Yvonne Wan, Continued from page 5

healthy Mexican-Americans. For ADH2*2 and ALDH2*2 the frequency of occurrence was found to be 6% and 0% respectively. This pattern is essentially the same as for Caucasians. In other words, in Mexican-Americans as a group, alcohol consumption will not result in the flushing and the discomfort seen in many Asians that are good deterrents to intoxication and hence to alcoholic liver disease. In contrast, the frequency for the Rsa I allele of CYP2E1 of 16% in Mexican-Americans is significantly greater than that of Caucasians (2-5% frequency).

These observations led Dr. Wan to propose that the high frequency of the Rsa I allele may play a role in the development of alcoholic liver disease in Mexican-Americans and has led to the current on-going study: “Alcohol Pharmacogenetics in Mexican-Americans.”

The goals of the study as stated by Dr. Wan are:
1. To establish a pharmaceutical and clinical database of alcohol abuse in the Mexican-American.
2. To identify candidate genes that might contribute to alcohol dependence and alcoholic liver disease in Mexican-American men.
3. To study the inducibility of CYP2E1 in relationship to alcoholic dependence and alcoholic liver disease.

The plan for the study is to enroll 200 men that have a clinical history of excessive alcohol intake (>80 g/day) for more than 5 years. To avoid confounding factors there are several exclusion criteria in place. Liver disease caused by hepatitis B or C, or by other biochemical or autoimmune causes, diabetes or use of drugs that may affect the activity of CYP2E1 are amongst the exclusion criteria. So far genotyping for 44 individuals has been completed.

The instrument used to assess drinking history is SEMI STRUCTURED ASSESSMENT FOR THE GENETICS OF ALCOHOLISM (SSAGA-II). An ultrasound exam is performed. Blood is drawn for liver panel tests, to detect viral hepatitis for DNA and other tests. Dr. Wan and colleagues so far found no difference in the frequency of ALDH2*2 or ADH2*2 alleles in alcoholics when compared to 108 healthy volunteers. For the CYP2E1 Rsa I allele the frequency increased in alcoholics (21.4% versus 16% for healthy controls). Intriguingly the frequency of another CYP2E1 allele (CYP2E1 TaqI) was decreased (13.6% versus 19% for healthy controls). In agreement with this finding, a study in Britain has looked at the relationship between CYP2E1 Taq I polymorphism and susceptibility to alcoholic liver disease. In this study, the authors found that possession of Taq I cytochrome P4502E1 was associated with a lower risk of developing alcoholic liver disease.

Dr. Wan and colleagues at Harbor-UCLA have also started to examine the effect of alcohol on the induction of CYP2E1 by phenotyping (measuring the activity of CYP2E1) in a sub-set of volunteers and patients with varying alleles. This requires patients staying in hospital for at least a period of five days. In normal subjects, the metabolism of chloroxazone is being assessed before and after the consumption of alcohol. For alcoholic liver disease patients’ phenotyping is done before (12 hours after admission to allow alcohol levels to drop to non-interference with the assay) and after a five-day abstention from alcohol. Fifteen patients have been studied so far, with only one exception, for all patients CYP2E1 activity is higher after recent consumption of alcohol than after five days of abstinence. The extent of induction of CYP2E1 by alcohol varies between alcoholic patients: in one case being nearly twenty-fold. In these alcoholic patients, the relative contribution of this enzyme to the overall metabolism of alcohol will be significant.

When these studies are completed the relationship between genotype, inducibility of enzyme activity by alcohol and the development of alcoholic liver disease in Mexican-American men will be established. The long-term objective is to understand the molecular mechanisms underlying the development of and the resistance to alcoholic liver disease in Mexican-Americans.

As expected for such an ambitious multi-faceted endeavor, many other talented investigators from Harbor-UCLA are contributing to this study directed by Dr. Wan with support from the Research and Education Institute, the Center for Psychobiology and Ethnology and the General Clinical Study Center.

