THE NORTHERN HOSPITAL

PROTEIN S DEFICIENCY

Emperor Leo III defending the Empire, during The Second Arab Siege of Constantinople, 717 - 718 AD - Bulgarian 14th Century manuscript copy the 12th Century Greek Manasses Chronicle.

.... I shall briefly represent the founder of a new dynasty, who is known to posterity by the invectives of his enemies, and whose public and private life is involved in the ecclesiastical story of the Iconoclasts. Yet in spite of the clamors of superstition, a favourable prejudice for the character of Leo the Isuarian may be reasonably drawn from the obscurity of his birth and the duration of his reign….Even in the corruption and debility of the modern Greeks, the elevation of a plebeian from the last to the first rank of society supposes some qualification above the level of the multitude…..

The name of Theodosius might recommend him to the senate and people; but after some months he sank into a cloister, and resigned, to the firmer hand of Leo the Isuarian, the urgent defense of the capital and empire. The most formidable of the Saracens, Moslemah the brother of the caliph, was advancing at the head of one hundred and twenty thousand Arabs…..and the presumption of Moslemah was exulted by the speedy approach and invincible force of the navies of Egypt and Syria. They are said to have

amounted to eighteen hundred ships….This huge armada proceeded on a smooth sea, and with a gentle gale, towards the mouth of the Bosphorus; the surface of the straight was overshadowed, in the language of the Greeks, with a moving forest, and the same fatal night had been fixed by the Saracen chief for a general assault by sea and land….

Edward Gibbon, "The History of the Decline and Fall of the Roman Empire", Volume 5, 1786.

With the usurpation and accession of a factional puppet of the army of the Opsikian theme, by the name of Theodosius III, the Byzantines had seen no less than six Emperors over the previous twenty years. Not since the foundation of Constantinople itself had there been such a protracted period of ungoverned anarchy. The Empire was at one of its weakest moments, and the Umayyads saw their chance to storm the bulwark of Christendom. In 717 AD, the Caliph Umar II, sent two immense armies across the Imperial border.

Maslama ibn Abd al-Malik, the Caliph's brother, led overland an army said to have numbered over 100,000 men, while a general named Suleiman, led a fleet of 1800 ships into the Marmara. By the 15th of August 717, 80,000 men were encamped around Constantinople, while the Saracen fleet completed a total blockade by sea. For the second time in its history Constantinople was under siege by a huge Arab army. Though its walls were deemed impregnable from the weaponry of the day, it appeared only a matter of time before the great city of Constantine would be starved into submission. In the long history of the West, eight times its very existence was seriously threatened, only to be saved by remarkable leaders and commanders. The Byzantines never really appreciated how closely their empire came to annihilation in 717 AD, saved only for the fact that greatest Emperor since Heraclius, ascended the Imperial throne at this critical moment.

He is known to history as Leo the Isuarian, although he was almost certainly nothing of the sort. As far as modern scholars can tell he was born in the district of Commagene, beyond the Taurus Mountains, and he was of simple peasant stock. Though born to humble circumstances, he did not lack in either intelligence or ambition. Legend has it that he had ridden out to the Emperor Justinian II when the Emperor was marching on Constantinople to regain his throne from the usurper Tiberius III. Leo offered no less than 500 sheep to Justinian, for use by his army. Justinian was so impressed by Leo's loyalty that he immediately invited him to join the Imperial Guard. It was a prescient decision. Leo proved staggeringly capable, cunning, manipulative, a master of intrigue against the enemies of the Empire. Justinian used him in diplomatic missions to the east, where amoung the barbarian tribes of the buffer states in Syria and the Caucasus, he incited one against the other while on the other hand created alliances between them in opposition to the Arabs. So brilliant was he in what he did, the short lived Emperor Anastasius II appointed him Governor of the critically important military province of the Anatolikon Theme that bordered with the Umayyad Empire.

