THE NORTHERN HOSPITAL

PROTEIN C DEFICIENCY

"Self-Portrait on the Borderline Between Mexico and the United States" oil on canvas, 1932, Frida Kahlo.

"...In Mexico one always has to go around with ones thorns sharp....to defend oneself from all the cabrones (bastards)....who get into hot arguments wanting always to get ahead and to screw the next person....In the US on the other hand one could relax because the people are dumber and more malleable....What's more in relation to Diego's work the people here in Mexico always respond with obscenities and dirty tricks, and that is what makes him most desperate since he has only to arrive and they start attacking him in the newspapers, they have such envy for him that they would like to make him disappear, as if by enchantment.

On the other hand in Gringolandia it was different, even in the case of the Rockefellers, one could fight against them without being stabbed in the back. In California everyone treated him very well, also they respect the work of anyone, here he does no more than finish a fresco and the next week it is already scratched or spat upon with phlegm. This as you must understand would disillusion anyone above all when one works like Diego, using all the effort and energy of which he is capable, without taking into consideration that art is "sacred" and all that series of pendejadas (stupidities), but on the contrary, toiling like any bricklayer.

On the other hand, and this in my personal opinion, in spite of the fact that I understand the advantages that the United States have for any work or activity, I don't like the gringos with all their qualities and their defects which are very great, their manner of being, their disgusting puritanism, their Protestant sermons, their endless pretension, the way that for everything one must be "very decent" and "very proper" seems to me rather stupid. I know that the people here are thieves, hijos de la chingada, cabrones, etc. But I don't know why, they do even the most horrible things with a little sense of humour, while the gringos are sagrones (dullards) by birth, although they are very respectful and decent. Also their system of living seems to be the most repugnant, those damned parties, in which everything from the sale of a painting to a declaration of war is resolved after swallowing little cocktails (they don't even know how to get drunk in a spicy way) they always take into account that the seller of the painting or the declarer of war is an "important" personage, otherwise they don't give one even a nickel's worth of attention.

In the US they only suck up to the "important" people it doesn't matter to them that they are unos hijos de su mother and like this I can give you a few other little opinions of those gringo types, you might tell me that you can also live there without little cocktails and without "parties" but without them one never amounts to anything, and it is irritating that the most important thing for everyone in Gringolandia is to have ambition, to succeed in becoming "somebody" and frankly I no longer have even the least ambition to be anybody, I despise the conceit and being the gran caca does not interest me in any way....

Frida Kahlo, letter to Dr Leo Eloesser, 1940

Diego Rivera believed that by amalgamating the natural riches and the ancient cultures of Central and South America with the might of the modern technology and industry of North America, a new and better pan-American culture could be created. While he saw little difficulty in the concept, Frida his wife, could see only conflict and contradiction. While she recognized the merits of both cultures she also clearly saw the drawbacks of

both. She believed that the values of the two were so distinct that an amalgamation of them was simply impossible. While in the great industrial city of Detroit she produced a fascinating work, "Self-Portrait on the Borderline Between Mexico and the United States" where she depicted the stark contrasts of the two cultures.

Frida herself stands on a pedestal straddled between two starkly different worlds. She is clad in an elegant salmon pink gown and wears fingerless lace gloves, appropriate dress for Fifth Avenue haute couture. But in her right hand she carries a small Mexican flag, while in her left she holds a cigarette as if to emphasize the billowing smoke of a Detroit factory. Inscribed on the pedestal on which Frida stands are the words, "Carmen Rivera painted her portrait in the year 1932". Carmen was the name Frida first used when she was in America, Frida apparently being a little too Germanic, for American sensibilities, during the period that spanned the two World Wars.

