

# III Jornada sobre ALCOHOL y ALCOHOLISMO

Patrocinadores:

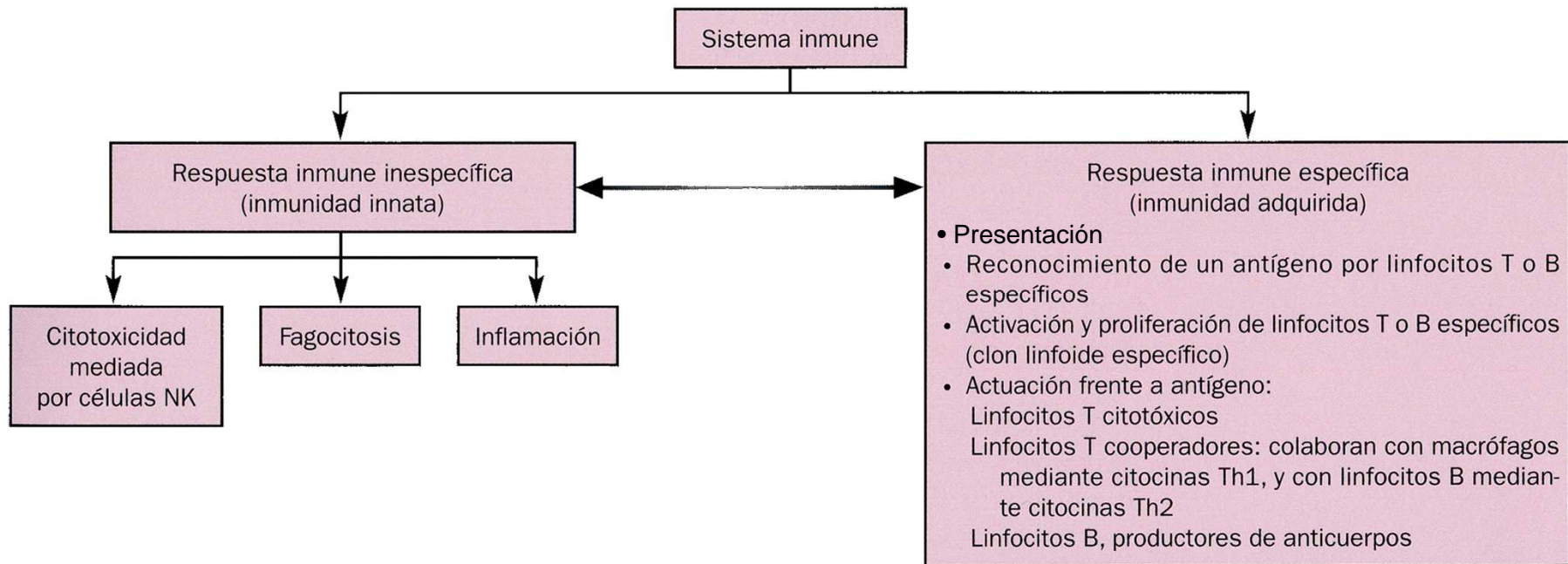


## Respuesta inflamatoria en el alcoholismo: lo esencial

F. Javier Laso

Unidad de Alcoholismo. Servicio de Medicina Interna  
Hospital Universitario de Salamanca

# Respuesta inmune



# Concepto clásico

El alcoholismo se asocia con inmunodeficiencia y, consecuentemente, con un mayor riesgo de infecciones y tumores

# Alcohol e inmunosupresión



Aumento de mortalidad en pacientes  
alcohólicos durante la epidemia de cólera  
de 1884 (R. Koch)

Mayor predisposición de los pacientes  
alcohólicos a desarrollar neumonía  
(W. Osler)



# Alcohol e inmunosupresión

## Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk

Wendy Y. Chen, MD, MPH

Bernard Rosner, PhD

Susan E. Hankinson, ScD

Graham A. Colditz, MD, DrPH

Walter C. Willett, MD, DrPH

**I**N MANY STUDIES, HIGHER CONSUMPTION of alcohol has been associated with an increased risk of breast cancer.<sup>1-3</sup> However, the effect of low levels of drinking as is common in the United States has not been well quantified. A few studies showed increased risk,<sup>1,4</sup> but in most, no significant association was observed.<sup>2,3,5-11</sup> Many of these studies did not regularly update assessments of alcohol intake, which may change over a person's lifetime, and may obscure the ability to detect associations. In addition, most lacked detailed information on drinking patterns, such as frequency of drinking and heavy episodic drinking. Because some

**Context** Multiple studies have linked alcohol consumption to breast cancer risk, but the risk of lower levels of consumption has not been well quantified. In addition, the role of drinking patterns (ie, frequency of drinking and "binge" drinking) and consumption at different times of adult life are not well understood.

**Objective** To evaluate the association of breast cancer with alcohol consumption during adult life, including quantity, frequency, and age at consumption.

**Design, Setting, and Participants** Prospective observational study of 105 986 women enrolled in the Nurses' Health Study followed up from 1980 until 2008 with an early adult alcohol assessment and 8 updated alcohol assessments.

**Main Outcome Measures** Relative risks of developing invasive breast cancer.

**Results** During 2.4 million person-years of follow-up, 7690 cases of invasive breast cancer were diagnosed. Increasing alcohol consumption was associated with increased breast cancer risk that was statistically significant at levels as low as 5.0 to 9.9 g per day, equivalent to 3 to 6 drinks per week (relative risk, 1.15; 95% CI, 1.06-1.24; 333 cases/100 000 person-years). Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk.

**Conclusions** Low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake throughout adult life. Alcohol intake both earlier and later in adult life was independently associated with risk.

JAMA. 2011;306(17):1884-1890

www.jama.com

# Factores de confusión

- Estudios en condiciones experimentales
- Exposición aguda al alcohol vs alcoholismo crónico
- Asociación o no de hepatopatía



# Alcohol y hepatitis C

Alcohol and Alcoholism Advance Access published May 19, 2013

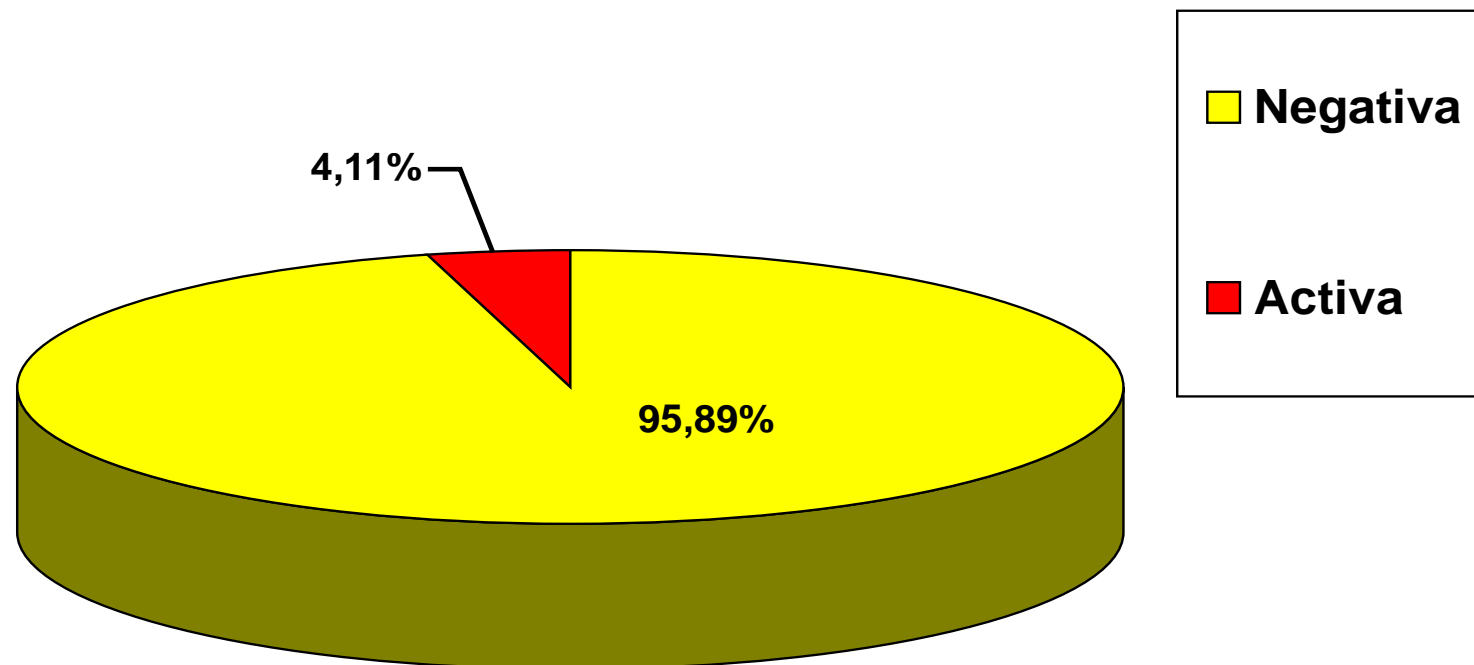
*Alcohol and Alcoholism* pp. 1–6, 2013

doi: 10.1093/alcalc/agt044

## ORIGINAL ARTICLE

Prevalence of Hepatitis C Virus Infection in Alcoholic Patients: Cohort Study and Systematic Review

Ignacio Novo-Veleiro, Cristina de la Calle, Susana Domínguez-Quibén, Isabel Pastor, Miguel Marcos<sup>†\*</sup>  
and Francisco-Javier Laso<sup>†</sup>



# Alcohol y hepatitis C

Alcohol and Alcoholism Advance Access published May 19, 2013

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Ignacio Novo-Veleiro, Cristina de la Calle, Susana Domínguez-Quibén, Isabel Pastor, Miguel Marcos<sup>†\*</sup>  
and Francisco-Javier Laso<sup>†</sup>

Table 1. Baseline characteristics and association of variables with the presence of HCV infection

