcised except one, who when last seen at age 40yrs remained uncircumcised. He had lost 3 older siblings from "a febrile illness" before the age of 5yrs, hence the parents chose not to circumcise him.

A positive family history of bleeding disorder was obtained in 46.5% of the haemophilic patients. The haemophiliacs were circumcised either by the traditional circumcisionist (or circumciser) or by a nurse-midwife or other community health worker. The incidence of post circumcision bleeding was 52.1%. Our findings were presented by me at the International Society of Haematology Conference in Cairo in the year 2000, particularly in relation to the incidence of post-circumcision bleeding (Shittu and Shokunbi 2001).

ABO Blood Group and Factor VIII level

It has been observed in several studies that the ABO Blood Group system is a major determinant of plasma levels of $FVIII^C$ and vWF. In a previous study, we observed that Blood Donors with Blood Group A have the highest $FVIII^c$ level (135 ± 12%) and a higher cryo yield of 72%, compared to $FVIII^C$ level in Group O individuals (of 92 ± 22%) and cryo yield of 67%. (Oluokun, Olaniyi and Shokunbi 2004) (see table 12).

Table 12: Blood groups and FVIIIc level in FFP and corresponding Cryoprecipitate

Blood group	Number of donors (%)	FFP ($FVIII^c$/ml)%	Cryo (FVIIIc/ml)%	Percentage yield%
O	27(52.94)	92 ± 22	313 ± 14	66.7
A	14(27.45)	135 ± 12	472 ± 63	71.6
B	9(17.65)	89 ± 37	313 ± 14	70.7
AB	1(1.96)	80.00	220	66.7
Overall	51			69.7

Olatunji, Okpala and Shokunbi (1990) observed that patients with severe haemophilia tend to have Blood Group O while those with mild haemophilia are usually of Blood Group A. These observations have implications in ensuring adequate stock level and policy formulation in the provision of transfusion services.

Clinical Manifestations of Haemophilia

Clinical manifestations in haemophilia include bleeding from the umbilical stump, cephal-haematoma, post-circumcision bleeding, dental (oral) bleeding (e.g. during tooth eruption) haemarthrosis, superficial haematoma, post-operative bleeds, haema-turia, retroperitoneal haematoma, muscle compartment bleeds (e.g. ilio-psoas haematoma) and intracranial haemorrhage. A recent review of 22 patients (with Haemophilia A or B) seen over the last 5 years, (and the earlier review covering 35 years (Shokunbi 2000) showed that the types of bleeds in our patients do not differ from those of the Caucasian patients. In this latest analysis (Shokunbi, Unpublished Observation), we observe in order of frequency, post-circumcision bleeding, haemarthrosis, dental bleeds, haematoma in muscle compartment, prolonged bleeding from sites of lacerations and intracranial haemorrhage (table 13).

Table 13: Classification of Clinical Severity and Pattern of Bleeding

Severity of Bleeding	Pattern of bleed
Severe haemophilia	Post circumcision bleeding, umbilical stump bleed. Joints usually weight bearing (e.g. knees, ankles) repeat bleeds (target joint), intracranial haemorrhage, muscle haemorrhages without obvious trauma;
Moderate haemophilia	Joint and muscle haemorrhages with minor trauma, surgery, haematuria.
Mild haemophilia	Haemorrhages with major haemostatic challenge e.g. major trauma, surgery surgery or serious trauma; a damaged joint may bleed repeatedly

Symptomatic Obligatory carriers may have bleeding from the mouth (e.g. after tooth extraction), epistaxis, post-partum haemorrhage, menorrhagia and prolonged bleeds after surgery. One of the obligatory carriers, whose brother was a haemophiliac bled profusely after a breast lumpectomy; her FVIIIC level was later shown to be 18% (see table 14). We have also reviewed clinical data on 11 Nigerian Obligatory carriers: 2 had menorrhagia, 7 had post partum haemorrhage (severe in 4, but mild in 3); one had epistaxis (Shokunbi, unpublished observation).

Table 14: Factor VIII evel in normal Population, Haemophiliacs and Obligatory Carriers

	FVIII^c %	FVIII^c 1unit/ml plasma
Normal person	100%	1 unit/ml plasma
Range in normal persons	40-200%	0.4 to 2 units/ml plasma
Severe haemophilia	< 1%	< 0.01 units/ml plasma
Moderate haemophilia	1-5%	0.01-0.05 units/ml plasma
Mild haemophilia	>5 but < 40%	0.05-0.39 units/ml plasma
Carrier of haemophilia (mean values)	50%	0.5units/ml plasma
Range in carriers of haemophilia	1-200%	0.01-2units/ ml plasma

Intra- and Post-Circumcision Bleeding in Nigerian Neonates: Correlation with Global Tests of Coagulation

Circumcision is a routine procedure in most African countries. In some communities, circumcision may be in the neonatal period or could be part of pubertal rites. During the last 50-100 years, routine neonatal circumcision became widespread in many developed countries. Kakli (1998) reported that only one in seven males in the world is circumcised. An upsurge in the circumcision rates is attributable to the observed advantage in the prevention of HIV and AIDS in communities where circumcision is routinely practised.

We assessed 244 male neonates undergoing circumcision at UCH and Oluyoro Catholic Hospital, Ibadan, noting the degree of intra- and post-circumcision bleeding. The rate of bleeding at circumcision was adjudged minimal (ie <10mls of blood) in 81.1% of the neonates and moderate bleed in 18.4%. As regards post-circumcision bleeding, 95.5% had minimal bleeding (considered satisfactory) while 4.5% had moderately severe bleed. The method of circumcision used was either with the Gomco clamp or with Plastibel, and the procedure was done by the Surgeons (UCH) or the nurse (Oluyoro Catholic Hospital).

The occurrence of intra-or post-circumcision bleeding had no significant correlation with the International Normalised Ratio (INR) values (P=0.534). There was no relationship between Activated Thromboplastin Time (APTT) and intra-operative bleeding (p = 0.276), however there was a significant correlation between APTT and post-circumcision bleeding (p = 0.001). We therefore concluded that APTT should be adopted as a screening test before circumcision particularly where there is a family history of bleeding disorder (Fakunle, Shittu and Shokunbi 2007).

Factor VIII^C in Nigerian Neonates undergoing Circumcision

The history of haemophilia and circumcision appear intertwined. A prospective study by Fakunle, and Shokunbi (2005) on FVIII^C level in 243 male infants pre-circumcision was undertaken so as to determine incidence of inherited deficiency of FVIII. We observed that 1.6% (4 neonates) of the 243 neonates had FVIII^C level between 20-26%, which is within the range seen in mild haemophiliacs (5-30%). All the 4 neonates with low levels of FVIII^C had no family history of bleeding disorders, and only one of the 4 had mildly elevated APTT of 55 secs, the other 3 patients had normal APTT (table 15).

Table 15: Low Factor VIII^{C} Levels in Some Nigerian Neonates and their Tendency to Intra-op or Post circumcision Bleeding

S/N	Family history	FVIII level (%)	PT(INR)	APTT value	Intra-op (circum-cision) bleeding	Post-op (circum-cision) bleeding
1	No	20.3	0.9	33	Yes	Yes
2	No	25.5	0.9	33	Yes	No
3	No	22.5	1.1	55	No	No
4	No	22.3	0.9	45	Yes	No

We concluded that these four neonates may either have mild haemophilia or vWD and need to be followed up for more comprehensive investigations including bleeding time, platelet function tests and von Willebrand factor assay.

Factors Leading to Flexion Deformity in the Nigerian Haemophiliac

Flexion deformity was found in 25% of haemophiliacs seen in UCH in a review covering a 35yr period—1961-1994 (Shokunbi 1994). Bleeding into the joint (haemathrosis) is the most characteristic feature of severe and moderately severe haemophilia, and if not promptly treated (i.e within 2hrs of the onset of the joint bleed), chronic synovitis, fibrosis and flexion deformities are the sequelae. The pathogenesis of the synovitis results from the release of oxygen radicals generated by the iron-laden macrophages within the joint space, as a consequence of the breakdown of red cells. This inflammatory reaction sets off a viscious cycle of synovial cell proliferation neo- vascularisation and repetitive bleeds into the affected joints (hence the term target joint). Factors identified as being responsible for the high incidence of flexion deformities in our patients include late presentation, inadequate coagulation factor replacement therapy, misdiagnosis and financial constraints (Shokunbi 1994; Abja et al. 2004). Occurrence of flexion deformity in a haemophiliac is now regarded as a failure of management.

Life threatening Haemorrhage in Nigerian Haemophiliacs

Intracranial haemorrhage remains the leading cause of death in the Nigerian haemophiliac (Shokunbi et al. 1997). Intracranial haemorrrhage tends to recur once an episode has occurred, and invariably becomes fatal. A fibrotic epileptic focus may be an outcome. One of our patients had an epileptic focus following an intracranial haemorrhage in childhood. In spite of antiepileptic drugs, he died at the age of 21years, following an epileptic attack while walking along a major road. He became unconscious and fell into a gutter. He died in UCH within 48 hours.

