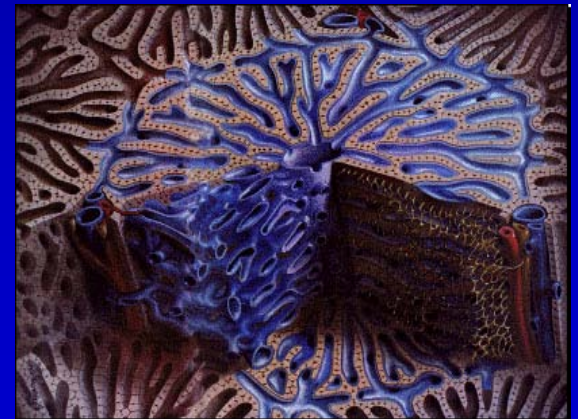
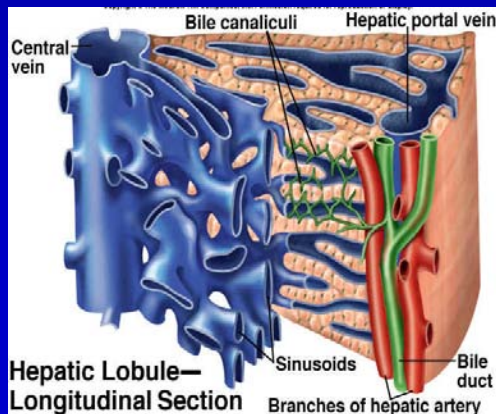


Practical Approach to Abnormal Liver Chemistries

Thomas Hargrave M.D.

May 20, 2011



**CONTRA COSTA REGIONAL MEDICAL
CENTER
NOON CONFERENCE SERIES**

DISCLOSURE OF CONFLICT OF INTEREST

- Speaker has nothing to disclose

“Liver Function” Tests

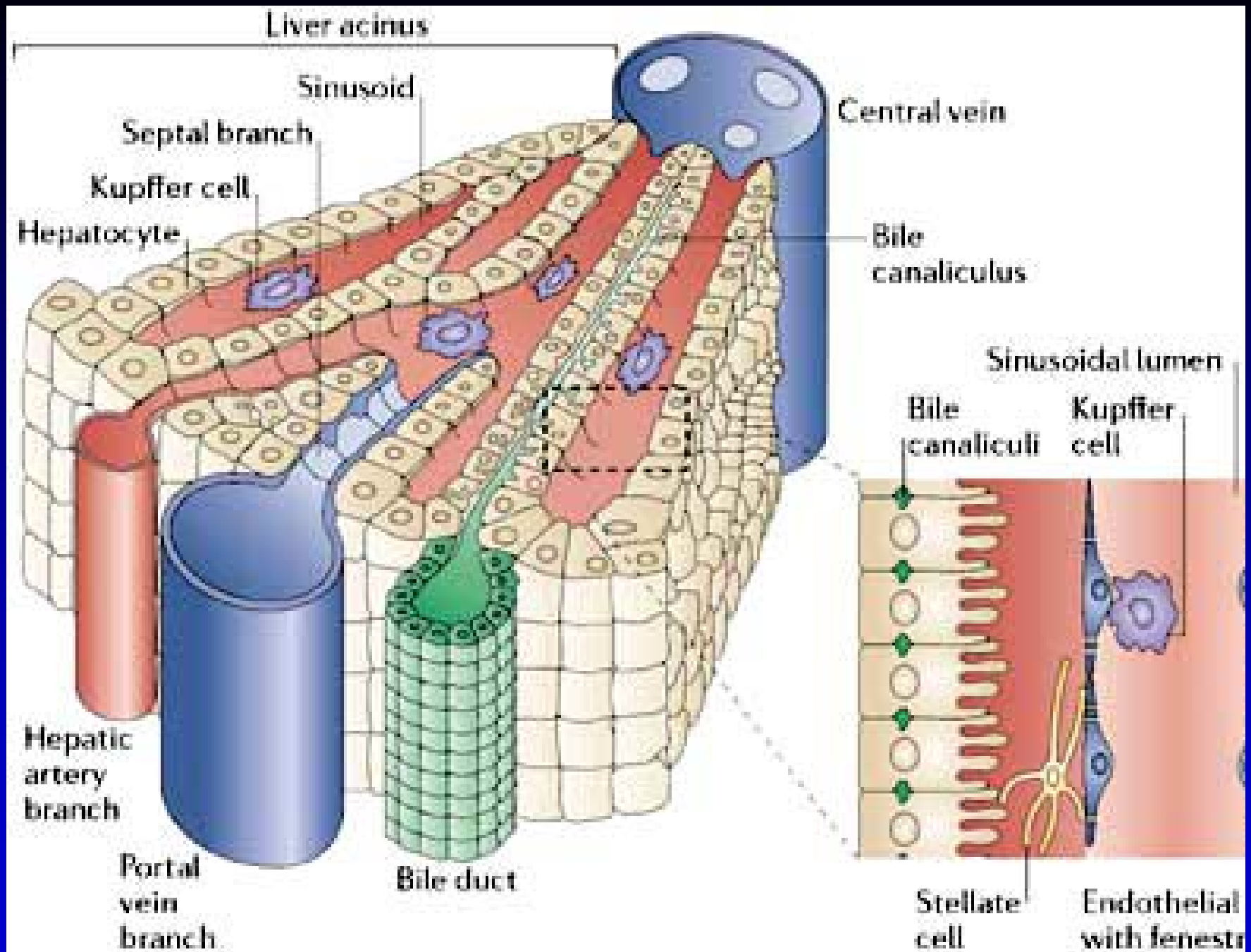
- **Aminotransferases: ALT/AST**
- **Bilirubin**
- **Alkaline phosphatase**
- **GGTP (Gamma-glutamyltransferase)**
- **Albumin**
- **Prothrombin time**
- **Platelet count**

“Liver Function” Tests

- **A misnomer**
 - **Elevated aminotransferases/alkaline phosphatase are markers of liver injury, not liver function**
 - **Albumin/Bili/PT can be affected by extrahepatic factors**
 - **nutritional state**
 - **hemolysis**
 - **antibiotic use**
- **Poor sensitivity and specificity for liver disease**

Three Categories

- **Markers of Hepatocyte Injury/Necrosis**
 - AST/ALT
- **Markers of Cholestatic Liver Disease**
 - Bilirubin/AP/GGTP
- **Markers of Liver Functional Reserve**
 - Albumin/INR/Platelet Count



Markers of Hepatocellular Injury:

Aminotransferases

- Serum aminotransferases are sensitive indicators of liver cell injury
- **AST**- (aspartate aminotransferase) liver>> heart> skeletal muscle> kidneys, brain, RBCs
- **ALT** –(alanine aminotransferase) more specific to liver, low concentrations also in kidney and skeletal muscles.
- Normal AST/ALT = 0.8
- AST>ALT occurs in setting of ETOH excess and advanced fibrosis/cirrhosis
- **ALT elevation is an scalable indicator of increased liver and general mortality**

Marker of Cholestasis: Alkaline Phosphatase

- ALP – predominate source = liver and bone (placenta, kidneys, intestines)
- Hepatic ALP present on surface of bile duct epithelia
- Elevated in the setting of infiltrative disease, biliary obstruction, or rising bile acids
- Takes time for induction of enzyme levels so may not be first enzyme to rise with acute biliary obstruction: half-life is 1 week.
- Gamma GT may be useful to evaluate the origin of ALP

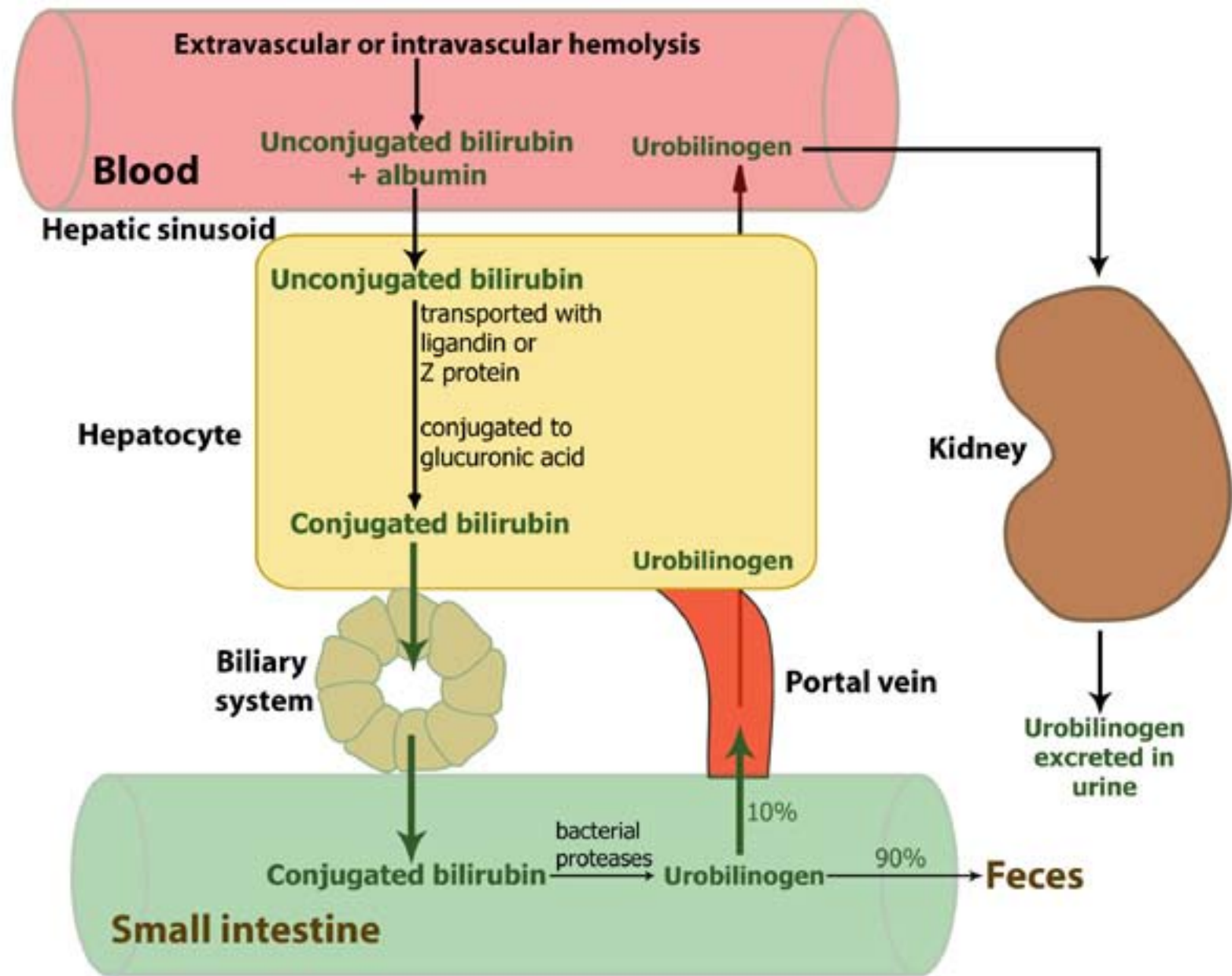
Markers of Hepatocellular Injury:

Gamma-GT

- Gamma-GT – hepatocytes and biliary epithelial cells, pancreas, renal tubules and intestine.
- Not present in bone
- Raised in virtually ANY liver disease, hepatocellular, cholestatic, and drug-induced
- Very sensitive but non-specific
 - A twofold elevation of the GGT in patients whose AST/ALT ratio is greater than 2:1 strongly suggests alcohol abuse
- Isolated GGT increase does not require any further evaluation, monitor periodically and investigate only if other LFT's become abnormal

Bilirubin

- Bilirubin is formed by breakdown of heme present in hemoglobin, myoglobin, cytochromes, catalase, peroxidase and tryptophan pyrrolase.
- Poorly soluble in water and highly toxic, transported in serum bound to albumin
- Glucuronidation occurs within hepatocytes prior to active secretion into bile canaliculi
- Normal serum bilirubin concentration in children and adults is less than 1 mg/dL
- In normal plasma, about 4 percent of bilirubin is conjugated



Hyperbilirubinemia

- The bilirubin normally present in serum reflects a balance between production and clearance.
- Elevated serum bilirubin concentrations can be due to three causes which can sometimes coexist:
 - Overproduction of bilirubin
 - Impaired uptake, conjugation, or excretion of bilirubin
 - Backward diffusion from damaged hepatocytes or obstructed bile ducts

Bilirubin

- **Total serum bilirubin is not a sensitive indicator of hepatic dysfunction.**
- **Concentrations of serum bilirubin may be normal despite moderate to severe hepatic parenchymal injury, including cirrhosis, or a partially or transiently obstructed common bile duct.**
- **This lack of sensitivity can be explained in part by the reserve capacity of the human liver to remove bilirubin**
 - **In patients who have hemolysis, the normal liver can remove at least twice the normal daily bilirubin load without the development of hyperbilirubinemia**

What is a True Normal Aminotransferase Value?



Determining the Definition of Normal ALT Values

- **Statistical definition**

- Standard practice to define normal lab values
- Middle 95% of healthy subjects
 - Abnormal: > 97.5th percentile
- Influenced by reference population

- **Biological definition**

- Risk of developing disease or complication
 - Cholesterol, glucose
- Abnormal ALT: level associated with disease



Updated Limits for Normal ALT

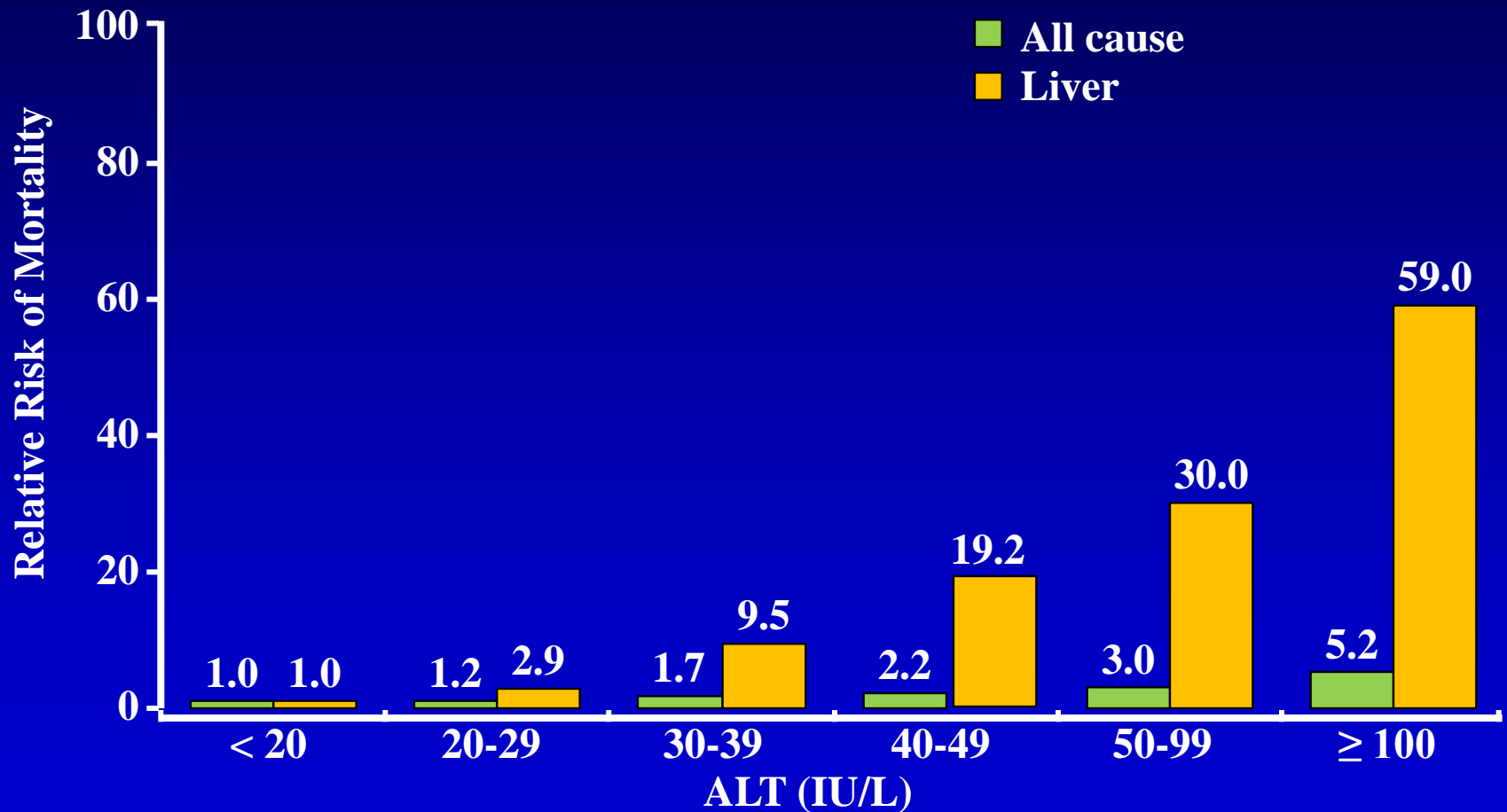
- 9221 first-time blood donor candidates
- 57% determined to be ‘low risk’ for liver disease
 - Negative viral serology
 - BMI < 25
 - Normal serum cholesterol, triglycerides, and glucose levels
 - Absence of concurrent medication use
- Updated healthy ALT ranges determined from the group of low-risk individuals
 - **Males: 30 IU/L**
 - **Females: 19 IU/L**