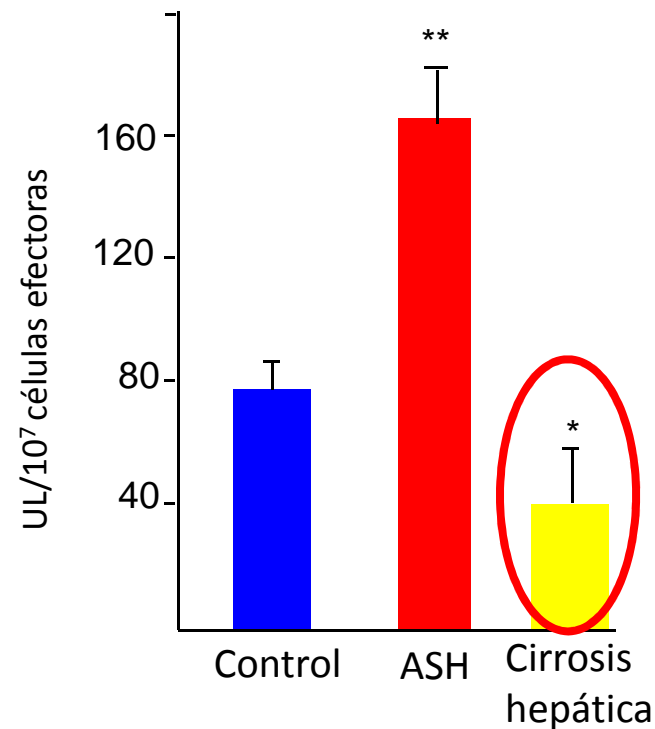
Variables	Total (n = 396)	HCV infected (n = 14)	Non-HCV infected (n = 382)	P-value
Age (years)	44.81 (11.54)	47.50 (16.09)	44.75 (11.35)	0.536
Male gender	347 (87.62)	10 (71.42)	336 (87.95)	
Female gender	49 (12.37)	4 (28.57)	46 (12.04)	0.062
Rural residence	74 (18.78)	1 (7.14)	73 (19.11)	0.213
Current smoker	333 (84.09)	10 (71.42)	323 (84.55)	0.865
Former smoker	49 (12.37)	4 (28.57)	45 (11.78)	
Never smoker	14 (3.53)	0 (0)	14 (3.66)	
Family history of alcoholism	203 (51.26)	4 (28.57)	199 (52.09)	0.021
Alcohol dependence	225 (56.81)	10 (71.42)	212 (55.49)	0.283
Alcohol abuse	171 (43.14)	4 (28.58)	170 (44.51)	0.283
Addiction to other drugs	43 (10.85)	6 (42.85)	37 (9.65)	0.001
IDUs	9 (2.27)	3 (21.42)	6 (1.57)	<0.001
Major psychiatric illness	46 (11.61)	1 (7.14)	45 (11.78)	0.588
HBV infection	46 (11.61)	4 (28.57)	42 (10.99)	0.044
Liver disease	120 (30.33)	9 (64.28)	111 (29.05)	0.005
Steatosis	50 (12.62)	0 (0)	50 (13.08)	
Hepatitis	6 (1.51)	0 (0)	6 (1.57)	<0.001
Undetermined	42 (10.61)	4 (28.57)	38 (9.94)	
Cirrhosis	22 (5.55)	5 (35.71)	17 (4.45)	



# Alcohol y citotoxicidad NK

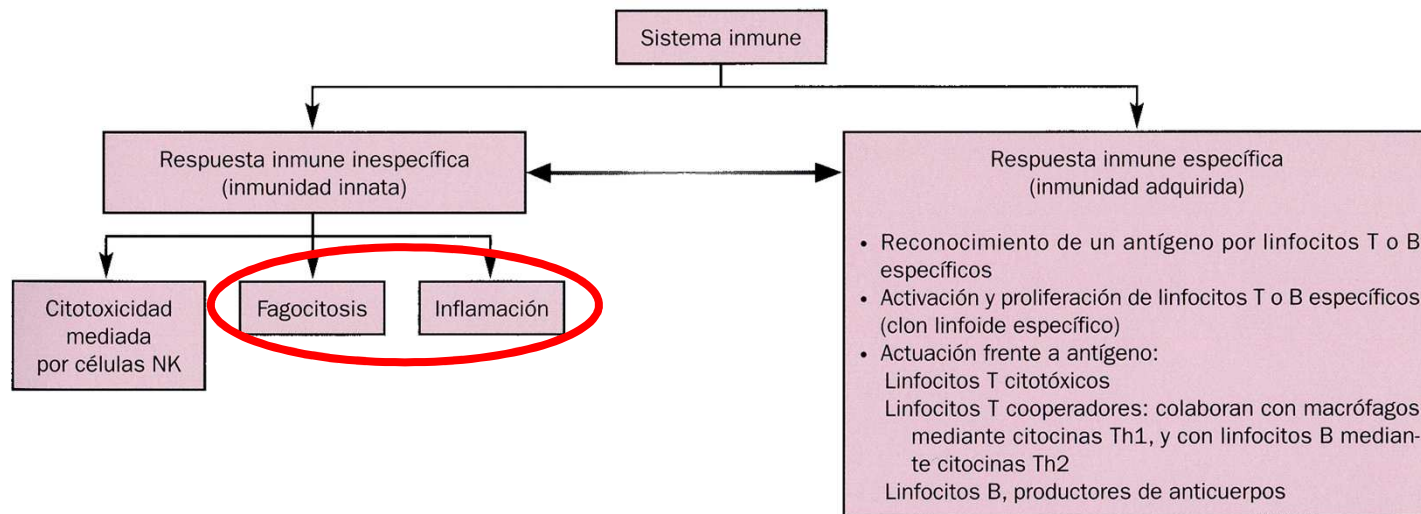
Decreased Natural Killer Cytotoxic Activity in Chronic Alcoholism Is Associated With Alcohol Liver Disease but Not Active Ethanol Consumption

FRANCISCO JAVIER LASO,<sup>1</sup> JOSÉ IGNACIO MADRUGA,<sup>1</sup> JOSÉ ANTONIO GIRÓN,<sup>2</sup> ANTONIO LÓPEZ,<sup>3</sup> JUANA CIUDAD<sup>3</sup>  
JESÚS FERNANDO SAN MIGUEL,<sup>4</sup> MELCHOR ALVAREZ-MON,<sup>5</sup> AND ALBERTO ORFAO<sup>4</sup>

