

# **Role of Inflammation in the Macroangiopathy of Diabetes**

**Professor John S Yudkin  
Professor of Medicine  
University College, London**

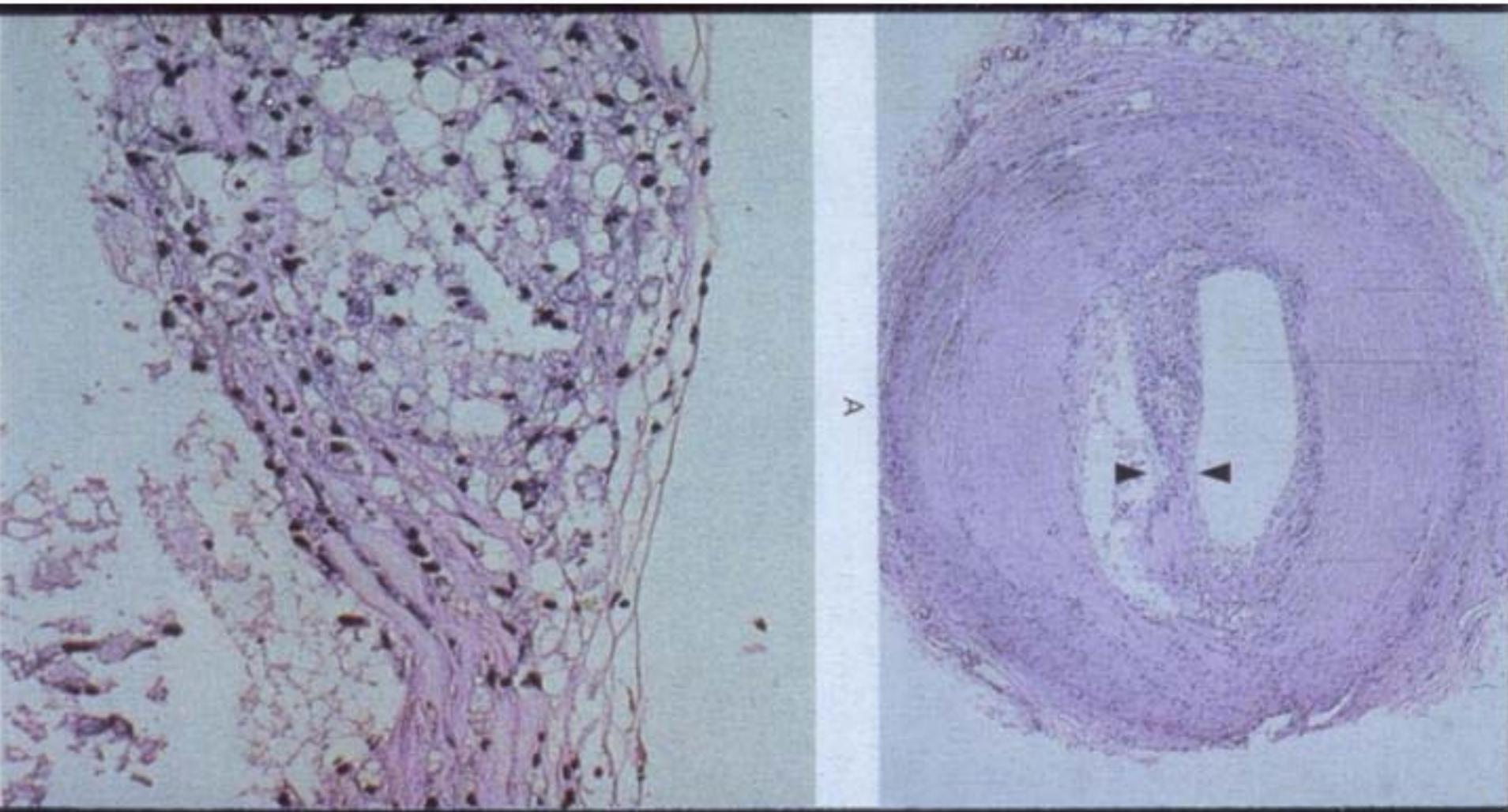


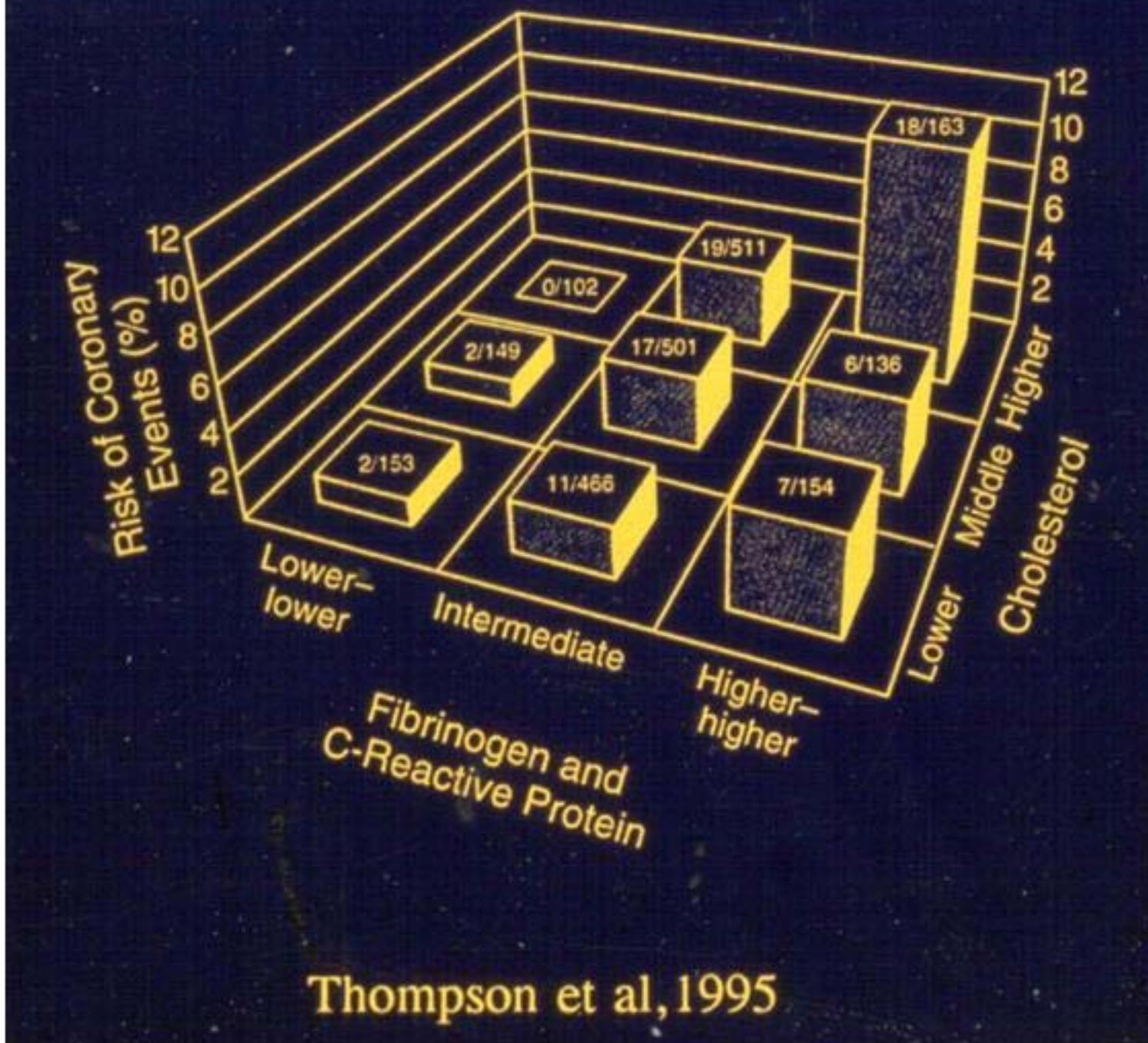
**Crossing Borders - A Challenge in the Y2K  
6th October 2000, Stockholm, Sweden**