Other life threatening haemorrhagic episodes seen in our patients include severe post-circumcision bleeding, massive cervical and sublingual heamatoma (Shokunbi et al. 1997), bleeding from the tongue following accidental bite while eating, mesenteric bleed associated with volvulus, severe gastro- intestinal bleed from heavy hookworm infestation, extensive scalp laceration during road traffic accident, relentless bleeding post-tooth extraction, crush injury of left foot , severe head and neck laceration from broken bottles during a brawl in a beer parlour, etc.

We also recall our experience with a 7-year old Prince from Ekiti who was brought in by his father, the King (Oba) and Queen (Olori). His past history revealed several episodes of spontaneous bleed, particularly haemathrosis. He also bled into the flank. He had Haemophilia A. On one of the hospital admissions, he fell off his bed in the paediatric ward and fractured his left femur, with serious consequences. He had to remain in the hospital for over 4 months, with orthopaedic care, blood transfusion and several units of daily cryo-precipitate infusion.

In every haemophiliac case note, we would have written "no aspirin, no intramuscular injection, bed rest (i.e. no exercise)". The social history of this Prince revealed the over-cosetting by his anxious parents, who because of his bleeding tendency found it difficult to assert discipline (similar to the social history of Alexis, the then heir to the Russian throne). The Ekiti Prince has been lost to follow-up.

Another remarkable case is that of a FIX deficient patient, diagnosed in infancy, had sound education and graduated as a

doctor from a Nigerian university. He then proceeded overseas for post-graduate training in haematology. Unfortunately, he fell in the snow and fractured his femur, thereby needing several months of orthopaedic care and factor concentrate infusion in England.

Haemophilia in a Set of Nigerian Twins

Haemophilia in identical twins is a very rare event and only a few anecdotal reports of haemophilia in twins or triplets exist. A set of twins was screened for haemophilia because the mother had given birth previously to a haemophiliac, who had prolonged bleeding post-circumcision on day 8 of life. This index patient later died at 18 years of age. His $FVIII^c$ level was 9%, while the twins had a FVIIIC level of 7% and 8% respectively. The mother had the first twin circumcised in a private hospital at the age of 2 years. The child bled profusely, requiring an emergency admission, blood transfusion and cryoprecipitate infusion until wound healing was complete (2 weeks). The 2nd twin was circumcised under general anaesthesia at the age of 6 years in UCH, with haemostatic support prior, during and after the surgery (Shittu and Shokunbi 2001). Both boys are now 17 years and alive and well.

$FVIII^c$ Yield in Cryoprecipitate prepared at UCH, Ibadan

Cryoprecipitate (cryo), a wet concentrate, remains the mainstay of treatment of haemophilia A in poor-resource countries. The UCH, Ibadan has been producing cryo for nearly four decades and we have usually observed good clinical response to cryo infusion in our FVIII deficient patients. Cryo preparation involves snap-freezing fresh plasma (at -40 to -70°C) within 6 hours of blood collection. The fresh frozen plasma is then thawed slowly in the cold at 2-4°C (Pool and Shannon 1965). This precipitate formed in the cold (hence the name cryoprecipitate) contains on the average, approximately 100iu of $FVIII^c$ per bag of the cryo (usually about 25mls). Other constituents of cryo include vWF, fibrinogen, FXIII and fibronectin.

The $FVIII^c$ level in normal plasma varies widely (Lane 1989). The level increases with age (donors above 45 yrs

have 23.6% more than those below 45 yrs (Coopberg and Teitebaun 1961)). Other factors such as exercise, pregnancy, menstruation, use of contraceptives, blood group A are associated with increased level of FVIIIc (Bidwell 1972; Preston 1964).

Our study showed that the fresh plasma obtained in our donors in UCH contained mean FVIIIc level of 105±24% (i.e. 1.05±0.24iu/ml) and the mean $FVIII^c$ level in the corresponding cryo bag was 366±101% (i.e. 3.59±1.09iu/ml, representing a yield of 69.67±8.93% (Oluokun, Olaniyi and Shokunbi,1995). We concluded that the $FVIII^c$ yield of the cryoprecipitate prepared in UCH compares favourably with previous reports (Pool and Shonnon 1965). We also observed that blood donors with blood group A had 1.50 times the FVIII levels of blood group O donors.

Seroprevalence of HIV Infection in a Cohort of Nigerian Haemophiliacs

At the early phase of the HIV and AIDS pandemic, it was recognized in 1983 that haemophiliacs were at the risk of acquiring HIV through the use of blood products. While recombinant and viral inactivated lyophilized concentrate have been the safest choice of treatment for haemophiliacs in the last two decades in the developed countries, our patients are still receiving wet concentrate (cryoprecipitate) and FFP which, inspite of the screening for HIV, HBV and HCV, can still transmit viral agents.

We screened 15 patients with severe haemophilia A ($FVIII^C$ <1%) over a 24-month period and only one was HIV positive (confirmed by Western Blot). This 24 year old patient had received over 200 bags of cryo in his lifetime (corresponding to about 800 $FVIII^c$ units/year). He has flexion deformity in the left knee. He admitted to having casual sexual partners during the counselling session. He has been lost to follow-up. From this study, we deduced that HIV seroprevalence of 6.7% in haemophiliacs seen in UCH was higher than the national average, of 5.8% at that time (Shokunbi et al. 2004).

For the child with haemophilia, there is hope:

Weep not, my mum
Weep not, my mother
With this cryo, let my doctor remove my pain and your tears,
The unprovoked bleeds shall not be long victorious,
They shall not long posses your happiness, with the advent of my prophylactic concentrate infusion.

Bleed not, child
Bleed not, my son
With this factor concentrate, let the doctor remove your pain,
The relentless bleeds, shall not long be victorious,
They shall not long possess your health, with the advent of gene therapy

Concluding Remarks

At the 28th MWIA (Medical Women's International Association Conference) in Muënster, Germany, July 2010, there were over 180 female Nigerian doctors attending the conference. I was privileged to be one of them. I would like to share with you an observation made by Prof. William Schmitz, Dean of Medical Faculty, University of Muënster:

"Seventy percent of medical students in the University of Muënster are females, but there is the 'leaky pipeline' line effect along the ladder of advancement in professional career as women population drops to 20% of full professors and 32% of associate professors (i.e. Readers)."

To the Glory of God, I was not swept aside by the "leaky pipeline" phenomenon, hence the opportunity offered today to give this inaugural lecture at the University of Ibadan.

To my knowledge, this is the first inaugural lecture on haemophilia in Nigeria, and it is my fervent hope that this lecture will further raise public awareness on inherited bleeding disorders as well as encourage the Government of Nigeria to address the issues of funding and support for genetic disorders in general.

Recommendations

The current status of haemophilia care in various tertiary hospitals in Nigeria, with regards to patient load and type of haemostatic support is shown in table 16. Even though the number of patients per centre appears few, it should be borne in mind that majority of patients with mild haemophilia would probably not get to these tertiary institutions. In my own estimate, the haemophilia population in Nigeria would be about 6,000.

Table 16: Haemophilia in Nigeria: Treatment Centres, Patient Load and Haemostatic Support

Hospital	Number of haemophiliacs		Replacement therapy			
	A	B	WB	FFP	Cryo	rFVIII
UMTH Maiguguri	15	0	Yes	Yes	Yes	Yes*
AKTH Kano	10	0	Yes	Yes	Yes	Yes*
ABUTH Zaria			Yes	Yes	Yes	Yes*
UITH Ilorin	1	0	Yes	Yes	No	No
UCH Ibadan	92	10	Yes	Yes	Yes	No
OAUTH Ife	10	0	Yes	Yes	No	No
UBTH Benin	5	0	Yes	Yes	No	No
UNTH Enugu	5	0	Yes	Yes (from Lagos)	Yes (from Lagos)	No
UPTH Port Harcourt	1	0	Yes	Yes	Yes	No
FMC Gombe	6	0	Yes	No	No	No

*limited donation from Canada;
WB – whole blood;
FFP – fresh frozen plasma;
Cryo – cryoprecipitate.
rFVIII – recombinant Factor VIII concentrate;

The Government should support these treatment centres by designating some as Haemophilia Treatment Centres. I would suggest (at least for now) 6 regional Haemophilia Care Centres so as to encourage research and prompt treatment with factor concentrates.

Home therapy should also be encouraged for patients who can be supported by their family physicians. Family studies should also be done to identify obligatory carriers and conduct appropriate genetic counselling.

The Government needs to be self-sufficient in achieving greater blood safety and provision of factor concentrates, bearing in mind that haemophiliacs are obligate recipients of blood products. Recombinant factor concentrates are currently very expensive and majority of our patients cannot afford it.

In the interim, greater voluntary blood donor drive should be undertaken and plasma-derived viral inactivated manufacturing plants for factor concentrates should be established.