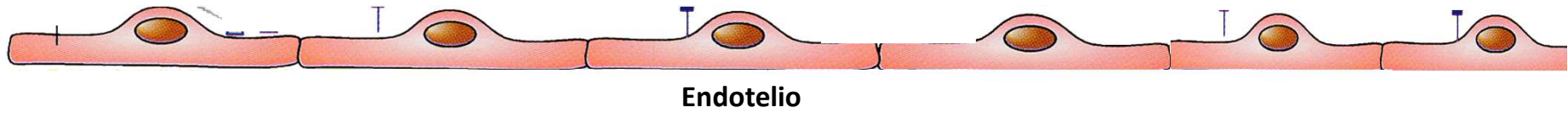


Hepatology 1997;25:1096-100

# Alcohol y respuesta inflamatoria

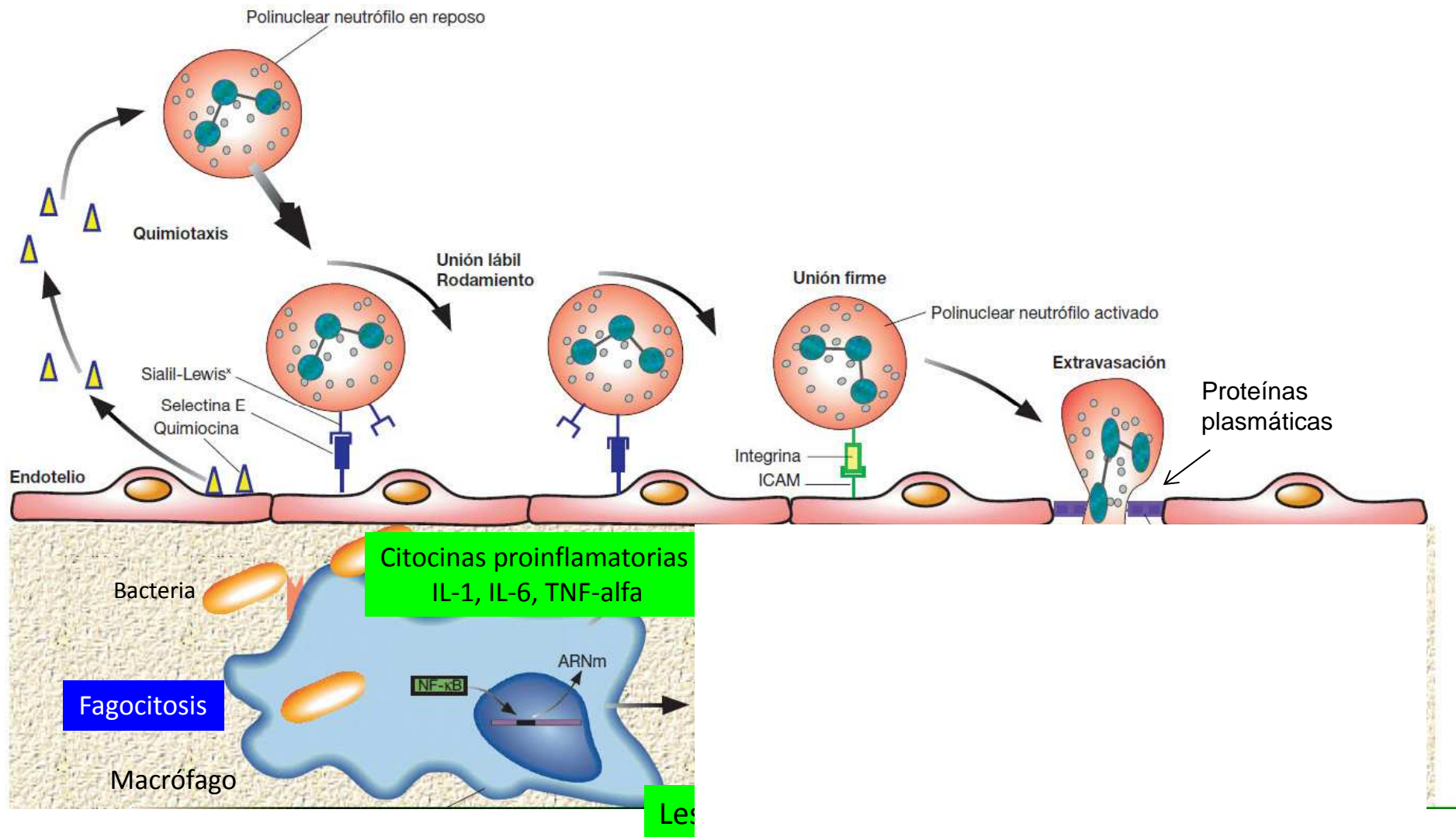


# Fagocitosis-inflamación



Microorganismos (PAMP)  
Restos celulares necróticos

# Inflamación



# Inflamación



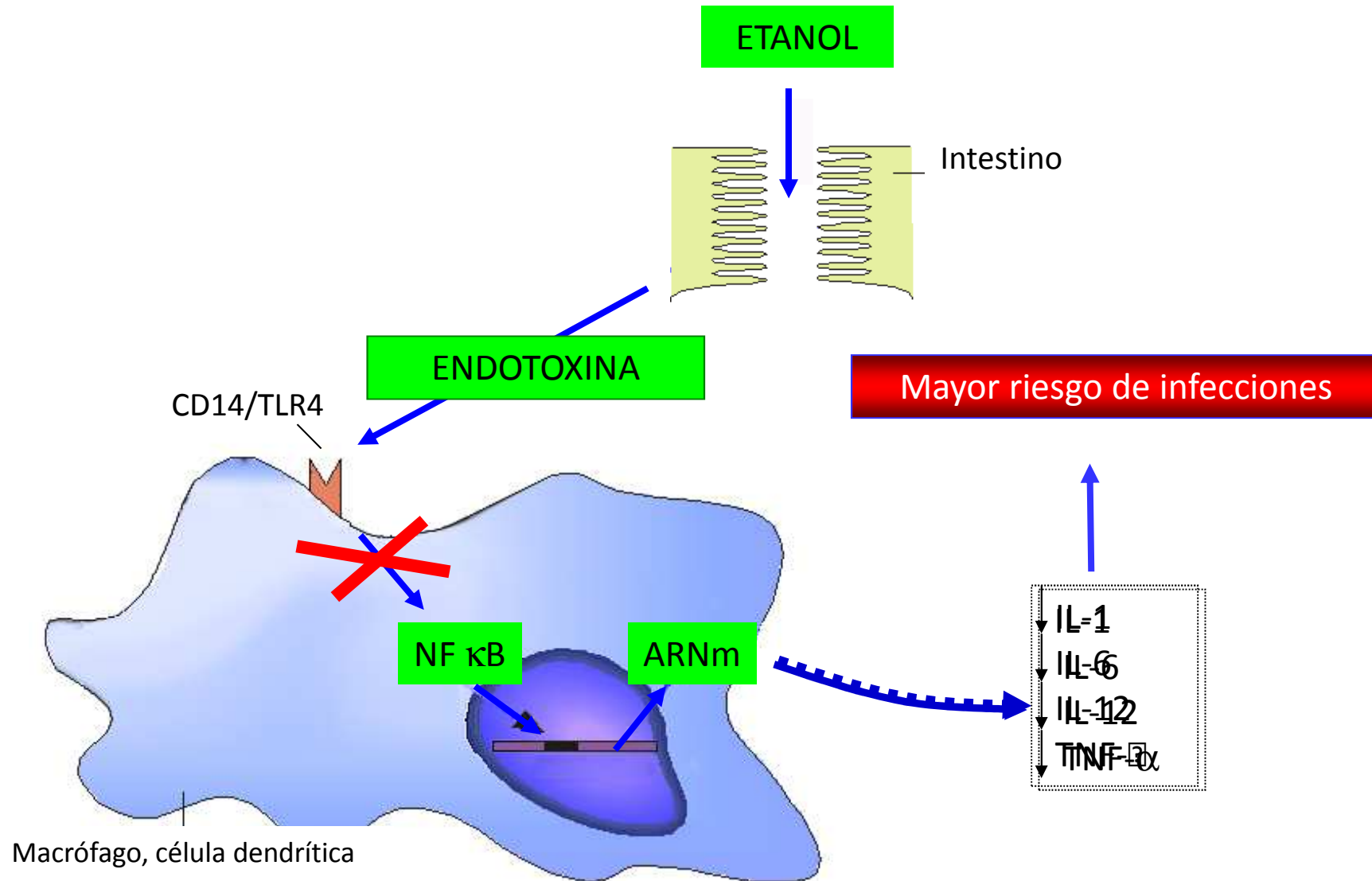
# Pregunta clave...



¿Qué relación existe entre el etanol y la inflamación?



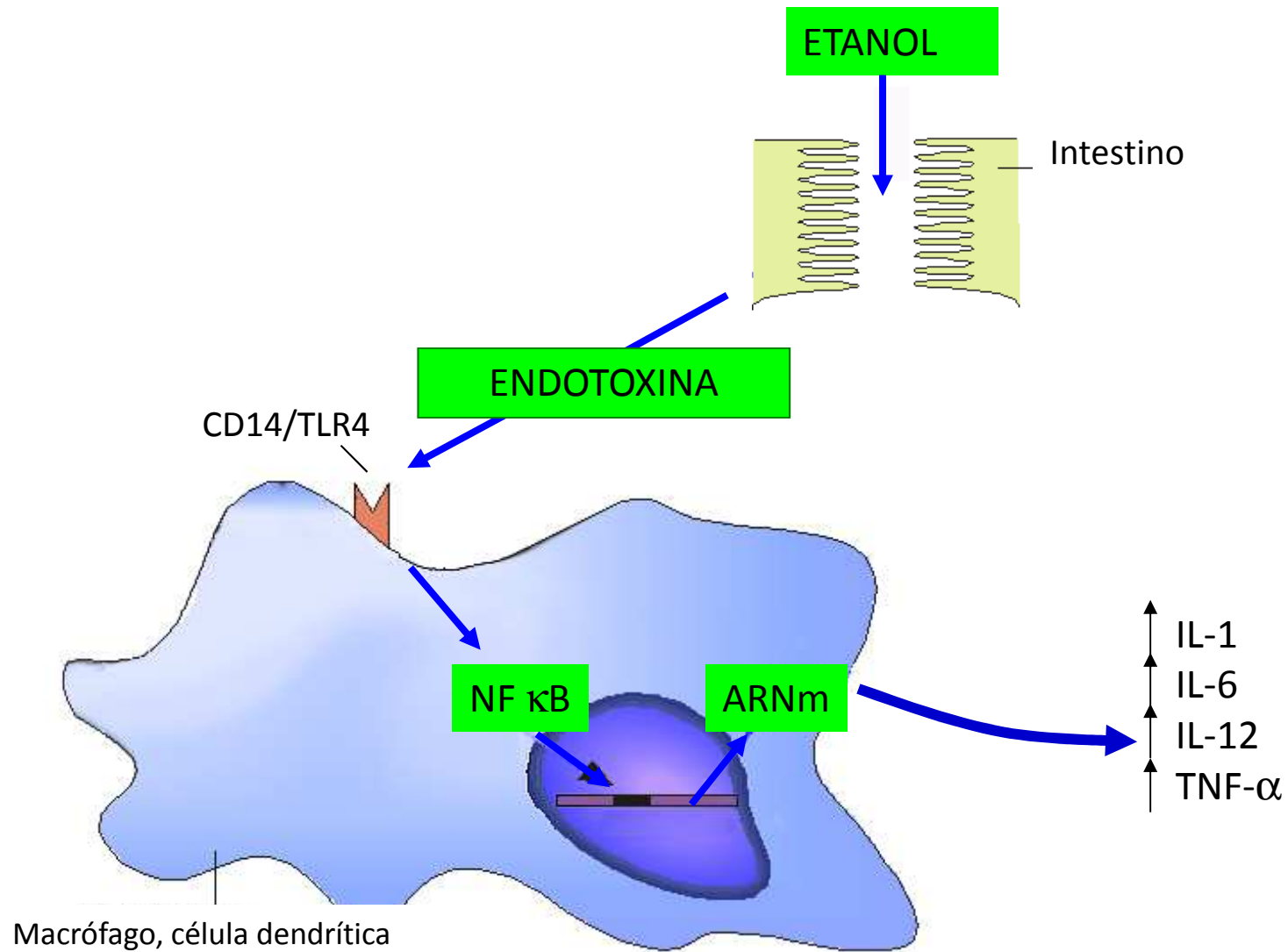
# Exposición aguda al alcohol



Mayor predisposición de los pacientes  
alcohólicos a desarrollar neumonía  
(W. Osler)

