THE NORTHERN HOSPITAL

D-DIMER

"The Delphic Oracle", (detail), John William Godward, oil on canvas, 1899, Fine Art Society, London, United Kingdom.

For over one and a half millennia the ancient world would consult the high priests of the oracle in important matters of state. Before any major decision could be made it was essential to consult the oracle in order to seek the prophecies of the gods themselves. The most famous oracle of all was that of Delphi, dedicated to the god Apollo. Its exact origins are uncertain, lost in the mists of deep antiquity.

It was believed that Apollo could talk through a medium, known as the Pythia. In the earliest times the Pythia would be a beautiful young virgin seated upon a tripod within the oracle. She would become engulfed in a mysterious mist that appeared to emerge from the very depths of the cavernous abyss of the Earth below. The Pythia would be sent into a trance or an ecstasy, and then Apollo would talk through her. Unfortunately Apollo only spoke through the Pythia in a very ancient and long lost Cretan tongue. Only the priests of the oracle could understand what was being said. Statesmen, generals, even emperors would listen to the Pythia, and hear only gibberish in answer to their questions. The priests would then translate to the enquirer what Apollo had said. Eventually the mist would clear and the Pythia would have no memory of what had occurred. It was said that so intense was the experience of the Pythia in being "possessed" by Apollo that many would go into convulsions, some would even die whilst giving their prophecy.

The prophecy had to be interpreted with extreme caution however. Sometimes the message was quite clear, but more often than not the message Apollo had given could be quite ambiguous. On many occasions it was no easy task to correctly interpret what had been said. The most famous example of this was when Croesus, the great Hellenic king of Lydia, consulted the oracle in 546 BC about what the outcome would be if he attacked the Persian Empire. He was informed that if he did attack, "a great empire would fall". Delighted with this he went ahead with his invasion, but his army was annihilated by the Persians, his kingdom was incorporated into the Persian Empire and he barely escaped with his life. Furious, he confronted the priests of the oracle about the prophecy he had been given. He was informed that the prophecy was entirely correct, he had destroyed a great empire…his own!

Despite the experience of King Croesus the power of the oracle of Delphi was still held in the highest regard. No less a figure than Alexander the Great, supreme in his own confidence of his abilities and destiny, hesitated before he embarked on his invasion of the Persian Empire in 333 BC. He did not believe he needed to consult anyone, even the oracle about his plans, so confident was he of the outcome. It was pointed out to him that perhaps it would nonetheless be prudent to alleviate the apprehensions of his soldiers by obtaining a divine endorsement for the enterprise from the oracle. Frustrated at the delay he went to the oracle only to find it was closed because of a religious holiday. Ceremony never stood in the way of Alexander. He sought out the Pythia, and dragged her forcibly to the oracle. She cried out in pain, "stop young man, you are invincible". This was good enough for Alexander, he released her and pronounced that the prophecy was favorable. The outcome of Alexander's attack on Persia is well known to history, he need not have bothered with the oracle.

By the first century AD, the powers of the oracle were being seriously questioned. Its popularity among the great and powerful was in steep decline, possibly in part due to the replacement of young and beautiful virginal Pthyians by old crones, as there had been

cases of the Pythia being "ravished" by clients during their trances. Plutarch interestingly ascribes the decline in the power of the oracle at this time as being due to a decline in the magical vapors emanating from the caverns below. Fascinatingly the geologists De Boer and colleagues in 2001 discovered that light hydrocarbon gases emanate from the bituminous limestone faults in the region of Delphi. Included among these gases were ethylene compounds, which are known to have anesthetic properties. In Godward's late Nineteenth century painting "The Delphic Oracle", the mysterious gases can be seen emerging from the ground at the bottom left hand corner of the work. They waft upward about to engulf the Pythia. Perhaps before the time of Plutarch these natural emissions were far more prominent, explaining the trance like states, convulsions, even occasional deaths of the Pythias. In 393 AD the Christian Emperor Theodosius I finally abolished the oracle, seen by that time as an archaic remnant of a distant pagan past.

In the 21st century, the oracle of Delphi is but an ancient memory. Rather than calling on Apollo, we now rely on the scientific method in order to make our prophecies. Although we pride ourselves on our miraculous scientific advances over the centuries, in some respects we have not far progressed from the days of the Pythia of Delphi. When we wish to make prophecies concerning our patients who may have venous thromboembolism we turn to our own oracle in the form of the d-dimer. Unlike King Croesus however we must interpret this prophecy with caution as the result may, like the pronouncements of the Pythia, be ambiguous. If the result is positive there could be a number of interpretations as to what this means. It is for this reason we must carefully consider beforehand what the result may be telling us. We do this by applying our Well's risk stratification criteria. In many cases, no prophecy will be necessary at all. When we are as confident of a positive result as was Alexander the Great, the d-dimer need not be consulted at all.

