

Abstracts

The following abstracts were presented by investigators at the Seventeenth Annual Samuel Bronfman Department of Medicine Research Day at the Mount Sinai Medical Center. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as The Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; Englewood Hospital and Medical Center, Englewood, NJ; and St. Joseph's Hospital and Medical Center, Paterson, NJ. The work outlined in three abstracts identified with an * were presented in the morning plenary session. Several additional posters were shown on Research Day, but the abstracts have been published elsewhere. Abstracts from Queens Hospital Center were presented as posters on Research Day held at that institution.

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Alcohol Research

Study on the Toxicity of β -Carotene and Acetaldehyde Combination in HepG2 Cells. R. Ni, M.A. Leo, J. Zhao, and C.S. Lieber. Alcohol Research Center, Section of Liver Disease and Nutrition, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

In rats and baboons, the hepatotoxicity of chronic ethanol consumption was shown to be exacerbated by β -carotene feeding, but the mechanism of this adverse effect is unknown. To study this, human hepatoma-derived HepG2 cells were incubated for 24 hrs with acetaldehyde (initial concentration of 179 μ M, maintained through repeated additions) and/or β -carotene (1-1.5 μ M). The latter was incorporated in phosphatidylcholine liposomes to yield hepatocyte concentrations equivalent to those measured by HPLC *in vivo* in human liver. Either acetaldehyde or β -carotene resulted in hepatotoxicity, documented by a release of lactic dehydrogenase from the cells into the media: (4.2 ± 0.4 and 3.9 ± 0.2 vs. 2.9 ± 0.2 in controls, % of total; $p < 0.01$ and < 0.05 respectively). Combination of the two resulted in an additive effect (5.0 ± 0.3 ; $p < 0.001$). The toxic effect of β -carotene was also documented by an alteration of mitochondrial function assessed by the tetrazolium dye MTT ($45.1\% \pm 0.99$ of controls; $p < 0.001$). In that respect, β -carotene was more toxic than acetaldehyde ($p < 0.001$).

Conclusion: β -carotene, in concentrations equivalent to those seen in human livers *in vivo*, is toxic to HepG2 cells *in vitro* and its effect is exacerbated by acetaldehyde, the toxic metabolite of ethanol. This model system now provides a tool to study the mechanism of this clinically relevant toxic interaction.

Polyenylphosphatidylcholine Attenuates the Oxidation of LDL Produced by Alcohol Feeding in Baboons. K.P. Navder, E. Baraona, M.A. Leo, and C.S. Lieber. Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

Alcohol taken in moderation may prevent atherosclerosis, whereas heavy drinking has the opposite effect, in part by promoting oxidation of low-density lipoproteins (LDL), a pathogenetic factor in atherogenesis. We assessed here (1) whether similar alterations can be reproduced in baboons fed 50% of energy as ethanol (the average intake of alcoholics) and (2) whether such alterations are affected by supplementation with polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines, shown to prevent alcoholic fatty liver, fibrosis and cirrhosis. Ten animals were given the ethanol-containing diet and ten were pair-fed isocaloric control diets for 7-8 years. In half of the pairs, the diets were supplemented with 2.8 g of PPC/1000 kcal. Alcohol feeding increased LDL-lipoperoxides and made LDL-proteins more negatively charged, changes that were attenuated or prevented by PPC. The oxidizability of LDL was determined *in vitro* by the formation of conjugated dienes following oxidation with Cu^{++} . Alcohol shortened the lag time

(which measures LDL antioxidant capacity); this effect was normalized by PPC supplementation. By contrast, PPC produced no significant changes in the controls. LDL oxidation with either Cu^{++} or 2,2'-azobis (2-amidino-propane) dihydrochloride was prevented by dilinoleoyl-phosphatidyl choline, a major PPC component. Thus PPC, by markedly attenuating the ethanol-induced increase in LDL oxidation, opposes one of the effects whereby atherosclerosis is being promoted.

Circulating Markers of Fibrosis Effects of Alcohol Intoxication. Y. Ponomarenko¹, M.A. Leo¹, W. Kroll², and C.S. Lieber¹. ¹Section of Liver Disease and Nutrition, Alcohol Research and Treatment Center, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY; and ²Bayer AG, Wuppertal, Germany.

In recent years, a number of circulating breakdown products of collagen or other components of the extracellular matrix (ECM) have been proposed as markers of hepatic fibrosis. In addition, matrix degrading metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) have been considered to be key determinants of ECM deposition. However, the published results lack consistency. Since many of the patients with fibrosis studied were alcoholics, the question was raised whether the presence of alcohol may have affected the results obtained and whether some of the variability reflects drinking at the time of blood sampling. Indeed, in a preliminary study, we had observed that serum values of laminin, the major noncollagenous glycoprotein of basement membranes, decrease with abstinence. Using sandwich-type assays or RIA technology with corresponding antibodies, we now completed this observation and extended it to 7 additional markers. A group of ten alcoholics were studied while intoxicated and during the following 2 weeks of abstinence, verified with repeated breath alcohol measurements. In addition to laminin, measurements were carried out of tenascin, a molecule expressed in proliferating ECMs; undulin, a glycoprotein associated with the surface of mature fibrillar collagen; TIMP-1; collagen VI, a molecule that forms filaments between large collagen fibrils; the N-terminal propeptide of procollagen type III (PIIINP), considered a marker of fibrogenesis; hyaluronic acid (HA), a ubiquitous glycosaminoglycan with high extraction by the liver sinusoidal endothelium; and MMP-2. Laminin was significantly reduced at 1 week (22%, $p = 0.013$) and at 2 weeks (30%, $p = 0.02$). Similarly, tenascin and undulin also significantly decreased ($p = 0.03$). By contrast, TIMP-1, collagen VI, PIIINP, HA and MMP-2 did not significantly change. The mode of action of alcohol on these tests is unknown, but regardless of the mechanism involved, the present results indicate that the presence of alcohol in the blood should be taken into account in assessing the significance of the proposed markers of fibrosis.

Summary: Of the 8 circulating markers of liver fibrosis studied, 3 (laminin, undulin and tenascin) appeared to decrease upon withdrawal from alcohol intoxication, whereas the 5 other tests (TIMP-1, collagen VI, PIIINP, HA and MMP-2) remained unaffected; these differences, if confirmed in a larger series, must be considered when using those measurements to assess fibrosis.

Polyenylphosphatidylcholine (PPC) Corrects Alcohol-Induced Oxidative Stress and Associated Depletion of Dilinoleoyl-phosphatidylcholine (DLPC). S. Aleynik, M.A. Leo, L.M. DeCarli, and C.S. Lieber. Alcohol Research Center, Section of Liver Disease and Nutrition, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

As we showed before in baboons, both hepatic alcohol-induced oxidative stress and associated depletion of DLPC can be attenuated by the administration of PPC. We now determined whether this is associated with corresponding systemic changes assessed in the plasma. Baboons (*Papio hamadryas*) were fed Lieber-DeCarli liquid diets containing 50% of energy as ethanol (equivalent to the average consumption of the alcoholic) or isocaloric carbohydrates, with or without 2.8 grams of PPC per 1000 kcal for a period up to 8.3 ± 0.5 years. Alcohol resulted in a three-fold decrease of circulating DLPC (determined by HPLC). We found the same trend for some other phosphatidylcholines, whereas total plasma phospholipids, tocopherol and reduced glutathione (GSH) were not changed. PPC administration increased circulating DLPC and some other phosphatidylcholines to levels above those in untreated animals ($p < 0.01$). Alcohol feeding also resulted in a 3.5-fold ($p < 0.001$) elevation of plasma 4-hydroxynonenal (4-HNE, measured by GC/MS), reflecting the alcohol-induced systemic oxidative stress. This increase was fully prevented by PPC. There was only a trend for corresponding changes in plasma malondialdehyde. In conclusion, the alcohol-induced oxidative stress and the associated depletion in DLPC, shown previously in the liver, is also found in the plasma and can be fully prevented by PPC administration.

Alcohol-Induced Apoptosis of Hepatocytes and Its Modulation by Polyenylphosphatidylcholine (PPC) in a Rat Model. L-J. Mi, K.M. Mak, and C.S. Lieber. Alcohol Research and Treatment Center, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

Alcohol consumption increases apoptosis of hepatocytes. The alcohol-induced apoptosis appears to be mediated by cytochrome P450 2E1, oxidative stress and cytokines. PPC, a soybean extract rich in polyunsaturated phosphatidylcholines, decreases alcohol-induced oxidative stress and fibrosis in baboons, modulates cytokine production and attenuates fatty liver in rats. To assess whether PPC attenuates the alcohol-induced apoptosis of hepatocytes, formalin-fixed and paraffin-embedded liver tissues from 28 male Sprague-Dawley rats were studied using TUNEL (terminal transferase dUTP nick end labeling) assay. These rats were divided into four groups and pair-fed for 21 days with Lieber-DeCarli liquid diets containing 36% of energy as alcohol or an isocaloric amount of carbohydrate with PPC (3 g/L) or equivalent amounts of linoleate as safflower oil and of choline. An additional dose of alcohol (3 g/kg) was given intragastrically 90 minutes before the livers were removed. Apoptotic hepatocytes were identified by positive TUNEL staining and/or nuclear chromatin condensation or margination. 20,000 to 60,000 hepatocytes in each rat were counted by light microscopy using an Image-Pro Plus program. In alcohol-fed rats, the percentage of apoptotic hepatocytes was about three times greater than in control rats ($0.205 \pm 0.047\%$ vs. $0.077 \pm 0.008\%$, $p < 0.01$, $n = 7$). PPC feeding decreased the alcohol-induced apoptosis by half ($0.116 \pm 0.034\%$, $p < 0.05$, $n = 7$). No difference in apoptosis between the control and PPC-fed rats was found. Apoptosis appeared to be distributed randomly in the liver lobules. The liver from rats fed alcohol (with or without PPC) exhibited varying degrees of fatty changes, but no correlation between the severity of steatosis and the apoptosis was observed. The apoptotic hepatocytes did not show fatty changes. Apoptosis was seen in both mononuclear and binuclear hepatocytes.

Conclusion: PPC attenuates alcohol-induced apoptosis of hepatocytes; this protective effect may provide a potent mechanism against liver injury, possibly in association with PPC's antioxidative action.

Gastric Oxidation of Ethanol Accounts for Its First-Pass Metabolism. E. Baraona, C.S. Abittan, and C.S. Lieber. Alcohol Research and Treatment Center, Bronx VA. Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

Oral alcohol consumption results in lower blood ethanol concentrations than intravenous infusion of the same dose, even when the latter is given at a rate equal to that of alcohol absorption. No such first pass metabolism

(FPM) occurs when alcohol is administered by the duodenal or portal routes, which bypass the stomach. However, there is a controversy on whether the stomach can metabolize a sufficient amount of ethanol and to what extent gastric alcohol dehydrogenase (ADH) activity is responsible. To study this, we used 21 normal baboons, a species close to man. In 8 baboons, the aorta and the hepatic vein were cannulated percutaneously to estimate the splanchnic blood flow by the Fick principle (using indocyanine green) with an appropriate dose of alcohol. In 3 additional baboons, the aorta and the portal vein were cannulated non-occlusively to assess the conversion of ethanol to acetate *in vivo*. Thirty minutes after closing the abdomen, ^{14}C -ethanol (300 mg/kg as a 15% solution) was given intragastrically (IG) and ^3H -acetate was infused intravenously (IV) at a constant rate (1 mCi/mL). Simultaneous sampling of portal and arterial blood was carried out for 3 hours. The stomach content was then removed and alcohol (300 mg/kg) was given IV in 30 min. The ethanol left in the stomach at 3 hours was 73 ± 8 mg/kg. Michaelis-Menten analysis of the IV and IG ethanol curves revealed an FPM of 94 ± 11 mg/kg. The porto-arterial differences were negative for ^3H -acetate (indicating net extraction) and positive for ^{14}C -ethanol and ^{14}C -acetate (indicating net output). ^{14}C -acetate was calculated from the ^{14}C -radioactivity after exhaustive evaporation of ethanol in an alkaline solution. To calculate the production of acetate, its porto-arterial differences were multiplied by the portal plasma flow, considered to be 2/3 of the splanchnic plasma flow. Total acetate production (extraction plus net output) increased with time and continued beyond the 3-hour measurements; the production of acetate over the first 3 hours (82 ± 13 mg/kg) corresponded to a substantial fraction (87%) of the FPM of alcohol. In 10 animals, the capacity for gastric ADH to mediate ethanol oxidation was determined *in vitro*. The ADH activity of gastric mucosa (53 ± 14 mg/kg in 3 hours) was insufficient to account for the FPM, suggesting a contribution of a much higher activity in the esophagus or the participation of non-ADH systems.

Conclusion: The oxidation of ethanol by gastric ADH, measured *in vitro*, as well as the conversion of ethanol to acetate, measured *in vivo*, can account for most of the first pass metabolism of ethanol.

Cardiology

Have We Overestimated the True Value of Contrast Echo? A Quantitative Echo Study. T. Nahar, L. Croft, R. Shapiro, S. Buckley, M. Henzlova, J. Machac, J. Diamond, E. Stern, and M.E. Goldman. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Harmonic (H) contrast (C) echo improves subjective LV endocardial border definition, which should translate into better quantification (quant) of LV ejection fraction (EF). However, C requires additional time, expense and an IV. To determine the incremental benefit of H and C imaging, we analyzed 50 2-D echoes obtained in four modes: fundamental (F), H, each with (C+) or without (C-) Optison® boluses. Each study was analyzed subjectively and biplane 2-D EF was blindly quantified and compared to radionuclear (RNC) EF. We defined an accurate 2-D EF to be = RNC EF $\leq \pm 5\%$.

	F:C-	F:C+	H:C-	H:C+
Visual Good	6	17	29	44
Poor	44	33	21	6
Quant $\leq \pm 5\%$	22	22	24	36
$\geq \pm 5\%$	28	28	26	14

Subjective assessment of LV function and cavity was significantly better with addition of C and H imaging (Poor = ≥ 2 continuous segments poorly seen in 2 or 4 chamber view). If endocardium was visualized better by H+C, objective quant should reflect the improvement. C+ improved F quant ($\leq \pm 5\%$ to RNC) in 9 patients, while H:C+ improved quant in 21 patients. About 1/2 the benefit of H:C+ was from H alone. No parameter studied (age, sex, height, weight, LV, EF, LV size, blood pressure), predicted who benefited from H, C or both.

Thus, while the impact of H:C+ on quant is less than for subjective reading, H:C+ significantly improves quant compared to F:C+ or H:C-. Previous reports based on subjective readings may have overestimated the relative value of contrast echo.

Accurate Quantitative Echocardiography Requires Harmonic Contrast Imaging. T. Nahar, L. Croft, R. Shapiro, S. Buckley, M. Henzlova, J. Machac, J. Diamond, E. Stern, and M.E. Goldman. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Quantitative LV ejection fraction (EF) measurement by 2-D echo is limited by subjective visual endocardial borders detection. Both harmonic (H) and contrast (C) echo provide better LV wall and cavity definition. To determine the incremental benefit of the newer technologies, we calculated modified Simpsons's biplane 2-D echo LV EF in 50 subjects, mean age = 48 ± 16 years, by fundamental (F) and H imaging, (Acuson Sequoia & ATL HDI 5000 CV) each with (C+), or without (C-) Optison® contrast boluses. Of the 50 echo studies, 44 qualified as technically difficult. Radionuclear (RNC) gated LV EF's done within 12 hours of the echo ranged from 18–72%, mean = $51 \pm 17\%$. Blinded measurements were done on digitally stored images by 3 independent readers (Readers1-3) and were correlated with RNC EF's.

TABLE

Correlation of Echo LV EF with RNC Performed by 3 Independent Readers

	F:C-	F:C+	H:C-	H:C+
Reader 1	0.68	0.78	0.84	0.95
Reader 2	0.60	0.68	0.84	0.96
Reader 3	0.66	0.80	0.83	0.95
Mean	0.65	0.75	0.84	0.95
Bias \pm S.D.	3.4 ± 15	5.0 ± 11	2.8 ± 9	-1.2 ± 5

Contrast provided a similar increment in accuracy for F and H imaging, though the correlation of H alone was significantly better than F alone. Harmonics alone provided roughly $1/2$ the advantage gained by contrast combined with harmonic imaging. Thus, quantitative echo is possible with newer imaging methods and is most accurate when harmonic imaging is performed with contrast.

Use of Microdialysis to Assess Interstitial Fluid Angiotensin II (Ang II) Concentration in the Rat Heart. F.M. Siri and S.A. Atlas. Hypertension Research Laboratory and Cardiology Section, Bronx VA Medical Center, Bronx, NY; and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

There is controversy regarding the extent to which tissue Ang II levels are derived from circulating blood, since a number of tissues, including the heart, are in theory capable of local Ang II synthesis. Furthermore, the beneficial effects of drugs that block the renin-angiotensin system in cardiac disease extend to patients with normal circulating Ang II levels, leading some to postulate the existence of high tissue levels due to local synthesis.

Aim: To estimate cardiac interstitial fluid levels of Ang II using microdialysis in the intact beating rat heart *in situ*.

Methods: A dialysis probe (10 mm length, 0.5 mm OD) was inserted into the anterior myocardial wall (apex to base) of normal open-chest, pentobarbital-anesthetized rats. Krebs solution with 0.5% BSA was then perfused at 2 μ L/min for 30–60 min periods, and samples were collected on ice into tubes containing EDTA. Blood samples were collected in EDTA prior to and following dialysate collection. Ang II in dialysates and in plasma was measured by radioimmunoassay following extraction on C₁₈ SepPak cartridges. Further analysis of immunoreactive (ir) Ang II was performed using reversed-phase high performance liquid chromatography (rpHPLC) using a C₁₈ column eluted isocratically with 22% acetonitrile in water.

Results: In initial studies (n = 5) irAng II levels averaged 72 ± 53 (mean \pm SD) pg/mL in cardiac interstitial fluid and 51 ± 4 pg/mL in plasma. By rpHPLC analysis the irAng II in plasma and interstitial fluid had retention times (9.5 min) corresponding to that of authentic Ang II octapeptide. In subsequent studies somewhat higher interstitial fluid levels (as high as 500 pg/mL) were found on occasion, but generally in proportion to (and never more than double) that in plasma. Preliminary experiments indicate a prompt rise in both plasma and cardiac interstitial fluid Ang II levels during high-dose Ang II infusion.

Conclusions: These results contrast markedly with a report that interstitial fluid Ang II in the dog heart *in situ* is several orders of magnitude higher than plasma Ang II and is uninfluenced by exogenous Ang II

infusion (Dell'Italia et al. J Clin Invest 1997; 100:253). The present results do not suggest such striking compartmentalization of Ang II in normal rat hearts. The data suggest that cardiac interstitial fluid Ang II is derived in part from the blood and/or that it is synthesized at a rate similar to that in blood. Further study is needed to determine whether interstitial fluid Ang II might be disproportionately elevated in the diseased heart.

Antihypertensive Efficacy of Omapatrilat: A Novel Vasopeptidase Inhibitor. S.A. Atlas¹, J. Baruth¹, P. Kumar¹, C. Rosendorff¹, R. Zusman², E. Adler³, and E. Levy³. ¹Hypertension Unit and Cardiology Section, Bronx VA Medical Center, Bronx, NY; and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY; ²Massachusetts General Hospital, Boston, MA; and ³Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ.

Omapatrilat, representative of a new class of antihypertensive agents termed "vasopeptidase inhibitors," is a single compound that simultaneously inhibits both neutral endopeptidase (NEP, K_i 8.9 nM) and angiotensin converting enzyme (ACE, K_i 6.0 nM). Inhibition of NEP slows the degradation of a number of endogenous vasodilatory and natriuretic peptide hormones, including the A- and B-type natriuretic peptides (ANP and BNP), bradykinin and adrenomedullin.

Aim: To determine the antihypertensive efficacy and safety of omapatrilat in patients with uncomplicated, mild-to-moderate essential hypertension.

Methods: Following a placebo washout period, subjects with seated diastolic blood pressure in the 95–110 mm Hg range were randomly assigned, in double-blind fashion, to receive either placebo (Pbo) or single daily doses of omapatrilat (Oma, 20–80 mg) for a 9-week period. Blood pressure was routinely measured at trough (i.e., 24 hours post dose) but also measured at peak (7 ± 1 hours post dose) on selected occasions.

Results: Administration of omapatrilat caused clear evidence of ACE inhibition (i.e., stimulation of plasma renin levels and decreases in plasma angiotensin II and aldosterone) as well as dose-dependent increases in urinary ANP and urinary cGMP excretion, consistent with effective NEP inhibition. Reductions in systolic (SBP) and diastolic (DBP) blood pressure were evident within 2–4 hours of administration and were sustained throughout the 9-week treatment period. Dose-dependent changes in trough BP were highly significant ($p < 0.001$ for all doses) compared to Pbo:

	Pbo	Oma 20 mg	Oma 40 mg	Oma 60 mg	Oma 80 mg
[n]	[99]	[111]	[104]	[107]	[296]
Δ SBP	-4.2	-12.7	-17.3	-17.8	-19.5
Δ DBP	-5.7	-10.2	-12.1	-13.7	-14.2

Peak reductions in SBP/DBP ($-25.8/-16.9$ mm Hg for 80 mg) suggest an excellent trough-to-peak ratio. At 80 mg/day, trough DBP was <90 mm Hg in 69% of all subjects (83% of mild hypertensives).

Conclusions: Omapatrilat administered once daily is a well-tolerated and highly effective antihypertensive agent with a very high normalization rate for monotherapy. This and other studies suggest unusual efficacy at lowering SBP, and greater BP reduction compared to ACE inhibitors in African Americans, the elderly and other typically low-renin subsets. These features suggest that vasopeptidase inhibitors may provide a significant advance in the treatment of hypertension.

Marked Stimulation of Brain Natriuretic Peptide Gene Expression in Left Ventricular Myocardium of Rats with Chronic Ascending Aortic Banding. S.M. Dolgilevich, F.M. Siri, and S.A. Atlas. Hypertension Research Laboratory and Cardiology Section, Bronx VA Medical Center, Bronx, NY; and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Brain natriuretic peptide (BNP) is a cardiac hormone with a longer biological half-life than atrial natriuretic peptide (ANP) and qualitatively similar natriuretic, diuretic and vasorelaxant activity. Although ANP is the major hormone secreted by the cardiac atria, both ANP and BNP are synthesized by ventricular muscle, and it has been suggested that plasma levels of BNP may provide a more reliable marker for congestive heart failure and ventricular hypertrophy.

Aim: To determine the extent to which the genes for BNP and ANP are transcriptionally regulated in a model of chronic pressure overload hypertrophy.

Methods: Samples of left (LV) and right (RV) ventricular myocardium were obtained from male Sprague-Dawley rats with ascending aortic constriction (n = 10) and normal controls (n = 6). Changes in gene expression were quantitated by Northern blot analysis using cDNA probes for ANP and BNP, and all values (presented as mean \pm SD) were normalized to the level of expression of G3PDH measured simultaneously.

Results: Aortic constriction caused a marked increase in LV mass to body mass ratio after 5–7 days. This hypertrophy was accompanied by a greater than 30-fold increase in BNP expression in LV but not in RV. The level of BNP mRNA (arbitrary units, normalized to G3PDH expression) in LV rose from 0.05 ± 0.02 in controls to 1.45 ± 0.3 in rats with aortic constriction ($p < 0.01$), whereas levels in RV were no different in the two groups (0.22 ± 0.06 vs. 0.38 ± 0.09). Results were qualitatively similar for ANP expression in hypertrophied hearts, which was far greater in LV compared to RV (1.1 ± 0.5 vs. 0.09 ± 0.06 arbitrary units).

Conclusions: These results indicate that left ventricular synthesis of BNP is, like that of ANP, highly responsive to increases in systolic pressure. These findings suggest that these locally expressed cardiac hormones, which via stimulation of particulate guanylate cyclase (i.e., the type A natriuretic peptide receptor) are thought to have anti-mitotic actions, could play an important compensatory role in the progression of afterload-induced left ventricular hypertrophy.

Colocalization of Annexin V with Tissue Factor in Human Atherosclerotic Plaques — A New Thrombomodulatory Mechanism. J.T. Fallon, V.E. Gulle, X.X. Wu, and J.H. Rand. Mount Sinai School of Medicine, New York, NY.

Background: Annexin V is an anionic phospholipid binding protein with potent anticoagulant properties, which blocks tissue factor (TF) activity on membrane surfaces. Atherosclerotic plaques are rich in TF protein but even ruptured plaques are variable in their thrombogenicity. We examined the hypothesis that annexin V is present in plaques and may modulate plaque thrombogenicity following plaque rupture.

Design: Human atherosclerotic coronary, carotid, and aortic segments were fixed and processed for paraffin embedding. Sequential sections were stained with H&E, trichrome, and immunostained with specific antibodies against annexin V, macrophage CD68, smooth muscle cell α -actin, tissue factor, and von Willebrand factor.

Results: Normal arterial wall did not contain annexin V antigen except on endothelium. Lipid-rich atherosclerotic lesions contained focal areas of annexin V staining in the fibrous cap, shoulder and base regions. These areas were rich in intact macrophage foam cells. In sections of ruptured plaques, annexin V staining was evident at the base of the overlying thrombus associated with macrophages. All areas of annexin V staining also showed TF staining. Annexin V antigen was not associated with regions rich in smooth muscle cells.

Conclusion: Annexin V is present in plaques and colocalizes with macrophages and TF at the sites of rupture. Annexin V may be an important modulator of TF activity and thrombosis following plaque rupture.

***High-Resolution Magnetic Resonance Imaging of Complex *In Situ* Coronary and Aortic Atherosclerosis *Ex Vivo*.** S.G. Worthley¹, G. Helft¹, V. Fuster¹, Z.A. Fayad^{1,2}, J.I. Osende¹, J.T. Fallon^{1,3}, M. Roque¹, O.X. Rodriguez¹, A.G. Zaman¹, and J.J. Badimon¹. ¹Cardiovascular Institute and Departments of ²Radiology and ³Pathology, Mount Sinai School of Medicine, New York, NY.

Acute coronary syndromes are the result of atherosclerotic plaque disruption and subsequent thrombosis. Atherosclerotic plaque composition is central in the pathogenesis of this process. Thus, there is a need for accurate imaging and characterization of atherosclerotic lesions. The porcine model is considered to closely resemble human atherosclerosis and has comparable coronary artery anatomy.

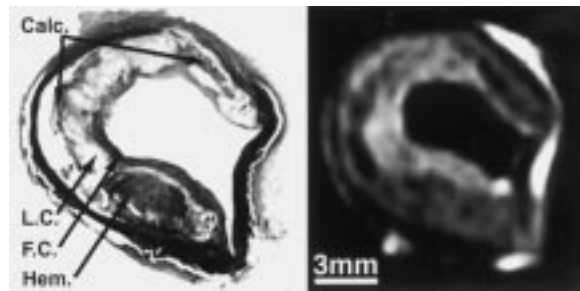
Aim: To validate *ex vivo* magnetic resonance imaging (MRI) characterization of atherosclerotic lesions from *in situ* coronary arteries and aortas in a novel model of complex porcine atherosclerosis and validate this with histopathology.

Methods: Coronary and aortic atherosclerosis was induced in Yucatan mini-swine (n = 4) by a combination of atherogenic diet (2% cholesterol) for 6 months and sequential balloon injury. All coronary arteries were imaged *ex vivo* on the intact heart, preserving the curvature of their

course. The aortas also underwent MRI. The MR images were correlated with the matched histopathology sections for both the coronary arteries (n = 54) and the aortas (n = 43).

Results: Mean wall thickness for the coronary arteries (r = 0.94, slope = 0.81) and aortas (r = 0.94, slope = 0.81) was accurately determined by MR imaging ($p < 0.0001$). MR imaging accurately characterized complex atherosclerotic lesions, including calcified (Calc.), lipid-core (L.C.), fibro-cellular (F.C.) and hemorrhagic (Hem.) regions (see figure of aorta).

Conclusions: MRI accurately quantifies and characterizes coronary and aortic atherosclerotic lesions in this experimental porcine model of complex atherosclerosis. This model may be useful for future studies of MRI of complex atherosclerosis *in vivo*.



High-Resolution *In Vivo* Magnetic Resonance Imaging of Experimental Coronary Artery Plaques. S.G. Worthley¹, G. Helft¹, V. Fuster¹, Z.A. Fayad^{1,2}, O.X. Rodriguez¹, J.T. Fallon¹, A.G. Zaman¹, and J.J. Badimon¹. ¹Cardiovascular Institute, and Departments of ²Radiology, and ³Pathology, Mount Sinai School of Medicine, New York, NY.

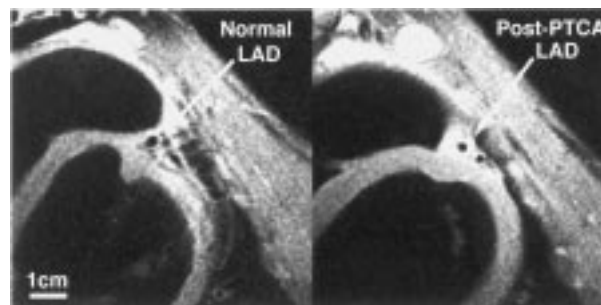
Atherosclerotic plaque composition modulates its vulnerability and thrombogenicity. *In vivo* magnetic resonance imaging (MRI) has been used to characterize and quantify non-coronary lesions. The major limitation of MRI has been the inability to translate this to atherosclerotic lesions within the coronary arteries. This is due to cardiac and respiratory motion artifacts, as well as the size and non-linear course of these arteries.

Aims: To develop and validate a novel MRI technique in a clinical 1.5 Tesla system that permits, for the first time, high-resolution imaging and characterization of lesions in coronary arteries in a porcine model.

Methods: Lesions were induced in Yorkshire albino swine (n = 5) in all 3 major epicardial coronary arteries with balloon angioplasty. *In vivo* MRI was performed 4 weeks post-angioplasty, with a standard phased array surface coil in a clinical 1.5 Tesla MR system (GE). A unique double inversion recovery fast spin echo sequence was used, allowing high-resolution (0.39 – 0.48 mm in-plane resolution, slice thickness 5 mm) proton density and T2 weighted imaging, while nulling flow signal. The figure shows an MR image of a fibrocellular coronary lesion in the left anterior descending artery (LAD). Included is an MR image of the coronary wall of a normal LAD for comparison. Cardiac gating and breath-holding (<30 seconds/image) was used to suppress motion artifacts.

Results: An excellent correlation ($p < 0.001$) between matched *in vivo* images and histopathology sections (n = 24) was observed for mean wall thickness (r = 0.93, slope = 0.96). Intralésion hematoma was readily identified from the fibrocellular components with MRI.

Conclusions: The non-invasive characterization of coronary lesions using MRI raises new therapeutic possibilities allowing risk stratification for plaque disruption and selection of therapeutic strategies based on plaque composition.



Do Patients with Primary Autonomic Failure Have Target Organ Damage? T. Vagaonescu¹, D. Saadia², A. Butkevich¹, R. Phillips¹, and H. Kaufman². ¹Hypertension Section, Cardiovascular Institute, and ²Department of Neurology, Mount Sinai School of Medicine, New York, NY.