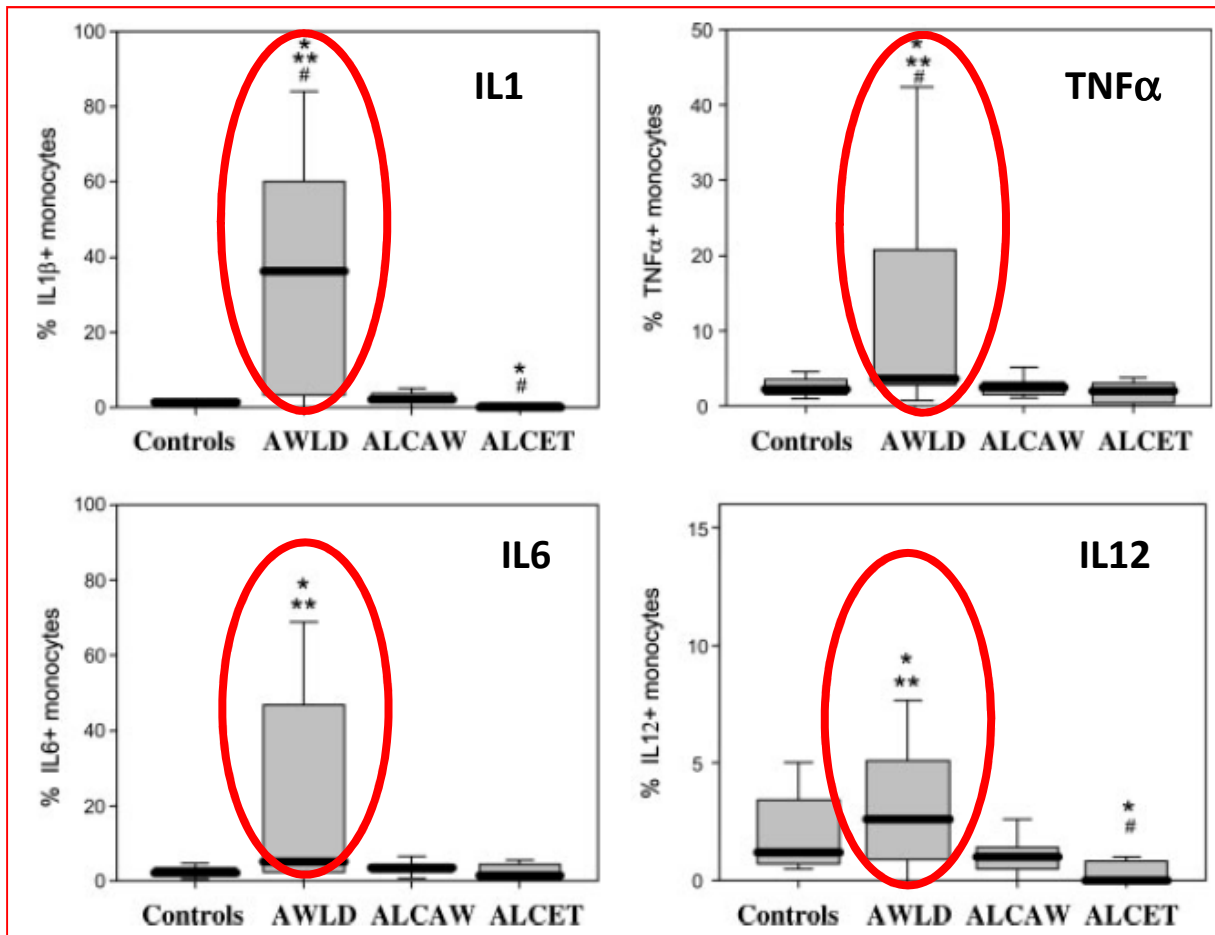


# Consumo crónico de alcohol



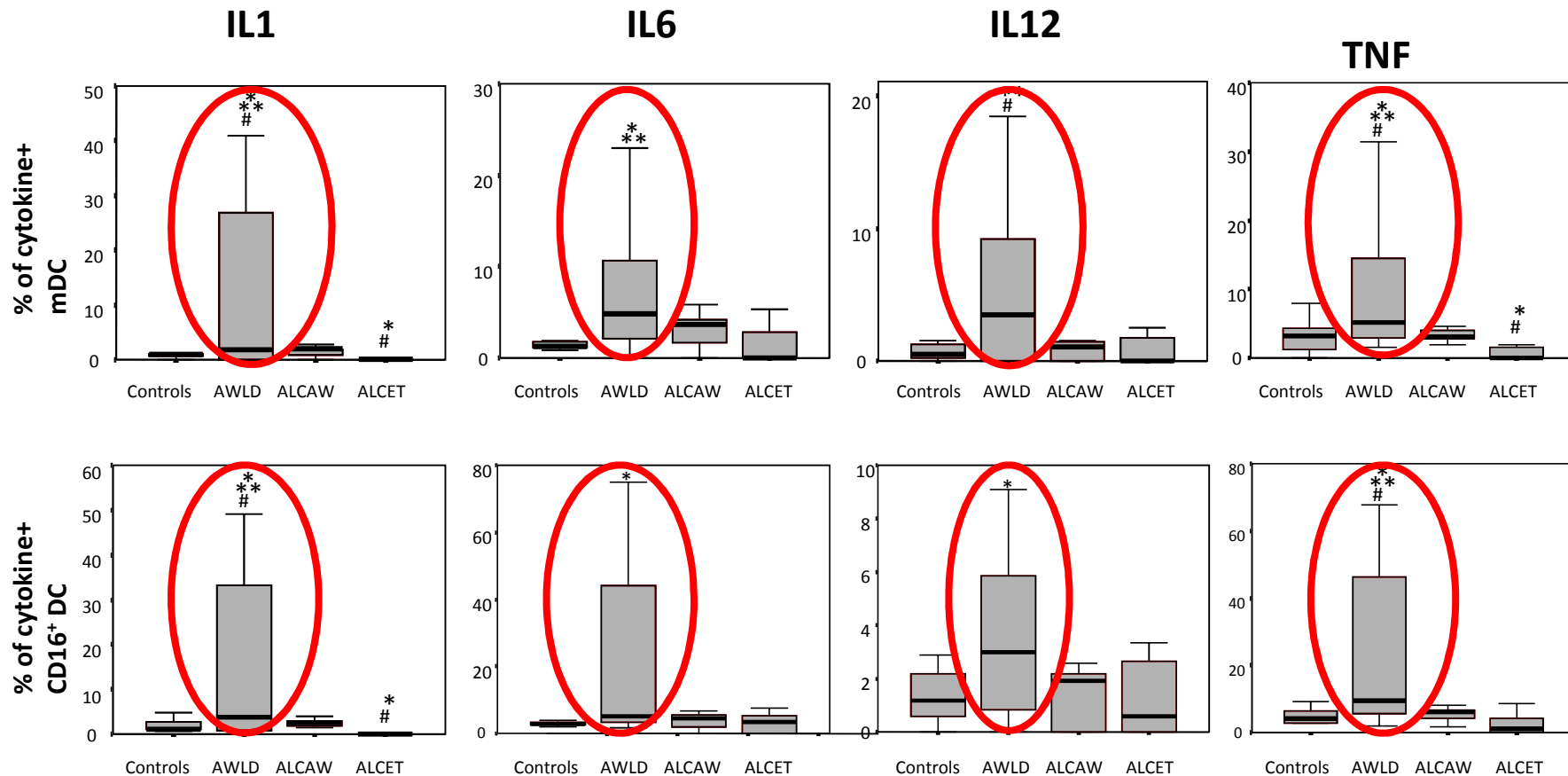
## Production of Inflammatory Cytokines by Peripheral Blood Monocytes in Chronic Alcoholism: Relationship with Ethanol Intake and Liver Disease

Francisco Javier Laso,<sup>1\*</sup> José Miguel Vaquero,<sup>2</sup> Julia Almeida,<sup>3</sup>  
Miguel Marcos,<sup>1</sup> and Alberto Orfao<sup>2</sup>

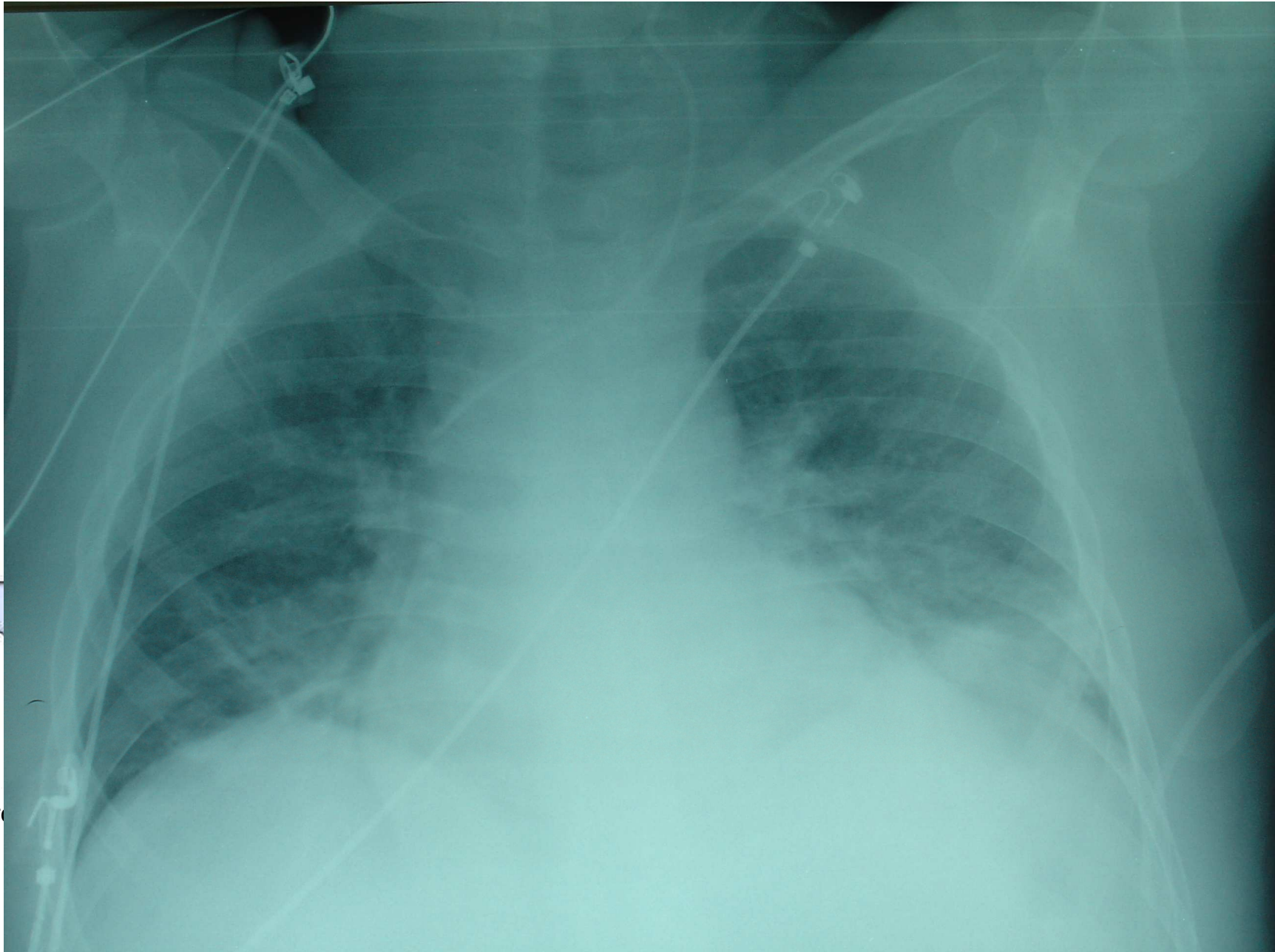


# Chronic Alcohol Consumption Is Associated With Changes in the Distribution, Immunophenotype, and the Inflammatory Cytokine Secretion Profile of Circulating Dendritic Cells

Francisco Javier Laso, José Miguel Vaquero, Julia Almeida, Miguel Marcos, and Alberto Orfao

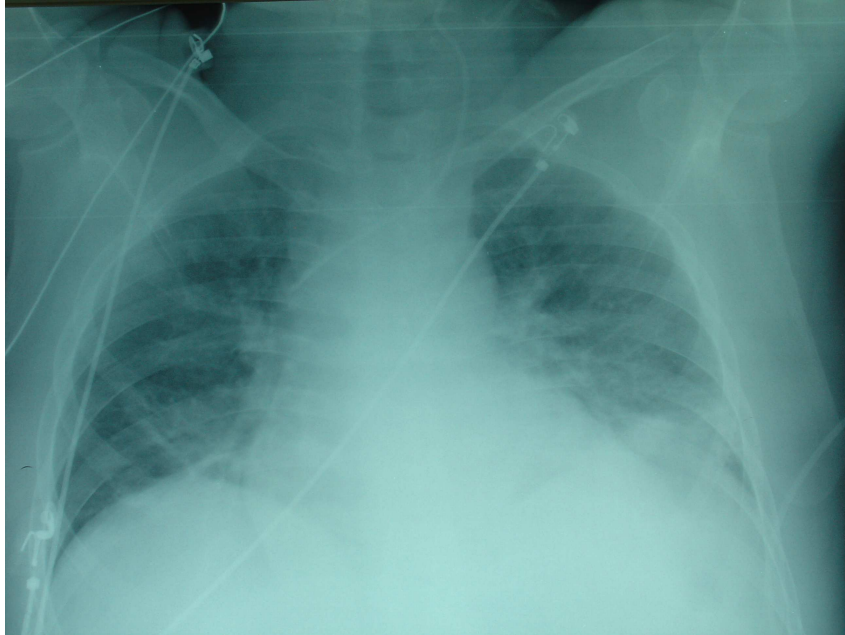


# Consumo crónico de alcohol



Macro





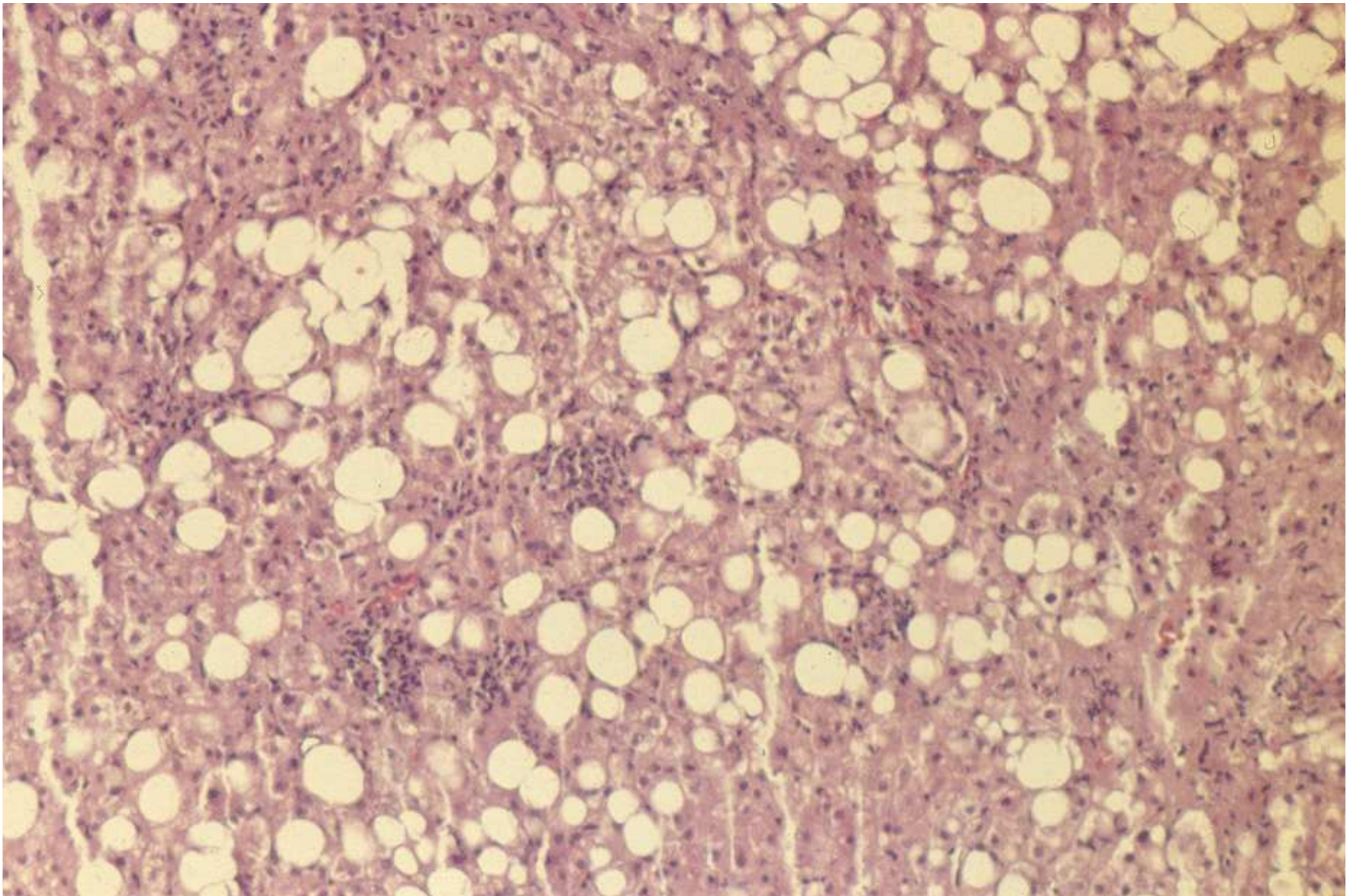
Mayor predisposición de los pacientes  
alcohólicos a desarrollar neumonía  
(W. Osler)