Ruins of the Temple of Apollo at Delphi, 4th century B.C, built on ruins of original 7th century B.C temple, (Author's photograph, 1986).

D-DIMER

Introduction

D-dimers are very sensitive but non-specific markers of venous thromboembolism, (VTE).

VTE in this sense refers specifically to the diagnoses of deep venous thrombosis or pulmonary embolism.

There is good evidence to show that when the **pre-test probability of VTE is low,** a normal d-dimer level can be used to rule out VTE, and hence avoid the need for further imaging investigations. [1, 2]

Elevated levels of d-dimers cannot however **make the diagnosis** of VTE as a large range of conditions may cause this elevation. So when the pre-test probability of VTE is *not low*, **an imaging investigation** must be done to make the diagnosis.

Physiology

D-dimers will be elevated when ever the process of clot formation is occurring. The process involving clot formation is a dynamic one that also concurrently involves fibrinolysis once clot forms. A dynamic equilibrium forms between the coagulation and the fibrinolytic processes.

Fibrin degradation products (FDPs) are the end result of the fibrinolysis process. One of the products is the readily measurable, d-dimer.

An elevation in the level of d-dimers therefore indicates that the process of clot formation (and concurrent fibrinolysis) is occurring.

A summary of the biochemical pathways of these two processes is given in appendix 1 below.

Normal Values

The normal values of d-dimers are (frustratingly) *variously* quoted as:

- **< 500 micrograms / L**

Or

- **< 0.5 mg / L**

Or

- **< 0.5 micrograms / ml**

Or

- **< 500 ng / ml**

Normal values however can be higher than this with age **≥ 50 years**.

Over the age of 50 years, the upper limit of age adjusted normal can be taken as:

- **Age (in years) × 10 µg/L.** [4]

  (For example, for a patient aged 78 years, the D-dimer concentration would be considered normal below 780 µg/L).

Or

- **Age (in years) x 0.01 micrograms / ml**

  (For example, for a patient aged 78 years, the D-dimer concentration would be considered normal below 0.78 µg / ml).

D-dimers are usually detectable as soon as one hour after thrombus formation.

The dynamic process of fibrinolysis in acute VTE results in elevated plasma D-dimer levels for at least one week. [3]

Larger clot burdens result in higher d-dimer levels.

Causes of an Elevated D Dimer

1. **Venous thromboembolism:**
   - **DVT**
   - **Pulmonary embolism.**

Others causes include:

2. **Infection in general.**
3. **Inflammatory conditions in general including vasculitis.**
4. **Malignancies**
5. **Myocardial infarction.**
6. **Stroke.**
7. **Recent surgery or trauma**

8. **Thrombolytic therapy.**

9. **Increasing age.**

10. **Aortic dissection.**

11. **DIC.**

12. **Pregnancy**

13. **Liver/ Renal disease**

14. **Sarcoidosis.**

Causes of a False Negative Value [3]

These include:

1. D-dimer levels fall with heparin therapy.

2. Levels may be reduced by as much as two thirds in patients on oral anticoagulants.

   Anticoagulation treatment (heparin or warfarin) prevents intravascular fibrin formation.

3. D-dimer levels may normalize in patients with VTE of longer than 7 days duration.

Indications for Testing

The utility of d-dimer testing is to help rule out VTE**, when the pre-test probability of VTE is low.**

Interpretation of D-Dimer Results

D-dimer levels must be interpreted in the light of the pre-test probability of VTE.

D-Dimer can be used in conjunction with clinical assessment for the evaluation of:

1. **Possible DVT**:

   - A Wells score < 2 + a normal D-dimer makes DVT very unlikely. [1]

2. **Possible PE**:

- A Wells score of < 2 + a PERC score > 0 + a normal D-dimer makes PE very unlikely.

- A Wells score 2-6 and + a normal D-dimer makes PE very unlikely.

