

# Nutrition and Immune Function – The Acute Phase Response and Assessment of Nutritional Status

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# Outline

## Biology of the Acute Phase Response (APR)

- A coordinated physiologic response to infection or injury that clears pathogens and repairs tissue damage. Nutrient metabolism is redirected to support these functions.

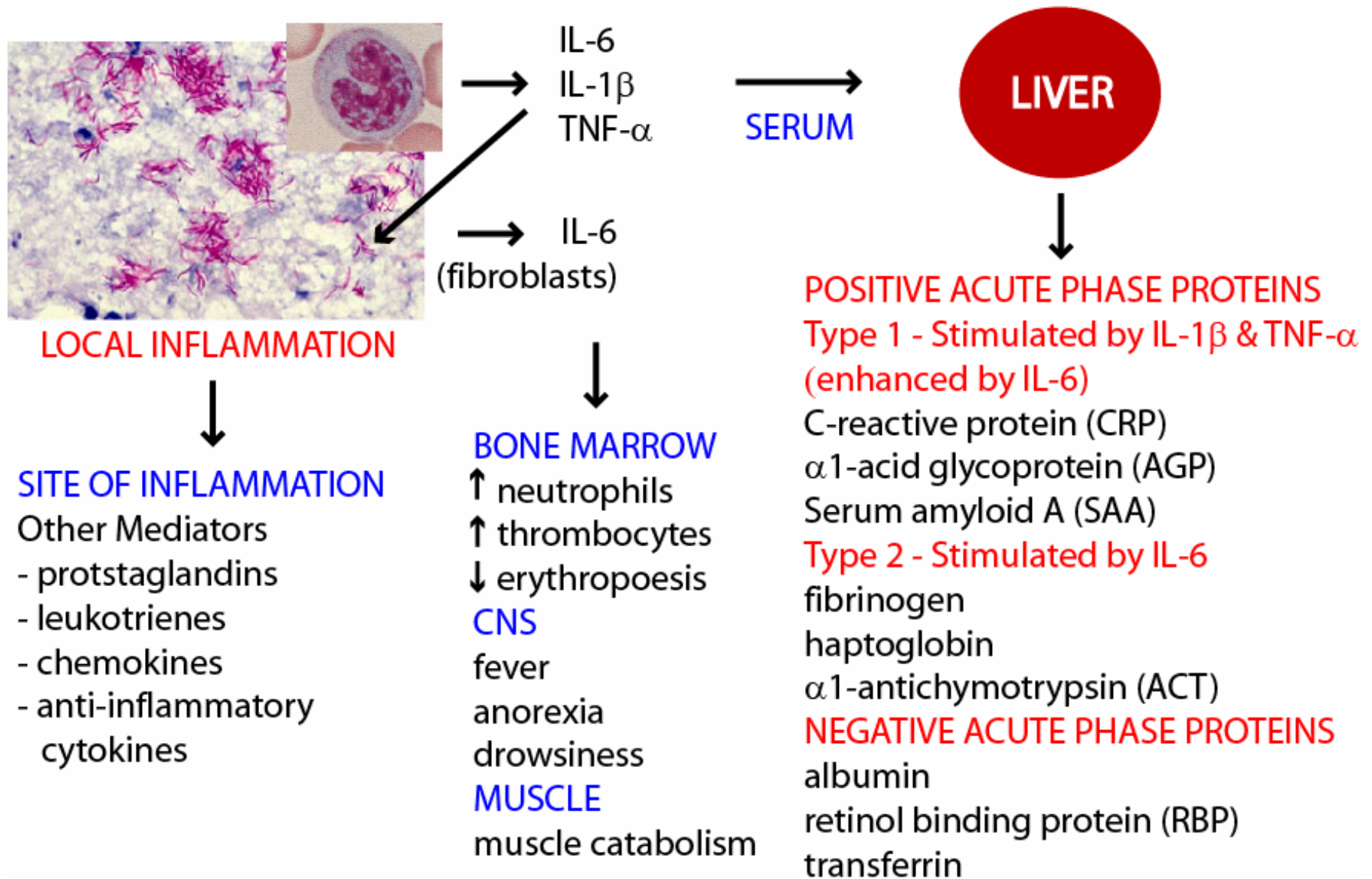
## The APR is a Nuisance for Nutritionists

- During the APR serum iron, zinc and vitamin A (retinol) decrease while serum ferritin increases. This complicates nutritional assessment because it alters the estimated prevalence of micronutrient deficiencies, or potentially obscures the impact of a nutritional intervention on micronutrient status.