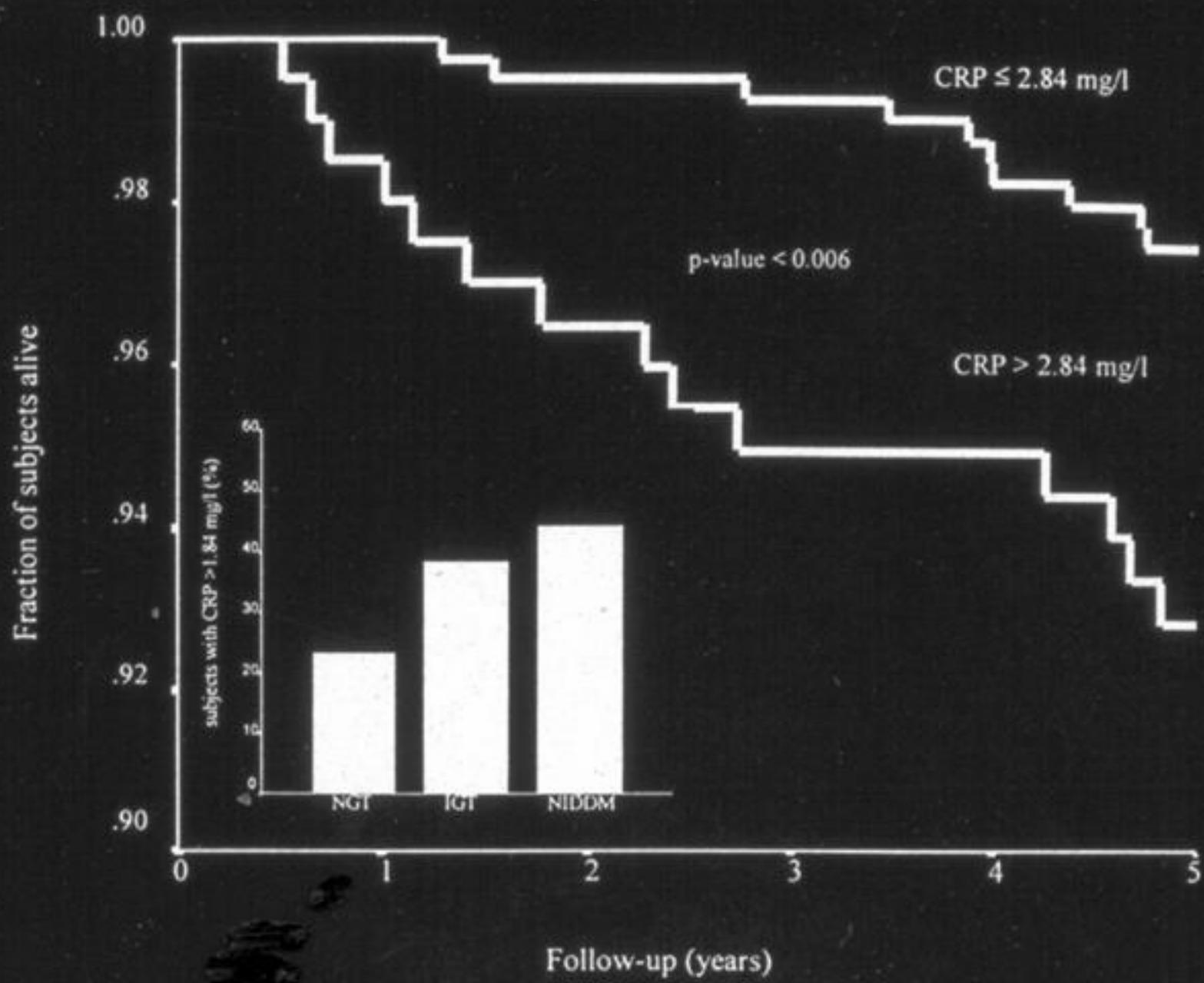
# INTRODUCTION

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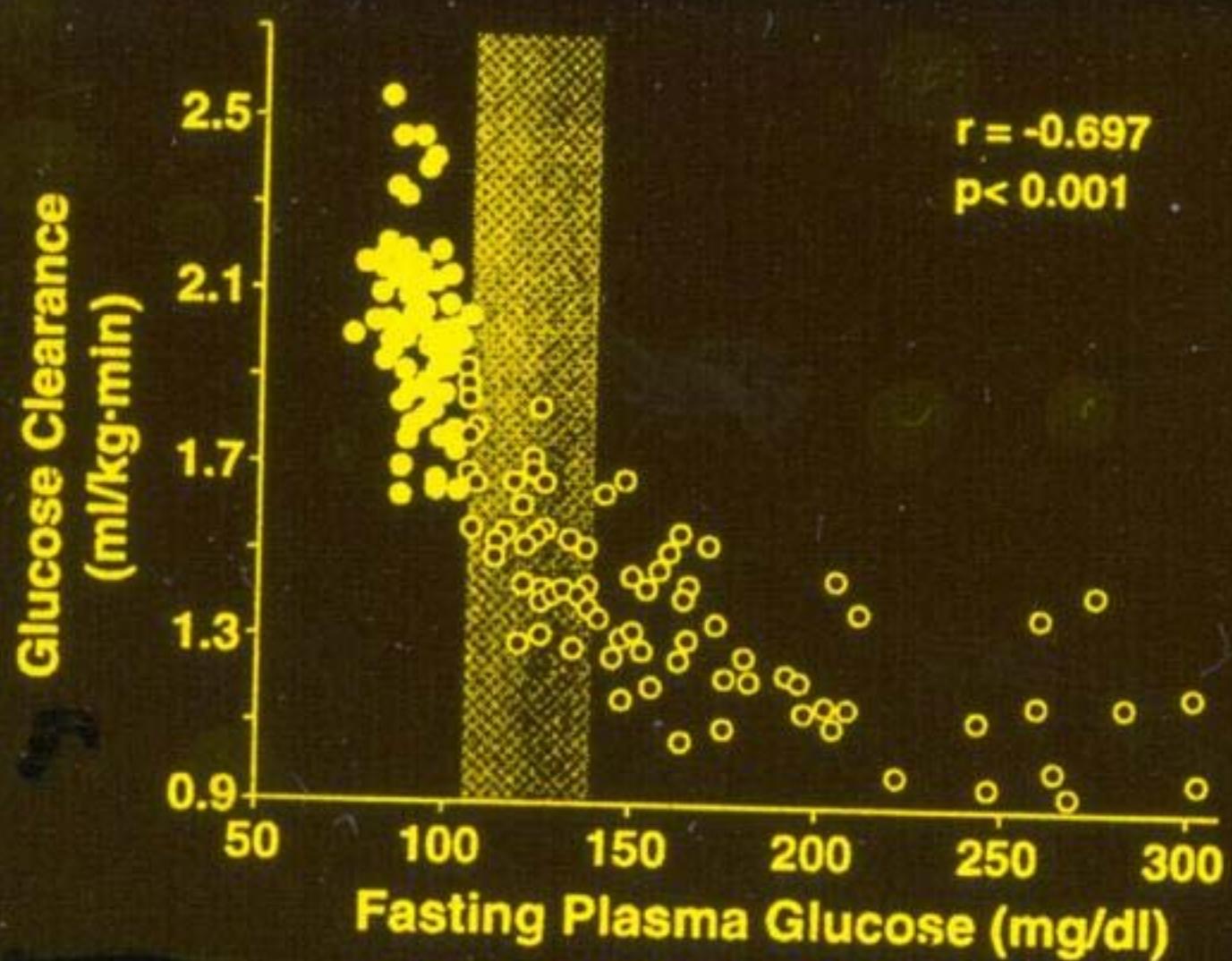
- Inflammation, infection and coronary heart disease
- Insulin resistance and the high risk phenotype
- Insulin resistance and vascular disease - cause, consequence or common antecedent?
- Proinflammatory cytokines, insulin resistance and vascular disease
- Fat as an inflammatory tissue