The most apparent problem in patients with primary autonomic failure (PAF) is orthostatic hypotension. However, this occurs only when the patient is sitting or standing. When supine, most patients with PAF have hypertension. Whether the supine hypertension, occurring only a few hours a day, is associated with target organ damage is unknown.

Aim: To assess if patients with PAF have left ventricular hypertrophy (LVH) and if the LVH correlates with their 24-hour blood pressure profile.

Methods: Ten patients with PAF (all treated with fludrocortisone and midodrine) were matched for sex and age with 10 normotensives (NT) and 10 essential hypertensives (EH). Ambulatory blood pressure monitoring and LV mass measurement (echocardiography) was performed in all patients.

Results: PAF patients had 24-hour and daytime systolic BP (DSBP) within normotensive range, but their nighttime SBP (NSBP) and LV mass index (LVMI) were similar to those of EH. PAF patients had a reversed nocturnal BP change when compared to EH and NT (Table). LVMI correlated with the 24-hour SBP in PAF patients ($r = 0.70$; $p = 0.01$).

	PAF (x ± SD)	NT (x ± SD)	EH (x ± SD)
24-hr SBP	128 ± 15	125 ± 5	140 ± 91,2
DSBP	125 ± 16	128 ± 5	142 ± 81,2
NSBP	138 ± 181	115 ± 7	135 ± 141
DiffSBP	-12 ± 171	13 ± 5	8 ± 7
LVMI	74 ± 291	40 ± 13	58 ± 11

Diff SBP = DSBP-NSBP

¹ $p < 0.001$ vs. NT; ² $p < 0.01$ vs. PAF; ³ $p < 0.001$ vs. NT and EH (ANOVA)

Conclusions: Although PAF patients had 24-hour SBP within normotensive range, their NSBP and LVMI were significantly higher than in NT and similar to EH. The increased NSBP in patients with PAF is responsible, most likely, for their LVH. This finding may have further therapeutic implications.

Contrast Harmonic Echo Is the “Great Equalizer” for Quantitative Echo. L. Croft, T. Nahar, R. Shapiro, S. Buckley, M. Henzlova, J. Machac, J. Diamond, E. Stern, and M.E. Goldman. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Accurate LV ejection fraction (EF) calculation by 2-D echo requires experience in endocardial border detection. Contrast (C) and harmonic (H) imaging, which both enhance cavity delineation, may improve LV EF quantification by less experienced users. Thus, 2-D imaging was performed on 33 patients in 4 different modes: fundamental (F), H (Acuson Sequoia & ATL HDI 5000 CV) with (C+) and without (C-) Optison® contrast bolus injections. Radionuclear (RNC) gated EF's were obtained within 12 hours of the echo, and ranged from 18–72% (mean = 51 ± 16%). 2-D biplane EF's (modified Simpson's), calculated by both a junior FELLOW and experienced echocardiologist (EXPERT) independently and blinded to RNC, were correlated with RNC EF.

TABLE

Correlation of Echo to RNC LV EF Measurements by Expertise

	F:C-	F:C+	H:C-	H:C+
FELLOW	0.59	0.68	0.69	0.91
Bias	-2.8 ± 13.8	-2.8 ± 12.2	-3.6 ± 12.6	-3.8 ± 6.9
EXPERT	0.66	0.80	0.83	0.95
Bias	-1.3 ± 13.9	-5.3 ± 11.1	-3.9 ± 10.3	-2.6 ± 5.8

Contrast and harmonic modes each significantly improved the EXPERT reader's accuracy, while only when harmonics and contrast were used together did FELLOW's EF's reach acceptable results. Thus, con-

trast harmonic imaging may empower less experienced users with the ability to assess and quantify LV function as accurately as more experienced echocardiologists.

Coronary Angiographic Findings and Effect of Coronary Artery Disease on Left Ventricular Function among Minorities at North General Hospital. J. Desueza and M. Maw. Cardiology Section, Department of Medicine, North General Hospital, New York, NY.

Objective: To evaluate the difference in coronary angiographic findings among African Americans and Hispanics in a community hospital, and correlate the effects of coronary artery disease on left ventricular function.

Design: Retrospective cohort study based on reviewing hospital reports of coronary angiographies performed at four tertiary teaching hospital in the City of New York, from February 1992 to June 1998.

Setting: A private voluntary community hospital located in East Harlem, New York.

Patients: The study included 241 patients, consisting of African Americans (n = 178) and Hispanics (n = 63) who underwent coronary angiography at four different specialized facilities. Also echocardiograms done at North General Hospital were reviewed. Statistical analysis was done with Stata Quest 4 software, Chi square test used for categorical variables and Student test for continuous variables. A p value ≤ 0.05 was used to identify statistically significant results.

Results: More African Americans underwent coronary angiography as compared to Hispanics (74% vs. 26%). Also noted is predominance of females as compared to males (56.8% vs. 43.2%). Coronary artery disease (CAD), defined as 70% or greater reduction in cross-sectional area of a major coronary artery, was found in 46% of African Americans (AA) and 56% of Hispanics (Hisp); but difference was not statistically significant ($p = 0.1$). Also, when comparison by multivessel (2 to 3 vessels affected) was done, no significant difference was found (AA: 31% vs. Hisp: 34%).

After exclusion of patients with valvular disease, a 50% increase in left ventricular mass (LVM) was found in Hispanics with CAD compared with those without CAD (158 g/m² vs. 104 g/m², $p = 0.003$).

Also found was a 23% decrease in ejection fraction (EF) (41% vs. 53%). Similar findings were observed in the African-American population but these were not as striking as in the Hispanic population. There was a 10% decrease in EF (CAD: 48% vs. no CAD: 52%, $p = 0.01$) and 7% increase in LVM (137 g/m² vs. 127 g/m², $p = 0.4$).

Conclusion: There was no significant difference in angiographic findings among African Americans and Hispanics, although it was significant by gender (males > females). The Hispanic population had a greater significant worsening of the left ventricular function, as measured by ejection fraction and increased left ventricular mass, when coronary artery disease was present, as compared to African Americans. These findings may partially explain the slower decrease in coronary artery disease mortality among Hispanics than among African Americans. Also, previous studies (5) have found a worse type of left ventricular hypertrophy (concentric hypertrophy) among Hispanics, a finding confirmed in our present study. The above findings indicate the need for more aggressive therapy in this ethnic group, as it is well known that they have a higher incidence of obesity, dyslipidemia and diabetes mellitus (6).

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Imaging of Atherosclerotic Lesions with ^{18}F FDG PET in Rabbits. G. Helft¹, S.G. Worthley¹, Z.Y. Zhuang², C. Tang^{3,4}, O.J. Rodriguez¹, J.T. Fallon⁵, Z.A. Fayad^{1,4}, J. Machac², M. Buchsbaum³, V. Fuster¹, and J.J. Badimon¹. ¹Cardiovascular Institute, and Departments of ²Nuclear Medicine, ³Neuro-Psychiatry, ⁴Radiology, and ⁵Pathology, Mount Sinai School of Medicine, New York, NY.

Acute thrombosis on disrupted atherosclerotic plaques plays a key role in the onset of acute coronary syndromes and atherosclerosis progression. Macrophages are critical in plaque vulnerability and modulate its thrombogenicity upon rupture. Quantification of macrophage accumulation would assist in the determination of plaque vulnerability. ^{18}F FDG has been reported to have high affinity for macrophages within tumors. Given its good imaging characteristics, ^{18}F FDG PET could be a useful non-invasive *in vivo* imaging technique for quantifying macrophage content within atherosclerotic plaques.

Aims: To correlate uptake of ^{18}F FDG with histopathological macrophage accumulation in atherosclerotic lesions.

Methods: Normal (n = 3) and atherosclerotic rabbits (n = 6) were studied. Aortic atherosclerosis was induced by a combination of cholesterol-rich diet (0.2% cholesterol for 9 months) and double balloon denudation with a 4 Fr. embolectomy catheter. *In vivo* imaging was performed with a GE brain PET camera 30 min after injection of 34–72 MBq of ^{18}F FDG. Macrophage area was estimated by RAM-11 positive staining on histopathology and uptake of the ^{18}F FDG by the thoracic aorta using standard uptake values (SUVs) and ratio of aortic-to-cardiac uptake were analyzed. ^{18}F FDG uptake and RAM-11 antibody stainings were averaged for the proximal 4 cm of the thoracic aorta of each rabbit.

Results: Atherosclerotic aortas showed an intense focal uptake of ^{18}F FDG. A highly significant correlation ($r = 0.71$, $p < 0.05$) was observed between macrophage-positive areas assessed by histopathology and ^{18}F FDG uptake by SUV. The aortic-to-cardiac uptake ratio also correlated significantly ($r = 0.81$, $p < 0.001$) with the macrophage area.

Conclusions: Thus, ^{18}F FDG PET quantifies *in vivo* macrophage burden within aortic atherosclerotic plaque. This promising imaging tool could serve to serially monitor changes in the cellular content of atherosclerotic lesions and thus stratify patients at risk for plaque rupture.

Benefits of Clopidogrel on Inhibition of Platelet Aggregation and Activation in Patients on Chronic Aspirin Therapy. G. Helft, J.I. Osende, O.J. Rodriguez, S.G. Worthley, A.G. Zaman, E. Lev, S. Palencia, V. Fuster, J.J. Badimon, and J.H. Chesebro. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

The antiplatelet drug clopidogrel has been shown to be at least as effective as aspirin in clinical trials. The additive antiplatelet effects of the two agents are yet to be accurately quantified in patients with known cardiovascular disease.

Aims: To compare platelet aggregation in patients with cardiovascular disease (n = 15) on chronic aspirin (325 mg per day) before and after one week of additional clopidogrel (75 mg per day).

Methods: Assessment of platelet function and activation was performed at baseline (aspirin alone) and after 7 days on clopidogrel (plus aspirin). Thus, each patient served as their own control. Platelet aggregation was determined in platelet-rich plasma (PRP) using ADP (10, 5, 2.5 μM) and collagen (5, 3 mg/mL). Platelet activation was assessed by flow cytometric determination of ADP-induced (0.12 and 0.6 μM) platelet surface binding of fibrinogen.

Results: There was a significant decrease ($p < 0.001$) in platelet aggregation at all doses of ADP tested, after 7 days of additional clopidogrel therapy. The respective mean percentage decreases in ADP-induced platelet aggregation were 26.6% (10 μM), 32.8% (5 μM) and 41.6% (2.5 μM). Interestingly, we also observed an inhibitory effect on collagen-induced platelet aggregation ($p < 0.01$) after 7 days of additional clopidogrel therapy, and at all doses tested. The respective mean percentage decreases in collagen-induced platelet aggregation were 18.6% (5 mg/mL) and 24.8% (3 mg/mL). Platelet activation was also significantly decreased ($p < 0.01$) after the addition of clopidogrel. ADP-induced fibrinogen binding to glycoprotein IIb/IIIa receptors was significantly reduced by clopidogrel: 26.81% to 6.89% with 0.12 μM ; 54.56% to 23.88% with 0.6 μM . There were no hemorrhagic complications noted during the study period.

Conclusions: The addition of clopidogrel to chronic aspirin therapy significantly increases inhibition of platelet aggregation and activation. This data supports the added clinical benefit of combining clopidogrel and aspirin in patients with cardiovascular disease.

Non-invasive Magnetic Resonance Imaging Detects and Quantifies Atherosclerotic Plaque Components in Rabbits. G. Helft¹, S.G. Worthley¹, V. Fuster¹, Z.A. Fayad^{1,2}, J.I. Osende¹, J.T. Fallon^{1,3}, A.G. Zaman¹, M. Roque¹, O.J. Rodriguez¹, and J.J. Badimon¹. ¹Cardiovascular Institute and Departments of ²Radiology and ³Pathology, Mount Sinai School of Medicine, New York, NY.

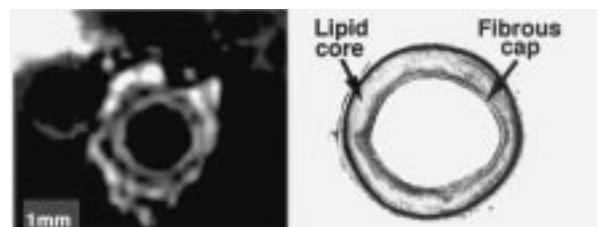
Non-invasive, high-resolution MRI may be used to serially study the effects of therapeutic interventions on atherosclerotic plaque stabilization *in vivo*. This stabilization results from changes in lesion composition.

Aims: To validate for the first time the ability of MRI to quantify lipidic and fibrotic components of lesions in a rabbit model.

Methods: Thoracic and abdominal aortic atherosclerosis was induced in New Zealand white rabbits (n = 15) by a combination of atherogenic diet (0.2% cholesterol) and double balloon aortic denudation. MRI of the entire aorta was performed in a clinical 1.5 T system (GE). Fast spin echo sequences were obtained with in-plane resolution of 0.35 mm and slice thickness of 3 mm. T2 (TR/TE 2300/55 msec) and proton density weighted (PDW) images (TR/TE 2300/17 msec) were acquired. After euthanasia, histopathological sections were matched with MR images.

Results: A significant correlation ($p < 0.05$) between MRI and histology (Oil Red O staining) for analysis of lipidic (low signal on T2w, $r = 0.81$) and fibrous (high signal on T2w, $r = 0.86$) areas was observed. Mean wall thickness correlated significantly ($p < 0.001$) between MRI and histology (CME) for the thoracic ($r = 0.75$) as well as the abdominal aorta ($r = 0.87$) (see Figure). Despite the cardiac and respiratory motion, we found that the thoracic aorta was relatively spared from these artifacts.

Conclusions: Non-invasive, high-resolution MRI allows qualitative and quantitative analysis of aortic atherosclerotic composition in this rabbit model. The *in vivo* feasibility of this technique permits the serial analysis of therapeutic strategies for atherosclerotic plaque stabilization.



Early Inflammatory Response and Intimal Hyperplasia after Mouse Femoral Artery Endothelial Denudation. M. Roque¹, J.T. Fallon^{1,2}, J.J. Badimon¹, M.B. Taubman¹, and E.D. Reis³. ¹Cardiovascular Institute, and Departments of ²Pathology and ³Surgery, Mount Sinai School of Medicine, New York, NY.

Techniques of arterial injury commonly used in animals to mimic endovascular procedures are not suitable for small-sized mouse arteries. This has limited the examination of the response to arterial injury in genetically modified mice. We have developed a reproducible model of transmural arterial injury in the mouse that results in substantial intimal hyperplasia.

Aims: To examine early inflammatory events and the time course of the proliferative response after injury.

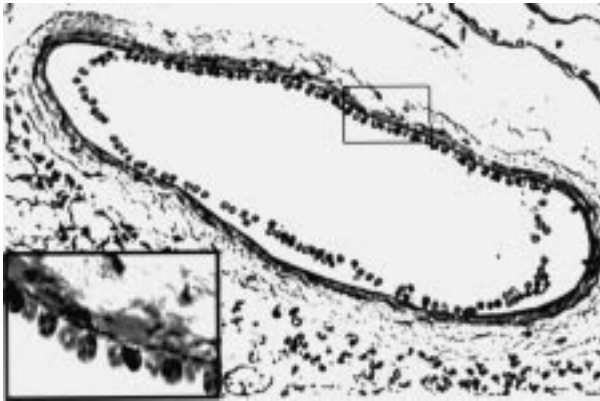
Methods: C57BL/6 mice (n = 100) underwent denudation of the femoral artery by passage of a 0.01" angioplasty guidewire.

Results: After injury, intimal hyperplasia was noted in 10% of arteries at 1 week, 88% at 2 weeks, and 90% at 4 weeks. Regenerated endothelium covered 7% of the luminal surface at 24 hours, 28% at 1 week, 49% at 2 weeks, and 91% at 4 weeks. The intima-to-media ratio reached 1.1 ± 0.1 at 4 weeks. Morphometry data are summarized in the Table.

	1 hour	24 hours	1 week	2 weeks	4 weeks
n (arteries)	10	10	20	66	58
Intimal hyperplasia (%)	0	0	10	88	90
Endothelial regeneration (%)	0	7 \pm 0.2	28 \pm 3.7	49 \pm 1.7	91 \pm 1.8
I/M ratio	0	0	0.2 \pm 0.05	0.5 \pm 0.1	1.1 \pm 0.1

One hour after injury, the denuded surface was covered with platelets and leukocytes, predominantly neutrophils (see Figure), associated with the presence of P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). These adhesion molecules were absent in the underlying media and normal endothelium.

Conclusions: These findings suggest that early leukocyte adhesion to the injured surface may be promoted by functional adhesion molecules derived from the circulation. Used in genetically modified mice, this model will be valuable for studying the role of specific molecules in mediating the arterial response to injury.



Clinical Immunology

Thyroid Amyloidosis in a Patient with Common Variable Immunodeficiency. J. Lee and C. Cunningham-Rundles. Division of Clinical Immunology, Mount Sinai School of Medicine, New York, NY.

Amyloidosis in patients with common variable immunodeficiency (CVI) is rare. There have been fewer than 20 reported cases of amyloidosis in patients with CVI or agammaglobulinemia. The pathogenesis of amyloidosis in CVI is not clear but may be due to recurrent infections triggering the deposition of amyloid A (AA) protein in the tissues. We report a 43-year-old male with recurrent pneumonia and bronchiectasis due to CVID on intravenous gammaglobulin (IVIG) replacement. He was diagnosed at the age of 8 years with low serum IgG, IgA and IgM. He was initially treated with intramuscular injections of immunoglobulins. He was switched to IVIG in 1980 but still had pneumonias, although less frequently. He was on IVIG every 3 weeks and rotating antibiotics when he presented with large, painful neck mass of 1-week duration. Computed tomography (CT) scan showed a large loculated mass in the thyroid, which was encroaching on the airway. He underwent total thyroidectomy that revealed an enlarged thyroid with amyloidosis along with focal necrosis and abscess formation. Immunohistochemical staining was positive for AA protein, suggesting that chronic lung infection and bronchiectasis may be the etiology of the amyloidosis. Since the most common mode of presentation of amyloidosis in hypogammaglobulinemic patients is with nephrotic syndrome, 24-hour urine protein measurement was done; it showed 2 gm/day proteinuria. Serum creatinine was slightly elevated to 1.6 mg/dL. The patient had normal renal ultrasound and no evidence of cardiac involvement seen on echocardiogram. To determine the systemic involvement, abdominal fat pad biopsy was done, but Congo red staining of the specimen was negative. Patient is to be started on colchicine, which may prevent further progression of his renal disease. This is the first reported case of CVI patient presenting with thyroid amyloidosis. His presentation may allow slower progression of his renal disease.

A Mouse Model of Cow Milk Hypersensitivity Induced by Oral Sensitization and Challenge. G.I. Kleiner¹, C.K. Huang², D. Serenbrisky², B. Schofield³, H. Sampson², and X.-M. Li². Divisions of ¹Clinical Immunology and ²Pediatrics, Department of Medicine, Mount Sinai School of Medicine, New York, NY; and ³Johns Hopkins University, Baltimore, MD.

Cow milk is one of the leading causes of food allergy in children. The lack of suitable animal models has hampered the development of new

therapeutic strategies for treating cow milk allergy (CMA). Utilizing cholera toxin (CT) and cow milk (CM) proteins, we developed a mouse model of IgE-mediated CM hypersensitivity. Three-week-old C3H/HeJ mice were sensitized orally with various doses of homogenized cow milk (HCM) and CT, and boosted 5 times at weekly intervals. Sera were collected weekly and CM-specific IgE, IgG1 and IgG2a antibodies were quantified by ELISA. Levels of CM-specific IgE were significantly increased at week 3 and peaked 6 weeks following initial sensitization. Mice were challenged orally with CM on week 6.

Symptoms of systemic anaphylaxis were evident within 15–30 minutes of challenge. Mice sensitized with a medium dose (1 mg/g body weight) of HCM had the highest levels of serum IgE and experienced the most severe systemic anaphylactic reactions. Plasma histamine levels increased significantly following challenge, indicating that mast cell activation was involved in the induction of anaphylaxis in this model. Intestinal permeability to casein was also found to increase. Th2 responses were likely to be responsible for the development of CM hypersensitivity in this model, since *in vitro* stimulation of spleen cells from CM-allergic mice lead to significant secretion of IL-4 and IL-5, but not IFN. These results demonstrated that under certain conditions, oral sensitization and challenge of mice can induce IgE-mediated CM allergy, which closely mimics clinical features seen in humans. This model should provide a useful tool for evaluating immunopathogenic mechanisms involved in CM allergy and for exploring novel therapeutic approaches.

The Inhibitory Receptor Complex CD94/NKG2A May Down-Regulate the Activation of IEL by gp180. L.S. Toy¹, B. Jabri-Bendelac², N. Cerf-Bensussan³, N.A. Campbell¹, and L. Mayer¹. ¹Division of Clinical Immunology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; ²Department of Microbiology, Princeton University, Princeton, NJ; and ³Department of Pediatric Gastroenterology, Hôpital Necker, Paris, France.

We have previously demonstrated that gp180, an intestinal epithelial cell (IEC) surface glycoprotein, is important in the activation of CD8+ suppressor T cells and results in the activation of CD8-associated p56lck. Furthermore, we have shown that gp180 can associate with non-classical class I restriction elements. The non-classical class I molecule HLA-E binds to the natural killer (NK) cell inhibitory receptor complex CD94/NKG2A, resulting in the inhibition of T cell activation and NK killing. Up to 30% of intestinal intraepithelial lymphocytes (IEL) express this complex. In addition, others have documented that IEL can recognize non-classical class I molecules.

Aim: In previous studies, we have shown that, in contrast to peripheral blood T cells, IEL neither proliferate nor manifest p56lck activation when co-cultured with IEC. We sought to determine whether one component of this failure to activate p56lck might occur through CD94/NKG2A.

Methods: CD94 high/NKG2A+ and CD94 low/NKG2A- clones derived from normal TCRab+ CD8+ IEL were incubated with anti-CD8 mAbs or gp180. Activation of lck was determined by lysis of T cells followed by an anti-phosphotyrosine Western blot.

Results: Unlike freshly isolated IEL, in which activation of CD8-associated p56lck is down-regulated in this system, all IEL clones could be activated (p56lck phosphorylation) with anti-CD8 mAbs. Thus in the absence of IEC, CD8 mediated signal transduction can be restored. However, when these same clones were co-cultured with gp180, p56lck phosphorylation was only noted in the CD94 low/NKG2A- cells.

Conclusions: These results may indicate a direct interaction of gp180 with the C-lectin like CD94 molecule, or alternatively, gp180 associates with a non-classical class I molecule which interacts with the CD94/NKG2A complex, activating the tyrosine phosphatases SHP-1 and SHP-2. This complex interaction may prevent T cell activation and potentially inhibit cytolytic T cell function in the epithelium.

Endocrinology

Prolongation of Thyroiditis in the Murine Post-Partum Period. M. Imaizumi¹, A. Pritsker¹, P. Unger², and T.F. Davies¹. Departments of ¹Medicine and ²Pathology, Mount Sinai School of Medicine, New York, NY.

Many human autoimmune diseases, including autoimmune thyroid disease, are affected by immune changes during pregnancy and the postpartum

tum period. Moreover, the severity of autoimmune diseases may be associated with a disparity in HLA class II antigens between mother and fetus. To investigate the influence of a disparity in HLA class II between mother and fetus on the development of thyroglobulin (Tg) induced experimental autoimmune thyroiditis (EAT), we examined the intrathyroidal histological changes of CBA/J (H-2k) female mice which were mated with BALB/c (H-2d) males. Fifty-six (56) female CBA/J mice were immunized with IV Tg (50 :g). Three hours later, they were injected with 20 :g of lipopolysaccharide (LPS). Twenty-six (26) female Tg immunized mice were mated with BALB/c males one week after the second immunization and were sacrificed in late pregnancy, 2 weeks post-partum and 5 weeks post-partum. Thyroid histology by H&E staining was graded as follows; 0.5: small focal areas of inflammatory cells; 1.0: focal collections of mononuclear cells with some follicular destruction; 2.0: diffuse infiltration of thyroid follicle involving approximately 40% or less of thyroid tissue examined; 3.0: destruction of 40% to 80% of thyroid tissue; 4.0: destruction of more than 80% of thyroid tissue. There was no statistical difference in the rate of development of thyroiditis between the non-pregnant group and late pregnancy (5 weeks after first immunization); the percentage being 50% and 60%, respectively. However, 75% of the pregnancy group maintained thyroiditis at 5 weeks post-partum (10 weeks after first immunization), compared with only 20% of the non-pregnant group ($p < 0.02$ by chi-square test). The average thyroiditis grade at 5 weeks post-partum was 0.44 in the pregnant group and 0.10 in the non-pregnant group. We concluded that the severity of EAT was prolonged during the postpartum period in this mouse model.

Evidence for CC Chemokine Receptor #5 (CCR5) Involvement in Homing of T Cells to the Thyroid Gland. M. Imaizumi¹, A. Pritsker^{1,2}, P. Unger², and T.F. Davies¹. Departments of ¹Medicine and ²Pathology, Mount Sinai School of Medicine, New York, NY.

Lymphocytic infiltration is associated with secretion of chemokines and expression of their receptors, as well as various adhesion molecules, at the sites of autoimmune disease. The CC chemokine receptor #5 (CCR5) has been described as one of the chemokine receptors which induce lymphocyte chemotaxis and may also be a marker of Th1 type (cytotoxic) T cells. To investigate the expression of CCR5 in autoimmune thyroiditis, we examined CCR5 expression by intrathyroidal lymphocytes and cultured spleen cells from thyroglobulin (Tg) induced experimental autoimmune thyroiditis (EAT) in which cytotoxic T cells are known to predominate. CBA/J female mice were immunized intravenously with 50 µg of murine Tg and 20 µg of lipopolysaccharide (LPS) at the beginning of the study, and one week later. Animals were sacrificed 5 weeks after the first immunization and control mice were injected with only LPS. Histological assessment of the mouse thyroids at week 5 showed a mean grade of 0.75. In animals in which EAT was induced, 20–40% of intrathyroidal lymphocytes expressed CCR5 as determined by immunohistochemical analysis (by antibody CKR5, Santa Cruz, CA). No CCR5 positive cells were observed in control thyroids. In contrast, spleen cells, even when stimulated *in vitro* by concanavalin A, were <5% CCR5 positive by flow cytometry. These results indicated that the intrathyroidal lymphocytic infiltrate in EAT was made up of primarily Th1 cells which expressed CCR5. We conclude that the low percentage of CCR5 positive spleen cells was highly suggestive evidence that CCR5 is the thyroid lymphocyte homing molecule.

An Unusual Variant of the Mouse TSH-Receptor Lacking the First Transmembrane Segment and Intracellular Loop. C. He, P. Graves, and T. Davies. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

We have recently employed recombinant mouse TSHR ectodomain as an immunogen for the induction of murine Graves' disease (GD). The immune response, however, produced TSHR blocking rather than stimulating autoantibodies (Clin Exp Immunol 1998, 113:111). In order to employ intact, full-length, mouse TSHR to provide a more appropriate immunogen, we set about cloning the mouse TSHR. Northern analysis using a human TSHR probe indicated the presence of multiple mTSHR mRNA splicing variants, including 4.3 Kb, 3.5 Kb, 2.9 Kb and 1.0 Kb. Using CBA/J thyroid mRNA we observed that PCR-amplified mTSHRs contained the expected variety of product lengths. Cloning and sequencing, likewise, revealed both full-length clones and clones which lacked portions of the cDNA. One of the most unusual clones lacked the coding

region for the first transmembrane segment and the first intracellular loop. Using specific primers for this receptor variant, we confirmed the presence of this variant in normal mouse thyroid mRNA, and semi-quantitative analysis suggested that the variant made up ~ 10% of mTSHR transcripts. The cDNA was subcloned into the pCDNA expression vector under the CMV promoter and used to establish stable CHO transfectants. The resulting cells showed no TSHR signal transduction as evidenced by the lack of cyclic AMP generation. In conclusion, the normal mouse thyroid cell contains many different TSHR transcripts, including variants which fail to effect signal transfer. Whether normal and abnormal receptor structures interact or not in the control of thyroid function deserves exploration.

Lymphocytic Hypophysitis: A Case Report and Review of the Literature. J. Najjar, C. Asta, and R. Rizzo. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Lymphocytic hypophysitis (LH) is a rare autoimmune pituitary disorder characterized by pituitary enlargement and insufficiency. One hundred twenty-eight cases, many without histological evidence, have been reported since 1962, occurring predominantly in women during late pregnancy or the postpartum period.

We describe a case of a 19-year-old female who presented, 2 months after a spontaneous vaginal delivery, with headaches and bilateral visual field deficits. On physical examination, pertinent findings included bilateral dilated pupils, absent pupillary reflex in the left eye, blindness of the left eye and restricted visual field to only the upper nasal quadrant of the right eye. Neuroimaging with computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a large, homogeneously enhancing pituitary tumor. The patient underwent transeptal transphenoidal subtotal resection of the mass. The pathology report confirmed LH. The patient's vision improved dramatically postoperatively, but the patient developed diabetes insipidus.

The epidemiology, pathogenesis, clinical presentation and natural history of LH are discussed, as well as the importance of including LH in the differential diagnosis of females with pituitary enlargement presenting in the peripartum period. A review of the management of this entity with corticosteroid therapy versus surgical treatment will be presented.

Prostaglandin E₂ Upregulates Vascular Endothelial Growth Factor Expression in Prostate Cancer Cells. X.H. Liu, A. Kirschenbaum, S. Yao, J.F. Holland, and A.C. Levine. Departments of Medicine and Urology, Mount Sinai School of Medicine, New York, NY.

We have previously demonstrated that androgens upregulate vascular endothelial growth factor (VEGF) expression in human prostate cells. Most prostate cancers become androgen-insensitive, and we postulate that hypoxic upregulation of VEGF *in vivo* plays an important role in tumor progression. We further hypothesize that hypoxic effects on VEGF expression are mediated by cyclooxygenase-2 (COX-2), and one of its major derived products, prostaglandin E₂ (PGE₂). PC-3 ML human prostate cancer cells (a highly invasive subline of androgen-insensitive PC-3 cells) were treated with 100 µM cobalt chloride (to induce hypoxia) ± NS398 (a selective COX-2 inhibitor) and/or PGE₂, and the effects on VEGF and COX-2 mRNA and protein expression measured by Northern blot, Western blot and ELISA. Hypoxia upregulated both COX-2 (5 fold induction beginning at 16h) and VEGF (7-fold induction beginning at 20h) protein expression. Hypoxia also resulted in a 4-fold increase in PGE₂ secretion at 48h. The hypoxia-driven increases in VEGF mRNA and protein expression were blocked in a dose-dependent fashion by the selective COX-2 inhibitor, NS398 (10–100 µM) for 3 days. Further addition of the COX-2 product, PGE₂, completely restored the VEGF response to hypoxia in the presence of COX-2 inhibition. These data indicate that COX-2 and its major derived product PGE₂ are mediators of hypoxic effects on VEGF expression. COX-2 inhibitors may serve as antiangiogenic therapy for androgen-insensitive human prostate cancers.

Neurological, Ethnic, and Gender Considerations in the Oral Glucose Tolerance of Persons with Chronic Immobilization. W. Bauman^{1,2}, R. Adkins³, A. Spungen^{1,2}, B. Kemp³, and R. Waters³. ¹Mount Sinai School of Medicine, New York, NY; ²Bronx VA Medical Center, Bronx, NY; and ³Rancho Los Amigos Medical Center, Downey, CA.

