

Erythrocyte Sedimentation Rate

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Disclosure Information

Tests I wish You Had Not Ordered

- I have no financial relationships to disclose.
 - I will not discuss off label use or investigational use in my presentation.



75 YEARS OF DEDICATION TO OUR MEMBERS

Timothy J Barreiro, DO, MPH

Objectives

- Learn how to stop doing this.

Case Presentation

- You are asked to consult on a 50-year-old female admitted with the weak and dizzies that started three weeks ago. Her exam is normal.
- A SED rate was obtained on admission and was noted to be 35 ml/hr.
- What does your consulting desired wish to convey?

Erythrocyte Sedimentation Rate

- Few laboratory tests are performed more frequently, yet none may be more difficult to interpret.
- Elevated levels lead to unnecessary testing.
 - No diagnosis can be made by an SED rate.
 - Mildly elevated ESR are typically ignored.
 - High levels attract attention, may not indicate serious disease.

Your Consult

CC: Elevated What?

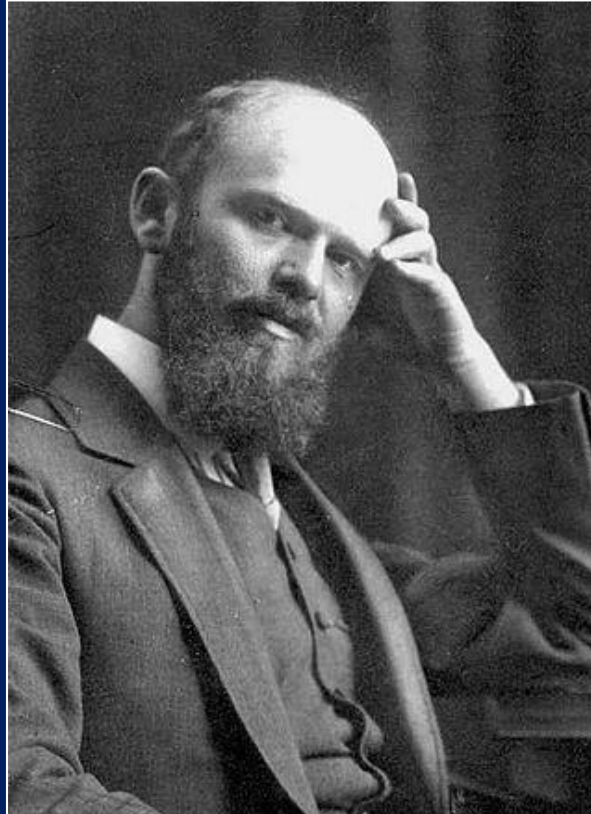
Dear Donald T.

Did you know that the SED rate was 1st discovered in 1866 by _____ . Your pleasant 50 year old woman states she developed the “weak and dizzies” from sitting on the couch in a awkward position during a meeting, that discussed the rating of a “bad apprentice.” in the office.

Erythrocyte Sedimentation Rate



Edmund Faustyn Biemacki
(1866 -1911)



Swedish hematologist,
Robert Sanno Fåhræus
(1888-1968)



Swedish internist
Alf Vilhelm Albertsson
Westergren (1891-1968).

Erythrocyte Sedimentation Rate

From the Stockholm Hospital for Tuberculosis at Söderby.

Acta Med Scand 54: 247-282. 1921

Studies of the Suspension Stability of the Blood in Pulmonary Tuberculosis¹

by

ALF WESTERGREN.

I. Introduction.

When a substance in a state of fine division is silted up in a liquid, we call this a suspension. The blood corpuscles, in this connection primarily the red ones, may thus be described as suspended in the plasma. A suspension is called stable, if the matter silted up for a long time keeps evenly distributed in the medium. The principal cause of a decrease of the stability is to be found, when the matter silted up has a

Erythrocyte Sedimentation Rate

It is the rate of downward descent of RBCs in a vertical column of blood.

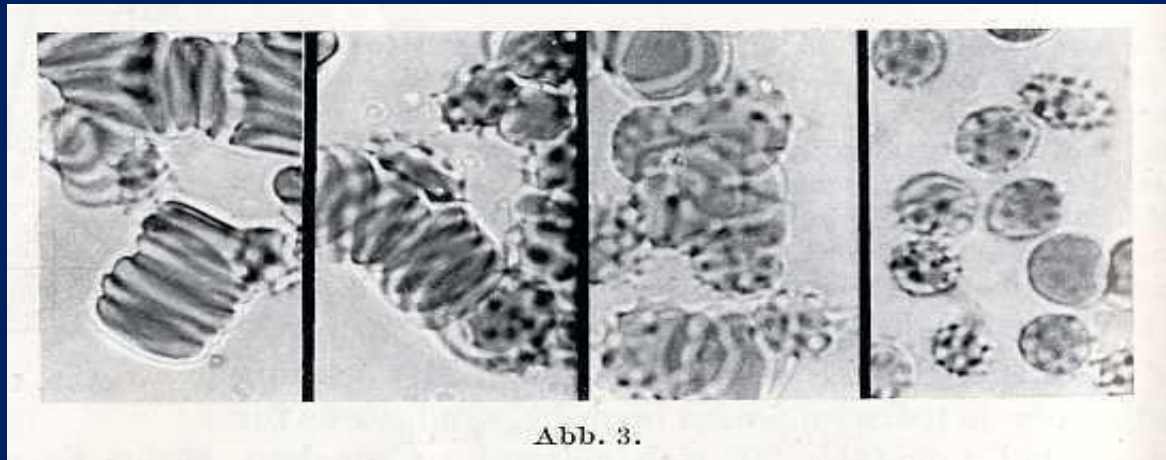
Principle: If anti-coagulated blood is allowed to stand vertically in a narrow tube, the red cells will settle progressively to the bottom leaving clear plasma above.

