

Rainer Gross Award Ceremony

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Hildegard-Grunow Foundation Award Criteria

1. Researchers pursuing innovative ideas and projects in nutrition and health in developing countries in the last 5 years
2. Practical solutions for urgent nutritional challenges

We describe innovative methods as practical solutions to remove the effect of inflammation and improve the measurement of iron and vitamin A status

Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis¹⁻³

David I Thurnham, Linda D McCabe, Sumanto Halder, Frank T Wieringa, Christine A Northrop-Clewes, and George P McCabe

ABSTRACT

Background: The World Health Organization recommends serum ferritin concentrations as the best indicator of iron deficiency (ID). Unfortunately, ferritin increases with infections; hence, the prevalence of ID is underestimated.

ulations (5). However, ferritin is also a positive acute phase protein (APP) that is elevated in the presence of inflammation (6, 7). Therefore, the WHO working group recommended that ferritin measurements should be accompanied by the analysis of one or more APPs to detect the pre

AJCN 2010;92(3): 546-55.

Interpretation of serum retinol concentrations

- Serum retinol in apparently-healthy men and women in Linxian Province (PRC).
- No evidence of VAD in the community.
- Jim Olson reported that serum retinol concentrations are
 - physiologically controlled,
 - do not fall until liver reserves are very low,
 - unaffected by VA supplements

	Serum retinol μmol/L mean (SD)	
	Rural Chinese ¹	National Survey UK ²
Men	1.47 (0.38)	2.21 (0.57)
Women	1.17 (0.35)	1.90 (0.529)

1. Thurnham et al Eur J Clin Nutr 1988;42:647-660
2. Gregory et al Diet & Nutrition Survey of British Adults 1990

Marginal malnutrition

- What are the implications of slightly abnormal nutrient values
- Low albumin initially considered a measure of protein status; now a negative acute phase protein
- Prospective British Regional Heart Study* n=7731 men (Phillips et al Lancet 1989 ii 1434)
- Low Alb associated with mortality from CHD, cancer and all causes even when deaths in first 5 years excluded
- But my main interest was in vitamin A

Sub-Clinical Infection and Intestinal Permeability

Intestinal permeability, mucosal injury, and growth faltering in Gambian infants

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P. G. LUNN C. A. NORTHROP-CLEWES R. M. DOWNES

There is controversy over whether children in developing countries can catch up on their growth rates after bouts of diarrhoea. A factor influencing catch-up growth is the extent and duration of mucosal injury. To explore the relation between intestinal disease and growth performance, a non-invasive test of intestinal integrity, the lactulose:mannitol permeability test, was done regularly on children aged 2–15 months, whose growth was monitored over a mean of 7.5 months. The study revealed persistent abnormalities in the small bowel mucosa of 2–15 month old Gambian infants and a negative correlation between these abnormalities and growth. Up to 43% of observed growth faltering can be explained on the basis of these long-term intestinal lesions.

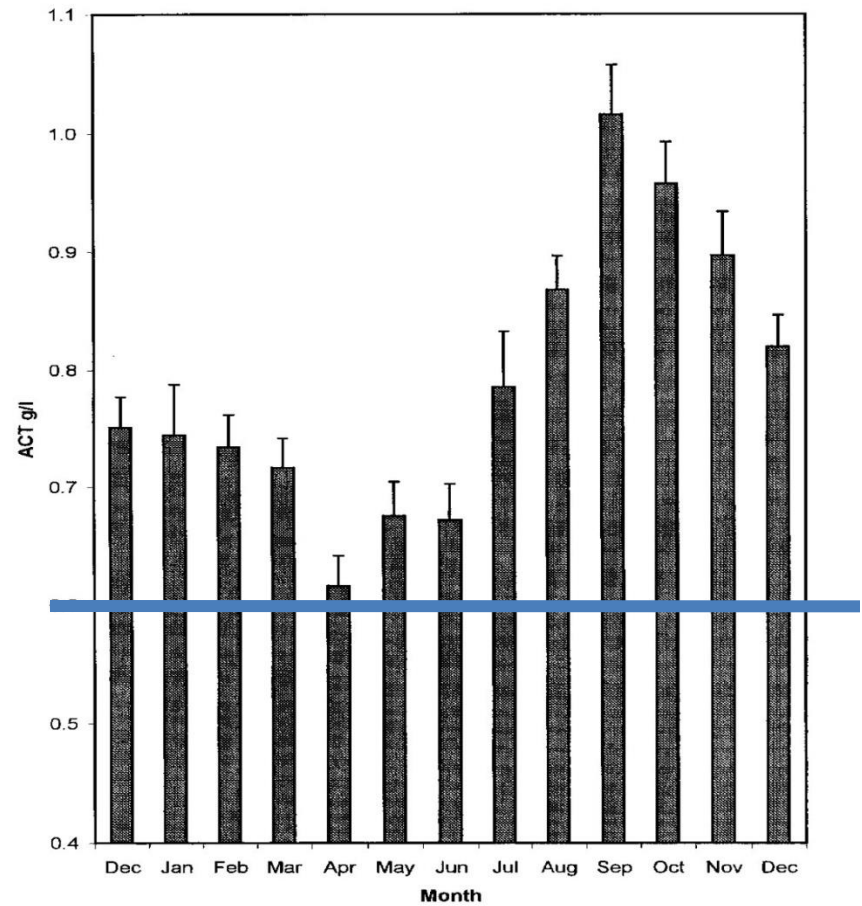
Lancet 1991; 338: 907–10.