The Greeks could not have been blessed with a better Governor, when in 1716 AD the Umayyads invaded with one of the largest armies they ever assembled. The exact details of the extraordinary events that followed are obscure, to say the least. Our primary

source, Theophanes, gives an account so tangled in labyrinthine detail as to render his story virtually incomprehensible. The only thing to emerge with any certainly is that Leo had immediately entered into complex negotiations with the two Arabian generals with the astonishing result that they both withdrew their forces from Byzantine territory towards the end of 716. To have achieved this remarkable result it appears that Leo had come to some type of "agreement" with the Saracens. It seems that the Arab leaders were quickly led to believe that Leo was no friend of Theodosius III…which he wasn't. They tried to manipulate him into an alliance, no doubt with promises of immense riches, but in fact it was Leo who was manipulating them. Arab sources suggest that Leo had agreed to accept the Arabian generals as his paymasters, if they helped him seize the Imperial throne from Tiberius. Leo enthusiastically accepted, but pointed out that his path to deposing Tiberius would be a good bit more difficult if he was seen to be backed by a Saracen army, and by so doing he succeeded in persuading the generals into a "tactical retreat", allowing Tiberius to do the work himself. Leo, although more than willing to depose Tiberius with the Anatolian army on the one hand, had absolutely no intention, on the other, of then betraying the Empire to the Saracens. From this point onwards, Leo's profound understanding of Arab psychology and his fluent mastery of Arabic enabled him to repeatedly deceive and -outmaneuver them at every turn. Indeed this latter talent, the magisterial John Julius Norwich has suggested, may, given his origins, have stemmed from the fact that Arabic had been his first language, with Greek only being acquired at a later time.

Thus unhindered, Leo led the Anatolian legions towards, Constantinople, when he was met by an army led by Theodosius's son at Nicomedia. Leo won an easy victory, taking the Emperor's son prisoner in the process. Knowing that Constantinople was virtually impregnable, Leo then opened up negotiations with the Senate and the Patriarch. They needed little persuading. With the insipid Tiberius III and the coming Arab invasion, they knew who they would rather be leading them. In early 717, Theodosius, having been given assurances that neither him nor his son would be harmed, abdicated the throne and retired with much relief to a monastery. Leo was crowned the new Byzantine Emperor, in Saint Sophia. Then, possibly in accordance with a pre-orchestrated plan the two vast Saracen armies again began to move towards Constantinople, no doubt anticipating an easy victory now with the treacherous collusion of Leo, who would retain nominal power as their puppet emperor. In the meantime however Leo had had five months to prepare for a defense of the city as well as a protracted siege. He had greatly strengthened the already formidable walls, stockpiled enough grain to last every citizen for three years, but most importantly of all, he rebuilt and expanded the Greek navy and ordered the large scale production of the most terrifying secret weapon in the pre-gun powder age - the Greek Fire - a volatile pitch formula that virtually exploded on contact with the air and was delivered via by a powerful and ingenious mechanism installed on Greek ships.

When the Saracens arrived outside the walls of Constantinople and saw its bristling defenses, they realised by then they had been taken for a ride by Leo. Enraged Maslama and Suleiman heavily invested the city intending to conduct a siege to the death. But now numbers did not count for so much. The Byzantines could survive for three years, but the Saracens, would be sorely tested supplying such an immense army so far from their homelands. Leo had engineered this situation to perfection. In previous centuries most fighting had been limited to the summer months, but now fighting had to continue into the

winter and the winter of the year 717 would prove to be the severest in the living memory of even the oldest Byzantine citizens. Snow lay thick on the ground for over ten weeks, and the ground itself froze solid. These were not conditions the Saracens were used to, more accustomed as they were to the desert Sun. Their light tents were no protection against the cold, and while the Byzantines remained warm with fires roaring in their homes, the Saracens began to starve and to freeze. Men and animals began to die from the cold and from starvation. Theophanes describes the desperate Arabs as being reduced to eating their horses, donkeys and camels, and even, he claims, each other. With famine, inevitably came disease, especially enhanced Theophanes tells us, by meat that was contaminated with their own excrement. By the end of the winter the Saracens unable to bury their dead in the frozen ground, were daily tossing hundreds of corpses into the Marmara. Meanwhile on the sea, although the Greek ships were hopelessly outnumbered, they possessed the most terrifying weapon of the age. Daily the Greek Fire took a fearful toll on Saracen ships, incinerating men and material in minutes. Arab naval morale understandably began to plummet, just as it rose in inverse proportion amoung the Greeks. However with the coming of Spring, the defenders on the walls of Constantinople were horrified to see on the horizon a second Saracen armada that appeared to be almost as immense as the first. It seemed that even despite the Greek Fire, they would eventually be overwhelmed by sheer weight of numbers. Then something remarkable happened. This second fleet was largely driven by Christian galley - slaves, (probably not the best strategy having them in battle against their co-religionists) and as soon as they entered the Bosphorus, there was a general uprising and desertion en masse, that spread chaos throughout this second seaborne army.