Ronald G. Thurman, Ph.D. (1941-2001)

By Hide Tsukamoto

University of Southern California

Center friend, Dr. Ronald Thurman died of a massive heart attack on July 11, 2001. An exceptional scientist, he will be missed by his colleagues that study alcoholic liver injury and will be dearly remembered as someone that made many contributions to the understanding of hepatic alcohol metabolism and injury. Shared to the right is a wonderful note penned by his family after his death.

www.usc.edu/medicine/alcohol_center
By Maria Runnegar

University of Southern California

Dr. Wan is Professor of Pathology in the UCLA School of Medicine. She joined the Faculty of the Harbor-UCLA Medical Center in Torrance in 1989. In looking at Dr. Wan’s academic and scientific career what stands out is the ease with which she has fused apparently disparate fields of research into a unifying theme. After a degree in Pharmacy from Taipei Medical College where she received a solid grounding in pharmacology and drug interactions, she came to the U.S. to do a Ph.D. in Pathology at Pennsylvania University in Philadelphia. During this time Yvonne added embryology and in depth morphology to her skills. This was followed by a postdoctoral appointment at the National Institutes of Health (NIH) in Bethesda. Here Dr. Wan mastered the molecular biology techniques necessary to successfully investigate gene expression and regulation.

Dr. Wan’s independent research career is truly a synthesis of all the areas of training she received. This is reflected in the very extensive range of topics in her publications.

The central theme of Dr. Wan’s work is the study of the action of retinoic acid (vitamin A) through its nuclear receptors on liver gene regulation, hepatocyte differentiation, proliferation, and programmed cell death.

Dr. Wan’s lab has shown a complex pattern of induction and repression of retinoic acid of gene expression of α-fetoprotein and albumin as well as of retinoic acid receptors in hepatoma cell lines and in the developing rat liver.

The physiological and pathological importance of retinoic acid and its receptors has been clearly established in a mouse model where the retinoic acid receptor (RARα) gene has been knocked out. Dr. Wan has shown that mice lacking hepatic RARα have elevated serum cholesterol and triglyceride levels (particularly in males) because liver homeostasis is lost. She has also shown that hepatic retinoic acid receptors (RARs) are essential for maintaining normal levels of many cytochrome P450 enzymes (including CYP1A1, CYP2C9, CYP3A1 and CYP3A2) of liver fatty acid binding protein and of some apo-lipoproteins. The consequences of these changes are perturbations in fatty acid, cholesterol, bile acid, and drug metabolism.

In alcoholism, vitamin A levels (retinol and hence retinoid acid) that are essential for growth and maintenance of normal epithelial function are decreased. Furthermore, ethanol has been shown to inhibit the effects of retinol to retinoic acid (the active form of vitamin A) by competing for access to alcohol dehydrogenases (ADH). It has been proposed that ethanol-induced reduction in retinoid acid during gestation results in the distinctive features of fetal alcohol syndrome.

The activity of enzymes involved in alcohol metabolism determines the time course and mode of disposition of alcohol. Oxidation of alcohol through to acetic acid is catalyzed by alcohol and acetaldehyde dehydrogenases. Alcohol can also be metabolized by the cytochrome P450 CYP2E1. This activity is important in alcoholism since the enzyme is induced by alcohol itself, making its contribution to alcohol metabolism more significant in heavy drinkers. The metabolism of alcohol by CYP2E1 could play a role in the pathogenesis of alcoholic liver disease through the formation of reactive oxygen leading to lipid peroxidation.

It has been shown in many studies that in humans there is functional polymorphism in both the alcohol and acetaldehyde dehydrogenases and in CYP2E1. The frequency of polymorphism varies in individuals within a group but that there are also overall patterns of allele expression that differ between ethnic groups. For instance, the alcohol dehydrogenase allele ADH2*2 (most common in East Asians) results in an enzyme that has the ability to metabolize alcohol much faster than the usual enzyme, ADH2*1. This suggests an increased ability to metabolize alcohol and hence to maximize consumption with ensuing alcoholic disease.

Continued on page 5

Center Adds $3M to Research Base, Continued from page 1

Lastly, the Center was awarded an additional quarter of a million dollars from NIAAA as supplemental funding to create a new Research and Prevention program. These new components will be spearheaded by Dr. Malcom Pike, Professor of Preventive Medicine at the University of Southern California. Dr. Sussman will collaborate with Drs. Bruce Runyon and Michelle Meador of the Rancho Los Amigos National Rehabilitation Center to develop a new preventive program for the Hispanic community. Dr. Yuen will collaborate with Drs. Malcolm Pike and Brian Henderson, internationally acclaimed epidemiologists to help define the risk factors for alcoholism. We hope that the addition of these new components will set a stage for the Center’s transition from a research center to a comprehensive center.

SCARG Conference, Continued from page 4

Visceral adipose tissue act as signal molecules for the changes in insulin and glucose levels that characterize insulin resistance. The pathogenesis of NASH is also not understood. Free fatty acids are thought to directly injure the liver or make it more susceptible to injury such as oxidative stress but this has not been conclusively proven.