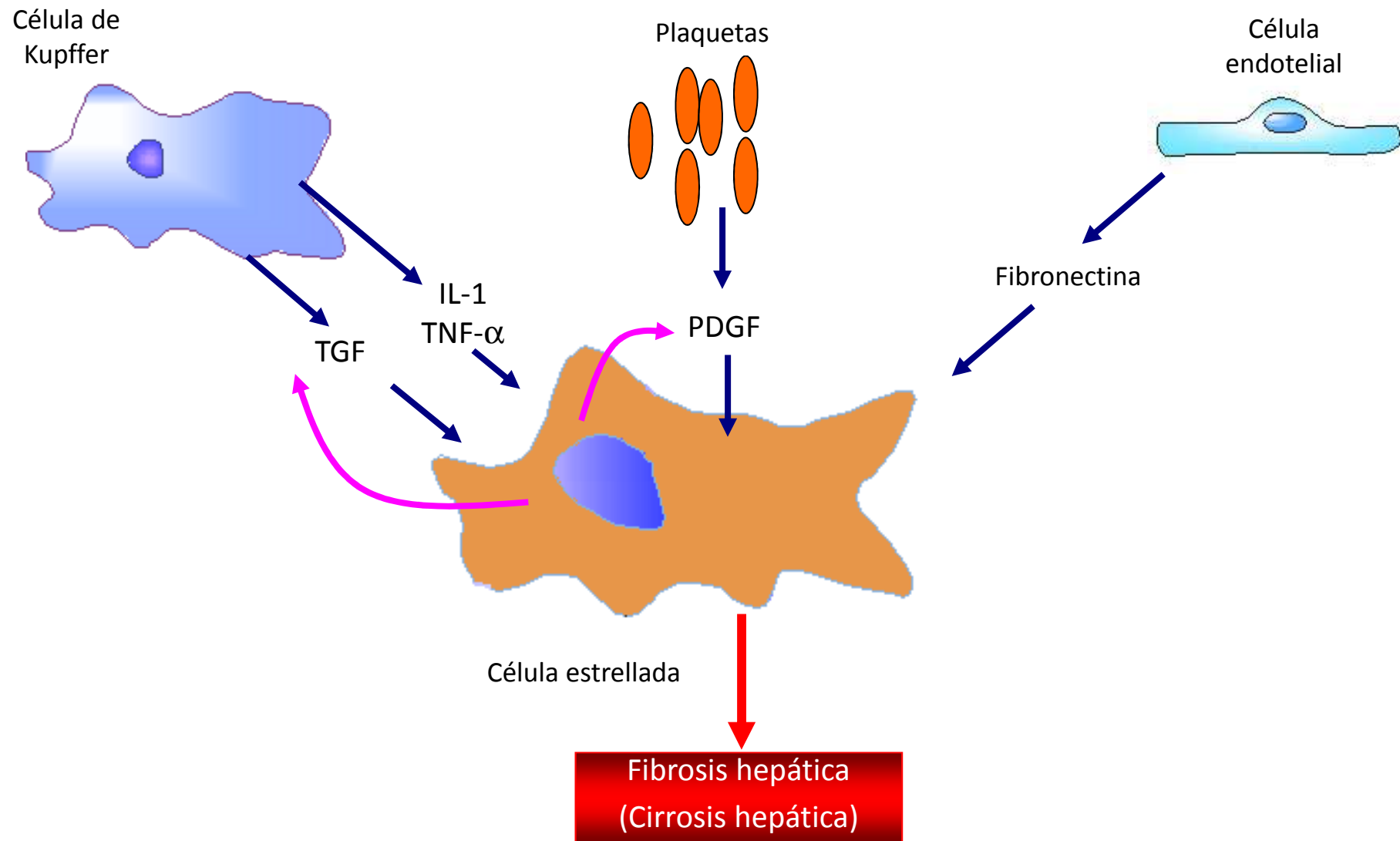
# Otras repercusiones inflamatorias del alcohol