Even so, with the warming sun of Spring Saracen spirits began to rise, but just as they did yet another disaster befell them. All the while the Bulgar Khan, Tervel, who had been a friend of the late Emperor Justinian II, but no particular friend of subsequent Emperors, had been closely monitoring the siege probably in order not to jump in too early on the losing side. The Byzantines seemed to have the upper hand, but yet with the end of the winter, perhaps the Saracens would with their seemingly inexhaustible supply of men begin the regain the initiative. The Bulgars had little love for the Byzantines, however they at least preferred them to the prospect of having Infidels in Constantinople. The Greeks may have been holding their own on the seas, but they could not challenge the Saracens on land without a powerful ally. It was at this critically important crossroads that Tervel decided to throw in his lot with the Greeks. As Spring turned to Summer a huge Bulgar horde descended onto the weakened, totally surprised and demoralized army of Maslama, delivering a crushing coup de grâce. We are told by Theophanes that over 22,000 Saracens were slaughtered. Maslama, had finally had enough. He immediately withdrew his army, what was left of it, all the way back to Syria. Nature herself next smiled on the Byzantines. A series of ferocious summer storms on the Marmara and the Bosphorus virtually annihilated the Saracen fleet, already weakened by relentless attack from the Greek fire ships. Only five of the original 1800 vessels, it was said, ever returned to their home ports. The Byzantine victory was total.

In the ensuing years the Arabs would conduct raids into Imperial territory, but they would never again reach Constantinople itself or seriously threaten the survival of the Empire. Had the Saracens succeeded in taking Constantinople in 717, the Byzantine Empire would have fallen to the Umayyad caliphate, with unimaginable consequences for

the West. It was one man that saved the desperate situation. Arab sources make it clear that Leo was in virtually continual contact with Maslama and Suleiman during the time of their invasion, making them endless promises which he had not the slightest intention of ever keeping, and offering copious advice he knew would lead them into disaster. He played them well in the finest tradition of underhanded and duplicitous Byzantine scheming. Eventually the Arabic generals came to realize they had been totally fooled, and Leo cheerfully admitted as much, but by then it was all too late for the invaders. John Julius Norwich believes that in fact there is some good evidence that Leo himself orchestrated the Christian galley-slave uprising as well as the incredibly fortuitous timing of the Bulgar attack on Maslama in the early Summer of 718.

Leo III was the savior of the West in the early Eighth century, although surprisingly he is little remembered today in this light. The Greeks, of his day did not fully appreciate the magnitude of, nor the stupendous consequences of, their victory. Rather in the decades that followed the siege, they seemed to forget their debt to Leo and became embroiled instead within that age old curse of the Greeks, the bitterness and divisiveness of obscure and arcane points of theology. Leo, perhaps by dint of his close ties with the Arabic world in his youth, held an abhorrence for the worship of idols, a practice very strong in the culture of the Byzantines in the Eighth century. He introduced the philosophy of Iconoclasm, that is, the forbidding of the worship of idols which had by then evolved into such a refined practice that parents were nominating sacred icons as Godparents for their children. Leo was so disgusted with these superstitions he attempted to have the worship of idols, as in the Muslim world, banned. The issue become so heated that it would curse and divide the empire for generations following his death. The Greeks remembered Leo the Isuarian, not so much as the savior of their Empire (and in consequence of the West0, but rather as the father of a dynasty of detested Iconoclasts.

In the biochemical evolution of the human coagulation and fibrinolysis systems, the pathways are legion and complex. For every procoagulation factor there seems to be an equal and opposite anticoagulant factor. These factors themselves are influenced by a bewildering kaleidoscopic array of cofactors and feedback loops, both positive and negative in endless cascades progressed step by step, not by absolutes, but by more subtle degrees.

Like the labyrinthine machinations of the great Byzantine Emperor, Leo III, the Isuarian, in his dealings which so cofounded the Saracens at the Siege of Constantinople in the second decade of the Eighth century, we may never quite appreciate or fully comprehend the intricate complexities of the coagulation - fibrinolytic cascades. Amoung the most complex hematological disease states is Protein S deficiency, and although the details may be obscured the important point is to understand the final outcome. A deficiency of Protein S signifies a victory of the empire of the procoagulants over that of the fibrinolytics.