Acknowledgements

My father Chief Joseph Adeoba Olaofe, the Baba Ijo of St. Andrews Church Are-Ekiti was the crown prince of the Olaofe Royal family of Are-Ekiti, a grandson of the late Alare (Oba) and a grandson of the daughter of Ewi of Ado-Ekiti. A most loving father, Chief Adeoba was passionate about education of the girl child and would not accept the pressure mounted on him then by his friends, who believed that no matter how educated a girl is, she would still end up in the kitchen as a cook. All my brothers and sisters, besides having a University undergraduate education, have post-graduate degrees as well (except one). Three of us became Professors in relatively rare fields:

Professor Gabriel Oluremi Olaofe: Mathematics
Professor Femi Olaofe: Chemistry
Professor Wuraola Shokunbi (nee Olaofe): Haematology

My mother, Chief Racheal Yelola Olaofe (the Iya Ijo of St. Andrews Church Are-Ekiti), was the granddaughter of the Oloye of Oye-Ekiti Mama was full of wisdom. She was gentle and compassionate, long-suffering, very peaceful and she was an eternal optimist. To ensure we had the best education, she sold her gold possessions and material goods. Even with the passing of time, your sweet memory will never fade in our hearts.

Gabriel Oluremi Olaofe (1937-1994), Professor of Mathematics of this great institution fought for truth and justice throughout his years as a university teacher. I was very fortunate to have lived with him and his wife, Mrs. Katherine Olaofe during my teenage years and into adulthood. The archives of this University would reveal the numerous memoranda he wrote in quest for justice and fairplay.

When I later joined the teaching staff of the University of Ibadan, I began to understand fully why my late brother kept on with his campaign against injustice. In the book *The song of the Bird* by Anthony De Mello (2009), the author wrote:

> "I could hardly believe my eyes when I saw the name of the shop: THE TRUTH SHOP. The salesgirl was very polite: what type of truth did I wish to purchase, partial or whole? The whole truth of course. No deception for me, no defences, no rationalizations, I wanted my truth plain, and unadulterated; she waved me to another side of the store. The salesman there pointed to the price tag. "The price is very high, sir he said, what is it? I asked, determined to get the whole truth, no matter what it cost, "your security, sir" he answered. I came away with a heavy heart, I still need the safety of my unquestioned beliefs"

I wished my brother, Prof. Gabriel Oluwaremilekun Olaofe was still alive today.

Mrs. Kathie Olaofe nurtured me as if I were her daughter. In my teenage years I wondered for quite a while how someone can leave the greener pastures of England and would choose to live in this country. In "Weep not, child", Ngugi Wa Thiong 'O wrote:

> "I wonder why he left England, the home of learning, and came here. ' He must, be foolish. I don't know. You cannot understand a white man"

Later in life, I came to realize that when you love someone, nothing is too big to sacrifice.

I was born in a small town called Are-Ekiti which even in an enlarged map of Nigeria, would not be listed. However, having not been born in a big city, my Good Lord chose to send me to a large family from 3 royal descents.

An inaugural lecture is meant to be a celebration but I believe those who should be celebrated are the people who made enormous sacrifice so that I could attain the peak of my career. In this regard, I thank with all my heart my brothers and sisters and my cousins from the three royal families of Are-Ekiti, Ado-Ekiti and Oye-Ekiti. In particular the following people are well appreciated: Chief Peter Akinwande (late Building Contractor), Engineer Frederick Olaofe (late, former V.I.O. Old Western Region), Mr. & Mrs. Adegoke Olaofe, Chief & Mrs. Peter Olaofe (retired school principal), Mrs. Yetunde Akinsete (Retired Librarian), Reverend and Mrs. Timothy Olaofe, Mr. & Mrs. Adeleye Olaofe (accountant), Rev. & Jide Ajayi and his wife Mrs. Victoria Yemisi Olaofe, High Chief B.S.O. Olaofe (late) and Pastor Titi Olaofe. Prof. & Mrs. I.O. Orubuloye, Madam Adetuberu (Mama Eleja), all my nieces and nephews (Kemi, Jide, Foluke, Femi, Funke and others too numerous to list, most of whom are engineers, computer scientists or lawyers) - I appreciate you all. I salute my teachers particularly Prof. Niyi Osundare, Prof. G.J.F. Esan (current Provost, College of Medicine, University of Ado-Ekiti), Prof. E.M. Essien, Prof. Aba Sagoe, Prof. Ibironke Alarisete, Prof. C.K.O. Williams, Prof. T.A. Junaid, and Dr. O.M. Jeje. I am indebted to Prof. Martin J. Inwood, and all the staff of the Department of Heamatology, St Joseph's Hospital London, Ontario Canada (as well as the staff of the South Western Ontario Regional Haemophilia Centre, Technologists in Haematology Laboratory, particularly Bernice in St. Joseph's Hospital, Okeefe, and Paul Harris.

My immense gratitude goes to the Dean of FBMS, Prof. E.O. Farombi, all past Deans and Sub- Deans, in addition to all the staff of the Faculty.

I am indebted to Prof. O.O. Akinkugbe, Prof. O.O.O. Oyediran, Prof. O. Ajayi, Prof. Akande, Prof. Ladipo, Prof. Gbola Ajao and Dr. (Mrs.) Bimpe Okunade, for their constant support.

I thank Prof. Bankole Oke, Prof. Akibo Adesomoju, and Prof. Ekundayo. I am grateful to Prof. & Mrs. Kujore and all the friends of my late brother, Prof. Remi Olaofe.

My gratitude to all members of AGRAA (Alalubosa GRA Association) for their constant support to our family and to all my prayer partners, Mrs. Moji Shittu, Prof. Gbemi Oke, Mrs. Oye Gureje, Mrs. Bose Omololu and others.

I sincerely appreciate the co-operation given me by my colleagues, Prof. Yetunde Aken'Ova, Prof. Philip Olatunji, Prof. M.A. Durosinmi (Past President, NSHBT) Dr. Taiwo Kotila, Dr. Titi Akingbola, Dr. Foluke Fashola and Dr. J.A. Olaniyi. I appreciate the intellectual challenge from Dr. A. Raji, Dr. Tayo Fakunle, Dr. E.U. Eze, Dr. Omolade Awodu, (Benin). I am grateful to Dr. Muktar (Zaria) Dr. Aisha Mamman (Zaria), Dr. U. Abjah (Maiduguri), Prof. C. Nwauche (Port Harcourt), for providing information on haemophiliac population under their care.

My experience with my past postgraduate students has greatly made the statement by Paolo Freore (in Pedagogy of the Oppressed) very meaningful to me; "I teach because I search". In this regard I thank my current group of postgraduate students Dr. Kapoona Eteng, (Chief Resident), Dr. Tola Ojo, Dr. Yuguda, Dr. Fowodu, Dr Olutogun, Dr. Busairi, Dr. Ogundeji, Dr. Oke, Dr. Shonde Adebola and a host of Rotating Residents from Pathology, Chemical Pathology, Micro-biology, and Internal Medicine. For Laboratory support in coagulation, I thank Mr I. Saliu, Mr. Olomu, (Chief Labora-tory Scientist), Miss Kemi Abraham, Mr. S.A. Oladipo, Mr. Akpan and all the laboratory scientists in the Department. I appreciate the research collaboration with Dr. A.J. Ajuwon (on Peer Education in HIV and AIDS prevention among U.I Students) and the project staff. I am immensely grateful to Prof. Tamashiro and his team for the training on HIV prevention at Hokkaido University, Japan.

I thank the current head of Surgery Department, Prof. V.O. Adegboye, as well as Prof. Ade Malomo, Prof Shittu, Dr. Adeleye, Dr. Adeolu, Dr. Bade Omololu and all our colleagues in Surgery Department. I cannot forget the support of Prof. Yombo Bolarinwa, Prof. Gbola Ajao, Prof. Femi Ogunbiyi and Dr. Bola Ogunbiyi, and Engr. Osiberu and his group.

My gratitude to Rev. Fr. Wilfred Chiwetalu, Rev. Fr. Alfred, Rev. Fr. Henry (and all the Redemptorists community), Rev. Fr. Joseph Akanbi (St. Lukes Chapel UCH) and the congregation for their spiritual support.

My appreciation to all my classmates in the MBBS class of 1978 particularly Prof. I.F. Adewole, (the Vice-Chancellor), Prof. Segun Akinyinka (the Provost), Prof. Tunde Ajaiyeoba (Dean Clinical Sciences), Prof J.U. Ohaeri, Prof. Yemi Akanji, Prof. Kayode Akinbami, Dr Tayo Denton, to mention a few. I thank all Christ's School Alumni particularly Dr. Kayode Obembe, Mrs. Moji Osonubi, Dr. Niyi Adenipekun and all the 67/71-73 set. I appreciate the technical support from Mrs. Bunmi Ojelade, Miss I.F Francis, Mrs. Dunni Popoola, Mr Mohammed Buseri, Miss Lola Allo, Mrs. Hope Onwubiko, and Miss Deyo Adebiyi. We are indebted to Mr I.M Silva for the artwork within this presentation.

Prof. M.T. Shokunbi (Tayo mi), I am lost for words in attempting to describe what you mean to me. Trenchard will always hold fond memories for the two of us—we wrote some of our examinations here together, had our graduation ceremony same day here and had our wedding reception here too in 1979. I can only pray to God; "Please be merciful to us and grant that we may grow old together" Amen (Tobit 8:8). My sincere gratitude to all members of the Shokunbi family, particularly the head of the family Alhaji and Alhaja Shokunbi. Our late mother Madam Aduke Shokunbi was a highly devoted mother. I thank you for your devotion to the care of the children while you were alive.