- Enfermedad hepática por alcohol
- Lesión y muerte neuronal: neuroinflamación

# Hepatitis alcohólica



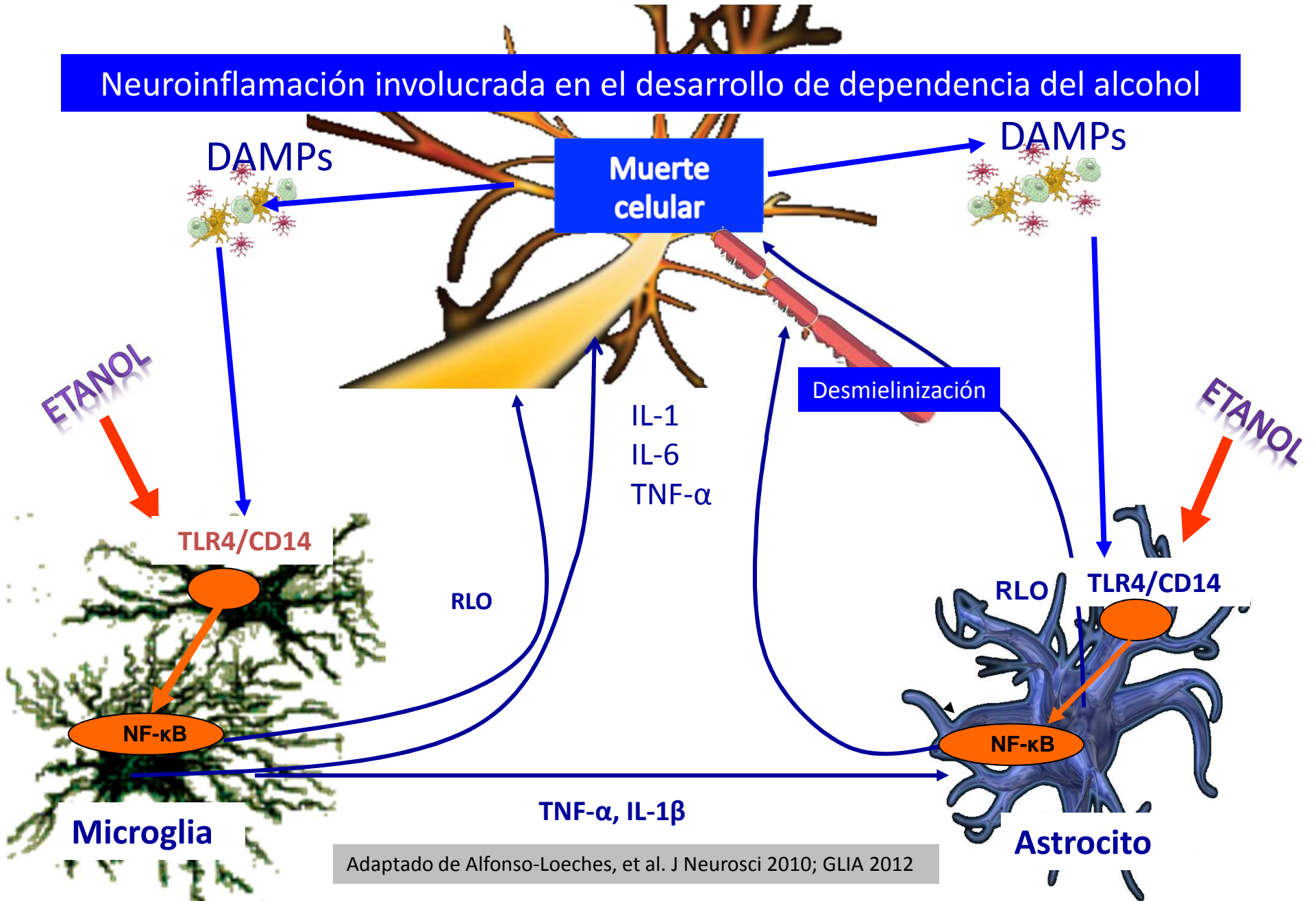
# Fibrogénesis hepática





# Alcohol y neuroinflamación: lesión y muerte celular

Neuroinflamación involucrada en el desarrollo de dependencia del alcohol



Adaptado de Alfonso-Loeches, et al. J Neurosci 2010; GLIA 2012

# Regulación de la respuesta inflamatoria en el alcoholismo





# Regulación de la respuesta inflamatoria



Linfocito T  
(CD4+)  
virgen

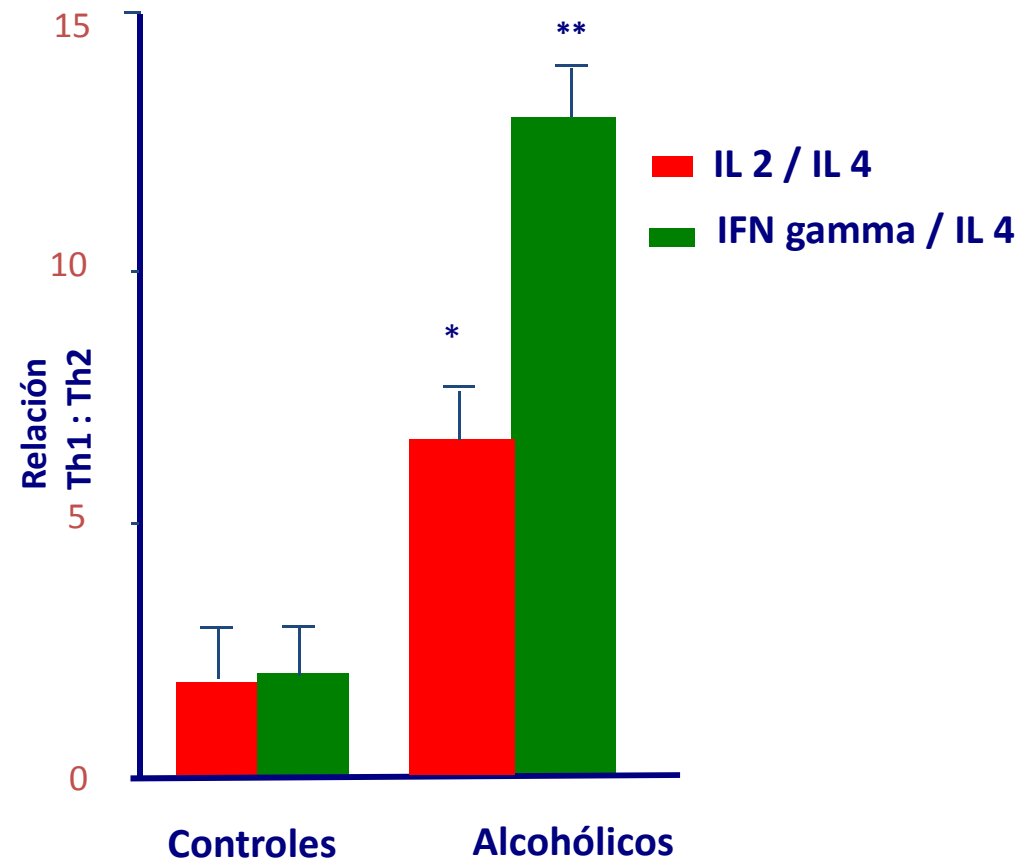
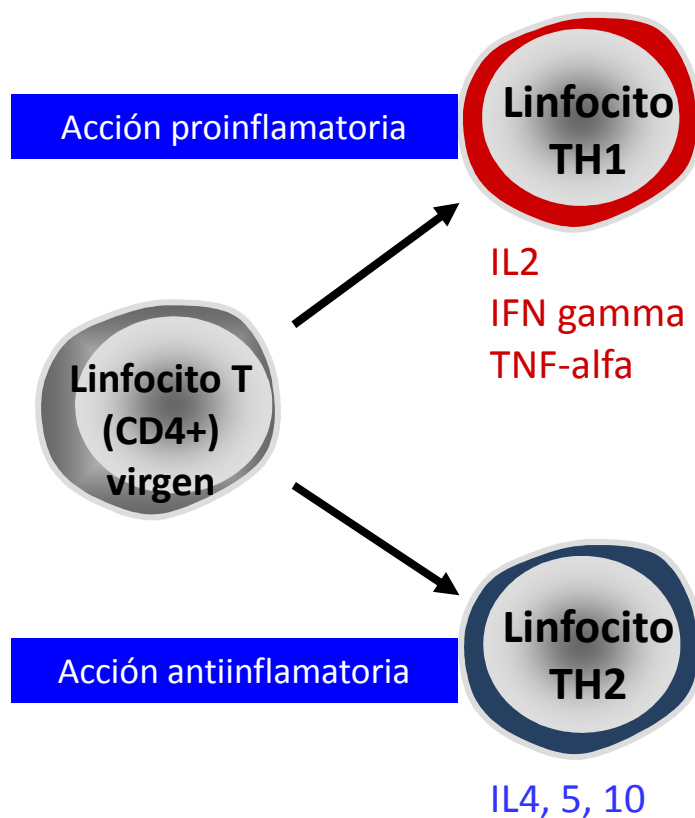
# Linfocitos T reguladores y alcoholismo

0145-6008/99/2308-1306\$03.00/0  
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

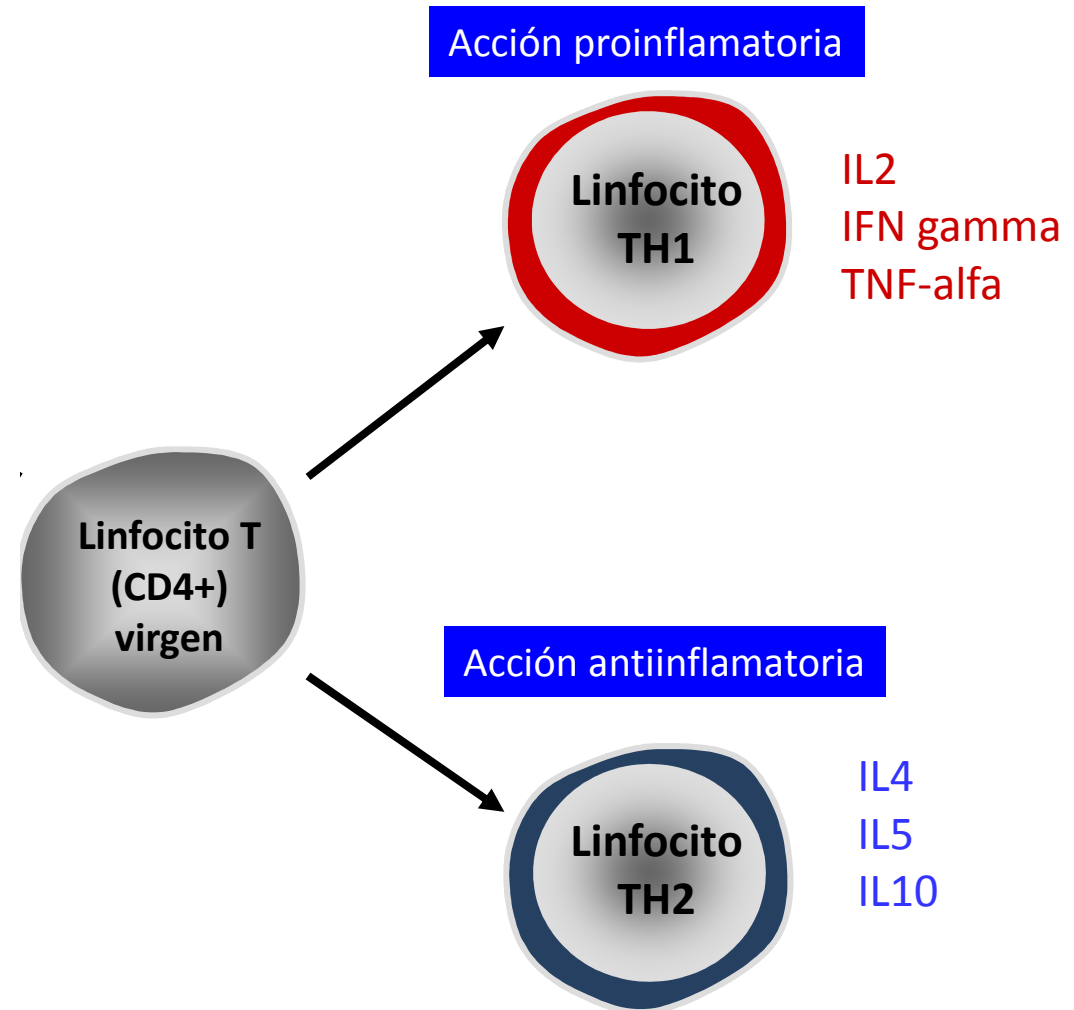
Vol. 23, No. 8  
August 1999

## Chronic Alcoholism Is Associated With an Imbalanced Production of Th-1/Th-2 Cytokines by Peripheral Blood T Cells

Francisco Javier Laso, Carmen Iglesias-Osma, Juana Ciudad, Antonio López, Isabel Pastor, and Alberto Orfao