It is important to the argument that diarrhoea be regarded as a symptom, not a disease. Just as the pathophysiology of diarrhoea varies with precipitating agents, so will the impact of the illness on weight and height growth and the extent of mucosal injury. Episodes associated with a systemic inflammatory reaction can be expected to result in severe growth faltering during the acute phase of the illness, but in the absence of intestinal injury, catch-up growth could be rapid. In contrast, if the diarrhoea is accompanied by damage to the mucosa of the small intestine then full catch-up growth cannot be expected until such injury has been repaired.

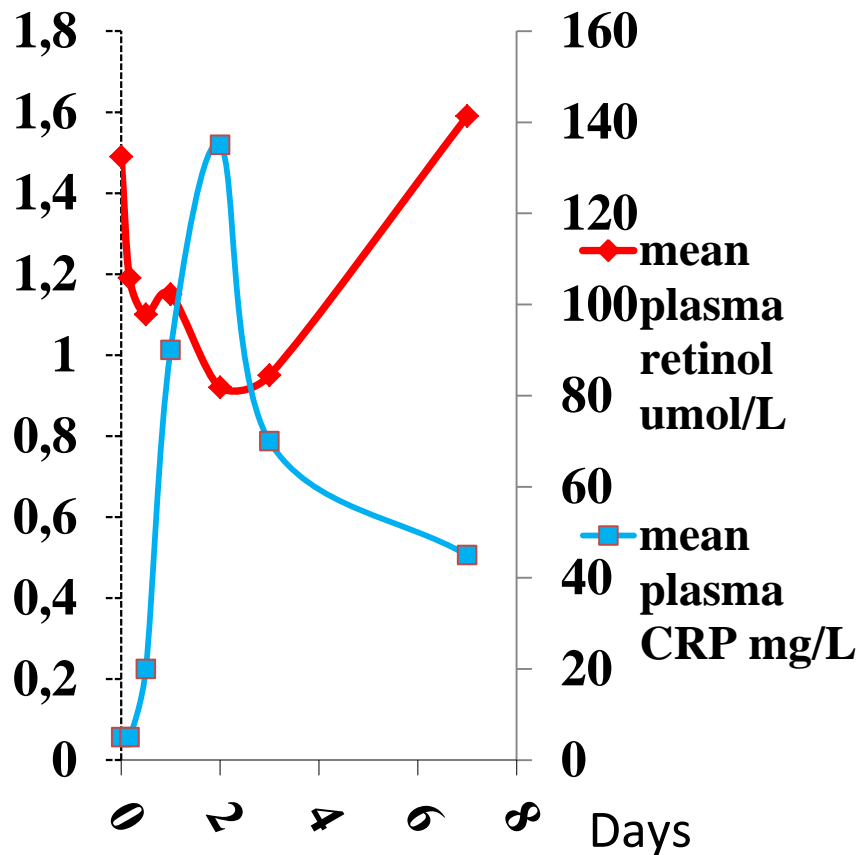
Little is known about the time taken for restoration of normal mucosal structure and function following injury mainly because of difficulties in measuring intestinal status. Until recently mucosal damage could be assessed only by endoscopy and/or biopsy of the small intestine, but the introduction of non-invasive techniques for estimating specific aspects of mucosal function and integrity has enabled repeated measurements to be made even under field

Eureka Moment 1989-'93

- The data (n>1000) revealed that >50% infants had sub-clinical inflammation every month throughout the year
- Least inflammation in April-June correspond with the mango season
- VAD in The Gambia
- What is the relationship between inflammation and VA?