Erythrocyte Sedimentation Rate

The cells settle due to :

- Density of RBCs is greater than that of plasma.
- RBCs tend to aggregate to form Rouleaux.

(Rouleaux differs from agglutination that agglutinated cells are irreversibly bound together and can not be separated)



Westergren method for estimation of ESR:

Equipment:

- Westergren tube (straight glass tube 30 cm in length, 2.5 mm in diameter and graduated from 0 - 200 mm)
- Special stand.
- 3.8% Sodium Citrate.
- 5 ml disposable syringe.

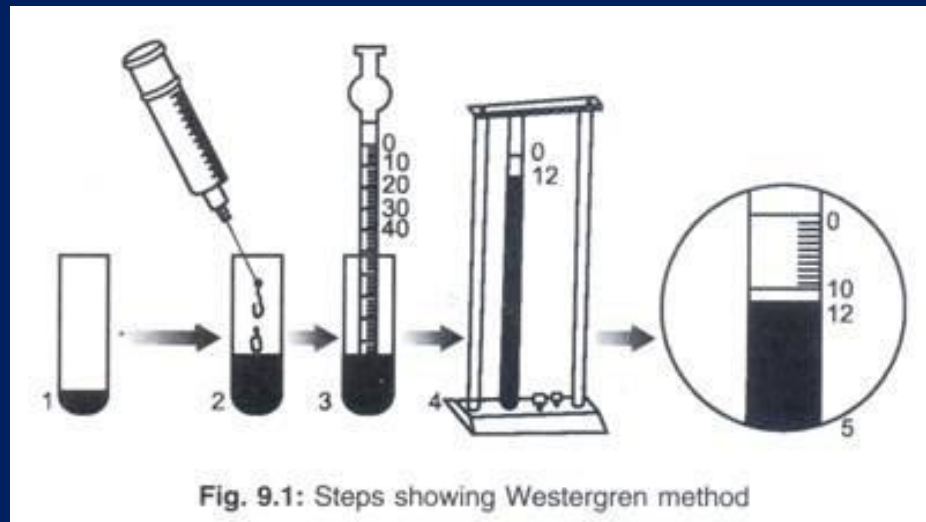
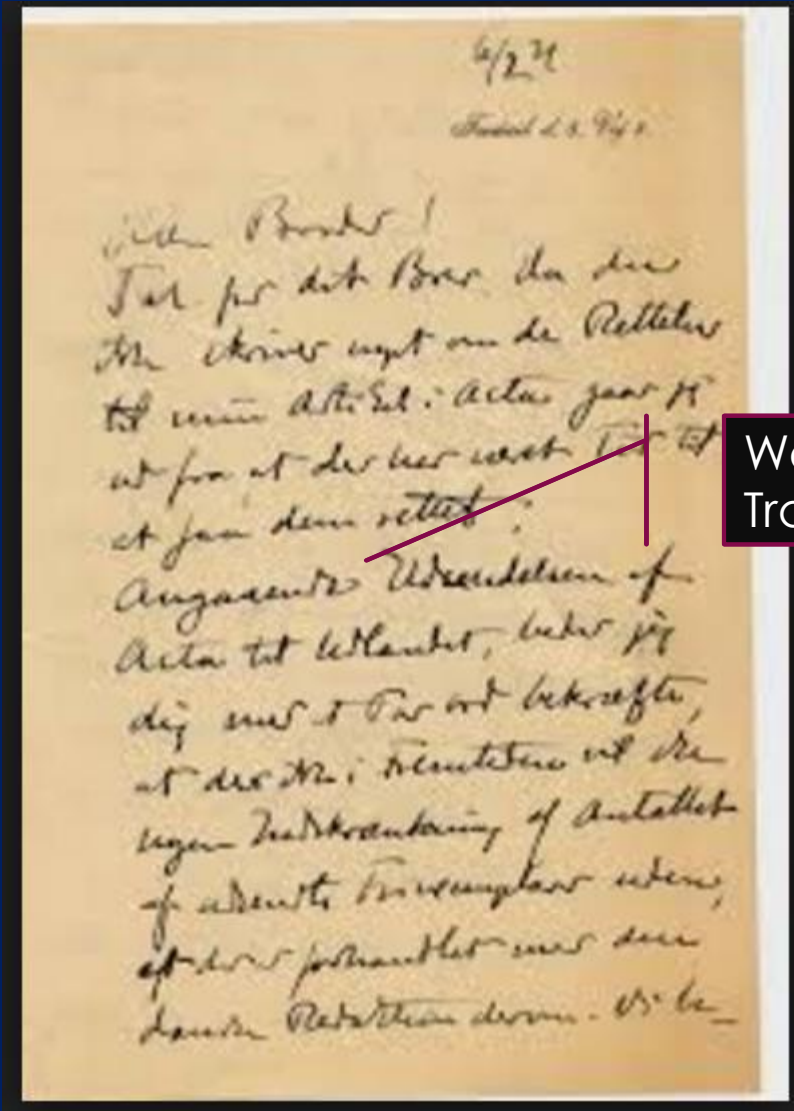


Fig. 9.1: Steps showing Westergren method

The "Letter" to Holmgren



Title: [Letter] 1921-02-06 [to] Israel Frithiofsson Holmgren

Description:

- The Waller Manuscript Collection, Uppsala University Library

Westergren

Translated: Don't order this test

- Alf Vilhelm Albertsson Westergren
1891-1968

Your Consult

CC: Elevated What?