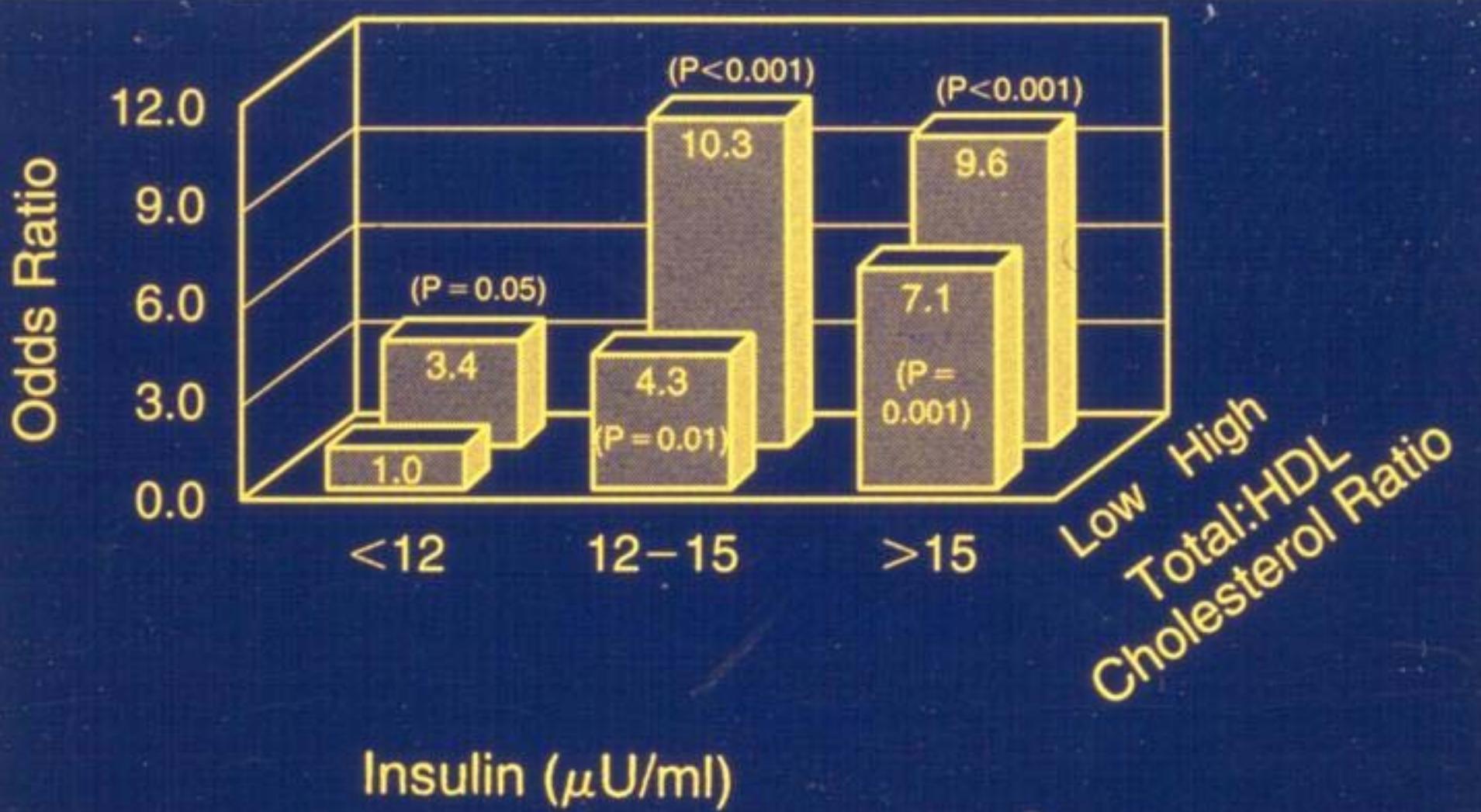




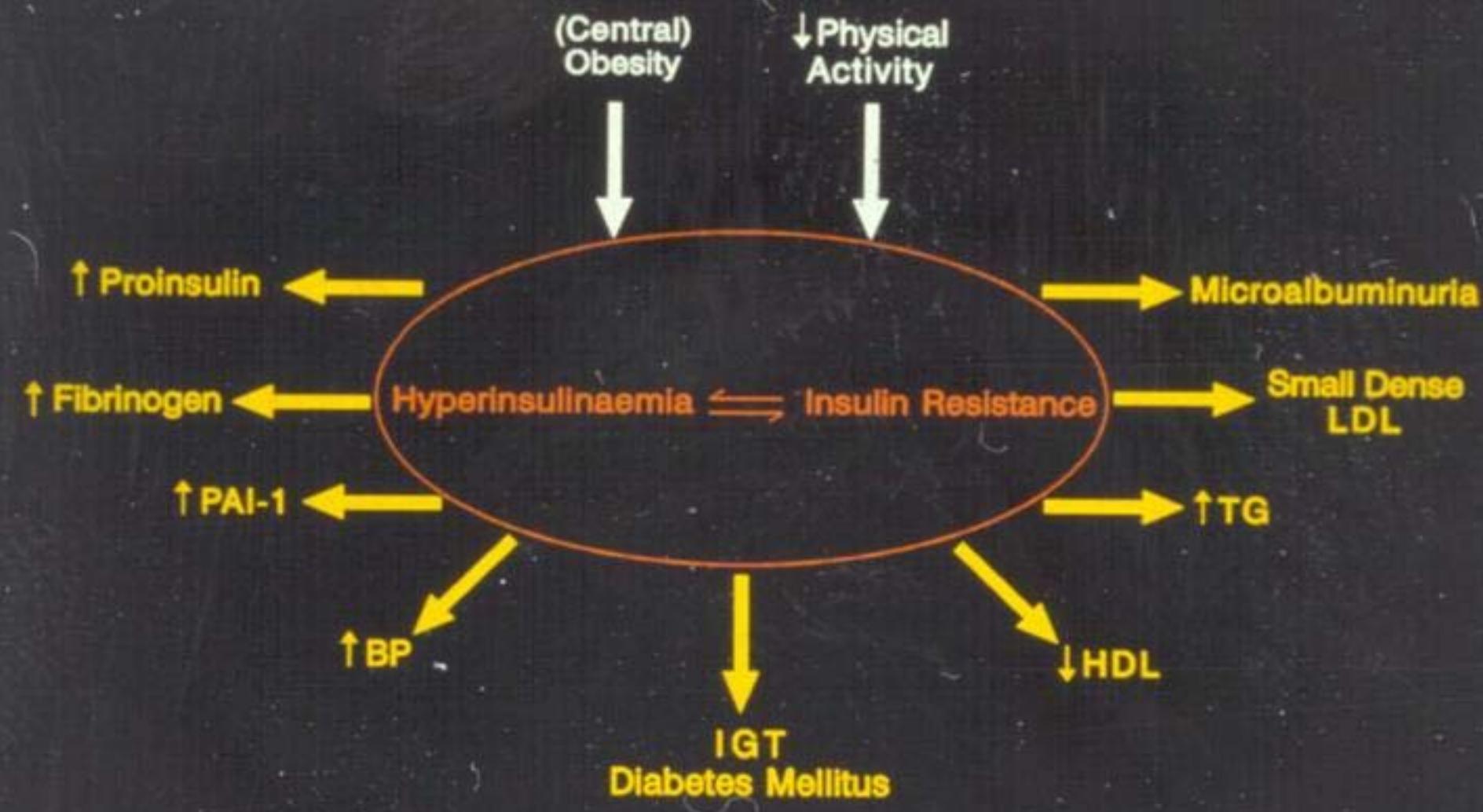
Jager et al, 1999



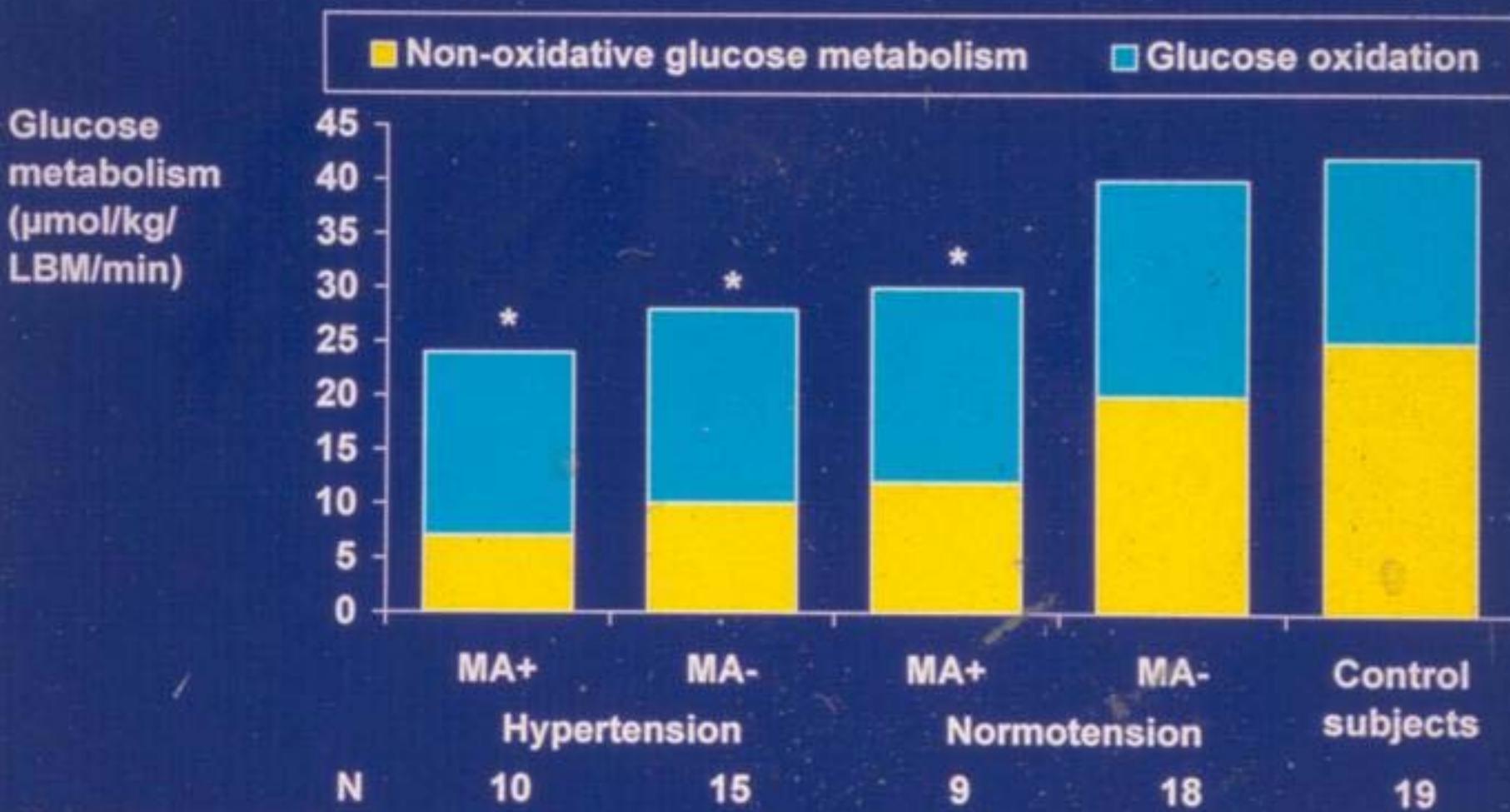
DeFronzo, 1988



Després et al, 1996

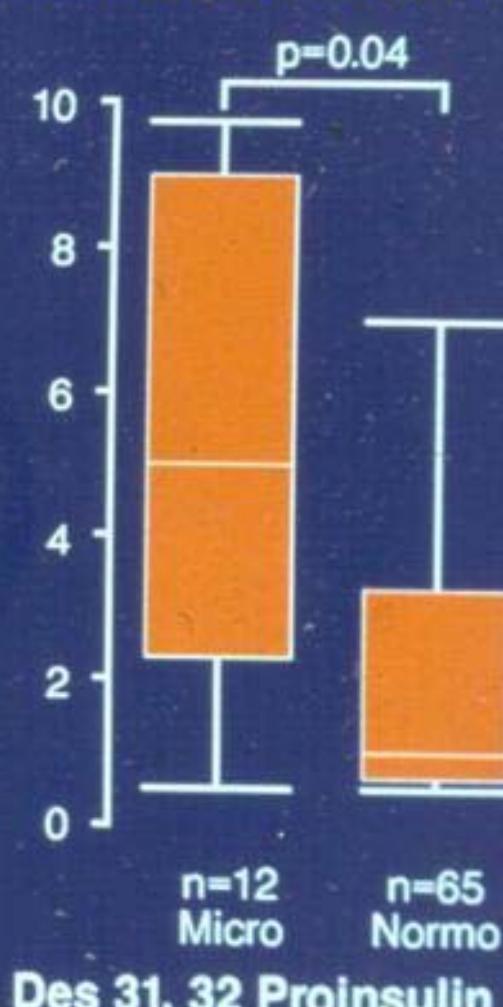
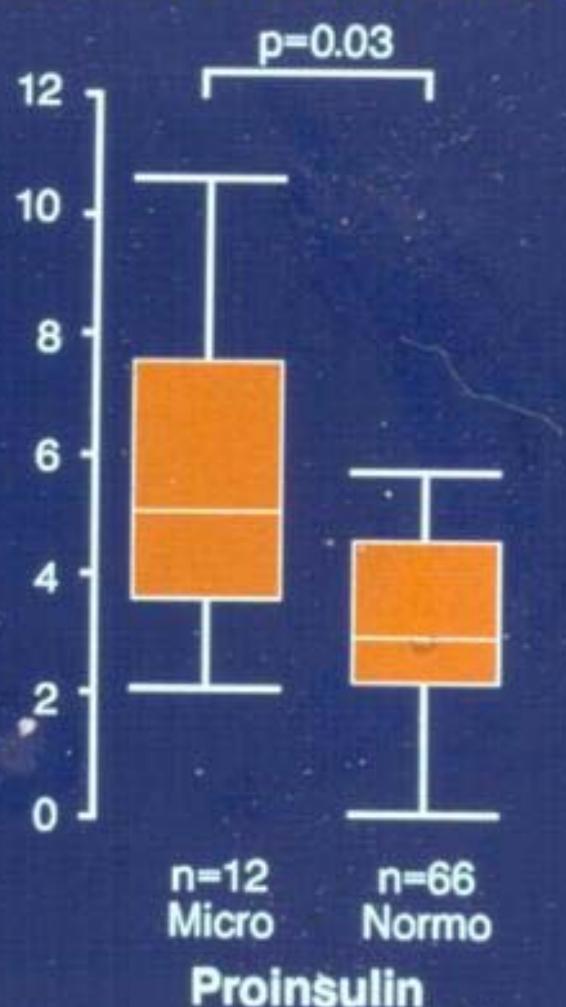