Changes in retinol and CRP following uncomplicated orthopaedic surgery

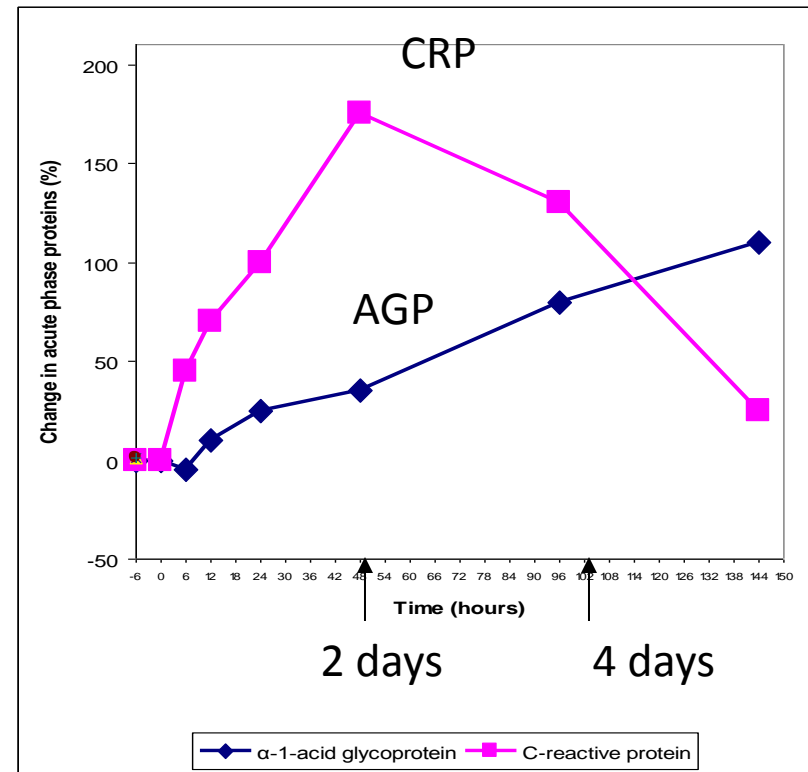


- Shows rapid fall in plasma retinol in first 48 hr in parallel with the rise in CRP
- Fall in retinol ~40%
- Dietary deficiency will take months