Dear Donald T.

Did you know that the SED rate was 1st discovered in 1866 by Edmund Faustyn Biemacki. Your patient's "weak and dizzies" from sitting awkward on a couch in a meeting. The test appears to have been done by the historical method called the Westergen method. It appears she has no history and is not anemic. However, despite the 'news' - comparisons in laboratory techniques don't seem to change the test results. Her ESR test was found to be 35 mm/hr. This result is an uncorrected value.

What is a Normal ESR Value

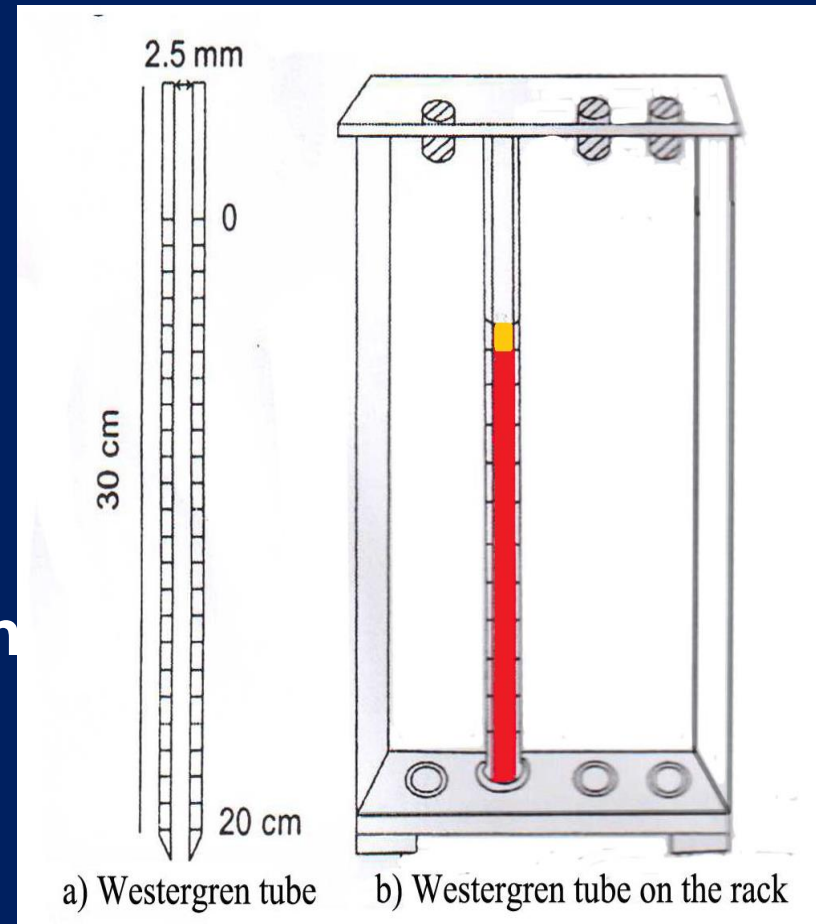
Normal values:

In males: 1st hr : 3 - 5 mm

2nd hr : 6 - 10 mm

In females: 1st hr : 8 - 10 mm

2nd hr : 16 - 20 mm



Calculating Normal Erythrocyte Sedimentation Rate

- Measurement of the ESR requires adjustments.
- Westergren method in 27,912 adults (1,076 non pregnant woman) aged 20 – 65 years old during routine exams in 10 London teaching hospitals.

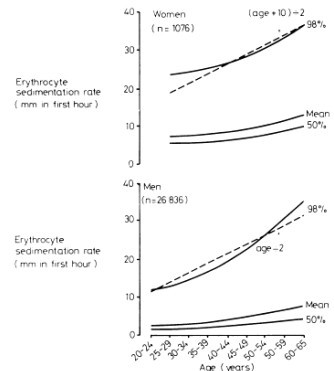
SHORT REPORTS

Simple rule for calculating normal erythrocyte sedimentation rate

Measurement of the erythrocyte sedimentation rate is a commonly performed blood test, so it might be expected that the reference range would have been well established. Several surveys¹⁻³ suggest that the upper limit of normal in a person aged under 50 may be as high as 15-20 mm in the first hour in men and 25-30 mm in the first hour in women, whereas a recent authoritative review⁴ recommended, on the basis of results "derived from several publications," values of 10 and 12 mm in the first hour respectively. Even so, the haematology departments at 10 London teaching hospitals quote the reference ranges as only 0.5 and 0.7 mm in the first hour in men and women respectively, following a standard textbook.⁵ We set out to clarify the upper limit of the normal range on the basis of a wide survey.

Subjects, methods, and results

The erythrocyte sedimentation rate was measured by the Westergren method⁶ in 27 912 adults (20 836 men and 1076 non-pregnant women) aged 20-65 as part of a routine health screening. None of the subjects was anaemic. Results, expressed to the nearest mm in the first hour, were stored on computer and subsequently analysed. A series of curves of erythrocyte sedimentation rate versus age (in blocks of five years) was constructed separately for men and women; these are shown in the figure, with maximum values for 50% (the median) and 98% of the population, and the mean values.



Erythrocyte sedimentation rates in men and women, with mean values and maximum values for 50% and 98% of the population. Broken lines are given by formulae and approximate to upper limits of normal.

Comment

The data for men came from a normal population 10 times the size of that in any previous study, and confirm other observations¹⁻³ that the erythrocyte sedimentation rate rises with age. Although only 1076 women were studied, the results in these women were broadly similar to those in the men but with higher values at each age. Possibly a few of these apparently healthy men and women had occult disease

that might have contributed to some of the high values, but this is unlikely to have influenced the results materially.