# Insulin-stimulated glucose metabolism in microalbuminuric NIDDMs and controls

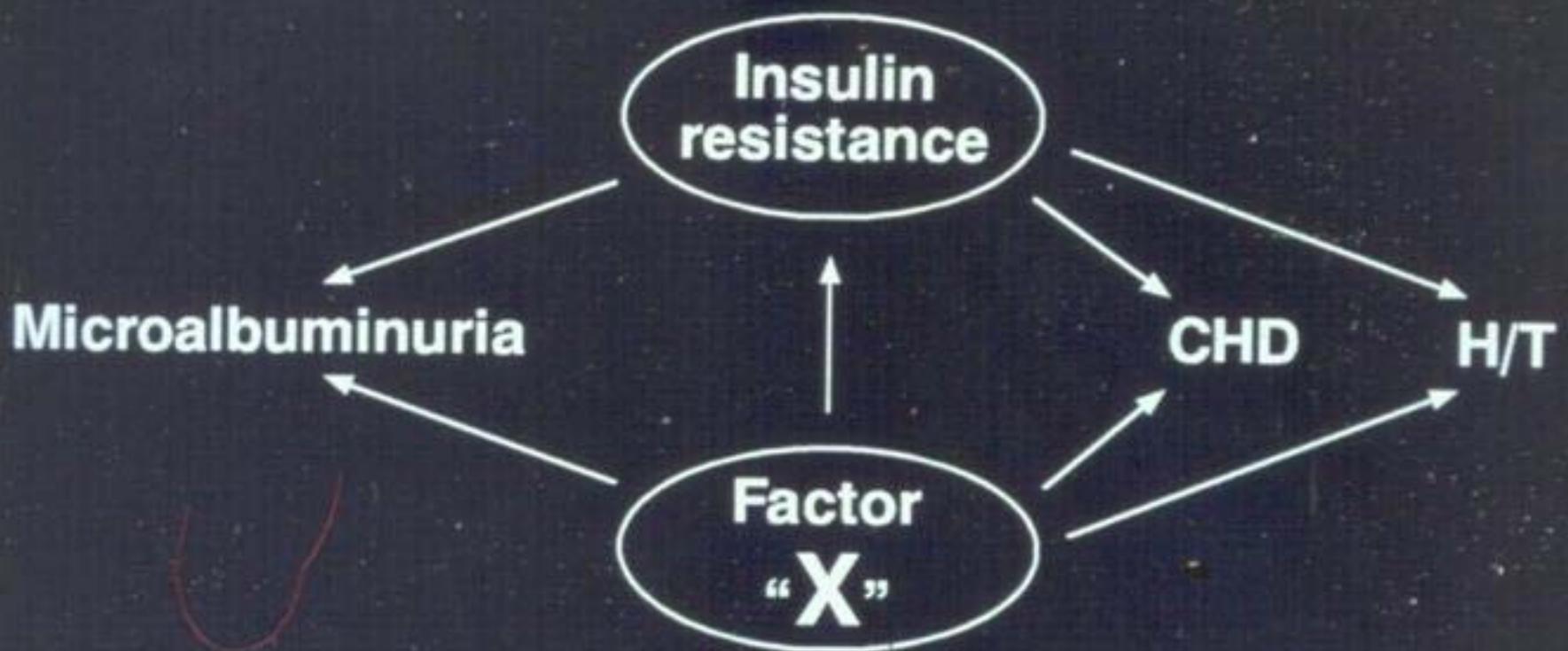


Groop et al 1993

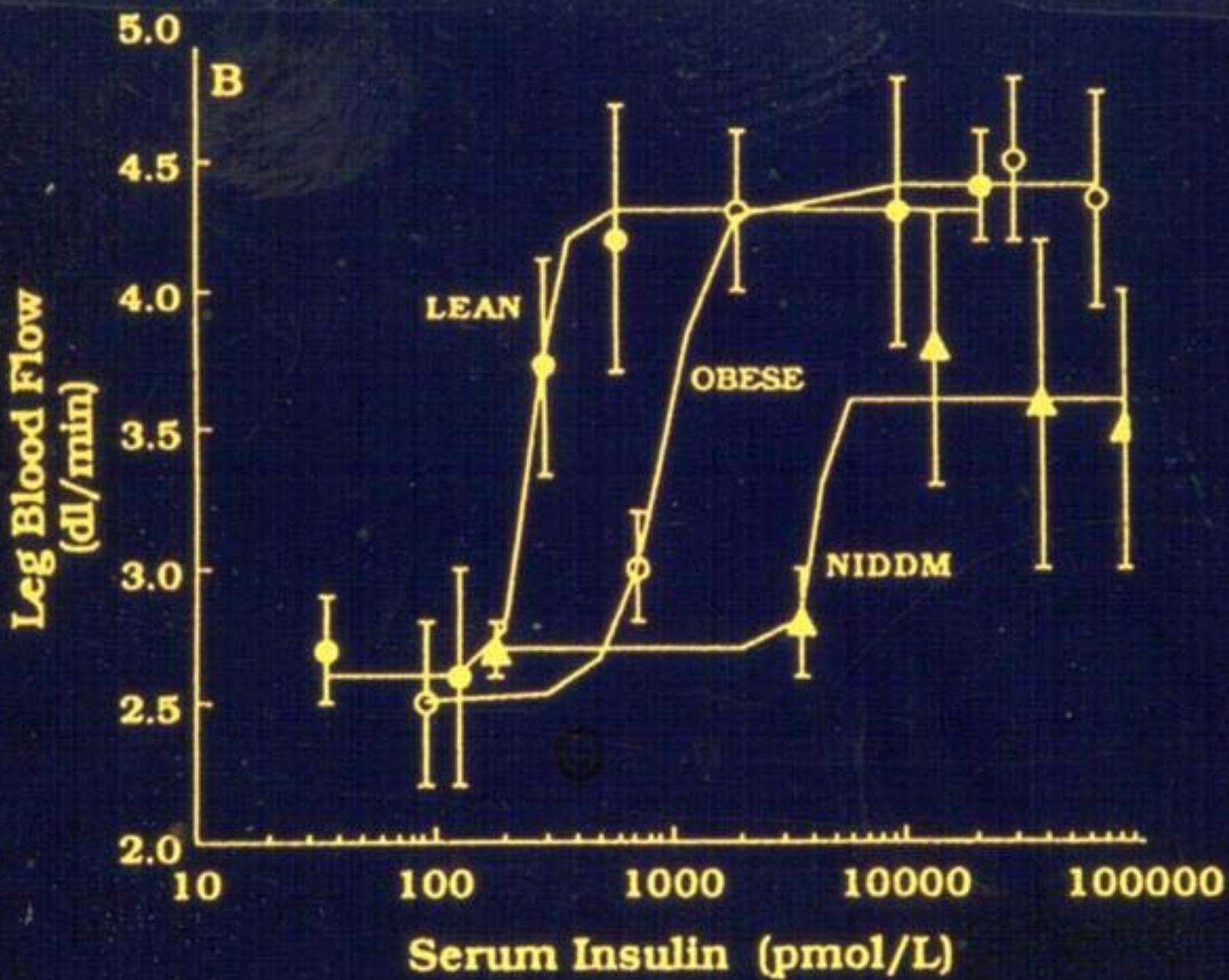
**Concentrations of insulin-like molecules ( $\text{pmol.l}^{-1}$ ) in microalbuminuric and normoalbuminuric non-diabetic subjects**



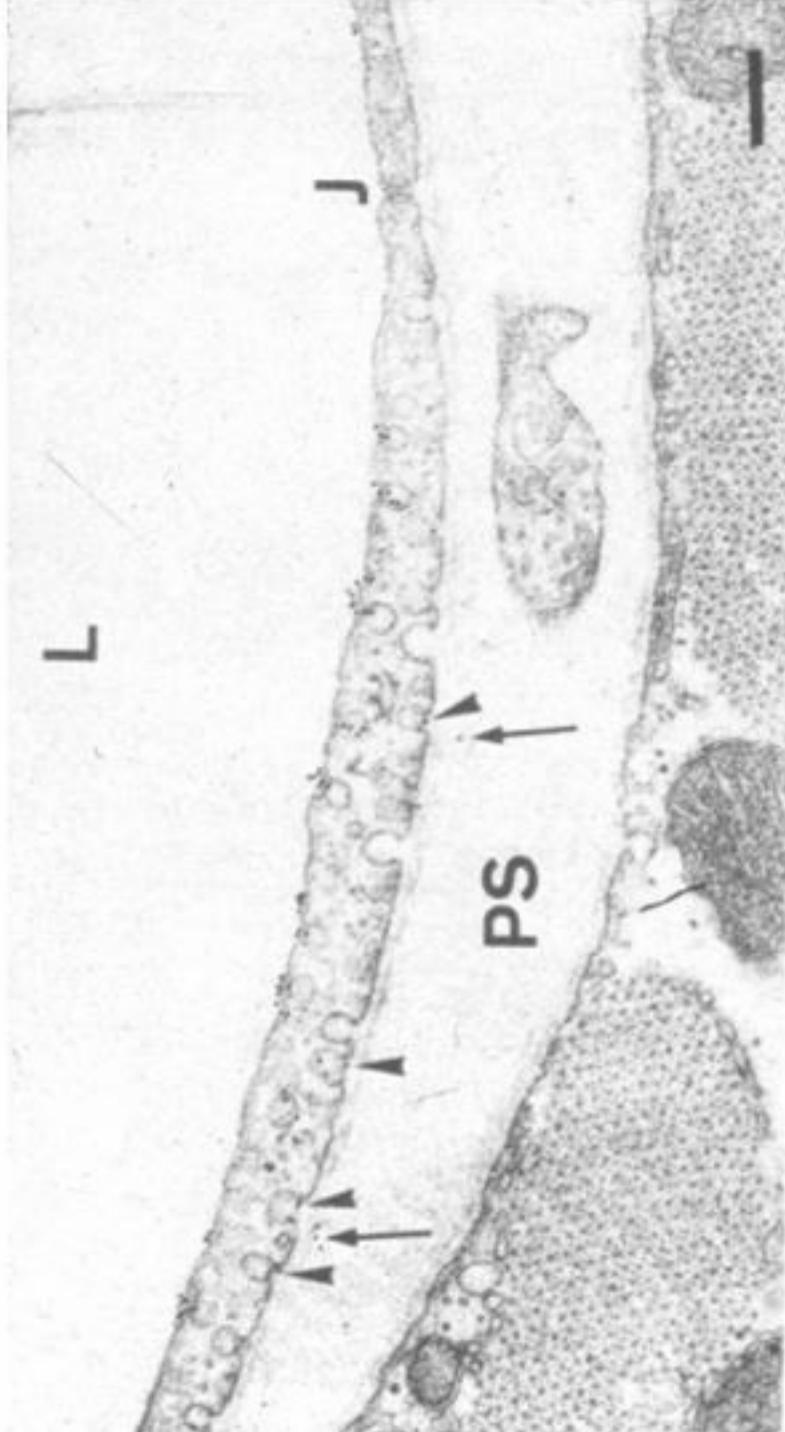
# Microalbuminuria and insulin resistance - cause and effect?