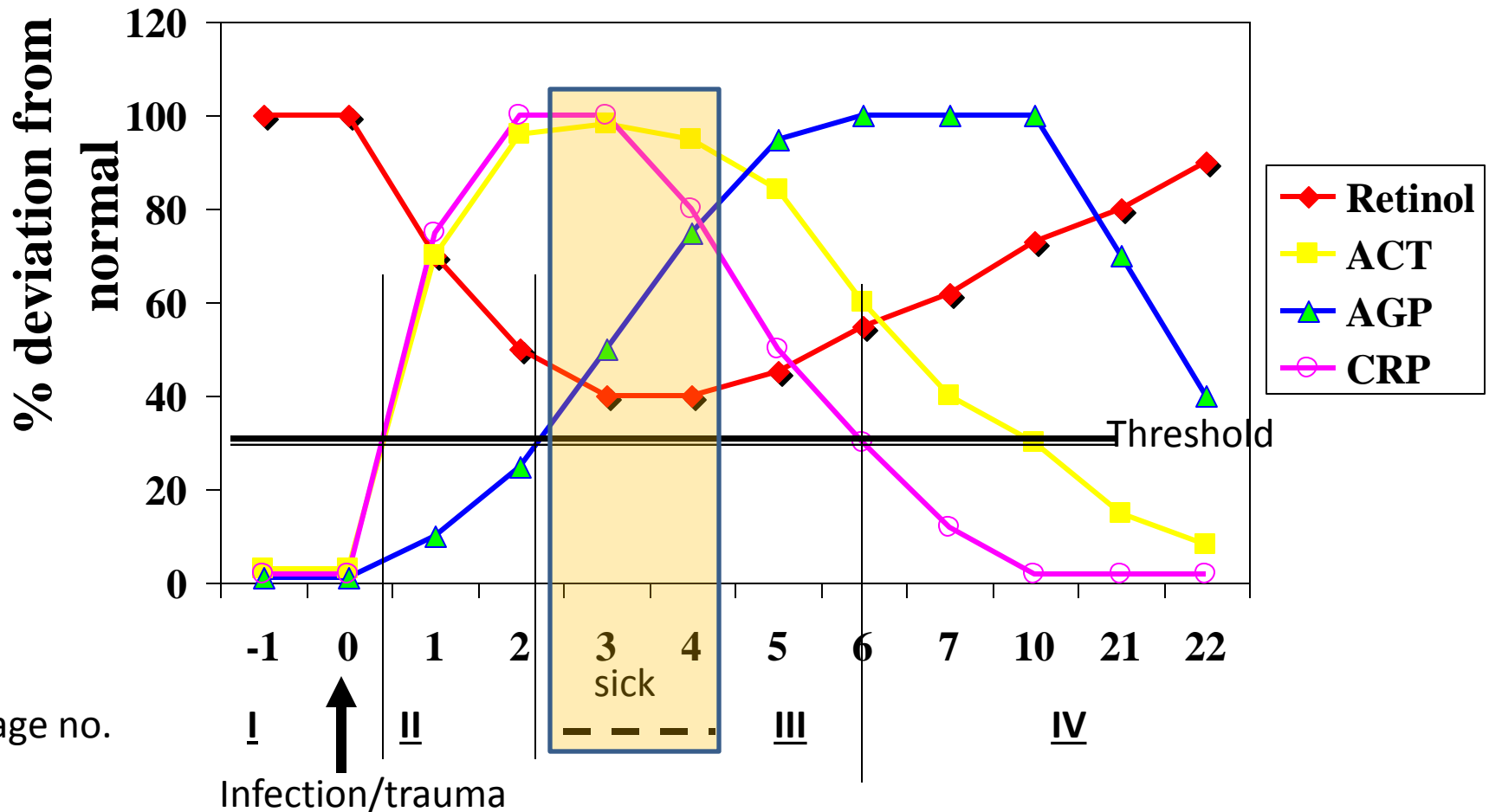
Louw et al 1992 Clin Care Medicine

Useful acute phase proteins to monitor disease

- In first 24 hours following infection on CRP is elevated
- CRP max at 48 hr and falling as clinical signs disappear
- ACT is very similar to CRP but is elevated for longer
- AGP slow to rise, not max until 4-6 d
- Increase in AGP not noticeable until 4 days



Model of behaviour of acute phase proteins and retinol during course of infection



Use of APP to interpret VA status

AJCN 2000;72:1164-9

Interpretation of vitamin A status in apparently healthy Pakistani children by using markers of subclinical infection¹⁻³