To the right we see the cold sterile world of industry depicted largely in dull greys and blues, while to the left we see her native Mexico, depicted in warm, earthy colours, the flowers are brightly coloured. The natural plants send their roots into the earth from which they draw their nourishment, while on the right we see only electrical machines, whose "roots" seem not to draw energy from the earth, but rather discharge excess power into it. However the machine directly under Frida appears to be connected to the roots of one of the plants. It is drawing its energy from them. In turn it plugs into the pedestal upon which Frida is standing, and so Frida while in "Gringoland" still draws her energy and life from her home.

The contrast between nature and artificial is a strong motif. For the first time in her work we see the appearance one of Frida's most powerful symbols - the image of the Sun adjacent the Moon, representing the unity between cosmic and terrestrial forces. The image also echoes the ancient Aztec concept of the deep duality of life. There is an eternal war between light and dark, the one chasing the other across the sky. The duality, like the ancient Chinese concept of Yin and Yan, extends to all aspects of the Universe, male and female, day and night, past and present, good and evil, proton and electron, velocity and position, matter and antimatter. The American scholar Bertram Wolfe explained this duality; "In most nature religions, as in ancient Mexican mythology, the lords of the heavens are the Sun and the Moon; the Sun being the masculine principle, the fertilizer and life-giver, and the Moon (or in some Mexican traditions, the Earth), the feminine principle, the mother of gods and men". The Sun and Moon symbolism was also one of Medieval Christianity, often flanking the cross in medieval paintings. This may represent the solar eclipse that Astronomers say happened at around the time of Christ's death - the Moon covered over the Sun. This symbolism persisted into the period of the Renaissance, a period which Frida had studied intensely, then on into early colonial Mexico brought with the conquistadors. Frida knew both Christian and pre-Columbian symbolism and frequently combined the two in her works.

As for the American side, the sky is filled with the billowing smoke of industrial pollution. The Sun is eclipsed by a giant Stars and Stripes, the whole terrain in dominated by factories, soaring suffocating windowless skyscrapers, machines and the pipes that feed them. The Mexican landscape on the other hand is nature strewn with the ancient relics of a pre-Columbian world. While the American industrial world appears lifeless, in

Mexico there is life and symbols of life everywhere. There are two ancient fertility statues lying beside the ubiquitous death mask of the Day of the Dead - symbols of the eternal cycles of life and death. In contrast to the faceless American deities of bankers and captains of industry who dwell in the towering tombstones, in Mexico we see the ruins of great and ancient pyramids, where the gods of day and night, Quetzalcoatl and Tezcatlipoca, dwelt.

While her husband Diego Rivera saw the best of both cultures, Frida, was more pragmatic seeing the good and the bad in both She did not idealize either country. She clearly saw them both as separate and contradictory, a view that would have caused Diego some distress, with his vision of a new pan-American culture. Frida, in contrast to Diego who depicted only idealized images to covey his political views, depicted universal images of the human condition that transcended time and space.

One of Frida Kahlo's most powerful motifs, the Sun and the Moon, represented the constant battle of the complex dualities of nature and of life, a motif mirroring the ancient Chinese philosophy of Yin and Yan. This battle of duality permeates virtually every mechanism of the ancient hierarchy of the physics, biochemistry, physiology and biology of life. A balance of power between opposing forces is reached in a homeostasis that maintains the harmony of life evolved over untold eons of deep geological time. We may see no better example of the duality of forces at play in the incredibly complex coagulation system of the blood - the constant battle between coagulation and anticoagulation. When this delicate balance of duality is lost, then catastrophe looms!

Frida, painting "Self-Portrait on the Borderline" Detroit 1932.

Behind her is Diego, in front of one his vast murals.
It was in America that Frida first became noticed as a painter in her own right.

PROTEIN C DEFICIENCY

Introduction

Protein C has an anticoagulant function following its conversion to "**activated**" **protein C** (**APC**)

Hereditary protein C deficiency is an uncommon condition that may result in the following 4 pathologies:

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

Protein C deficiency can be either an inherited or an acquired condition.

Any actual or suspected case of a complication of Protein C deficiency should be urgently referred to a Clinical Haematologist.