There is no generally accepted medical treatment for NASH. It is thought that weight loss and exercise would be beneficial since they improve the degree of obesity and insulin resistance that is found in the majority of cases. Studies examining the relationship between weight loss and the severity of NASH have so far yielded mixed results: in some cases showing improvement and in others a worsening of liver fibrosis. Because of this, a number of small studies have combined medications known to play a protective role in the liver with weight reduction. Unsaturated fatty acid (UFA) has shown promise in a placebo-controlled study with a large scale placebo-controlled study with this drug in CYP2E1. The frequency of polymorphism varies in individuals within a group but that there are also overall patterns of allele expression that differ between ethnic groups. For instance, the alcohol dehydrogenase allele ADH2*2 (most common in East Asians) results in an enzyme that has the ability to metabolize alcohol much faster than the usual enzyme, ADH2*1. This suggests an increased ability to metabolize alcohol and hence to maximize consumption with ensuing alcoholic disease.

The effect of polymorphism of CYP2E1 on alcohol consumption and on the incidence and severity of alcoholic disease is still controversial with as many studies showing positive correlation as negative ones. Some of these conflicting findings could be explained by CYP2E1 having different significance in the pathogenesis of alcoholic liver disease in different ethnic groups. For this reason Dr. Wan, who has been funded by NIAAA (National Institute for Alcohol Abuse and Alcoholism, part of NIH) to study in Mexican-Americans the functional polymorphism in alcohol metabolizing enzymes and determine its association with the development and/or resistance to alcoholic disease.

This study is particularly important in Los Angeles because of the large proportion of Mexican-Americans in the population (42% in L.A. County) and the higher prevalence rate of heavy drinking and hence alcoholic liver disease in this group when compared to others. Nearly 20% of Mexican-American men have experienced three or more alcohol-related problems. Deaths from chronic liver disease are also about 70% greater for this group when compared to residents of Caucasian or African-American ethnicity.

The only publication that addresses polymorphism in alcohol metabolizing enzymes in this very significant ethnic group is by Dr. Wan. In 1998, she with her coworkers determined genetic polymorphism of alcohol metabolizing enzymes in a group of Mexican-American men.

Continued on page 6
Tao Recipient of Summer Student Research Fellowship Award

By Anne Taguchi
University of Southern California

Nico Tao, graduate student in the Keck School of Medicine of USC, Department of Pathology, is the 2001 recipient of the Center’s first Summer Student Research Fellowship Award. Nico’s outstanding research during the summer of 2001 involved doing an analysis of California State Health Department hospital discharge data to determine the demographic distribution of ALD and pancreatitis in Los Angeles County.

Nico received the Center’s first Summer Student Research Fellowship Award along with a check for $1,000.

Nico’s analysis of hospital discharge data has revealed that cases of Alcoholic Liver Disease costs the healthcare system over $280 million in Los Angeles county alone. The number of Alcoholic Liver Disease diagnoses in L.A. county is also 50% higher than that reported for the nation. Furthermore, primary ALD diagnosis is more prevalent among: 1) the middle-aged (45-65 yr old); 2) male; 3) Hispanic; 4) those with lower median household income (<$25,000 per year). Twenty percent of liver transplantations performed in California is due to alcoholic cirrhosis. Finally, ALD is the 8th leading cause of hospital death, claiming more deaths than HIV or diabetes.

In contrast, the diagnosis frequency for acute or chronic pancreatitis does not show a gender difference and is highest among Blacks. Pancreatitis diagnosis frequency is also closely associated with lower household income. ♦

See more about Nico’s research at www.usc.edu/medicine/alcohol_center.

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Dr. Steve Sussman, Professor in the Institute for Preventive Research at USC presented strategies for the prevention of ALD through education and outreach. The long-term goal of this program is to achieve a better understanding of why ALD is relatively high among Latinos. The aim is to develop educational programs that are likely to prevent or decrease the occurrence of ALD in Latinos and later expand the programs to other ethnic groups.

Initially, a pilot study of the effectiveness of educational intervention in a group of 100 male Hispanics with a family history of drinking or ALD will be set up. The educational program will have sessions on the nature of ALD and its consequences. It will emphasize the need and the means to establish and maintain a lifestyle that minimizes the use of drugs, tobacco and alcohol.