“X” = ?Low birthweight  
?Endothelial dysfunction  
?Proinflammatory cytokines



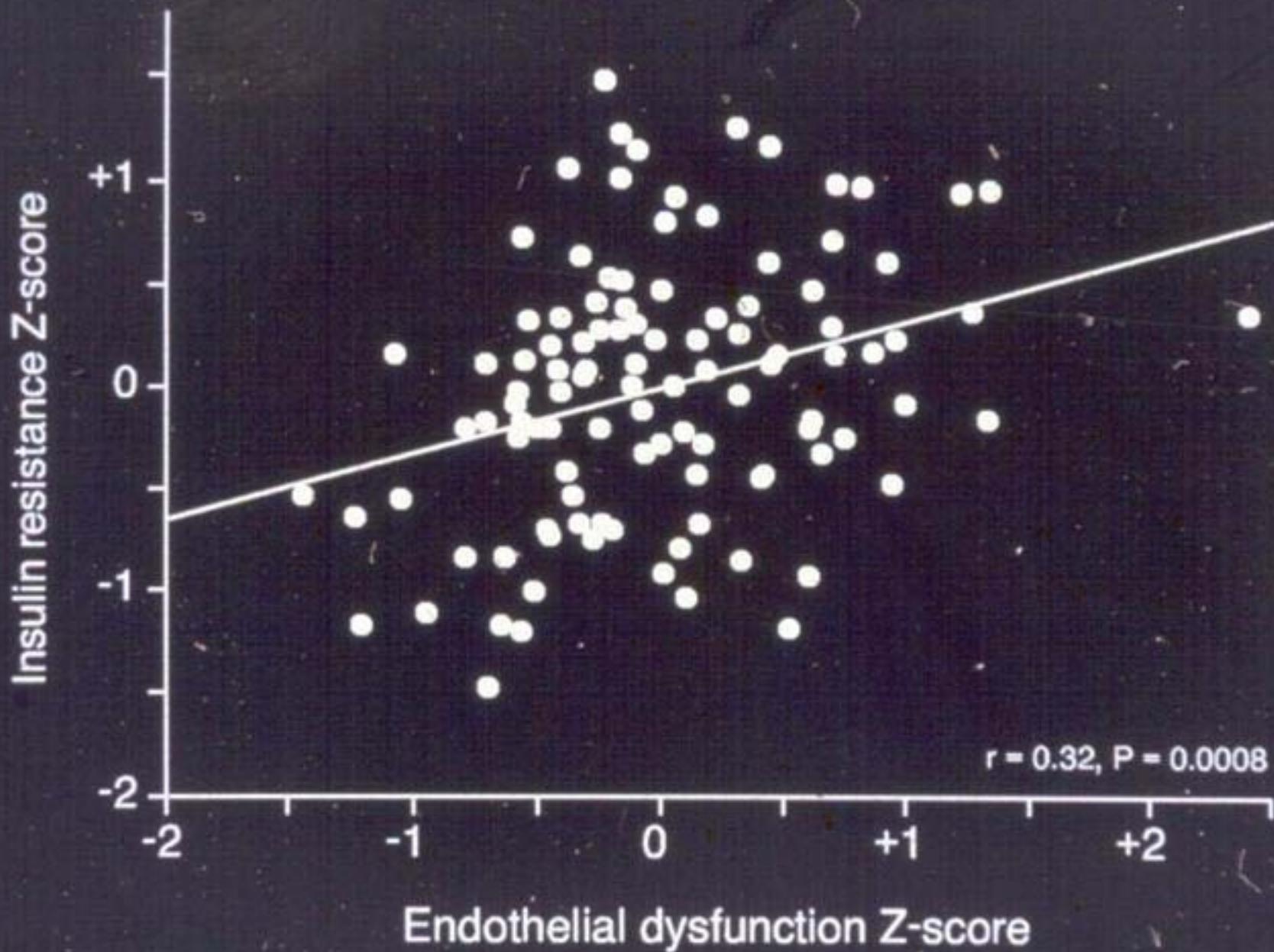
Laakso et al, 1992

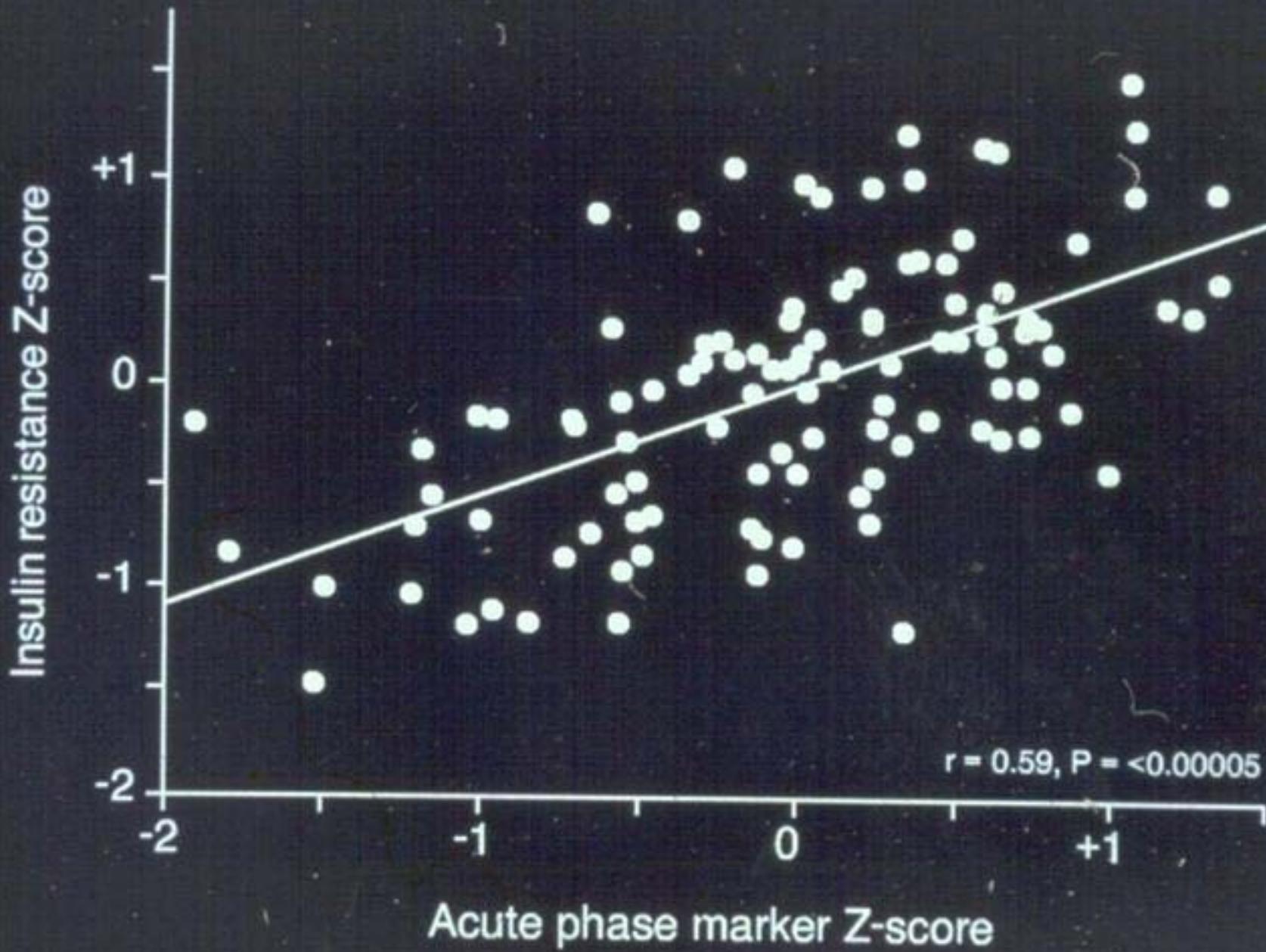


# RELATIONSHIPS OF INSULIN RESISTANCE, ENDOTHELIAL AND ACUTE PHASE VARIABLES

|                      | Triglyceride | Diastolic<br>BP | Cellular<br>fibronectin | Thrombomodulin | C-reactive<br>protein | Fibrinogen |
|----------------------|--------------|-----------------|-------------------------|----------------|-----------------------|------------|
| Insulin              | 0.39***      | 0.34***         | 0.23*                   | 0.07           | 0.22*                 | 0.16       |
| Triglyceride         | -            | 0.25**          | 0.33**                  | 0.24*          | 0.27**                | 0.13       |
| Diastolic BP         | -            | -               | 0.20*                   | 0.07           | 0.27**                | 0.27**     |
| Cellular fibronectin | -            | -               | -                       | 0.21*          | 0.28**                | 0.12       |
| Thrombomodulin       | -            | -               | -                       | -              | 0.13                  | 0.07       |
| C-reactive protein   | -            | -               | -                       | -              | -                     | 0.22*      |