As a laboratory Physician, I have always enjoyed the Oscillation in my work-schedule between Clinical Haematology and Laboratory Heamatology i.e. from bed-side to

bench work, and vice versa. Clinical care will only continue to improve with sound Basic Science research, in line with Research and Development.

My children Tiwatayo (Mechanical Engineer), Aanuoluwapo (Structural Engineer) and Atoke (Chemical Engineer), I thank you for your patience, love, understanding, prayers, pampering and perseverance. The educational journey has been long, but having you made it all worthwhile. May you see your children's children Amen.

I thank God for the opportunity of education, for journey mercies over the years and giving me the enablement to moderate this rich educational journey so far.

I would recommend this poem by Ngugi (1965) to every Nigerian child particularly the girl-child:

Father,
I do not want a spear
I do not want a shield
I want the shield and spear of learning

Father,
The war of shields and spears
Is now ended
What is left?
The battle of wits,
The battle of the mind.
I, we, all want to learn

I stand before you and openly declare that God has been merciful to me and my loved ones. Praise, honour, glory and adoration to our Lord Jesus Christ. Those He chooses, He anoints.

Thank you and God bless you all.

Glossary of Terms

1. Factor VIII^{C} (Coagulant activity) – the coagulant activity of factor VIII as determined by the ability to correct the clotting defect of a haemophilia A plasma. This activity is specifically neutralized by homologous antibody occurring in some patients with haemophilia A (WHO 1977).

2. Factor VIII R.ag (factor VIII-related antigen) – the antigen that can be identified by specific precipitating antibodies raised in animals against factor VIII (WHO 1977).

3. Factor VIII R:RCF (factor VILL- related ristocetin cofactor) – the activity associated with factor VIII that is needed for aggregation by ristocetin of normal washed or fixed platelets.

4. Obligatory haemophilia carriers are women
   (i) whose fathers are haemophiliacs.
   (ii) who have had more than one heamophilic son at separate births.
   (iii) with an affected son and a well documented haemophilic relative on the material side of the family (WHO 1977).

5. Possible haemophlia carriers are –
   women who have a haemophilic relative on the maternal side.
   women, who without a family history of haemophilia, have given birth to a haemophilic son (WHO 1977).

6. DDAVP (1-desamino- 8 – D- arginine vasopressin) is a synthetic analogue of vasopressin. DDAVP induces a dose-dependent increase in all the FVIII related activities (Kobayashi 1979). It is currently being used in the management of mild haemophilia A and in some patients with von Willebrand's disease. It may be administered intranasally, subcutaneously or intravenously.

7. T-cell subsets. The various stages of T-cell development is under the influence of the thymus and is characterized by changes in their surface antigens. These changes result in segregation of T-cells into two major subsets, helper/inducer and suppressor/cytotoxic T-cells. Several systems of nomenclature are available depending on the source of the monoclonal antibodies used in identification of the subsets e.g. the OK-T series. The T-helper cells (or T4 subsets since it is identified by OKT4 monoclonal antibody) augment B-cell immune response while suppressor cells (T8 subset) suppress an immune response. Thus a normal antibody response cannot be obtained in the absence of the regulatory roles of T4 and T8 subsets. OKT3 identifies a common T-cell marker.

8. Natural killer (NK) cells are a sub-population of lymphocytes with the spontaneous ability to lyse a wide variety of tumour cells. They are non-phagocytic but they share some markers with macrophages and T-cells. Their functions include resistance against metastatic spread of tumours, natutal resistance against infections by some microbial agents and against bone marrow transplants. They possibly contribute to the development of certain diseases including some cases of aplastic anaemia, GVH (graft- versus-host) disease and atopic dermatitis.

Bibliography

Abjah Uma, Ocheni, S., Raji, A.A. and Shokunbi, W.A. (2004) Factors leading to flexion deformity in the Nigreria Haemophiliac-A Case Report. *Borno Medical Journal.* **1** (1):36-38.

Anwar MS, Munawar, F. and Anwar, Q. (2010) Circumcision: A religious obligation or the crulest of cuts? *British Journal General Practice*: Jan 59-61.

Aronova – Tiuntseva and Herreid Freeman C. Haemophilia: "The Royal Disease" *http://www.sciencescases.org/hemo/hemo/asp 20.01.11.*

Ajuwon, A.J., Brieger, W.R., Oladepo, O. and Adeniyi, J.D. (1995) Indigious surgical practices in rural Southwestern Nigeria: Implications for disease prevention. Health Promotion Research **10**: 379 – 384.

Biggs, R., Douglas, A.S., Macfarlane, R.G., Dacie, J.V., Pitney, W.R., Merskey, C. and O'Brien, J.R. (1952) Christmas disease: a condition previously mistaken for haemophilia. *Brit Med J* **2**: 1378.

Birch, C.L.A.F (1937) Haemophilia. Clinical and genetic Aspects. Urbana. University of Illinosis.

Bithel, T.C., Pizzaro, A. and Macdiarmid, W.D. (1970) Variant of factor IX deficiency in females with 45X Turner's syndrome. *Blood* **36**: 169-179.

Boyer, S.H. and Graham, J.B. (1965) Linkage between the X-chromosome loci for glucose-6-phosphate dehydrogenase electrophoretic variation and haemophilia A. *American J Human Genetics* **17**: 320-324.

Bulloch, W. and Fildes, P. (1911) Treasury of Human Inheritance, Parts V and VI, Section XIVa, Haemophilia Francis Galton Laboratory for National Eugenics, University of London (UCH), London. Dulau and Co. Ltd., 37 Soho Square, London.

Christie, D.A. and Tansey, E.M. (editors) (1998) Haemophilia: Recent History of Clinical Management. Wellcome Witness to Twentieth Century Medicine, vol. 4. The Wellcome Trust, London.

Cohn, E.J. (1941) Properties and functions of plasma proteins with consideration of methods for their separation and purification. *Chemical Reviews* **28**: 395-417.

Essien, E.M. (1974) Studies on the haemophilic diseases in Ibadan, Nigeria – with a note on the prevalence of haemophilia in Ibarapa District. MD Thesis, University of London, 164.

Fakunle, E.E., Shittu, O.B., Shokunbi, W.A. (2007) Incidence of factor FVIIIC deficiency in live male infants undergoing circumcision in South West, Nigeria. *Haemophilia* **13**, 567-569.

Graham, J.B., Barrow, E.S. and Elston, C.R. (1975) Lyonization haemophilia: A cause of error in direct detection of heterozygous carriers. *New York Acad of Sciences* **240**: 141-146.

Harrison, J.F. (1964) Haemophilia, Christmas desease and Xg blood groups. Observations based on the haemophiliacs of Birmigham. *Br J Haematol* **10**: 115-121.

Hopff, (1828) Cited by Bulloch and Fildes 1911.

Ikkala, E., Helske, T., Myllyla, H.R., Nevanlinna, H.R., Pitkanen, P. and Rassi, V. (1982) Changes in the life expectancy of patients with severe hemophilia A in Finland in 1930-1979. *Br J Haematol* **52**: 7-12.

Ingram, G.I.C. (1976) The history of haemophilia. *J. Clinical Pathology*. **29**: 3-13.

Jeffery, S.S., Paula, H.B.B., Michael, J.S., Irwin, Marb B. (2010) A study of variation in the reported haemophila A prvalencearoung the world. Haemophilia **16**: 20-32.

Kavakli, K., Alerdof, L.M. (1998) Circumcision and Haemophilia: A perspective. Haemophilia Jan 4 (1) 1: 1-3.

Kernoff, P. B., Rizza, C. R. (1973) Factor-VIII-related antigen in female haemophilia. *Lancet* **ii**: 734.

Kerr, C.B. (1963) The fortunes of haemophiliacs in the nineteenth century. *Med History* **7**: 359-370.

Kessler, C.M. (2008) Advances in the treatment of Haemohilia. *Clinical Advances in Haemotherapy and Oncology*.**6** (3): 184 – 187.

Konig, (1890) Cited by7 Bulloch and Fildes (1911). Kreiss, J.K., Lawrence, D.N., Kasper, K.C., Goldstien, A.L., Naylor, P.H., Mclane, M.F., Lee, T. and Essex, M. Antibody to human T-cell leukaemia virus membrane antigens, Beta 2-microglobulin levels and Thymosin Alpha-1 levels in haemophiliacs and their spouses. Annals of Int Med 1984; 100: 178-182.

Lang, S. (1840) Haemorrhagic diathesis. Successful transfusion of blood. *Lancet* **i**: 185-188.

Levine, P.H. (1974) Efficacy of self therapy in haemophilia. *N Eng J Med* **291**: 1381-1384.

Lyon, A.S. and Petrucelli, J. (1978) Medicine: an illustrated history. Abrams HN Inc. New York 432-436.

Lyon, M. (1962) Sex chromatin and gene action in the mammalian X-chromosome. *Am J of Human Genetics*. **14**: 135-148.

Macfarlane, R.G., Barnett, B. (1934) On the relative potency of certain snake-venoms to coagulate haemophilic blood. *Proceedings of the Zoological Society* **4**: 977-978.

Macfarlane, R.G., Barnett, B. (1934) The haemostatic possibilities of snake venom. *Lancet* **ii**: 985-987.