PROTEIN S DEFICIENCY

Introduction

Protein S Deficiency is an uncommon inherited thrombophilia associated with an increased risk of thromboembolism.

In some situations **protein S deficiency** may also be due to **acquired** causes.

Protein S then serves as a **cofactor** for *activated* **protein C,** which **inactivates procoagulant factors Va and VIIIa, reducing thrombin generation**, thus resulting in an reduction of the conversion of **Prothrombin to Thrombin**

A *deficiency* of Protein S, therefore can result in **procoagulation** pathologies, similar in large part to those seen in **Protein C Deficiency**.

Conditions that may be seen with Protein S deficiency may therefore include:

1. **Thrombophilia, leading to Venous thromboembolism**
2. **Warfarin-induced skin necrosis**
3. **Neonatal purpura fulminans.**
4. **A possible weak association with pregnancy loss.**

Protein S deficiency is usually an **inherited** condition, but there are also some **acquired** causes.

As with other inherited thrombophilias, protein S deficiency may be *suspected* in an individual with venous thromboembolism (VTE) in association with one or more of the following:

- Strong family history of VTE
- Known familial protein S deficiency
- First VTE event before age 50
- VTE in an unusual site such as portal, mesenteric, or cerebral vein
- Recurrent episodes of VTE

Protein S deficiency is the most difficult of the hereditary thrombophilias to document with certainty.

Free protein S level (measured with an immunoassay) is probably the **best screening test**.

The initial management of acute venous thromboembolism (VTE) in patients with inherited protein S deficiency is not different from that in patients without an inherited thrombophilia and typically includes anticoagulation for at least 3 - 6 months.

Protein S deficiency does not alter the choice of anticoagulant or dosing.

All cases of Protein S deficiency related complications should be urgently referred to a Clinical Haematologist.

History

Protein S is named for the city of **Seattle**, Washington, where it was originally discovered and purified.

The first descriptions of **familial protein S deficiency** were reported by **C.P Comp** et al. in 1984.

Epidemiology

The exact prevalence of **hereditary** protein S deficiency has been difficult to determine due to:

- The variability of protein S levels among different individuals
- The use of different tests that may measure different pools of protein S
- The lack of a clear threshold below which protein S deficiency can be diagnosed reliably.

In general terms however, its incidence is now thought to be significantly lower than previously believed, and it probably only accounts for **< 1%** of individuals with venous thromboembolism (VTE).

Classification

Heritable thrombophilia conditions include:

1. Anti-thrombin III deficiency
2. Protein C deficiency
3. **Protein S deficiency**
4. Factor V Leiden mutation (or Activated Protein C (APC) resistance).
5. Prothrombin 20210A gene mutation.

6. Increased plasma concentration of fibrinogen or other coagulation factors.

7. Hyper-homocysteinaemia, (may be partly determined by environment).

Physiology

Protein S is synthesized by **hepatocytes, endothelial cells,** and **megakaryocytes**.

It is a **vitamin K-dependent** *glycoprotein* (i.e it needs vitamin K for it to become active).

Protein S then serves as a **cofactor** for *activated* **protein C,** which **inactivates procoagulant factors Va and VIIIa, reducing thrombin generation**, thus resulting in an reduction of the conversion of **Prothrombin to Thrombin**

In overall effect therefore, it prevents coagulation, and as such can be described as a **natural anticoagulant**, (**see Appendix 1 below**).

A *deficiency* of Protein S, therefore can result in **procoagulation** pathologies.

Protein S circulates in 2 states:

1. Free, (the *active* form) - around 30 - 40 %

2. Bound to the complement component C4b binding protein (a non-active form) - around 60-70%.

Pathophysiology

Genetics of Hereditary Protein S Deficiency:

Protein S deficiency is an **autosomal dominant** condition due to mutations in the **PROS1 gene**, a large gene on **chromosome 3**.

The majority of individuals with hereditary protein S deficiency are **heterozygous** for a PROS1 mutation, although rare homozygous or compound heterozygous individuals with much more severe clinical features have been reported.

Types of Protein S deficiency:

Inherited protein S deficiency can be subdivided according to whether the abnormality affects **total protein S level**, **free protein S level**, and/**or protein S function**.

Note that the distinction among types is important for research purposes but does not affect disease severity or (current) clinical management.