\* $p<0.05$ , \*\*  $p<0.01$ , \*\*\* $p<0.001$

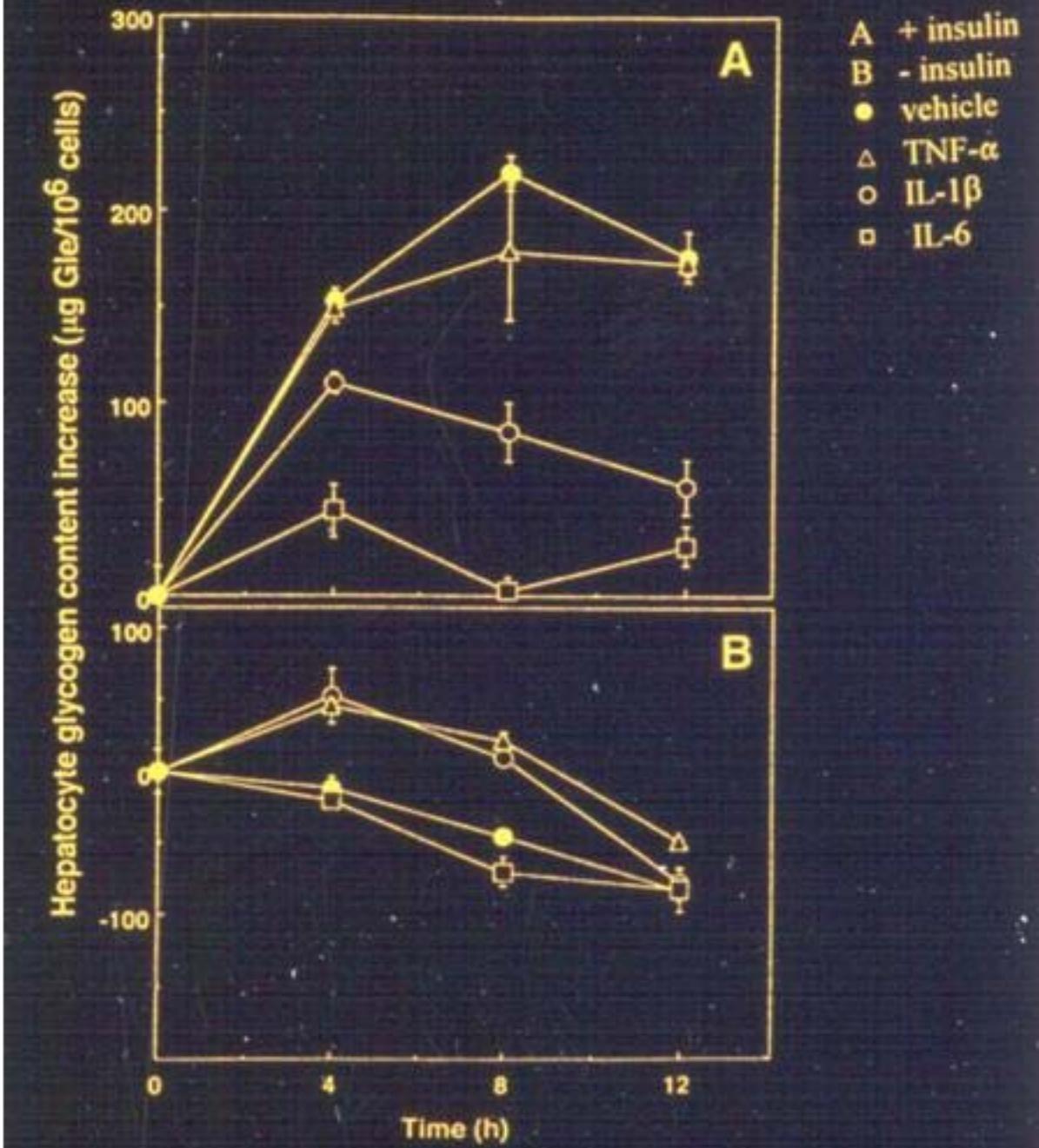
**a**

**b**

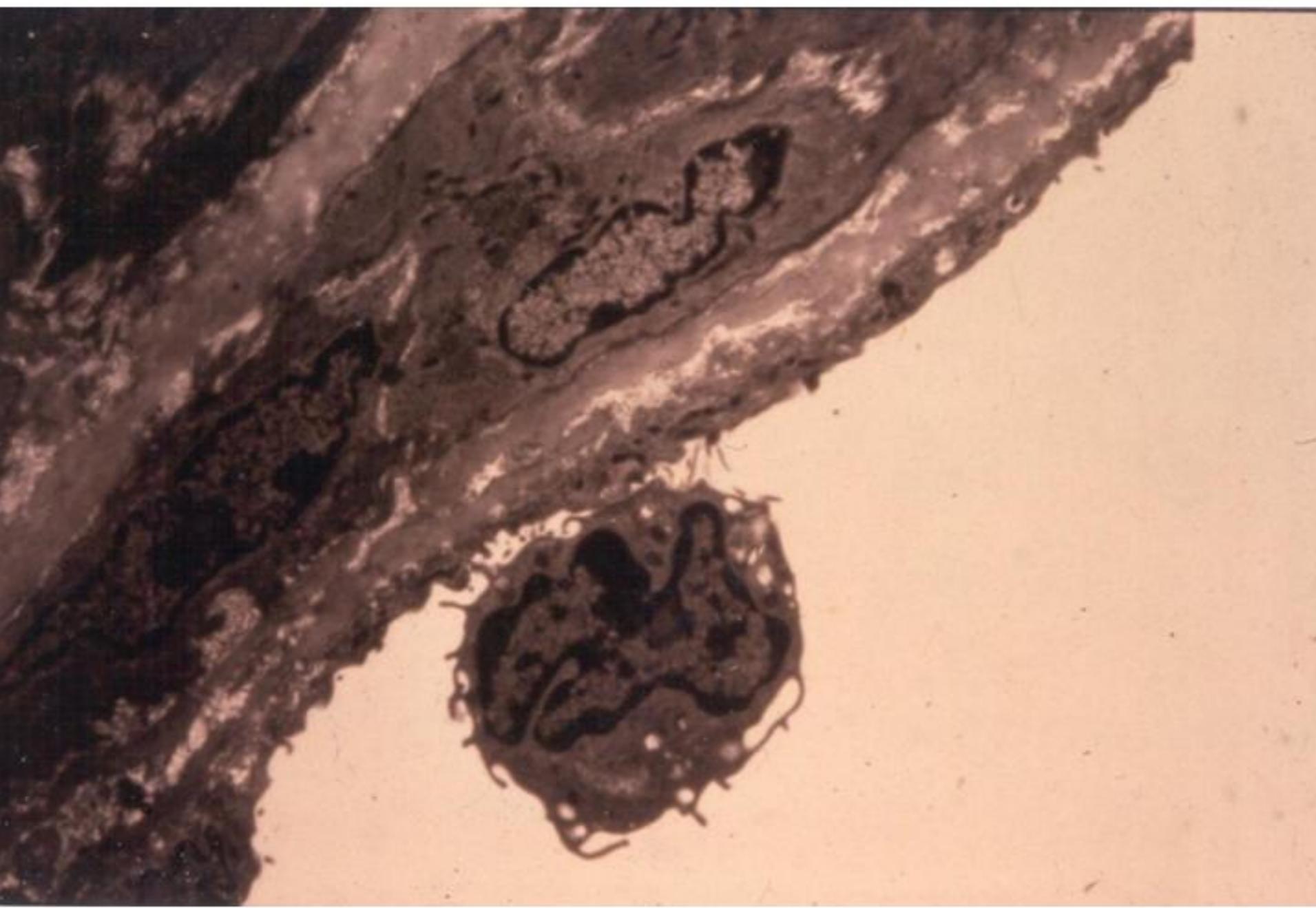
# RELATIONSHIP OF PROINFLAMMATORY CYTOKINES AND COMPONENTS OF INSULIN RESISTANCE CLUSTER

|                                  | TNF- $\alpha$ <sup>+</sup> | IL-6 <sup>+</sup> | C-reactive protein <sup>+</sup> |
|----------------------------------|----------------------------|-------------------|---------------------------------|
| Insulin sensitivity <sup>†</sup> | -0.35***                   | -0.09             | -0.22**                         |
| Triglyceride <sup>†</sup>        | 0.37**                     | 0.03              | 0.27**                          |
| HDL-cholesterol                  | -0.27**                    | -0.26**           | -0.21*                          |
| Systolic blood pressure          | 0.33***                    | 0.31**            | 0.34***                         |
| PAI-1 antigen                    | 0.35***                    | 0.18              | 0.19                            |

\* $p<0.05$ , \*\*  $p<0.01$ , \*\*\* $p<0.001$



Kanemaki et al, 1998



# RELATIONSHIP OF PROINFLAMMATORY CYTOKINES AND ENDOTHELIAL MARKERS

|                                   | TNF- $\alpha$ <sup>+</sup> | IL-6 <sup>+</sup> | C-reactive protein <sup>+</sup> |
|-----------------------------------|----------------------------|-------------------|---------------------------------|
| tPA antigen                       | 0.40***                    | 0.32**            | 0.40***                         |
| vWF                               | 0.38***                    | 0.11              | 0.31***                         |
| Thrombomodulin <sup>†</sup>       | 0.32**                     | -0.05             | 0.13                            |
| Cellular fibronectin <sup>†</sup> | 0.36***                    | 0.13              | 0.28**                          |
| Mean AER <sup>†</sup>             | 0.25*                      | 0.20*             | 0.07                            |

\* $p<0.05$ , \*\*  $p<0.01$ , \*\*\* $p<0.001$

# EFFECT OF WEEKLY INTERLEUKIN - 6 INJECTIONS ON FATTY STREAK FORMATION IN ATHEROSCLEROSIS - PRONE MICE

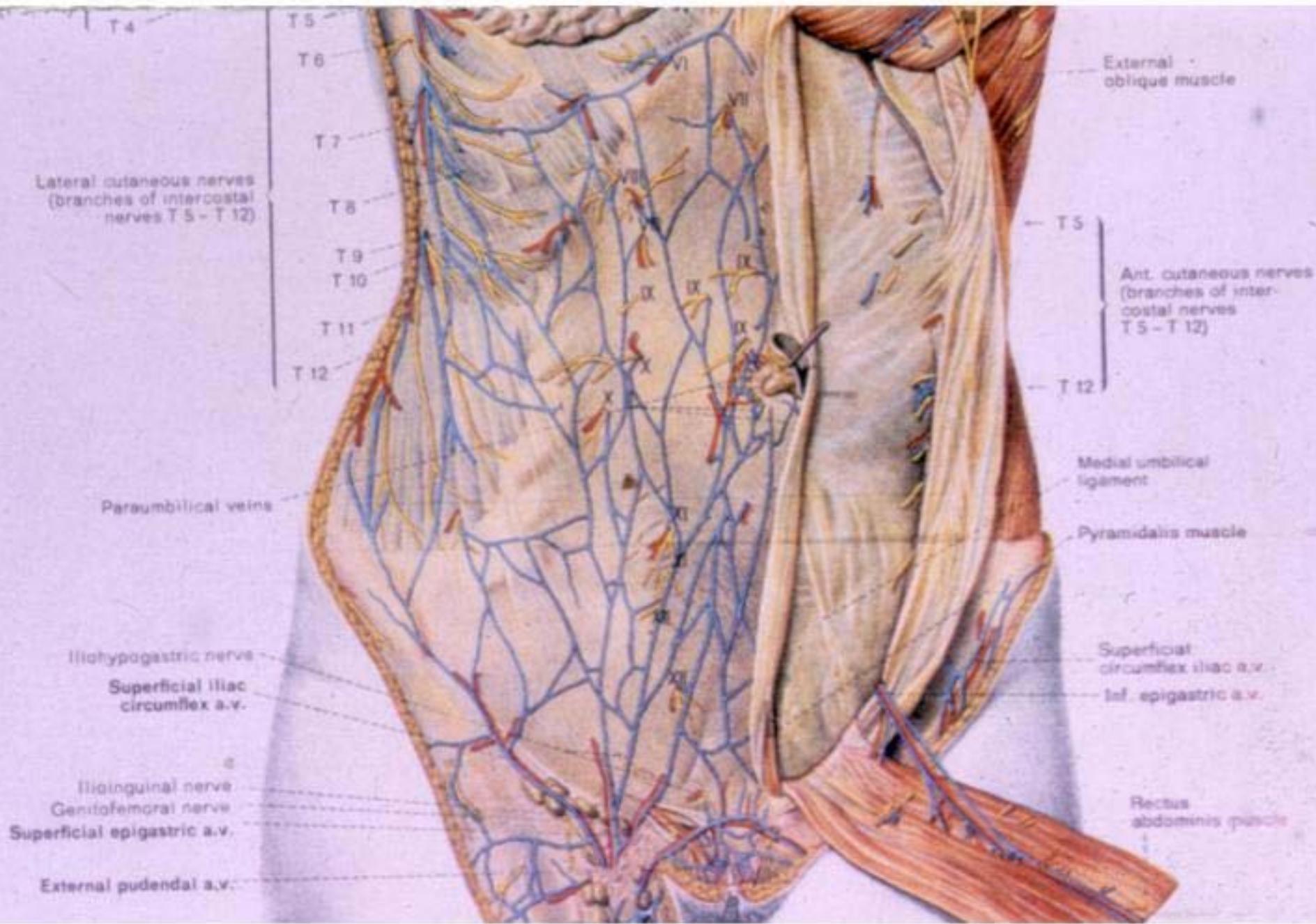
| <u>Mice</u>        | <u>Diet</u> | <u>IL-6</u> | <u>Lesion<br/>Size (μm<sup>2</sup>)</u> | <u>Circulating<br/>TNF<math>\alpha</math><br/>(ng/ml)</u> | <u>Fibrinogen<br/>(mg/l)</u> |
|--------------------|-------------|-------------|---|---|------------------------------|
| Apo-E<br>Deficient | High fat    | -           | 27409                                   | 0.24  | 660                          |
|                    |             | +           | 51964                                   | 0.78  | 810                          |