Merskey, C., Macfarlane, R.G. (1951) Female carrier of haemophilia: a clinical and laboratory study. *Lancet* **1**: 487-490.

Merskey, C. (1950) The laboratory diagnosis of haemophilia. *Journal of Clinical Pathology* **3**: 301-320.

Merskey, C. (1951) Haemophilia associated with normal coagulation time. *British medical journal* **1**(4712): 906-912.

Miyoshi et al. (1978) Cited by Bloom AL and Thomas DP. Haemostasis and Thrombosis. Edinburgh: Churchill Livingstone 1981; 332-334.

Nasse, (1820) Cited by Bulloch and Fildes (1911).

Ngugi, W.T. (1964) Weep not Child, Heinemann Educational Books Ltd. New Hamphshire USA.

Ngugi, W.T. (1965) The River between. Heinemann Educational Books, Gaborone, Bostwana.

Olatunji, P.O., Okpala I.E. and Shokunbi W.A. (June 1990). ABO blood groups and haemophilia A. Nigeria Medical Association Annual Conference Booklet. Page 4.

Oluokun, A.O., Olaniyi, J.A. and Shokunbi, W.A. (2004) Factor VIII coagulant yield of the cryoprecipitate prepared at the University College Hospital Ibadan, Nigeria. Archives of Ibadan. Medicine, **4**:26-29.

Otto, 1803. Cited by Bulloch and Fildes (1911)

Patek, A.J., Taylor, F.H.L. (1937) Haemophilia II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of haemophilic blood. *Journal of Clinical Investigation* **16**: 113-124.

Patek, A.J. and Stetson, R.P. (1936) Cited by Ingram (1975).

Pitney, W.R. and Arnold, B.J. (1959) Plasma antihemophilic factor (AHF) concentrations in families of patients with heamorrhagic states. *Br J Haematol* **5**: 184 – 188.

Polakova, H., Kadasi, L., Filova, A. (1998) FVIII Gene inversions in Haemophilia A patients of Slovakia. Human Heredity **48**: 34-37.

Pool, J.G. and Shannon, A.E. (1965) Production of antihaemophilic globulin in a closed-bag system. *N Eng J Med* **273**: 141 – 147.

Pool, J.G., Hershgold, E.J. and Pappenhagen, A.R. (1964) High potency Antihaemophilic factor concentrate prepared from cryoglobulin precipitate. Nature **203**: 312.

Quick, A.J., Stanley-Brown, M., Bancroft, F.W. (1935) A study of the coagulation defect in hemophilia and in jaundice. *American Journal of the Medical Sciences* **190**: 501–511.
Quick, A.J. (1943) On constitution of prothrombin. *American Journal of Physiology* **140**: 212–220.
Quick, A.J. (1941) The diagnosis haemophilia. *Am J Ned Sci* 469-471.
Quick, A.J. (1935) The Prothrombin in haemophilia and in Obstructive jaundice. *J Biol Chemistry* **109**: 73-74.
Rabiner, S.F. and Tefler (1970) Transfusions for patients with haemophilia A. *N Eng J Med* **283**:1011-1015.
Rizza, C.R. (1961) Effect of exercise on antihaemophilic globulin in human blood. *Journal of Physiology* **156**: 128-135.
Rizza, C.R. (1975) The first patient to receive factor IX concentrate in the UK: a recollection. *Haemophilia* **1**: 201-212.
Rizza, C., Spooner, R.J.D. (1977) Home treatment of haemophilia and Christmas disease: five years' experience. *British Journal of Haematology* **37**: 53–66.
Rizza, C., Spooner, R.J.D. (1983) Treatment o f haemophilia and related disorders in Britain and Northern Ireland during 1976–80; report on behalf of the directors of haemophilia centres in the United Kingdom. *British Medical Journal* **286**: 929–933.
Rosner, F. (1969) Haemophilia in the Talmud and Rabbinic writings *Annals of Int Med* **70**: 833-837.
Shittu, O.B. and Shokunbi, W.A. (2001) Circumcision inn Haemophiliac. The Nigerian Experience: Haemophilia **7**:534-536.
Shokunbi, W.A. and Inwood, M.J. (1987) Lymphocyte Mitogenic response in Obligatory Carriers of Haemophilia. IX Congress of the International Society of Haematology (European and African Division): Abstract No. 68 Page 77.
Shokunbi, W.A. and Inwood, M.J. (1987) Low Natural–Killer Cell Counts in obligatory carrriers of Haemophilia. IX Congress of the International Society of Haematology (European and African Division): Abstract No. 81 Page 90.
Shokunbi, W.A. and O' keefe, B., Schauss, M.R. (1985) effect of evacuated sample tubes on of Haemostasis and Thrombosis. Canadian Journal of Medical Technology-47,171, 176.
Shokunbi, W.A. (1985) Lymphocyte function tests in obligatory carriers for Haemophilia and their haemophilic relatives-relationship of sex-linked bleeding disorders to host defence and to the Acquired Immune Deficiency Syndrome. FMC Path-November.

Shokunbi, W.A. (1993) Haemophilia in common Haematological Problems in Nigeria ed. Akinyanju O.O. The Nigeria Family Practice, 3:53-56.

Shokunbi, W.A., Aken'Ova, Y.A., Adewoye, H., Sanusi, A.A. and Essien, E.M. (1997) Life-threatening sublingual and cervical haemorrhage in haemophilia in Ibadan, Nigeria. *Nigeria Quarterly Journal of Hospital Medicine*; 7: 101-103.

Shokunbi, W.A., O'keefe, B. and Schauss, M.R. (1989) The effects of varying the amount of blood added to a constant volume of 3.2% sodium citrate ofr global tests Haemostasis and thrombosis. Society of Haematology (European and African Division): Abstract No. 121 Page 136.

Shokunbi, W.A., Paul Harris and Sam Thompson, variability in the amount of blood drawn into evacuated tubes (1989) IX Congress of the International Society of Haematology (European and African Division): Abstract No. 1231 Page 136.

Shokunbi, W.A., Saliu, I. and Essien, E.M. (December 1993) Incidence of antibodies to HIV 2 gene Product in Seropositive cas4es seen in Ibadan, Nigeria. 1st National Conference onn human retroviruses and related infections: Abstracts No. 627.

Shokunbi, W.A., Shittu, O.S., Koledoye, V.O. and Ajuwon, A.J. (2002) a 35-year Retrospective Review of Circumcision in Nigerian Haemophiliacs. Absract Book of the XVIth meeting of the International Society of Haematology of the Egyptian Journal of Haematology (supp); 27: pg 52.

Shokunbi, W.A. and Inwood M.J. (1996) Lymphocyte Mitogenic Response in Obligatory Carriersof Haemophilia. Nigerian Postgraduate Medical Journal3:1-4.

Shokunbi, W.A. and Essien, E.M. (1991) The treatment of haemostatc disorders in: Sagoe A.S. Guidelines on appropriate use of blood products in Nigeria Federal Ministry of Health, 32-38.

Stevens, R.F. (1999) The history of Haemophilia in the Royal families of Europe. *British Journal of Haematology*. 105, 25 – 32.

Stirling, Y., Woolf, L., North, W.R.S., Seghatchian, M.J., Meade, T.W.: (1984) Haemostasis in normal pregnancy. Thrombosis and Haemostasis **52**:176-182.

Strumia, M.M. and McGraw, J.J. Jr. (1941) The development of plasma Preparations for transfusion. *Annals of Intern Med* **15**: 80-84.

Tuddenham, E.G., Lane, R.S., Rotblat, F., Johnson, A.J., Snape, T.J., Middleton, S., Kernoff, P.B. (1982) Response to infusions of polyelectrolyte fractionated human factor VIII concentrate in human haemophilia A and von Willebrand's disease. *British Journal of Haematology* **52**: 259–267.

Tuddenham, E.G., Trabold, N.C., Collins, J.A., Hoyer, L.W. (1979) The properties of factor VIII coagulant activity proposed by immunoadsorbant chromatography. *Journal of Laboratory and Clinical Medicine* **93**: 40–53.

Tuddenham, E.G.D., Goodall, A. (1985) Monoclonal antibodies and coagulation. In: Hoffbrand, A.V., ed. Recent Advances in Haematology (4). Edingburgh: Churchill Livingstone 285-307.

Whitaker, D.L., Copeland, D.L. and Graham, J.B. (1962) Linkage of colour Blindness to haemophilias A and B. *American J Human Genetics* **14**: 149-158.

Williams, C.K.O., Alabi, G.O., Junaid, T.A., Saxinger, C., Gallo, R.C., Blaney, D.W., Blattner, W.A. and Greaves, M.F. (1984) Human T-cell leukemia virus associated lymphoproliferative disease: a report of two cases in Nigeria. *Br Med J* **288**: 1495-1496.

Williams, W.J., Beutler, E., Erslev, A.J. and Lichtman, M.A. (1983) Haematology 3rd ed. New York: McGraw-Hill 1381-1392.

Wintrobe, M.M., Lee, G.R., Boggs, D.R., Bithell, T.C., Foerster, J, Athen, J.W. and Lukens, J.N. (1981) Clinical Hematology 8th ed. Philadelphia: Lea and Ferbinger 1160-1169.