History

Protein C deficiency was first described by J.H Griffin et al. in 1981

Epidemiology

The incidence of inherited protein C deficiency varies depending on the population but in general it is low

Healthy individuals in the general population have an incidence of approximately 0.2 - 0.5 %.

Individuals with venous thromboembolism have an incidence of Approximately 2 - 5 %.

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 C is a **vitamin K-dependent anticoagulant** protein.

It is synthesized in the liver with the assistance of vitamin K

Thrombomodulin, is a specific receptor on vascular endothelium that binds **thrombin.** It is the **thrombomodulin** - **thrombin** complex that "activates" Protein C, (i.e converts Protein C to activated Protein C)

APC then acts to inhibit:

- F5a
- F8a

By the inhibition of these **coagulation** factors, APC acts as an **anti**-coagulation factor.

The inhibitory effect of APC is further enhanced by another vitamin K-dependent anticoagulant protein known as **protein S.**

A deficiency in Protein C therefore will lead to **pro-**coagulation problems.

See also Appendix 1 below.

Pathophysiology

Protein C deficiency is an **inherited** condition, but it can also be an **acquired** one.

Hereditary protein C deficiency:

Protein C deficiency is associated with a small percentage of cases of inherited thrombophilia (see above)

Hereditary protein C deficiency is an uncommon condition that may result in the following 4 pathologies:

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

2. Warfarin-induced skin necrosis:

- The combined effects of **protein C deficiency** *and* **vitamin K antagonism** with **warfarin** may explain the occurrence of warfarin-induced skin necrosis in some individuals with protein C deficiency who are treated with a vitamin K antagonist.

  This procoagulant state results in the thrombosis of skin vessels.

3. Neonatal purpura fulminans:

   - Levels of protein C take some time to reach the normal adult level after birth.

     Preterm infants may have protein C levels of only 7- 18% percent of normal.

     Full term newborns have protein C levels of approximately 20 - 40 % of normal

     Severe Protein C deficiency can lead to neonatal purpura fulminans at birth

4. A possible weak association with pregnancy loss.

Inherited Protein C deficiency is caused by mutations in the **PROC gene**, the gene that encodes for Protein C

The defective gene has autosomal dominance.

Acquired Protein C deficiency:

Protein C deficiency can *also* be an **acquired problem**.

The causes of acquired Protein C deficiency include:

1. Acute liver injury:

   Protein C is synthesised in the liver

   Circulating levels of protein C may be reduced in liver disease including:

   - Right heart failure with hepatic congestion
   - Severe liver disease in general

2. DIC:

   - Patients with DIC have ongoing consumption of both coagulation factors and natural anticoagulants.

3. Infection

- Protein C levels are **not** generally affected by infection unless the infection is severe.

  Acquired protein C deficiency has been described in certain patients with acute severe viral, bacterial, and other infections (such as malaria).

  Meningococcemia is probably the best characterized of these

4. Drugs:

Cancer chemotherapy agents:

- Some cancer chemotherapeutic agents such as asparaginase can cause reductions in protein C levels

Warfarin:

- Vitamin K antagonist anticoagulants (i.e warfarin) can interfere with protein C and protein S production.

  The half-lives vary among the vitamin K-dependent coagulation factors (factors II, VII, IX, and X) and natural anticoagulants (protein S and protein C), and as a result, the factors with the shorter half-lives (half-lives for factor VII and protein C of 8 and 14 hours, respectively) are depleted more rapidly than the others.

Clinical features

Hereditary protein C deficiency is an uncommon condition that may result in the following 4 pathologies:

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:

Individuals with protein C deficiency can develop venous thromboembolism (VTE) at any site including:

Most commonly:

1. DVT

2. PE

3. Mesenteric veins

Less commonly:

4. Cerebral veins

5. Portal veins

6. Superficial skin veins

7. Other unusual sites can also occur, but are much less common.

The **absolute risk** of VTE in a patient with protein C deficiency is difficult to estimate because other modifying factors also contribute to risk such as family history of VTE or other clinical events.