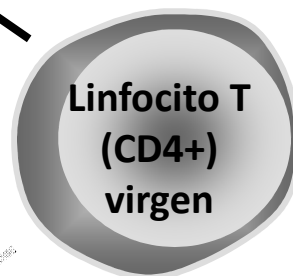


# Regulación de la respuesta inflamatoria



# Linfocitos T reguladores y alcoholismo

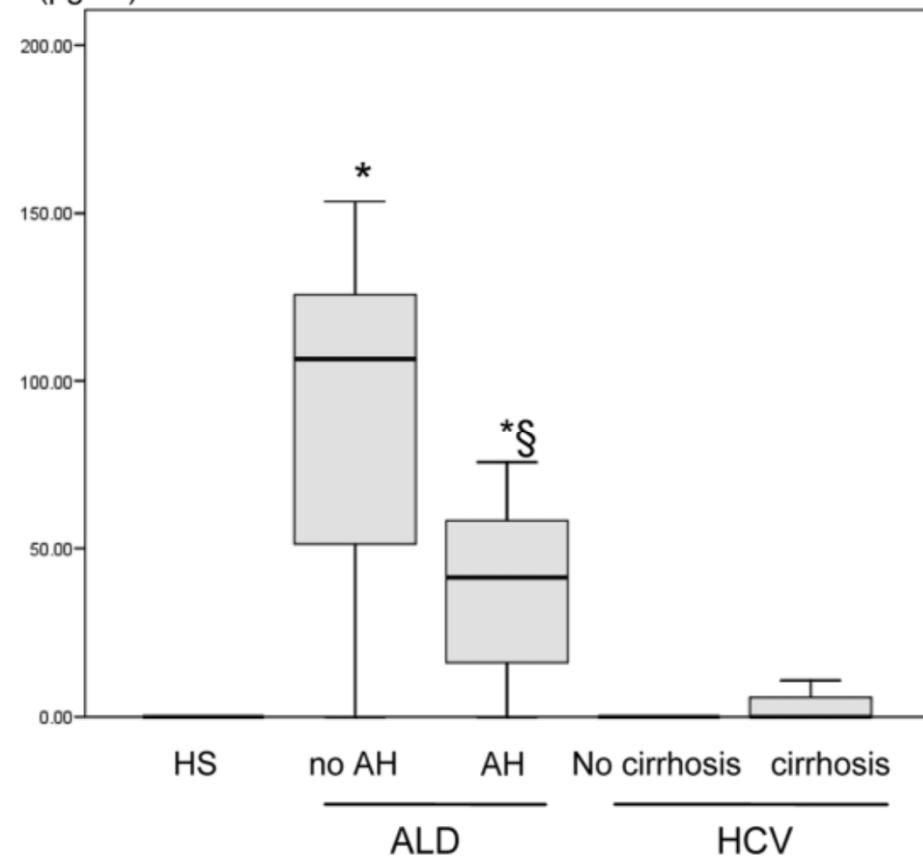
Acción proinflamatoria



## The Interleukin-17 Pathway Is Involved in Human Alcoholic Liver Disease

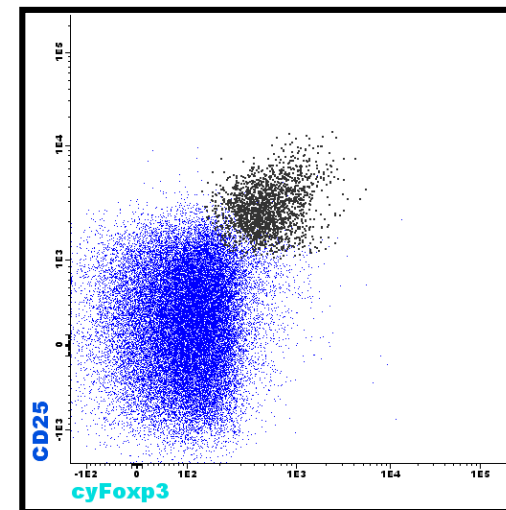
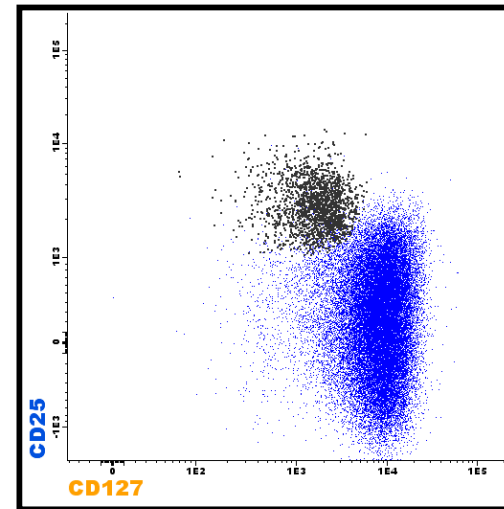
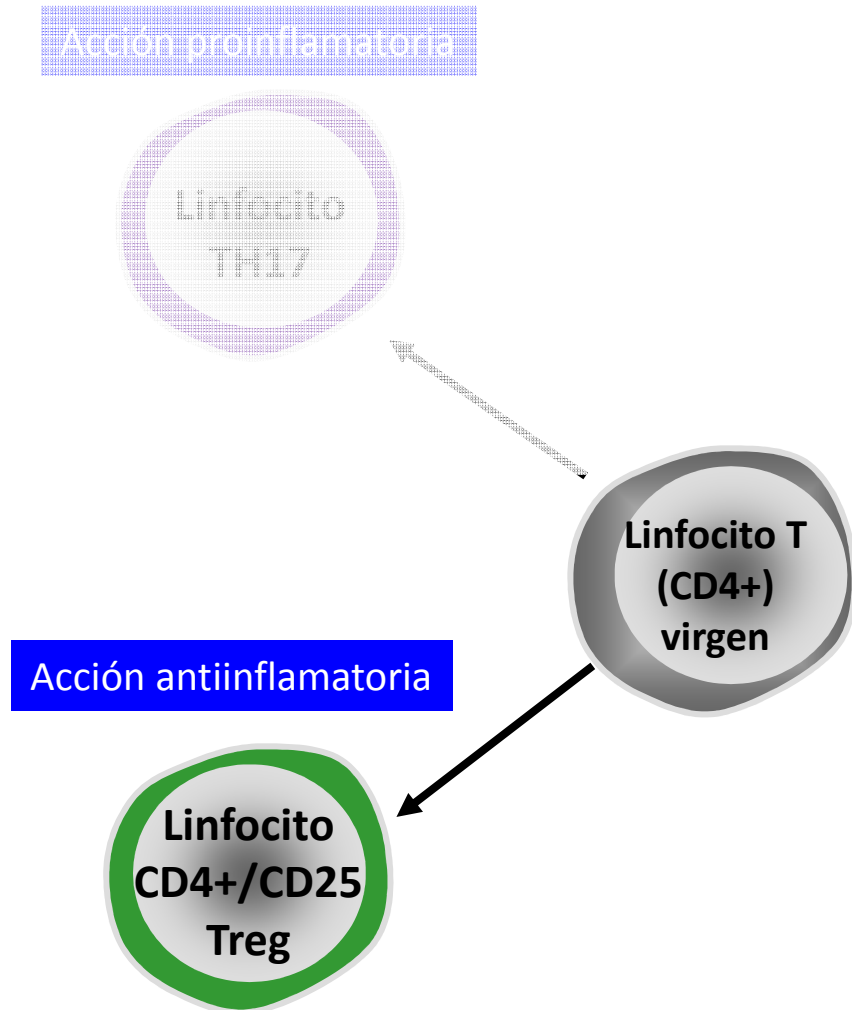
Arnaud Lemmers,<sup>1,2</sup> Christophe Moreno,<sup>1,2</sup> Thierry Gustot,<sup>1,2</sup> Raphaël Maréchal,<sup>1,2</sup> Delphine Degré,<sup>1,2</sup> Pieter Demetter,<sup>4</sup> Patricia de Nadai,<sup>5</sup> Albert Geerts,<sup>3</sup> Eric Quertinmont,<sup>2</sup> Vincent Vercruysse,<sup>2</sup> Olivier Le Moine,<sup>1,2</sup> and Jacques Devière<sup>1,2</sup>

IL-17 (pg/ml)



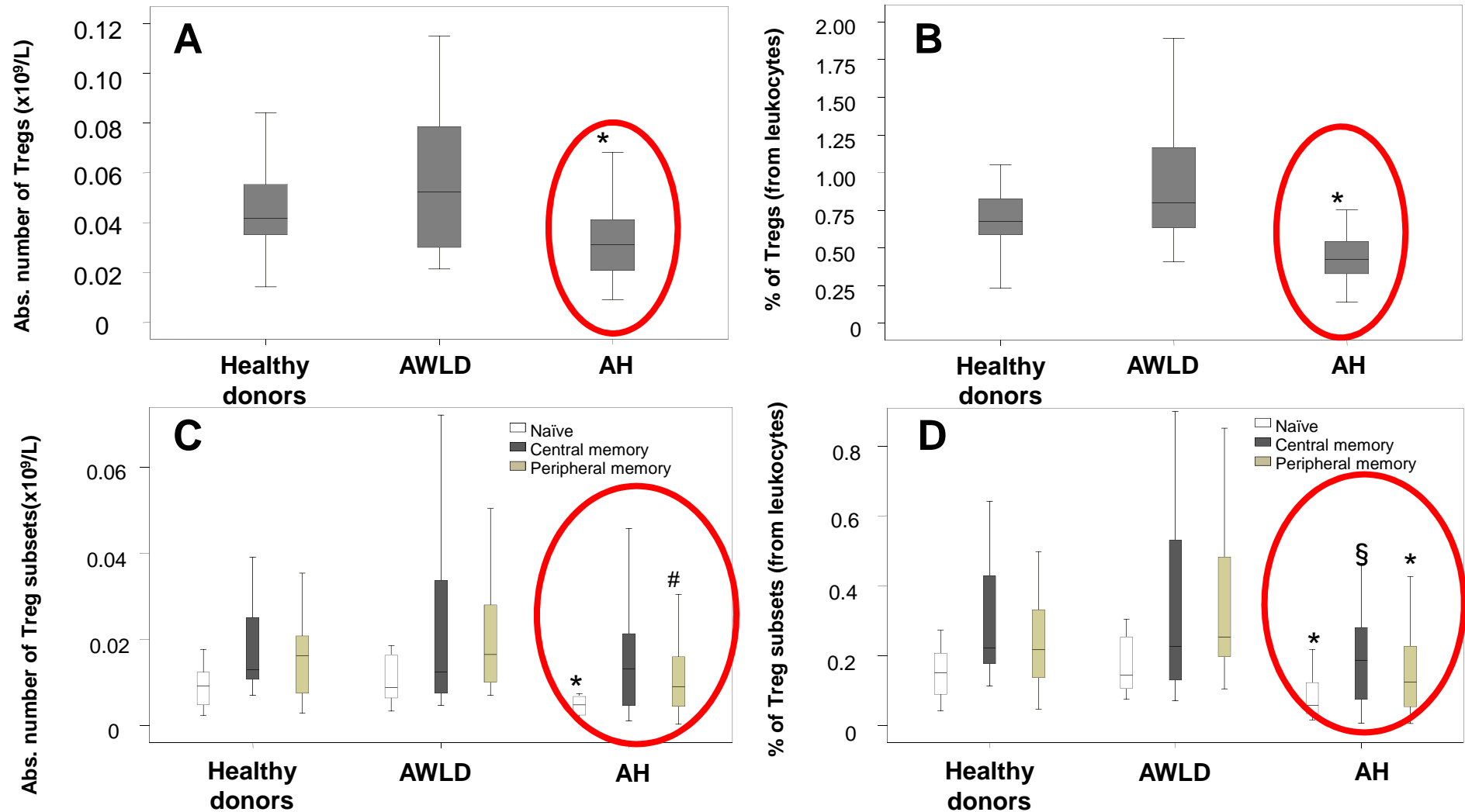
Hepatology 2009; 49: 646-657

# Linfocitos T reguladores y alcoholismo



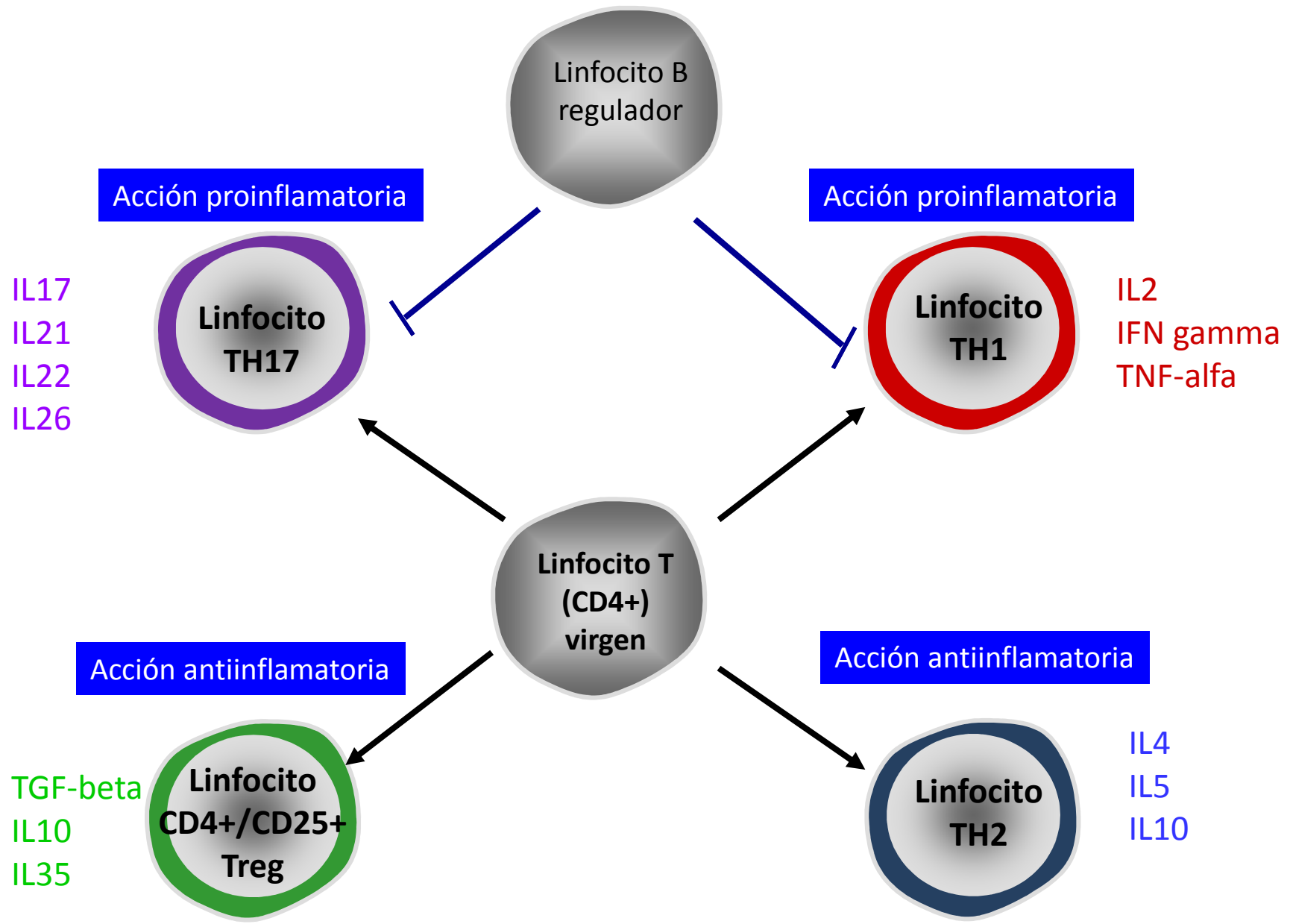
# Decreased Peripheral Blood CD4<sup>+</sup>/CD25<sup>+</sup> Regulatory T Cells in Patients with Alcoholic Hepatitis