Wright, I.S. (1962) The nomenclature of blood clotting factors. Thrombos Diathes Haemorrh (Stuttg.) 7: 381-388.

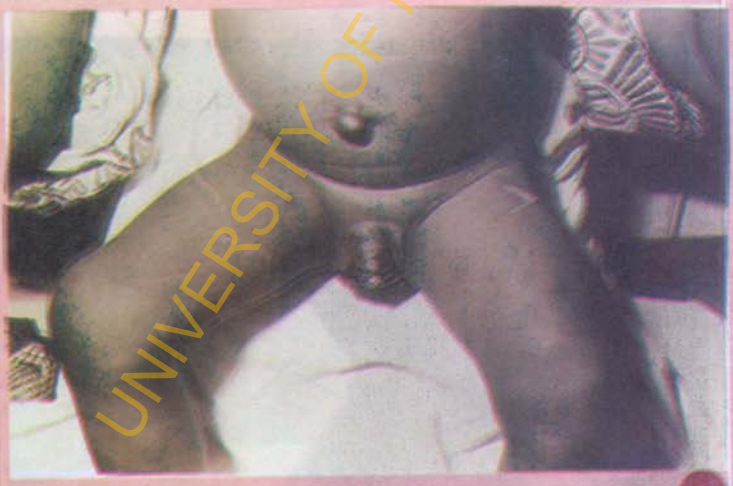
Young, N.S., Gerson, S.L. and High, K.A. pg 817. Mosby 2006.

APPENDIX

"SCENE DE LA CIRCUMCISION DE JESUS": A SCULPTURE IN THE CATHEDRAL OF CHARTES

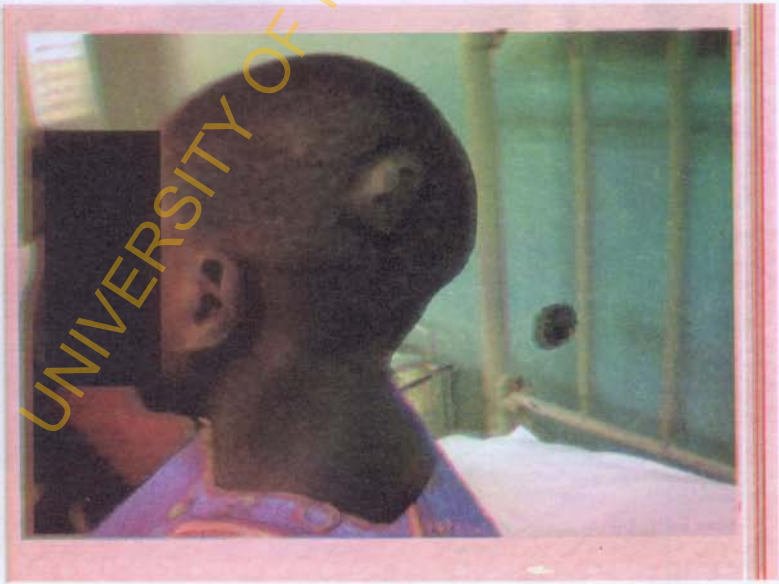
IDENTICAL TWIN HAEMOPHILIACS, TAKEN AT AGE 14 IN SS1

- One of identical twin haemophiliac (Factor VIII^{C} level 7 %), post-circumcision. The second twin was circumcised in a private clinic at age 2 years and had severe post-circumcision bleeding necessitating admission, haemostatic support, and red cell transfusion. The private practioner was therefore unable to proceed with the circumcision of this patient, and was then referred to UCH. The patient had cryoprecipitate infusion at the rate of 200 iu of Factor VIII per 10 kg every 12 hours, 24 hours before circumcision and for 10 days post-circumcision. There was complete wound healing by day 14 of the surgery.
- The mother of the twins has had two older sons (2 previous marriages) with haemophilia A with Factor VIII level 9 %. Her factor level is 15 % consistent with obligatory carrier status.

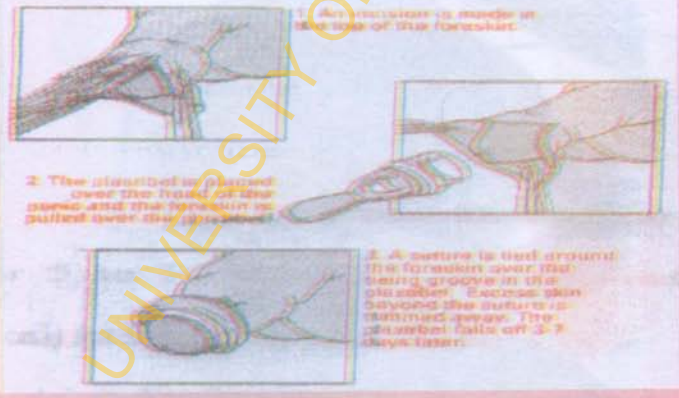


6 YEAR-OLD (IDENTICAL) TWIN HAEMOPHILIAC

- 14 years old haemophiliac presented with pain and swelling in the left parieto-occipital region following corporal punishment by a school teacher. The patient at the start of school age had a medical report indicating the status of his inherited bleeding disorder. Note the haematoma and the overlying scabs in the left parieto-occipital region. He received cryo-precipitate on out-patient basis for a week and the swelling resolved.
- 3 years later, he was brought into accident and emergency (A&E) in a coma following a scuffle with a school mate. A diagnosis of intra-cranial haemorrhage was made. He died within 24 hours of admission.
- One of the twin haemophiliacs shown previously.



HOLLISTER PLASTIBELL:
(CIRCUMCISION INSTRUMENT)

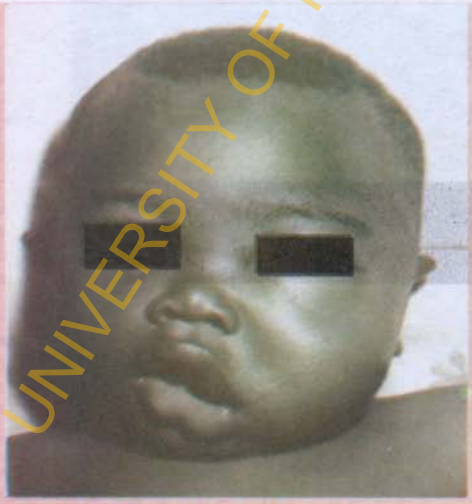


CIRCUMCISION PROCEDURE (ONE OF OUR HAEMOPHILIACS DEVELOPED A HAEMATOMA WHEN CIRCUMCISED WITH THIS PROCEDURE)

- A 9 month old boy with Factor VIII level < 1% and a swelling of the left cheek preceded by mild trauma. He had post-circumcision bleeding. He responded to cryo-precipitate therapy and the haematoma resolved completely after 10 days of haemostatic support.

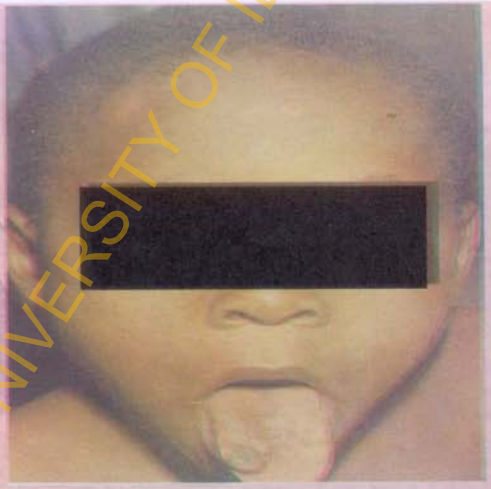
SUBCUTANEOUS BLEED IN THE LEFT CHEEK FOLLOWING MILD TRAUMA

- 7 month old baby with haemophilia A Factor $VIII^C$ level < 1 % with spontaneous swelling (no preceding trauma) on the face (left). Examination revealed peri-orbital swelling and swelling of the left cheek with loss of left naso-labial fold. Diagnosis was major haemorrhage peri-orbital region and left maxillary region. The haematoma resolved completely after 7 days treatment with cryo-precipitate.



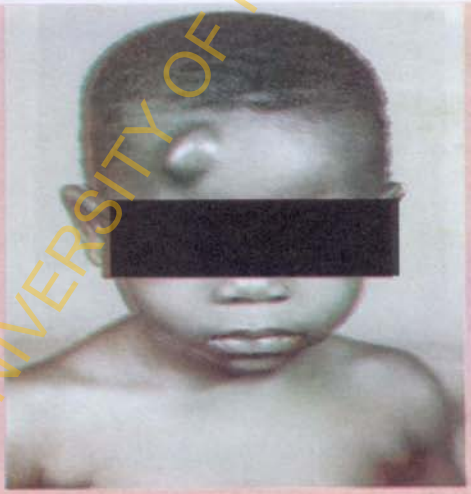
7 MONTH OLD BABY WITH SUBCUTANEOUS BLEED; LEFT PERIORBITAL AND CHEEK

- 5 year-old haemophilia A patient Factor VII level of 7 % who presented with severe bleeding from the tongue 2 days after injury from a fish bone. He was severely pale (note the pallor of the tongue). A haemorrahgic bullae measuring 2x2 cm was seen on the anterior surface of the tongue. He responded to cryo-precipitate given for 2 weeks before complete healing was achieved. He was also given packed red cells to correct the anaemia followed by oral iron therapy. Patient is now 20 years old and in a tertiary institution.