Parvez I Paracha, Abdul Jamil, Christine A Northrop-Clewes, and David I Thurnham

ABSTRACT

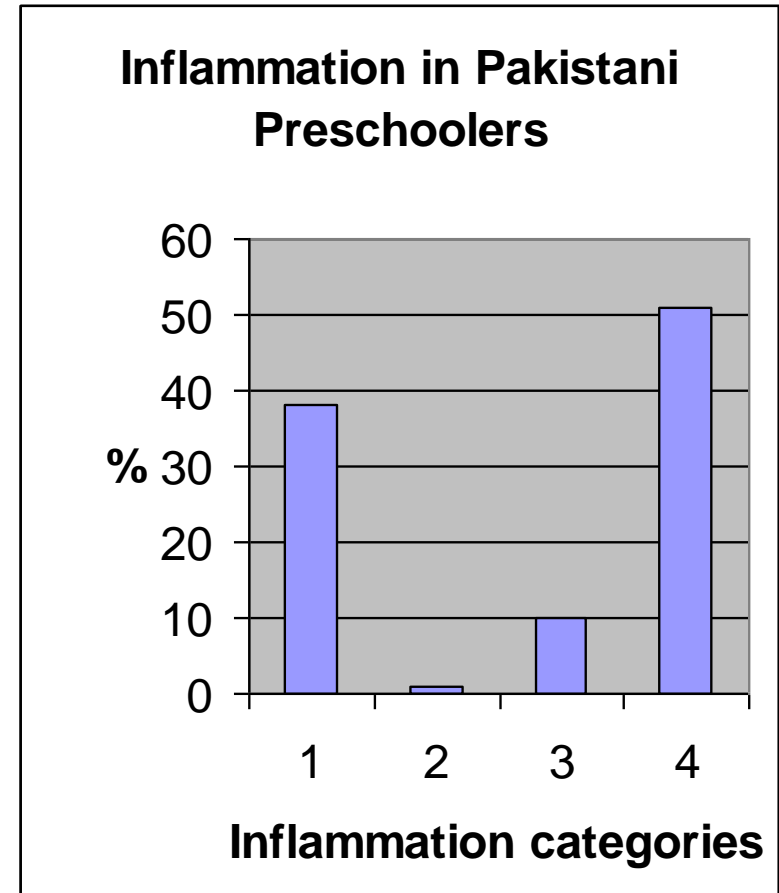
Background: Plasma retinol concentrations are depressed by infection but are commonly used to assess vitamin A status.

Objective: We measured 2 acute phase proteins, α_1 -antichymotrypsin (ACT) and α_1 -acid glycoprotein (AGP), to determine whether they could be used to assist in interpreting vitamin A status.

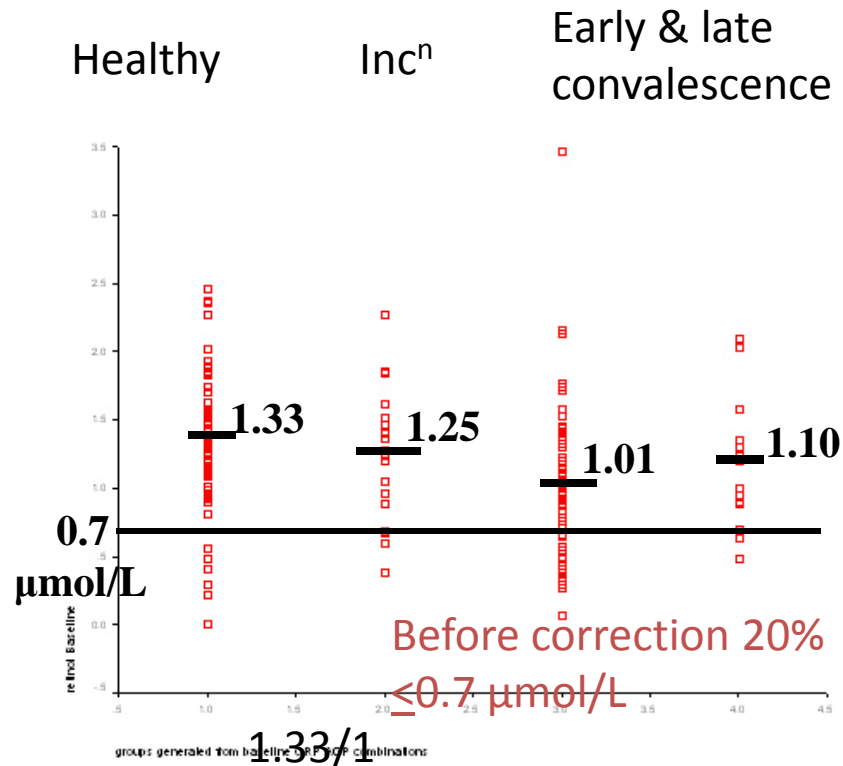
dren (2, 3). These estimates of vitamin A status are based predominantly on dietary or biochemical data, particularly plasma retinol, but both are difficult to interpret because the bioavailability of provitamin A carotenoids is in doubt (4) and plasma retinol concentrations are depressed by concurrent disease (5, 6). The interpretation of other nutrient concentrations is also made more difficult by disease (7, 8), but it has been suggested that