The 50% and 98% levels show that the results were distributed with considerable skewness,⁷ and this is the reason for the difference between the mean and median curves. Statistics that assume a normal distribution¹⁻⁴ are thus misleading, as are the popularly quoted normal ranges of 0.5 mm in the first hour in men and 0.7 mm in the first hour in women.⁵ Upper limits of the normal range such as those of Lewis¹ (10 and 12 mm in the first hour in men and women respectively aged under 50, and 14 and 20 mm in the first hour in men and women respectively aged over 60) and of others² are more accurate but hard to remember. It would seem reasonable to define the upper limit of the normal range as that value above which less than 2% of the normal population lies. On the basis of our results we propose the following formulae for calculating the maximum normal erythrocyte sedimentation rate at a given age: in men, age in years - 2; in women, (age in years + 10) ÷ 2. When these calculated values are plotted against age (the broken, straight lines in the figure) the results give a good approximation to the 98% curves. These formulae are both realistic and easy to remember.

¹ Böttiger LE, Svedberg CA. Normal erythrocyte sedimentation rate and age. *Br Med J* 1967; **1**: 85-7.
² Wilhelm WF, Tillisch JH. Relation of sedimentation rate to age. *Med Clin North Am* 1951; **25**: 1209-11.
³ Rafnsson V, Bengtsson C, Lænnarsson J, Linquist O, Noppa H, Tibblin E. Erythrocyte sedimentation rate in a population sample of women with special reference to its clinical and prognostic significance. *Acta Med Scand* 1979; **206**: 207-14.
⁴ Lewis SM. Erythrocyte sedimentation rate and plasma viscosity. *Association of Clinical Pathologists Broadsheet* 1980; **94**: 1-7.
⁵ Dacie JV, Lewis SM. *Practical haematology*. Edinburgh: Churchill Livingstone, 1975.

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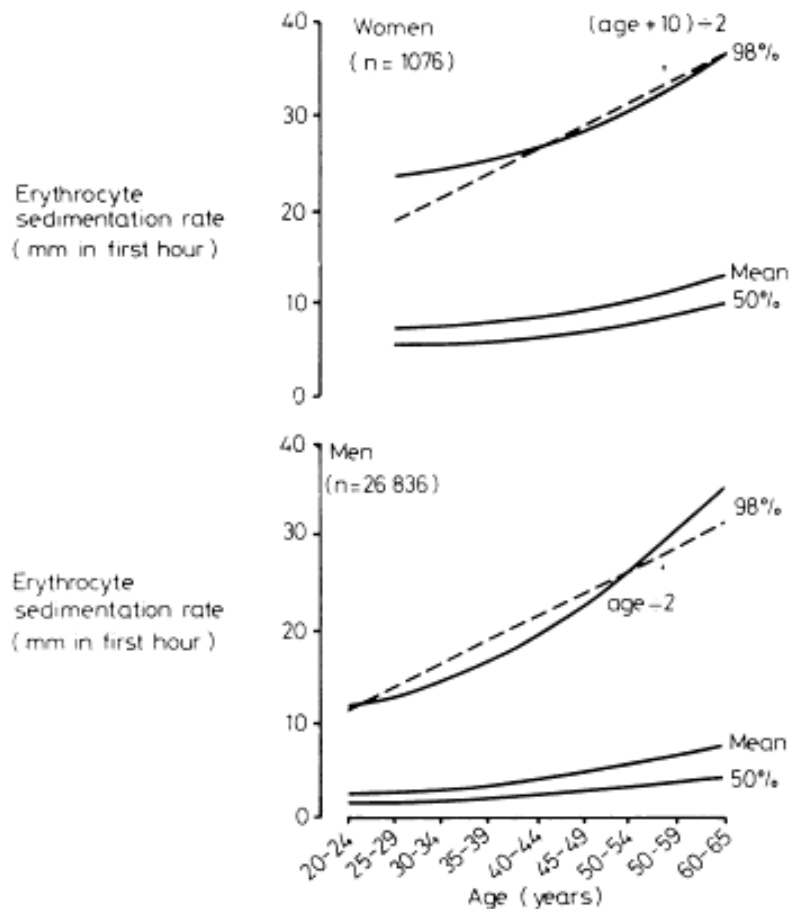
Acebutolol-induced hypersensitivity pneumonitis

Episodes of bronchoconstriction induced by beta-blocking agents in patients with asthma or chronic bronchitis are well known. To our knowledge side effects with the features of hypersensitivity pneumonitis have not been reported. We describe a case in which hypersensitivity pneumonitis appeared to be related to administration of acebutolol.

Case report

A 69 year old man with coronary heart disease was treated with acebutolol (200 mg daily) for six months; an x-ray film taken one year earlier had been normal. At the end of the six months' treatment a routine x-ray film showed bilateral pulmonary infiltrates; physical examination was normal, and a tuberculin skin test negative. There were no symptoms of cardiac failure (normal heart rate, with neither dyspnoea nor cardiac enlargement). Tests of respiratory function yielded normal values except for the carbon monoxide pulmonary diffusing capacity, which was low (transfer coefficient 0.92 mmol/min kPa); 3.3 ml/min/mm Hg/l). Serum activity of angiotensin-converting enzyme was normal; and bronchial, salivary gland, and hepatic biopsy specimens showed no abnormality. In the bronchoalveolar lavage fluid the proportions of lymphocytes, macrophages, and polymorphonuclear leucocytes were respectively 88%, 13%, and 4%. Acebutolol was withdrawn for 54 days, after which a chest x-ray film was normal and the diffusing capacity still low; the cell differential in bronchoalveolar lavage fluid showed 46% lymphocytes, 46% macrophages, and 8% polymorphonuclear leucocytes; the OKT₁, OKT₄; ratio was 0.16. Thirty-seven days after acebutolol treatment was resumed, with the