Among thrombophilic families, the risk of thrombosis in individuals with protein C deficiency is:

- Similar to that of protein S deficiency and antithrombin (AT) deficiency (approximately 1 thrombosis per 100 patient-years)

- Higher than individuals with the factor V Leiden mutation (approximately 0.3 thromboses per 100 patient-years).

The *relative* risk of thrombosis with protein C deficiency is approximately seven times that of individuals without an inherited thrombophilia.

The *absolute* risk of VTE in individuals with a **positive family history** may be as high as:

- 75 % in **severely** affected families

- 30% percent in other families

Regardless of family history, the risk of VTE in individuals with protein C deficiency is expected to be **increased** by *additional inherited or acquired* VTE risk factors, e.g. factor V Leiden mutation, prolonged immobility, surgery, oral hormonal contraceptive use etc.

The **initial** episode of VTE in patients with protein C deficiency is apparently spontaneous in approximately two-thirds of cases, and the remaining third have the usual risk factors.

The median age of a **first thromboembolic** event is typically in **young adulthood**.

Individuals with a positive family history are more likely to have a first VTE in their 20s - 30s, while individuals without a family history of thrombophilia are more likely to have a first VTE in their 30s - 40s

The risk of **recurrent thrombosis** depends on the clinical setting but is thought to be approximately 60% in patients from **thrombophilic** families *without* prophylactic anticoagulation.

Warfarin-induced skin necrosis:

Warfarin-induced skin necrosis is a complication of warfarin therapy used in patients who also have Protein C deficiency.

Despite the warfarin therapy there is paradoxical thrombosis due to the overriding simultaneous depletion of the natural anticoagulant, Protein C, in patients who are already Protein C deficient.

The patient develops **demarcated** areas of **purpura** and **necrosis** due to vascular thrombosis.

The appearance can be similar to that of neonatal purpura fulminans.

It may affect one or more areas of skin including the extremities, breasts, trunk, or penis

The skin lesions in warfarin-induced skin necrosis typically form during the **first few days** of warfarin therapy, often in the setting of large loading doses of 10 or more milligrams of warfarin per day.

The lesions typically marginate over a period of **hours** from an initial central erythematous macule, (similar to neonatal purpura fulminans).

The incidence of warfarin-induced skin necrosis in individuals with protein C deficiency is unknown, as most descriptions are in the form of case reports.

Note that warfarin-induced skin necrosis is **not** "pathognomonic" for protein C deficiency, as it has been described in individuals with **other inherited thrombophilias** such as factor V Leiden mutation, protein S deficiency and *transient* reductions of protein C levels

Neonatal purpura fulminans:

Neonatal purpura fulminans in newborns is a **rare**, **life-threatening** condition characterized by disseminated intravascular coagulation (DIC), extensive venous and arterial thrombosis, and hemorrhagic skin necrosis.

It usually is caused by **homozygous** or compound heterozygous (i.e in combination with another inherited thrombophilia) deficiency in protein C.

Laboratory testing reveals evidence of disseminated intravascular coagulation and extremely low protein C levels of < 1 % of normal values.

Pregnancy loss:

Protein C deficiency has been linked to fetal loss, however thrombophilia from Protein C deficiency is currently not thought to be a major factor **in itself** in adverse pregnancy outcomes e.g. miscarriage, fetal loss, preeclampsia, fetal growth impairment.

However, it is important to note that pregnancy itself increases the risk of VTE due to a number of physiologic and anatomic changes, and prophylactic anticoagulation during pregnancy and the postpartum period to reduce the risk of VTE is likely to be appropriate for certain individuals with protein C deficiency where this risk is additive.

Arterial thrombosis:

The risk of **arterial** thrombosis (and so stroke or myocardial infarction) in patients with protein C deficiency *may* be increased **slightly**, but high quality data is lacking to support or refute an association - and, if one exists, to establish the magnitude of the effect.