5 YEAR OLD BOY HEMOPHILIA A WITH HAEMORRAGHIC BULLAE ON THE TONGUE

- 5 year old boy with severe haemophilia A and swelling on the forehead after mild trauma to the head during a fall. Examination showed a non-tender fluctuant mass of about 6 x 4 cm in the frontal region (right). The haematoma resolved completely within 1 week of cryoprecipitate therapy.

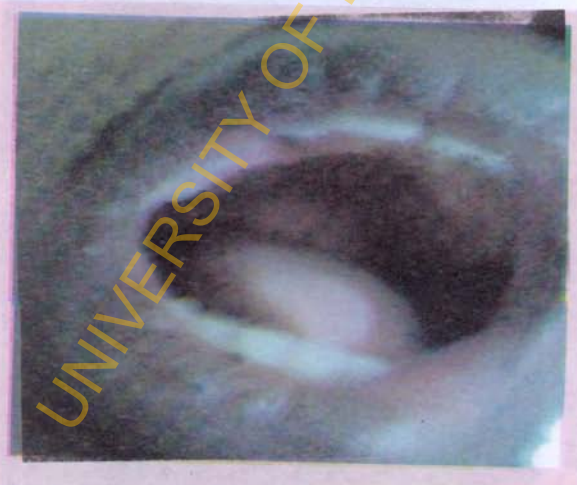


5 YEAR OLD HAEMOPHILIA A WITH A HAEMATOMA RIGHT FRONTAL REGION

- 12 year old haemophilia A patient factor level 1 % with swelling right flank preceded by minor trauma. There was a huge haematoma of about 20 x 18 cm. He responded to cryo-precipitate therapy and the swelling resolved completely with 12 days.

12 YEAR OLD HAEMOPHILIAC (A PRINCE), FACTOR VIII <1% AND HAEMATOMA LEFT FLANK

P: Patient presenting with severe toothache associated with mild bleeding (occasionally) from the tooth socket of 4 weeks duration. The dental surgeon had advised extraction of the lower right first and second molars in view of the caries and pulpal involvement. He was therefore admitted and transfused with cryoprecipitate 24 hours preoperation. He also received cryoprecipitate intra-operation. Post-op, he developed a huge haematoma over the two empty sockets as shown by the arrow. In addition to the haemostatic support, he received DDAVP (Des-amino D-arginine vasopressin), anti-fibrinolytic agents, haematinix, and broad spectrum antibiotics. The bleeding, in spite of all these measures, became troublesome on day 6 because the patient chose to chew cola nut against medical advice. The dose of the haemostatic support had to be stepped up. The 2 sockets eventually healed after 3 weeks wet factor VIII concentrate infusion.



SEVERE HAEMOPHILIA A PATIENT (A UNIVERSITY UNDERGRADUATE) WITH HAEMATOMA AT THE OPEN SOCKET POST TOOTH EXTRACTION.

- 19-year old haemophiliac with a 2-day history of trauma to the right handpalmar surface following a fall while riding an "okada". The laceration was sutured in private clinic (notice the silk sutures just above the right wrist), but patient continued to bleed.
- He was admitted and transfused with cryo-precipitate or FFP when the former was not available and the response was satisfactory.

19 YEAR OLD HAEMOPHILIAC PATIENT WITH LACERATION ON THE RIGHT PALM FOLLOWING A FALL WHILE RIDING AN "OKADA".

SAME HAND, DAY 10

- 17 year old severe haemophiliac factor level < 1% with a crush injury to the left foot 3 days prior to presentation. He was seen in a private clinic where the left big toe was amputated , but patient continued to bleed and was then referred to UCH. Notice the amputated left big toe with profuse bleeding and extensive laceration at the base of the toe.

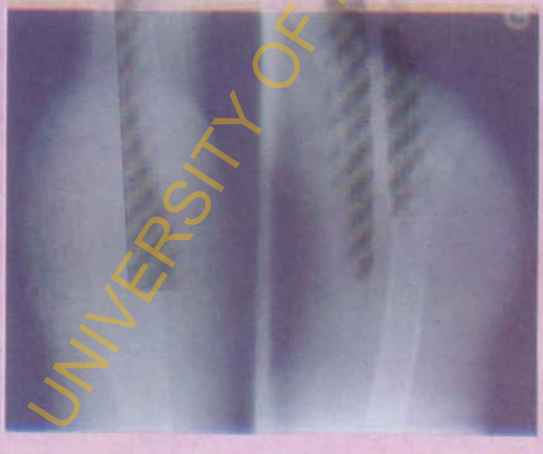
HAEMOPHILIA A PATIENT WITH CRUSH INJURY TO THE LEFT FOOT 3 DAYS PRIOR TO PRESENTATION

SAME HAEMOPHILIAA PATIENT ABOVE WITH IMPROVED WOUND HEALING FOLLOWING HAEMOSTATIC SUPPORT, ANTIBIOTICS AND WOUND DRESSING

- 19-year old known haemophilia A patient Factor VIII level < 1 % with acute haemathrosis left knee which resolved gradually with infusion of cryoprecipate during 2 weeks of admission. The patient had complained of limitation of movement, pain, and persistent swelling of the right knee. He also had in the same left knee, mild flexion deformity and chronic synovitis (see knee X-ray on next page). He had had repeated haemathroses on the same knee since childhood.

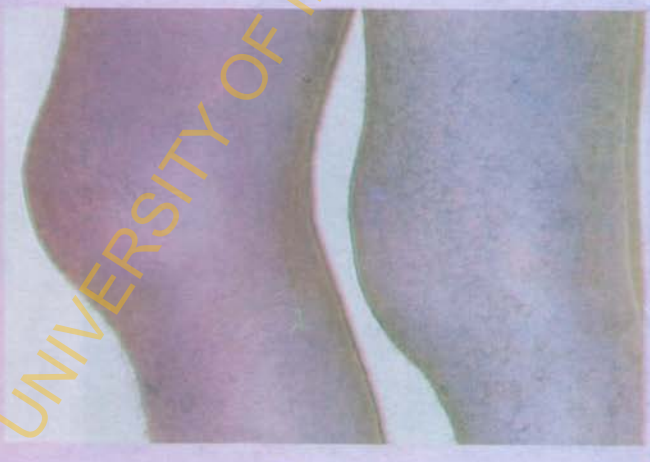
LEFT KNEE SHOWING MASSIVE SWELLING IN A TARGET JOINT WITH RECENT BLEED AND CHRONIC SYNOVITIS IN A 19-YEAR OLD SEVERE HAEMOPHILIAC

LATERAL VIEW OF SAME PATIENT



X-RAY OF THE SAME PATIENT ABOVE

- A 32-year old man with severe haemophilia A factor VIII level <1 %. He complained of persistent swelling and pain of the left knee and limitation of movement since his last episode of haemathroses 6 months earlier. Examination revealed extensive fluctuant mass, mildly tender and with engorged superficial veins overlaying the medial surface of the knee (see black arrow). Patient felt some relief with ibuprofen and hydrotherapy when reviewed three months later. There was about 25 % reduction in the new effusion. He has been lost to follow-up



- 21 year old known Haemophilia A patient Factor level < 1 % with haemathrosis left knee following a fall into a gutter preceded by generalized seizure. The patient also had flexion deformity of the left knee which had become the target joint for recurrent haemathroses.
- He was diagnosed as a haemophiliac in infancy. He had post-circumcision bleeding. And at about 1 year of age, he fell from the staircase and had intra-cranial haemorrhage which was managed with cryo-precipitate for several weeks and surgical evacuation of the intra-cranial bleed by the neurosurgeon. He subsequently developed an epileptic focus which was managed by the neurology team with phenobarbitone until time of death.
- Note the blister and the cellulitic area on the medial surface of the knee associated with the fall, and the cellulitis resolved with antibiotics. The patient died about a year later from intra-cranial bleed preceded by status epilepticus.

HUGE HAEMARTHROSIS, LEFT KNEE IN A 21-YEAR OLD WITH SEVERE HAEMOPHILIA A; POST-MILD TRAUMA IN A TARGET JOINT. NOTE THE ULCERATION OVER THE CELLULITIC AREA.

- 21 year old undergraduate with severe haemophilia A had massive haemorrhage from scalp laceration following a road traffic accident. Further haemorrhage occurred post-suturing in a private clinic before referral to UCH. Only on admission management by a neuro-surgical team involved only pressure bandaging which slowed down the bleeding considerably as well as appropriate doses of cryoprecipitate. There was complete healing of the laceration at 2 weeks with haemstatic support. He is still alive and well.

21 YEAR OLD MAN WITH SEVERE HAEMOPHILIA, UNIVERSITY UNDERGRADUATE WITH MASSIVE HAEMORRHAGE FOLLOWING A ROAD TRAFFIC ACCIDENT

- 23-year old university undergraduate with haemophilia A factor level < 1 % with a history of a cut from a kitchen knife (while trying to cut plantain). At the time of presentation, he had lost about 200 ml of blood. Examination revealed a laceration of about 4 cm in the right frontoparietal region. Patient was managed with compression bandage without suturing and transfused with cryo-precipitate. There was complete healing by day 16.