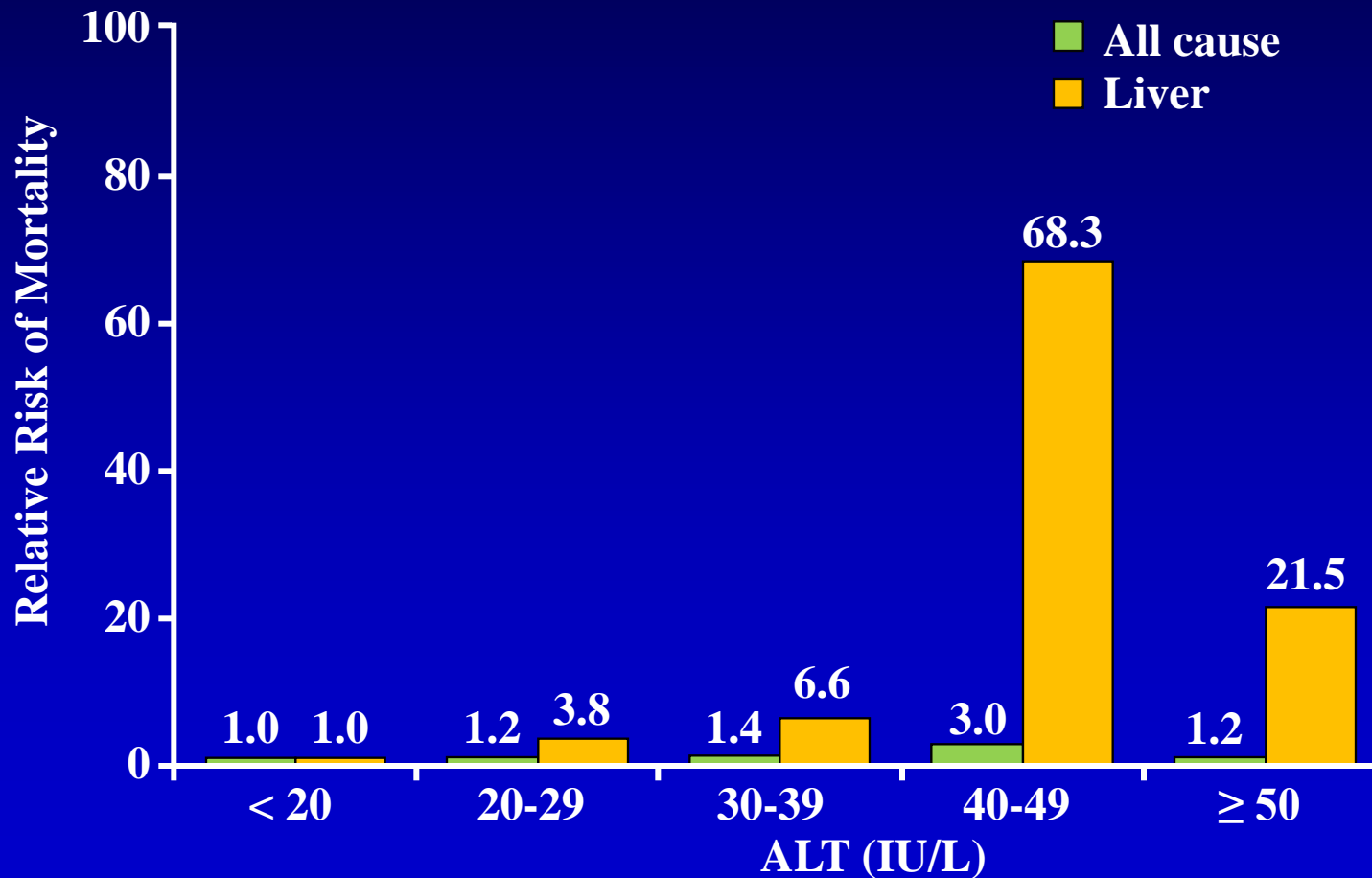
Biologic Definition of Normal ALT

- Cohort study of 142,055 S. Korean health insurance participants
 - Aged 35-59 years
 - Baseline ALT measured 1990-1992
 - Follow-up through 2000
 - Death certificates used to determine date of death and cause of death
 - Limitation: hepatitis B diagnosis unknown

ALT and Subsequent 10-Year Mortality in Men

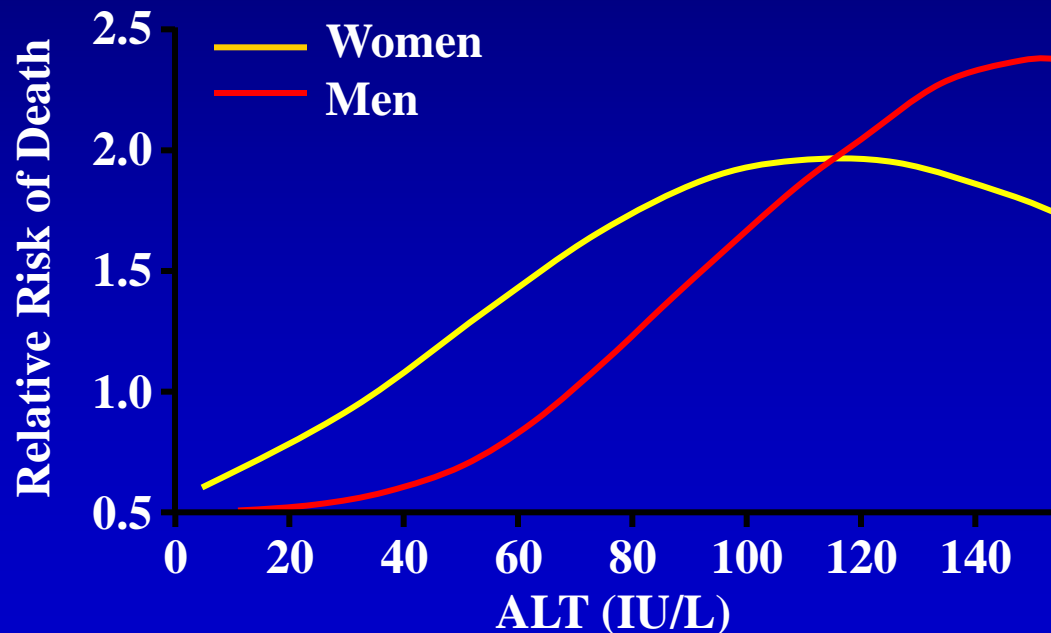


ALT and Subsequent 10-Year Mortality in Women



ALT and 11-Year Mortality in Olmsted County Cohort

- Adults from Olmsted County, Minnesota, who came to Mayo Clinic in 1995 included (N = 6823)
 - Followed from January 1995 to April 2006



Serum aminotransferase activity and mortality risk in a United States community. Lee TH, et al. 2008. Hepatology. 2008;47:880-887.

Disadvantages of Using a Lower ALT ULN Cutoff

- Unclear health benefit
 - i.e., NAFLD with minimally elevated ALT
- Potential unnecessary testing and consultation
- Rejection of blood donors
- Anxiety
- Medico-legal



Evaluation of Liver Abnormalities

History

- **Systemic symptoms**
- **Family Hx**
 - Hemochromatosis, Wilson's Disease, alpha₁ antitrypsin deficiency
 - Gilbert's syndrome, Dubin-Johnson Syndrome, Rotor's syndrome
- **Infectious risk**
 - Sexual History
 - Tattoos
 - Illicit drug use
 - Travel history

History

- **Occupational exposures**
 - Chemicals (vinyl chloride, dimethylformamide, 2-Nitropropane, Trichloroethylene)
- **Other co-morbid illnesses**
 - Autoimmune diseases, Thyroid disease, Celiac disease, IBD, Diabetes Mellitus
- **Medications**
 - Prescription
 - OTC
 - Herbals, Vitamins

Drug-Induced Liver Injury

- **Hepatocellular injury (serum aminotransferase elevations)**
 - Acetaminophen
 - Alpha-methyldopa
 - Amiodarone
 - Dantrolene
 - Diclofenac
 - Disulfiram
 - Fluconazole
 - Glyburide
 - Heparin
 - Isoniazid
 - Ketoconazole
 - Labetalol
 - Lovastatin
 - Nitrofurantoin
 - Propylthiouracil
 - Trazodone
- **Cholestatic injury (serum ALP and bilirubin elevations)**
 - Androgenic anabolic steroids
 - Captopril
 - Chlorpropamide
 - Erythromycin
 - Estrogenic steroids
 - Floxuridine
 - Gold salts
 - Methimazole
 - Phenothiazines
 - Tolazamide
 - Tolbutamide
 - Trimethoprim-sulfamethoxazole
- **Mixed hepatocellular-cholestatic injury**
 - Flutamide
 - Phenylbutazone
 - Phenytoin

Acetaminophen Can Cause Aminotransferase Elevation Among Healthy Adults

- Placebo controlled study of 145 healthy volunteers given acetaminophen (4 g daily for 14 days)
- An increase from 1 to 2 times the upper limit of normal was observed in 50 to 70 percent of patients.
- An increase > 3 times the upper limit of normal was observed in 33-41 percent of patients.
- About 20 percent experienced an ALT elevation more than five times the upper limit of normal (compared with 3 percent taking placebo)

Routine Monitoring of LFTs no Longer Considered Necessary for Statin Use

- Clinical studies have found ALT elevations in 0.5% to 3% of patients who take statins.
- No case reports of chronic liver damage (i.e. cirrhosis) from statin use
- Acute liver failure resulting from statin therapy is idiosyncratic and exceedingly rare (0.2/million)
- Routine LFT monitoring is not necessary.
- Statins should not be withheld in patients with preexisting liver disease or baseline abnormal LFTs (mostly due to NAFLD).

Herbal and Dietary Supplement Hepatotoxicity

- **42% of American use some form of alternative medical therapy**
- **Approx. 19% use dietary supplements (DS)**
- **20-40% of chronic liver patients use herbal supplements**
- **21% of adults taking prescriptions use DS**
- **69% do not disclose DS use to their primary care provider**

Hepatotoxic Herbals

- Black Cohosh
- - Buckthorn (*Rhamnus cathartica*).
- - *Callilepis laureola* (*Impila*)
- - Cascara Sagrada
- - Celandine
- • Chaparral
- • Comfrey and other herbs containing pyrrolizidine alkaloids (*heliotropium*, *senecio*, *crotalaria*, *symphytum*)
- - Doxidan
- • Germander (*Teucrium chamaedrys*).
- - Green tea leaf
- • Groundsel (*Senecio vulgaris*).
- - *Impila* root
- • Jin Bu Huan.
- - Kava (
- - Kombucha
- • Lobelia (*Lobelia inflata*).
- Ma huang (*ephedra*).
- Mate
- Mistletoe (*Viscum album*).
- Nutmeg (*Myristica fragrans*).
- Pau d'arco (*La pachol*).
- Pennyroyal (*Mentha pulegium*).
- Poke root (*Phytolacca americana*).
- Ragwort (*Senecio jacoboea*).
- Sarsaparilla (*Smilax species*).
- Sassafras (*Sassafras albidum*).
- Saw palmetto –
- Senna (*Casio acutifolia*).
- Skullcap (*Scutellaria laterifolia*).
- Soy phytoestrogen
- Sweet clover (*Melilotus officinalis*).
- Tansy (*Tanacetum vulgare*).
- T'u-san-chi.
- Valerian (*Valeriana offinalis*).
- Woodruff (*Galium odorata*).

How Prevalent Are Aminotransferase Elevations?

**Very, and increasing significantly
over the last two decades.**

Prevalence of Diseases Associated with Elevated ALT

• NAFLD	45-60%
• NASH	9-20%
• Drugs/Herbs	???
• ETOH > 2/day	5-6%
• Hepatitis C	1.8% (2-15%)
• Hepatitis B	0.4% (0.4-15%)
• Hemochromatosis	0.25%
• AIH	0.017%

Prevalence and Etiology of Elevated Aminotransferases in USA 1988-1994

- Data on adults ages 17 yr and older (n = 15,676) from the Third National Health and Nutrition Examination Survey (1988–1994).
- Participants were classified as having elevated aminotransferase levels if either AST or ALT was elevated above normal.
 - Men: ALT >40 AST > 37
 - Women ALT > 31 AST > 31
- “Unexplained” ↑ALT defined as the absence of HBV, HCV, abnormal iron saturation, and no alcohol excess

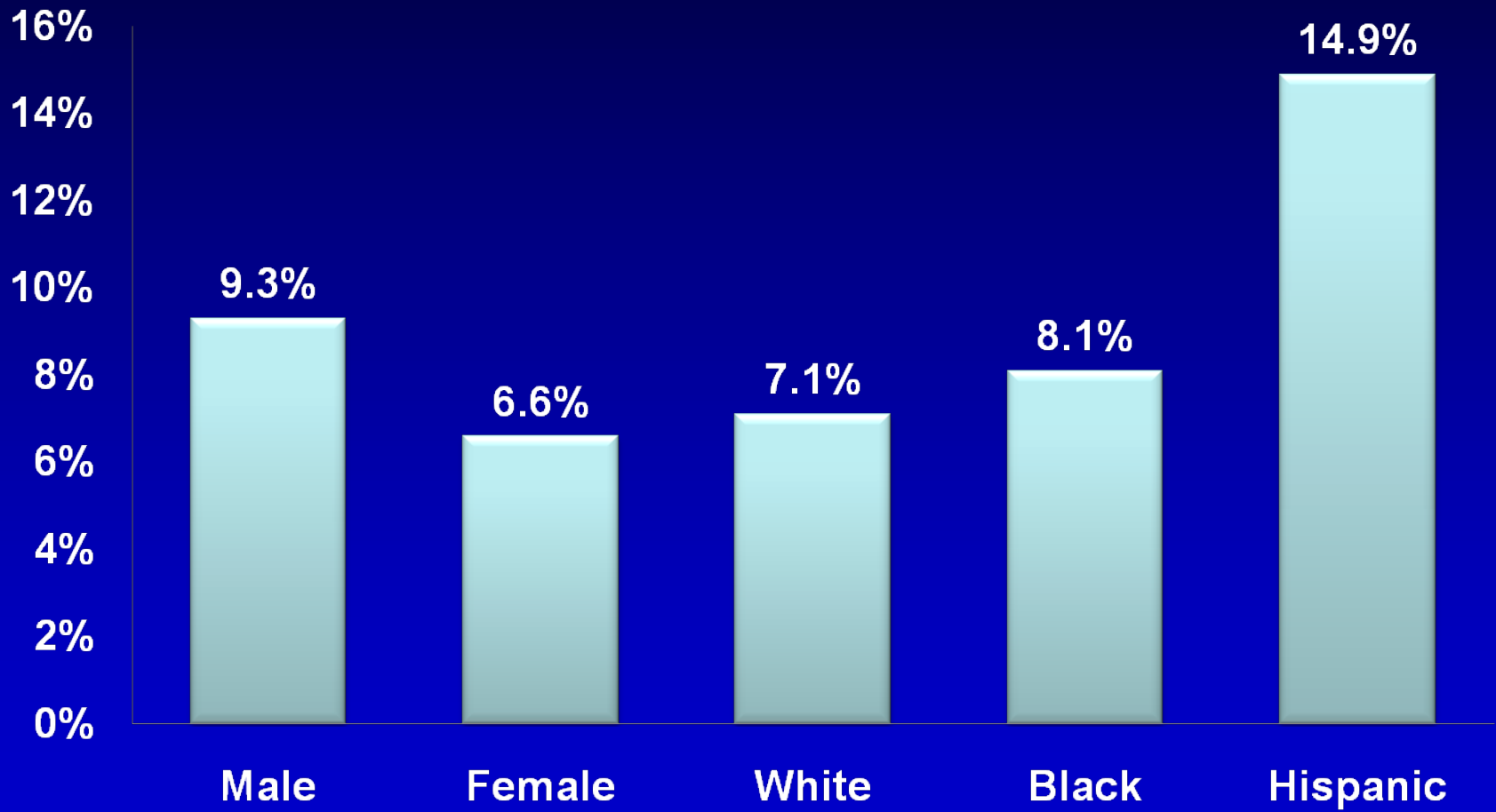
Prevalence and Etiology of Elevated Aminotransferases in USA 1988-94

- The prevalence of aminotransferase elevation in the United States was 7.9%.
- Aminotransferase elevation was more common in men compared to women (9.3% vs 6.6%, $p = 0.002$), in Mexican Americans (14.9%) and non-Hispanic blacks (8.1%) compared to non-Hispanic whites (7.1%) , $p < 0.001$.
- Hepatitis B or C infection, high transferrin saturation, and/or alcohol use accounted for only 31.0% of cases.