Studies have thus far, not *convincingly* demonstrated that protein C deficiency is a risk factor for the development of **arterial** thrombosis

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.

Protein C testing:

The diagnosis of protein C deficiency is established in a patient for whom there is an **appropriate clinical suspicion** and laboratory evidence of low protein C levels.

In most cases levels are approximately 50% of normal (or less).

However, the **absolute threshold** for defining a deficiency is uncertain.

It is important to note that protein C levels can be transiently reduced in certain settings, such as acute liver injury (see above).

Further, there is a wide range of "normal" protein C values in the general population, making diagnosis difficult in individuals with "borderline-low" levels.

Levels may fluctuate somewhat over time in the same individual. Those with **severe deficiency** will continue to show severe deficiency over time, but those with **borderline** values in the high 55 - 60% range may occasionally cross the threshold into the normal range.

Testing ideally should be done after the patient has recovered from an acute event such as an **acute thrombosis** or **severe inflammatory illness**. If the result was obtained at the time of one of these events, the testing should be repeated.

The **possible interference** from an anticoagulant, especially **warfarin**, should be taken into account when ordering protein C testing, based on the medication list and the patient's prothrombin time (PT) and international normalized ratio (INR).

Age-appropriate and laboratory-specific normal values should be consulted for **infants** and **young children** because protein C levels are lower at birth and take time to reach adult levels.

Genetic testing:

Genetic testing for mutations and other defects in the **PROC gene**, which encodes for protein C is possible.

This testing however is only performed in specialized laboratories and is not currently available for routine clinical use.

Management

Thromboembolism:

Anticoagulation is undertaken for individuals with protein C deficiency who develop a thromboembolic event.

Management is essentially similar to other individuals with a thromboembolism, with the exception of measures to reduce the risk of warfarin-induced skin necrosis.

These measures may include:

1. The use of an anticoagulant other than warfarin

    - **DOAC**
    - **Enoxaparin**

2. **Judicious** use of warfarin with a lower-than-average starting dose, and/or longer duration of overlapping heparin or low molecular weight (LMW) heparin administration.

    Commence at 2 mg daily for the first three days followed by *gradually* increasing increments of an additional 2 to 3 mg until therapeutic anticoagulation is achieved.

The duration of anticoagulation is individualized according to the age of the patient, site and clinical significance of the thromboembolism, and whether the thromboembolism was provoked or unprovoked.

Indefinite anticoagulation is recommended for many patients with an unprovoked thromboembolic event, regardless of whether an inherited thrombophilia is identified; the documentation of protein C deficiency may strengthen the case for indefinite anticoagulation particularly if there is a strong family history of VTE.

Warfarin-induced skin necrosis:

Warfarin-induced skin necrosis is a potential paradoxical complication of **warfarin therapy** in patients with **protein C deficiency** caused by transient hypercoagulability during warfarin initiation

It is important to establish that skin necrosis is due to protein C deficiency rather than another cause such as vasculitis, or heparin-induced thrombocytopenia (HIT).

In patients with known protein C deficiency (or a known family history of protein C deficiency) and skin necrosis, a presumptive diagnosis of warfarin-induced skin necrosis can be made while protein C levels are being obtained.

In patients without a known personal or family history of protein C deficiency, consultation with a specialist with expertise in thrombophilia may help in determining the likelihood of protein C deficiency.

Once the diagnosis is made, immediate intervention is required to prevent rapid progression and to minimize complications.

Treatment then consists of:

1. Ceasing warfarin therapy.

2. Administration of vitamin K intravenously (enhances protein C activity)

3. For ongoing anticoagulation, use heparin/ enoxaparin / DOAC

4. Administer a source of protein C:

    - Protein C concentrate (if available)

    Or

    - Fresh Frozen Plasma (FFP)

      The required volume of FFP may be significant depending on the patient's baseline protein C activity level.