Calculating Normal Erythrocyte Sedimentation Rate



- ESR increases with age.
- 50% and 98% levels show that the results are skewed.
- Corrected values thus adjusted to be within 2% of the population:
- Adjustments needed:
 - ESR ♀ = $(\text{age} + 10) / 2$;
 - ESR ♂ = $\text{age} / 2$

Clinical significance of ESR

- Because the ESR is changed in a great variety of conditions , Its alteration is not specific and not diagnostic.
- It is a prognostic test :
 1. It detects the presence and severity of disease.
 2. It gives an idea about the activity of disease.
 3. Repeated ESR estimation may help in prognosis and follow up of disease.

Factors Effecting ESR Testing

Factors determining the rate of sedimentation of RBCs :

- Plasma proteins :
 - Albumin : If plasma albumin level is increased the ESR decreases.
 - Fibrinogen and globulins : If plasma fibrinogen or globulins level is increased the ESR increases.
- Red cell count :
 - If RBCs count is increased the ESR decreases.

Factors Effecting ESR Testing

Physiological factors :

ESR is increased in :

- 1- Old age.
- 2- Females.
- 3- Pregnancy.
- 4- Menstruation.

ESR is decreased in :

- 1- Newborn.
- 2- Males.
- 3- High altitude.

Your Consult

CC: Elevated What?

An uncorrected value

Edmund Faustyn Biemacki

Dear Donald T.

... It appears that her ESR test is actually fairly normal and not “fake” which is typically good for patients. We calculated her adjusted level to be 30 mm/hr, which is close to the 35 mm/hr test. However, since the symptoms started weeks ago – this may or may not be a “RED flag.”

Lucky for us, we can “tap” into the computer and see if a CRP was also drawn at the same time.

Case Presentation

- On the same 50-year-old female admitted with the weak and dizzies.
- A CRP was drawn and was noted to be **8 mg/L**.
- What does your consulting desired wish to convey?

C Reactive Protein

- C-reactive protein (CRP) belongs to the pentraxin family of proteins, which has five identical subunits. It was named because it reacts with the somatic C polysaccharide of *Streptococcus pneumoniae*, and was first discovered in 1930 by Tillet and Francis.