Prevalence and Etiology of Elevated Aminotransferases in USA 1988-94

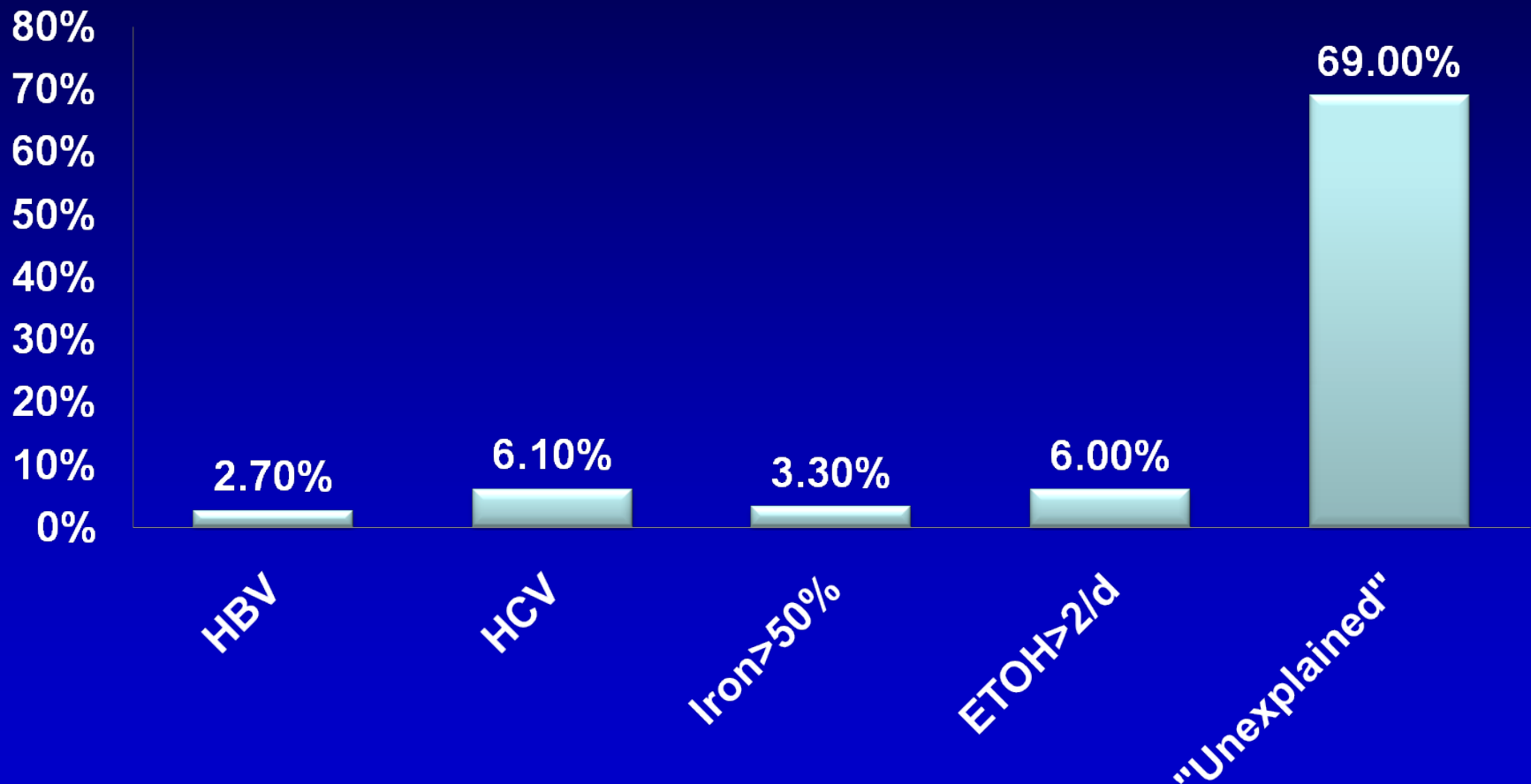
- Aminotransferase elevation was “unexplained” in the majority (69.0%).
- In both men and women, unexplained aminotransferase elevation was significantly associated with higher body mass index, waist circumference, triglycerides, fasting insulin, and lower HDL; and with type 2 diabetes and hypertension in women (all $p < 0.05$).
- I.e. Metabolic Syndrome/NAFLD

Prevalence of Elevated Aminotransferases in USA 1988-94



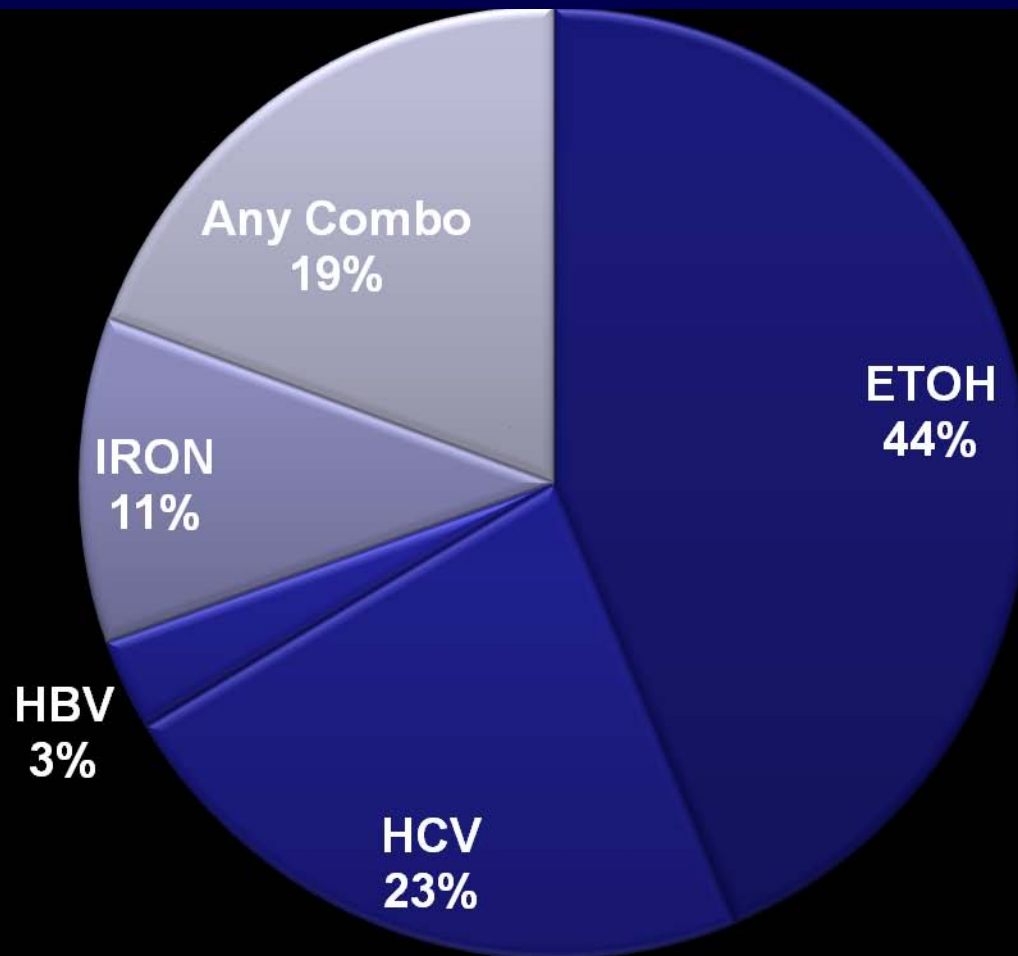
The American Journal of Gastroenterology (2003) 98, 960–967

Etiology of Elevated Aminotransferases in USA 1988-94



The American Journal of Gastroenterology (2003) 98, 960–967

“Known” Etiologies of Elevated Aminotransferases in USA: NHANES 1988-94

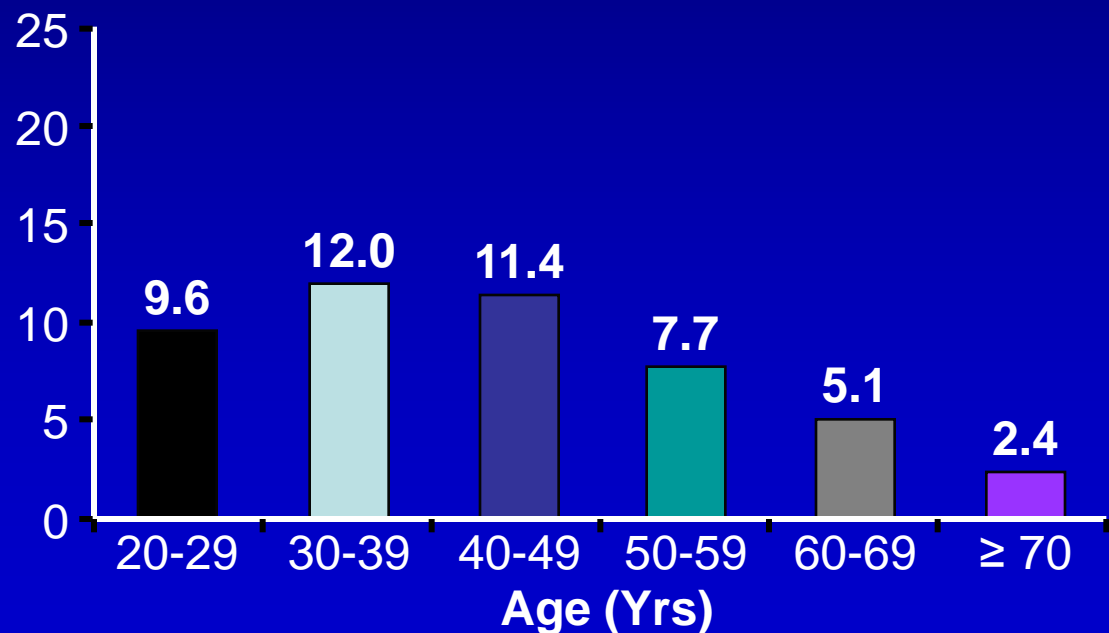
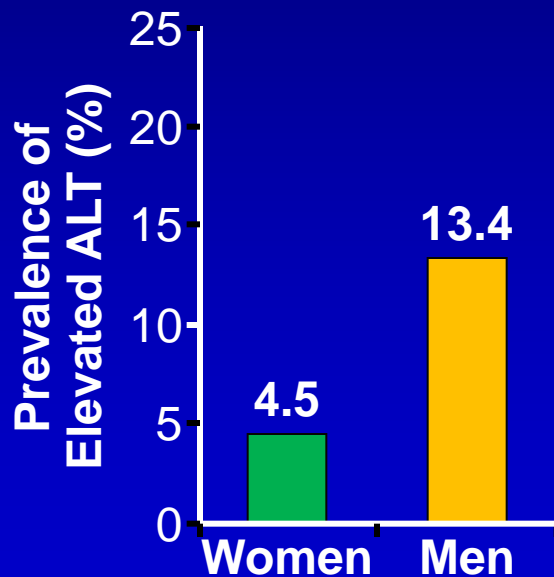


The American Journal of Gastroenterology (2003) 98, 960–967

Ten Years Later...

Prevalence and Etiology of Elevated Aminotransferases in USA 1999-2002

- Prevalence of elevated ALT (> 43 IU/L: men and women) from 1999-2002 NHANES database evaluated (N = 6823)