5. In some cases, skin lesions may continue to progress despite these interventions due to tissue infarction.

The therapies should be continued but involvement of a dermatologist and/or surgeon may also be required.

Neonatal purpura fulminans:

Neonatal purpura fulminans is *initially* treated with a source of exogenous protein C:

- A highly purified concentrate of protein C (Ceprotin)

Or

- FFP

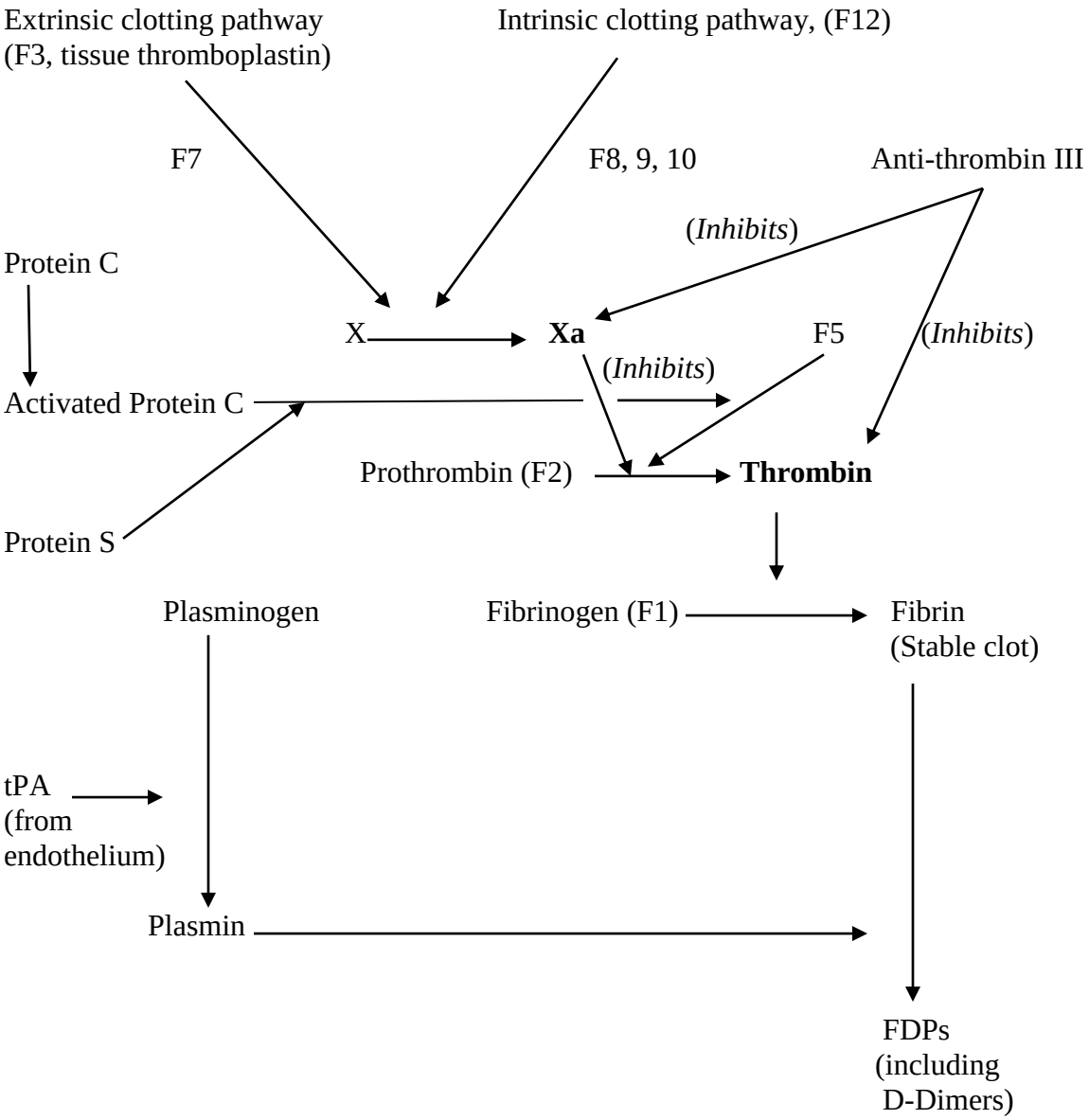
Heparin and antiplatelet agents are ineffective