In the general population, abnormal oral carbohydrate tolerance is associated with increased risk for coronary heart disease. A few reports have demonstrated that persons with spinal cord injury (SCI) have abnormal glucose tolerance, hyperinsulinemia and insulin resistance.

Aims: This study addressed the overall effects of SCI on carbohydrate metabolism in subgroups of subjects categorized by level of lesion, gender and ethnicity.

Methods: A standard 75 g oral glucose tolerance test was performed on 201 subjects with SCI (169 male and 32 female; 54 white, 28 black, 114 Latino, and 5 Asian/American Indian) who were outpatients being seen for routine annual physical examination at Rancho Los Amigos Medical Center.

Results: The results were reported as mean \pm SEM. The age of the group was 39.1 ± 0.77 years, duration of injury, 14.0 ± 0.65 years, and body mass index (BMI), 25.3 ± 0.43 kg/m². There were no significant differences for any of the aforementioned demographic determinations between the subgroups of neurological deficit within the SCI sample (complete tetraplegia, incomplete tetraplegia, complete paraplegia, incomplete paraplegia). For the total group, subjects with complete tetraplegia had significantly higher plasma glucose values, at 60, 90, and 120 minutes, and plasma insulin levels, at 90 and 120 minutes, than the other three subgroups of neurological deficit, and had a greater frequency of disorders of glucose tolerance (73% vs. 44%, 24% and 31%, respectively; $X^2 = 36.9$, $p < 0.0001$). Males and females had similar serum glucose concentrations, but the plasma insulin levels were significantly higher in the males, at 30, 60, and 90 minutes. By ethnicity, there was no significant difference in the serum glucose or plasma insulin response.

Conclusion: Subjects who were the most neurologically impaired exhibited the worst oral carbohydrate tolerance. Furthermore, for the same BMI, men were more insulin resistant than women were.

Treatment with Calerol and Providine Supplemental Calcium Reduces Serum PTH Levels in Persons with SCI. W. Bauman^{1,2} and A. Spungen¹. ¹Mount Sinai School of Medicine, New York, NY, and ²Bronx VA Medical Center, Bronx, NY.

Spinal cord injury (SCI) results in disuse osteoporosis. Further loss of bone secondary to readily reversible metabolic conditions should be avoided. Persons with SCI are at an increased risk of being vitamin D deficient (Bauman, Metabolism 1995) due to several predisposing factors, including avoidance of milk, reduced sunlight exposure, and medications that accelerate hepatic metabolism. In a prior study, daily intake of vitamin D (800 IU) for two weeks failed to significantly change the vitamin D level (unpublished observation).

Aims: To study the effect of 2 weeks of therapy with 25 hydroxyvitamin D [25(OH)D; Calderol 50 g BIW] and calcium supplementation (1.5 g elemental calcium/day) in 10 subjects with vitamin D deficiency (i.e., levels less than 16 ng/mL).

Methods: Serum was drawn for 25(OH)D and intact immunoreactive parathyroid hormone (iPTH) (Nichols Institute) at baseline and on days 1 and 14 of therapy.

Results: The results are expressed as mean \pm SD. The mean age of the subjects was 53 ± 15 years and the duration of injury, 27 ± 14 years. From baseline to day 14, the mean serum calcium concentration increased from 8.9 ± 0.4 to 9.2 ± 0.5 mg/dL, n.s., and the urinary calcium excretion increased from 103 ± 81 to 184 ± 145 mg/24 hr, $p < 0.01$. The mean serum 25(OH)D levels increased on therapy: 8.7 ± 2.1 to 12.5 ± 3.3 to 14.7 ± 3.6 ng/mL, $p < 0.0005$. However, the therapy prescribed was insufficient to raise the vitamin D levels into the normal range in 8 of 10 subjects. Of note, mean serum iPTH levels decreased while on therapy: 35 ± 26 to 23 ± 14 to 17 ± 12 pg/mL, $p < 0.01$.

Conclusion: In persons with SCI, replacement of 25(OH)D and supplementation with oral calcium will reduce the secondary increase in iPTH levels, which may be expected to decrease skeletal turnover and bone loss in a skeleton already regionally osteoporotic.

Analysis of the BTK Gene on Chromosome X as a Candidate Gene in Graves' Disease. R. Villanueva¹, Y. Tomer¹, S. Tucci¹, D.A. Greenberg², E.S. Concepcion¹, and T.F. Davies¹. ¹Division of Endocrinology and Metabolism, Department of Medicine, and ²Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Graves' disease (GD) develops as a result of genetic susceptibility and environmental triggers. The disproportionately higher prevalence in

women suggests mechanisms related to pregnancy or susceptibility genes on the X-chromosome. Since women have two X chromosomes, they are twice as likely to inherit an X-chromosome susceptibility gene. We recently screened the X-chromosome using a set of polymorphic microsatellite markers. In the region Xq21.33-22, we found a locus — DXS8020 (designated GD-3) — which was linked to GD with a maximum LOD score (MLS) of 2.5. Among the genes mapped to this region is the Bruton's tyrosine kinase (BTK) gene which encodes for a tyrosine kinase protein important in B cell ontogeny. Inactivating mutations of the BTK gene cause X-linked agammaglobulinemia. It is also possible that mutations of BTK may influence susceptibility to autoimmunity. Indeed, the mouse gene homologous to BTK (*xid*) has been shown to modulate the expression of collagen autoimmunity in susceptible mouse strains. Therefore, we investigated the BTK gene as a candidate susceptibility gene for GD. We performed an association study comparing the frequencies of two single stranded conformation polymorphism (SSCP) alleles of the BTK gene resulting from a single base polymorphism (C or A) at position 2228. Seventy (70) Caucasian patients with GD (60 females and 10 males) and 67 healthy Caucasian controls (57 females and 10 males) were studied. The region containing the C/A polymorphism was amplified using P-32-labeled alpha-dCTP. The fragments were separated by polyacrylamide gel electrophoresis (PAGE) according to standard protocols. Twenty-four percent (24%) of the samples were analyzed by direct sequencing using an ABI 310 to confirm findings on the SSCP assays. In all cases complete concordance was obtained between the SSCP analysis and the direct sequencing results. Forty-eight percent (48%) of the patients and 49% of the controls had the C allele demonstrating no association between the BTK SSCP alleles and GD ($p = 0.89$). We conclude that the BTK gene is unlikely to be the GD susceptibility gene on Xq21.33-22.

Relationship Between the Appearance of a Novel Prostacyclin Receptor Antibody and Duration of Spinal Cord Injury. N. Kahn, Z. Jingbo, A. Sinha, and W. Bauman. ¹Mount Sinai School of Medicine, NY; and ²Bronx VA Medical Center, Bronx, NY.

Coronary artery disease (CAD) is accelerated in subjects with chronic spinal cord injury (SCI). We have shown a novel circulating IgG in SCI that specifically blocks the high-affinity PGI₂ receptors on the platelet surface without affecting the low-affinity PGI₂ receptors.

Aims: In this study we determined the time required to develop measurable amounts of the IgG to the high-affinity prostacyclin receptor as a function of duration of SCI.

Methods: Blood samples were collected 1, 3, 5, 10 and >10 (15 \pm 4) years after SCI (n = 36). Plasma samples (50 g) were analyzed by polyacrylamide gel electrophoresis (PAGE) followed by densitometry.

Results: The optical density (OD) of the IgG (47,000 K) at 1 year was 1.65 ± 0.08 versus the controls; 1.33 ± 0.04 ($p < 0.01$). A progressive increase of antibody levels for the first 5 years after injury was observed in both paraplegia (n = 25) and quadriplegia (n = 11). The level of antibody appeared to plateau after 5 years of SCI; after 5, 6–10 years and >10 years of injury the OD's were 1.85 ± 0.12 , 1.82 ± 0.13 and 1.84 ± 0.15 , respectively. The increase of IgG was directly related to the decrease of binding of prostacyclin to its high-affinity receptors in SCI platelets. Scatchard analysis of ³H-PGE₁ binding showed a significant loss of high-affinity receptor numbers ($n_1 = 43 \pm 12$ vs. $n_1 = 172 \pm 25$ sites/platelet, $p < 0.001$) with no significant change in receptor affinity ($kd_1 = 6.1 \pm 2.15$ vs. $kd_1 = 8.1 \pm 2.7$ nM). The level of the high-affinity PGI₂ receptor antibody observed in individuals with SCI was directly associated with the duration of injury, not the level of injury.

Conclusion: An early, aggressive approach aimed at preventing elevations in high-affinity PGI₂ receptor IgG may be advantageous in reducing the progression of vascular diseases in SCI subjects and hence the atherogenic potential of the SCI platelets.

Synaptophysin Immunoreactive Contacts onto GnRH Cells in Hypogonadal Mice Grafted with Normal Preoptic Area: Correlation to Functional Recovery. G. Rajendren and M.J. Gibson. Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

The integration of gonadotrophin-releasing hormone (GnRH) neurons grafted into the third cerebral ventricle (3V) of hypogonadal (HPG) female mice was investigated. HPG females grafted in the 3V with preoptic area

(POA) obtained from normal fetal mice were assessed for gonadal development. HPG/POA mice with signs of gonadal development ($n = 4$) or those without any noticeable gonadal activation ($n = 4$) were primed with estrogen and progesterone and were paired with sexually active males. Two hours after the mating tests, the brains were fixed and were processed for triple immunohistochemical staining for Fos, GnRH, and synaptophysin. Fos immunoreactivity was observed in the GnRH cells in 3 out of 4 HPG/POA mice with gonadal development, whereas GnRH cells in the non-responders did not exhibit Fos in their nuclei. The number of synaptophysin immunoreactive contacts onto GnRH cells in HPG/POA mice with gonadal development was 6.47 ± 1.05 (mean \pm sem) vs. 3.53 ± 0.56 in HPG/POA mice showing no signs of activation of the reproductive axis. The difference was statistically significant ($p < 0.05$). The results suggest that activation of reproductive functions in HPG/POA mice may be dependent on synaptic inputs to the transplanted GnRH cells.

The Effect of Anabolic Steroid Therapy on Healing of Long-Standing Pressure Ulcers: Case Reports of Nine Individuals with SCI. A. Spungen¹, M. Rasul², K. Koehler², A. Cytryn², and W. Bauman^{1,2}. ¹Mount Sinai School of Medicine, New York, NY; and ²Bronx VA Medical Center, Bronx, NY.

Non-healing pressure ulcers are a frequent and debilitating problem for individuals with spinal cord injury (SCI). Anabolic steroid therapy combined with increased protein intake has been successful in promoting weight gain, reversing catabolism and increasing the rate of skin closure from burns.

Aims: To evaluate the effect of oxandrolone 20 mg/day and glutamine 20 g/day use in the treatment and healing time of non-healing stage III pressure ulcers (4x4 cm in surface area) in nine individuals with SCI.

Methods: Nine patients were selected based on having at least one of the following two criteria: severity of the wound (full thickness through fascia into muscle, tendon and/or bone) and duration of non-healing status (self-reported or hospitalized documentation of no change or worsening status of greater than 2 months). Patients were administered: oxandrolone 20 mg/day (BTG Corp, Iselin, NJ) and glutamine 20 g/day dissolved in applesauce or juice (Cambridge Nutraceuticals, Boston, MA). Liver function tests and lipid profile analyses were performed by routine methods in the Bronx VA Medical Center Clinical Chemistry Laboratory.

Results: After treatment with oxandrolone and glutamine: two subjects healed in 12 months, one healed in 6 months, two healed in 4 months, three healed in 3 months, and one patient's progress was unknown due to a self-requested discharge from the hospital. Mild elevation in liver function tests (ALT and AST) was observed.

Conclusion: Prior attempts to promote wound healing by topical pharmacological interventions have had marginal effects. Although clinical case studies have limited usefulness for determining a drug effect, these initial observations have been promising. Our group has planned a double-blind placebo trial to test the efficacy of treatment with oxandrolone in individuals with SCI and non-healing pressure ulcers.

New Insights into the Genetic Susceptibility to Autoimmune Thyroid Diseases. Y. Tomer¹, G. Barbesino¹, D.A. Greenberg², E. Concepcion¹, and T.F. Davies¹. ¹Division of Endocrinology and Metabolism, Department of Medicine and ²Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The autoimmune thyroid diseases (AITDs) include two related disorders, Graves' disease (GD) and Hashimoto's thyroiditis (HT), in which perturbations of immune regulation result in immune reaction to the thyroid gland. In Graves' disease, the autoimmune process results in the production of thyroid-stimulating antibodies and leads to hyperthyroidism, while in Hashimoto's thyroiditis the end result is destruction of thyroid cells and hypothyroidism. The AITDs appear to develop as a result of a complex interaction between inherited predisposing genes and environmentally encountered triggering agents. Even though GD and HT have different clinical presentations, it is likely that similar mechanisms lead to the immune attack on the thyroid in both diseases, since they appear in the same families. Thus, it has been postulated that a similar genetic contribution is involved in their development. In order to identify the susceptibility genes for GD and HT, and to examine whether they are unique to each disease or common to both diseases, we performed a whole genome linkage study in patients with AITD. We studied a data set of 56 multiplex, multi-

generational AITD families (354 individuals), using highly polymorphic and densely spaced microsatellite markers (inter-marker distance < 10 cM). Linkage analysis was performed using two-point and multipoint parametric methods (classical LOD score analysis). We identified 5 loci which were linked with AITD. Three loci were linked with GD but not with HT and were termed GD-1, GD-2, and GD-3. One locus was linked with HT only in a subgroup of the families (HT-1), and one locus was linked with both GD and HT (AITD-1). We found no linkage to the HLA and CTLA-4 regions which previously were reported to be weakly associated with GD. These results demonstrate that unique and common genes confer susceptibility to GD and HT. It is possible that the wide range of clinical phenotypes of HT caused the lack of identification of more susceptibility loci for HT.

Gastroenterology

Intravenous Conjugated Estrogen for the Control of Recurrent Gastrointestinal Bleeding from Angiodysplasia in a Patient with Chronic Renal Failure (CRF). E.Y. Baghal, N.J. Dababneh, G. Pavlou, and W.J. Baddoura. Division of Gastroenterology, St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University School of Graduate Medical Education, South Orange, NJ.

Introduction: Gastrointestinal (GI) bleeding from angiodysplasia associated with chronic renal failure is not uncommon. Management of such cases can be quite challenging and problematic, as demonstrated in the following report.

Case Report: A 52-year-old male with a history of CRF and hypertension presented with a one-week history of tarry stools not associated with pain or diarrhea. The patient had upper and lower endoscopic examinations, including small bowel enteroscopy, which failed to reveal a definite source of bleeding. Angiogram was negative but bleeding scan showed trace uptake of radionuclide in the proximal duodenum. The patient continued to bleed intermittently over a period of approximately three months, during which he received a total of 85 units of packed red blood cells in addition to other blood products for correction of prolonged bleeding time. On subsequent examinations, several bleeding angiodysplastic lesions were identified in the duodenum, and despite endoscopic electrocoagulation therapy, hemostasis could not be achieved. Combined oral estrogen and progesterone therapy also failed to stop bleeding. As a last resort, conjugated estrogen was administered intravenously at a dose of 0.6 mg/kg/day for five consecutive days. The hemogram remained stable with no further bleeding over the next three months, at which time the patient expired of unrelated causes.

Conclusion: Conjugated estrogen given intravenously can be effective in the control of recurrent GI bleeding in patients with chronic renal failure. The exact mechanism of action remains undetermined, though beneficial effect on platelet function has been demonstrated in the past.

The Role of Nitric Oxide in Cerulein Pancreatitis: Studies in iNOS KO Mice. M.A. Korsten¹ and J.J. Ma². ¹Bronx VA Medical Center, Bronx, NY; and ²Beijing Medical University, Beijing, People's Republic of China.

Microcirculatory alterations appear to play an important role in the pathogenesis of cerulein pancreatitis (CP). Recent studies suggest that these changes in the microcirculation may be mediated by nitric oxide (NO), a potent vasodilating substance. Genetically engineered mice lacking the iNOS (inducible nitric oxide synthase) gene now permit a direct assessment of the importance of NO production in this rodent model of pancreatitis.

Methods: 6–8 week old male mice (C57BL/6 and iNOS KO) were administered cerulein (Sigma) by IP injection (at doses of 0, 10, 30, 60 and 90 g/kg BW) at hourly intervals for 7 hours and sacrificed 24 hours after the last dose. Pancreatic weight (mg/g BW), plasma nitrite (mM), plasma amylase (U/l) and myeloperoxidase activity (MPO) were assessed as measures of pancreatic injury.

Results: In genetically intact C57BL/6 mice ($n = 6$ in each group), we observed a significant (using ANOVA) dose-dependent increase in pancreatic wt. (C0: 7.4 ± 0.29 ; C10: 8.2 ± 0.34 ; C30: 8.9 ± 0.51 ; C60: 10.5 ± 0.58 ; C90: 11.1 ± 0.76), plasma nitrite (C0: 4.6 ± 0.4 ; C10: 5.2 ± 0.6 ; C30: 6.0 ± 0.7 ; C90: 7.6 ± 0.8) and plasma amylase (C0: 63.6 ± 5.4 ; C10: 72.1 ± 6.2 ; C30: 94.3 ± 7.1 ; C60: 126.5 ± 8.4 ; C90: 148.2 ± 9.6) after cerulein. Based on this initial data, a cerulein dose of 60 g/kg was used for

studies in which the pancreatic response to cerulein was compared in normal and iNOS KO mice. Pancreatic wt. was greater (12.8 ± 0.74 vs. 10.5 ± 0.58 , $p < 0.05$), plasma nitrite was lower (4.5 ± 0.5 vs. 6.8 ± 0.6 , $p < 0.05$) and plasma amylase was higher (162.5 ± 9.7 vs. 126.5 ± 8.4 , $p < 0.02$) in iNOS KO mice as compared to C57bl/6 mice. Finally, the level of MPO was enhanced in iNOS KO mice (26 ± 2.8 vs. 18 ± 2.4 , $p < 0.05$). These differences were attenuated by the administration of isosorbide dinitrate to iNOS KO mice.

Conclusion: NO production plays a protective role in CP, in part, by preventing the accumulation of leukocytes. To the extent that this rat model resembles events in early human pancreatitis, measures that increase NO levels may have clinical value.

Geriatrics

Knowledge and Attitudes of Geriatricians Regarding Dementia Patients Who Drive and Are a Danger to Others on the Road: A National Survey of Geriatricians. S. Gerges, G. Cable, M. Reisner, and V. Thirumavalavan. Mount Sinai School of Medicine, New York, NY; and The Jersey City Medical Center, Jersey City, NJ.

Objectives: To determine geriatricians' attitudes and knowledge about the steps to take with their dementia patients who drive and may be dangerous on the road.

Design: A survey sample of geriatricians in the United States.

Results: Nearly 3 of 10 geriatricians (28.7%; 95% Confidence Interval [CI], 24.3% to 33.1%) do not know what steps to take in their state to report dementia patients who drive and may be a danger to others on the road. Most geriatricians in all states (74.8%; 95% CI, 70.5% to 79.1%) agreed that physicians are responsible for reporting dementia patients who drive and may be a danger to others. Similarly, over 90% (92.7%; 95% CI, 90.1% to 95.3%) of geriatricians said that they would contact the appropriate authority to recommend that patient driving privileges be revoked. Moreover, geriatricians would be willing to recommend revocation over the objections of patients (86.9%; CI, 83.6% to 90.2%), though a smaller percentage would recommend revocation of driving privileges over the objections of the patient's family (74.5%; 95% CI, 70.5% to 78.8%).

Comment: Although large majorities of geriatricians believe they are responsible for reporting dementia patients who drive, and will act to have driving privileges revoked, only a minority of geriatricians know what steps to take to report patients who drive.

Hematology

GPIIb/IIIa-Dependent Platelet-Platelet Interactions Come Before Rather than After Platelet Adhesion and Spreading for Most Platelets Depositing on Collagen under Static Conditions. D. Patel, H. Vaananen, C. Boger, and B.S. Collier. Mount Sinai School of Medicine, New York, NY.

The traditional description of platelet interactions with collagen-coated surfaces is that platelets (P) first adhere and spread to form a monolayer, and then this first layer of P recruits additional layers of P to commence platelet thrombus formation.

Objective: To study this phenomenon of platelet-platelet interactions and the role GP IIb/IIIa has in this process.

Methods: We developed a microchamber allowing concurrent time-lapse recording of 12 separate samples using phase contrast microscopy. The chamber consists of a silicone elastomer-coated glass slide, a silicone elastomer gasket, and a #1.5 coverslip coated with polystyrene. The microscope system consists of an inverted microscope, a 100 X 1.4 N.A. objective, a video camera, and a mechanical stage under computer control. Images were obtained automatically for 2 hrs from each channel at 2.4 min intervals and stored on a video disk recorder. Each acquired image was an average of 2 video frames from the camera. Chambers were coated with purified type 1 lathyritic rat skin collagen at 33 g/mL in 0.05% HAc, blocked with 0.5% BSA, and washed with modified Tyrode's buffer (MT) containing Mg^{++} . Human P were prepared from ACD blood either by gel filtration in Tris-saline (T-S), pH 7.4, or by combining PRP with platelet-rich buffer obtained from buffy coats using MT. P in MT or T-S with Mg^{++} were added to the chambers, either with or without pretreatment with mAb 7E3 (anti-GPIIb/IIIa + v3) at 10 g/mL for 15 min at 22°C.

Results: The results with untreated P differed from the traditional description, in that soon after the initial adhesion of relatively few P, additional P appeared to be recruited via their filopodia to the adherent P, and then the recruited P went on to: (1) adhere and spread nearby, (2) continue to interact laterally and vertically with the recruiting platelet, and in some cases (3) recruit additional P that then went on to adhere and spread. In the presence of mAb 7E3, platelet-to-platelet recruitment was nearly eliminated, but a monolayer formed nonetheless by direct adhesion to collagen, although with little evidence of lateral or vertical cohesion between P.

Conclusion: These data indicate that, at least under static conditions, platelet adhesion, spreading and recruitment on collagen are not rigidly sequential processes, but rather concerted processes; moreover, although GPIIb/IIIa is not required for P to deposit on collagen, the deposition process is fundamentally different in the absence of functional GPIIb/IIIa receptors.

The AML/ETO Fusion Protein Modulates the Transcriptional Effects of Histone Deacetylases, PLZF and Other Corepressor Proteins. A. Melnick¹, J.J. Westendorf¹, S. Arai¹, B. Lutterbach¹, H.J. Ball¹, A. Polinger¹, S.W. Hiebert², and J.D. Licht¹. ¹Mount Sinai School of Medicine, New York, NY; and ²Vanderbilt University School of Medicine, Nashville, TN.

The promyelocytic leukemia zinc finger (PLZF) protein is a transcriptional factor disrupted in a subset of patients with acute promyelocytic leukemia (APL). PLZF has been demonstrated to interact with a transcriptional repression complex which includes the nuclear receptor co-repressors N-CoR and SMRT, Sin3-A and histone deacetylases (HDACs). ETO, involved in the (8; 21) AML-M2 translocation, also associates with the same transcriptional repression complex. These commonalities led us to ask whether ETO and PLZF associate together, and if this interaction has functional significance. Using the yeast-two-hybrid system and mammalian cell co-immunoprecipitation assays and immunofluorescence assays, we demonstrated for the first time that these two proteins do interact. This occurred both for overexpressed and endogenous proteins. Furthermore, we found that ETO is able to enhance the ability of PLZF to repress transcription. This effect was further increased when co-repressors and HDACs were titrated into these reactions. The interaction was mapped to the N-terminal region of ETO and is not dependent on the PLZF POZ/BTB repression domain. We conclude that ETO is a co-repressor for PLZF repression, by virtue of its ability to recruit a transcriptional repression complex which depends at least in part on HDAC chromatin condensation. This is further supported by the fact that HDAC inhibitors abrogated the combined transcriptional repression of PLZF and ETO. We then wished to know if the AML/ETO fusion protein, product of the t(8;21) translocation, could disrupt ETO and PLZF functions. We found that: (1) AML/ETO is able to partially antagonize transcriptional repression mediated by PLZF; (2) AML/ETO completely abrogates the cooperative effect of PLZF and ETO; (3) AML/ETO is able to block the transcriptional cooperation between PLZF and other co-repressors such as N-CoR and SMRT; (4) AML/ETO is able to antagonize transcriptional repression mediated by HDACs 1, 2 and 3; and (5) AML/ETO can antagonize the transcriptional repression mediated by the aberrant PLZF/RAR fusion partner on its binding sites. Thus, we conclude that AML/ETO behaves as a dominant negative factor, not only for ETO but for other myeloid specific transcriptional regulators. This dysregulation suggests a common pathway of leukemogenesis in several myeloid leukemias.

The HMG Domain Protein SSRP1 is a Cofactor in Transcriptional Activation. P.J. Hayes, D. Dias, M.A. Dyer, and M.H. Baron. Divisions of Hematology and Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Globin gene switching in humans is a process in which embryonic, fetal, or adult globin genes are sequentially activated and then silenced in erythroid cells at distinct stages of development. We have focused on the earliest-expressed human b-like globin gene, ϵ , and have previously shown that activation of the gene requires the cooperation of a collection of positive and negative regulatory elements termed PREs and NREs, respectively. PRE II synergizes with at least two other elements, PRE V and PRE I, to activate a minimal promoter. Its activity requires the binding of a nuclear factor of ~85–90 kDa, termed PREIIBF, that specifically inter-

acts with a novel 19 bp region within PRE II. Nuclear extracts prepared from adult erythroid cells contain a PRE II binding activity that exhibits faster mobility in electrophoretic mobility shift assays. A number of biochemical and molecular criteria suggest that embryonic and adult forms of the two proteins are very similar. The distinct forms of PREIIBF are expressed from a single gene, do not appear to be translated from alternatively spliced transcripts, but may result from differential post-translational modifications such as phosphorylation, proteolysis, and/or glycosylation. PREIIBF was extensively purified from a human erythroid cell line and shown to introduce a bend into its target PRE II site. We have previously proposed that PREIIBF acts as an architectural transcription factor to bring together distantly bound proteins upstream of the human ϵ -globin gene in a process that might involve DNA bending and/or looping. cDNA expression cloning followed by biochemical and immunological characterization revealed that PREIIBF is the HMG domain SSRP1. We have shown that SSRP1/PREIIBF lacks a classical activation domain. Therefore, at least in the context of non-erythroid cells, SSRP1/PREIIBF does not function as a classical activator. Yet, the amino-terminal two-thirds of the protein is very highly conserved from yeast to humans. On the hypothesis that one function of this domain may be to interact with and recruit other proteins to the DNA, we have isolated several potential SSRP1 partners in erythroid cells using a yeast two-hybrid screen. Recently we have shown that SSRP1 stimulates both DNA binding and transcriptional activation by the Serum Response Factor (SRF) transcription factor (Spencer, MHB and Olson, 1999 JBC 274:15686). It seems likely that SSRP1/PREIIBF functions at least in part through interactions with other proteins, perhaps through recruitment of proteins that contain activation domains (which might function in an erythroid-specific manner) or by promoting higher-order assemblies of proteins, thereby promoting interactions with the basic transcriptional machinery.

***Development of a Murine Endothelial Cell Line with Multilineage Potential Derived from Adult Murine Bone Marrow.** I.S. Meeus, R.S. Weinberg, and G.F. Atweh. Division of Hematology, Mount Sinai School of Medicine, New York, NY.

In the course of performing gene transfer experiments, we observed the development of an unusual lymphoproliferative disease in a set of 5 W/W^v mice. These mice were previously transplanted with C57BL/6J bone marrow that was plated *ex vivo* in Dexter-type, long-term bone marrow culture and transduced with an ecotropic murine moloney leukemia retroviral construct carrying the human-globin gene. The disease first manifested 4 months after transplantation as massive hepatosplenomegaly with severe itching. One of the 5 mice died spontaneously and was found to have a malignant lymphoma (with features of plasmacytoid differentiation) that infiltrated the liver and spleen. The other four animals were sacrificed as they became moribund, and their bone marrows were harvested. Bone marrow cells from these mice were plated *in vitro* in the presence of erythropoietin and developed into a factor-independent cell line (DC2) that had striking endothelial characteristics. The cell line grew in culture as a mixture of adherent and non-adherent cells. The non-adherent cells showed morphological features typical of plasma cells. The attached cells had a tendency to line up in long highway-like structures that extended from one end of the tissue culture plate to another. When the DC2 cells were plated in Matrigel[®] (a semisolid medium rich in extracellular matrix proteins), they gave rise to branching tubular structures that resembled blood vessels. When the cells were maintained in culture until they reached confluence and arrested their growth, some cells in the adherent layer accumulated cytoplasmic lipid-rich vacuoles typical of adipocytes. The same spectrum of morphological features was seen in multiple clonal cell lines that were isolated from the primary cell line by limiting dilution. Cell surface phenotypic analysis showed positive staining for Flk-1, also known as murine VEGF-2 receptor, (endothelial marker), Tie-2 (endothelial marker), CD34 (endothelial/hematopoietic marker) and CD31 (endothelial marker). The cells were also positive by flow cytometry for the myeloid marker CD45 (5.7%), CD34 (84%), the endothelial/megakaryocytic marker CD61 (15%), the hematopoietic marker CD38 (7%) and the B-cell marker B220 (3.3%). We believe that the bone marrow cell that gave rise to this established cell line represents a primitive cell capable of differentiation along several distinct lineages that include endothelial, lymphoid, myeloid and adipocytic lineages. The potential for this cell line to contribute to vasculogenesis and hematopoiesis *in vivo* is currently being tested. This cell line may provide unique opportunities to clarify the developmental lineage of the different cell types that constitute

the adult bone marrow. It may also serve as a valuable tool in the investigation of the molecular events that underlie lineage commitment and differentiation of endothelial and hematopoietic cells.

Binding of Complement Component C1q to β_2 GPI Antibodies from Patients with Antiphospholipid Syndrome. M. Odorcuk, L.B. Keil, and V.A. DeBari. Laboratory of Experimental Medicine, Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Antibodies to β_2 GPI and other phospholipid-binding proteins are associated with and may contribute to the pathogenesis of antiphospholipid syndrome (APS). Several mechanisms have been proposed whereby the β_2 GPI-anti- β_2 GPI reaction would lead to the thrombotic state characteristic of APS. We are interested in exploring whether complement activation by these complexes contributes to the physiology of APS.

Objective: To determine if anti- β_2 GPI reactive with surface-bound β_2 GPI can bind C1q, i.e., to determine whether surface-bound β_2 GPI-anti- β_2 GPI immune complexes can initiate the classical pathway of complement activation.

Methods: β_2 GPI was bound to chemically activated microtiter plates which had previously been shown to promote anti- β_2 GPI reactivity with bound β_2 GPI. Wells with surface-bound β_2 GPI (capped with bovine serum albumen) were then reacted with complement-inactivated (C_{in}) sera from patients (pts) or with C_{in} control sera. Following removal of unbound serum components, the wells were incubated with biotinylated C1q and probed with peroxidase-conjugated streptavidin. Bound C1q was detected at 450 nm using tetramethyl benzidine/peroxidase as a substrate system and expressed as Absorbance units (Abs).