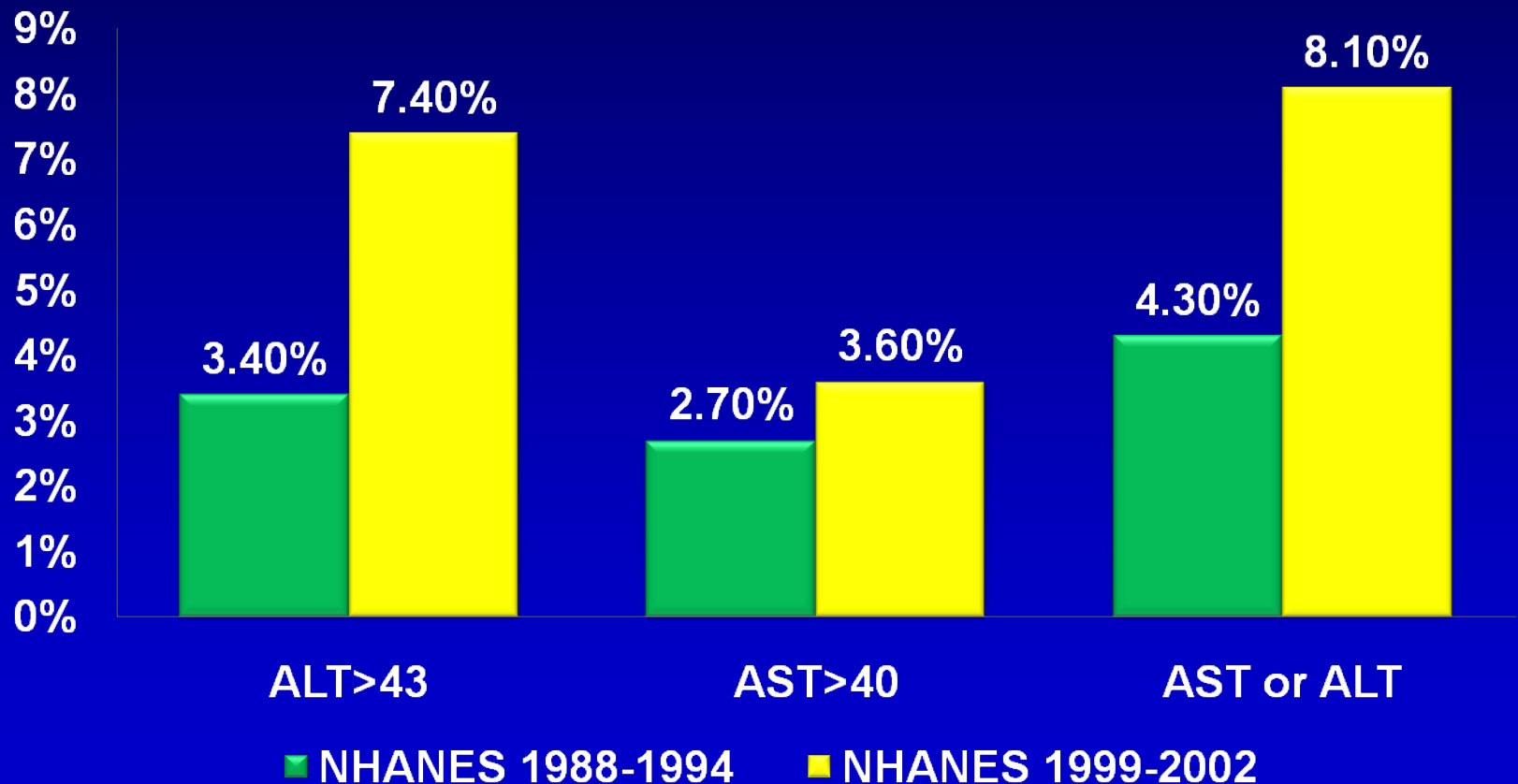


Prevalence and Etiology of Elevated Aminotransferases in USA 1999-2002

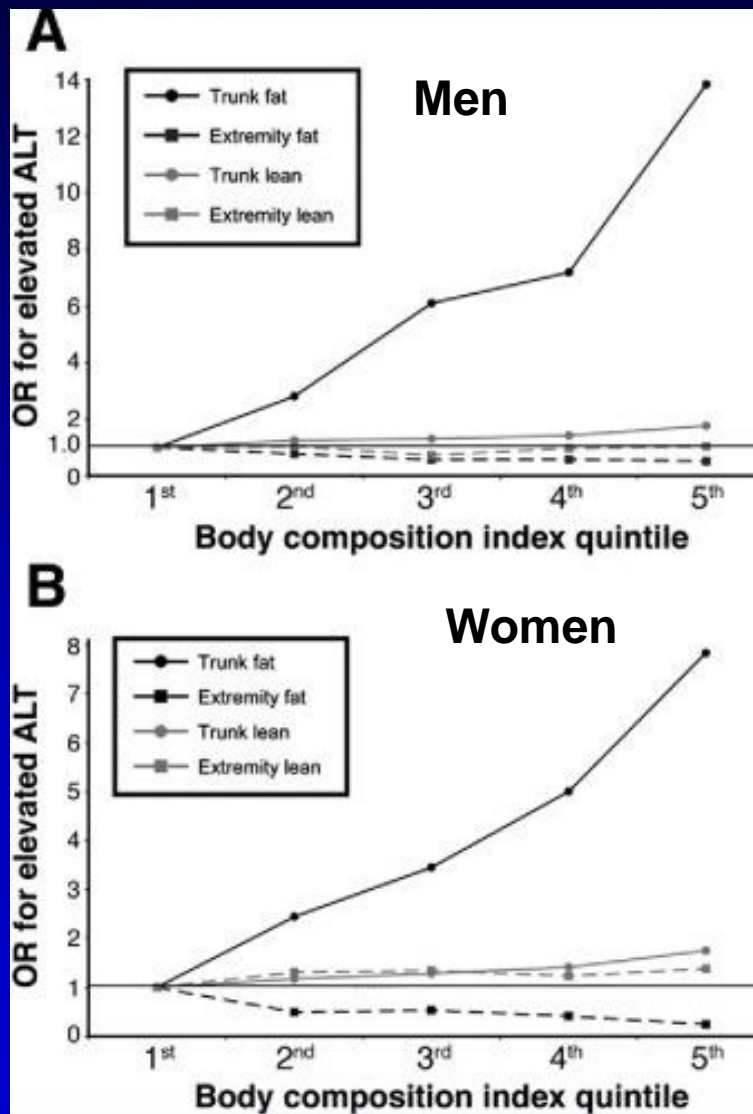
- In NHANES 1999–2002, the prevalences of elevated ALT, AST, or either ALT or AST were 8.9%, 4.9%, and 9.8%,
- In NHANES 1988–1994, which employed a different assay methodology, the prevalences of elevated aminotransferases were approximately half of the prevalences described in NHANES 1999–2002, but the predictors of elevated ALT activity were similar. (i.e. BMI, DM, hyperlipidemia, visceral fat, metabolic syndrome)

Prevalence of “Unexplained” Elevated Transaminases

After exclusion of viral hepatitis and more the one alcoholic drink per day



Trunkal Fat is a Major Body Composition Determinant of Increased ALT



When BMI, waist circumference, and trunk fat were considered together, only trunk fat remained independently associated with increased ALT.

Gastroenterology. 2010;138(4):1346-1356

Prevalence of Diseases Associated with Elevated ALT

• NAFLD	45-60%
• NASH	9-20%
• Drugs/Herbs	???
• ETOH > 2/day	5-6%
• Hepatitis C	1.8% (2-15%)
• Hepatitis B	0.4% (0.4-15%)
• Hemochromatosis	0.25%
• AIH	0.017%

Prevalence of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among a Largely Middle-Aged Population Utilizing Ultrasound and Liver Biopsy: A Prospective Study

Christopher D. Williams, Joel Stengel, Michael I. Asike, Dawn M. Torres, Janet Shaw, Maricela Contreras, Cristy L. Landt and Stephen A. Harrison

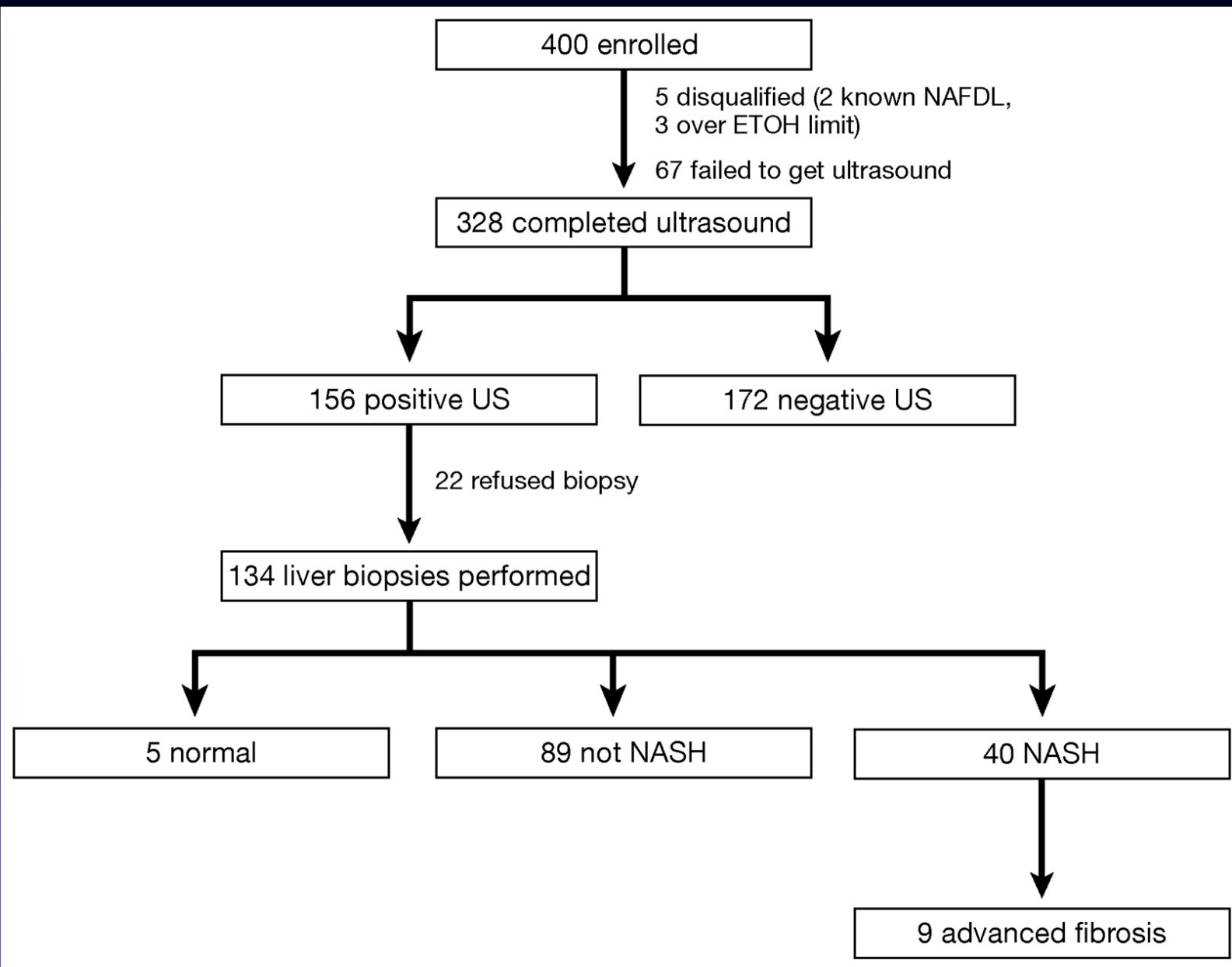
Gastroenterology

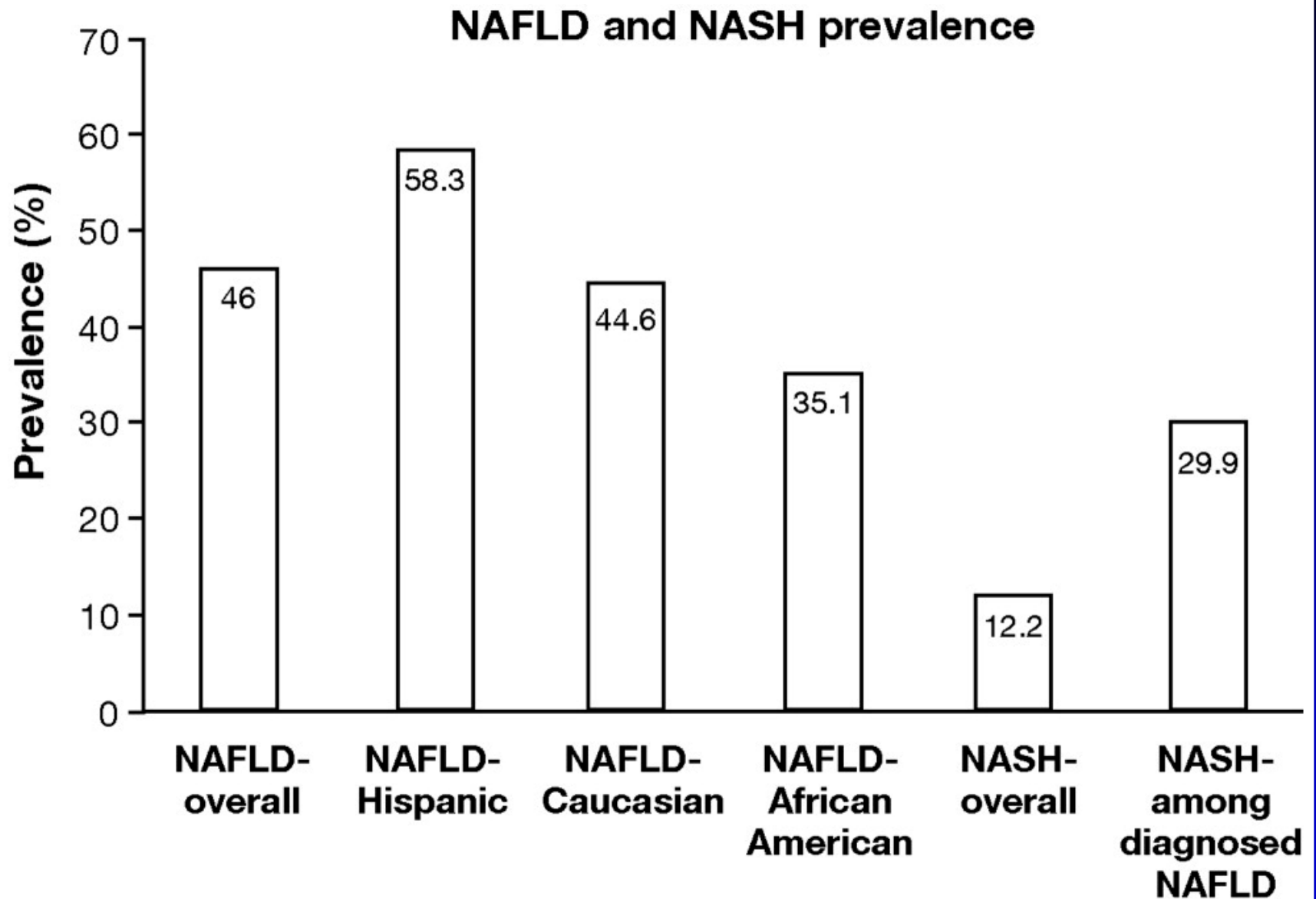
Volume 140, Issue 1, Pages 124-131 (January 2011)

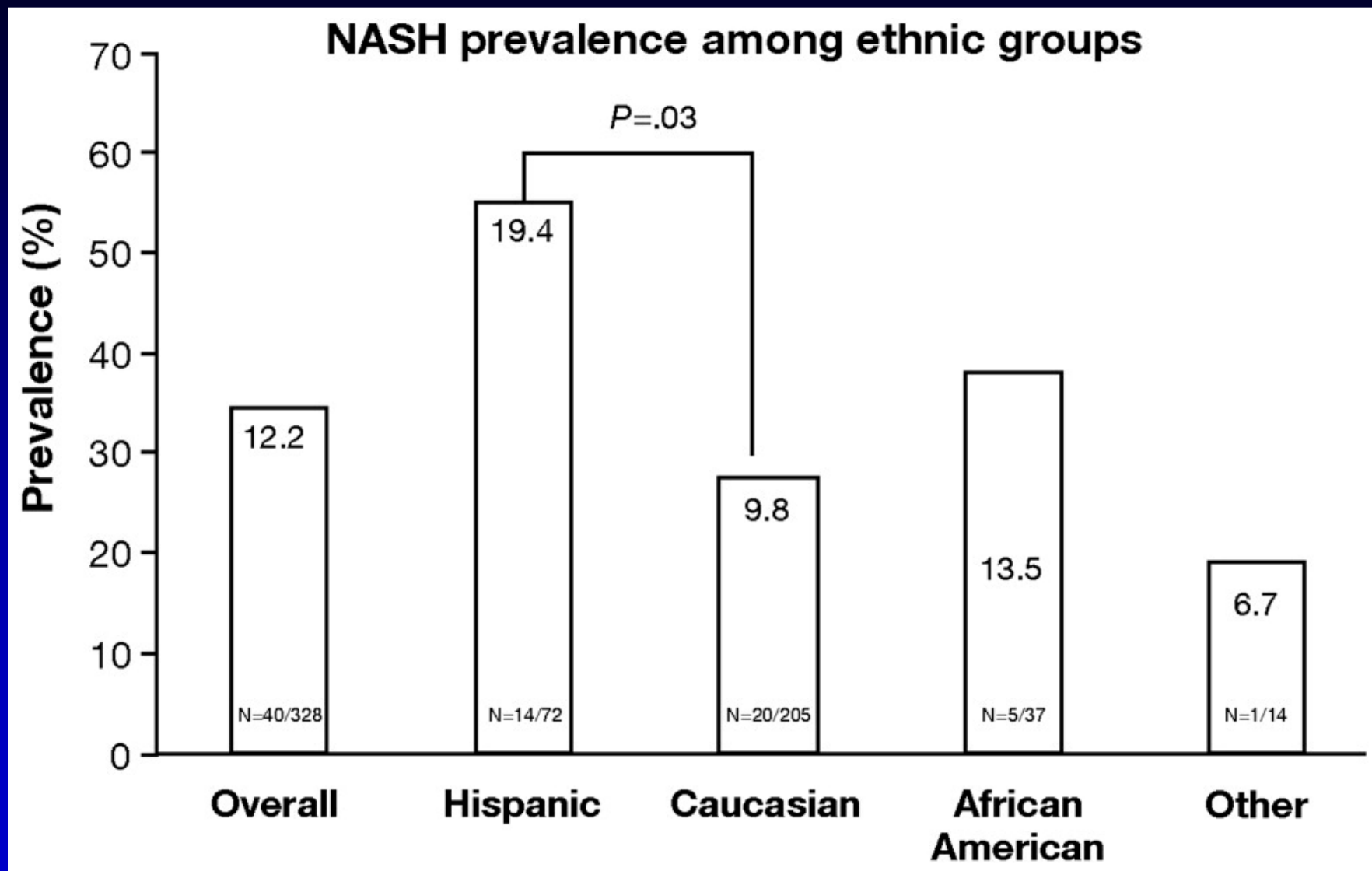
DOI: 10.1053/j.gastro.2010.09.038

High Prevalence of NAFLD/NASH in Urban Population

- **Brooke Army Medical Center Primary Care Clinic in Dallas: include all active duty personnel, their dependents, and military retirees (to include spouses)**
- **328 pt underwent a right upper quadrant ultrasound.**
- **Mean age: 54.6 ± 7.35 years; range, 28–70 years**
- **50.9% were female.**
- **Caucasian (62.5%), Hispanic (22%), African American (11.3%), and other (4.3%).**
- **The mean body mass index was 29.8 ± 5.64 with 45.4% of the patients meeting criteria for obesity ($\text{BMI} \geq 30$)**