Dr. Michel Mendler of the Liver Unit at Ranch Los Amigos National Rehabilitation Center and Assistant Professor of Clinical Medicine in the Division of Gastrointestinal and Liver Diseases at USC described his current and proposed work on the effect of S-adenosylmethionine (SAM) in the progression of liver disease. This is a collaborative work with Center members Shelly Lu and Hide Tsukamoto, assisted by Alice To and Zongzhi Huang, and supported by Pharmavite Corporation. The significance of SAM metabolism in ALD has been the focus of a previous SCARG conference. SAM is the principal methyl donor in all biological reactions, directly impacting nucleic acid, protein and polyamine synthesis. Methylation by SAM of phospholipids is a determinant of membrane properties such as transport of metabolites and signal transmission across the membrane. Its formation is catalyzed by the enzyme methionine adenosyltransferase (MAT). It is the nature and expression of the MAT isozymes in liver that determines SAM levels and degree of methylation of DNA. This influences liver growth and perhaps carcinogenesis. MAT is not the only enzyme that defines SAM and its activity. In fact, SAM metabolism is regulated by the interplay of many enzymes and cofactors like folic acid, vitamin B12 and B6. A number of these enzymes as well as MAT and cofactors are modified in ALD. Decrease in the activity of liver specific MAT, fall in GSH, elevated homocysteine levels through reduced metabolism are all found in ALD patients. These changes set the stage for the onset of fibrosis through the induction of collagen synthesis. SAM administration blocks the increase in homocysteine and could therefore impact the development of liver fibrosis in ALD. Rats that have decreased levels of hepatic SAM are more sensitive to liver injury caused by LPS and have elevated levels of TNF. It is well known that serum TNF levels are elevated in ALD patients, SAM administration may lead to lower serum TNF levels.

In 1999, Jose Mato et al. in the Journal of Hepatology published the findings from a randomized, placebo-controlled double-blind, multicenter clinical trial of the effect of SAM in alcoholic liver cirrhosis. Significant increase in survival of the SAM treated group versus placebo was shown for patients with less advanced liver disease, leading the authors to conclude that long-term treatment with SAM may be beneficial in ALD with mild cirrhosis.
The present study by Dr Mendler and colleagues will test the effect of SAM administration over a period of one year to a group of patients that are chronic alcohol users: > 80g/day for women and >120 g/day for men for more than 5 years. Liver biopsies will be taken to establish the presence of acute alcoholic hepatitis, excluding among others severe cirrhosis, chronic active hepatitis B and C as well as other known causes or confounders of liver disease. The hypothesis being tested is that SAM administration combined with abstinence will normalize methionine metabolism resulting in increases in GSH and SAM, levels, in decreases in TNFα with less hepatic apoptosis and proliferation. This should translate in significant decrease in the severity of the alcoholic hepatitis.

A total of 30 patients will be enrolled: 15 placebo and 15 receiving 1200 mg/day of SAM. At baseline routine labs will be done as well as measurements of TNF, methionine, homocysteine, GSH and SAM levels. Changes in these parameters will be determined at 1, 2, 4, 6, 8, 10 and 12 months. At baseline a liver biopsy will be done to determine the grading of alcoholic hepatitis. This will be repeated at the end of the 12-month period. At the end of the study, changes in the severity of alcoholic hepatitis will be compared with changes in levels of TNF, methionine and metabolites over the year period. It is hoped that the study will show that treatment with SAM is therapeutically beneficial to patients with less advanced ALD. It will also show the relative significance of changes in the levels of methionine metabolites and progression or regression of disease. It will also define the parallels between findings in well-characterized animal models and man.

In the second part of his presentation, Dr. Mendler introduced his other area of major research interest: nonalcoholic fatty liver disease (NASH) which has led to the establishment of the USC Clinical Research Center in Nonalcoholic Fatty Liver Disease dedicated to the study of this disease. Hepatic steatosis (the accumulation of fat in liver) is frequently seen in liver biopsies. Many different insults and conditions result in fatty liver, excessive alcohol consumption being often the cause. It has become clear that fatty livers often occur in the demonstrated absence of alcohol consumption hence the term NASH for a fatty liver with inflammation. A recent issue of Seminars in Liver Disease covered the clinical and pathophysiological aspects of NASH stressing how much still needs to be worked out. Apart from alcohol, other liver diseases can result in fatty livers and NASH. These include viral hepatitis, autoimmune disease and Wilson's disease. Many NASH cases most likely occur in response to extra-hepatic disease. Malnutrition, corticosteroids and other drugs can cause fatty livers, but obesity, hyperlipidemia, diabetes mellitus type II and syndrome X (a syndrome associate with insulin resistance) are most often associated with NASH. Findings at biopsy of a fatty liver without inflammation indicate rather benign changes and often do not progress to the more severe changes of NASH where there is inflammation that can progress to fibrosis and cirrhosis.