Results: We identified 17 pts with elevated anti- β_2 GPI: 4 pts with IgG only, 4 with IgM only, 1 with IgA only, 1 with IgG and IgA, 6 with IgG and IgM, and 1 with IgG, IgA and IgM. C1q binding from 15 normal controls (con) was 0.05 ± 0.03 (SD). Of the APS pts, 13/17 (76%) had Abs > 5 SD above con. The 4 pts with C1q Abs within normal limits had, respectively, IgM only (2), IgA only (1), and both IgG and IgM (1). Statistical analyses (ANOVA followed by Neuman-Keuls) suggest differences IgG and IgG + IgM groups compared to con (ANOVA: $p < 0.0001$; Neuman-Keuls: con vs. IgG, $p < 0.05$; con vs. IgG + IgM, $p < 0.001$).

Conclusions: Anti- β_2 GPI from APS appear to have a variable degree of C1q affinity. Although this is most likely a function of anti- β_2 GPI Ig isotype and titer, those patients with strong C1q binding responses are likely to have an inflammatory component to their disease processes.

Properties of the Hololipoprotein Complex Formed from β_2 glycoprotein I and Dicaproyl Phosphatidylserine. J.D. Kohles^{1,2}, M. Petersheim², and V.A. DeBari¹. ¹Laboratory of Experimental Medicine, Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ; and ²Department of Chemistry, Seton Hall University, South Orange, NJ.

Several phospholipid (PL) binding proteins have been implicated as the targets for autoantibodies from patients with antiphospholipid syndrome (APS) including β_2 glycoprotein I (β_2 GPI), a 54 kDa glycoprotein consisting of five "sushi" domains. Within the fifth domain is a region from cys 281-cys 288 which contains 4 lys residues which can bind anionic PL.

Objective: To clarify the role of the lipid-binding site in the presentation of the autoepitope of β_2 GPI by generating a hololipoprotein in solution, thus segregating the surface-binding requirement from the chemical alteration of the apoprotein by lipid.

Experimental Approach: We describe our studies of the holoprotein generated by reacting β_2 GPI with dicaproyl phosphatidylserine (DCPS).

Results: The formation of the β_2 GPI-DCPS complex is accompanied by inhibition of β_2 GPI binding to PL-coated (dimyristoyl phosphatidic acid, 80%/dimyristoyl phosphatidyl choline, 20%) polystyrene surfaces (fit to sigmoidal dose response model was: $r^2 = 0.995$). DCPS at concentration > 10 mM also displaces β_2 GPI bound to anionic PL surface. When the β_2 GPI-DCPS complex bound to untreated polystyrene was probed with human APS autoantibodies, a slight increase in apparent binding was observed with maximum activity at a ratio of DCPS/ β_2 GPI of 7.2×10^4 . However, the apparent binding observed in this system was only 22% of that shown by β_2 GPI-anti- β_2 GPI on activated polystyrene.

Conclusions: These data demonstrate that, although binding of a low molecular weight anionic PL to β_2 GPI might minimally enhance bind-

ing of autoantibodies from APS serum, the extent of this binding does not compare favorably to that observed when β_2 GPI is bound to a surface with characteristics which elicit optimal autoepitope exposure. This suggests that lipid binding itself is not a sufficient condition for the generation of the autoepitope.

A Pre-Clinical Study of the Stability of Reconstituted Urokinase Solutions. H. Asa¹d¹, J.D. Kohles¹, J.R. Sterrett², M. Weld³, P. Gunning³, and V.A. DeBari¹. ¹Laboratory of Experimental Medicine and ²Division of Nephrology, Department of Medicine, and ³Pharmacy Department, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Urokinase, a plasminogen activator (PA) from cultured kidney cells, has been used extensively in clinical situations requiring clot lysis. The stability of reconstituted urokinase solutions is an issue of considerable importance to health care facilities, especially tertiary-level medical centers, because of the potential cost savings derived from the use of stored aliquots of this enzyme.

Objective: To investigate the *in vitro* activity of urokinase over a two-month period at temperatures (C \pm range) of -70 ± 4 , -20 ± 2 , 7 ± 1 and 37 ± 1 .

Methods: Urokinase was reconstituted with normal saline and stored in polypropylene syringes with polyisoprene plunger tips. Aliquots were assayed for PA activity by the Sigma method using casein as a substrate for proteolysis. Immediately after t₀ (initial time) assay, aliquots were stored at the temperatures indicated. At intervals up to 56 days, specimens were withdrawn and assayed.

Results: Over the period from t₀ to 56 days, no significant decrease in activity was observed; slopes indicated a % activity/day = -0.18 ± 0.27 , -0.08 ± 0.22 , 0.05 ± 0.21 and -0.20 ± 0.26 , for aliquots maintained at -70°C , -20°C , 7°C and 37°C , respectively. Neither slopes nor intercepts varied significantly as assessed by ANOVA (p = n.s.). Studies of urokinase activity at 60°C demonstrated 21% decrease in activity after 3 hr. An aliquot heated to 100°C for 30 min demonstrated obvious denaturation; a suspension of this specimen showed no activity.

Conclusion: These data strongly suggest that thrombolysis with urokinase solutions stored for extended periods should be possible and should be examined in an *in vivo* clinical trial.

Anti-phospholipid Antibody Syndrome: A Case Report with Critical Review. L.M. Sheldon, S. Grossman, and A.D. Rubin. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

We report a case of Anti-phospholipid Antibody Syndrome (APS) in an adult male, with thrombocytopenia, followed by a review of the literature on APS.

Case Report: A 63-year-old male with a past medical history of diverticulitis, peptic ulcer disease, and recent coronary artery bypass surgery was readmitted for treatment of psychosis and depression after he presented confused and complaining of depression and insomnia. He had no previous personal or family history of hypertension, diabetes, autoimmune diseases, or thrombotic tendencies. His previous hospitalization was complicated only by a mild thrombocytopenia, and his medications were Lopressor, Ecotrin, Pepcid, and Pravachol. On re-admission, his vital signs were stable and his physical exam unremarkable. Lab results showed platelets of $78,000/\mu\text{L}$, PT of 13.9, PTT of 54.1 and an INR of 1.2. There were no new EKG changes. A computed tomography (CT) scan of the head was negative. Over the next few days, renal function deteriorated, with BUN and creatinine climbing to 38/3.3. Laboratory tests were negative for ANA and RF, but anti-cardiolipid antibodies were positive. ESR was 82. Administration of high dose corticosteroids resulted in normalization of renal function within two days. However, patient's thrombocytopenia worsened, with platelets falling to a low of $13,000/\mu\text{L}$. Platelet transfusions, intravenous immunoglobulin, and steroids had a limited and transient effect on his platelet counts. On day 17, the patient developed focal weakness and the diagnostic workup revealed a CVA. Warfarin anticoagulation was considered and rejected because of the patient's bleeding history and refractory thrombocytopenia. To raise his platelet count, a course of plasmapheresis with fresh frozen plasma was begun. His platelet count rebounded, with increased counts showing a strong temporal association with plasmapheresis sessions. After three months, platelet counts were sustained at or above 30,000; the patient no longer required plasmapheresis and had experienced no further thrombotic episodes.

Antiphospholipid syndrome is characterized by recurrent venous or arterial thromboses, spontaneous abortion, and/or thrombocytopenia accompanied by positive antiphospholipid antibody titers. Approximately 25% of APS patients have thrombocytopenia and are at risk for both thrombosis and bleeding at very low platelet counts. The pathogenesis of APS is not fully understood and is an area of active research. Potential mechanisms may involve antibody interaction with 2GPI, the Protein C pathway, eicosanoids, and endothelial cells. Warfarin is the recommended treatment for thromboses, and corticosteroids are the drugs of choice to raise platelet counts prior to the introduction of warfarin.

Induction of Hematopoiesis and Vasculogenesis by Diffusible, Non-mesodermal Signals and Potential Stem Cell Targets in the Developing Mouse Embryo. M.H. Baron^{1,2}, M.A. Dyer¹, M. Minou¹, H. Snoeck², and J. Zavadil¹. ¹Divisions of Hematology and Medical Oncology, Department of Medicine, and ²Institute for Gene Therapy and Molecular Medicine, Mount Sinai School of Medicine, New York, NY.

Blood formation and vasculogenesis in the yolk sac of the mammalian embryo are processes that begin during gastrulation and first require the induction of mesoderm during gastrulation. The first blood and vascular endothelial cells form when the extraembryonic mesoderm is induced to differentiate. However, little is known about the molecules involved in these processes during embryonic development. To examine the possibility that epithelial-mesenchymal interactions play an important role in yolk sac hematopoiesis and vasculogenesis in the mouse, we devised a novel transgenic embryo explant culture system. Transgenic embryos harvested prior to the formation of blood (i.e., before or early in gastrulation) are stripped of their surrounding primitive endoderm (epithelium) and grown in collagen drop cultures alone or together with the isolated endoderm tissue. Using this system we have demonstrated that primitive (visceral) endoderm signaling is essential for activation of primitive hematopoiesis and embryonic vasculogenesis. The signals mediating these epithelial-mesenchymal interactions are short-range, diffusible and stage-dependent, becoming less potent around late gastrulation and eventually undetectable. Remarkably, primitive endoderm signaling can reprogram (reprogram) hematopoiesis and vasculogenesis in tissue that is not fated to form blood or vascular cells. For example, anterior embryonic ectoderm (prospective neuroectoderm) can be respecified along hematopoietic and vascular lineages when cultured with visceral endoderm tissue. We are currently pursuing two major lines of experimentation: the identification of the endodermal signaling molecules, and the characterization of stem cells that arise during gastrulation. To simplify the assay for testing of recombinant signaling proteins, we have generated transgenic mice in which a green fluorescent protein (GFP) reporter gene is expressed only in embryonic blood cells. Cultured gastrulating embryos activate expression of the GFP gene as mesoderm and then erythroblasts are produced, resulting in green fluorescence that can be detected under UV light. To identify possible target cells of endodermal signaling, we have begun to carry out cell sorting by flow cytometry. We find a surprisingly large population of cells that are Sca1+lin- (a characteristic of adult and fetal stem cells), and the Sca1+ population also expresses both CD34 and c-kit. We are beginning to analyze the developmental potential of these populations using *in vitro* progenitor/stem cell assays.

Endothelial Selectins and VCAM-1 Promote Hematopoietic Progenitor Homing to Bone Marrow. P.S. Frenette¹ and D.D. Wagner². ¹Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; and ²Department of Pathology, Harvard Medical School, Boston, MA.

The adhesive mechanisms allowing hematopoietic progenitor cells (HPC) homing to the bone marrow after bone marrow transplantation are poorly understood. We investigated the role of endothelial selectins and VCAM-1 in this process. Lethally irradiated recipient mice deficient in both P- and E-selectins (P/E^{-/-}), reconstituted with minimal numbers (5×10^4) of wild-type bone marrow (BM) cells, survived the procedure poorly compared to wild-type recipients. Excess mortality in P/E^{-/-} mice, after a lethal dose of irradiation, was likely due to a defect of HPC homing. Indeed, we observed that the recruitment of HPC to the BM was reduced in P/E^{-/-} animals, either splenectomized or spleen-intact. Homing into the BM of P/E^{-/-} recipient mice was further compromised when a function-blocking VCAM-1 antibody was administered. Circulating HPC, 14 hours

after transplantation, were greatly increased in P/E-/- mice treated with anti-VCAM-1 compared with P/E-/- mice treated with just IgG or wild-type mice treated with either anti-VCAM-1 or IgG. Our results indicate that endothelial selectins play an important role in HPC homing to the bone marrow. Optimal recruitment of HPC after lethal doses of irradiation requires the combined action of both selectins and VCAM-1 expressed on endothelium of the bone marrow.

G-CSF Primed Bone Marrow Improves Delayed Engraftment Produced by MTX Containing GvHD Prophylaxis Regimens. L. Isola, E. Scigliano, D. Skerrett, and S. Fruchtman. BMT Service, Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Administration of G-CSF leads to increased number of progenitors in harvested bone marrow. We previously demonstrated that G-CSF primed bone marrow (pBM) is a suitable source of stem cells for allogeneic transplantation. Combinations of methotrexate (MTX) with cyclosporin A (CSA) or tacrolimus (FK) are commonly used for graft versus host disease (GvHD) prophylaxis after allogeneic transplantation. Prednisone and CSA or FK regimen results in more rapid hematopoietic reconstitution, but steroids have undesirable side effects.

Aims: We examined whether the use of pBM can offset the delayed engraftment seen with MTX containing GvHD prophylaxis.

Methods: Seventeen (17) patients received pBM from matched sibling donors who received G-CSF at 10 mcg/kg/day for 2–4 days prior to harvesting. Conditioning was total body irradiation/cyclophosphamide (CY), busulfan/CY or total lymphoid irradiation/CY/ATG. All grafts contained $3.5-4 \times 10^8$ MNC/kg. Ten out of 17 patients received MTX as part of their GvHD prophylaxis. IBMTR definitions of ANC > 500 and plts > 20,000 were used. Historical controls for engraftment were 112 consecutive pts who received allogeneic bone marrow transplant (BMT) at our institution with unstimulated BM (BM). For length of stay, controls were the subset transplanted during 1996.

Results: Neutrophil and platelet engraftment occurred more rapidly in both groups of patients receiving pBM as compared to controls, and this shortened hospitalization (see table). Peritransplant mortality was 18% (3/17). Fourteen patients remain alive on day 57–1014 post-BMT. One patient in the pBM group who received CSA/PRD has extensive chronic GvHD. One who received MTX/CSA had an isolated central nervous system leukemic relapse and is now in complete remission.

Graft/MTX	ANC > 500*	ANC > 1,000*	Plt > 20,000*	Hospital Stay*
BM/yes	24 ± 12	26 ± 13	26 ± 19	46 ± 15
pBM/yes	18 ± 3	21 ± 6	21 ± 6	34 ± 8
pBM/no	14 ± 4	17 ± 3	17 ± 3	36 ± 10

*Mean ± SD

Conclusion: The use of primed bone marrow allografts resulted in more rapid engraftment and shorter hospitalization in this group of patients. Bone marrow priming can partially offset the delay in neutrophil and platelet recovery seen with the use of MTX containing GvHD prophylaxis. G-CSF pBM transplants did not result in higher than expected GvHD, disease relapse and/or peritransplant mortality.

Proteasome-Mediated Degradation of Integrin Receptor Subunits. D.L. French and J.C. Unkeless. Department of Medicine and Immunobiology Center, Mount Sinai School of Medicine, New York, NY.

Integrins are a family of adhesion receptors that mediate cell-cell and cell-extracellular matrix interactions, in both normal and pathologic situations. These interactions are essential for cell survival and are required for functions that include cell adhesion, spreading, migration, and proliferation. Integrin receptors are synthesized in the endoplasmic reticulum (ER) as two single-chain precursor molecules that associate to form a complex that is transported to the cell surface. Subunits may be synthesized at different rates and in different stoichiometric amounts. Mechanisms must be available both for the assembly and transport of stable complexes, and for the orderly degradation of unassembled subunits in the ER. To study the

mechanisms of ER-mediated retention and degradation of integrin subunits, we are using transfected CHO cell lines expressing normal and mutant integrin subunits of the prototype integrin receptor, platelet GPIIb/IIIa (IIb 3). This receptor plays a critical role in both hemostasis and thrombosis, and the absence of the platelet integrin GPIIb-IIIa receptor manifests in the bleeding disorder Glanzmann's thrombasthenia. In preliminary studies, a panel of cell-permeable protease inhibitors, including MG132 (10 M) which inhibits the chymotrypsin-like activity of the proteasome, calpains, and cysteine proteases; lactacystin (10 M) which specifically inhibits the chymotrypsin-like activity of the proteasome; NH₄Cl (50 mM) which inhibits lysosomal proteases; and E64d (10 M) which inhibits cysteine proteases, were tested. The results suggested that degradation of GPIIb/IIIa is mediated solely by the proteasome. In addition, the accumulation of normal and mutant integrin subunits expressed in three cell lines incubated in the presence of MG132 showed an ~1.3-fold increase in the amount of a normal GPIIIa subunit, an ~11-fold increase in the amount of a mutant GPIIIaC374Y subunit, and an ~2-fold increase in the amount of another mutant GPIIIaC374-386A subunit. These findings extend our original observations and provide evidence that the proteasome is not only involved in degradation of mutant integrin subunits, but is also involved in degradation of normal integrin subunits. To dissect the effect of inhibitors and chaperone binding proteins on integrin biosynthesis and degradation, an *in vitro* transcription/translation system has been established. This system will complement the *in vivo* system and provide a mechanism to decipher the complexities of ER-mediated retention and degradation of integrin subunits.

Immunobiology

STAT 1 and STAT 3 Activation by a Novel B Cell Differentiation Factor. T. Kraus, C. Horvath, and L. Mayer. Immunobiology Center, Mount Sinai School of Medicine, New York, NY.

We have previously described a novel B cell differentiation factor, termed 446-BCDF, that is secreted by anti-CD3-stimulated T cells. This factor results in a 3–10-fold increase in secreted immunoglobulin (Ig) from SAC-activated B cells and cannot be neutralized by antibodies to other cytokines that induce B cell differentiation. We now report that 446-BCDF stimulation of peripheral B cells results in the activation of STAT 1, and to a lesser degree, STAT 3.

Aim: To study the activation of Ig transcription elements by our novel cytokine.

Methods: We employed an electrophoretic mobility shift assay (EMSA) of whole cell lysates from B cells stimulated with 446-BCDF and a DNA probe that contains the consensus binding sequence of STAT 1 and STAT 3, to access the DNA binding elements associated with the probe. Supershifts and western blots were used to confirm the identity of the proteins.

Results: The EMSAs revealed the activation of both STAT 1 and STAT 3. STAT activation could not have resulted from contaminating cytokines in our BCDF prep, since neutralizing antibodies to STAT activators IL-10 and IL-6 did not ablate the signal. Anti-IFN γ did reduce, but did not ablate the STAT 1 signal, verifying a small contamination of IFN γ in our BCDF prep. Further studies were done using antibodies against these transcription factors. Supershift analysis revealed that the STAT 1 was the major DNA binding protein and the STAT 3 a minor contributor. In addition, the same B cell lysates were analyzed by western blot and probed with anti-phospho-STAT 3. This experiment confirmed the activation of STAT 3.

Conclusions: STAT 1 and STAT 3 are activated by the novel B cell differentiation factor 446-BCDF. The importance of these proteins in the transcription of immunoglobulin is now under investigation.

gp180, a Novel CD8 Ligand Expressed by Intestinal Epithelial Cells, Inhibits the Activation and Priming of Cytolytic T Cell Responses. K. Becker¹, C. Korsten¹, N. Campbell¹, T. Moran², and L. Mayer¹. ¹Immunobiology Center and ²Department of Microbiology, Mount Sinai School of Medicine, New York, NY.

gp180 is a novel CD8 ligand expressed by normal intestinal epithelial cells (IECs); it appears to selectively activate CD8⁺ suppressor T cells in IEC:T cell co-cultures. Since purified gp180 binds to CD8 at sites that are dis-

tinct from where classical class I binds, we wanted to determine whether this molecule might affect classical cytolytic T cell priming and effector function. Purified gp180 was added to allo-CTLs during a 4-hour cytotoxicity assay. While mAbs to CD8 and MHC I completely inhibited killing, gp180 mediated inhibition was negligible (15%) and comparable to the glycoprotein control CEA. These findings were confirmed using IEC targets (HT29), expressing native gp180, in an influenza-driven cytotoxicity assay. Influenza-infected HT29 cells were readily killed when HLA matched primed anti-flu CTLs were used. We then added purified gp180 to T cells at the onset of the priming culture using influenza-infected PBMC as stimulator cells. gp180 completely inhibited the activation of anti-flu CTLs. These results were extended using 2 cell lines. HT29 cells were flu-infected and used to activate an anti-flu response in HLA-A9 matched PBT cells. While normal APCs could prime a response, no similar activation was seen when HT29 cells were used. HT29 cells were then transfected with HLA-A*0201 used to prime an A2 restricted anti-flu response. Similarly, no activation of anti-flu CTLs was detected. These data suggest that IECs can process viral Ags appropriately (i.e., they can serve as targets for CTL responses) but that the expression of surface molecules such as gp180 may alter the ability of either primary or memory CTL responses to be generated. gp180 effects appear to be in the inductive rather than the effector phase.

Infectious Diseases

Hydatid Cyst Disease: A Clinical Vignette and Review of the Literature. N. El-Dairi, A. Alshrouf, and M. Rabbat. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Hydatid cyst disease is a parasitic infection caused by *Echinococcus granulosus*. It remains a serious health problem in many parts of the world, especially in the Mediterranean countries.

We report a case of a 26-year-old native Macedonian male who was brought to the emergency room in a state of acute respiratory distress. He was found to have an oxygen saturation of 47% at respiratory rate of 37/min; 100% oxygen failed to increase his saturation to more than 75%, so he was subsequently sedated, paralyzed, and intubated. His history indicated that he was recently diagnosed in Macedonia with liver cyst, and was to have surgical evaluation as an outpatient shortly after admission to the hospital. Chest x-ray on admission to the hospital showed a large cyst occupying the right lower lobe, and x-rays taken later showed air filling the cyst. Other diagnostic measures, including CT-scan of the abdomen, were normal. The patient was evaluated by thoracic surgical consultant, and the diagnosis of a ruptured lung hydatid cyst was made. The patient was taken to the operating room, where he underwent thoracotomy and lobectomy and was started on albendazole. The patient improved quickly and was discharged from the hospital after one week. He was continued on albendazole for two more weeks.

With recent events in the Balkans, where hydatid cyst disease is endemic, and with the fact that many people from that area might be coming to live in the United States, we hope that this clinical vignette will help health professionals to recognize, treat, and prevent this disease.

Acute Suppurative *Salmonella* Type B Thyroiditis Associated with Hyperthyroidism in a Patient on Immunosuppressive Therapy for Crohn's Disease. J.L. Galan, S. Tummala, J. Farkas, and W. Baddoura. Division of Gastroenterology, St Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University School of Graduate Medical Education, South Orange, NJ.

Introduction: Immunosuppressive drugs play a significant role in the management of Crohn's disease. Opportunistic infections are known complications of such therapy. We present an unusual case of thyroid abscess resulting from long term-use of immunosuppressants.

Case Report: The patient was a 38-year-old diabetic female maintained on 6-mercaptopurine and corticosteroids for active Crohn's disease. She presented with neck swelling, dysphagia, and tremulousness, and was found to have hyperthyroidism associated with a thyroid abscess. Blood and abscess cultures grew *Salmonella* type B. The patient improved after drainage and appropriate antibiotic therapy. Thyroid studies were normal when she was checked three weeks after discharge.

Discussion: Bacterial infections of the thyroid gland are rare and potentially life threatening. If one excludes underlying anatomic defects and previous thyroiditis, the most likely setting in which one may encounter pyogenic thyroiditis is in immunocompromised hosts. Review of the literature reveals one case report of pyogenic thyroiditis due to *Salmonella enteritis* in a patient with acquired immune deficiency syndrome. We strongly suspect that the combination of active colonic inflammation and immunosuppressive therapy contributed to this unusual opportunistic infection in our patient.

Conclusion: To our knowledge, this is the first report of acute suppurative thyroiditis due to *Salmonella* type B in a patient with Crohn's disease on immunosuppressive therapy.

Program to Reduce Usage of Vancomycin: Impact on Antimicrobial Resistance. M.H. Mendelson, F. Wallach, L. Finkelstein, C. Petrec, S. Jones, G. Kogan, G. Papanicolaou, A. Gurtman, P. Duncsak, M. Levin, and M. Klotman. Mount Sinai School of Medicine, New York, NY.

Aim: In an effort to promote judicious usage of vancomycin, an antimicrobial utilization pilot project was initiated by the departments of epidemiology, infectious diseases (ID) and pharmacy at an 1100-bed metropolitan hospital.

Method: Use of vancomycin (i.v. and per os [po]; total grams, g/100 patient days) and nosocomial vancomycin-resistant enterococci (VRE) incidence (new clinical cases excluding urine/1000 pt. days) were analyzed for a baseline and post-intervention period: A - baseline - 7/97 - 5/98, B - post-intervention analysis - 8/98 - 3/99. Interventions included development, distribution and training of Medical Board-approved usage guidelines; daily (weekday) microbiologic laboratory review of all patients on vancomycin; as indicated, daily chart reviews by ID attendings, and direct communication of recommendations for alterations in treatment if usage was not consistent with approved guidelines or other clinical indications.

Results: Results of the pilot are illustrated in Table.

TABLE
Vancomycin Usage

	A - (July '97 - May '98)		B - (Aug '98 - March '99)	
	gm/100 pt days	incidence of VRE	gm/100 pt days	incidence of VRE
MSH	17.2	0.67	12.6	0.58
Oncology I	32.5	0.72	16.0	0.17
Oncology II	39.5	1.16	31.7	0.53
Cardiac Surgical ICU	94.1	2.4	72.4	1.7
Cardiac Surgical	30.5	0.5	15.4	0.15
Surgical ICU	40.3	4.87	33.4	4.1
Medical ICU	37.4	3.57	35.3	5.64

Results in the Medical ICU were not comparable: vancomycin IV (37.4, 35.3), VRE (3.57, 5.64).

Conclusion: At The Mount Sinai Hospital, the vancomycin utilization program appears to have reduced the incidence of VRE in those units in which the amount of vancomycin administered was reduced. The impact that changes in other antimicrobial usage patterns may have on the incidence of VRE also needs to be evaluated.

Internal Medicine

Follow-up of Inpatient and Outpatient Endoscopic Biopsy Results in Elmhurst Hospital Center (EHC). S. Banerjee¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: There have been anecdotal reports at EHC of positive biopsy results for which a responsible M.D. could not be identified.

Aim: This study was conducted to determine whether endoscopic biopsy results are available in the chart and if they are appropriately followed up.

Method: At EHC, bronchoscopy, colonoscopy, sigmoidoscopy, and esophagogastroscope are performed in a dedicated endoscopy suite. Medical record numbers of all patients who had biopsies done during the months of March–May, 1998 were obtained from the computer database of the endoscopy suite. A systematic random sample was obtained by taking every third qualifying patient. Each patient's chart was reviewed for presence or absence of note on biopsy procedure, official biopsy report from the Pathology Department, and acknowledgment of the biopsy report by any physician within a 3-month period from the date the biopsy was performed. A biopsy result is considered not acted upon if (a) there is a procedure note mentioning a biopsy being done, or (b) there is an official biopsy result in the chart, and (c) there was no acknowledgment of the biopsy report by any physician.

Results: A total of 56 charts were reviewed: ten (18%) patients did not have an official biopsy report in the charts; however, all of these patients were inpatients, and physicians acknowledged all of their biopsy results. Only 1 (10%) of these 10 patients had a normal biopsy result. Of the total sample of 56 patients, 21 patients (38%) did not have their biopsy report acknowledged by any physician, although 19 (90%) of these did have their biopsy reports in the chart. Nineteen patients (90%) had their procedures done as outpatients; 13 (61%) patients had a normal biopsy report. Seven of nine (78%) bronchoscopic biopsy results were unavailable in the charts.

Conclusions: It appears that physicians do not always acknowledge biopsy results in the chart, or that the results may not always be available in the charts in a timely manner. Patients whose procedures were performed as outpatients appear to be at higher risk for non-acknowledgment. The system of handling biopsy documentation may need to be reviewed. Biopsy results delivered via the computer information system may yield better tracking. More extensive study is needed to see if acknowledgment of the biopsy report by the physician(s) improves with conversion to an electronic medical record.

Lipid Profile in Patients from Indian Subcontinent, Further Results. S. Parikh¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: Studies have shown that people of Indian-subcontinent ancestry are at higher risk for coronary artery disease and for more severe disease at a younger age than any other ethnic groups in the United States (US) and elsewhere.

Methods: Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center serves many patients of South Asian ancestry (Indian/Pakistani, Bangladeshi and Caribbean patients of Indian ancestry [CPIA]). A study was conducted to examine lipid profiles from these patients. Results of the first fifty patients have been reported (1); data on an additional eighty patients are presented in this report. The methodology was unchanged. These data were compared with data from the general US population and from a healthy rural Indian population (HRIP) (2). Chi-square analyses was performed using EpiInfo software to compare proportions.

Results: Cholesterol level of >240 mg/dL was seen in 43% of CPIA, (compared to 63% in previous study), 24% of Indian/Pakistani and 21% of Bangladeshi patients as compared to 8% of HRIP. LDL level of >160 mg/dL was seen in 30% of CPIA (compared to 54% in previous report), 11% of Indian/Pakistani and 25% of Bangladeshi population as compared to 67% of HRIP. HDL level of <35 mg/dL was seen in 37% of Bangladeshi, 22% of Indian/Pakistani and 19% of CPIA patients as compared to 29.7% of HRIP. Triglyceride level of > 400 mg/dL was seen in 4% of Indian/Pakistanis, 2% of Bangladeshi and 0% of CPIA patients as compared to 0.7% of HRIP. Although the original sample showed a statistically significant risk of having cholesterol level of > 200 mg/dL for CPIA (odds ratio 9.5), odds ratio in larger sample was 1.3 and this was no longer statistically significant.

Conclusion: As compared to HRIP, the immigrant Indian population had higher cholesterol, LDL and triglyceride levels; HDL level <35 mg/dL was seen more frequently in HRIP than in immigrant Indians. In comparison to the previous report of fifty patients, this combined study of 130 patients does not show a significant difference in lipid profiles of South Asian patients and CPIA. A larger study is needed to confirm these findings and to investigate the associated environmental and dietary factors.

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Helicobacter pylori Infection in Peptic Ulcer Disease, Elmhurst Hospital Center (EHC). S. Ibrahim¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Helicobacter pylori (HP) plays a principal role in the pathogenesis of peptic ulcer disease (PUD); 45–100% of patients with duodenal ulcers and 75–85% of patients with gastric ulcers harbor the organism. Infection may be associated with acute complications of PUD, as well as long-term sequelae like recurrence of PUD and gastric carcinoma. In the United States (US), rates of *H. pylori* increase with low socioeconomic status, increasing age and residence in custodial institutions, and are higher in blacks and Hispanics. In developing countries, *H. pylori* is generally acquired in childhood; prevalence rates are much higher than in the US.

Aim: To examine factors associated with *H. pylori*-positivity in PUD at EHC.

Methods: Medical records were reviewed for all patients who underwent esophagogastroduodenoscopy (EGD) for dyspepsia and/or hematemesis from January, 1998 to March 1999. From a chronological list of those patients diagnosed with PUD who underwent a diagnostic test for *H. pylori* (biopsy and/or serology), every fourth patient was selected. Demographic and clinical variables were extracted. Insurance status was noted as an indicator of socioeconomic status. Complications were defined as serious recurrent bleeding or need for major surgical procedure.

Results: A total of 1101 patients underwent EGD, of which 164 patients (14.9%) had PUD and a test for HP. Forty-two patients (25.6%) were selected. Of these, 27 (64.3%) had HP infection: 19 (70.3%) newly diagnosed by positive biopsy on this EGD, 1 (3.7%) with a positive biopsy despite prior treatment, and 7 (26%) who had been successfully treated. Further review of the charts of the 15 HP-negative patients revealed 9 (60%) had a history of NSAID use. Infected patients comprised 12 of 18 Hispanics (66.7%), 9 of 16 Asians (56.3%), 4 of 5 whites (80%), and 2 of 3 African-American patients (66.7%). Of 23 uninsured patients, 9 of 12 Hispanics (75%), and 6 of 11 Asians (55%) had HP infection. Gastrointestinal bleeding was the presenting symptom in 25 patients (59.5%); 13 of these (52%) were positive for HP. Of 20 currently infected patients, 14 (70%) had a complication vs. 12 of 22 (55%) uninfected patients (odds ratio = 1.94, chi-square = 1.1, p = NS). Fourteen of 20 currently infected patients (70%) experienced relief of symptoms after anti-HP therapy; three (15%) were lost to follow-up.