Ultrasound and NAFLD

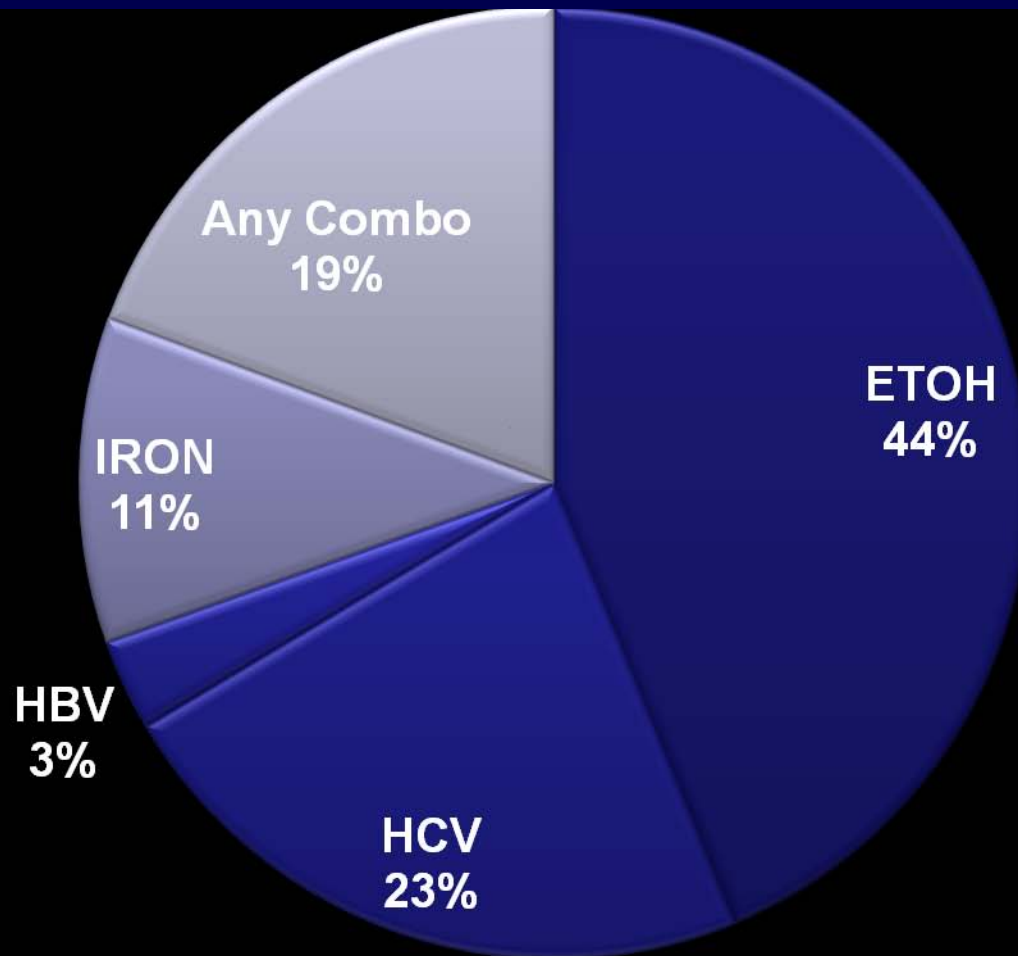
- Although US is an acceptable first-line screening procedure for NAFLD in clinical practice, it underestimates the prevalence of hepatic steatosis when there is $< 20\%$ fat.
- For the presence of macrovesicular hepatic steatosis of any degree had a sensitivity of 60.9% and a specificity of 100%.
- The sensitivity increased to 100% and the specificity to 90% when there was $> 20\%$ of fat

Prevalence of Diseases Associated with Elevated ALT

• NAFLD	45-60%
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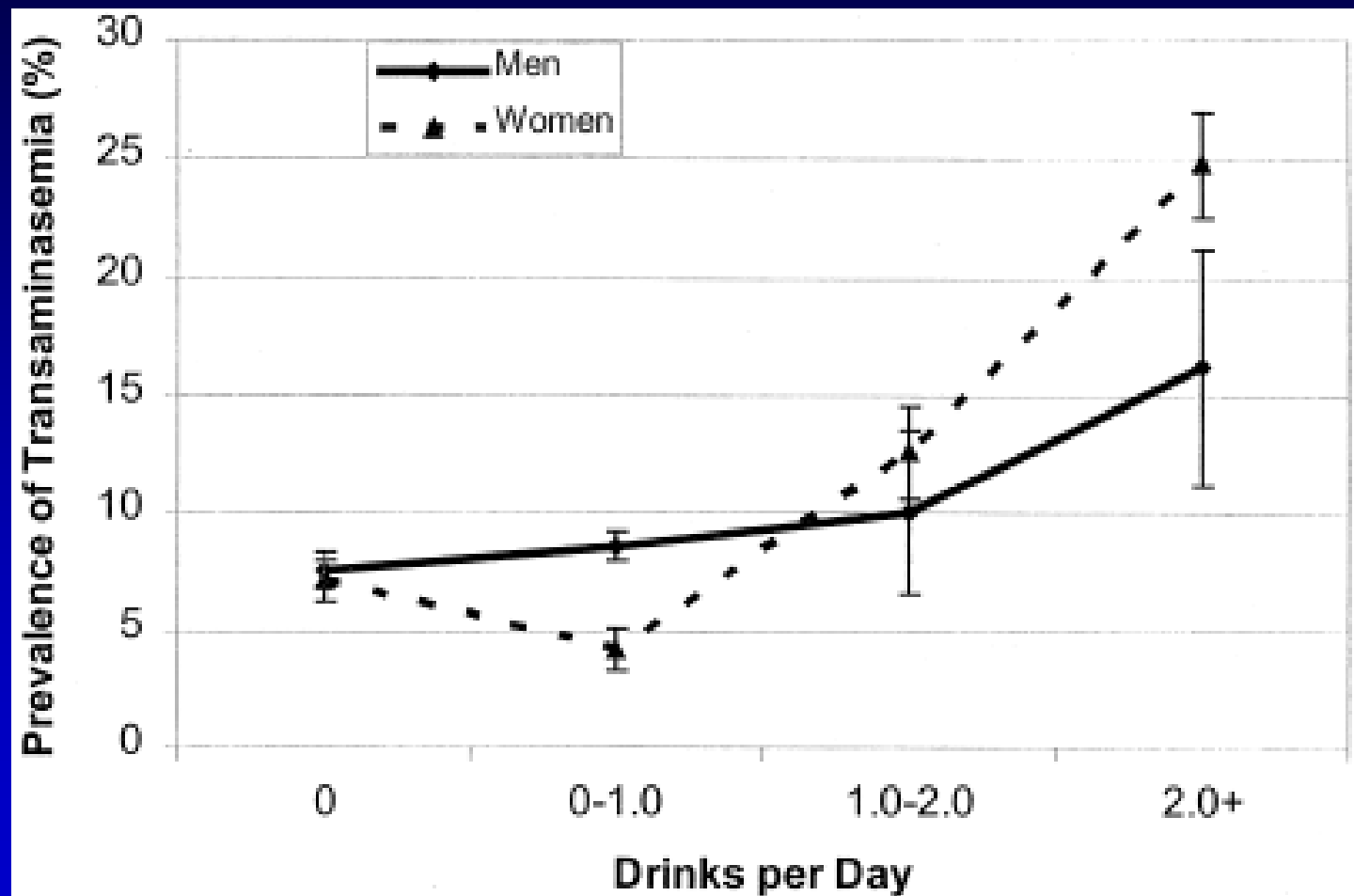
Alcohol

“Known” Etiologies of Elevated Aminotransferases in USA: NHANES 1988-94



The American Journal of Gastroenterology (2003) 98, 960–967

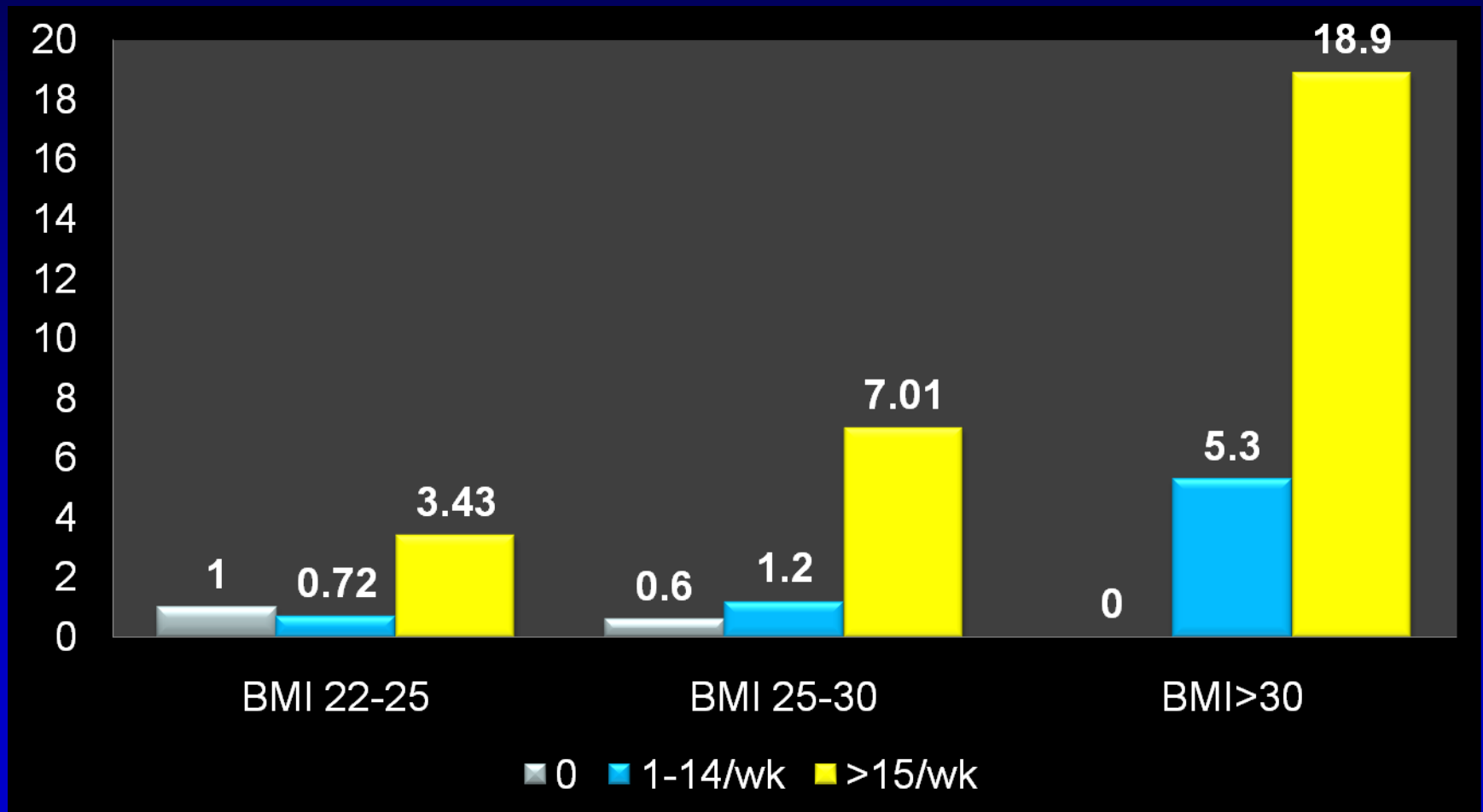
Prevalence and Etiology of Elevated Aminotransferases : Role of ETOH



The American Journal of Gastroenterology (2003) 98, 960–967

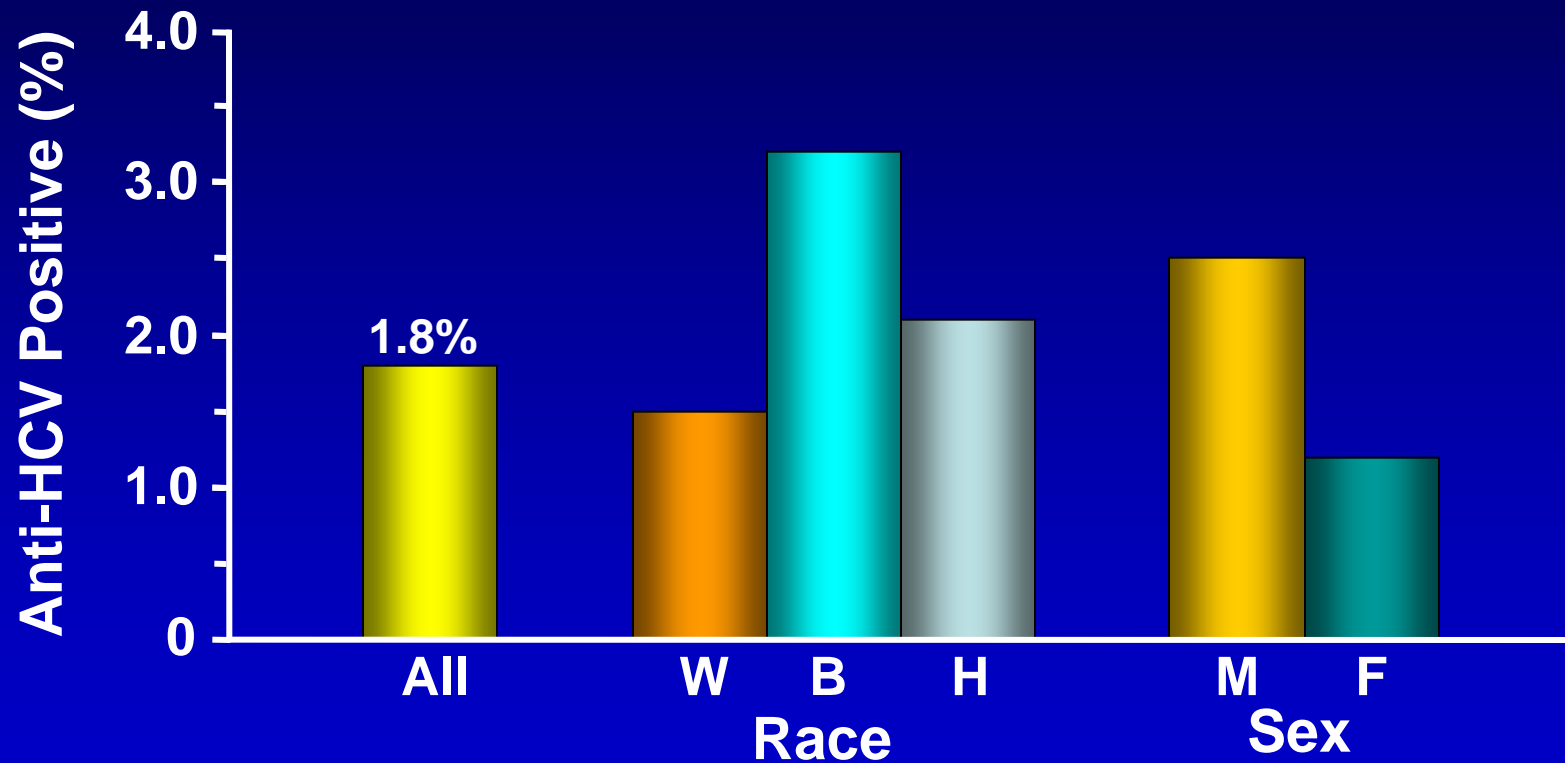
Effect of BMI and Alcohol on Relative Risk of Liver-Related Death

Prospective cohort study of 9558 men followed for average of 42 years.