Julia Almeida, Maria Angeles Polvorosa, Arturo Gonzalez-Quintela, Miguel Marcos, Isabel Pastor, Maria Luisa Hernandez Cerceño, Alberto Orfao, and Francisco-Javier Laso





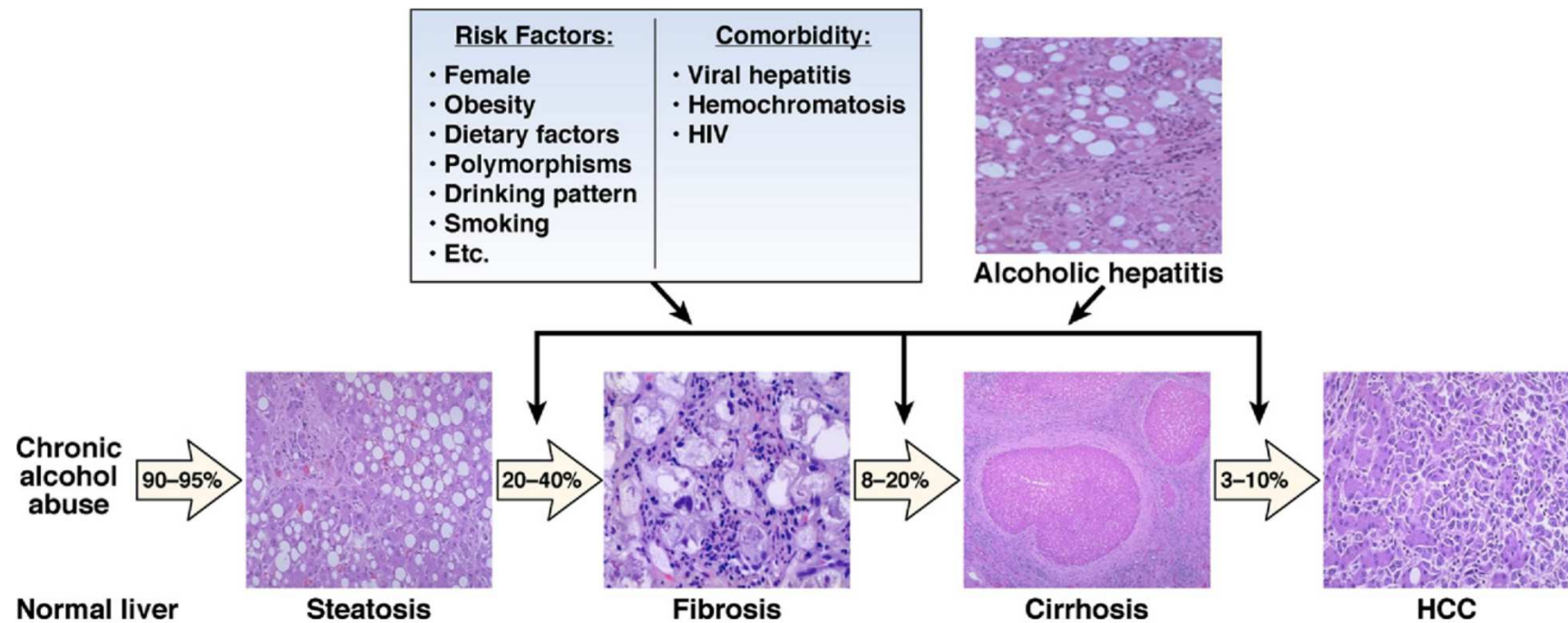
# Regulación de la respuesta inflamatoria



# Variabilidad individual a los efectos del alcohol

- No todo consumidor de alcohol llega a ser dependiente del tóxico
- Sólo algunos alcohólicos crónicos desarrollan enfermedad hepática debida al alcohol

# Evolución de la enfermedad hepática por alcohol





***"El triunfo de Baco o Los borrachos"***

**Diego Velázquez (1629)**



***"El triunfo de Baco o Los borrachos"***

**Diego Velázquez (1629)**

# Evolución de la enfermedad hepática por alcohol

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 37, No. 4  
April 2013

## Binge Ethanol and Liver: New Molecular Developments

Shivendra D. Shukla, Stephen B. Pruetz, Gyongyi Szabo, and Gavin E. Arteel

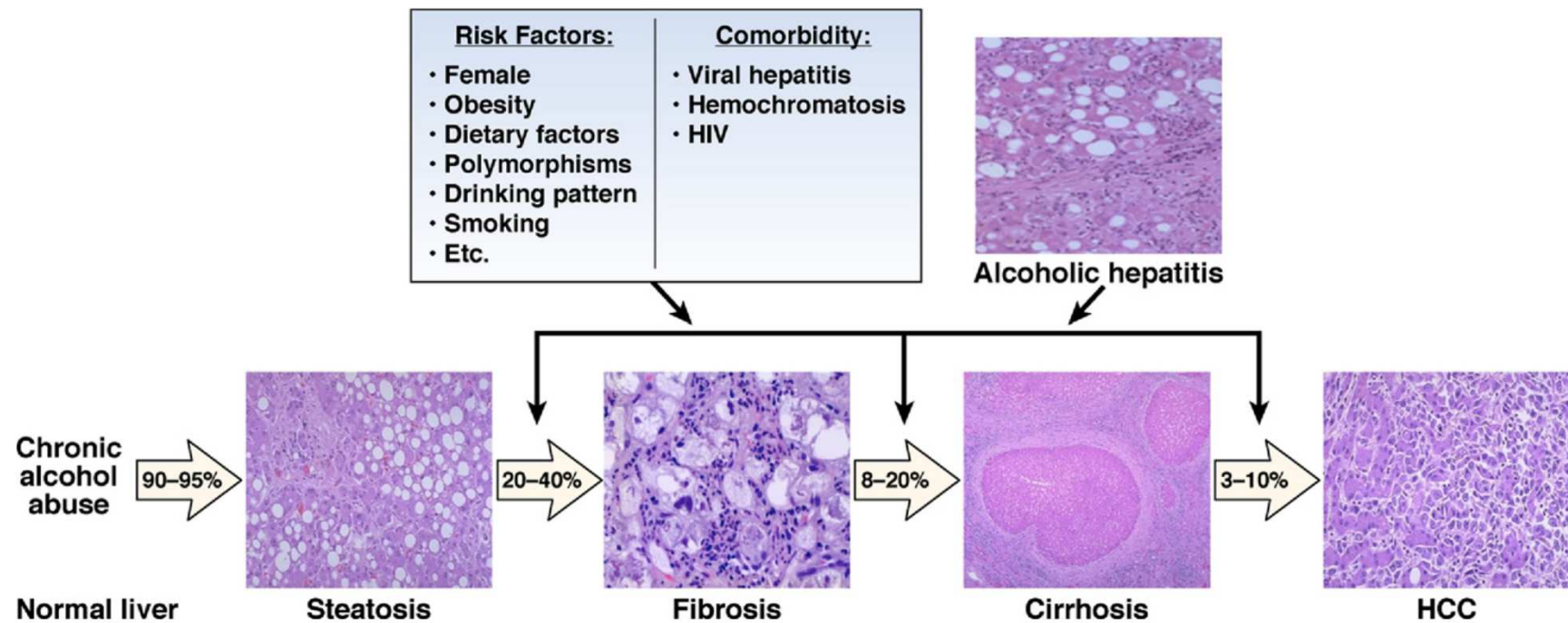
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Binge consumption of alcohol is an alarming global health problem. Binge (acute) ethanol (EtOH) is implicated in the pathophysiology of alcoholic liver disease (ALD). New studies from experimental animals and from humans indicate that binge EtOH has profound effects on immunological, signaling, and epigenetic parameters of the liver. This is in addition to the known metabolic effects of acute EtOH. Binge EtOH alters the levels of several cellular components and dramatically amplifies liver injury in chronically EtOH exposed liver. These studies highlight the importance of molecular investigations into binge effects of EtOH for a better understanding of ALD and also to develop therapeutic strategies to control it. This review summarizes these recent developments.

**Key Words:** Acute Ethanol, Alcoholic Liver Disease, Binge Ethanol, Liver Injury.



# Evolución de la enfermedad hepática por alcohol





# Genes y respuesta inflamatoria en el alcoholismo

## Respuesta inflamatoria

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 286, NO. 2, pp. 1436–1444, January 14, 2011  
© 2011 by The American Society for Biochemistry and Molecular Biology, Inc. Printed in the U.S.A.

### Up-regulation of MicroRNA-155 in Macrophages Contributes to Increased Tumor Necrosis Factor $\alpha$ (TNF $\alpha$ ) Production via Increased mRNA Half-life in Alcoholic Liver Disease\*

Received for publication, May 18, 2010, and in revised form, November 7, 2010. Published, JBC Papers in Press, November 9, 2010, DOI 10.1074/jbc.M110.145870

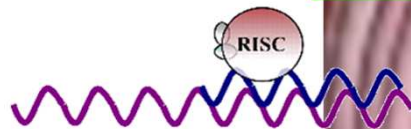
Shashi Bala<sup>1</sup>, Miguel Marcos<sup>1</sup>, Karen Kodys, Timea Csak, Donna Catalano, Pranoti Mandrekar, and Gyongyi Szabo<sup>2</sup>

From the Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01605

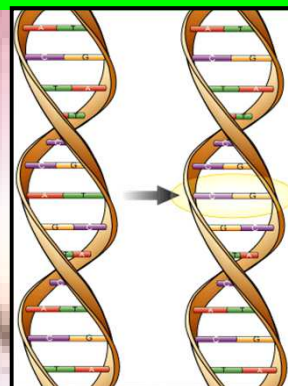
. 170, No. 8  
/aje/kwp236  
er 15, 2009

microARN

Miguel Marcos, Mercedes Gómez-Munuera, Isabel Pastor, Rogelio González-Sarmiento, and Francisco-Javier Laso



Genes





Robert Koch  
(1843-1910)

Aumento de mortalidad en pacientes  
alcohólicos durante la epidemia de cólera  
de 1884

Mayor predisposición de pacientes  
alcohólicos a desarrollar neumonía



William Osler  
(1849-1919)

# FRANCE

## ROUTIÈRE KILOMÉTRIQUE

(Préférence N° 75)

Grands Itinéraires  
Kilomètres

Routes Numérotées

Nouvelle  
Classification  
des Routes Nationales



Echelle :  
1/1.300.000

Tirage en 5 couleurs

Sur papier  
simili-japon :

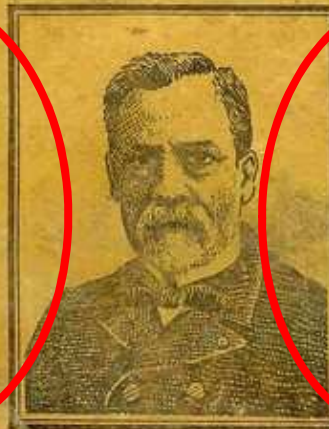
Prix : 6 fr.

Donnez la préférence aux Restaurants qui comprennent  
le vin dans le prix du repas.

MOYENNE  
de la  
VIE HUMAINE

59 ans  
pour un  
buteur d'eau

65 ans  
pour un  
BUVEUR  
DE VIN



87 % des  
centenaires sont  
des buveurs de  
vin.

Le Vin  
c'est le lait  
des vieillards

" Le Vin est la plus saine et la plus hygiénique  
des boissons. "

(Pasteur.)

# Grupo de trabajo de Salamanca



[laso@usal.es](mailto:laso@usal.es)