Conclusions: A substantial proportion of patients with PUD on EGD required treatment for *H. pylori* infection. Prevalence may differ by nationality, socioeconomic class, age and other variables; a larger sample is needed to further delineate the risk of infection in the multi-ethnic, predominantly low-income population served at EHC. In a population with high prevalence, early and aggressive measures to diagnose infection may be warranted.

Likelihood of Coronary Artery Disease (CAD) in Patients Admitted to Elmhurst Hospital Center (EHC) with Chest Pain (CP): Racial and Gender Differences. S. Aytug¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Chest pain (CP) is one of the most common reasons for hospital admission. In an ethnically diverse inner city hospital, initial evaluation of patients from different cultures and genders can be difficult due to language barriers and possibly different clinical presentations.

Aim: To determine whether race and gender are significant determinants of the presence of CAD in-patients with CP.

Methods: From January 1, 1996 to April 30, 1998, all patients who were admitted to EHC with a CP-related diagnosis were identified, and a sample was selected using random numbers generated by EpiInfo software. Presence of CAD is defined as having a positive exercise thallium

stress test, present or past myocardial infarction, positive cardiac catheterization, prior percutaneous transluminal coronary angioplasty or coronary artery bypass graft. CAD was classified as newly diagnosed or prior CAD. Absence of CAD is defined as having a negative stress thallium test, normal coronary arteries.

Results:

1. There were 1759 admissions; 150 were selected for the sample, of these, 33 (22%) did not meet inclusion criteria. Of the remaining 117, 63 had CAD (53%), 54 (47%) did not. Of the 63 CAD patients, 31 (49%) were newly diagnosed CAD and 32 (51%) had prior CAD.

2. In the new CAD group, there was no significant difference according to gender. The odds ratio of a male having new CAD was 0.81 (95% CI: 0.3, 2.21), $p = NS$. The presence of CAD was not associated with race (chi-square = 1.33, $p = NS$).

3. Of smokers, the odds ratio of females having new CAD vs. no CAD was 3.08, $p = NS$.

4. Of the patients who had CAD, the odds ratio for females having diabetes was 2.35 (95% confidence interval = [0.88, 6.36]; chi-square = 3.58, $p = 0.058$ [NS]); the odds ratio for males being smokers was 2.48, $p = NS$.

Conclusions:

1. Patients admitted with CP and subsequently diagnosed with CAD were just as likely to be of either gender or any ethnic group.

2. Forty-seven percent of patients admitted with CP did not have CAD.

3. Among smokers without known CAD, gender was not statistically significantly associated with being diagnosed with CAD.

4. Among those with CAD, females were more than twice as likely to be diabetic (this approached statistical significance).

Management of Hyperlipidemia in the Medicine Primary Care Clinic (MPC) at Elmhurst Hospital Center (EHC). R. Kumar¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

The National Cholesterol Education Program (NCEP) has developed recommendations for the management of patients with hyperlipidemia.

Aim: To study identifying patients with hyperlipidemia, the implementation and length of non-pharmacologic therapy, and the initiation of pharmacologic therapy in compliance with the NCEP guidelines.

Methods: A database of all patients with a Low Density Lipoprotein (LDL) of ≥ 160 mg/dL seen in different clinics between January 1, 1995 and December 30, 1996, was obtained; from those patients followed in the MPC clinic, every tenth patient was selected. One hundred charts were reviewed for age, ethnicity, gender, number of risk factors for CAD, time period between diagnosis of hyperlipidemia and the start of non-pharmacologic and pharmacologic therapy and compliance with NCEP guidelines.

Results: The total number of patients was 100. Gender: 28% male and 72% female. Ethnicity (male patients): Caucasian 7 (25%), East Asian 3 (10.71%), Hispanic 10 (35.70%), South Asian 6 (21.42%), Other 2 (7.14%). Ethnicity (female patients): African-American 10 (13.88%), Caucasian 6 (8.33%), East Asian 3 (4.16%), Hispanic 35 (48.61%), South Asian 8 (11.11%), and Other 10 (13.88%). Fifteen percent (15%) of patients had documented CAD, 85% did not. Risk factors for CAD: 0: 19%, 1: 11% and 2 or more: 70%. The start date of non-pharmacologic therapy was not documented in 47 (47%). The time frame between start of pharmacologic therapy and initial documentation of diagnosis was stratified: < 3 months: 5, 3–6 months: 12, 6–12 months: 14, 12–24 months: 14, 24–36 months: 9, 36–48 months: 0, > 48 months: 7, not documented: 13 and not started: 26. Of 100 patients, 74 were started on pharmacologic therapy, 26 were not. Of the latter, 12 had improved LDL with non-pharmacologic measures, 2 charts had insufficient data; the remaining 12 were then stratified on the basis of risk factors (zero: 2 patients, one: 0 patients, 2 or more: 9 patients and one patient with documented CAD). The two patients with no risk factors had LDL of >190 mg/dL, the only patient with CAD had LDL of 160 mg/dL, the nine patients with 2 or more risk factors had LDL >160 mg/dL. Ethnicity of these twelve patients was Hispanic 6 (50%), African American 2 (16%), Caucasian 2 (16%), other 2 (16%). Gender distribution: male 1 (9%) and females 11 (91%).

Conclusions: Despite knowledge about the effects of hyperlipidemia and the need for early treatment, there are still patients not receiving appropriate therapy as per NCEP guidelines. Physicians have yet to

embrace NCEP guidelines; medical education should include training on treatment of hypercholesterolemia.

Patient Satisfaction with Education at the Medical Primary Care Clinic of Elmhurst Hospital Center (EHC). M.G.O. Rabin¹, A. Lyman², and L. Ares². ¹Housestaff Alumnae, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Patients obtain information on medical conditions and their treatment from many sources. Their satisfaction with education obtained at the Medical Primary Care (MPC) Clinic at EHC may influence their overall perception of quality of care.

Aim: To study (a) sources of information on medical conditions and treatment, and (b) evaluate knowledge developed from and satisfaction with patient education at MPC.

Methods: A questionnaire was developed to collect information on demographic variables, educational attainment, knowledge about the patient's medical condition and medications, sources of such knowledge, and factors affecting the comfort of patients in discussing compliance and psychosocial issues with the primary care physician. The questionnaires were distributed at session registration to all English-speaking patients known to MPC. Patient identifiers allowed linkage to the surveyed record, but confidentiality was assured. Diagnoses and medications indicated by patients were confirmed by review of the medical record.

Results: Ninety consecutive surveys were distributed. Eighty-one (90%) questionnaires were returned. Of respondents, 44% were over 60 years, 62% were female, 32% were Black non-Hispanic, 27% were Hispanic, 19% were White non-Hispanic, 17% were Asian, 5% ethnicity not given. Fifty-five percent (55%) had a high school or greater educational attainment; 7% had a grade school education and 7% had never attended school. Seventy-two percent (72%) stated they knew what medical conditions they had, 19% did not know, and 9% did not answer. A variety of sources of medical information were provided by patients; 59 (66%) stated that their main source was their physician, 18% indicated print media, and 13% indicated TV. Sixty-five percent (65%) knew the medications they were taking, but only 22% knew the possible side effects. Those with higher educational attainment were more likely to know their conditions and medications. Sixty percent (60%) stated they had adequate time to tell their physician all their complaints; 57% felt they were given enough information about their medical condition and 25% did not. Fifty-three percent (53%) felt comfortable discussing alternative medicines with their physician, 40% felt comfortable discussing the influence of their religious beliefs on their compliance with medical treatment and 49% were comfortable discussing personal problems affecting their health; 21% had discussed or planned to discuss advance directives with their physician. Seventy percent (70%) were satisfied with their physician. Female patients were more likely to be comfortable in discussions with the physician, (OR = 2.77, chi square = 4.09, $p < 0.05$).

Conclusions: Subgroup analyses were limited by the study's sample size, and patient participation may have been affected by the lack of anonymity of the response. Further investigation is warranted.

Factors Associated with Appointment Compliance at Medical Primary Care Clinic (MPC), Elmhurst Hospital Center (EHC). V. Shah¹ and Andrea Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Failure to keep an appointment may affect care of the patient, and also influence productivity of primary care sites. Data are inconclusive regarding the association of gender, race, age, time of visit, language barriers, and other factors with appointment compliance.

Aim: To study demographic and other variables of patients who miss appointments in a public hospital clinic with an ethnically diverse patient population.

Methods: A list of all patients scheduled to visit the Medical Primary Care Clinic (MPC) during a representative week was obtained. Patient characteristics were obtained from the computerized database. Patients who missed an appointment were contacted by telephone by the investigator or an interpreter for Spanish- or Mandarin-speaking patients. Frequencies were tabulated using Systat software; odds ratios were calculated and chi-square and Fisher's exact test were performed using SPSS and EpiInfo.

Results: There were 728 scheduled visits in the selected time period; 464 visits (63.7%) were kept and 264 (36.3%) were missed. A total of 113 males (39.1%) with appointments failed to keep them, as compared to 151 females (44.5%) (odds ratio [OR]=1.25, chi-square = 2.02, $p = ns$). There was no statistically significant difference in appointment-keeping based on race/ethnicity (chi-square = 8.72, $p = ns$) or by English-speaking status. The OR for missed appointments for patients new to MPC was 1.91 (chi-square = 7.5, $p = 0.006$); for patients with psychiatric diagnoses, the OR was 1.93 (chi-square = 8.09, $p = 0.005$); for daytime appointments vs. evening, the OR was 2.24 (chi-square = 4.65, $p = 0.031$). Of those who missed appointments, 154 (57.3%) could be contacted by telephone; 110 (42.7%) could not be contacted. Of the 154, 99 (64.2%) spoke English and 55 (35.8%) did not. Reasons for missing appointments were: forgot (20.6%), had to work (18.8%), perceived a language barrier (14.9%), and other reasons (32.1%); 13.6% had changed their appointment, but this fact was not noted in the MPC computer scheduling system.

Conclusions: A substantial proportion of appointments is not kept at MPC, especially by new patients, patients with psychiatric diagnoses, and patients with daytime appointments. Compliance with appointments, an important factor in providing primary care, may be affected adversely by many factors in a low-income, multi-ethnic population. Further research is needed to elucidate modifiable risk factors of missed appointments.

Complications of Central Venous Catheterization in a Medical Intensive Care Unit and the Necessity of a Postprocedural Chest Radiograph: A Retrospective Study. F. Mankarios¹, S. Baffic², D. Benz², E. Erickson¹, and M. Moore². ¹Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ; and ²University of Medicine and Dentistry, Newark, NJ.

The placement of a central venous catheter (CVC) is one of the most common procedures that have been associated with low morbidity and mortality when performed in the medical intensive care unit (MICU). It has been a routine practice to order a postprocedural chest radiograph to ensure the absence of complications.

Aim: To study the incidence and complications of the CVC in the ICU population and correlate that with the cost and necessity of the postprocedural chest radiograph.

Methods: We retrospectively reviewed the charts, postprocedural radiographs and reports of the patients in the MICU who were subjected to a triple lumen CVC at St. Joseph Hospital and Medical Center during 1997 and 1998. Our population consisted of 131 subjects, 49.6% female and 50.4% male. The ages of the subjects ranged from 19 to 94 with a mean age of 58.4%. The postprocedural complications were 3.9%. They included one case of pneumothorax (0.75%) that required the placement of a chest tube. Unsuccessful catheterization was encountered in 3.8%. The review of 131 postprocedural radiographs showed one pneumothorax and a malposition rate of 5.3%.

Conclusion: Complications associated with CVC were limited and comparable to the previous studies. We do not advocate the performance of a postprocedural chest radiograph routinely.

Epidemiology of Lymphomas in Elmhurst Hospital Center (EHC). A.R. Thummala¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Lymphomas are heterogeneous malignancies arising from T or B cells. Studies have shown that the risk of lymphoma among HIV patients is rising, possibly due to increasing survival of the population treated with highly active anti-retroviral therapy.

Aim: To study the patterns of lymphomas in EHC.

Methods: A retrospective cohort study was done. All patients who were diagnosed with lymphoma from January 1994 to December 1997 were included. Cancer registry data and patient charts were reviewed for demographic and clinical data. The list of patients was then compared to the registry of the Infectious Diseases Clinic in order to identify any additional patients known to be HIV-positive. Frequencies were tabulated and Epi-Info was used to compare proportions.

Results: One hundred patients were diagnosed with lymphoma during the study period. More cases occurred in males (62%); this was true for all ethnic subgroups except Asians. Cases were more likely to be

White or Hispanic, and the peak age group was between 30–40. Thirty-nine percent (39%) presented with advanced disease; Whites constituted 46.15% of this group. Thirty percent (30%) of the patients were HIV positive, with Hispanics being in greater proportion (46.60%) compared to other groups. Lymph nodal disease accounted for 63% of the cases in the group of HIV-negative or HIV-unknown compared to 33% in the HIV-positive group. CNS lymphomas comprised 56% of the cases in the HIV-positive group, compared to 2.9% in the other group (HIV-negative and -unknown). In the HIV-negative/unknown group, 29.62% died, compared to 66.66% in the HIV positive group (through December 1998). HIV-related lymphomas decreased from 10 (38.4%) in 1994 to 4 (16%) in 1997. On comparing the data between 1994 and 1997, we noted a highly statistically significant decrease in the proportion of HIV-related lymphomas (chi-square = 19.52, $p = 0.0058$).

Conclusions: These results suggest that the risk of lymphoma is decreasing among HIV-positive patients (anecdotal evidence indicates this may be seen at other New York City clinical sites as well). However, earlier access to insurance coverage may affect where patients seek care, and thus these results must be viewed with caution. Additional studies are needed to further define this risk.

Clinical Predictors of Mood and Anxiety Disorders in Medical Primary Care Clinic (MPC) Patients. G. Tangarorang¹, S. Mariano¹, L. Ares¹, and P. Leong². ¹Department of Primary Care-Internal Medicine and ²Department of Psychiatry, Elmhurst Hospital Center, Elmhurst, NY.

Mood and anxiety disorders are among the most common mental disorders in the community and in primary care clinics (1). They cause significant patient morbidity and mortality and impose a heavy economic burden (2). These disorders are largely undiagnosed and therefore undertreated by primary care providers (3).

Aims: To identify clinical predictors of mood and anxiety disorders in medical primary care clinic patients.

Methods: Patients in MPC were interviewed to collect demographic variables and were administered the Primary Care Evaluation of Mental Disorders, PRIME-MD, a validated instrument to determine the presence or absence of mood and/or anxiety disorder (4). Major medical diagnoses, medications and clinic visits for all participants were then extracted from the patients' chart. Statistical analyses were performed on data from groups with and without these disorders, using Student's *t* test for comparing means and Fisher's exact test to compare proportions.

Results: Thirty-four of 88 randomly selected patients met the inclusion criteria and agreed to participate. A mood or anxiety disorder was present in 12 (35%). Of these, 6 (50%) had a known disorder, (5 of them were under therapy) while the other 6 (50%) were diagnosed by the investigators. Six (50%) had pure mood disorder, 3 (25%) had mood and anxiety disorder, 1 (8%) had mood and binge eating disorder and 2 (16%) had pure anxiety disorder. Patients with mood disorders reported more recent stressors (75% vs. 4%, $p < 0.001$), physical complaints (7.33 vs. 4.27, $p = 0.006$), history of drug use (16% vs. 0%, $p = 0.036$) and suicidal tendencies (32% vs. 0%, $p = 0.011$). There was no significant difference among patients with and without these disorders in terms of age, race/ethnicity, education, smoking habits, alcohol abuse, family history of any psychiatric disorder, sense of well-being, perceived level of care, number of concurrent major medical diagnoses or number of clinic visits.

Conclusion: Mood or anxiety disorders are commonly found among patients in the MPC. Predictors of these disorders (multiple physical complaints, recent stressors, drug use and history of prior suicidal ideation/attempt) should trigger further evaluation.

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Microscopic Hematuria, Medical Primary Care Clinic (MPC), Elmhurst Hospital Center (EHC). M. Alam¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Normal individuals may excrete some red blood cells (RBC) in the urine. Hematuria, whether gross or microscopic in nature, may be a sign of serious underlying urologic disease including malignancy. Microscopic hematuria (MH) is an incidental finding that is frequently discovered as part of routine examination. Three or more RBC/high-power field on at least two of three properly collected and properly performed urinalyses (U/A) require evaluation. In studies of adults with MH, the likelihood of finding urologic cancer is 5%, versus 23% in those patients with gross hematuria.

Aim: To examine demographic and clinical variables associated with MH at EHC.

Methods: A retrospective cohort study of microscopic hematuria was done in MPC. A list of all patients followed by a subset of providers was obtained. Charts were reviewed, and demographic data were collected on age, sex, ethnicity, comorbid risk factors, duration of microhematuria, number of abnormal U/A, findings on U/A, renal function, evaluation/investigation done, and final diagnosis. Of approximately 500 patients, 75 had MH; of these, 45 charts (60%) were available for review.

Results: Twenty-nine (29) patients were over 55 years old (64.44%), 38 patients were female (84.44%), 27 patients were Hispanic (60%), 25 patients had hypertension, (55.55%), 26 patients had MH for more than 24 months (35%). Urine cytology was performed on 13 patients, renal ultrasound on 28 patients, intravenous pyelography (IVP) on 4 patients, computed tomography on 3 patients, cystoscopy on 6 patients, renal biopsy on 2 patients. Final diagnosis: 1 patient (2.2%) was found to have renal cell carcinoma, 2 patients (4.4%) had glomerulonephritis (GN) (1-IgA nephropathy, 1-membranous GN), 1 (2.2%) each with interstitial nephritis, nephrolithiasis, and prostatic hyperplasia, 3 patients (6.6%) with renal cysts. Eight patients were found to have other diagnoses (1 patient with Evan's syndrome, 5 patients with recurrent urinary tract infection had microhematuria when asymptomatic, 2 patients with probable diabetic nephropathy). No pathology was found in 6 patients (13.3%). No patient was found to have bladder cancer. Seven patients had pending evaluation (15.55%). Sixteen patients (35%) had no evaluation of abnormal U/A.

Conclusions: A substantial proportion of patients did not have diagnostic evaluation of MH, which may be a clue to serious urologic disease, including malignancy, and should be evaluated.

Acute Myocardial Infarction due to Mediastinal B-Cell Non-Hodgkin's Lymphoma in a Young Woman. K. Chennapragada¹, V.M.K. Bhaskarabhatla², and M. Kelly¹. ¹Saint Joseph's Hospital and Medical Center, Paterson, NJ; and ²Internal Medicine Associates, Mount Sinai School of Medicine, New York, NY.

A 26-year-old woman was brought to the emergency room (ER) in a state of shock (BP 71/28 mm Hg) and acute respiratory distress. She had a long history of autism, seizure disorder, and treatment by phenytoin and carbamazepine. In addition, there was a one-month history of progressive dyspnea, cough, anorexia, fatigue and weight loss. Chest radiograph and computed tomography (CT) scan had revealed a large mediastinal mass, infiltrating the heart and the great vessels, with pleural effusion. She had electrocardiographic signs of acute antero-lateral myocardial infarction with posterior extension and inferior subendocardial ischemia (Q waves in I1, aVL, V2, and V3; poor progression of R waves in precordial leads; ST segment elevations > 0.20 mV in leads I1, aVL, V4 -V6; ST segment depressions in L2, aVF, and V1; and inverted T waves in leads L2, L3, and aVF). An echocardiogram in the ER showed antero-apical akinesia, focal anterior pericardial effusion, and a solid mass in the pericardial cavity. Her cardiac enzymes were markedly elevated, and there was severe hypoxia (paO₂: 22 mm Hg), hypercapnia (paCO₂: 35 mm Hg) and acidosis (arterial blood pH: 7.17). She had immediate artificial ventilation and was transferred to the intensive care unit. Following informed consultations with her family, a "Do-Not-Resuscitate" decision was made. On day 9, she suffered cardiac arrest and died.

At autopsy, the mediastinal mass was found to be a B-cell non-Hodgkin's lymphoma with malignant lymphomatous infiltrations of the heart and the coronary arteries. The ventricles showed extensive areas of infarction and necrosis of the myocardium.

Great progress has been made in the treatment of lymphomas in recent decades by radiotherapy and/or chemotherapy, with significant cure rates even in the advanced stages. Patients who relapse following treatment have been known to present with lymphomatous pericardial and cardiac infiltration, especially in the terminal stages. However, to our knowledge, this was the first known instance of acute myocardial infarction due to lymphomatous infiltration as an initial presenting feature in a previously untreated patient with lymphoma. Had the nature of her disease been recognized ante-mortem, emergency radiotherapy and/or chemotherapy might have been successful in altering the course of her disease.

Xanthogranulomatous Pyelonephritis: A Case Report with Critical Review. I.G. Abadeer and R. Marton. Department of Internal Medicine, St. Joseph Hospital and Medical Center, Paterson, NJ.

We report a case of unilateral xanthogranulomatous pyelonephritis (XPN) in an adult, diagnosed after right nephrectomy, followed by a review of the literature on XPN.

Case Report: A 44-year-old man with a history of hemophilia A was admitted with complaints of fever and suprapubic pain for 1 week. Nine years prior to admission he had developed complications resulting from a lumbar puncture. His medical history also included asthma, depression and arthritis. The patient's medications were lactulose, acetaminophen, Duragesic®, patch, Dilaudid®, Ativan®, and Cipro®. On physical examination, he had temperature of 103.2°F, a pulse rate of 124/min and blood pressure of 137/86 mm Hg. He was in his usual mental status. He had dry, warm skin and diffuse abdominal tenderness, especially around the suprapubic catheter. Laboratory results showed white blood cell count of 9000/mm³, prothrombin time of 14 seconds, and partial thromboplastin time of 47.2 seconds. Routine urinalysis revealed turbid appearance, large amount of blood and protein, positive nitrite, large leukocytes, >100 RBC, >100 WBC, and many bacteria. Catheterized urine culture had colony count of 100,000 colonies/mL, identifying *Proteus mirabilis* and methicillin-resistant *Staphylococcus aureus*. (The patient was started on IV Vancomycin and ceftazidime, according to sensitivity.) Blood culture was negative. Renal ultrasound showed very thin cortex and hydronephrosis in the right side, no abnormalities in the left side. On IVP, the right kidney was not visualized. No uptake of technetium in the region of the right kidney indicated nonperfused and non-functioning right kidney. The patient was given factor VIII one day prior to and ten days after the right nephrectomy. The pathological report showed hydronephrosis with xanthogranulomatous pyelonephritis.

Genitourinary obstruction and urinary tract infection are strongly implicated in the development of XPN. Because the clinical presentation of the disease is variable and nonspecific, it is frequently misdiagnosed either as renal neoplasms, abscesses or tuberculosis. CT scan is the best radiological imaging technique for discovering the extent of inflammation. Diagnosis requires renal tissue for special pathological staining. Lipid-laden macrophages called "xanthoma cells" characterize the disease. Treatment by nephrectomy or partial nephrectomy has been the mainstay of therapy for XPN, although a trial of antibiotics prior to surgery is warranted in cases of focal XPN.

Evaluation of a Community-Based Clinical Experience, and the Resident's Role in Curriculum Development. L.M. Reich and R.A. David. Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

In a previous report, we described the creation of a community-based clinical experience in a primary care internal medicine residency program. The development of this curriculum relied on the residents' assessments of their learning needs and their retrospective identification of learning objectives. The clinical experience consisted of five components: a community-based geriatrics practice, a mobile-van outreach facility, an urgent-care walk-in center, and home visits to homebound geriatrics and AIDS patients.

Aim: To evaluate this curriculum in terms of how well we (1) met clinical learning objectives; (2) helped improve the residents' clinical performance; and (3) achieved the goal of including residents in curriculum development.

Methods: The thirty-six residents (12 per PGY level) who had rotated through one or more of the five components of the community-based clinical experience were surveyed regarding the educational and

clinical value of the rotation and their role in curriculum development. Residents were asked to respond to a series of statements along a five-point Likert scale.

Results: Twenty-eight of 36 residents (78%) returned completed surveys. A total of 31 resident-rotations were evaluated (mean of 1.11 sites per resident). Residents gave positive ratings to all components of the curriculum, with Home Care-Geriatrics receiving the highest ranking and Home Care-AIDS the lowest. Despite this, Home Care-Geriatrics received the lowest ranking for "new clinical experience" and Home Care-AIDS among the highest. Home Care-Geriatrics was also ranked highest in terms of causing the residents to "think differently" and "change their attitudes" about "certain clinical situations." The community-based practices (geriatrics and urgent-care center) were ranked as the strongest learning experiences. In terms of their role in curriculum development, residents gave positive responses only for the urgent care center, although overall they felt that their "input was important in terms of curriculum development" (more so for PGY-III's than for PGY-I's).

Conclusions: The addition of community-based clinical experiences provided residents with new learning experiences and resulted in a self-perceived change in clinical thinking and attitude (an independent educational goal of residency training). Overall, the residents felt that they played a significant role in curriculum development, although they could not identify specific aspects of the curriculum for which they felt they had done so. It is not known at this point to what extent the residents' experience in curriculum development contributed to the positive impact of this curriculum on their training.

Training in Nicotine Addiction Treatment in Internal Medicine and Family Practice Residency Programs. A. Lyman. Department of Ambulatory Care, Mount Sinai Services, Elmhurst Hospital Center, Elmhurst, NY.

Studies have demonstrated that physicians feel unprepared to treat nicotine addiction (1); integrating specific training into graduate medical education may improve specific skills and overall efficacy of physicians in this area.

Aim: To ascertain current practices of residency programs, a survey was conducted in conjunction with a program (funded by a Project ASSIST grant to the Coalition for a Smoke-free City/NYC Department of Health) to develop a network of "tobacco control physician liaisons" (residency program faculty who would (a) coordinate training and tobacco control advocacy for their programs, (b) serve as media spokespersons, and (c) provide cessation materials for their institutions' Employees' Health Services).

Methods: A list of all residency programs in internal medicine (IM) and family practice (FP) in New York City was obtained. Each program was sent a packet containing the survey and curricular, scientific and patient education materials. Survey responses were tabulated and frequencies calculated with EpiInfo software.

Results: Sixty-three (63) eligible residency programs were identified and sent packets; 56 (89%) that did not respond were remailed the survey. Fifteen programs (24%) responded to the survey; representing 19 tracks (4 FP, 6 traditional IM, 8 primary care IM, 1 ambulatory care IM). Of fourteen programs, 13 (93%) taught nicotine addiction treatment; 6 (43%) taught 100% of residents; 8 (57%) as part of a formal curriculum, 13 (93%) informally during precutting, 10 (71%) at an occasional lecture. Nine (64%) taught brief counseling techniques, 12 (86%) taught use of pharmacologic agents, 7 (50%) provided curricular materials for physicians (NCI:5, AHCPR:2, American Academy of Family Practice:2, other:2); only 4 (29%) found these useful. Twelve of 15 programs (80%) had had residents who smoked; 10 (67%) had had faculty who smoked; only 2 respondents (15%) had intervened (referral and/or counseling). Three (20%) institutions had smoking cessation groups for employees; and 3 (20%) had groups for patients. The most frequently perceived barriers to training were lack of time, rotation of residents, and perceived failure of cessation by patients; most frequently cited need was for new curricula.

Conclusions: A program offering limited assistance with smoking cessation training is not an effective method of increasing residency program involvement with local tobacco control infrastructure, or for assessing residency program practices. Further study is needed to ascertain and improve graduate medical education in nicotine addiction treatment.

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Epidemiology of *Burkholderia cepacia* Colonization in a Cohort of Cystic Fibrosis Patients. S. Seward¹, P. Walker², P. Tietjen², M. Burdella², W. G. Batte³. ¹Internal Medicine-Pediatrics Associates, Mount Sinai School of Medicine, New York, NY; ²Cystic Fibrosis Center, St. Vincents Medical Center, New York, NY, and ³Department of Radiology, Durham Veterans Administration Medical Center, Durham, NC.

Burkholderia cepacia was first recognized as a significant pathogen in the cystic fibrosis (CF) population in 1979. It is known to colonize patients earlier in life than other gram-negative bacteria. Colonization has been anecdotally reported to lead to a more rapid deterioration in lung function, and ultimately death, than would otherwise be expected. We characterize a cohort of 24 patients colonized with *B. cepacia*.

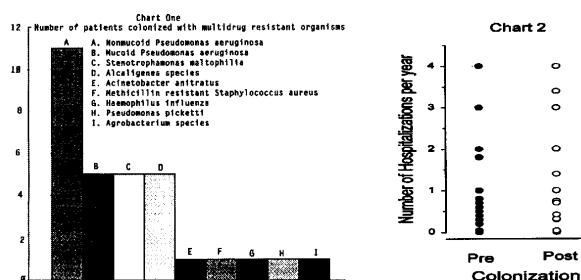
Aim: To evaluate the impact of *B. cepacia* colonization on the clinical course of CF patients.

Methods: A retrospective chart review was undertaken. The Brasfield Scoring System (1) was used to evaluate chest radiographs. It assigns demerit points in each of five categories: nodular densities; linear markings; large lesions (e.g., subsegmental and lobar infiltrates, atelectasis); complications (e.g., pneumothorax); and overall severity. Annual films from up to five years before and five years after *B. cepacia* colonization were evaluated by five independent investigators, blinded to patient name, respiratory status, and date of colonization. Repeat evaluations were completed on three patients to establish an internal intraobserver control. For each patient, a mean of the five observers' Brasfield scores was calculated and recorded.

Results: A total of 24 patients, ages 2 to 31 years, were evaluated. There were 3 sets of siblings. Four patients were colonized with *B. cepacia* for 10+ years; only one of them has died. Another patient, colonized for 2.5 years, has also died. Sixteen (16) patients were colonized with other multidrug-resistant (MDR) organisms (Chart 1). Six (6) patients grew *Aspergillus* species from their sputum. The mean albumin level at time of colonization was 4.2 g/dl (range 3.1 - 5.3). The mean Body Mass Index (BMI) was 19.4 kg/m² (range 15.6 - 22.8). The number of hospitalizations per year for each patient before and after colonization was calculated (Chart 2). There was no statistically significant change in the number of hospitalizations after colonization (pre-colonization mean 1 ± 1; post-colonization mean 1 ± 1; p > 0.5). Sixty-three percent (n = 15) of our patients became colonized with *B. cepacia* in the two-year period November, 1994 to November, 1996, during which all of these patients were hospitalized at least once. Brasfield scores were also evaluated before and after colonization. No statistically significant change in scores was found (pre-colonization mean 18.49 ± 3; post-colonization mean 15.36 ± 3; p > 0.5).

Conclusions: We evaluated 24 CF patients colonized with *B. cepacia* over a 10-year period, during which only two have died. We found that CF patients can become colonized with *B. cepacia* as early as two years of age. Three patients have survived colonization for greater than 10 years. A large percentage of our patients had either a sibling with *B. cepacia* or were hospitalized during a 2-year period when over 60% of our patients became colonized. No significant change in morbidity, in terms of number of hospitalizations or CXR findings, was found after the time of colonization.