Applying the Inflammation Model

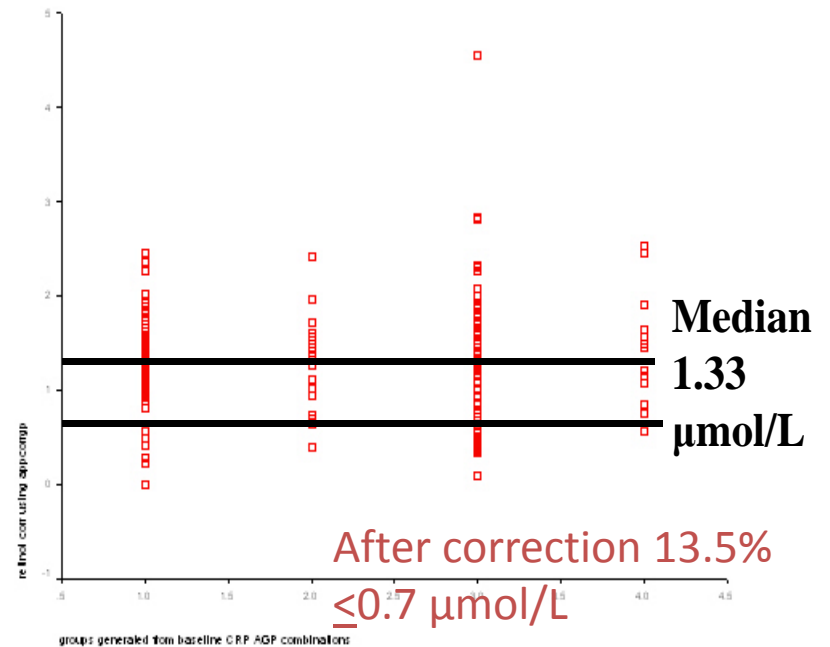
- First applied the model in Paracha et al 2000
- 2519 preschool children
- 39% with no raised APP (VAD 28%; retinol <math><0.7 \mu\text{M}</math>)
- 61% displayed inflammation (VAD 36%)
- most late convalescence
- Subsequently showed how to correct the data



Influence of APP correction on plasma retinol concentrations



Factors .25 1.11, 1.32, 1.21



Meta-analysis to correct plasma retinol concentrations

ARTICLES

Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A deficiency: meta-analysis

D I Thurnham, G P McCabe, C A Northrop-Clewes, P Nestel

Summary

Background Vitamin A deficiency adversely affects child morbidity and survival. This deficiency is estimated by

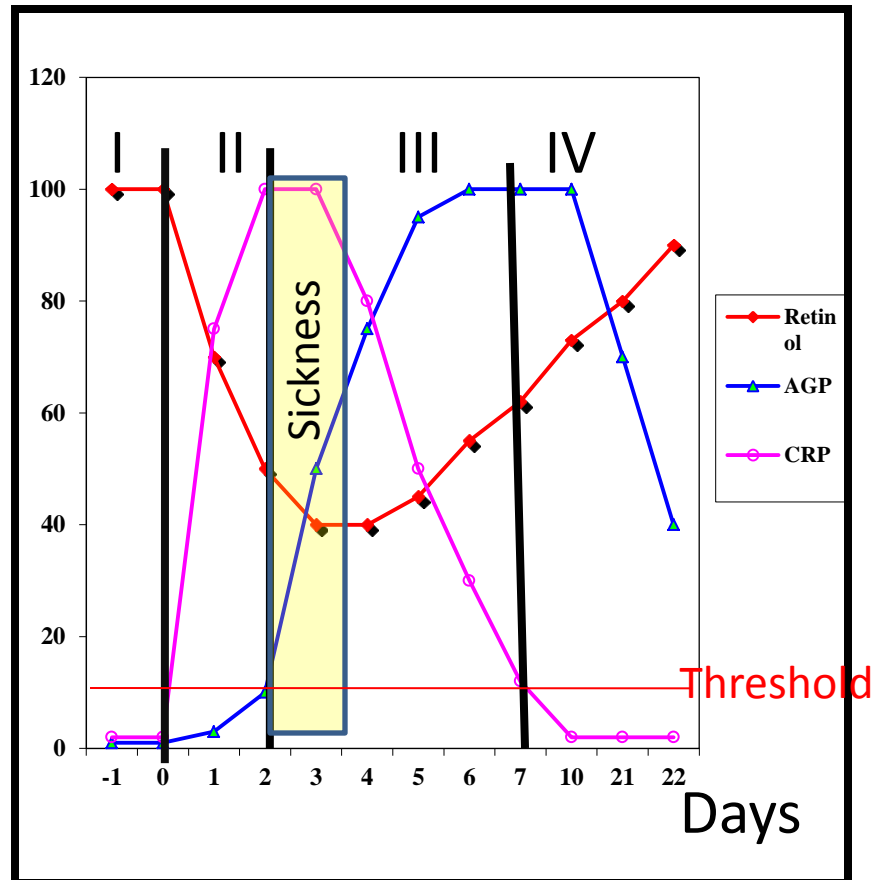
retinol concentrations to be corrected where sub-clinical infection exists, and the healthy sub-group to be identified.