We have come to realize that the prevalence of NASH has major public health implications. Dr Mendler presented projected numbers for the incidence of fatty livers and NASH in the American population. These projections arise from studies that have shown that up to 80% of obese people (Body Mass Index of more than 30) have fatty livers. The number of obese adults in the US is estimated to be 32 million, therefore 26 millions would have fatty livers. The more severe changes of NASH (fatty liver with inflammation) would be present in 16 million, 13 million of which will have some degree of portal fibrosis, with cirrhosis in 3 million. Fatty livers and NASH are present in up to 75% of diabetic patients (Type II). Syndrome X, a metabolic syndrome characterized by hepatic and peripheral insulin resistance has also been associated with nonalcoholic fatty liver disease in over 50% of cases. Insulin resistance as seen in Syndrome X is often associated with obesity, more particularly with a male pattern of visceral adipose tissue. Syndrome X predisposes also to non-insulin dependent diabetes (Type II) and is accompanied by dyslipidemia and hypertension.

The pathogenesis of the insulin resistance that is at the basis of syndrome X is not fully understood. Many groups are actively investigating the problem: foremost among them the laboratory of Richard Bergman, Professor of Physiology at the Keck School of Medicine of USC. It is proposed that increased free fatty acids, particularly from the more rapidly turning over
ALKYTOXIC” at the SCARG Meeting on September 1st, 2001.

By Maria Runnegar
University of Southern California

Dr. Wan is Professor of Pathology in the UCLA School of Medicine. She joined the Faculty of the Harbor-UCLA Medical Center in Torrance in 1989. In looking at Dr. Wan’s academic and scientific career what stands out is the ease with which she has fused apparently disparate fields of research into a unifying theme. After a degree in Pharmacy from Taipei Medical College where she received a solid grounding in pharmacology and drug interactions, she came to the U.S. to do a Ph.D. in Pathology at Hahnemann University in Philadelphia. During this time Yvonne added embryology and in depth morphology to her skills. This was followed by a postdoctoral appointment at the National Institutes of Health (NIH) in Bethesda. Here Dr. Wan mastered the molecular biology techniques necessary to success fully investigate gene expression and regulation. Dr. Wan’s independent research career is truly a synthesis of all the areas of training she received. This is reflected in the very extensive range of topics in her publications. The central theme of Dr. Wan’s work is the study of the action of retinoic acid (vitamin A) through its nuclear receptors on liver gene regulation, hepatocyte differentiation, proliferation, and programmed cell death. Dr. Wan’s lab has shown a complex pattern of induction and repression of retinoid acid of gene expression of a-fetoprotein and albumin as well as of retinoid acid receptors in hepatoma cell lines and in the developing rat liver.

The physiological and pathological importance of retinoid acid and its receptors has been clearly established in a mouse model where the hepatocyte RXRα gene has been knocked out. Dr. Wan has shown that mice lacking hepatocyte RXRα have reduced levels of both cholesterol and triglyceride levels (particularly in males) because liver homeostasis is lost. She has also shown that hepatocyte RXRα is essential for maintaining normal levels of many cytochrome P450 enzymes (including CYP3A4, CYP2C5, CYP3A1 and CYP2B) of liver fatty acid binding protein and of some apo-lipoproteins. The consequences of these changes are perturbations in fatty acid, cholesterol, bile acid, and drug metabolism. In alcoholism, vitamin A levels (retinol and hence retinotic acid) that are essential for growth and maintenance of normal epithelial function are decreased. Furthermore, ethanol has been shown to inhibit the efficacy of retinoid acid (the active form of vitamin A) by competing for access to alcohol dehydrogenase (ADH). It has been proposed that ethanol-induced reduction in retinotic acid levels during gestation results in the distinctive features of fetal alcohol syndrome.