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Improvement in Quality of Care through Utilization of an Electronic Medical Record. R.A. David¹, D. Carr², J. Dimitrakakis², C. White², D. Danzig¹, E.Kanner², M. Camacho¹, M. Brewer¹, P. Velez², and J. Moshirpur¹. ¹Elmhurst Hospital Center, Elmhurst, NY; and ²Mount Sinai School of Medicine, New York, NY.

The Joint Commission for Accreditation of Healthcare Organizations requires there to be a summary list in the medical record. This list must include four elements: diagnoses (and problems), medications, allergies, and significant historical data (hospitalizations and procedures). This has been a notoriously difficult task to achieve in hospital settings, due to problems involving chart management.

Aim: To evaluate whether conversion of the chart summary list from a paper record to an electronic medical record would improve compliance with summary list completion. Our site was the ambulatory practices unit of a large acute care municipal hospital with nearly 500,000 patient visits yearly.

Methods: Compliance with summary list completion was monitored before and after the summary list was converted from a paper medical record to an electronic medical record. All four elements of the list were required to be complete in order for compliance to be achieved in any individual record. Charts were sampled in random fashion on an ongoing basis throughout the study in numbers proportional to the visit frequencies of the various primary care and specialty practices at the hospital site.

Results: Before conversion to an electronic medical record, the completion rate for the summary list was $91/2485 \times 100 = 3.7\% \pm 5\%$ (99% confidence interval) over a baseline 3-month period. After all four elements of the summary list were moved to the electronic medical record, the completion rate was $680/680 \times 100 = 100\% \pm 5\%$ (99% confidence interval) over a 6-month period.

Conclusions: Implementation of an electronic medical record led to a substantial and sustained improvement in compliance with summary list completion. This allows immediate access to vital clinical information with much greater reliability. It also satisfies Joint Commission for Accreditation of Healthcare Organizations requirements.

Liver

Characteristics of Oleic Acid Uptake by Rat Adipocytes and Binding to Rat Adipocyte Plasma Membranes Indicate Two Distinct Pathways for Cellular Uptake. D.D. Stump¹, X. Fan¹, and P.D. Berk^{1,2}. ¹Department of Medicine, Division of Liver Disease and ²Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

Despite identification of seven proteins as putative long-chain (LC) free fatty acid (FFA) transporters, facilitated LCFFA transport mechanisms remain controversial. Others report that LCFFA "flip-flops" very rapidly across synthetic lipid bilayers, with msec T-1/2s, making a need for facilitated transport unlikely (1). However, using the same methods, researchers found that LCFFA uptake by adipocytes, studied at non-physiologic conditions with respect to LCFFA and albumin concentrations, was much slower, with a T-1/2 of ~40 sec (1).

Aim: To determine the mechanisms of LCFFA uptake by adipocytes.

Methods: Rat adipocytes and adipocyte plasma membranes were isolated by standard methods. Initial cellular [3H]-oleate uptake velocity (2) and equilibrium binding studies were conducted at 37°C in the presence of bovine serum albumin (BSA), at LCFFA:BSA ratios of 0.1:1 - 4:1. Unbound oleate concentrations (Ou's) were calculated according to Spector et al. (3).

Results: Both uptake and binding consisted of the sum of a saturable plus a non-saturable component of the form:

$$F(Ou) = P1.Ou/(P2 + Ou) + P3.Ou,$$

where F(Ou) represents either uptake or binding at a given Ou. By assuming that the substrates for saturable and non-saturable uptake, respectively, were the separate LCFFA pools bound either saturably or non-saturably to the membrane, it was possible to calculate rate constants of transmembrane movement of LCFFA by the separate saturable ($k_s = 2.9 \text{ sec}^{-1}$, T-1/2 = 0.2 sec) and non-saturable ($k_{ns} = 0.13 \text{ sec}^{-1}$, T-1/2 = 5.3 sec) uptake processes. The calculated k_s is similar to others reported for protein-mediated transport; that for non-saturable uptake (k_{ns}) is much slower. Both are similar to results in hepatocytes (4).

Conclusions: LCFFA uptake by adipocytes consists of two components: a rapid, saturable process reflecting protein-mediated transport and a slower, non-saturable one reflecting passive "flip-flop."

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Promoter Analysis of Mitochondrial Aspartate Aminotransferase (mAspAT) to Localize Regions Responsive to Adipocyte Differentiation. M.W. Bradbury¹, D.D. Stump¹, and P.D. Berk^{1,2}. ¹Division of Liver Diseases, Department of Medicine, and ²Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

Mitochondrial aspartate aminotransferase is a well-studied enzyme with a role in nitrogen balance and the malate-aspartate shuttle, which passes reducing equivalents across the mitochondrial membrane. The enzyme is also found on the surface of adipocytes, hepatocytes, and other cells with high transmembrane free fatty acid (FFA) fluxes, and was isolated and described as plasma membrane fatty acid binding protein (FABPpm). Certain fibroblast cell lines, such as 3T3-L1, can be induced to differentiate into adipocytes *in vitro*. During this differentiation there is an increase in FFA uptake, and in the case of 3T3-L1, a large increase in the amount of mAspAT mRNA in the cell and FABPpm on the surface. An increase in gene transcription is a likely source of some of these changes.

Aim: To determine if the mAspAT promoter responds to pre-adipocyte differentiation and identify putative responsive regions or elements.

Methods: We designed a promoter construct containing a zeocin-resistance selectable marker, a secreted alkaline phosphatase (SEAP) reporter gene, and a 1.7 kb fragment of the rat mAspAT promoter. Full-length plasmid and plasmids with deletions of the promoter were transfected into 3T3-L1 fibroblasts with SuperFect® (Qiagen, Santa Clara, CA). Stable transfectants were prepared by Zeocin selection. Individual clones or mixed populations of transfectants were induced to differentiate into adipocytes. Medium was changed every 48 hrs and assayed for SEAP activity. Endogenous phosphatases were inhibited by heat inactivation and l-homoarginine.

Results: Clones of 3T3-L1 bearing the full-length mAspAT promoter construct were analyzed and showed significant SEAP expression in a similar pattern. Expression was increased above background on day 0 of differentiation, followed by a slight increase on day 2, and a significant increase by day 4. The level of expression either remained stable through day 8 or showed a slight decrease. The first two deletion constructs analyzed suggest that there may be negative as well as positive regulatory elements in the promoter. A construct deleted to position -251 showed an increase in expression on day 2, and a decrease to the level of day 0 thereafter. A construct with a longer promoter region, to -441, however, showed no expression above background in six clones analyzed. Further deletion constructs are being constructed and analyzed.

Conclusions: The mAspAT promoter is responsive to pre-adipocyte differentiation. The 1.7 kb fragment produces an expression pattern consistent with studies of mRNA expression. The different expression patterns of deleted constructs suggest that there are both positive and negative regulatory elements within the promoter. Further analysis should locate these elements and allow for the identification of binding sites for either known or novel transcription factors.

Histopathologic Analysis of the Progression to Cirrhosis in Patients with Recurrent Hepatitis C Viral (HCV) Infection after Liver Transplantation. T.D. Schiano¹, M.I. Fiel², M.Q. Ye², A.D. Min¹, L. Kim-Schluger³, P.A. Sheiner³, S.H. Sigal^{1,4}, S.N. Thung², and H.C. Bodenheimer¹. ¹Division of Liver Diseases, Department of Medicine, and Departments of ²Pathology and ³Surgery, Mount Sinai School of Medicine, New York, NY, and ⁴Division of Gastroenterology and Gastrointestinal Immunology, Department of Medicine, Columbia University/St. Luke's-Roosevelt Hospital, New York, NY.

Progression of histologic damage in recurrent HCV appears to occur at an accelerated rate in allograft livers. HCV reinfection of the allograft occurs frequently, and it is feared that with increasing time from transplantation (LT), many patients will ultimately develop cirrhosis.

Aim: In order to better predict patient outcome and indications for treatment, we sought to establish a timeline for the progression of fibrosis in HCV patients developing cirrhosis post-LT.

Methods: Using the RMTI and pathology databases, all HCV patients with documented histologic recurrence up until 4/99 were identified. Those who had serial liver biopsies and chronic hepatitis (CH) with either stage 3 or stage 4 fibrosis were studied. Using current CH nomenclature, these biopsies were blindly staged (0 = no fibrosis, 1 = portal fibrosis, 2 = fibrous septa, 3 = transition to cirrhosis, 4 = cirrhosis) and graded (1 = mild, 2 = moderate, 3 = severe lobular activity) by a liver pathologist.

Results: HCV was the indication for LT in 468 patients, with 231 (49%) having documented histologic recurrence. Forty-two (18%) had stage 3–4. After excluding patients with concurrent vascular/biliary complications or cellular/ductopenic rejection, 30 patients (mean age 47.4 yrs, 16 males) were studied. Recurrent HCV infection was diagnosed on biopsies an average of 10.5 months post-LT in these patients. Progression from initial biopsy-proven diagnosis of hepatitis to stage 2 took 17.1 months (n = 8, range 2–55 months, though in 4 patients within 4 months), from stage 2 to 3 fibrosis, 27.5 months (n = 9, range 10–43), and from stage 3 to 4 fibrosis, 12 months (n = 7, range 1.5–16). Twelve patients progressed from initial biopsy-proven diagnosis of hepatitis to stage 3 on consecutive biopsies (mean 27.3 months, range 7–58), while 5 others progressed to stage 4 (mean 24.8 months, range 11–51). The average inflammatory activity was moderate to severe (grade 2.6/3) throughout all stages. Patients reaching stage 3–4 (n = 18) not requiring re-LT had mean PT 13.1 seconds, total bilirubin 2.6 mg/dL, serum albumin 3.4 g/dL, alkaline phosphatase 296 IU/L, ALT 120 IU/L and AST 142 IU/L. At the first clinical evidence of portal hypertension, PT was normal with only minor abnormalities in serum bilirubin and albumin. Thirteen of 16 (81%) HCV patients progressing to stage 2–3 within 2 years of LT ultimately developed portal hypertension and/or required re-LT.

Conclusions: HCV patients who develop cirrhosis post-LT typically have early reinfection of their allograft with significant inflammatory activity. The development of stage 2–3 within 2 years of LT may be predictive for the ultimate development of portal hypertension and need for retransplantation. Hepatic synthetic function appears to be well preserved until patients develop signs of portal hypertension.

Role of Body Composition and Resting Energy Expenditures in Fatigue among Patients with Chronic Hepatitis C. N. Lau^{1,2}, K. Gardilla², S. Sigal^{1,2}, and D.P. Kotler². ¹Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY; and ²Division of Gastroenterology and Gastrointestinal Immunology, Department of Medicine, Columbia University/St. Luke's-Roosevelt Hospital, New York, NY.

Fatigue is a commonly reported symptom among patients with chronic hepatitis C (HCV) infection.

Aim: To assess fatigue using the Fatigue Impact Scale (FIS) and to correlate fatigue with body composition, exercise tolerance, and resting energy expenditure.

Method: Twenty-seven (27) patients with stable, non-cirrhotic chronic hepatitis C (9F, 18M) with mean age 45 years (range 28–55) were evaluated. Patients who were active alcoholics or receiving treatment with interferon were excluded. Patients rated their fatigue level using a self-reporting questionnaire that evaluated 3 dimensions: physical, cognitive and psychosocial. Body composition measurements (BCM) were made by bioelectrical impedance (BIA). Resting energy expenditure (REE) was measured by indirect calorimetry. A sub-maximal exercise test was performed using a modified bicycle test to estimate aerobic capacity.

Results: Total fatigue score, as assessed by the FIS, was associated with depletion of weight (p = 0.04) and body cell mass (BCM, p = 0.007). Patients who rated fatigue high, especially along the physical dimension, did well on the exercise bicycle test (p = 0.012). The predicted REE was calculated according to the Harris-Benedict equation. There was no difference found between the measured REE by indirect calorimetry and the predicted REE, indicating that the patients were normo-metabolic. Aminotransferase levels and REE did not correlate with fatigue. Patients scored highest in fatigue along the psychosocial dimension. Women scored higher fatigue levels along every dimension compared with men.

Conclusion: Subjective fatigue is associated with nutritional depletion as assessed by decreased weight and BCM, but not by objective evidence of impaired exercise capacity. This finding indicates that subjective fatigue is a poor predictor of physical capacity.

Inadequacy of Non-invasive Assessment in Detecting Significant Inflammation in Patients Undergoing Liver Transplantation for Chronic Hepatitis B. S.H. Sigal^{1,2}, A.D. Min¹, T.D. Schiano¹, M. Ye³, K.B. Hussain¹, S.N. Thung³, C.M. Miller⁴, and H.C. Bodenheimer¹.

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Recent reports indicate that lamivudine improves liver function in patients with decompensated cirrhosis associated with chronic hepatitis B (HBV). Theoretically, only patients with significant inflammation would benefit from such therapy.

Aim: To assess the activity of inflammation in liver explants from patients undergoing liver transplantation for chronic HBV, and the sensitivity of the biochemical and serologic assessment in detecting moderate-to-severe inflammation.

Methods: Liver chemistries, serologies (HBeAg, HBV DNA by liquid hybridization assay) and liver size (% predicted liver volume) of patients undergoing liver transplantation for chronic HBV from 1994 to 1999 were correlated with inflammatory activity in the liver explants. Pediatric patients and those with recent alcohol use, fulminant or subfulminant disease, portal vein thrombosis, hepatocellular carcinoma requiring pre-transplant treatment and concurrent HCV and HDV infection were excluded. Patients with recent use of anti-viral therapy were also excluded.

Results: 34 patients were available for review (29 male, 5 female). Mean age was 52.8 years (30–71), and 10 (29.4%) were Asian. Thirteen (38%) livers had minimal or mild inflammatory activity, while 21 (62%) had moderate or severe inflammation. The severity of inflammatory activity of those with minimal/mild vs. moderate/severe activity could not be predicted by ALT level (64.9 ± 12.9 vs. 63.9 ± 7.0 U/L), HBeAg+ status (5/12 vs. 5/16), ethnicity (3/13 vs. 6/21) or liver volume (70 ± 5 vs. 63 ± 4% predicted) (p = NS). Low but detectable HBV DNA levels (5.0 to 48.5 pg/mL) were more commonly present in patients with moderate/severe activity (7/19 vs. 1/12; p = 0.04). However, 12/23 (52%) patients with undetectable HBV DNA had moderate/severe inflammatory activity.

Conclusions: Moderate/severe inflammatory activity is present in 62% of patients undergoing liver transplantation for chronic HBV. Histologic inflammatory activity in patients with end-stage chronic hepatitis B is poorly predicted by biochemical, serologic or molecular markers of liver injury or viral replication.

Interferon alfa-2b and Ribavirin in Patients with Resistant Chronic Hepatitis C. A.D. Min¹, J.L. Jones¹, E. Lebovics², I.M. Jacobson³, F.M. Klon¹, I.S. Goldman⁴, S. Esposito⁵, J.M. Geders⁶, H. Tobias⁷, and H.C. Bodenheimer¹.

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The combination of interferon (IFN) and ribavirin has efficacy in previously untreated patients with hepatitis C or those relapsed after IFN alone. However, the effect of increased dose of IFN in combination with ribavirin is not known in resistant chronic hepatitis C.

Aim: Thus, this study was to evaluate the effect of an increased dose of IFN in combination with ribavirin on the efficacy of treating patients with chronic hepatitis C without sustained response to prior IFN therapy.

Methods: We randomized 159 patients with chronic hepatitis C to receive either 3 or 5 MU of IFN alfa-2b three times/week and ribavirin (1000–1200 mg/day) for 12 months, and followed them for an additional 6 months. Subjects were HCV RNA positive in spite of prior IFN therapy. Treatment was stopped at 6 months for subjects with less than a 90% reduction in viral load from the baseline. All subjects had liver biopsy within 2 years prior to study entry. Full follow-up data are available on 126 subjects. There were 100 nonresponders (NR) and 26 relapsers (R) to prior IFN therapy. Serum HCV RNA levels were measured using a quantitative PCR assay at baseline, 6, and 12 months of treatment and after 6 months post-treatment. Sixty-seven (53%) subjects were randomized to receive 3 MU IFN and 59 (47%) to 5 MU IFN.

Results: The mean age of the subjects was 47 years (range 28–68) and 91 (72%) were male. One-hundred-eight (86%) had genotype 1. Nineteen (15%) had cirrhosis on pre-study biopsy. The data at 12 months of treatment and at 6 months after the end of treatment are summarized in the Table.

At end of therapy	R (n=26)	NR (n=100)	3 MU (n=67)	5 MU (n=59)
HCV RNA (-)	13 (50%)	26 (26%)	18 (27%)	20 (34%)
HCV RNA (+)	13 (50%)	74 (74%)	49 (73%)	39 (66%)
At 6 months F/U	R (n=26)	NR (n=100)	3 MU (n=67)	5 MU (n=59)
HCV RNA (-)	9 (35%)	16 (16%)	11 (16%)	14 (24%)
HCV RNA (+)	17 (65%)	84 (84%)	56 (84%)	45 (76%)

There was a statistically significant difference in virologic response between the R and NR groups after 12 months of treatment ($p = 0.034$), but not after 6 months of follow-up ($p = 0.065$). There was no difference between subjects randomized to receive 3 MU and 5 MU of IFN alfa-2b, both at 12 months ($p = 0.51$) and at 6-month follow-up ($p = 0.42$). Fourteen of 39 (36%) subjects with (-) HCV RNA at 12 months subsequently had (+) HCV RNA at 6-month follow-up. Of those 14, ten (71%) were NRs to prior IFN monotherapy.

Conclusions: Although there was a significant difference in virologic response between relapsers and nonresponders at the end of 12-month therapy of combination treatment, there was no statistical difference in sustained response at the 6-month follow-up. When used in combination with ribavirin, 5 MU of IFN alfa-2b did not enhance the response rate compared with 3 MU.

Medical Oncology

Gastric Carcinoma at Elmhurst Hospital Center (EHC), 1990–1996. S.Khanwani¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Cancer of the stomach remains the second most common cause of cancer-related death in the world. The incidence is highest in East Asia, South America, and Eastern Europe. Gastric carcinoma is primarily a disease of the middle-aged and elderly; the proportion of patients ≤ 40 years of age has varied from 6–8%. However, a study done at an urban public hospital found that 15% of cases were in patients ≤ 40 years; young patients were more likely to be black.

Aim: A study was conducted at EHC, which has an ethnically diverse population with a large proportion of foreign-born patients, to examine the demographic, clinical and pathologic features of patients with gastric carcinoma.

Methods: From the Tumor Registry a list was obtained of all patients diagnosed from 1990–1996, and charts were reviewed. Odds ratios were calculated and chi-square analyses were performed using EpiInfo. One hundred and two patients had been diagnosed with gastric carcinoma; 90 charts (88%) were located and reviewed. The male:female ratio was 2:1. Thirty-five patients (39%) were Hispanic, 29 (32%) were Asian, 19 (21%) were white and 7 (8%) were black. Ten patients (11%) were ≤ 40 years; comparing these patients with older patients, clinical staging was as follows: localized: 0 ([0%] vs. 16 [20%]), regional: 4 (40% vs. 18 [22.5%]), distant metastases: 6 ([60%] vs. 29 [36.3%]), unknown: 0 ([0%] vs. 17 [21.3%]). The odds ratio of males having local/regional disease as compared to distant/unknown was 2.54, which approached statistical significance (95% confidence interval = 0.89, 7.41], chi-square = 3.76, $p = 0.053$); corresponding odds ratio for Asians vs. Hispanics was 3.14 (95% confidence interval = 1.00, 10.02; chi-square = 4.92, $p = 0.027$). Epigastric pain was the presenting complaint in 54 patients (60%); 48 cases (54%) had proximal lesions.

Conclusions: Young patients accounted for a higher proportion of patients than is generally found; they were all Asian or Hispanic, and were more likely to have advanced disease. A substantial proportion of patients had proximal lesions; males may be more likely to be diagnosed at an earlier stage. Additional study is indicated to further define the risk in younger and foreign-born patients; physicians should have a high index of suspicion when treating patients from areas of high incidence.

Breast Carcinoma at Elmhurst Hospital Center (EHC). N. Adya¹ and A. Lyman². ¹Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and ²Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Breast cancer is the most common life-threatening malignancy in North American women; mortality differences by race are known to exist.

Aim: To study the demographic characteristics of women with breast cancer in Elmhurst Hospital Center.

Methods: This is a retrospective cohort study of breast cancer patients with newly diagnosed breast cancer from January 1995 to December 1996. The patient list was obtained from the hospital tumor registry. Sixty-four patients were randomly selected from 114 patients, and hospital and tumor registry records were reviewed.

Results: The most common age category was 50/64 years (50%). Racial distribution: Caucasian 12 (18.75%), African American 12 (18.75%), Hispanic 19 (29.68%), East Asian 6 (9.37%), South Asian 5 (7.81%), Other 3 (4.68%) and not in chart 7 (10.93%). Family history of breast cancer: positive in 5 (7.81%), negative in 37 (57.81%), and not documented in 22 (34.37%). Menopausal status: postmenopausal 20 (31.25%), premenopausal 15 (23.43%), unknown 29 (45.31%) and late menopause 4 (6.25%). Early menarche was present in 10 (15.62%) and not documented in 30 (46.87%). Late age at first pregnancy: present in 9 (14.06%) including nulliparous, not documented in 26 (40.62%). Parity: nulliparous 4 (6.25%), one-two 12 (18.75%), three-four 13 (20.31%), five or more 6 (9.37%) and not documented in 29 (45.31%). History of benign breast disease: present in 1 (1.56%) and unknown in 57 (89.06%). History of radiation exposure: negative in one patient (1.56%) and unknown in 63 (98.43%). Oral contraceptive use: present in 1 (1.56%) and not documented in 63 (98.43%). Hormone replacement therapy: not documented in 61 (95.31%) and negative in 3 (4.68%). Estrogen receptor/progesterone receptor (ER/PR) status: +/+ in 20 (31.25%), +/- in 7 (10.93%), -/+ in 1 (1.56%), -/- in 7 (10.93%) and unknown in 29 (45.31%). Of 20 postmenopausal patients, ER and PR were positive in 11 (55%) and 7 (35%) respectively. Of 15 premenopausal patients, ER and PR were positive in 2 (10%) each. Grading: well differentiated in 3 (4.68%), moderately differentiated 15 (23.43%), poorly differentiated 10 (15.62%), undifferentiated 2 (3.12%) and unknown 34 (53.12%). Histology: carcinoma in situ (CIS) 3 (4.68%); infiltrating- ductal 41 (64.06%), lobular 5 (7.81%), ductal/lobular 3 (4.68%), adeno 2 (3.12%) and others 4 (6.25%). Staging: 0: 8 (12.5%), 1: 16 (25%), 2A: 7 (10.93%), 2B: 9 (14%), 3A: 7 (10.93%), 4: 1 (1.56%) and unknown: 13 (20.31%). Comparing stage 0-4 at time of diagnosis, there was no significant difference between these data and data for 1992. Majority presented with lump- 25 (39.06%); 16 (25%) were self-reported. Screening mammogram diagnosed 8 (12.50%) patients; 57.81% patients were uninsured.

Conclusions: The most common presentation at diagnosis was a self-reported breast lump (25%); 12.5% were diagnosed by mammogram; stages 0, 1, 2 constitute 62.5%; a majority of the patients were uninsured, which could contribute to late presentation at diagnosis. Patients at EHC are not being diagnosed at an earlier stage than was found a few years earlier. Improved availability of screening mammography to this population might considerably improve outcome. Better documentation in hospital charts would facilitate future research.

Identification of PLZF Transcriptional Targets by Expression Profiling. M. McConnell and J. Licht. Derald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY.

PLZF, a zinc finger transcription factor, is one of several fusion partners for the retinoic acid receptor alpha gene that is rearranged in acute promyelocytic leukemia. This rearrangement has been shown to disrupt normal cellular retinoid response pathways and presumably also disrupts PLZF pathways, although these latter pathways have not been established. The identification of genes altered by PLZF expression is the first step in deciphering these pathways. In order to find these genes, a tetracycline-regulated PLZF-expressor cell line was developed. At several time points after expression of PLZF was induced, mRNA was isolated and used to query a cDNA array (Research Genetics, Huntsville, AL). A temporal expression profile of genes both up- and down-regulated by PLZF was derived and confirmed by Northern blot. The validity of the Genefilter system, the list of identified genes, and their putative roles in growth suppression and tumorigenesis will be discussed.

Investigation of MMTV-like LTR in Human Breast Cancer. Y. Wang, J.F. Holland, and B.G.T. Pogo. Department of Medicine, Division of Medical Oncology, Mount Sinai School of Medicine, New York, NY.

The mouse mammary tumor virus (MMTV) has been regarded as a potential model for human breast cancer (BC). We have previously reported that a 660 bp MMTV-like env gene sequence was present in about 38% human BC, but not in the normal breast and normal tissues. We also found that 66% of the positive samples expressed this gene. The 3N long terminal repeats (LTR) sequence of the MMTV plays a very important role in mouse mammary tumorigenesis, since it contains several important elements, such as enhancers, promoters, glucocorticoid responsive element (GRE) and an open reading frame (ORF) for potential superantigen. These all have critical functions during the MMTV infection. Therefore, we have focused our research on LTR identification and expression. By using PCR, cloning and sequencing, a 630 bp fragment was first amplified from 32 human BC and breast cancer cell lines. It showed over 90% homology to MMTV LTR, but very low homology to any other known sequences in the genebank. Using an extra-long PCR and a nested PCR, a longer 1.2 Kb sequence was detected, and complete ORF and GRE elements have been identified. The results from the preliminary experiments also indicated that the LTR gene is expressed in BC. This human MMTV-like LTR has been cloned into a bacterial and a mammalian expression vectors to be used for detection in human tissues and functional assays. The results obtained from this research will help researchers understand the molecular mechanism(s) of human breast carcinogenesis, and identify new genetic markers possibly useful for diagnosis, prognosis and therapy.

Effect of Trehalose on Cell Kill Effects of Anticancer Agents or Hyperthermia against Human Tumor Cell Lines. L-T. Song, T. Ohnuma, and J.F. Holland. Division of Medical Oncology, Mount Sinai School of Medicine, New York, NY.

Trehalose is a non-reducing disaccharide found in organisms as diverse as insects, bacteria, fungi and algae, but absent from mammals. In these organisms trehalose serves not only as an energy source but also as a protectant against damage imposed by physical/chemical stresses such as poor nutrition, heat, dehydration, and exposure to hyperosmotic shock or to heavy metals. Thus, among insects and plants living in desert or subzero temperature, trehalose acts as an important anti-desiccant and anti-freezing substance. Trehalose has been successfully utilized as a storage solution for cells and organs for transplantation.

Aim: In view of the unique protective characteristics of trehalose on the host under stress, we attempted to determine whether trehalose plays a role on cell kill effects of anticancer agents or hyperthermia against human tumor cells, with a goal of eventually expressing a trehalose gene in host cells.

Methods: We examined the effect of trehalose on three human tumor cell lines using MTT assay on day 3 after adding the compound to culture medium.

Results: Increasing concentrations of trehalose in culture medium resulted in progressive inhibition of cell growth of Daudi lymphoma, HEP-2 laryngeal cancer and MOLT-3 ALL cells due to hypertonicity. Among the 3 cell lines, HEP-2 cells were able to tolerate the highest concentration of trehalose. Next, we examined the ability to support cell growth in media with decreasing glucose concentrations supplemented with increasing trehalose concentrations, making the media essentially isotonic. We observed that medium containing 0.007M glucose supported cell growth as efficiently as the original medium which contained 0.011M glucose. In the presence of 0.007M glucose, trehalose concentrations up to 0.04M supported optimal HEP-2 cell growth. In the presence of 0.004M – 0.04M of trehalose, cell kill effects of 0.3 µg/mL doxorubicin or 0.5 µg/mL vincristine on HEP-2 cells were essentially identical to those of no-trehalose control. At the trehalose concentration of 0.04M, doxorubicin concentration-cell kill curves overlapped with those with no-trehalose control. We also exposed HEP-2 and Daudi cells at 42°C for up to 3 hrs or at 0°C for up to 4 days with or without trehalose, and compared the cell kill effects. Presence of trehalose had no effects on hyperthermia- or hypothermia-induced cell kill effects.

Conclusions: Our study failed to show that trehalose, which had modulating effects in prokaryotes and lower animal forms, had any protective effects on human tumor cell lines when exposed to anticancer agents or to high or low temperatures under experimental conditions employed.

Study of Reovirus-Induced Cytopathic Effect (CPE) and Ras Protein in Human Tumor Cell Lines. L-T. Song¹, Irwin Gelman², J.F. Holland¹, and T. Ohnuma¹. ¹Division of Medical Oncology and ²Department of Microbiology, Mount Sinai School of Medicine, New York, NY.

Lee and his colleagues recently reported that reovirus selectively kills cells with an activated Ras pathway (Science 282:1332, 1998). Since Ras expression is a common phenomenon of a variety of human tumors, reovirus might serve as an effective anticancer agent. This information is of such importance that the relationship between the reovirus-induced CPE in a variety of human tumors and Ras expression needs to be thoroughly evaluated.

Aim: To examine the relationship between the degree of reovirus-induced CPE and the degree of Ras expression.

Methods: Reovirus serotype 3 was obtained from ATCC and maintained through serial infection of LLC-MK₂ cells. We examined reovirus-induced CPE, Ras protein amounts and viral RNA on 7 human tumor cell lines, including DND-1A melanoma, 2780 ovarian carcinoma, HEP-2 laryngeal squamous cell carcinoma, U87 glioblastoma and sublines, U87wt and U87 EGFR, and MCF-7 breast cancer. NIH/3T3 mouse embryo fibroblast and LLC-MK₂ monkey kidney cell lines were also included. CPE was determined by cellular rounding, granular appearance, degeneration, detachment from the floor, and eventual cell lysis and necrosis under microscopy. Amounts of Ras protein were assayed by Western blot using pan-Ras antibody. Four days after infection, viral RNA was detected by silver staining after PAGE.

Results:	Cell lines	CPE*	Ras*	Viral RNA§
	DND-1A	++	+	+
	2780	++	+	+
	HEP-2	+	+++	±
	U87	+	++	+
	U87wt	+++	+++	+
	U87 EGFR	++++	++++	+
	MCF-7	++++	++++	+
	NIH/3T3	-	+	-
	LLC-MK ₂	+	+	+

(* graded from - to +, § presence + or absence - only)

Conclusions: All human tumor cell lines tested expressed Ras protein, and the intensity of protein expression appears to correlate with the CPE. In spite of identical very low expression of Ras in NIH/3T3 and LLC-MK₂ cells, reovirus produced CPE on LLC-MK₂ cells only. The nature of this difference is unknown, but the lack of CPE in NIH/3T3 cells may be related to PKR (dsRNA-activated protein kinase) phosphorylation after viral infection in this particular cell line.

Mass Spectrometric Identification of Intact Complexes of Etoposide with Albumin and Hemoglobin in Models and Serum. J. Roboz, L. Deng, and L. Ma. Division of Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Etoposide, a semisynthetic derivative of podophyllotoxin, has been widely used in the treatment of several malignancies. The drug strongly binds to proteins, but little is known about the nature of the complexes.