3 types are recognized:

Type I:

Type I deficiency consists of:

- Reduced total protein S
- Reduced free protein S
- Reduced protein S function

This is the "classic" type of inherited protein S deficiency.

Typical findings include:

- A total protein S of approximately 50% of normal

And

- Free protein S as low as 15% of normal.

Type II:

Type II deficiency consists of:

- Normal total protein S and normal free protein S, but with reduced protein S *function.*

This type is rare.

It is also referred to as a "**qualitative**" defect.

Type III:

Type III deficiency consists of:

- A normal total protein S but a **reduced** *free* protein S

With

- Abnormal (i.e decreased) protein S function

Acquired Protein S Deficiency:

In addition to PROS gene mutations reduced protein S levels have also been seen in the following settings:

1. Pregnancy
2. Oral hormonal contraceptive use.

However, postmenopausal hormone replacement therapy does not appear to alter protein S levels.

3. Coagulation disorders

    - Disseminated intravascular coagulation.
    - Acute thromboembolism in general.

4. Human immunodeficiency virus (HIV) infection;

    - There can be significantly reduced total and free protein S, however a correlation with increased thromboembolism risk has not been established.

5. Nephrotic syndrome:

    - Typically characterized by increased total protein S levels but reduced protein S function.

      This pattern is in part due to urinary loss of *free* protein S and elevated plasma C4b-binding proteins.

6. Liver disease:

    - Moderate decreases in total and free protein S.

7. L-asparaginase chemotherapy

Note that C4b-binding protein is an **acute phase reactant**. As such, several of the conditions listed above may be associated with a shift of protein S from the free form to the bound (inactive) form, potentially leading to an erroneous diagnosis of protein S deficiency.

The **clinical consequences** of these **acquired** Protein S reductions may differ from **inherited** Protein S deficiency.

Some of these conditions are associated with multiple coagulation factor deficiencies, making it difficult to establish the relative contribution of Protein S deficiency to procoagulation problems.

Clinical features

A *deficiency* of Protein S, can result in **procoagulation** pathologies similar to those seen in Protein C deficiency.

Conditions that may be seen with Protein S deficiency may therefore include:

1. **Thrombophilia, leading to Venous thromboembolism**

2. **Warfarin-induced skin necrosis**

3. **Neonatal purpura fulminans.**

4. **A possible weak association with pregnancy loss.**

Thrombophilia, leading to Venous thromboembolism:

Venous thromboembolism, including DVT and PE, is the major clinical manifestation of protein S deficiency.

The **absolute** risk of VTE due to Protein S deficiency increases with:

- Younger age of presentation
- Typically seen in thrombophilic families
- Individuals with combined VTE risk factors.

Hereditary protein S deficiency is a **rare** risk factor for VTE in the **absence** of a family history.

As with other inherited thrombophilias, protein S deficiency may be *suspected* in an individual with venous thromboembolism (VTE) in association with one or more of the following:

- Strong family history of VTE
- Known familial protein S deficiency
- First VTE event before age 50
- VTE in an unusual site such as portal, mesenteric, or cerebral vein
- Recurrent episodes of VTE

Arterial thromboembolism:

There may be only a **slight** increased risk of arterial thrombosis in individuals with Protein S deficiency.

Warfarin-induced skin necrosis:

Warfarin-induced skin necrosis typically associated with Protein C deficiency has also been described with Protein S deficiency

Neonatal purpura fulminans:

Neonatal purpura fulminans, typically associated with Protein C deficiency, has also been described with Protein S deficiency

It may rarely be seen in newborns with **very low** protein S levels and is typically due to a **homozygous** deficiency.

A possible weak association with pregnancy loss:

The data is mixed regarding the role of protein S deficiency in miscarriage.

The increased risk, (if any), is small.

Pregnancy and the postpartum period **themselves** increase the risk of maternal VTE over and above anything that can be definitely attributable to Protein S deficiency.

Investigations

Tests for **heritable** thrombophilia are often used inappropriately and non-selectively.