Disposition:

All patients who have or who are suspected to have Protein C deficiency and have suffered a VTE event should be referred to e Clinical Haematologist.

Appendix 1

The coagulation cascade and fibrinolytic system:



VISITING HOMES OF INTERESTING PEOPLE

Wife of the Master Mural Painter Gleefully Dabbles in Works of Art

By FLORENCE DAVIES.

SOMETHING about the hilarious incongruity of a stuffed lion, a plaster-of-Paris horse, and a colored chromo of George Washington draped in garlands of red, white and blue crepe paper, all jumbled in the same shop window, proved to be too much for the sense of humor of Senora Diego Rivera, and so she simply had to do something about it. What she did was to go home and paint it, which may surprise people who think that Diego Rivera, the great mural painter now at work at the Detroit Institute of Arts, is the only artist in the family.

That, however, is all a mistake, since his wife, Carmen Rivera, or "Freda," as her friends call her, is a painter in her own right, though very few people know it.

"No," she explains, "I didn't study with Diego. I didn't study with anyone. I just started to paint."

Then her eyes begin to twinkle. "Of course," she explains, "he does pretty well for a little boy, but it is I who am the big artist." Then the twinkles in both black eyes fairly explode into a rippling laugh. And that is absolutely all that you can coax out of her about the matter. When you grow serious she mocks you and laughs again. But Senora Rivera's painting is by no means a joke; because, however much she may laugh when you ask her about it, the fact remains that she has acquired a very skillful and beautiful style, painting in the small with miniature-like technique, which is as far removed from the heroic figures of Rivera as could well be imagined.