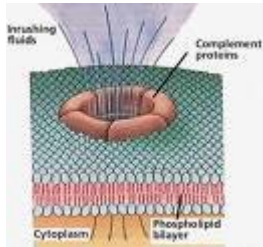
## What to do?

- Potential solutions (and their limitations)

# INDUCTION OF THE ACUTE PHASE RESPONSE



# Functional Groupings of Acute Phase Proteins



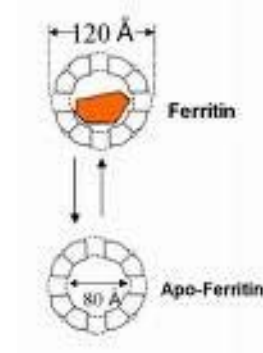
## COMPLEMENT SYSTEM

C3, C4, C9  
Factor B  
C1 Inhibitor  
C4b-binding protein  
Mannose-binding lectin



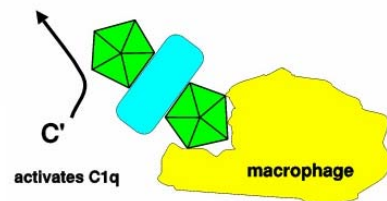
## COAGULATION & FIBRINOLYTIC

Plasminogen activator-inhibitor 1  
tissue plasminogen activator  
plasminogen  
fibrinogen  
urokinase  
protein S  
citronectin



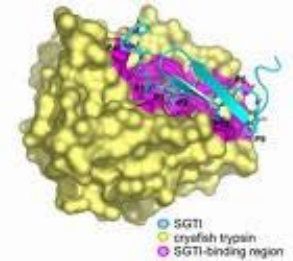
## OTHER (antibacterial; scavenger)

C-reactive protein  
serum amyloid A  
 $\alpha$ 1-acid glycoprotein  
ferritin



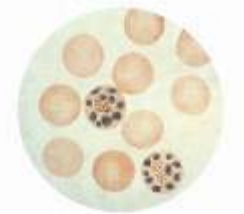
## ANTI-PROTEASES

$\alpha$ 1-protease inhibitor  
 $\alpha$ 1-antichymotrypsin  
pancreatic trypsin inhibitor  
 $\alpha$ -trypsin inhibitors



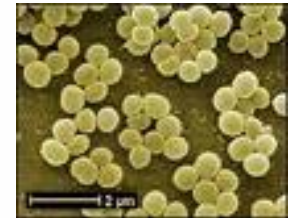
## TRANSPORT PROTEINS

ceruloplasmin (Cu)  
haptoglobin (Hgb)  
hemopexin (heme)



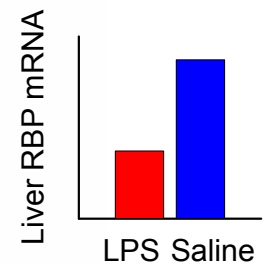
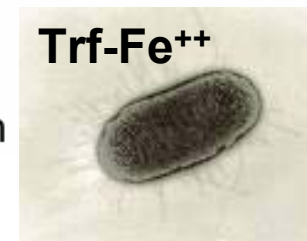
## INFLAMMATION

secreted phospholipase A2  
LPS-binding protein  
IL-1 receptor antagonist  
granulocyte colony stim. factor