For patients suspected of having a thrombophilia condition consider the following tests:

1. FBE
2. Clotting profile
    - INR
    - APPT
3. Fibrinogen
4. Anti-phospholipid syndrome (often an acquired condition) tests include:
    - Lupus anticoagulant
    - Anti-cardiolipin antibodies

When considering a hereditary cause the following thrombophilia screen should be done:

5. Factor VIII levels
6. Factor V (Leiden factor) mutation
7. Protein C.
8. **Protein S**.

9. Anti-thrombin activity.

Further test that may be specifically requested include:

10. Prothrombin gene G20210A

11. Methylene tetrahydrofolate reductase.

12 Homocysteine

As a general rule for patients above 45 years of age *routine* thrombophilia screening is not necessary.

Below the age of 45 it should be done.

Note that some individuals with Protein S deficiency and VTE also have a **second thrombophilic** defect, in particular, the Factor V (Leiden factor) mutation.

Protein S testing:

Establishing a specific diagnosis of **hereditary protein S deficiency** can be difficult, particularly in the setting of an acute thrombosis and/ or anticoagulant administration.

Normal value:

The *average* plasma concentration of **total** protein S in adults is:

- **23 mcg/mL**, which by definition is assigned a value of **100%,** or 1 unit/mL (100 units/dL).

  It should be noted, however, that protein S levels in the general population *can vary significantly* (more so than for Protein C or for Antithrombin).

Effect of age:

Total protein S levels change with **age**, but **free** protein S levels remain more constant:

- Total protein S levels in healthy **newborns** at term are 15 - 30 %of that in adults, while C4b-binding protein is markedly reduced to less than 20%. Therefore, **free** protein S predominates and so functional protein S levels are only *slightly* reduced compared with those in adults.

- Protein S levels **increase** with **advancing age**

  The increase with age is seen with total protein S but not free protein S; a finding that has been explained by an increase in C4b-BP levels during normal aging.

Effect of sex:

Protein S levels are lower and more variable in females than males however, no clinical significance has been ascribed to this finding.

Effect of serum lipids:

Serum lipids may affect protein S levels.

- Total protein S levels increase by as much as 10% with increasing cholesterol levels.
- Free protein S levels increase by as much as 30% with increasing triglyceride levels.

Interpretation:

Protein S deficiency is the most difficult of the hereditary thrombophilias to document with certainty.

Diagnosis is usually made with a combination of:

1. Total Protein S levels.
2. **Free Protein S** levels - this appears to be the best *screening* test for true deficiency.
3. Protein S functional assays:
    - Protein S function is measured in a coagulation-based assay in which the time to clot formation is proportional to the plasma protein S activity.

There is no ideal cut-off level that distinguishes between individuals with and without protein S deficiency.

The value ultimately used will depend on:

1. The assay
2. The clinical setting
3. The age of the patient:

In *general* terms:

- For patients who have had a VTE or those with a strong family history of VTE, plasma levels of total or free protein S antigen **< 60 - 65 international units/dL** are considered to be in the deficient range.

- For individuals who are asymptomatic or who have a first VTE in the absence of a strong family history, lower levels of free protein S (e.g. **< 33 IU/dL**) are more predictive for an increased risk of VTE.

- For newborns, it is important to used age-based norms for the specific laboratory performing the test, as these may differ from normal adult values, especially for total protein S levels.

The timing of thrombophilia testing relative to a VTE event and/or anticoagulation administration is an important consideration in laboratory testing for suspected protein S deficiency (as is also the case for suspected deficiency of antithrombin or protein C deficiency).

With respect to anticoagulant therapies:

- Vitamin K antagonists can cause reduced protein S levels.

- Heparin and low molecular weight heparins do not alter protein S concentration

- Direct oral anticoagulants DOACs) can affect the functional assays for protein S (which use a clotting endpoint

Genetic testing:

Genetic testing for Protein S deficiency is not readily available outside of a research setting.

Management

The initial management of acute venous thromboembolism (VTE) in patients with inherited protein S deficiency is not different from that in patients without an inherited thrombophilia and typically includes anticoagulation for at least 3 - 6 months.

Protein S deficiency does not alter the choice of anticoagulant or dosing.

Unlike Protein C deficiency there is no purified Protein S concentrate available for transfusion.

Individuals with Protein S deficiency who have *not* had a thromboembolic event are not *routinely* treated with anticoagulation.

Individuals with Protein S deficiency may benefit from the judicious use of prophylactic anticoagulation in **certain settings**, especially if they have a strong family history of thrombophilia or other VTE risk factors. The greatest benefit in this regard is likely to be seen in those at greatest risk of VTE such as those with a strong family history of thrombophilia or surgery/pregnancy associated with prolonged immobility. The benefit

may be lower (or absent) in those with less VTE risk such as those with an absent or weak family history of thrombosis and a briefer period of immobility.