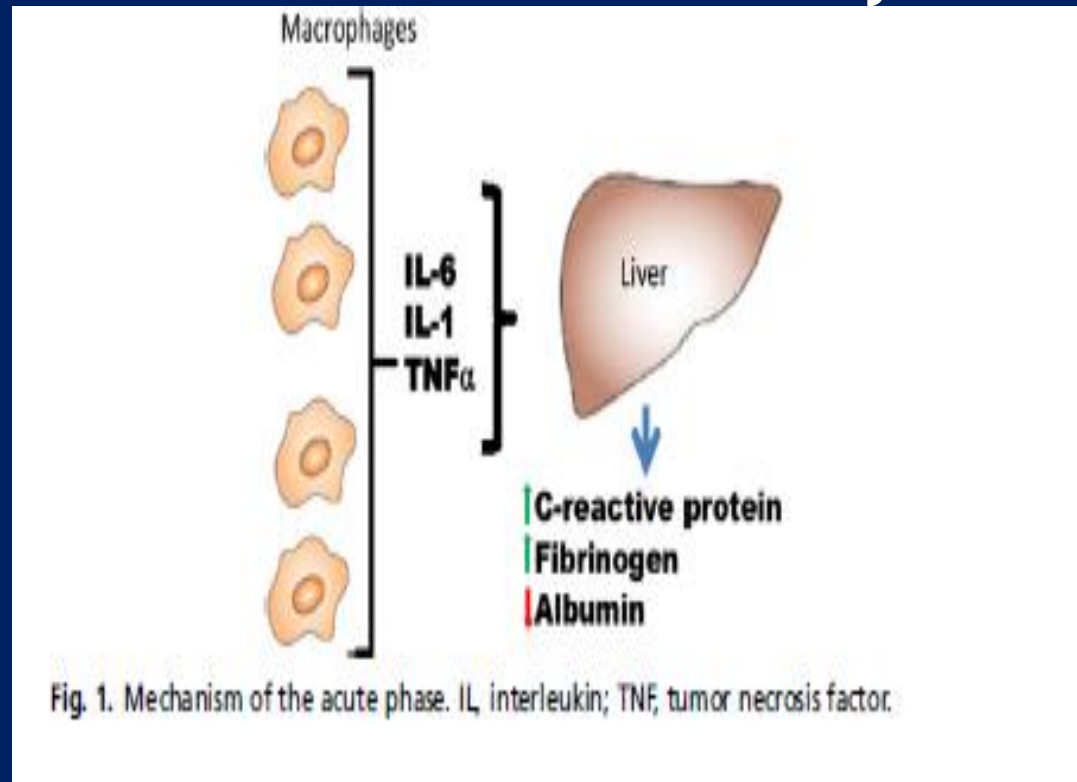
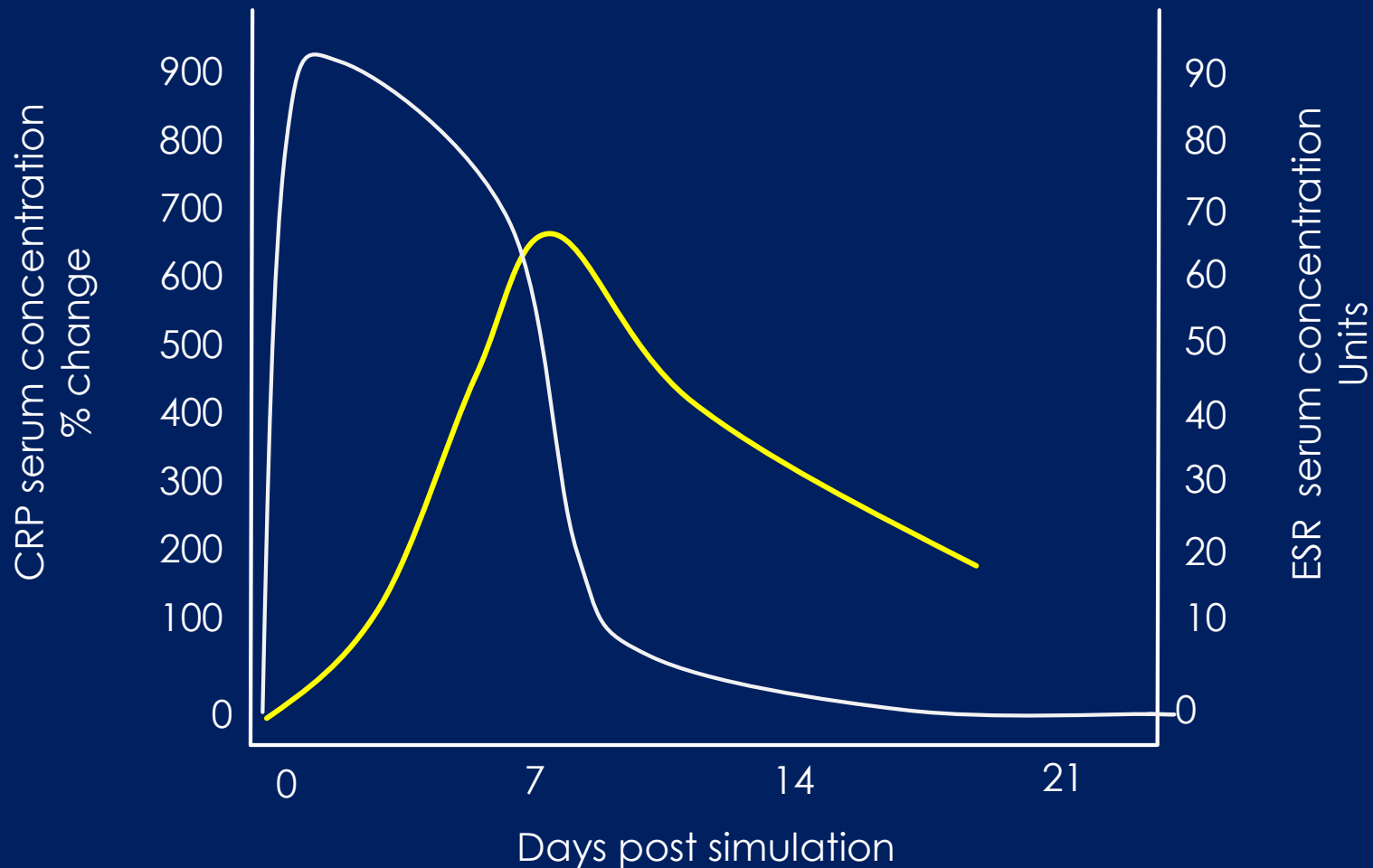


Fig. 1. Mechanism of the acute phase. IL, interleukin; TNF, tumor necrosis factor.