Hepatitis C

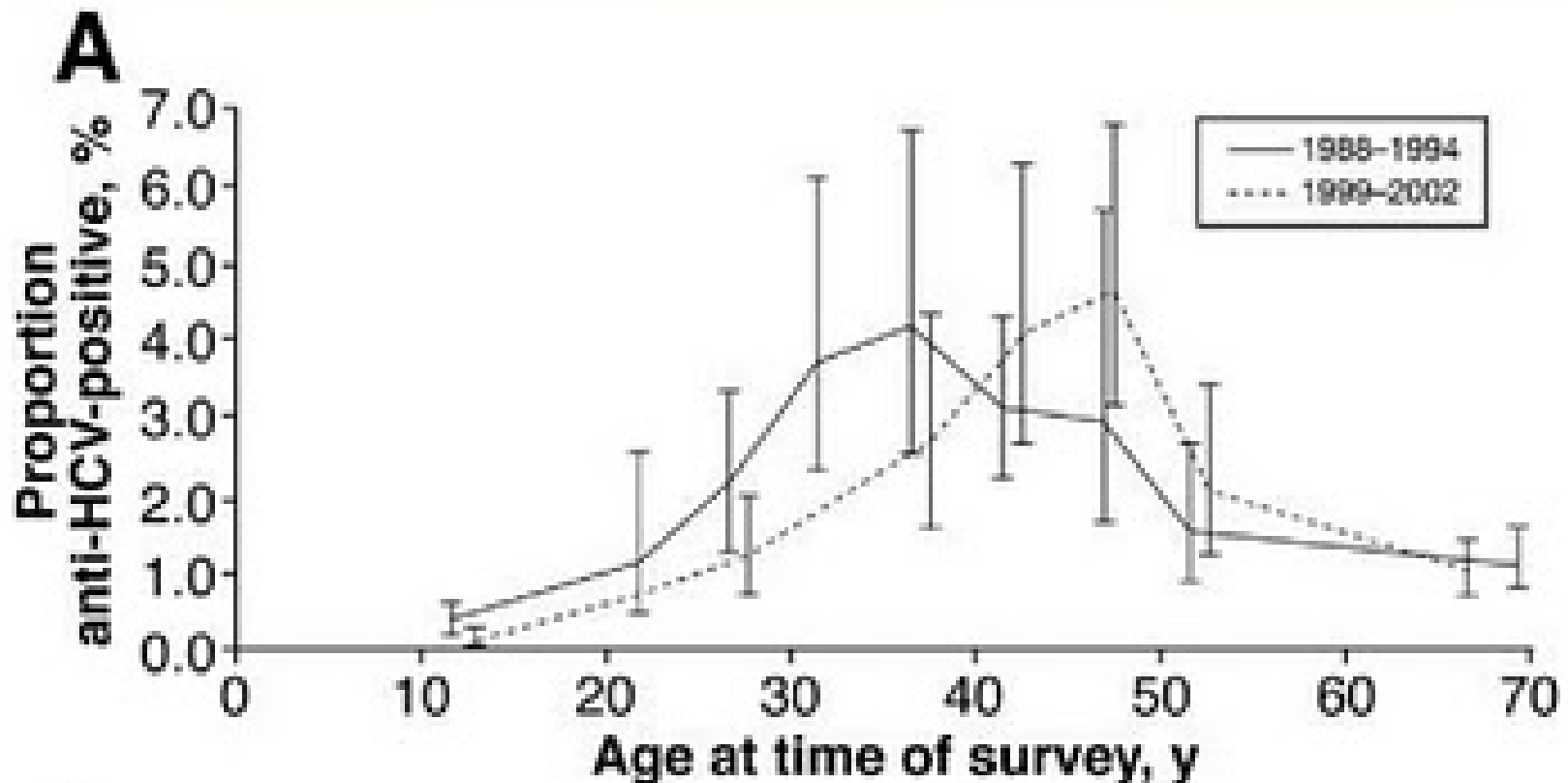
HCV Prevalence Varies by Race, Sex, and Age



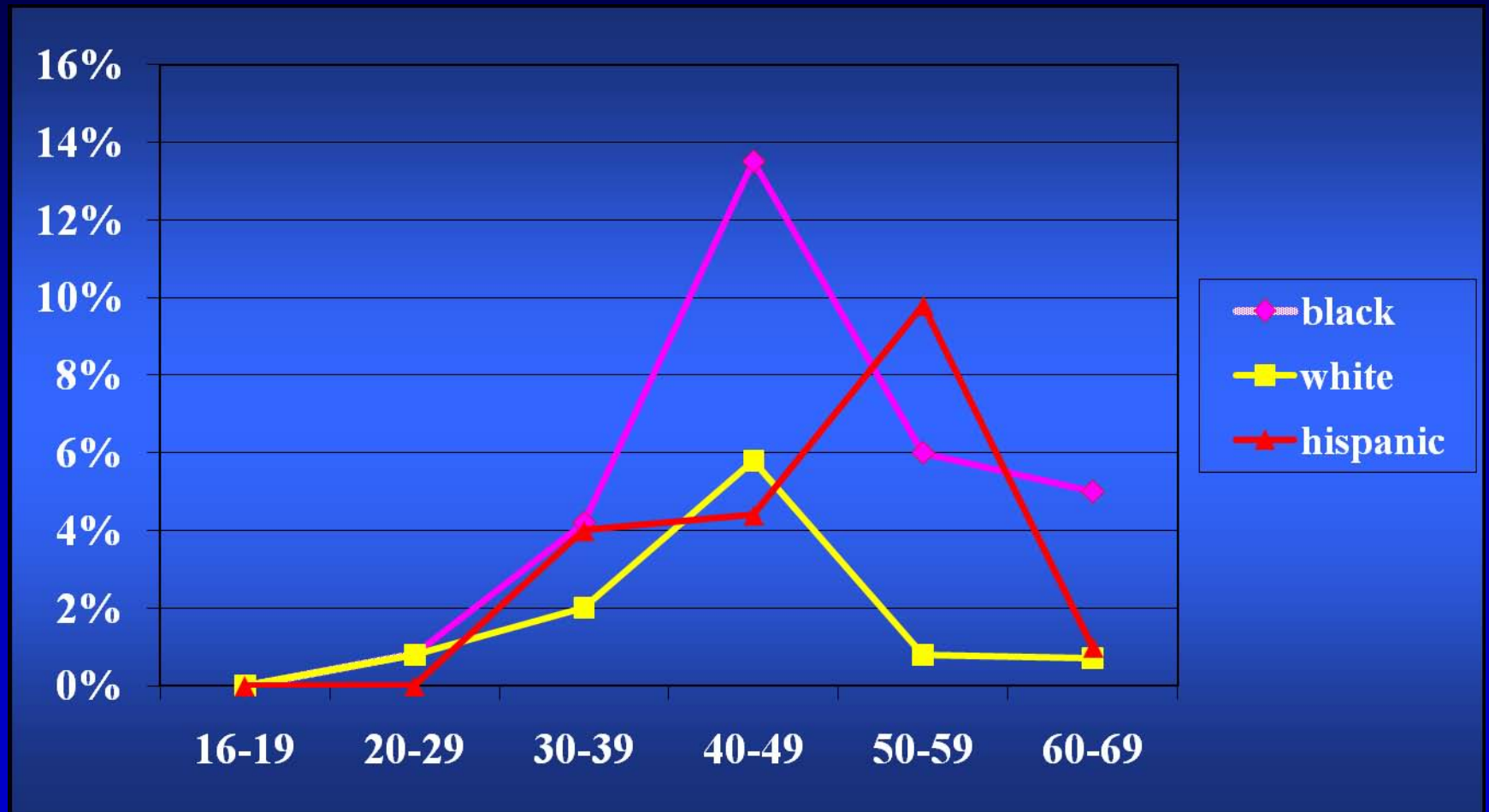
B, Blacks; F, female; H, Hispanic; M, male; W, Whites.

Prevalence of HCV 1988-2002

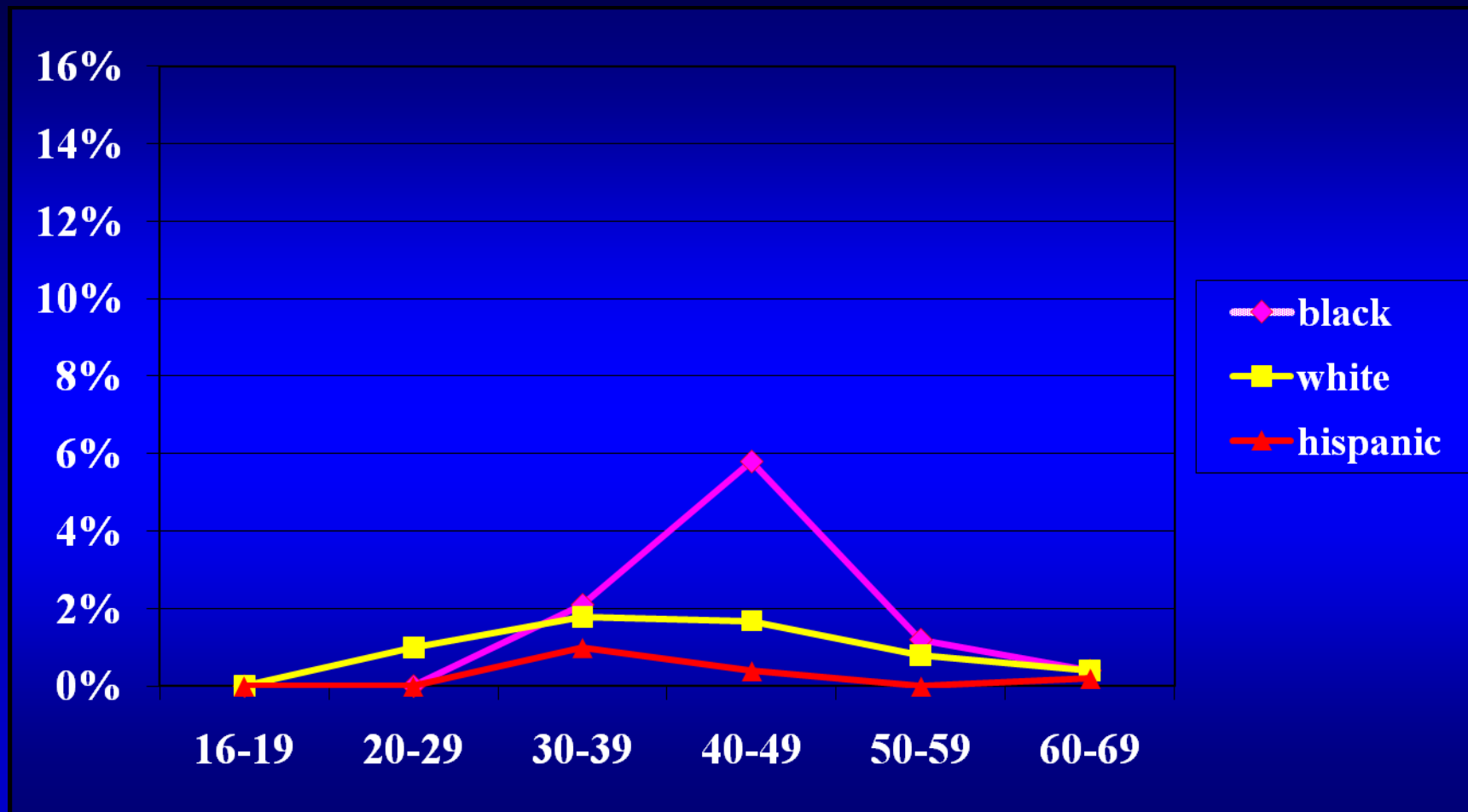
- Estimated 3.2-3.4 million Americans chronically infected with Hepatitis C



Prevalence of HCV in Males 1999-2002



Prevalence of HCV in Females 1999-2002



Hepatitis B

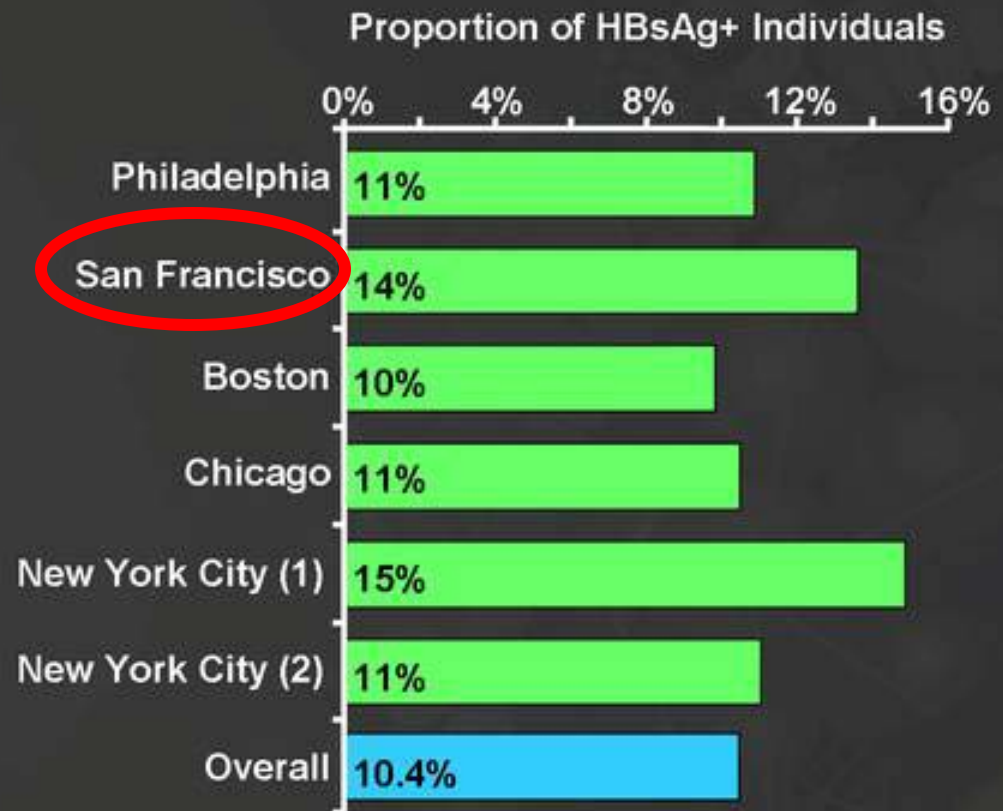
Estimated Prevalence of HBsAg-Positive Persons in the US by Population Segment

Population Group	CHB Prevalence, % ^[1,2]
US-born API	1.40
Foreign-born API	8.90
Non-Asian Americans	0.42
Correctional institutions	2.00
Other group living quarters	0.50

- Age-adjusted prevalence of anti-HBc and HBsAg in the US statistically similar during 1999-2006 vs 1988-1994^[3]
- ~ 40,000 persons with chronic HBV infection immigrate to US each yr^[4]

HBV Seroprevalence Among Asian Americans

- 5 large US cities (2001-2004)
 - Chinese
 - Korean
 - Vietnamese
- Median age
 - 43 yr (12-80)
- HBsAg+, overall
 - 558/5341 (10.4%)



Phases of Chronic HBV Infection

	Immune Tolerance	Immune Active/ HBeAg-Positive CHB	Nonreplicative (Inactive Carrier)	HBeAg-Negative CHB
Typical HBV DNA, IU/mL	> 200,000 and often > 10^{7-8}	200,000 - 2×10^9	< 2000	2000 - 2×10^7
HBeAg	Positive	Positive	Negative	Negative
ALT	Normal	Elevated or fluctuating	Normal	Elevated or fluctuating
Other observations	Liver biopsy typically normal or minimal findings	Active inflammation on liver biopsy	HBsAg may become undetectable	Active inflammation on liver biopsy
Treatment candidate?	No	Yes	No	Yes

1IU = ~5 copies/mL

Lok AS, et al. Hepatology. 2009;50:661-662.