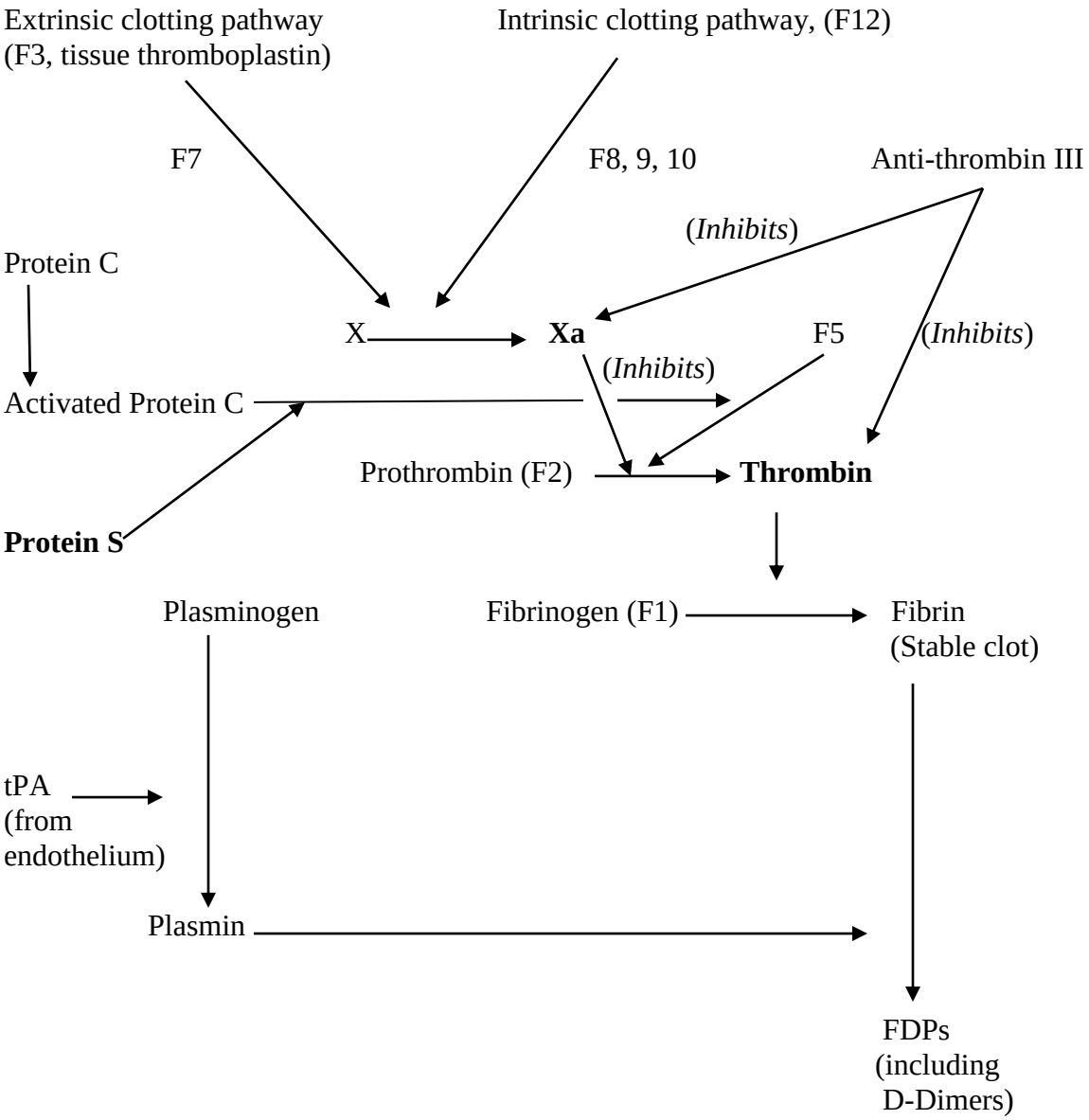
In all cases specialist Haematologist advice should be sort.

Disposition:

All cases or suspected cases of Protein S deficiency related complications should be urgently referred to a **Clinical Haematologist**.

Appendix 1

The coagulation cascade and fibrinolytic system:



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