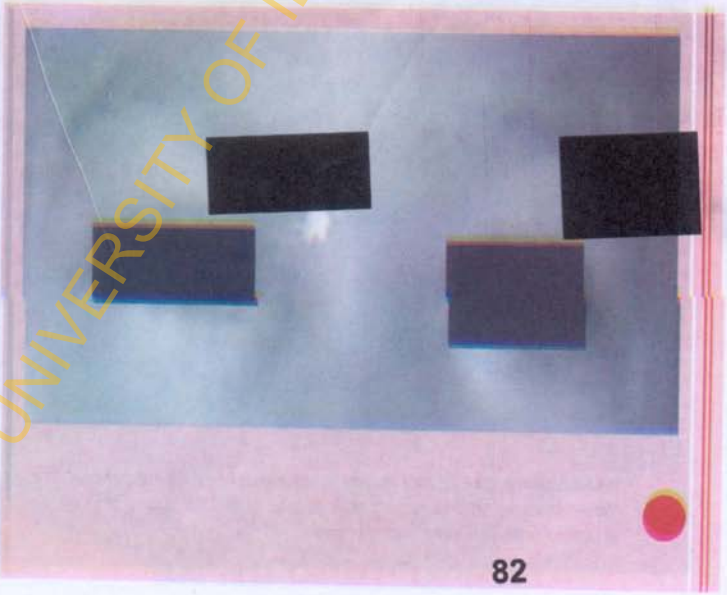
- 23 year-old haemophilia A patient with factor level 1 % presenting with massive swelling of the face and neck 2 days prior to presentation and stridor. Examination revealed an anxious young man in respiratory distress, massive diffuse swelling in neck (bull neck) and mandibula region (right > left). He was immediately put on intranasal oxygen and was transferred to intensive care unit (ICU), as this was a life threatening haemorrhage. Massive doses of cryoprecipitate were given every twelve hours until the respiratory distress subsided on the fifth day of ICU care. He was then transferred to the ward and maintained on further cryoprecipitate infusion. He was discharged on the 14th day. He remains alive and well.

HAEMOPHILIA A (23 YEARS OLD) WITH MASSIVE CERVICAL AND RETRO-PHARYNGEAL BLEED FOLLOWING MILD TRAUMA. [FACTOR VIII LEVEL < 1 %]

- Same patient as in previous slide, now 25 years old at time this picture was taken. He had severe facial haematoma and sub-conjuctival haemorrhage following a scuffle; factor level 1 %. Lesions resolved with cryoprecipitate infusion.

SAME PATIENT AS IN PREVIOUS SLIDE ON ANOTHER OCCASION WITH SEVERE SUB-CONJUCTIVAL HAEMORRHAGE AND FACIAL HAEMATOMA FOLLOWING A SCUFFLE

- 9 year old haemophilia A patient factor level 1 % with "spontaneous" swelling in right peri-orbital region. The mild haemorrhage resolved fully with cryo-precipitate therapy.



BIODATA OF PROFESSOR WURAOLA AGNES TITILOLA ADEBOLA SHOKUNBI

Wuraola Adebola Shokunbi was born on 7th August, 1953 in Are-Ekiti, Ekiti to the family of late Chief Joseph Adeoba Olaofe and late Chief Racheal 'Yelola Olaofe. Her elementary education was in Are, Ado-Ekiti, Ilorin and Effunrun. She had her Secondary School education at that exceptional School Christ's School, Ado-Ekiti between 1967 and 1971. Wuraola had Grade 1 distinction (with an aggre-gate of 7) in the WASC (West African School Certificate) examination and her result was the best in that set of more than 170 students. She gained admission into the Prelim class of 1972/73 at the University of Ibadan for Medicine. She graduated from Ibadan in June 1978 with MB.BS (with Distinction in Obstetrics and Gynaecology).

The Housemanship year (1978/79) was spent at Baptist Hospital, Ogbomosho under Dr. John Tarpley (Surgery), Dr Gilliland (Paediatrics) and others. She was posted to the Specialist (Central) Hospital, Benin as Casualty Officer during the NYSC (National Youth Service Corp) year (1979/80).

Postgraduate Professional training in Haematology commenced at the University College Hospital (UCH), Ibadan in October 1980, as a Senior House Officer. After passing the Part 1 Fellowship in 1983, she preceded to the Regional Centre for the South Western Ontario Haemophilia programme, at St Joseph's Hospital, London Onatario, Canada as a Research Fellow (1983-1985). In November 1985, she obtained the final Professional qualification in Haematology; *FMCPath* (Fellow of the Nigerian College of Pathology). She is also a Fellow of the West African College of Physicians *FWACP* (Laboratory Medicine, 1989).

She commenced teaching as Lecturer 1 at the University of Ibadan in 1988, became a Senior Lecturer in 1991, and a Professor in 1997. She was introduced to Basic Research as a

medical student by Prof. GJF Esan and Prof. O. Oluboyede, during which time she wrote her first paper on Non-Hodgkin's Lymphoma. Her Research experience expanded under Prof. M.J. Inwood when she obtained a Research Fellow Post at the St. Joseph's Hospital, London Ontario, one of the Teaching Hospitals under the University of Western Ontario, where she had the opportunity to conduct research on the Immune Status of Haemophiliacs and their Obligatory Carrier mothers. She was also given the opportunity to understudy how a Regional Transfusion Service was being run in South Western Ontario sub-region.

Wuraola has published over 100 papers in learned Journals (including booklets, chapter of a book) and over 30 abstracts for various conferences. Her Research Interests include Coagulation Disorders, particularly Inherited Bleeding Disorders, Haemostasis in Sickle Cell Disease (SCD) patients, Psychosocial Issues in SCD, Prevention of HIV and AIDS and Blood Transfusion Medicine. She has attended over 75 Conferences and Training Workshops both Locally and Internationally (London Ontario, Toronto, Montreal, Sapporo, Muenster, Jerusalem, Durban, Kadoma, Dakar, Cairo, etc) and presented in over 35 Conferences.

She won the Federal Government Scholarships for both Undergraduate and Postgraduate Education. She also was a beneficiary of the JICA (Japanese International Co-operation Agency) Fellowship. Apart from the basic qualification required to practise as a Haematologist, she has a Certificate in Immunology (University of Ibadan), Certificate in Ethics (WHO) and a Certificate in HIV Prevention (University of Hokkaido, Japan).

Wuraola has won several Honours and Distinctions including the Best Student in Physics (1972), Departmental Prize in Surgery (1978), Best Female Teacher (by the 1992 Graduating Medical Students), first female Professor of medicine from Christ's School Ado Ekiti, first female Chairman, Medical Advisory Committee and Director of Clinic Services, Research and Training to the UCH (1998-

2002), Member Board of Management, UCH (1998-2002), Chairman, Association for Reproduction and Family Health (ARFH) Ethics Committee (2002-2010) and Current Chairman, Board of ARFH.

She served as Treasurer, then Secretary, and later Chairman of the Medical and Dental Consultants Association of Nigeria (MDCAN), Oyo State Branch. She is the current President of the Nigerian Society of Haematology and Blood Transfusion, and the President-Elect of the Medical Women Association of Nigeria (MWAN), Oyo state Branch. She has been an External Examiner to several Universities in Nigeria and Ghana. She is the current Head of the Department of Haematology, and had done so on three previous occasions. She has also served the University in other capacities—(Sub-Dean Undergraduate, Chairman Board of Health (2002-2007), and Assistant Warden, Alexander Brown Hall (ABH), 1990-1997.

Wuraola (Principal Investigator) and Dr. A.J. Ajuwon (Co-Investigator) received the MacArthur Grant for HIV and AIDS prevention between January 2005 and December 2010. Through this activity, she received an award from the students in HAPPY (HIV/AIDS Prevention Promotion for Youth) Club. She has rendered Consultancy Services to IITA (Review of Clinical Services), Oyo State Government (on Review of Technical Report on HIV Seroprevalence in Oyo State; Working Paper on Blood Transfusion Safety in Oyo State in 2002; and on Proposals submitted by NGOs on HIV/AIDS for the World Bank Assisted Projects). She was appointed a member of the Presidential Project Implementation Committee (PPIC) since 2003, a committee saddled with the responsibility of overseeing the Rehabilitation of 16 Teaching Hospitals under the Federal Government/VAMED Project. She is a member of the Appointment and Promotion Committee of the SS Peter and Paul Catholic Seminary, Bodija, Ibadan.

She received an award from the Anglican Archbishop of Ekiti, Archbishop Abe for her positive role in the church and

recently from the Chaplain Committee, St. Lukes Catholic Chapel (UCH). She has given over 20 Public lectures on Radio, Television and Social clubs. She is a member of the World Federation of Haemophilia, the International Society of Haematology, Medical Women International Association (MWIA) and many other professional bodies.

She is married to Prof. M. T. Shokunbi, an Anatomist and a Neurosurgeon and their marriage is blessed with three wonderful and loving children (all Engineers).