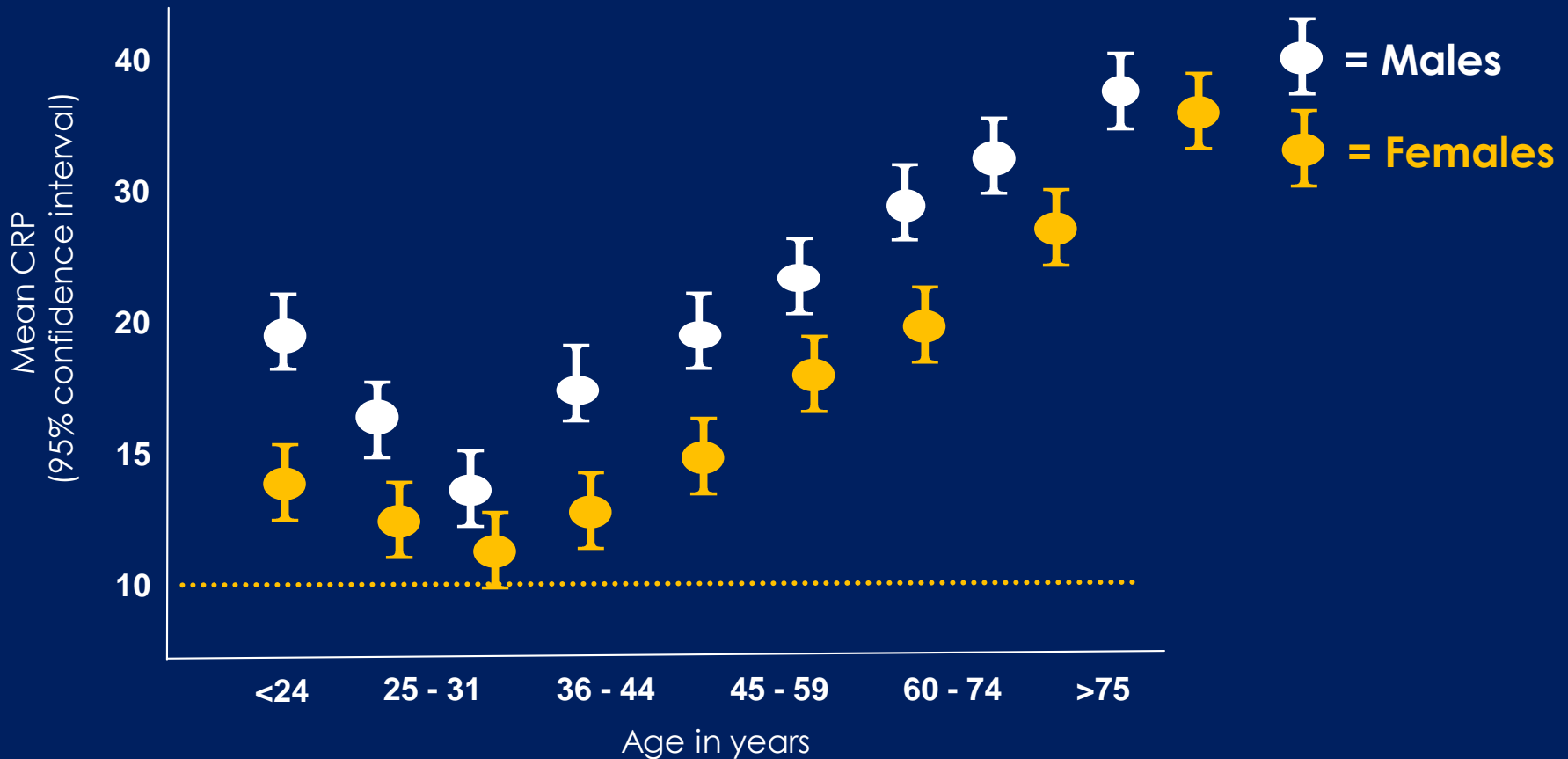
CRP & ESR Patterns of Response



CRP is reported to have several main functions

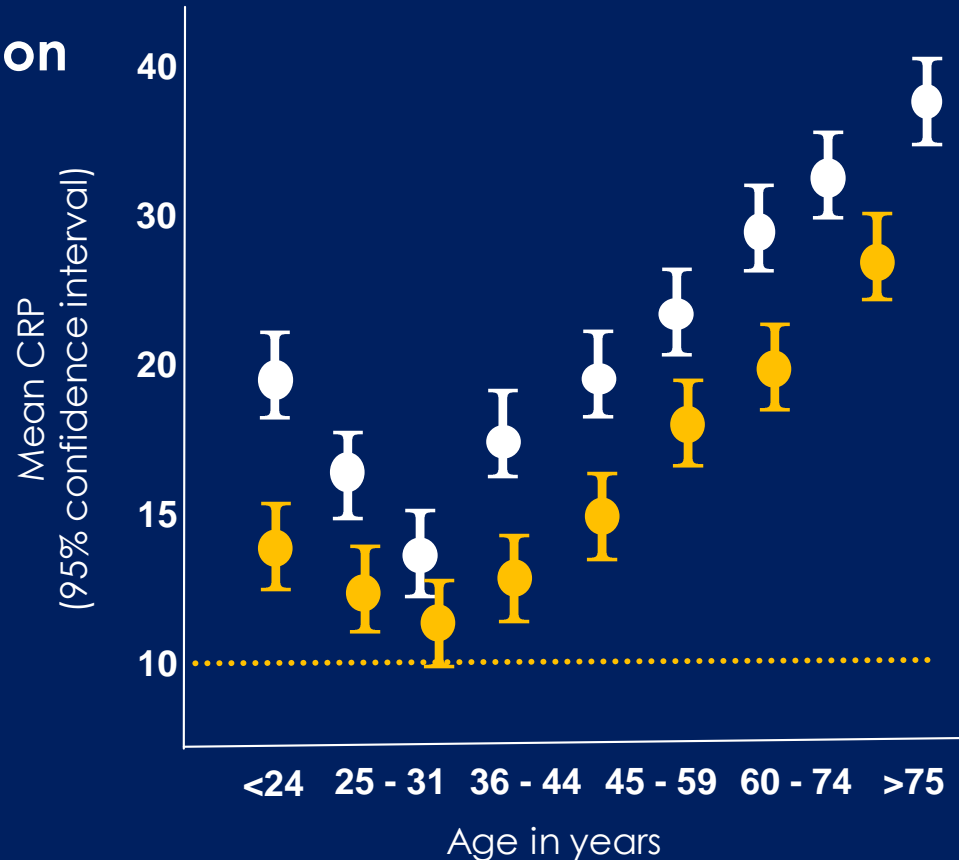
- CRP shows a rapid response to infection and inflammation: increasing within hours of stimulus, and returning rapidly to normal following resolution.
- CRP is not affected by conditions such as pregnancy, drug use, anemia and plasma protein variations.
- CRP reference ranges also have variations for age or gender.

What is a Normal CRP Value



What is a Normal CRP Value

- US National Health & Nutrition Examination Survey
- 9,000 adults
- Mean level as 2.1 mg/L
- 90 % had levels < 10 mg/L
- Corrected CRP
 - ♀ = (age +6) / 5
 - ♂ = age in years / 5



Woloshin S, Schwartz LM **Distribution of C-Reactive Protein in the US.**

N Engl J Med 2005; 352 (15): 1611- 3.