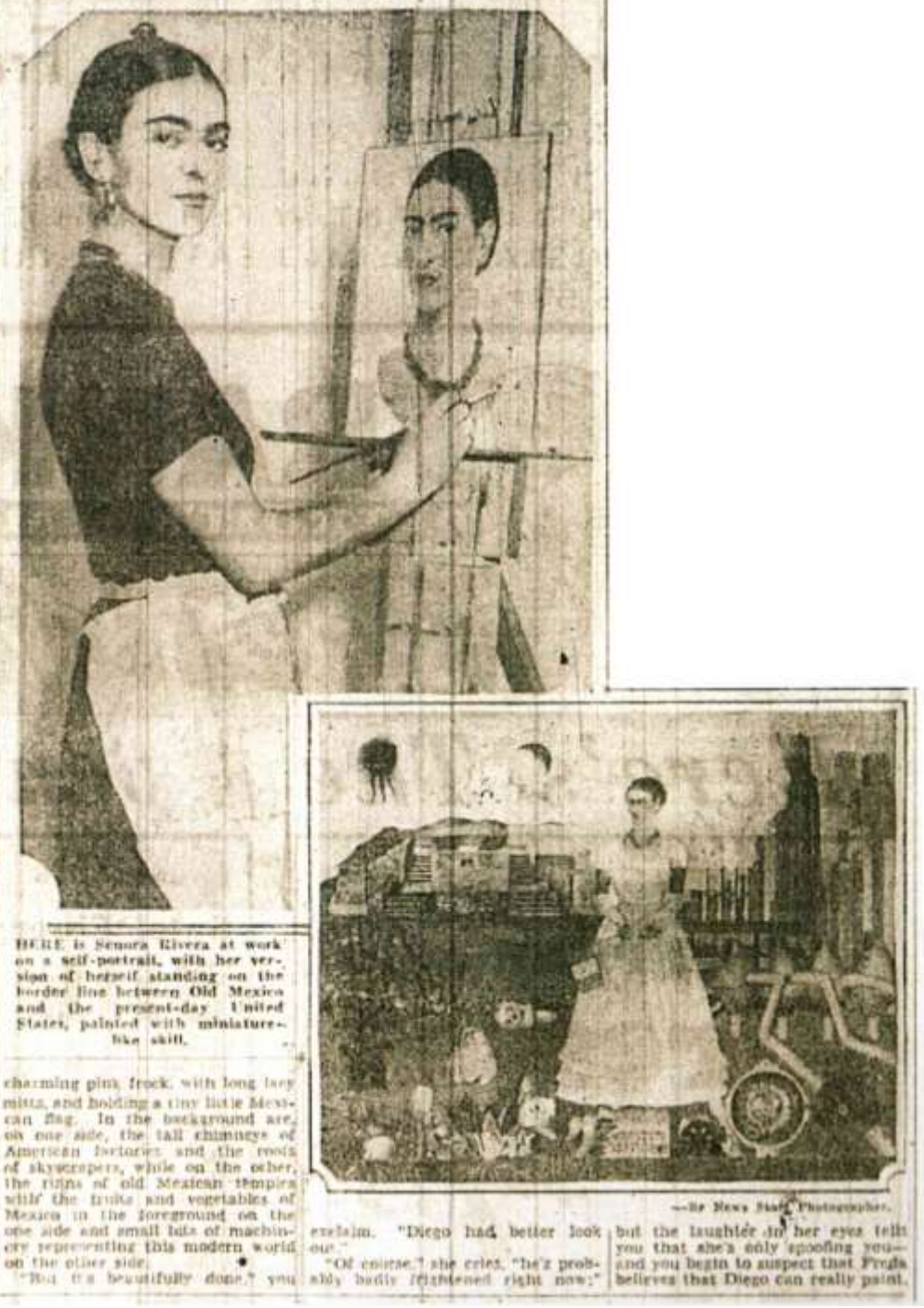
Thus, while her husband paints with large brushes on a huge wall surface, his wife, herself a miniature-like little person with her long black braids wound demurely about her head and a foolish little ruffled apron over her black silk dress in lieu of a smock, chooses a small metal panel and paints with tiny camel-hair brushes.

In Detroit she paints only because time hangs heavily upon her hands during the long hours while her husband is at work in the court. So thus far she has finished only a few panels. The window of the shop where street decorations are manufactured was obviously done in the spirit of humor. A little more seriousness however has gone into a portrait of herself standing on the border line between Mexico and the United States.

In the center of the picture, standing on a little gray stone bearing her name and date, is a full length portrait of herself clad in a charming pink frock, with long lacy mitts, and holding a tiny little Mexican flag. In the background are, on one side, the tall chimneys of American factories and the roofs of skyscrapers, while on the other, the ruins of old Mexican temples with the fruits and vegetables of Mexico in the foreground on the one side and small bits of machinery representing this modern world on the other side.

"But it's beautifully done," you exclaim. "Diego had better look out."

"Of course," she cries, "he'z probably badly frightened right now;" but the laughter in her eyes tells you that she's only spoofing you—and you begin to suspect that Freda believes that Diego can really paint.



HERE is Senora Rivera at work on a self-portrait, with her version of herself standing on the border line between Old Mexico and the present-day United States, painted with miniature-like skill.

—Be News Staff Photographer.

Detroit news, February 1933. With "Self-Portrait on the Borderline Between Mexico and the United States" Frida becomes noticed not only as the wife of Diego Rivera, but for the first time as an Artist in her own right. After her death in 1954, she would become far more famous than her husband.

Frida and Diego share an intimate moment at the Detroit Institute of Arts, 1932.

<u>References</u>

1. Kenneth A Bauer, “Protein C Deficiency” in Up to Date Website, December 2018.

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