Aim. Use electrospray ionization mass spectrometry to measure the molecular masses of intact complexes with albumin (Alb) and hemoglobin (Hb), to determine the number of bound molecules under different molar ratios and incubation times in models, spiked serum, and patient samples.

Methods: Etoposide and Alb or Hb were mixed (10:1 to 1:50 molar ratios) and incubated (0–24 hrs, 37°C). Human serum was spiked to therapeutic and toxic concentrations. Model samples were flow injected, spiked and patient serum samples were analyzed by LC/MS. Trace complexes were identified in the presence of large protein excesses by: (a) mass transformation scan-by-scan along the total ion current curve and (b) monitoring preselected multiply charged ions (m/z 1432, +47 charge and m/z 1463, +46 charge).

Results: With 2–10-fold excess Alb, the complex contained only 1 etoposide/Alb at all incubation times, molecular mass 67,326.3 ± 23.3 Da (n = 45), within 0.15% of the calculated value. Pickup of 1 etoposide was also detected in spiked serum at therapeutic doses. Increasing the quantity

of etoposide led to complexes containing up to 9 etoposides, e.g., at 1:1 molar ratio, masses were detected corresponding to +2 (67,752 Da), +3 (68,236 Da), and +7 (70,502 Da) etoposides. Complexes with up to 8 etoposides/Hb were detected using 1:1 to 1:50 ratios, e.g., 15, 727 Da (+1 etoposide) and 18,189 Da (+5). All measured masses were within 0.01 to 0.5% of the calculated values. A representative patient sample contained Alb complexes with 1 and 3 attached etoposides, Hb complex with 1 etoposide, and 0.34 mmole/L free etoposide.

Conclusion. This methodology determines molecular masses of intact protein-drug complexes in the presence of large protein excess in serum. Knowledge of quantity and half-life of the complexes will lead to a better understanding of the observed influence of binding (e.g., adults vs. children) on the therapeutically important free drug fraction, and the possible monitoring of complexes for toxicity.

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Acylating Reactivity of the -CO-NH-CO- Moiety, a Structural Element of Some Antineoplastic and Teratogenic Antiepileptic Agents. Weisz¹, J. Roboz¹, I. Wolf², L. Deng¹, and J.G. Bekesi¹. ¹Division of Medical Oncology, Department of Medicine, and ²Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

While investigating the chemical reactivity of the 3-(bromoacetyl)amino-benzoylurea, a new anticancer compound synthesized in our laboratory, we have found evidence that, in addition to the expected alkylating activity of the C-Br bond, acylating activity also appeared due to the presence of the diacylamino, -CO-NH-CO-, moiety.

Aim: To investigate the acylation reactions of cyclic diacylamines, cyclic acylureas and open-chain acylureas with the NH₂ and OH groups of nucleophiles.

Methods: The following diacylamino-containing compounds were investigated: (a) Cyclic diacylamines: succinimide, glutarimide, phthalimide; (b) Cyclic acylurea: dihydrouracil; (c) Open-chain acylureas: N-benzoyl-N'-phenethylurea, 3-(bromo-acetamino)-benzoylurea, phenylacetylurea. The compounds were reacted with: (a) 50- to 100-fold excess (weight) methanol or ethanol at 25 to 78°C for 0.5 to 3 hr; the reactions were catalyzed by NaHCO₃ or K₂CO₃; (b) butylamine, phenethylamine, putrescine or N,N-dimethyl-ethylenediamine (molar equivalents) in water at room temperature for 1 to 24 hr. The reaction products were analyzed either after purification, e.g., succinimide-phenethylamine, or in the crude reaction mixture, e.g., phenylacetylurea-methanol. Molecular masses (protonated molecules) were determined by electrospray ionization mass spectrometry. When authentic compounds were available, identities were also confirmed by TLC or HPLC.

Results: The following reaction products were detected and characterized:

(a) From cyclic diacylamines: succinamic acid methyl ester, succinamidyl-putrescine, succinamidyl-phenethylamine, succinamidyl-N,N-dimethyl-ethylenediamine, glutaramidic acid ethyl ester, glutaramidyl-putrescine, phthalimidic acid methyl ester.

(b) From dihydrouracil: β-ureidopropionic acid ethyl ester, β-ureidopropionyl-putrescine, b-ureidopropionyl-butylamine.

(c) From open-chain acylureas: benzoic acid methyl ester, 3-(methoxy-acetamino)benzoic acid methyl ester, phenylacetic acid methyl ester.

Conclusions: Acylation capability was confirmed for all compounds studied. Because the -CO-NH-CO- moiety appears in the structure of some antineoplastic agents, e.g., aminogluthetamide, aminofide, and teratogenic antiepileptic agents, e.g., phenoximide, phenacemide, there is a possibility that acylation may play an important role in their biological activity.

Pulmonary

* **Pulmonary Complications in Cardiac Transplant Recipients.** R. Lenner, G.J. Schilero, M.L. Padilla, A. Gass, and A.S. Teirstein. Department of Medicine, Division of Pulmonary and Critical Care and Cardiology, Mount Sinai School of Medicine, New York, NY; and Bronx VA Medical Center, Bronx, NY.

Introduction: The incidence of pulmonary complications in heart transplant recipients has not been extensively studied. We report pul-

monary complications in 159 consecutive adult orthotopic heart transplantations performed in 157 patients at our institution between 8/86 and 9/98.

Methods: Retrospective review of medical records.

Results: Forty-seven of 159 (29.9%) recipients suffered 81 pulmonary complications. Pneumonia was most common (27/159, 17.2%-18 bacterial, 4 viral, 5 fungal), followed by bronchitis (15/159, 9.4%), pleural effusion (10/159, 6.3%), pneumothorax (7/159, 4.4%), tracheostomy (7/159, 4.4%), and obstructive sleep apnea syndrome (6/159, 3.8%). All patients with late onset, community-acquired bacterial pneumonia presented with fever, cough and a new lobar infiltrate on the chest radiograph, and responded promptly to empiric antibiotics without undergoing invasive diagnostic work-up. In contrast, early onset, bacterial pneumonias were nosocomial in nature, and carried a 33.3% mortality rate. Patients whose pre-transplant skin tuberculin test was positive were more likely to develop pulmonary complications (62.5% vs. 26.8%), and this difference was statistically significant (p = 0.007). The 18 recipients who initially received FK-506 as opposed to cyclosporine tended to have fewer pulmonary infections (5.6% vs. 29.6%) and post-transplant malignancies (0% vs. 4.3%), but these differences did not reach statistical significance. Induction immunosuppression with OKT3 in 61 recipients was associated with a significantly higher rate of lung cancer and post-transplant lymphoproliferative disorder (8.1% vs. 0%). We found no association between the presence or absence of pulmonary complications and the patients' age, gender, underlying cardiac disease and smoking history. Pulmonary infections occurred with similar frequencies regardless of the CMV serology of the donor and the recipient. During a mean follow-up of 3.4 years (0-12), the mortality rate of 23.5% (37 patients) correlated significantly with a higher rate of pulmonary complications (56.7% vs. 24.1%) that directly contributed to mortality in 11 of 37 patients.

Conclusions: Pulmonary complications were common following heart transplantation occurring in 29.9% of recipients, and were attributed to pneumonia of primarily bacterial origin in one half of the cases. Late onset, community-acquired pneumonias had an excellent prognosis following empiric antibiotic therapy, and these patients may forego invasive diagnostic work-up. In contrast, early onset, bacterial pneumonias were nosocomial in nature and carried a high mortality rate. PPD positivity was a significant risk factor for pulmonary complications. Initial immunosuppression with FK-506 as opposed to cyclosporine may decrease infectious complications and post-transplant malignancies, while OKT3 induction therapy was associated with an increased incidence of lung cancer and post-transplant lymphoproliferative disorder.

Is the Incidence of Pleural Involvement in Sarcoidosis Under-reported? A Chest CT-CXR Comparison. J.B. Szwarcberg, N. Glajchen, and A. Teirstein. Pulmonary and Critical Care Division and Radiology Department, Mount Sinai School of Medicine, New York, NY

Pleural involvement in sarcoidosis has been reported to be 5-10% by conventional thoracic radiology. It is associated with severe disease and greater multiorgan involvement. Over a 6-month period, 61 patients from the sarcoidosis service at the Mount Sinai Medical Center, New York, NY, were observed. A computed tomography (CT) scan and chest X-ray (CXR), where available, were included in the observations. CT scans were independently evaluated by a masked radiologist and compared to a simultaneous CXR for absence or presence of pleural involvement (thickening or effusion). Pleural changes were compared to pulmonary function tests (PFT's), which were scored (1 = mild, 2 = moderate, 3 = severe). Twenty-five (25) (41%) of the 61 patients had pleural involvement by CT criteria (20 thickening, 5 effusion); only 7 (11%) had pleural involvement by CXR criteria (4 effusion, 3 thickening). Patients with CT pleural involvement had more fibrosis (stage IV CT 75% vs. 25% p = 0.008), worse restrictive impairment (54 vs. 46%), and a lower DLCO (68 vs. 32% p = 0.012) on PFT's. One patient had a pleural effusion on CXR, which was not present on a subsequent CT performed after furosemide.

	CT+	CT-	TOT
CXR+	6	1	7
CXR-	19	35	54
TOT	25	36	61

CXR showed a sensitivity of 24% and a specificity of 97% for pleural involvement. The incidence of pleural involvement by CT scan in sar-

coidosis was much higher than previously reported by conventional CxR. The presence of pleural involvement occurs in more advanced disease.

A Comparison Between the Frequency of Pneumothorax Complicating Transbronchial Lung Biopsy (TBLB) of the Upper and Lower Lobes. M. Ismail, R. Theerthakarai, C. Anselmi, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Aim: The incidence of pneumothorax complicating TBLB is estimated to be 1–4%. Which lobe is more vulnerable to this complication has not been determined. Since the upper lobes are relatively more distended than the lower lobes due to a more negative surrounding pleural pressure, pneumothorax may be more frequent following TBLB in an upper lobe. To assess the validity of this hypothesis, we retrospectively reviewed our experience with 160 patients who underwent TBLB.

Methods: We reviewed the medical records of all patients who underwent bronchoscopy and TBLB at our institution during a twenty-month period. We excluded patients who underwent more than one-lobe biopsy as well as those in whom the biopsy site was not defined.

Results: A total of 160 patients (90 males, 70 females; age range from 22 to 94 years, mean age: 56.8 years) were studied. The number of biopsies ranged from 1–4. There were 49 patients with an upper lobe biopsy, 94 patients with a lower lobe biopsy, 12 with middle lobe and 5 with lingular biopsy. Only two patients developed pneumothorax following a lower lobe biopsy and none after an upper lobe biopsy.

Conclusion: There is no increase in the risk of pneumothorax following an upper lobe TBLB as compared to a lower lobe biopsy.

A Comparison of Drug-Resistant Tuberculosis in US-Born and Foreign-Born Patients in an Inner-City Community. R. Theerthakarai, M. Ismail, C. Anselmi, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Aim: Comparatively high prevalence of drug-resistant tuberculosis (TB) is seen in foreign-born individuals. To assess the prevalence of drug-resistant TB in both the US-born and foreign-born patients in our community, we reviewed our experience over a four-year period.

Methods: We retrospectively analyzed the confirmed TB cases with culture positive disease from July, 1994 to June, 1998, at the Paterson Board of Health Chest Clinic. Two hundred and one (201) patients (108 US-born and 93 foreign-born; age range: 4 months – 93 years; mean age: 44; male: 108, female: 93) were found eligible for the study.

Results: The incidence of drug-resistance among the US-born and foreign-born was 8% (9 patients) and 26% (24 patients) respectively ($p = 0.005$). Multi-drug resistance was found in 1 (1%) in US-born and 7 (8%) in foreign-born patients. The resistance to individual drugs is as follows:

	INH	RIF	PZA	EMB	SM
US-born	4 (4%)	0 (0%)	0 (0%)	3 (3%)	3 (3%)
Foreign-born	18 (19%)	4 (4%)	3 (3%)	3 (3%)	10 (11%)

Conclusions: These results indicate that the rates of resistance to all first-line drugs except ethambutol were higher in foreign-born than in US-born patients. The incidence of single and multi-drug resistance was also higher in foreign-born than in US-born patients.

Pilot Study of IV Prostacycline in the Treatment of Pulmonary Hypertension Secondary to Pulmonary Sarcoidosis. M. Padilla¹, R. Lenner¹, S. Kushwaha², M. Poon², and A. Teirstein¹. ¹Division of Pulmonary and Critical Care Medicine, and ²Division of Cardiology, Mount Sinai School of Medicine, New York, NY.

Pulmonary hypertension (PH) is a devastating result of chronic lung disease and usually indicates approaching death. Lung and heart-lung transplantation have been successful in some patients. Recently, both primary pulmonary hypertension (PPH) and secondary PH have been treated medically with prostaglandin inhibitors.

Aim: To compare IV prostacycline in the treatment of patients with marked PH due to sarcoidosis and patients with PPH.

Material and Methods: Three patients from the sarcoidosis service of the Mount Sinai Medical Center, New York, NY with Stage IV chest radiographs and PH unresponsive to steroid and antimalarial medications (pulmonary arterial pressure [PAP] range 66–95/20–40 mm Hg, mean (m) 40–60 mm Hg) and 6 patients with PPH (PAP 70–105/25–57 mm Hg, m. 40–70 mm Hg) were treated with IV prostacycline (PC). Following initiation of PC, the patients were evaluated biweekly for any changes in clinical response.

Results: The 3 patients with sarcoidosis had no clinical response to treatment with PC. These 3 died 2 to 7 months after beginning PC therapy. In contrast, only one of 6 patients with PPH expired; the other 5 clinically improved 3 to 26 months after beginning PC treatment.

Conclusion: In this small pilot series, PC did not confer the same improved prognosis for patients with PH due to sarcoidosis as it did for those patients with PPH. Further studies of patients with PH and sarcoidosis, and PH secondary to other diseases may give insight into the apparent lack of benefit from prostacycline in patients with PH due to sarcoidosis.

The Effect of Inflammation on Airway Smooth Muscle Stretch-Induced Relaxation. R. Carrillo-Bislick, G.S. Skloot, D. Chandy, A. Enriquez, A. Gadgil, and E.N. Schachter. Mount Sinai School of Medicine, New York, NY.

Airway hyperresponsiveness in asthma may be a problem of limited smooth muscle relaxation with inspiration (Skloot et al. JCI 1995; 96:2393). We have previously studied the response of stretch-induced relaxation (SIR) in guinea pig trachea (AJRCCM, 1998; 157:A515), in order to evaluate the role of mediators in this response. In the current study, we evaluated the role of allergic inflammation in SIR. Guinea pigs were sensitized using 3 repeated intraperitoneal injections (0.5 mL of a 6 mg/mL solution of ovalbumin [OA]) given over a one-week period. On day 21, the guinea pigs were challenged with an aerosol of 2.5% OA. A control group of unsensitized animals, followed concurrently, received a sham challenge of double distilled water. Both groups were sacrificed 24 hours after challenge. Guinea pig tracheal rings were then suspended in physiologic buffer and maintained at a baseline tension of 2 g. Individual rings were then stretched by applying tensions 2.5, 5, 10 or 15 g. After equilibration, the tissues were washed and reset to 2 g tension. Carbachol (10^{-4} M) was added and the tissues allowed to reach maximal constriction. The response to stretch was again studied. A total of 5 sensitized and 3 control animals have been studied to date. The inflammatory response in sensitized animals was confirmed histologically by the presence of extensive infiltration of eosinophils into the mucosal epithelium (not seen in controls). The SIR response in inflamed tissue was not significantly different from that in uninflamed tissue, either in the absence or presence of carbachol. These initial data suggest that SIR in guinea pig trachea is not influenced by the inflammatory response elicited by a single challenge with OA in sensitized animals. Repeated antigen challenge may cause airway remodeling; its effect on SIR remains to be determined.

Differences Between the Bronchoprotective Effect of Fast and Slow Deep Inspirations. D. Chandy, R. Carrillo-Bislick, E.N. Schachter, and G.S. Skloot. Mount Sinai School of Medicine, New York, NY.

Deep inspiration (DI) protects against pharmacologically induced bronchoconstriction in healthy subjects (HS) but not in asthmatics. A possible mechanism in HS is that DI stretches airway smooth muscle and breaks crossbridges, while in asthmatics, inflammation impairs this ability. We hypothesized that in HS this effect is related to inspiratory velocity, i.e., a fast (F) DI is more bronchoprotective than a slow (S) DI. We studied 10 HS (mean FEV1 % pred \pm SE = 98 ± 3), screened on day 1 by standard methacholine (Mch) challenge ($PC_{20} > 75$ mg/mL). On day 2, subjects performed 3 FVC maneuvers and then underwent modified Mch challenge without DIs (0 DI); only partial forced expirations were done after each dose. The threshold dose (DT), defined by symptoms and/or partial FEV1/FVC < 0.65 , was followed by 3 FVC maneuvers. All subjects had $>20\%$ reduction in FEV1 from baseline, a prerequisite for further study. On days 3 and 4, the protocol was identical to that of day 2, except that immediately prior to DT, subjects performed either an FDI or an SDI respectively (mean maximal inspiratory flow rate [L/s] 5.58 vs. 1.15, $p < 0.01$; mean inspired volume (l) 3.02 vs. 3.23, $p = NS$). The % reduction (mean \pm SE) in FEV1 and FVC post-DT (compared to baseline) on days 2–4 is shown.

		% Reduction	
		FEV1	FVC
Day 2	0 DI	34 ± 4	23 ± 3
Day 3	SDI	31 ± 5	19 ± 4
Day 4	FDI	20 ± 3*	12 ± 3†

Significant differences were seen for FEV1 (*FDI vs. SDI, $p = 0.018$) and FVC (†FDI vs. SDI, $p = 0.009$). These results suggest that a fast DI is more bronchoprotective than a slow DI in HS. We speculate that this may be due to enhanced breakage of crossbridges.

Histamine Bronchoprovocation Testing: Comparison of Methods. D. Grimm^{1,2}, D. Chandy^{1,2}, G. Schilero^{1,2}, and M. Lesser^{1,2}. ¹Bronx VA Medical Center, Bronx, NY, and ²Departments of Medicine, Mount Sinai School of Medicine, New York, NY.

Previously, we demonstrated by use of a logarithmic/manual method (LMM) that most subjects with tetraplegia exhibited airway hyperreactivity (AHR) in response to aerosolized histamine. However, this method may be associated with inhalation of increased amounts of histamine as compared to more standard protocols.

Aim: The objective of this study was to compare our method with two standardized methods (2 minute tidal breathing [TBM] and dosimeter [DM]) in the determination of AHR in persons with tetraplegia.

Methods: Nine subjects with tetraplegia were randomized to perform 3 histamine challenges by the different methods, which were administered at least one week apart. Both standard methods used doubling concentrations of histamine, whereas our method used logarithmic concentration increments. For the TBM, aerosol was generated by a Salter 8900 nebulizer driven by air (50 psi) at a flow rate of 8 L/min with an output of 0.35 μ L/min. Particle size ranged from 1.6–3.4 μ m and was delivered via a face mask for 2 min. For the DM, aerosol was generated by a DeVilbiss dosimeter 646 nebulized attached to a Rosenthal-French dosimeter driven by compressed air (20 psi), for a duration of 1.42 sec, producing an output of 0.31 mL/min. Particle size ranged from 2.37–2.75 μ m. Five breath-actuated maximal inhalations were performed for each incremental dose. For the LMM, aerosol generation, flow rate and particle size were the same as the TBM. Nebulization was done by manual occlusion of a thumbport and 5 maximal inhalations were performed.

Results: No significant differences for mean baseline spirometry or mean LnPC20 values were found between the 3 bronchoprovocation challenge methods (TBM LnPC20 = 0.32 ± 1.31; DM LnPC20 = 0.21 ± 1.15; LMM LnPC20 = 0.59 ± 1.05 mg/mL). Significant correlations were found for all comparisons among the methods: TBM vs. LMM $r = 0.95$, $p < 0.001$; DM vs. LMM $r = 0.81$, $p < 0.009$; TBM vs. DM $r = 0.87$, $p < 0.005$.

Conclusion: The LMM for bronchoprovocation can be used as another reliable method for performing histamine challenge studies.

Pharmacologic Characterization of Organic Dusts from the Tobacco Industry. E.N. Schachter, E. Zuskin, N. Rienzi, S. Goswami, and H. Singh. Mount Sinai School of Medicine, New York, NY.

In a recent study we evaluated workers exposed to tobacco dust in a cigarette manufacturing plant. An excess of respiratory symptoms and lung function abnormalities was noted. Water soluble extracts from dusts collected from tobacco leaves (TDE) were prepared as a 1:10 w/v solution. Dose-related contractions of nonsensitized, guinea pig trachea (GPT) were demonstrated using these extracts. TDE was added to the GPT's in 1/2 log dose increments. Response was measured as a percent of maximal carbachol contraction. The effects of mediator-modifying drugs, as well as an angiotensin converting enzyme inhibitor (captopril), a calcium channel blocking agent (TMB8) and capsaicin were tested. Atropine inhibited TDE over the entire range of doses tested. Pyrilamine, indomethacin, acivicin, NDGA, and BPB (a phospholipase A2 inhibitor) had variable effects on TDE induced constriction. Pre-treatment with capsaicin depleted irritant nerves of bronchoconstricting mediators, and resulted in a modest reduction of TDE induced constriction. Additionally, we fractionated the crude TDE by molecular weight (< 10 Kd and > 10 Kd) and by lipid content. Most of the contractile effect of TDE was found in the low molecular weight delipidated fraction of the TDE. The lipid-containing

fraction was not found to have any constrictor activity. We conclude that TDE exerts a non-immunologic constrictor effect on guinea pig tracheal muscle. The mechanism of this contractile effect is complex and capable of being modulated by a wide variety of mediator-modifying agents. Anticholinergic agents in particular appear to exert a profound blocking effect on this extract. Partitioning studies of the extract indicate that the activity is concentrated in the low molecular weight, non-lipid fraction of the extract.

Very Elderly Critically Ill Patients: What Is a Good Outcome? D.M. Nierman¹, L.M. Cannon¹, C. B. Schechter², and D.E. Meier³. The Departments of ¹Medicine, ²Community Medicine and ³Geriatrics, Mount Sinai School of Medicine, New York, NY.

Purpose: Decisions regarding the value of critical care for very elderly patients (> 85 years) depend on the desired outcomes. However, what these patients and their surrogates consider to be an acceptable outcome is unknown.

Subjects and Methods: Telephone interviews were conducted with very elderly patients or their surrogates within 1 to 2 years following hospitalization and intensive care at a tertiary, academic medical center. The interview included the Mount Sinai Care Center Survey, Spitzer's Quality of Life Index, and Patrick's Perceived Quality of Life (PQOL) Scale.

Results: Of 222 very elderly patients, 171 (77%) survived the hospitalization. A total of 146 (66%) interviews were conducted. Eighty-eight percent (88%) of patients living at home would have been willing to repeat the ICU experience again, as would 87% of surrogates of patients living at home, 78% of surrogates of patients living in skilled nursing facilities (SNFs), 96% of surrogates of patients who died in the hospital, and 59% of surrogates of patients who died after hospital discharge. Patients living in SNFs had significantly worse function than patients living at home as assessed by Spitzer's Quality of Life Index; however, their Patrick's PQOL scores were comparable.

Conclusions: Independent of the outcome, respondents to these interviews felt that the ICU admission was worthwhile. For hospital survivors, patient-perceived QOL was acceptable independent of level of function or place of residence. The definition of a successful ICU outcome for this patient population deserves reexamination.

Psychiatry

Hemispheric Specialization for Selective Attention. S. Chokron, A.M. Brickman, T.C. Wei, and M.S. Buchsbaum. Neuroscience PET Laboratory, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The pulvinar, a major association nucleus of the thalamus, may mediate the selective filtering of non-pertinent information. Previous imaging studies have suggested a role of the pulvinar in selective attention, but have not examined visual hemifields separately. New studies are needed to test for a hemispheric asymmetry occurring at the sub-cortical level. The current project provides evidence for the suitability of a new neuropsychological task to demonstrate hemifield differences in selective attention. This selection requires a filtering process that would ensure an amplification of the target and/or an attenuation of the background information.

Aim: To test for a hemispheric asymmetry in selective visual attention.

Methods: Twenty (20) normal subjects performed a letter detection task in which the attentional demand was varied. The letter to be detected could appear alone as a big stimulus or small and surrounded by flankers. In order to test for hemispheric specialization in the filtering processes, the stimuli were displayed horizontally, either in the left or in the right hemifield, or vertically, either above or below the fixation point. Subjects were signaled as to whether they were correct or incorrect, by presenting a blue background for incorrect trials. The task was carried out without this feedback with the conditions in a counterbalanced order.

Results: A significant interaction between the type of stimulus (alone or surrounded by flankers) and the hemifield of presentation (left or right) was found only in the condition where subjects were presented stimuli horizontally without any feedback. In this condition, reaction times (RTs) were shorter in the left hemifield rather than in the right one for single large stimuli, while on the contrary for stimuli surrounded by flankers, RTs were shorter in the right hemifield rather than in the left one.

Conclusions: The present findings suggest a right hemifield (left hemisphere) advantage for visual analysis of complex visual displays and suggest that the current task will be useful in fMRI imaging studies of selective attention and pulvinar function.

Radiology

Magnetic Resonance Imaging Expands the Detection of Musculoskeletal Sarcoidosis. S. Moore¹, A. Teirstein², and L. DePalo². ¹Department of Radiology and ²Division of Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY.

Reviews of the clinical manifestations of sarcoidosis stress the frequency of intrathoracic disease and a few common extrathoracic sites such as eyes, skin, liver, and lymph nodes. Although musculoskeletal symptoms are among the patient's most common complaints, there has been little interest in the extent of bone, tendon, synovial and muscle involvement beyond the well-recognized "punched out" lesions of the small bones of the hands and feet, usually confirmed by standard radiographs. MR imaging optimizes soft tissue contrast and is sensitive for evaluation of marrow infiltration and subtle bony lesions occult on plain films. Accordingly, MR scanning promises to enlarge the visualization and characterization of musculoskeletal manifestations of sarcoidosis.

Aim: To assess the value of MR imaging in musculoskeletal sarcoidosis.

Materials and Methods: Ten patients with sarcoidosis proven by tissue biopsy and/or Kveim test, who presented with symptoms suggesting musculoskeletal sarcoidosis, were evaluated. Standard plain films, bone scan and MRI on 1.5 Tesla magnet were performed, focusing on the symptomatic area.

Results: Six patients demonstrated lesions detected with MRI which were underestimated, or not detected, on plain films. Manifestations included parosseous and marrow granulomatous infiltration, tenosynovitis, and myositis. In some cases, bone scans aided in localizing lesions prior to MRI scanning.

Conclusion: These preliminary data strongly suggest that musculoskeletal sarcoidosis is common and more extensive than previously detected, and may account for the high frequency of somatic complaints in sarcoidosis patients. MR imaging accurately assesses soft tissue involvement, as well as marrow infiltration in the axial skeleton, which may be radiographically silent. Further studies of MR imaging in patients with various presentations of sarcoidosis are indicated.

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Rheumatology

Occult Active Giant Cell Aortitis Requiring Surgical Repair. Y.J. Chang, L.D. Kerr, S. Flagg, K. Dowling, J. Weintraub, R. Sathyanarayanan, H. Spiera, and J. Fallon. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Aortitis complicated by aneurysm or dissection may be a more prevalent complication of giant cell arteritis (GCA) than has been previously recognized.

A retrospective chart review of 1069 aortic repairs or replacements performed at the Mount Sinai Medical Center uncovered 19 patients (n = 19) whose tissue demonstrated active GCA. Of these 19 patients, only one had a prior diagnosis of GCA by temporal biopsy. None had a recent history of symptoms referable to the temporal arteries. Cardiovascular symptoms consisting of dyspnea on exertion (12/19), angina (6/19) and orthopnea (4/19) predominated. Physical signs consisted of a new murmur in 14/19, with aortic insufficiency confirmed in 9/19. Erythrocyte sedimentation rates were not obtained.

At surgery, 17/19 had thoracic aortic aneurysms, 2 with dissection; 6/19 had aneurysms of both the thoracic and abdominal aortas; and 2/19 had aneurysms of the abdominal aorta alone. Of the nine aortic valves replaced, none had valvulitis. All patients were discharged without further treatment or follow-up.

These data document that clinically occult active GCA necessitating aortic repair occurs, perhaps with increasing incidence. Since GCA is a systemic rather than a localized disease, earlier identification of these patients and the use of immunosuppressive therapy may prevent this catastrophic complication.

Monoclonal (Type I) Cryoglobulinemia: Long-Term Follow-up of 8 Patients. Y.J. Chang, S. Glabman, S. Dickman, R.G. Phelps, and P.D. Gorevic. Departments of Pathology and Medicine, Mount Sinai School of Medicine, New York, NY.

Patients with monoclonal (Type I) cryoglobulinemia comprise only ~6% of a recent large series of patients with cryoglobulinemia. Although ~6% of IgG myeloma proteins and ~10% of macroglobulins are cryoglobulins, in as many as ~30% of patients no underlying plasma cell dyscrasia is apparent, even after detailed clinical and pathologic evaluations. We retrospectively collected data over 13 years (1986-1999) on 8 patients (5 men and 3 women; mean age 52 years) with type I ("essential") cryoglobulinemia, who did not have any underlying hematological malignancy or connective tissue disorder; 6 had IgGκ paraproteins, one IgM, and one a biclonal (IgMγ/IgGγ) gammopathy. Mean duration from the initial manifestations until the diagnosis of cryoglobulinemia was 28 months, and mean duration of follow-up after diagnosis of cryoglobulinemia was 8 years. Initial manifestations were: cutaneous (6); musculoskeletal (3); renal (2); and neurological (1). Mucocutaneous manifestations included macules/papules (4); petechiae (3); leg ulcers (3); livedoid skin lesions (5); purpura (5); acrocyanosis (4); bluing of ear helices (3); nasal erosions (1); and Raynaud's phenomenon (2). Symptoms were reproduced by ice cube test challenge in one patient. Musculoskeletal manifestations were frank arthritis (2), arthralgias (4); and myalgias (2). Neurological symptoms were paresthesias (5) and foot drop (1). Fifty percent (50%) of patients developed clinical or biochemical evidence of renal disease, including renal insufficiency (3), proteinuria (4), or nephritic syndrome (1). One patient had chronic irritative corneal deposits solubilized by the application of warm compresses to the lids.

Cryoglobulin concentration at diagnosis varied from 0.8–11 mg/mL, with a mean viscosity of 1.6 on routine testing; of the 7 IgG-containing cryoproteins, 4 were IgG1 and one each IgG2, IgG3 and IgG4; direct N-terminal sequence analysis of heavy and light chain bands immunoblotted from gels did not reveal selective VL or VH subgroup usage. No patient had positive serology for hepatitis B or C (HCV) virus initially, and no cryoprecipitate was positive for HCV by RT-PCR; ANA and Rheumatoid Factor were negative. Only one patient had low C3 and C4 on repeated testing. Leukocytoclastic vasculitis was apparent in skin (5/5), renal (1/2) and nerve (1/1) biopsies, with 40% of skin, both renal, and the nerve biopsy also showing prominent intravascular inclusions. One renal biopsy showed mesangiocapillary glomerulonephritis which recurred in an allograft following transplantation, during which the patient became infected by HCV; both renal biopsies had eosinophilic PAS-positive hyaline inclusions with crystalline ultrastructure.