The activity of enzymes involved in alcohol metabolism determines the time course and mode of disposition of alcohol. Oxidation of alcohol through to acetic acid is catalyzed by alcohol and acetaldehyde dehydrogenases. Alcohol can also be metabolized by the cytochrome P450 CYP2E1. This activity is important in alcoholism since the enzyme is induced by alcohol itself, making its contribution to alcohol metabolism more significant. The rate of alcohol oxidation by CYP2E1 could play a role in the pathogenesis of alcoholic liver disease through the formation of reactive oxygen leading to lipid peroxidation. It has been shown in many studies that in humans there is functional polymorphism in both the alcohol and acetaldehyde dehydrogenases and in CYP2E1. The frequency of polymorphism varies in individuals within a family. Continued on page 3

Center Adds SSM to Research Base, Continued from page 1

Lastly, the Center was awarded an additional quarter of a million dollars from NAAA as supplemental funding to create ALD Epidemiology and Prevention components. These new components will be spearheaded by Dr. Steve Sussman, Professor of Preventive Medicine. Dr. Sussman will collaborate with Drs. Bruce Runyon and Michel Mendler at Rancho Los Amigos National Rehabilitation Center to develop a new preventive program for ALD in the Hispanic community. Dr. Yuan will collaborate with Drs. Malcolm Pike and Brian Henderson, internationally acclaimed epidemiologists to help define the risk factors for ALD. We hope that the addition of these new components will set a stage for the Center’s transition from a research center to a comprehensive center.

SCARG Conference, Continued from page 4

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There is no generally accepted medical treatment for NASH. It is thought that weight loss and exercise would be beneficial since they improve the degree of obesity and insulin resistance that are frequent in the majority of patients. Studies examining the relationship between weight loss and the severity of NASH have so far yielded mixed results: in some cases showing improvement and in others a worsening of liver fibrosis. Because of this, a number of small studies have combined medications known to play a protective role in the liver with weight reduction. Unsideoxycorticoid (UDCA) has shown some promise for a large scale placebo-controlled study with this drug.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is funding the establishment of a network of centers focusing on the etiology, contributing factors, natural history, complication and therapy of NASH. Under this umbrella, Dr. Mendler’s group will be carrying out a “prospective, double-blind, placebo-controlled study of pioglitazone and metformin in adult non-diabetics with NASH.” This is a very extensive, ambitious study that will examine the effect of these drugs over a period of two years. Pioglitazone is an insulin-sensitizing agent, which decreases fasting plasma glucose, while metformin suppresses hepatic glucose output.

Patients will be recruited throughout the Los Angeles area from several locations that are connected to USC. Patients from Rancho Los Amigos Medical Center, the Roybal and Hudson CHCs, LAC+USC Medical Center, the USC University Hospital and Ambulatory Health Center as well as Children’s Hospital will take part in this study. 215 adults and 15 children representing a diverse ethnic background, but predominantly Hispanic, are going to be recruited each year. Extensive metabolic work-up including liver biopsies will be done on recruitment. In the following months a number of parameters of glucose and lipid metabolism and of liver function will be monitored. Liver biopsies will be taken at 22 and 24 months (the completion of the study). At the end of the study it is expected that in the placebo patients NASH would have worsened, while in those treated, NASH would have stabilized or improved.

Since there is also some evidence that there is a genetic component to NASH, an arm of the study will include genotyping for candidate genes that are relevant to NASH.

At the end of the study, Dr. Mendler and colleagues will have firmly established the role that impaired glucose metabolism plays in NASH progression, as well as get insight into the genetic background that predisposes to the disease. An overview of Alcohol Pharmacogenetics in Mexican Americans presented by Yvonne Wan is reviewed on Page 2.

Yvonne Wan, Continued from page 2

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Yvonne Wan, Continued from page 5

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development of alcoholic liver disease in Mexican-American men will be established. The long-term objective is to understand the molecular mechanisms underlying the development of and the resistance to alcoholic liver disease in

Mexican-Americans. As expected for such an ambitious multi-faceted endeavor, many other talented investigators from Harbor-UCLA are contributing to this study directed by Dr. Wan with support from the Research and Education Institute, the Center for

Psychobiology and Ethnology and the General Clinical Study Center.

Ronald G. Thurman, Ph.D. (1941-2001)

By Hide Tsukamoto

Center friend, Dr. Ronald Thurman died of a massive heart attack on July 11, 2001. An exceptional scientist, he will be
missed by his colleagues that study alcoholic liver injury and will be dearly remembered as someone that made many
cross-cultural breakthroughs the understanding of hepatic alcohol metabolism and injury. Shared to the right is a wonderful
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