Huber et al, 1999

# RELATIONSHIP OF LEVELS OF PROINFLAMMATORY CYTOKINES WITH ANTIBODY TITRES AND OBESITY

|  | TNF- $\alpha$ <sup>+</sup> | IL-6 <sup>+</sup> | C-reactive protein <sup>+</sup> |
|--|----------------------------|-------------------|---------------------------------|
| Helicobacter pylori titre <sup>†</sup> | 0.18                       | 0.28*             | 0.24*                           |
| Chlamydia titre <sup>†</sup>           | 0.21                       | 0.15              | 0.25*                           |
| Cytomegalovirus titre <sup>†</sup>     | 0.21                       | 0.17              | 0.23*                           |
| BMI                                    | 0.33***                    | 0.19*             | 0.41***                         |
| Waist-hip ratio                        | 0.51***                    | 0.41***           | 0.32**                          |
| Subscapular-triceps ratio              | 0.37***                    | 0.26**            | 0.21*                           |

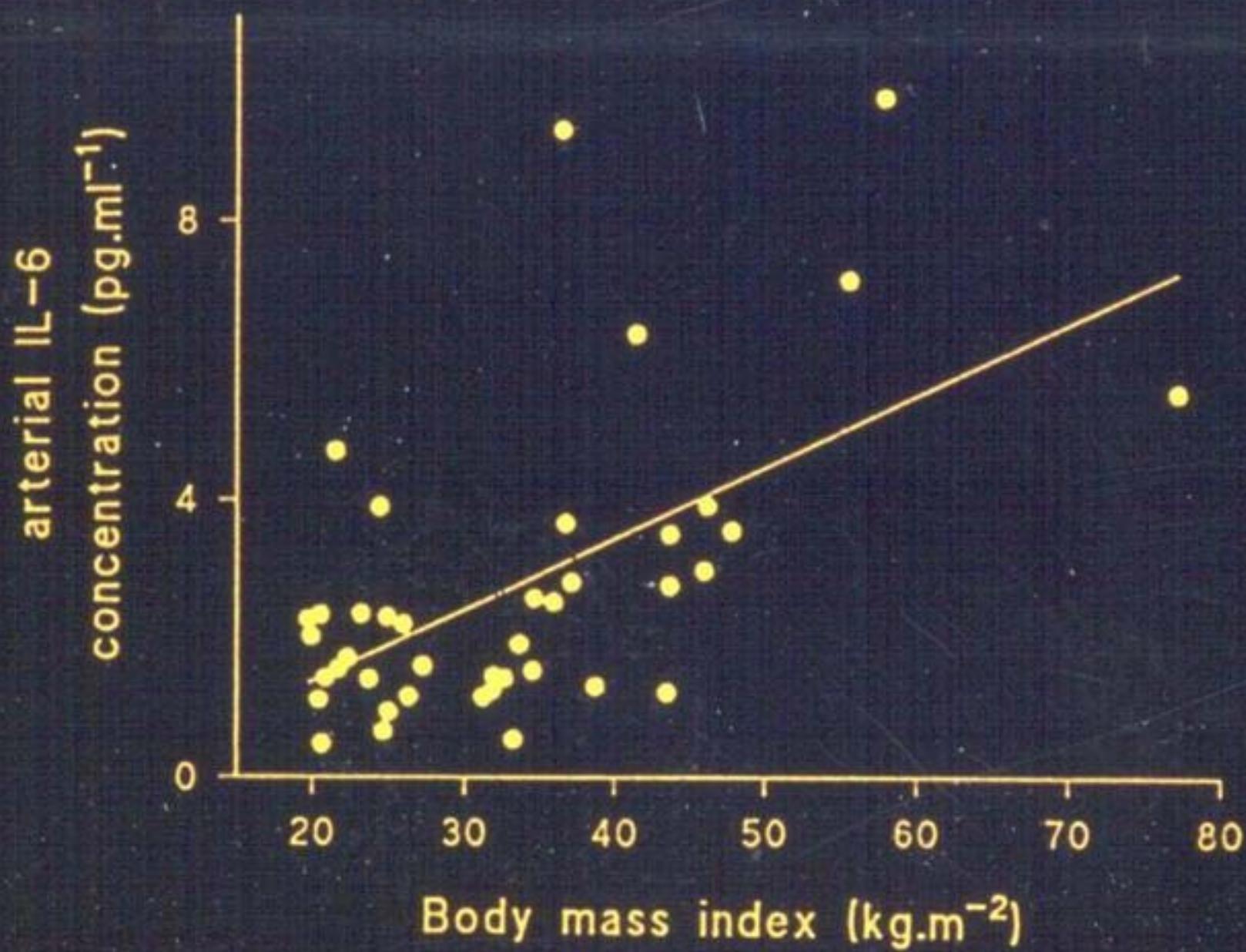
\* $p<0.05$ , \*\*  $p<0.01$ , \*\*\* $p<0.001$



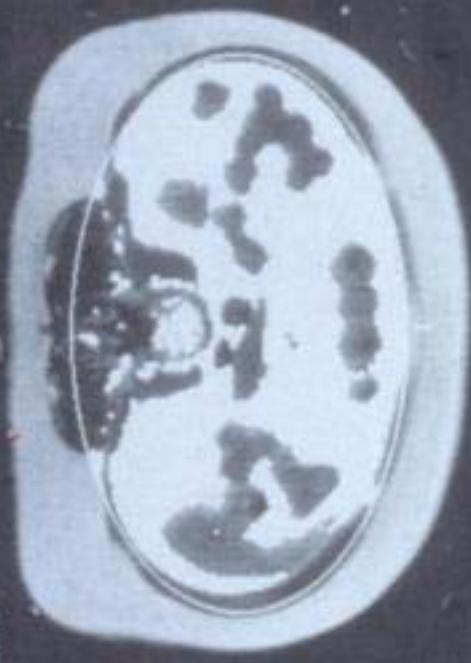
# FASTING ARTERIAL AND VENOUS CONCENTRATIONS OF IL6 AND TNF- $\alpha$ IN 24 SUBJECTS

|                       | Arterial         | Venous            | p value |
|-----------------------|------------------|-------------------|---------|
| Fasting IL6           | 2.02 (1.33-3.16) | 7.38 (2.79-11.73) | <0.001  |
| Fasting TNF- $\alpha$ | 1.26 (0.97-1.88) | 1.35 (1.09-2.02)  | 0.71    |

Data shown as median (interquartile range)



Mohamed-Ali et al, 1997



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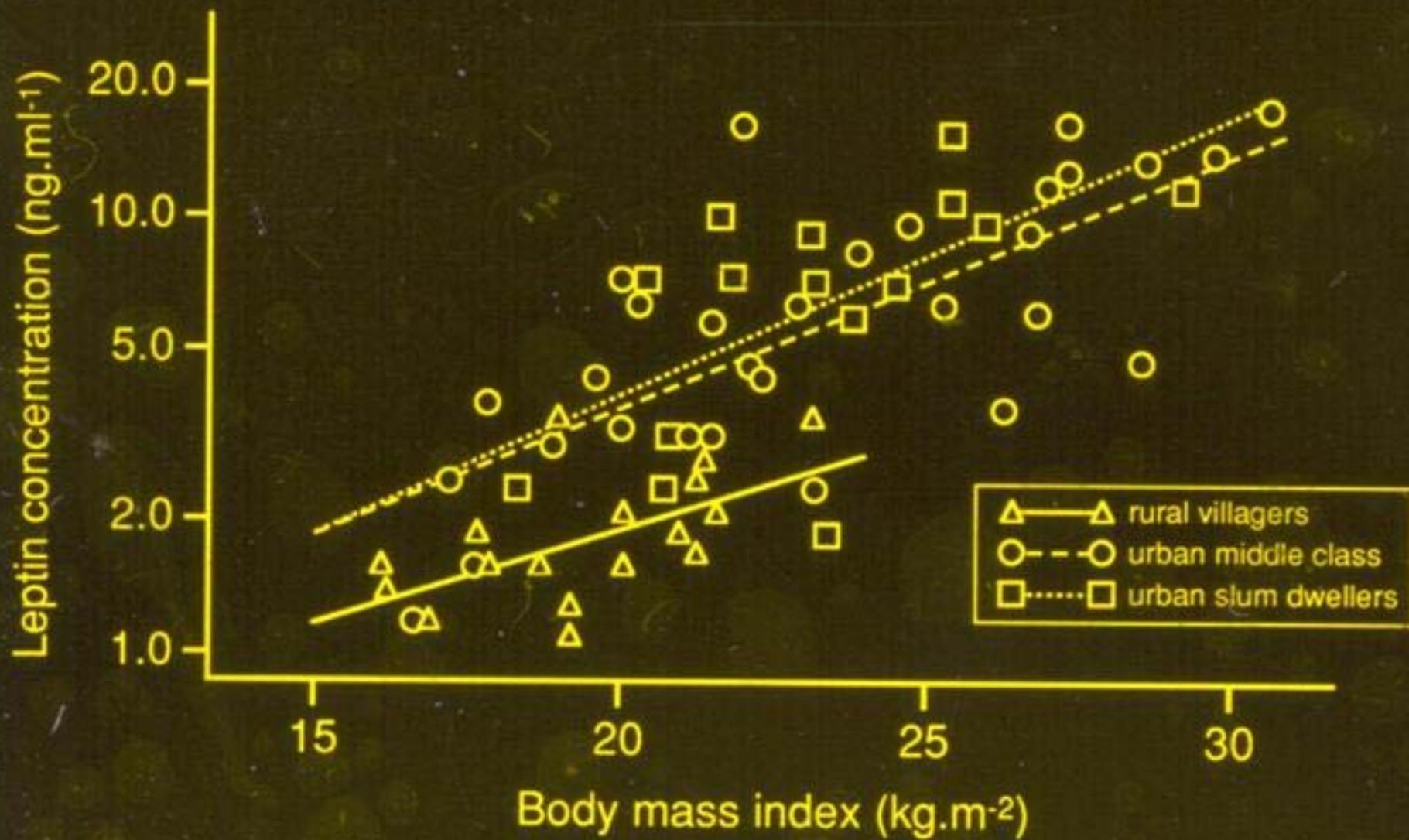
H.C.F. - Ecofjord