Prevalence of Diseases Associated with Elevated ALT

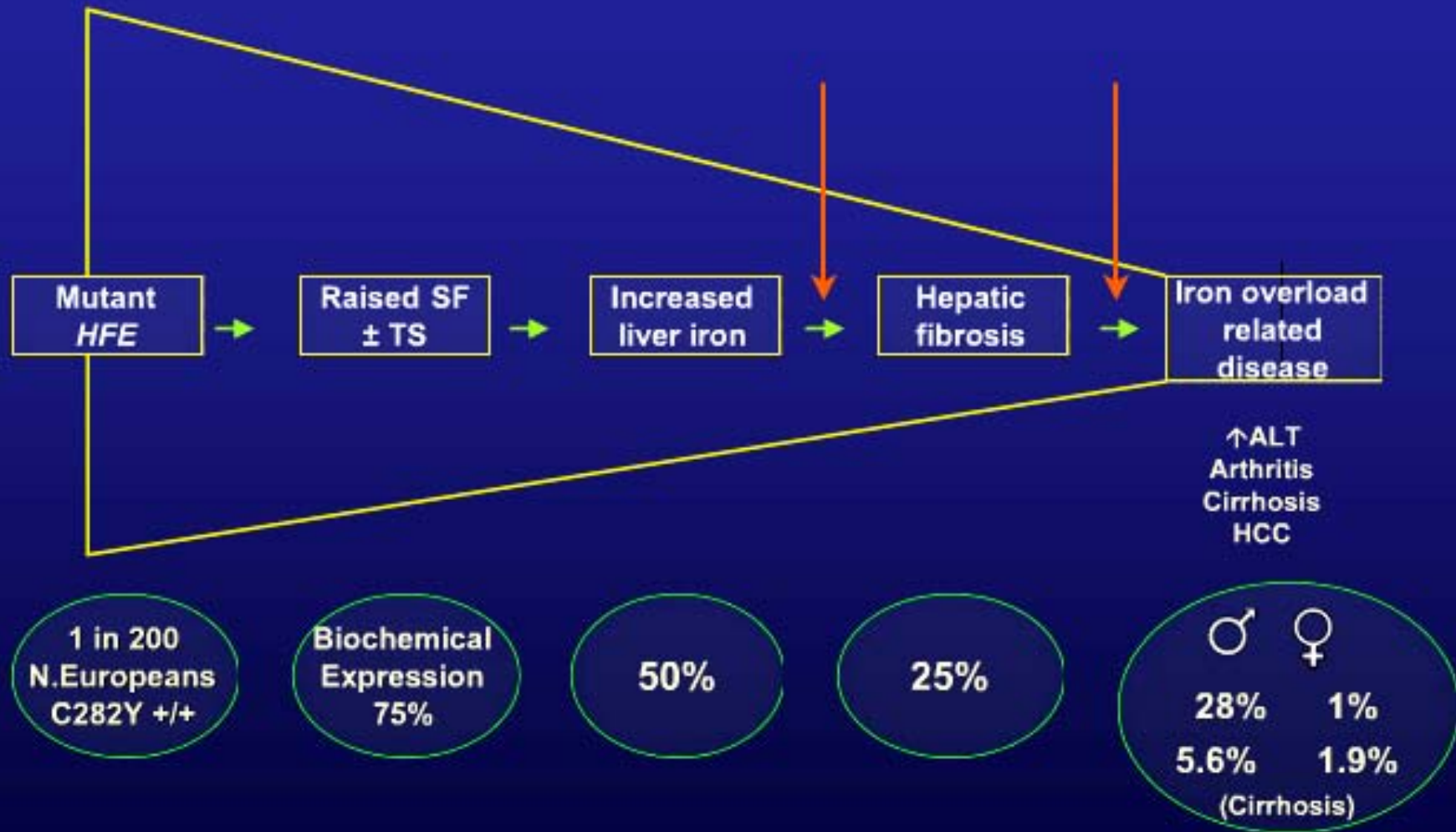
- NAFLD 45-60%
- NASH 9-20%
- ETOH > 2/day 5-6%
- Hepatitis C 2-15%
- Hepatitis B 0.4%-15%
- Hemochromatosis 0.25%
- AIH 0.017%
(17/100,000)

Prevalence of Inherited Liver Diseases

<u>Disease</u>	<u>Homozygote Frequency</u>	<u>Gene Frequency</u>	<u>Heterozygote Frequency</u>
Haemochromatosis	1:400	1:20	1:10
α_1 AT Deficiency	1:1600	1:40	1:20
Cystic Fibrosis	1:2500	1:50	1:25
Wilson's Disease	1:30,000	1:170	1:85

Leggett *et al* Brit J. Haem. 1990

The natural history and disease burden of HH



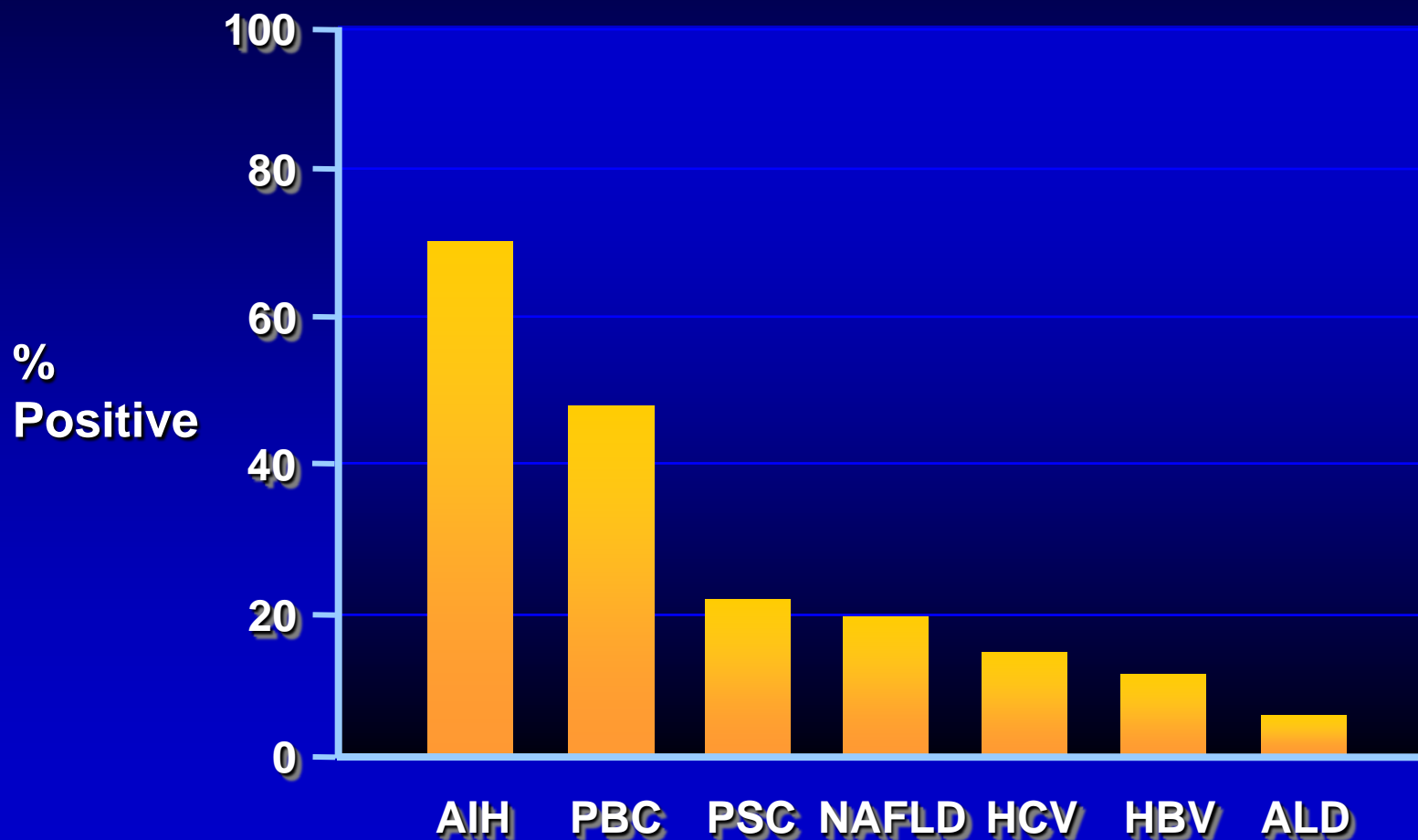
(from Beutler et al 2002, Pietrangelo, NEJM 2004;350:2383; Whitlock et al, Ann Intern Med 2006;145:209; Powell et al, Arch Intern Med 2006;166:294; Allen et al, NEJM)

[Allen et al.
Powell et al.]

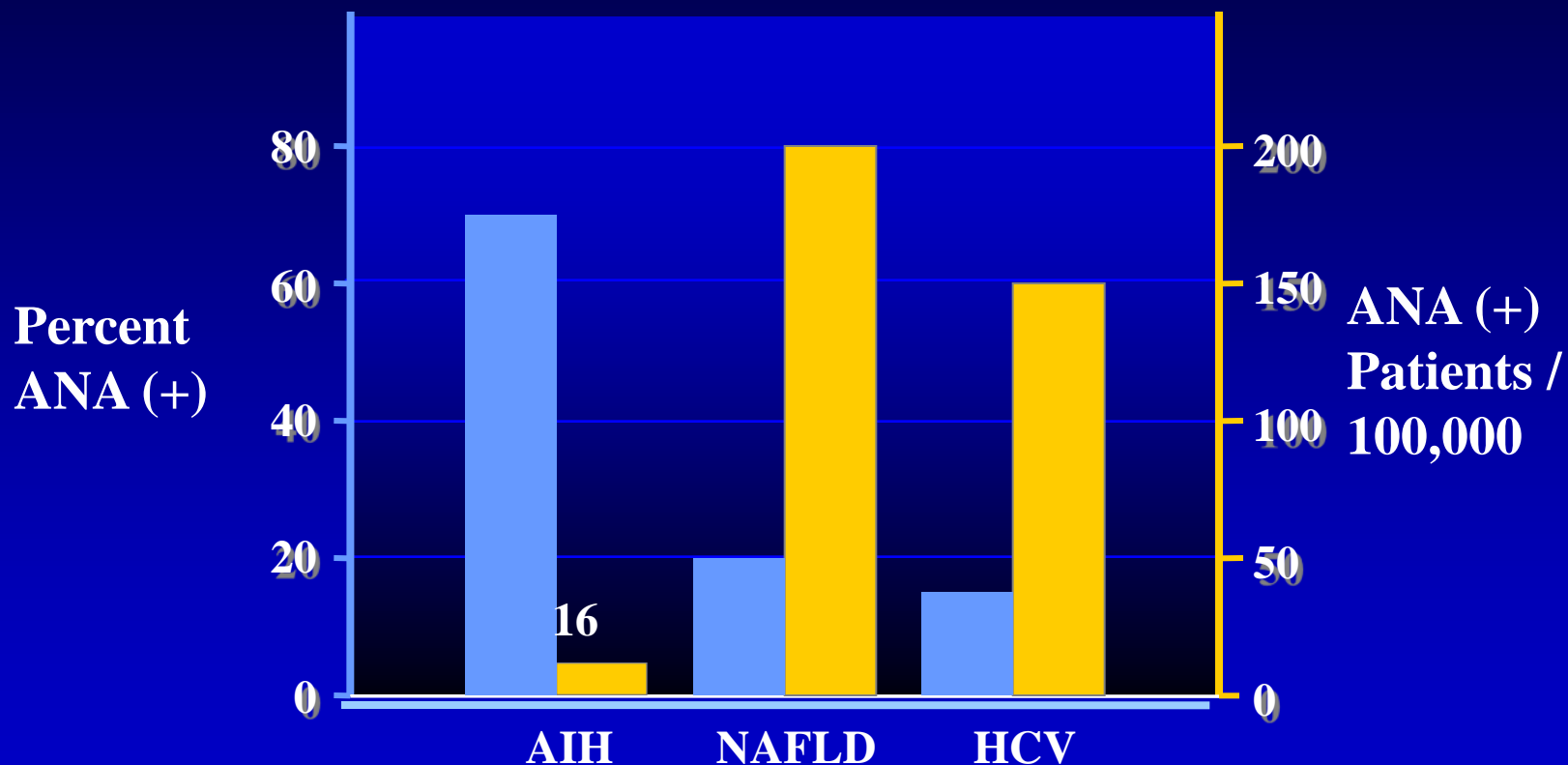
Hemochromatosis

- Screening should begin with a fasting serum iron and total iron binding capacity (TIBC), which permits the calculation of the iron or transferrin saturation (serum iron/TIBC).
- An iron saturation of greater than 45 percent warrants obtaining a serum ferritin.
- Ferritin should not be obtained as an initial test because it is an acute phase reactant and therefore less specific than the iron saturation.

Prevalence of ANA in Liver Disease



ANA Testing in Patients with Elevated Transaminases Has Low Specificity



A useful screening test for AIH is IgG or serum protein electrophoresis (SPEP). More than 80 percent of patients with autoimmune hepatitis will have hypergammaglobulinemia

*Sem. Liv. Dis 2002, 22:339 Amer. J. Gastro 2004, 99:1316 Hepatology 1995, 21:613

**J. Gastro. Hepatol. 2003 18:1118 Hepatology 2004, 40:1387 NEJM 1999, 341:556

Prevalence of ANA in Liver Disease

- **Low titers of ANA positivity are seen in up to a third of patients with NASH/NAFLD**
- **Low titers of anti-smooth muscle antibody (ASMA) and AMA have also been reported in patients with NASH/NAFLD**
- **In patients with suspected NAFLD, if ANA or ASMA titers are greater than 1:160 and 1:40 respectively, SPEP of total IgG and/or liver biopsy should be considered to exclude the presence of autoimmune hepatitis**

Initial Evaluation of Mild-Moderate Transaminase Elevation 2-5x

- Review possible link to medications, herbal therapies or recreational drugs
- Screen for alcohol abuse (screening instruments, AST/ALT ratio >2:1)
- Obtain serology for hepatitis B and C (HBsAg, HCV Ab)
- Screen for hemochromatosis (FE/TIBC >45 percent)
- Evaluate for fatty liver (obtain a RUQ ultrasound)
- If the above serologies are negative, the ultrasound is consistent with NAFLD, and the patient fits the profile for metabolic syndrome, no further work up indicated

Initial Evaluation of Mild-Moderate Transaminase Elevation 2-5x

- **Positive HCV antibody**
 - Hepatitis C viral load (Genotype optional)
 - Ultrasound
 - INR/CBC/platelets
- **Positive HBsAg**
 - Hepatitis B quantitative DNA
 - HB-E Antigen/ anti-E antibody
 - Ultrasound/AFP optional, based on age/HCC risk

Alkaline Phosphatase

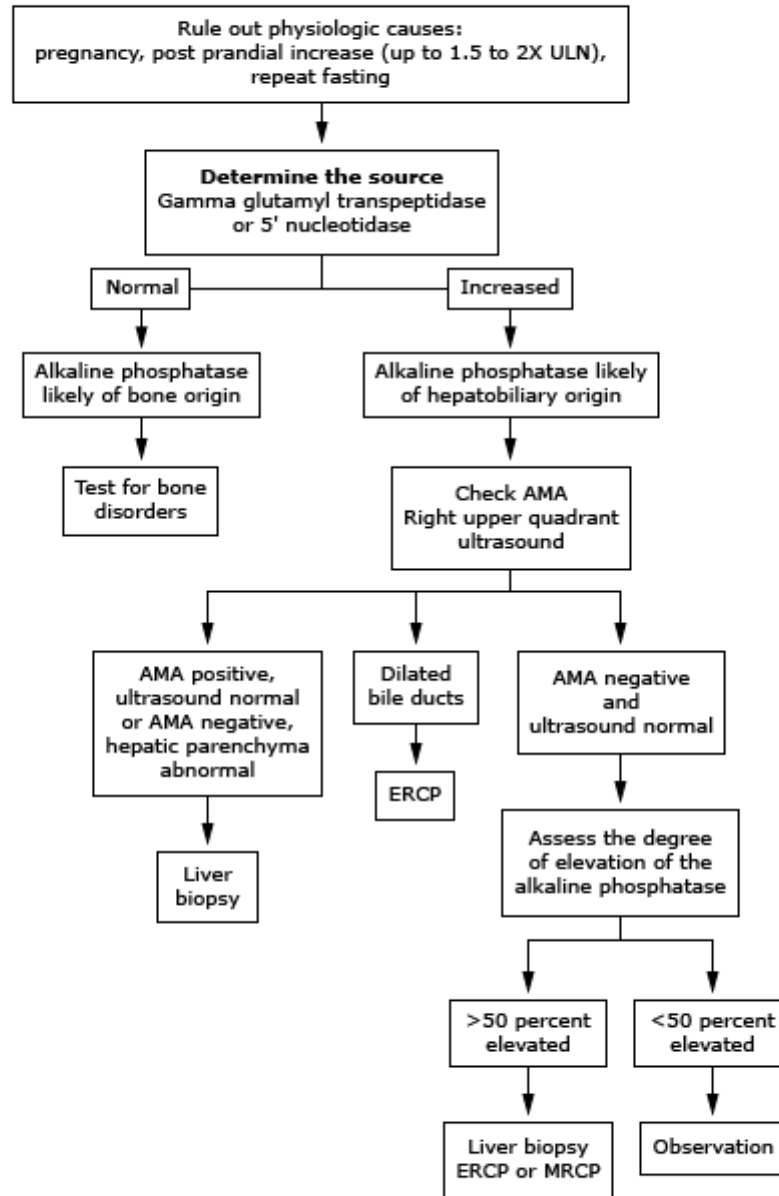
Mild-Moderate AP Elevation

- **Mild-moderate elevation in alkaline phosphates activity, up to three times the upper limit of normal, are nonspecific and occur in all types of liver disease, including viral hepatitis, chronic hepatitis, cirrhosis, infiltrative diseases of the liver, and congestive heart failure**
- **Elevations in hepatic alkaline phosphatase of this magnitude can also occur in disorders that do not directly involve the liver, such as Hodgkin lymphoma, myeloid metaplasia, intra-abdominal infections, and osteomyelitis**

Marked/Predominant AP Elevation

- Biliary Obstruction
 - Pancreatic or cholangio-carcinoma
 - CBD stones
 - Sclerosing Cholangitis
 - Primary Biliary Cirrhosis
- Infiltrative diseases: metastatic carcinoma, amyloidosis, sarcoidosis, hepatic abscesses, tuberculosis
- Drug-induced cholestasis

Evaluation of elevated serum alkaline phosphatase



AMA: antimitochondrial antibody.