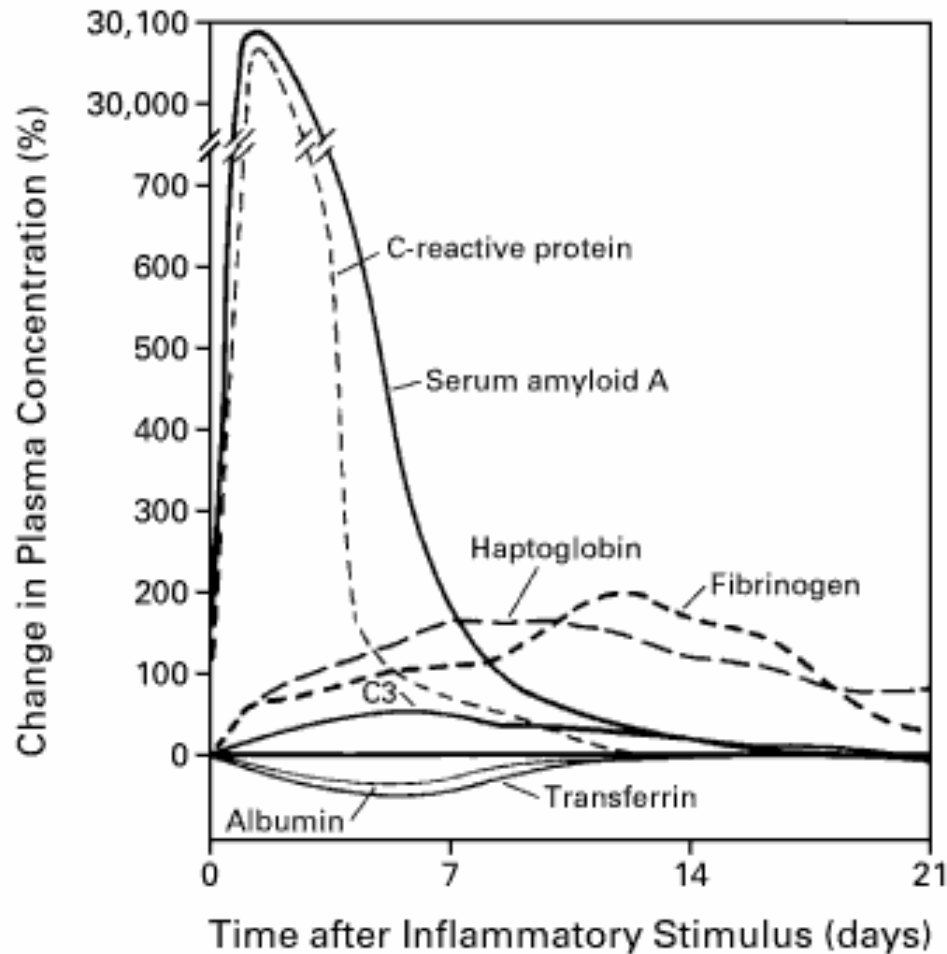


## NEGATIVE APP's (transport)

retinol binding protein  
albumin  
transferrin  
transthyretin



# Serum Levels of Acute Phase Proteins Determined by Severity of Inflammation



C-reactive protein (CRP):  
What is high? What is low?

Pneumonia (mg/L) >100

Clinically significant >10

Cardiovascular risk (but otherwise healthy) >3

“Healthy” 1

# Assessing Vitamin A Status in Populations: Impact of the Acute Phase Response (APR)

**Problem** – Subclinical infections induce the APR, depress serum retinol and inflate the estimated prevalence of deficiency. What to do?

**Solution # 1** – Use an acute phase protein (e.g., CRP) to identify subjects with and without an active APR. Report serum retinol levels and prevalence rates of deficiency in those with and without elevated CRP.

**Solution # 2** – Adjust serum retinol using correction factor based on difference between those with and without elevated CRP.

**Solution # 3** – Use multiple acute phase proteins to adjust for phase or severity of infection.

## Example of Solutions #1 and #2

Cross-sectional study of 577 healthy children, 3 - 7 yr in Dhaka (Mirpur). Multiple linear regression (MLR) used to develop correction factors based on C-reactive protein (CRP) categories.

Serum retinol ( $\mu\text{mol/L}$ )	Serum CRP, mg/L ( <i>n</i> )					P
	<1 (132)	1 to <2 (142)	2 to <5 (185)	5 to 10 (80)	$\geq 10$ (38)	
<b>Mean*</b>	<b>0.93<sup>a</sup></b>	<b>0.89<sup>a</sup></b>	<b>0.81<sup>b</sup></b>	<b>0.77<sup>b</sup></b>	<b>0.62<sup>c</sup></b>	<0.001
% "decrease"	0	4	13	17	33	
<b>&lt;0.70 (%)</b>	<b>16</b>	<b>24</b>	<b>36</b>	<b>39</b>	<b>74</b>	<0.001
0.70–1.05 (%)	54	53	47	50	21	
$\geq 1.05$ (%)	30	23	17	11	5	