Lancet 2003; **362**: 2052–58

Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A deficiency: meta-analysis (Lancet 2003;362:2052-8)

- Correction Factors
- Gp II (incubation) + 13%
- Gp III (early convalescence) + 24%
- Gp IV (late convalescence) +11%
- Net effect on serum retinol is to increase the concentration and so reduce the prevalence of vitamin A deficiency

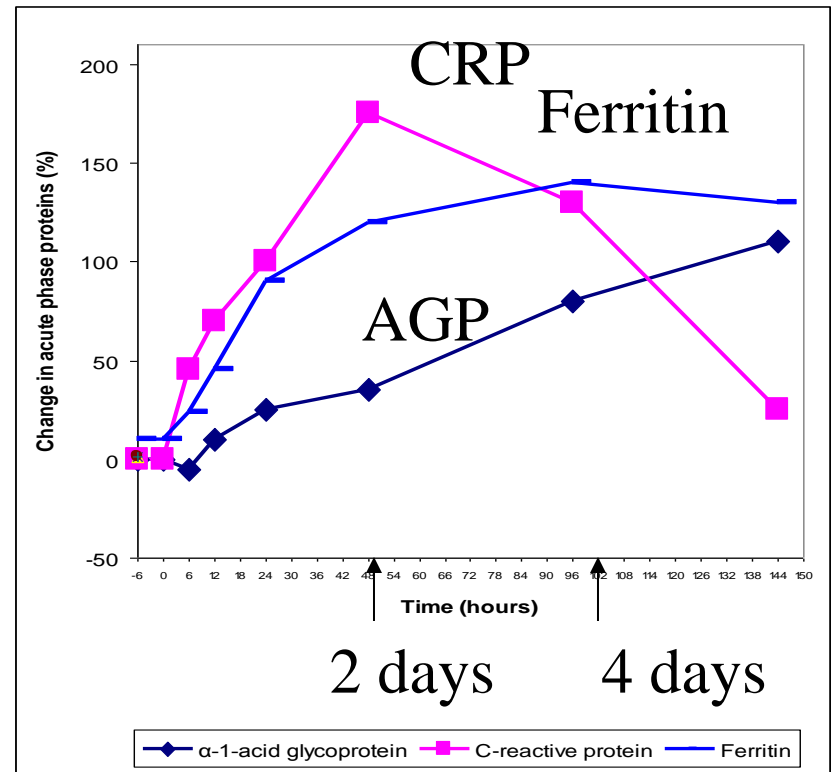
% deviation
from normal



The other important biomarker
which is influenced by
inflammation is serum ferritin

Serum Ferritin and the inflammatory response

- WHO and CDC suggested ferritin is the best marker of iron status but it increases during infection
- Similar rate of rise of CRP and ferritin to 24 hr
- CRP max at 48 hr and falling as AGP approaches max
- AGP slow to rise, not max until 4-6 d
- Ferritin remains high as CRP falls and plateaus bet. 2-6 days
- During convalescence increase in ferritin similar to AGP



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Correction Factors

Subjects in group 2 (incubation) – Reduce by 30%

Subjects in group 3 (early convalescence) – Reduce by 89%

Subjects in group 4 (late convalescence) – Reduce by 33%

The net effect of correction is to reduce serum ferritin concentrations i.e. increase the prevalence of iron deficiency

Acknowledgements

- Hildergard-Grunow Foundation
- My wife Christine Clewes whose initial work in The Gambia was an inspiration for this work
- George and Linda McCabe (Purdue University USA) whose statistical advice and efforts were invaluable .
- Colleagues and friends who freely lent their data for inclusion in the meta-analyses
- Sponsors
 - OMNI Research, US Agency International Development
 - Harvest Plus, Washington