Wener MH, Daum PR, McQuillan GM. **The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration.**

J Rheumatol 2000; 27(10): 2351- 9.

CRP as an Indication of Severity

Table 2: CRP as an indication of severity

CRP (mg/L)	
10 - 40	Mild Inflammation, viral or bacterial infection
40 - 100	Moderate Inflammation, viral or bacterial infection
100 - 200	Marked inflammation, bacterial infection
> 200	Severe bacterial infection or extensive trauma

How do ESR and CRP differ

Table: Comparison of ESR and CRP

Results affected by:	ESR	CRP
Gender	Yes	Yes
Age	Yes	Yes
Pregnancy	Yes	No
Temperature	Yes	No
Drugs (eg. steroids, salicylates)	Yes	No
Smoking	Yes	No

Comparison of ESR and CRP

Table 2
Comparison of ESR and CRP

	ESR	CRP
Cost	Low	Low
Throughput time	5 minutes to 2 hours	Typically less than 30 minutes
Measurement	<i>Indirect measure of proteins</i> Corresponds primarily with fibrinogen levels in acute inflammation	<i>Direct protein measurement</i> Measures specific acute-phase protein
Rises	Days to weeks	Hours to days
Peak level	1–2 weeks	48 hours
Declines	Slowly (1–2 weeks)	Rapidly
Age and gender	Significant effect	Mild to moderate effect
Accuracy for inflammation	Frequent false positives	Rare false positives
Affected by multiple confounding factors (eg, RBC abnormalities)	Often	Never/rarely

Data from Johnson HL, Chiou CC, Cho CT. Applications of acute-phase reactants in infectious diseases. *J Microbiol Immunol Infect* 1999;32(2):73–82.

What is the best test to use in different situations?

There are few studies that compare the use of ESR and CRP.

The best approach is to consider the various clinical questions that may be posed during the course of the consultation.

When these test might help?

Screening Asymptomatic patients

- CRP and ESR are *not suitable* as a screen in asymptomatic patients.
- They should only be requested on patients in whom the clinical evaluation has given some indication of a disease process.

Polymyalgia rheumatica

- There is little evidence to suggest CRP is a suitable diagnostic test for the diagnosis of PMR.
- It is recommended both ESR and CRP are requested when considering PMR as a diagnosis, CRP is recommended for the monitoring of PMR.

Temporal (giant cell) arteritis

- It is recommended that CRP and ESR should be tested simultaneously, which will result in a higher sensitivity for diagnosis.

CRP as a cardiovascular disease risk factor

- At this stage, High Sensitivity-CRP (Hs-CRP) is defining its role as a cardiovascular disease risk factor.

When these test might help?

Infection

- CRP is useful when considering an atypical infection, as it can be helpful in differentiating between bacterial and viral infections.
- AS the CRP increases above 100mg/L, the likelihood of a bacterial infection becomes greater than viral infection

Rheumatoid Arthritis

- Neither CRP or ESR are of use when diagnosing rheumatoid arthritis, as there are other defined diagnostic criteria.
- CRP is considered a better measure of the disease activity and it is known that sustained high levels of CRP are associated with worse outcomes.

Malignancy

- Given the non-specific nature of the acute phase response, a definite role of CRP measurements in the management of cancer patients, other than in cases of current infection has not yet been established.

Your Consult

CC: Elevated inflammatory markers

Dear Donald T.

... we reviewed the literature but only the ones with “large crowds” and “SO many people” and it appears that her CRP test is actually normal.

Her clinical exam and consultation questions did not reveal anything “illegal” under oath. Thus, we recommend that close monitoring of the clinical condition can be done.

Sincerely,

Vad

Conclusions

- Recognize the ESR as a indirect measurement of acute phase protein that responds slowly
- C-reactive protein test as a direct acute phase protein that response quickly.
- ESR is affected by many factors whereas CRP is affected by degree of inflammation.
- Adjust factors are needed: ESR ♀ = $(\text{age} + 10) / 2$; ♂ = $\text{age} / 2$
- Adjusted factor are needed: CRP ♀ = $(\text{age} + 6) / 5$; ♂ $\text{age in year} / 5$
- Use of these test for screening patient is not supported.
- ESR and CRP look at different processes of inflammation and data is mixed on the need for testing both.
- Both are incapable of making a diagnosis.

Consultation Questions

Question	CRP	ESR	Comments
Screening asymptomatic patients?			Unlikely to be useful
I know this patient is ill but I don't know why	✓		Actual level of CRP helpful
Could this patient have a significant bacterial infection	✓		CRP good, ESR slow response
Could the patient have post-op infection?	✓		CRP good, ESR slow response
Has the infection responded to this antibiotic	✓		CRP good, ESR slow response
Is this RTI more serious than it seems?	✓		Level of CRP useful
Is this patient responding to a trial of steroid therapy?	✓		CRP good, ESR slow response
Does this patient have PMR?	✓	✓	PMR with a normal ESR occasionally occurs

Consultation Questions

Question	CRP	ESR	Comments
Monitoring PMR	✓		CRP more sensitive indicator of activity
Does this patient have temporal arteritis/GCA?	✓	✓	GCA with a normal ESR occasionally occurs
Monitoring temporal arteritis/GCA?	✓		CRP more sensitive indicator of activity
What is the cause of this/these inflamed joints?	Little use	?	CRP more sensitive indicator of activity
Monitoring rheumatoid arthritis	✓		CRP better measure of the disease activity
Monitoring SLE?	✓	✓	CRP normal during flare, but elevated during infection
Why is the platelet count elevated?	✓	✓	Many different causes which may include inflammation
Prediction of cardiovascular disease	?		Role not yet established