\*different superscripts indicate means are significantly different

### Correction based on MLR:

For serum CRP (mg/L) levels

1 to < 2 add 0.04  $\mu\text{mol/L}$

2 to < 5 add 0.12

5 to < 10 add 0.16

$\geq 10$  add 0.32

### Effect of correction on % deficient in entire population

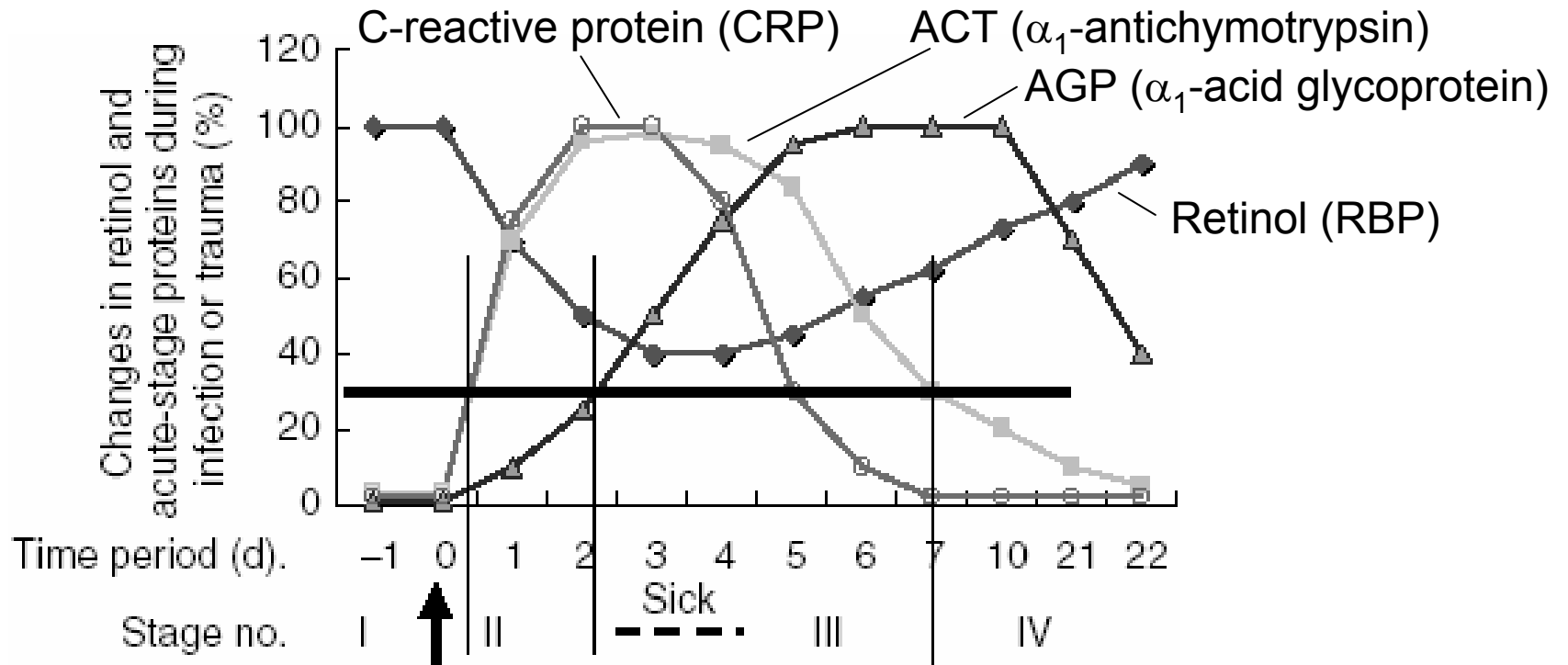
Serum retinol	Before	After
<b>&lt;0.70 (%)</b>	<b>31</b>	<b>16</b>
0.70–1.05 (%)	49	55
>1.05 (%)	20	29

# Interaction of Vitamin A Deficiency (VAD) With The Acute Phase Response (APR): Impact on Adjusted % Deficient

## *Percentage of Subjects Deficient by CRP Category*

<u>Effect of VAD on APR</u>	CRP Category		<u>Adjusted % Deficient</u>
	<u>Low</u>	<u>High</u>	
No effect	16%	↔ 16%	16% (OK)
↑ risk or magnitude	14%	→ 18%	14% (too low)
↓ risk or magnitude	18%	← 14%	18% (too high)

## Solution #3 - Correct Based on Stage (Severity?) of Infection Using Multiple Acute Phase proteins



Group	Stage of inflammation	Raised APP*	Retinol decrease
I	Healthy	None	None
II	Incubating or pre-clinical	CRP only	13 %
III	Early convalescence	CRP & AGP	24 %
IV	Late convalescence	AGP only	11 %

\*CRP > 5 mg/L; AGP > 1 g/L

Thurnham DI et al. Proc Nut Soc 64:502 2005.

# Conclusions

Report data in those with and without APR

Adjustment may be useful

- When prevalence of APR is high
- When necessary to adjust for seasonal variation of infections in longitudinal studies
- But beware of underlying assumptions!

Issues to address in a longitudinal study

- Determine how many “healthy” subjects with elevated APPs really are deficient
- Compare different APPs and their cut-offs

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