|                                  | Rural<br>Villagers<br>(n=43) | Urban slum<br>dwellers<br>(n=28) | Urban middle class<br>(n=40) |
|----------------------------------|------------------------------|----------------------------------|------------------------------|
| BMI                              | 18.7                         | 22.3***                          | 23.3***                      |
| WHR                              | 0.83                         | 0.86***                          | 0.85*                        |
| Interleukin-6                    | 2.50 (1.62, 14.5)            | 23.5 (6.60, 26.9)***             | 7.15 (3.92, 22.4)***         |
| Tumour necrosis factor- $\alpha$ | 2.57 (1.27, 5.52)            | 39.3 (10.3, 41.6)***             | 30.9 (7.44, 41.9)***         |

\*  $p<0.05$

\*\*  $p<0.01$

\*\*\*  $p<0.001$



**Endothelium-mediated  
vasodilatation**

$R=+0.76$

**Capillary recruitment**

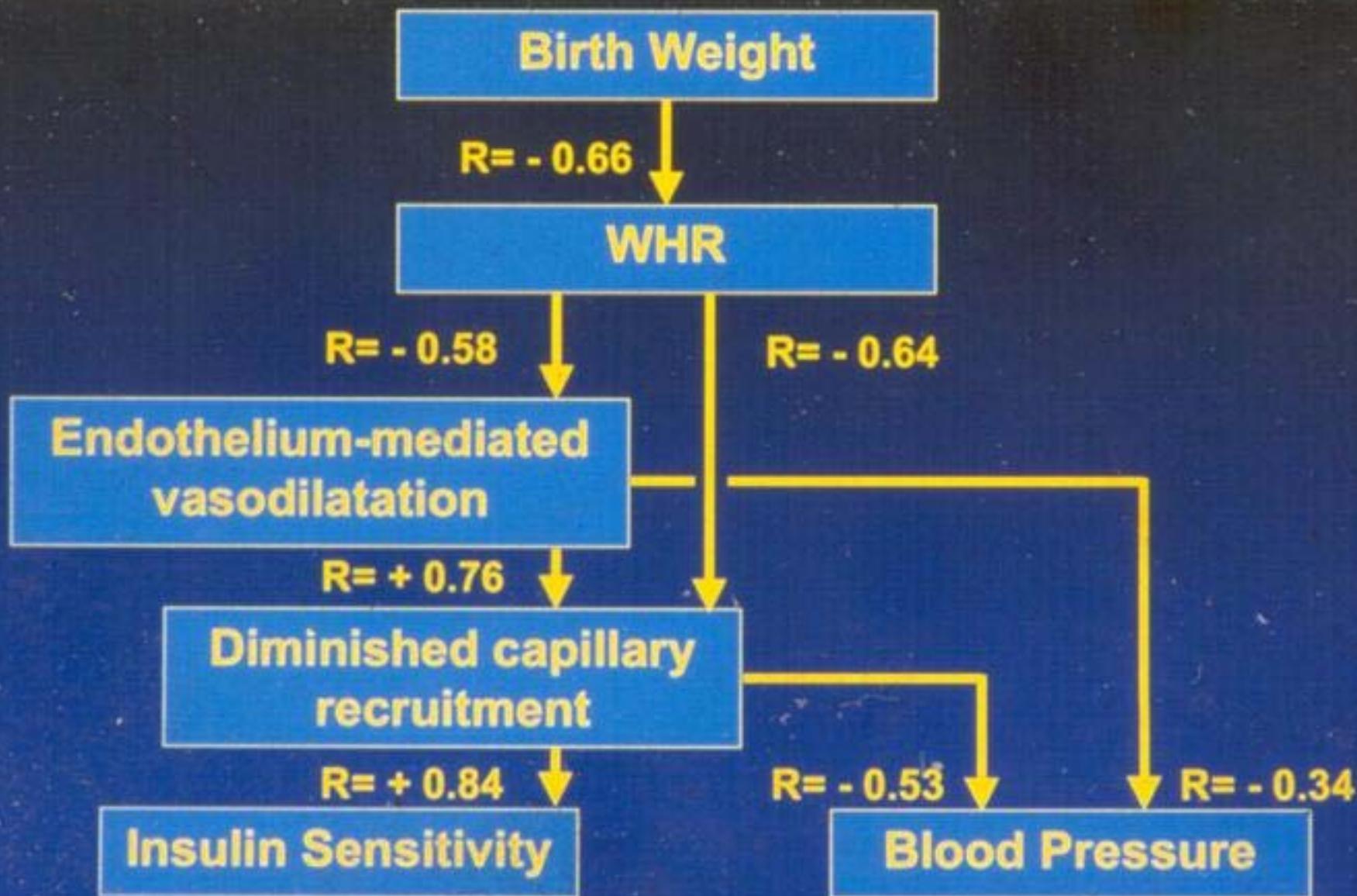
$R=-0.53$

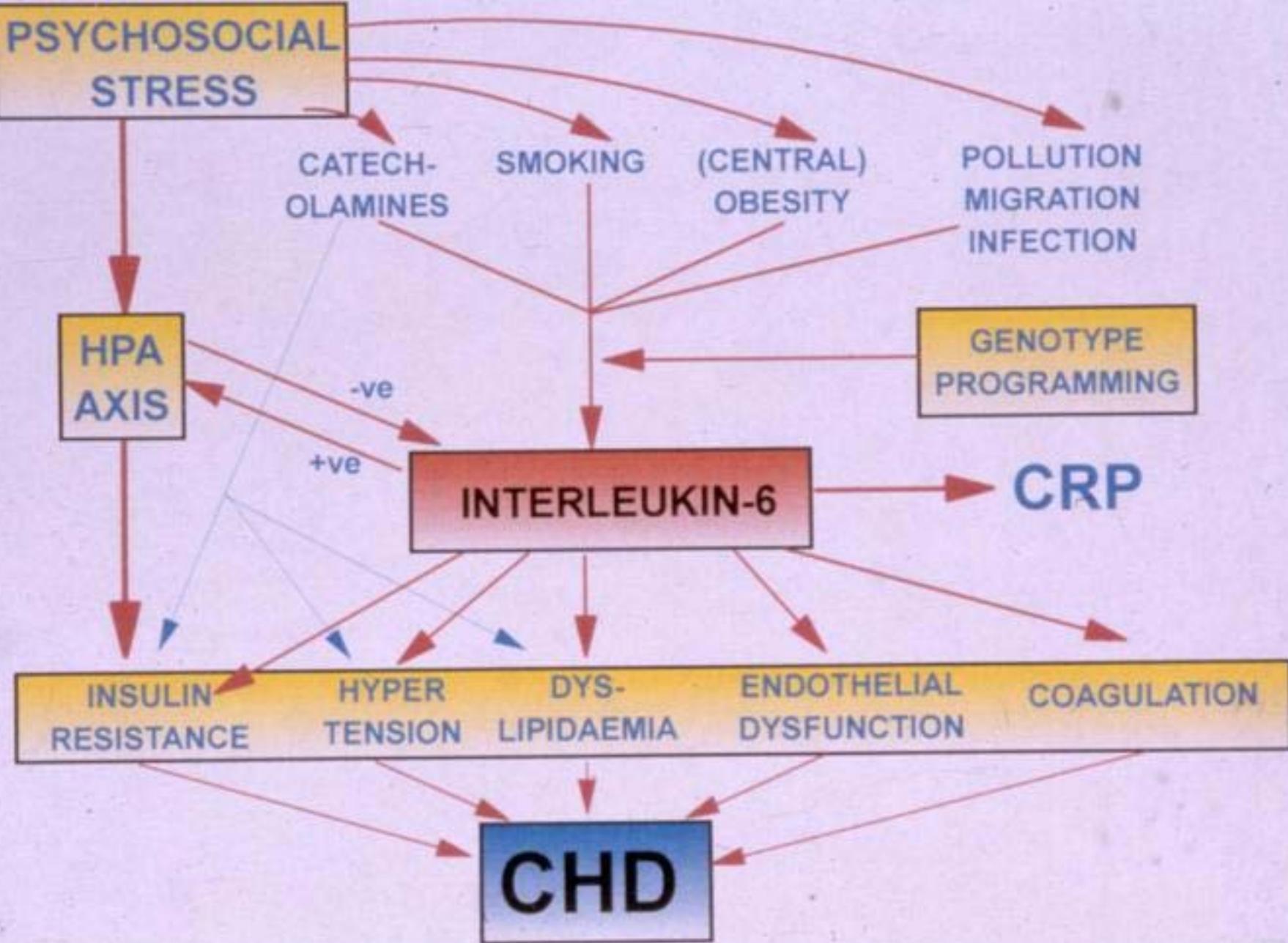
$R=+0.84$

**Insulin sensitivity**

$R=-0.34$

**Blood pressure**





# CONCLUSION

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- ▶ Adipose tissue expresses and secretes proinflammatory cytokines
- ▶ These influence insulin signalling through autocrine, paracrine, endocrine mechanisms
- ▶ Parallel effects on lipids, endothelium and coagulation
- ▶ Insulin resistance and vascular disease are linked through common antecedent