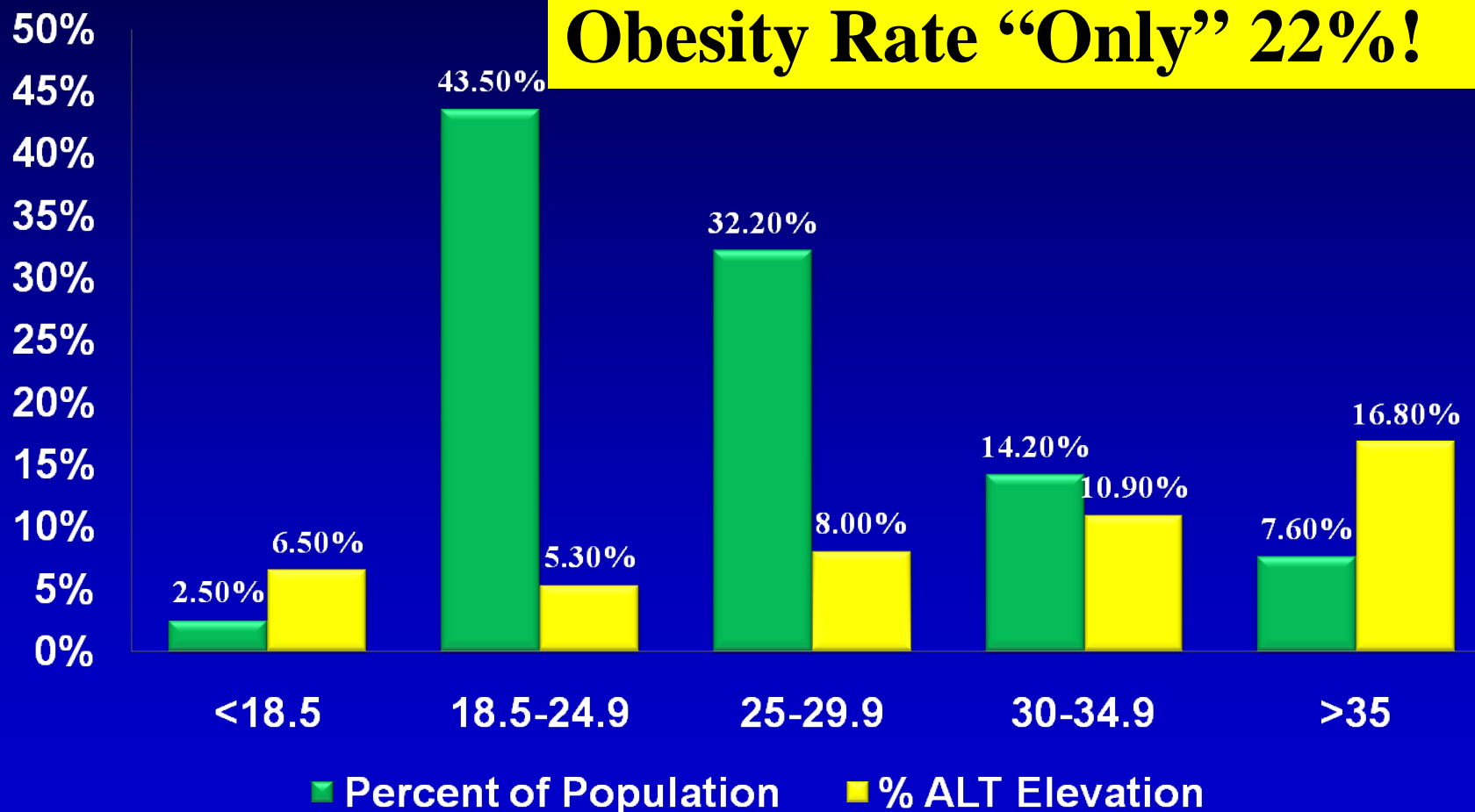
Unconjugated Hyperbilirubinemia: Overproduction

- **Overproduction of bilirubin**
 - Extravascular or intravascular hemolysis,
 - Extravasation of blood in tissues (large hematomas)
 - Dyserythropoiesis.
- The normal liver can remove at least twice the normal daily bilirubin load without the development of hyperbilirubinemia
- Uncomplicated hemolysis seldom causes a serum bilirubin value in excess of 5 mg/dL

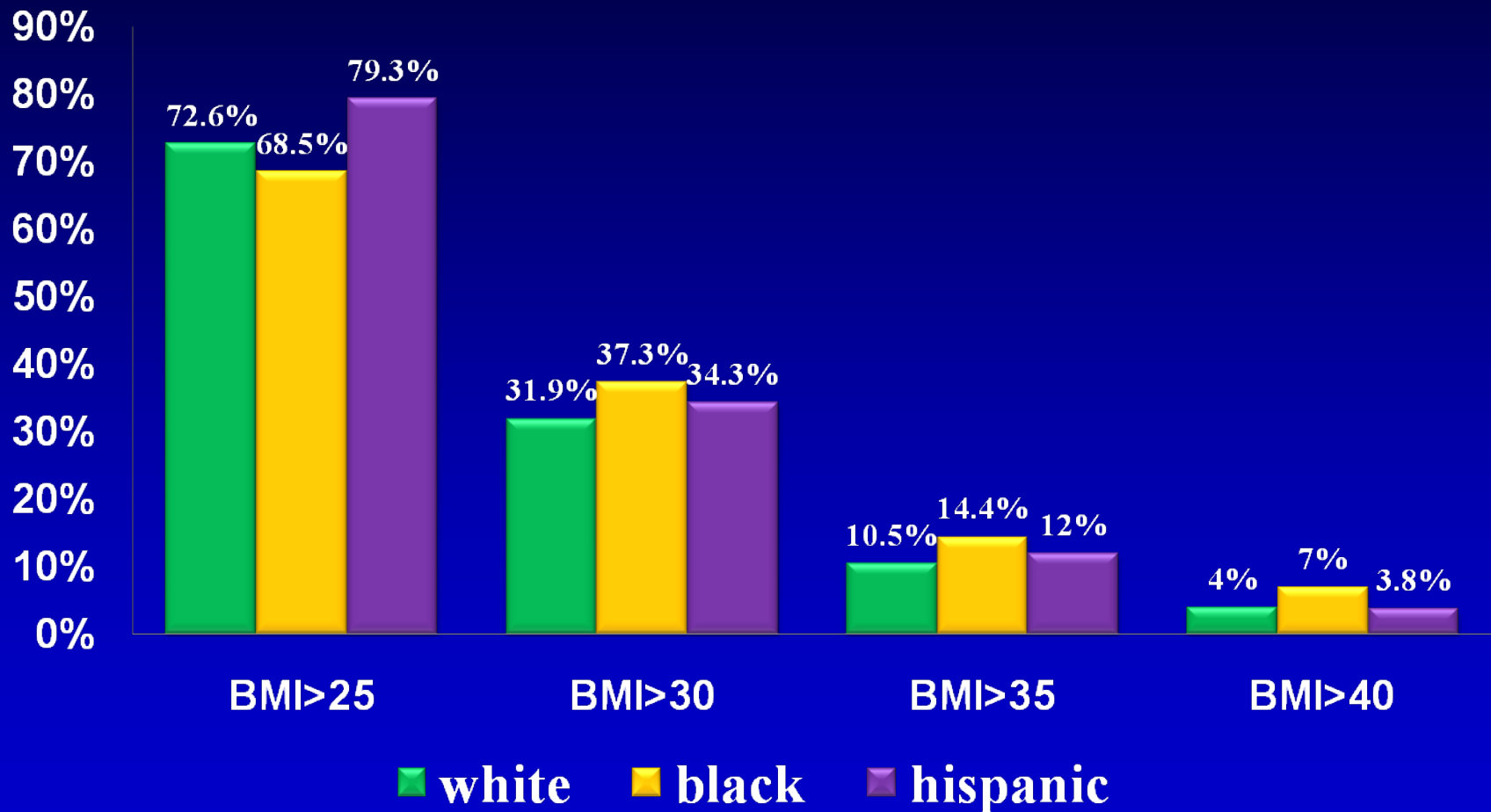
Unconjugated Hyperbilirubinemia: Impaired Hepatic Conjugation: Gilbert's syndrome

- Affects approximately 3 to 7 percent of the population, with white males predominating over females by a ratio of 2 to 7:1.
- Impaired conjugation of bilirubin is due to reduced bilirubin UDP glucuronosyl transferase activity.
- Affected patients have mild unconjugated hyperbilirubinemia with serum levels almost always less than 6 mg/dL.
- The serum levels may fluctuate and jaundice is often identified only during periods of illness or fasting.

NHANES Distribution of BMI: 1988-1994

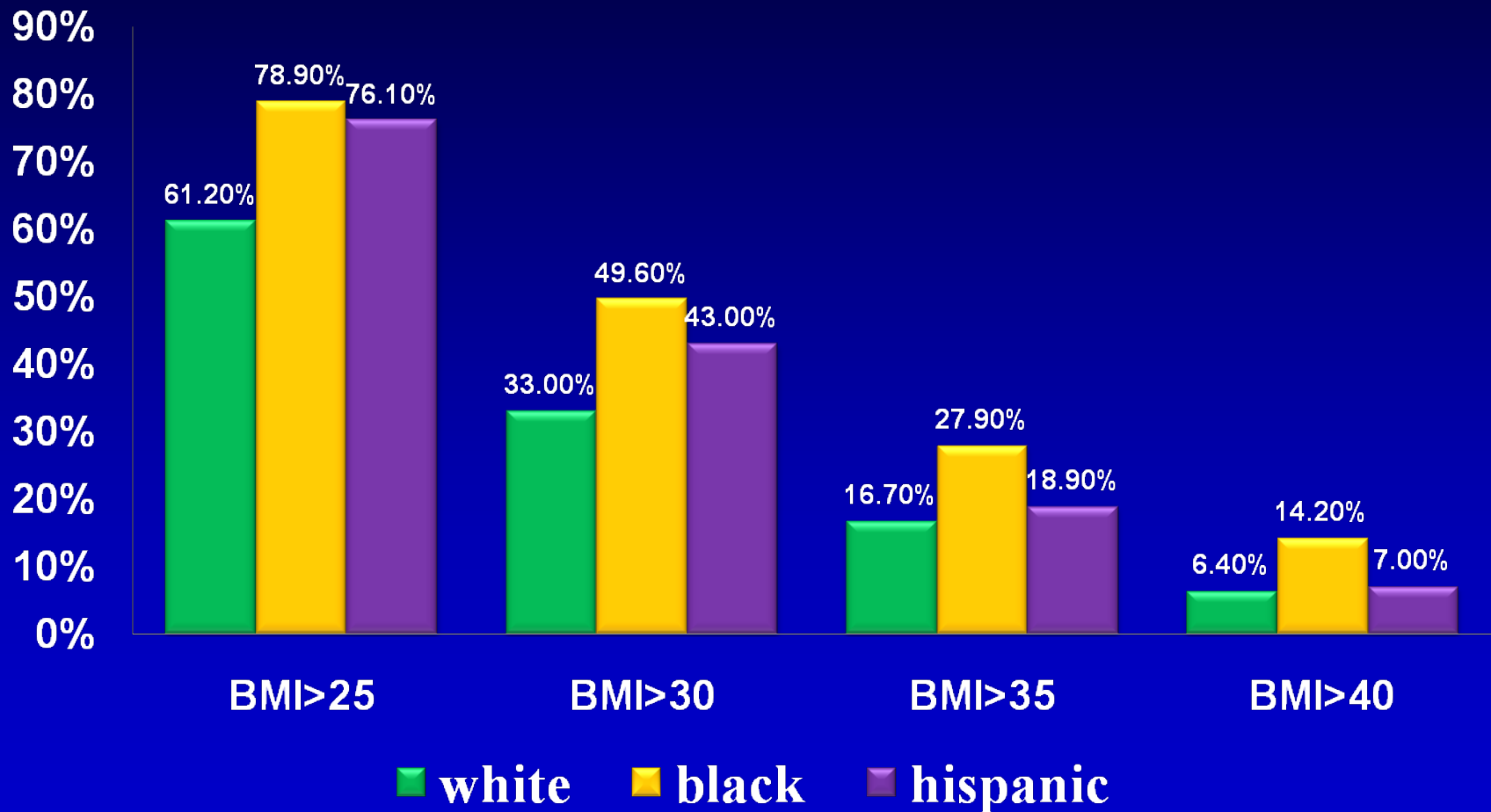


Obesity Statistics 2007-2008: US Males

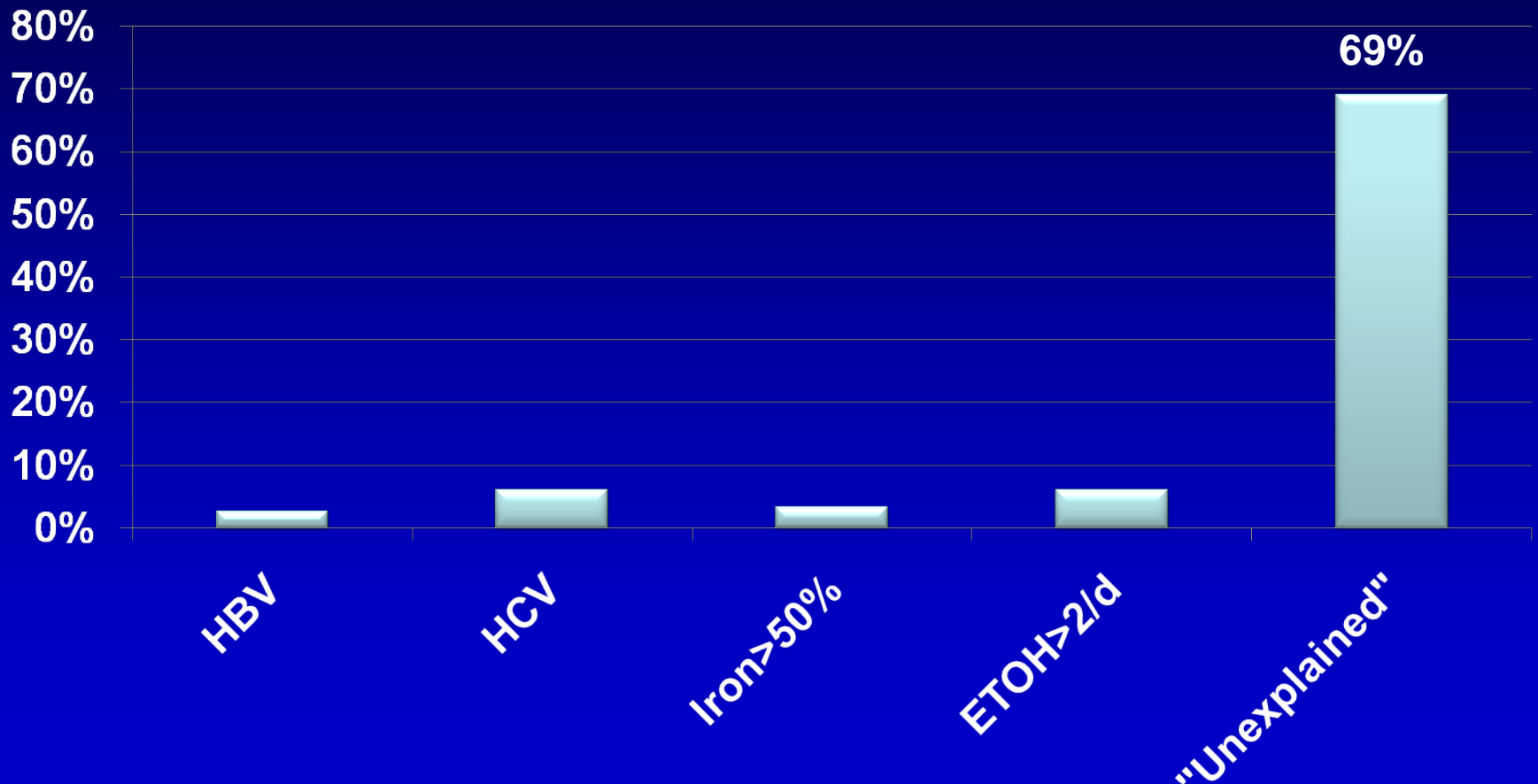


Obesity Statistics 2007-2008: US

Females



Etiology of Elevated Aminotransferases in USA 1988-94



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