  Additionally:

  A Wells Score < 2 + PERC Score = 0 makes PE very unlikely. [5]

3. **Possible Aortic Dissection**:

   - An aortic dissection detection score ≤ 1 + normal d-dimer makes aortic dissection very unlikely. [6]

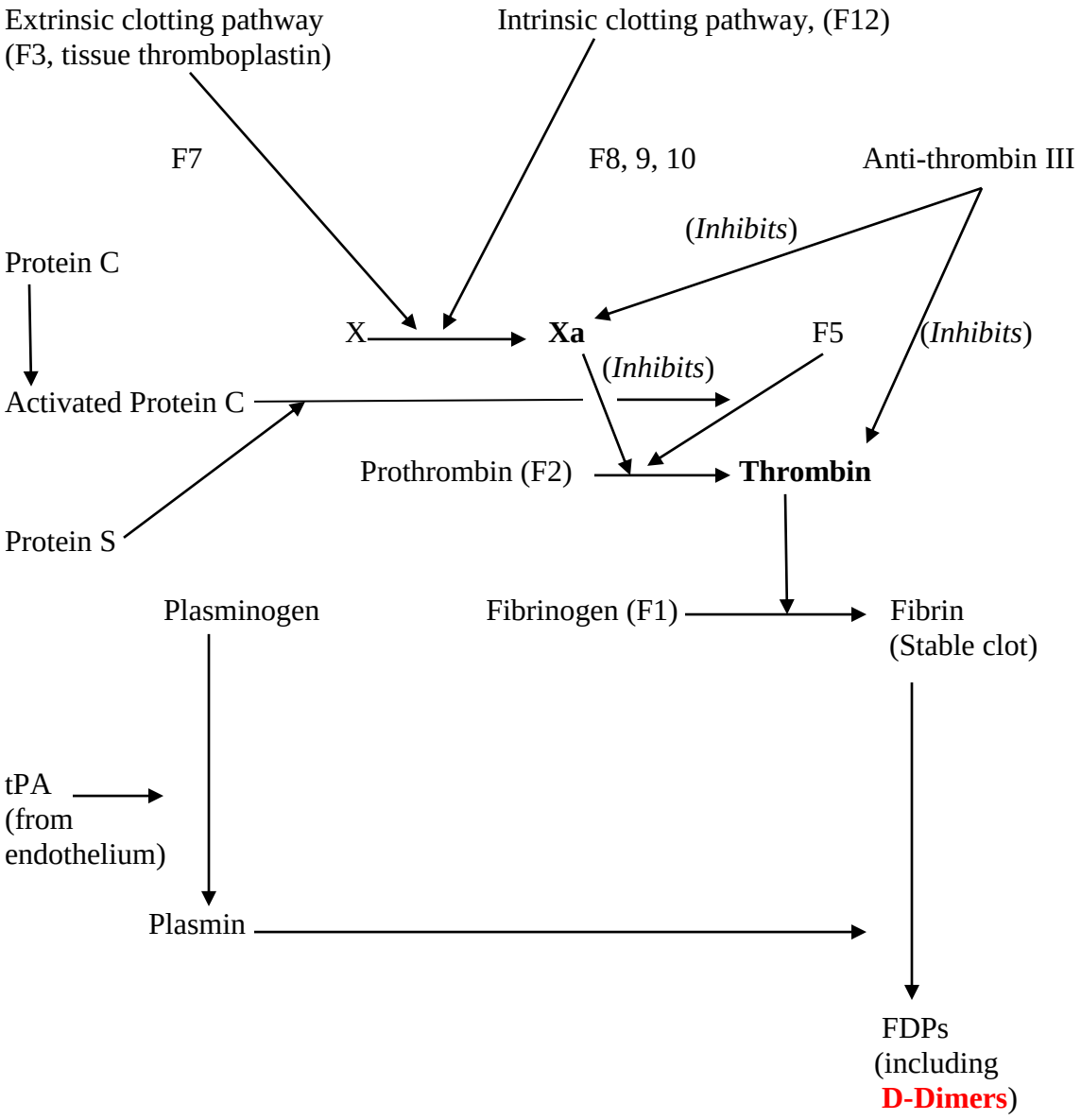
It is important to realise that the d-dimer level cannot *make a specific diagnosis* of VTE, only an *imaging* study can currently do this.

A negative d-dimer test can only be used to rule out VTE when the pre-test probability of VTE is **low**. A normal d-dimer level therefore *cannot rule out* VTE when the pre-test probability of VTE is *not low.*

Because of non-specificity, D-dimers should not be ordered indiscriminately without careful consideration and documentation of the pre-test probability of VTE.

Appendix 1

The coagulation cascade and fibrinolytic system:



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Further reading:

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