Therapies were: glucocorticosteroids (100%); immunosuppressive therapy (75%); plasmapheresis (62%) and intravenous immunoglobulin (IVIG) (37%). Over a 7-year period of follow-up, one patient has continued to require IVIG, and two others have remained clinically stable off all medication. There were 2 deaths, one from abdominal sepsis and the other from complication of bone marrow transplant. Type I cryoglobulinemia is clinically, biochemically, and serologically distinct from the more common Type II and Type III cryoglobulinemias and is only rarely associated with HCV infection; patients may not evolve to defined plasma cell dyscrasias or known lymphoproliferative disorders, even after long periods of follow-up. Disease pathogenesis involves both inflammatory and thrombotic mechanisms, and in some instances can be reproduced by direct cold challenge testing.

Renal Transplantation in Scleroderma. Y.J. Chang and H. Spiera. Division of Rheumatology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Although the outcome of renal transplantation in patients with SLE has been studied, there are few reports about the outcome of patients with PSS who have undergone renal transplantation. We retrospectively collected data from the United Network for Organ Sharing Scientific Renal Transplant Registry (UNOS) over a 10-year period. Eighty-six (86) PSS patients who underwent renal transplantation were identified. Of these 86 patients, 70% were women, 86% were Caucasians, with the mean age at transplantation 50.4 years. The overall mortality was 24% of the patient group; 44% (38/86) of renal grafts failed. First through fifth year graft survival rates were 62%, 60%, 57%, 50% and 47%, respectively. The causes of graft failure could not be ascertained in 25 of 38 patients (64%). Among the known causes, 5 had acute rejection, 4 had chronic rejection, 2

had recurrence of scleroderma (criteria accepted by UNOS), and 1 each had infection and graft thrombosis.

Immunosuppressive regimens utilized in the PSS patients consisted of anti-lymphocyte globulin in at least 25%. Sixty percent (60%) received a combination of steroids, azathioprine and cyclosporine. The use of cyclosporine was neither associated with improvement of graft survival nor an increase in the rate of the graft failure. A comparison of graft survival of PSS patients with that of SLE patients who received renal transplantation revealed comparable graft survival at 1 and 5 years.

Based upon this data, renal transplantation is as effective a treatment for restoring renal function in PSS patients as it is in SLE patients. Those PSS patients whose renal function did not improve with ACE-inhibitor treatments after scleroderma renal crisis, should be considered transplant candidates. Although the data are incomplete, the use of cyclosporine may not confer the advantage of improving graft survival in PSS patients as compared to SLE patients.

Spinal Cord Research

Venous Vascular Function in Subjects with Spinal Cord Injury Compared to Sedentary and Active Controls. J. Wecht^{1,2}, J. Weir⁴, A. Spungen¹⁻³, W. Bauman¹⁻³, and D. Grimm^{1,2}. ¹Spinal Cord Damage Research Center and Medical Services, Bronx VA Medical Center, Bronx, NY; ²Departments of Medicine and ³Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY; and ⁴University of Osteopathic Medicine and Health Sciences, Des Moines, IA.

Alterations in peripheral blood flow associated with spinal cord injury (SCI) are the result of both sympathetic denervation and the loss of an active muscle pump. Determining the contributions of autonomic denervation and the absence of orthostasis to alterations in peripheral circulation may have important clinical implications in persons with SCI.

Aim: To describe venous vascular function in subjects with SCI and in sedentary (S) and active (A) able-bodied controls.

Methods: Forty-eight (48) subjects were studied, 24 individuals with SCI, 12 S and 12 A. Venous vascular function was assessed by strain-gauge venous occlusion plethysmography.

Results: Venous vascular function is expressed as mean \pm S.D and is presented (Table 1). Maximal venous distention (VDm) was significantly reduced in the SCI group compared with both S and A groups, and also in the S relative to the A group. Total venous outflow (VOt) was significantly lower in the SCI group than in the S and A groups and in the S versus the A group. Venous emptying rate (VEi) was significantly higher in the S and A groups compared to the SCI group. When expressed as an index of VDm however, VEi was significantly higher in the SCI group compared with the S and A groups. Finally, venous resistance (VR), an indirect estimate of venous compliance, was significantly higher in the S and A groups compared to the SCI group.

	SCI	Sedentary	Active	p<0.05
VDm %	0.31 \pm 0.13	1.61 \pm 0.76	2.1 \pm 0.55	1,2,3
VOt % /sec	2.95 \pm 1.3	39.0 \pm 18.8	66.7 \pm 45.2	1,2,3
VEr % /sec	12.2 \pm 6.6	33.6 \pm 19.2	44.1 \pm 19.4	1,2
VEi %	39.3 \pm 13	21.2 \pm 8.9	21.2 \pm 4.9	1,2
VR %	0.22 \pm 0.12	0.75 \pm 0.15	0.78 \pm 0.20	1,2

1 = SCI vs. SED, 2 = SCI vs. ACT, 3 = SED vs. ACT

Conclusion: Regular orthostatic challenge and exercise may improve vascular compliance and peripheral circulation in individuals with SCI.

Surgery

Splenic Artery Aneurysm in the 1990s. S.P. Dave, E.D. Reis, A. Hossain, P.J. Taub, M.D. Kerstein, and L.H. Hollier. Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Splenic artery aneurysms (SAA), although rare, are the most common aneurysms of visceral arteries. Like most aneurysms, SAA are usually asymptomatic and diagnosed incidentally; however, rupture can cause

serious morbidity or death. Pregnancy and portal hypertension have been associated with an increased risk of SAA, but the mechanisms are poorly understood. Advances in non-invasive diagnosis and minimally invasive therapy have generated controversy regarding the optimal management of SAA.

Aim: Assess risk factors, management, and outcome of a recent series of patients with SAA.

Methods: A retrospective review performed at our institution identified nine patients with a diagnosis of SAA in the last 12 years (1988 to 1999). Demographics, clinical features, treatment, and outcome were analyzed.

Results: The mean patient age was 60.5 (range: 31 to 81) years. Six were women, three were men. Associated conditions were essential hypertension (6), smoking history (4), portal hypertension (3), diabetes (1), intracranial aneurysm (1), and polyarteritis nodosa (1). At the time of diagnosis, 6 SAA were asymptomatic (incidental findings), 2 were ruptured, and 1 was causing abdominal pain. Diagnosis was made by angiography (2), computed tomography (3), ultrasonography (3), and exploratory laparotomy (1). Aneurysm size varied from 2 to 9 cm. One patient had multiple aneurysms in the splenic artery, and the patient with polyarteritis nodosa had micro-aneurysms or dilations in other visceral arteries and iliac arteries. Six patients underwent open surgery (4, elective; 2, emergency [ruptures]); 5 with splenectomy. One patient had coil embolization; and 2 (with aneurysms <3 cm) had no intervention. Three patients died postoperatively, at 2 days (ruptured intracranial aneurysm), 4 days (myocardial infarction), and 9 months (overwhelming sepsis).

Conclusions: In this series, incidence of portal hypertension was a common factor related to SAA, perhaps because our institution has a large number of liver transplant patients. Despite predominance in women, no aneurysms were noted during pregnancy. Open surgical treatment often required splenectomy. Postoperative mortality correlated with presence of severe co-morbidity.

Thrombosis Research

Leukocytes Transfer Tissue Factor to Platelets during Thrombus Formation. U. Rauch¹, D. Bonderman¹, B. Bohrmann², J.T. Fallon², J.J. Badimon², M. Riederer³, and Y. Nemerson¹. ¹Division of Thrombosis Research, Department of Medicine and ²Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY; and ³F. Hoffmann La Roche Ltd., Basel, Switzerland.

Arterial thrombosis is known to occur after a vessel is damaged and blood is exposed to vessel-wall tissue factor (TF). Recent observations demonstrate that TF is also present in the circulating blood. Thrombi generated on collagen-coated slides by human blood stain heavily for TF. TF in thrombi appears mostly on membrane vesicles that are attached to platelets pointing to cells as the main source of blood-borne TF. TF-positive polymorphonuclear leukocytes can be isolated from the circulation and are also detectable in thrombi. Leukocytes cocultured with platelets generate more procoagulant activity than either cell alone.

Aims: To investigate whether human leukocytes transfer TF to platelets during thrombus formation. To identify the membrane adhesion molecules that mediate the TF transfer. To determine whether blocking antibodies to the identified membrane adhesion proteins inhibit the TF transfer from leukocytes to platelets.

Methods: A human monocytic cell line (THP-1) was induced with TNF to produce TF. THP-1 cells were mixed with washed human platelets and perfused over a collagen-coated slide at a shear rate of 500 sec⁻¹. Alternatively, a platelet carpet was deposited on the slide and then perfused with THP-1 cells. TF-transfer to platelets was identified by immunohistochemistry and flow cytometry. Immunoelectron microscopy was used to colocalize TF and leukocyte adhesion molecules in thrombi. The effect of antibodies (anti-CD15 and anti-TF) on TF transfer was tested by flow cytometry.

Results: THP-1 cells transferred TF to the platelets in both perfusion systems. TF was co-localized with CD15 on membrane vesicles that attached to platelet aggregates. Leukocyte-derived vesicles were assessed for surface proteins: 60% were positive for CD15, 14% for CD18, and 45% for TF. TF transfer to platelets was reduced 50% to 65% by blocking antibodies against anti-CD15. Monoclonal antibodies to TF inhibited the TF transfer to platelets by approximately 75–85%.

Conclusions: Leukocytes transfer TF-positive vesicles to platelets, which render the platelets capable of propagating coagulation. TF-transfer is mediated by the interaction of CD15 on leukocyte-derived membranes with P-selectin on platelets. The inhibition of TF transfer by CD15 antagonism may represent a therapeutic strategy for prevention of arterial thrombosis.

Queens Hospital Center

Lymphocytic Interstitial Pneumonitis in an HIV-Infected Adult. R. Ahmed, A. Goswami, N. Adhami, M. Hanif, V. Azueta, R. Ayinla, and J. Fleischman. Departments of Medicine and Pathology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Lymphocytic interstitial pneumonitis (LIP) was first described in 1966, and until 1980 most cases were associated with dysgammaglobulinemic states. In 1983, the disease was reported among Haitian adults and children with other manifestations of HIV. In 1985, the CDC identified histologically proven LIP as an AIDS-defining diagnosis in children under 13 years of age unless the serological tests for HIV are negative. In 1991, LIP was reported in 30–50% of children with pulmonary complication of AIDS. In contrast, LIP has only been described in 3% of HIV-infected patient who present with a pulmonary opportunistic infection. A recent review of pulmonary complications of AIDS noted that LIP has a tendency to occur earlier in the course of HIV infection prior to the occurrence of many other opportunistic infections. Because of the possibility in some patients of resolution of LIP either with or without retroviral therapy, there are no clear guidelines for treatment, although some authorities describe improvement with corticosteroid treatment.

Case Report: A 34-year-old male from Congo (an AIDS endemic area), a U.S. resident for 4 years, presented with chronic cough, hemoptysis and a 20-pound weight loss over three years. He was sexually promiscuous. On clinical examination, the patient had low grade fever and bilateral basal rales. His complete blood count and chemistry were remarkable for anemia. LDH was 180 IU/liter. Arterial blood gas on room air revealed — pH 7.46, pCO₂ 36.6, pO₂ 72.8, with an increased A-a gradient of 32 torr. CD4 count was markedly reduced (65) with elevation of viral load (55,000 copies). HIV serology was positive. Chest X-ray showed bilateral reticulonodular infiltration mostly in the mid and lower lung zones but sparing the apical areas. Transbronchial biopsy of the right lower lobe revealed hyperplasia of pneumocytes and interstitial infiltrate of lymphocytes, plasma cells and histiocytes without granuloma. Stains for acid fast bacilli, fungi and *Pneumocystis carinii* pneumonia were negative. These findings were consistent with LIP. Because of symptomatic dyspnea and troublesome cough, corticosteroid therapy was initiated. Four weeks later, significant improvement was noted on follow-up chest X-ray. Marked improvement in gas exchange (ABG pH 7.4, pCO₂ 40, pO₂ 95 and A-a gradient 4 torr) was noted after six weeks of therapy.

Discussion: This patient demonstrated typical radiographic and histologic features of LIP. LIP has not previously been reported as a first manifestation of AIDS in an adult. Since prior reports noted LIP to occur early in the course of HIV disease, our patient is also unique in that he presented with an advanced stage of HIV disease. His improvement with corticosteroid therapy, radiographically and physiologically, is noteworthy, particularly since there are no clear-cut guidelines for treatment of this disorder in the AIDS patient. Further studies are required to better define this noninfectious pulmonary complication of AIDS.

Cocaine-Induced Sick Cell Crisis in a Patient with Sick Cell Disease. A. Aziz¹, M. Undavia¹, A. Husain², T. Santucci Jr.¹, and F. Rosner². ¹Department of Medicine, Jamaica Hospital, Jamaica, NY, and ²Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Painful crises in patients with sickle cell disease are often precipitated by infections, hypoxia, metabolic derangements or dehydration. We report a case of painful sickle cell crisis in a 28-year-old woman with sickle cell disease induced by cocaine abuse.

Case Report: A 28-year-old African American woman with sickle cell disease presented to the emergency room complaining of generalized body aches especially in the back and the extremities. She denied fever, cough, diarrhea or urinary symptoms. She has had episodes of vaso-occlusive crisis about twice a year in association with recreational cocaine abuse.

The patient was alert and oriented but in moderate distress from pain. The only significant physical findings were pallor and icterus. The hematocrit was 27.8%, leukocyte count 17,300/mm³ with a normal differential, reticulocyte count 12.5%, Hgb S 91%, and serum lactate dehydrogenase 327 IU/L (normal range 100–200 IU/L). Chest roentgenograph

and urinalysis were normal. Urine toxicology screen revealed the presence of cocaine. The patient was treated with intravenous fluids and analgesics. Her previous hospitalization for painful crisis was also preceded by cocaine use confirmed by a positive urinary toxicology screen.

Conclusion: A fatal combination of cocaine overdose and a cocaine-induced sickle cell crisis was previously reported in a 38-year-old woman (1). In our patient, the presence of cocaine in the urine on two separate occasions during painful crises strongly suggests the association between cocaine and sickle cell crisis. The mechanism of the crisis may be related to cocaine-induced vasoconstriction.

Reference

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Guillain-Barré Syndrome and Babesiosis: A Case Report. N. Bharany, H. Dhingra, F. Rosner, and D. Brennessel. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Acute ascending paralysis in adults has many etiologies. Guillain-Barré syndrome (GBS) is the most common cause of acute ascending paralysis in adults and represents a demyelinating process of the peripheral nervous system. Abundant evidence points to the role of the immune system, although viruses (cytomegalo and Epstein-Barr), lymphoma, systemic lupus erythematosus, Rocky Mountain spotted fever and influenza vaccine have been reported in association with GBS.

Case Report: We report a case of GBS associated with babesiosis. The patient initially presented with fever, malaise, rigors and chills. Ring forms of babesia species were found on the peripheral blood smear. Indirect immunofluorescence was positive for *Babesia microti*. The patient responded well to quinine and clindamycin.

Three weeks later the patient developed gait disturbance, severe-to-moderate degree of weakness in distal and proximal muscles, respectively, in both upper and lower limbs, and areflexia. Both superficial and deep sensations were minimally impaired. Cerebrospinal fluid analysis revealed glucose 52 mg/dL, protein 91 mg/dL, and 7 leukocytes, mainly lymphocytes. Nerve conduction studies showed the evidence of a diffuse sensory-motor polyneuropathy with mixed features of axonal and demyelination pattern. Clinical diagnosis of GBS was made.

One day later, he developed respiratory weakness which required mechanical ventilation. The patient was treated with plasmapheresis and intravenous immunoglobulins for two weeks. Muscle power gradually improved, and he was weaned off the ventilator after three weeks. Twelve weeks later he had completely recovered.

Fatal Necrotizing Pancreatitis and Fasciitis in a Patient with Pulmonary Sarcoidosis (Stage III). A. Briones, G. Shidham, C. Saha, S. Chokhavatia, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Symptomatic gastrointestinal involvement in sarcoidosis is infrequent and severe pancreatic involvement is rare.

Case Study: A 31-year-old African American woman, a social alcohol drinker, treated intermittently with steroids for pulmonary sarcoidosis (stage III), was hospitalized for severe breathlessness. She was treated with intravenous steroids and improved. On the fourth hospital day, she developed severe persistent epigastric pain, with increased serum amylase (293 U/L) and lipase (314 U/L) levels. The patient's condition deteriorated rapidly. The severity of the pancreatitis and the increased risk for mortality were evidenced by (1) Ranson's criteria [four risk factors, namely: leukocytosis (26,500/mm³), hypoxemia (P₀₂ of 33 mmHg), high serum LDH (437 IU/L), and hypoalbuminemia (3.1 g/dL)], and (2) the Acute Physiology and Chronic Health Evaluation (APACHE-II) scoring system (score of 12 points). She developed methicillin-resistant *Staphylococcus aureus* pneumonia, empyema, and eventually respiratory failure necessitating endotracheal intubation and mechanical ventilation. Dynamic computed tomography (CT) scan of the abdomen revealed multiple pancreatic pseudocysts and ascites (Grade E on the CT grading system of Balthazar and Ranson). These findings prompted surgical explo-

ration which revealed a hemorrhagic and necrotic pancreas with necrotic posterior fascia requiring extensive debridement. Despite aggressive medical and surgical management, the patient failed to improve and eventually died on the fiftieth hospital day. Acute pancreatitis in patients with sarcoidosis is usually clinically benign and responds to steroid therapy. Our patient developed a severe fatal pancreatitis, despite aggressive medical and surgical treatment.

Lumbosacral Radiculopathy due to Rapid Fluid Retention and Acute Renal Failure. B. Chen and N. Paddu. Department of Physical Medicine and Rehabilitation, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Lumbosacral radiculopathy is a common clinical entity with many causes. To our knowledge, fluid retention as a cause for this disease has not been described.

Case Study: A 45-year-old man with major depression was hospitalized due to sedative Unisom (doxylamine) overdose. He was unresponsive with severe metabolic acidosis, impaired renal function and a markedly increased serum creatine kinase (CK) level (129,708 U/L). The patient was intubated and received a large amount of IV fluids as part of the treatment for rhabdomyolysis. His renal function deteriorated quickly, with total urine output of 1,880 mL, in spite of an intake of 19,928 mL in the first 3 days. As a result, dependent edema occurred, particularly in both thighs and left lumbosacral area (due to the supine position). When the patient became alert, he complained of pain, numbness and weakness of the left lower extremity but had no lower back pain. He was unable to move that limb. Electrodiagnostic studies (EMG) demonstrated left lumbosacral radiculopathy and sciatic nerve compressive neuropathy with an extensive denervation process. A non-significant diffuse central disc bulge was noted on a magnetic resonance imaging (MRI) scan. A computed tomography (CT) scan of the lower extremity demonstrated extensive fluid collection bilaterally along the iliac crest down to the knees. When edema subsided with hemodialysis, the symptoms gradually improved.

Conclusion: This patient developed radiculopathy and sciatic nerve compression due to rapid fluid retention and improper positioning. Recognition of this condition, proper positioning of the patient during the comatose state, and careful management of fluid intake may prevent this complication.

Metastatic Disease to the Patella from a Large Cell Carcinoma of the Lung: Case Report and Review of the Literature. J. Daly and I. Ashley. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We cared for a 45-year-old man with large cell carcinoma of the lung who complained of pain in the right knee and was found to have metastatic carcinoma to the patella. The patella is an extremely rare site of metastatic disease from cancer.

Method: The 32 reported cases of metastatic cancer to the patella were reviewed with analysis of the common primary sites of cancer, the prognosis, and response to therapy.

Results: The most common primary cancer site was the lung (9 cases), followed by breast cancer (5 cases), lymphoma (3 cases), and 2 cases each of melanoma, kidney, and esophagus. Other primary sites and histologies were varied. Histology included squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Treatment included patellectomy, radiotherapy and systemic treatments such as chemotherapy or hormone therapy. The ultimate prognosis depended on the responsiveness of the primary cancer to systemic treatment rather than local treatment (i.e., radiotherapy or patellectomy). The mean survival time was 7.5 months.

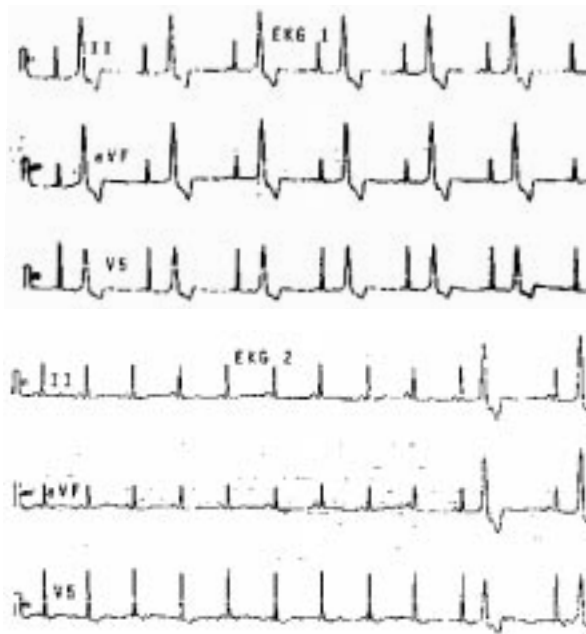
Conclusion: Metastatic disease to the patella should be considered in patients with cancer who develop significant pain in the knee. The prognosis is poor and various treatments are only palliative.

Bigeminy and Its Treatment in the Heroin Abstinence Syndrome. A.K. Goswami, Y. Khan, R. Ahmed, M. Morgan, and E. Johnson. Department of Emergency Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Abstinence syndrome from heroin is generally mild since the street drug is usually impure. Occasionally, however, the with-

drawal may include a manifestation requiring immediate attention. We report a patient with heroin withdrawal who developed bigeminal rhythm, along with symptoms which responded to intravenous morphine. Different arrhythmias have been described in withdrawal from substances like alcohol etc., but our Medline search did not reveal bigeminy in heroin withdrawal.

Case Report: A 32-year-old black female, a heroin addict, came to the emergency department a few hours after stopping heroin sniffing. The patient gave a history of hypertension and diabetes type II and was taking Glucotrol, Procardia and methadone. She had not taken her medication for two days. The patient was asymptomatic with a pulse of 68 beats per minute, BP 186/112 mmHg, normal size pupils and no piloerection. The patient was given Procardia 10 mg and clonidine 0.1 mg for her hypertension. After four hours she started vomiting, became restless, the pupils became dilated, piloerection was noted, the pulse was 70 and BP 160/94. The patient was given another dose of clonidine 0.1 mg. She also complained of palpitation, chest pain and difficulty in breathing. EKG revealed bigeminal premature ventricular contractions. Two mg of morphine was given intravenously and within minutes her symptoms abated and the rhythm became predominantly sinus (Figs. 1 and 2).



Discussion: Opioid inhibits adenylyl cyclase activity in the nucleus locus caeruleus and other centers in the central nervous system, resulting in decrease in cAMP levels. In an addict, there is progressive compensatory increase in adenylyl cyclase levels, so that normal cAMP levels are eventually maintained. On withdrawal, since adenylyl cyclase is no longer inhibited, cAMP activity and, therefore, noradrenergic activity is increased in these center resulting in withdrawal manifestations. This increased noradrenergic activity can be blocked by exogenous opioids, acting on opioid receptors or by clonidine acting on central presynaptic alpha 2 receptors. Clonidine has been extensively used for the withdrawal symptoms, as it is nonaddictive and less expensive. If opioid is selected, methadone is the drug of choice. Very rarely is it necessary to administer opioid acutely to treat opioid abstinence. Dysrhythmias, resulting from an excess catecholamine, as in our case, may represent such a situation.

Premature ventricular contractions (PVC) may occur in a variety of pathological and nonpathological states and as such are not an indication for treatment. However PVC of Lown class 3 and above may degenerate into ventricular tachycardia or ventricular fibrillation and need treatment in different clinical settings (1). Our case according to these criterion was of class 5 and hence needed prompt attention. In settings of ischemia, lidocaine can lessen or abolish PVCs and is recommended for Lown class 3 and above. In other situations beta blockers or calcium channel blockers may be more appropriate. Acutely administered opioid may be an appropriate treatment in PVCs of Lown class 3 and above in opioid withdrawal syndrome as exemplified by our case.

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Quinapril-Induced Pancreatitis. A. Goswami, T. Otrók, L. Kasturi, S. Chokhavatia, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and the Mount Sinai School of Medicine, New York, NY.

Introduction: Drugs are a relatively uncommon cause of pancreatitis in adult patients. There are very few reports of patients with pancreatitis-associated angiotensin converting enzyme (ACE) inhibitor therapy, such as captopril. We report an elderly woman with quinapril-induced pancreatitis.

Case Study: A 65-year-old nonalcoholic, white woman was hospitalized for severe upper abdominal pain radiating to the back, nausea and vomiting. A cholecystectomy for cholecystitis had been performed in 1974. Quinapril was started about eight months before this episode. Additional medications included pravastatin, glyburide, omeprazole, levothyroxine, risperidone and sertaline.

On admission, there was diffuse upper abdominal tenderness. The liver function tests were as follows: AST 29 U/L (2–40 U/L), ALT 22 U/L (2–50 U/L), total protein 5.1 g/dL (6.5–8.5 g/dL), albumin 2.0 g/dL (3.5–5.5 g/dL), total bilirubin 0.6 mg/dL (0–1.5 mg/dL), and conjugated bilirubin 0.1 mg/dL (0.1–0.4 mg/dL). The serum amylase was 5841 U/L (0–130 U/L), lipase 646 U/L (13–104 U/L) and triglyceride 274 mg/dL (52–97 mg/dL). On abdominal ultrasound, the common bile duct was normal with no stone. Computed tomography of the abdomen showed an enlarged pancreatic head and extensive peri-pancreatic infiltration with edema consistent with mild acute pancreatitis. All medications were discontinued. The patient gradually improved over the next eight days with resolution of the abdominal pain. The serum amylase decreased to 74 U/L and the lipase level to 34 U/L.

All medications, except quinapril, which was thought to be the cause of the acute pancreatitis in the absence of any other etiology, were restarted. At six-month follow-up, the patient had no further episode of pancreatitis.

Discussion and Conclusion: Definite proof that a drug causes pancreatitis requires that: (1) pancreatitis develop during treatment with the drug; (2) other likely causes of pancreatitis are not present; (3) pancreatitis resolves upon discontinuing the drug; and (4) pancreatitis usually recurs upon re-administration of the drug. Our patient met the first three criteria. We did not re-administer quinapril. Drug-induced or drug-related pancreatitis is remarkably uncommon, especially in view of the fact that there has been a dramatic increase in the number of new drugs during the last 25 years. A listing of drugs with definite association, probable association and possible association has been reported. Our patient's other drugs are not included in this listing. The relative rarity of drug-induced pancreatitis requires the gradual accumulation of information, by case reports such as ours.

Neuropsychological Assessment of Older Adults: Differentiation of Dementia from Normal Age-Related Decline. Bret S. Grube. Department of Psychiatry, Division of Psychology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

One of the most difficult challenges for neuropsychological assessment is determining whether changes in cognitive functioning in older adults are normal age-related changes, or are indicative of a dementing process. This is especially true in borderline situations, in which there is decline in cognitive functioning that warrants clinical attention, but the decline is not significantly below that which is expected following normal age-related cognitive changes. In fact, a new nosology is developing to characterize these instances, and it consists of such categories as "Benign Senescent Forgetfulness" for those people less likely to become demented, and "Incipient Dementia" for those more likely to progress toward dementia. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) includes research criteria for "Mild Neurocognitive Disorder" that might apply in such borderline cases and which does not imply a par-

ticular prognosis. There is currently no easy way to determine whether somebody who is experiencing mild or moderate memory problems in older age will go on to develop severe problems associated with dementia (as in Alzheimer's Type), or whether these problems will remain static and subclinical (as in normal age-related decline), or even improve or remit (as when due to other problems such as depression, hypothyroidism, or another medical condition that may partially or fully remit). While standardized neuropsychological testing provides objective evidence of problems in memory and other areas of cognitive functioning (e.g., "executive," language), and scanning techniques such as functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), and single photon emission computed tomography (SPECT) provide complementary evidence of brain functioning, other methods are available to help determine the extent to which these problems are progressive and may result in dementia. Repeat testing six months to one year following initial ("baseline") neuropsychological assessment can provide objective data pertinent to the rate of progression of cognitive decline; in addition, assessment in the form of careful history taking from the examinee and those who know the examinee well can also shed light on the rate of decline. In some cases, it is helpful to estimate earlier, "premorbid" levels of functioning in the absence of objective data collected at that time, and methods are available to accomplish this based on careful analysis of newly collected data and on prior psychosocial functioning and demographic information. There is also new normative information emerging on the nature of changes in cognitive functioning that are expected across the lifespan and in older age; these norms are essential when interpreting test data in this context. Refinement of assessment and diagnostic procedures is critical in light of recent advances in the pharmacological and rehabilitative treatments for dementia and other cognitive disorders, and in light of the aging of the population.

Prevalence of Thrombocytopenia in the Intensive Care Unit of a Municipal Hospital. A. Husain, R. Jamshidian, and I. Ashley. Department of Internal Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Study Objective: To identify the incidence and risk factors of thrombocytopenia in a community hospital intensive care unit (ICU).

Method: Charts of patients admitted to the ICU during a 12-month period (1998) were reviewed. Patients with platelet counts less than 100,000/mm³ were selected for further assessment. This group was studied with respect to the lowest platelet count they had during the ICU stay, the length of ICU stay, and other associated risk factors. The clinical significance of thrombocytopenia was also assessed.

Results: Charts of 400 patients were studied, with 42 patients having platelet counts less than 100,000/mm³.

The major underlying diagnoses leading to ICU admission in these 42 patients were delirium tremens (13), respiratory failure (7), cardiac arrest (6), cancer (6), AIDS (4), liver disease (3) and miscellaneous (3). Risk factors included alcoholism (15 patients), heparin use (9 cases), furosemide (7 cases), penicillin analogue use (6 cases), renal disease (6 cases), cardiac arrest (6 cases) and cancer (4 cases).

The lowest platelet count for the 42 patients is indicated in the Table.

Discussion and Conclusions: The incidence of significant thrombocytopenia in our ICU was 10%. Seventeen patients had platelet counts less than 50,000/mm³. The majority of these patients had two or more risk factors. Thus, the severity of thrombocytopenia correlates with the number of risk factors. The major diagnoses among these patients were delirium tremens, respiratory failure, cancer, AIDS and liver disease. The significant risk factors identified were drugs (alcohol, furosemide, heparin, penicillins and cimetidine); disease states such as renal disease, cancer and sepsis; and clinical conditions requiring central lines and mechanical ventilation. (Heparin was not used to maintain patency of the central line, neither was subcutaneous heparin used for deep vein thrombosis prophylaxis.) A large number of patients had alcohol-related thrombocytopenia; none had less than 50,000 platelets. All, however, had good prognoses with subsequent normalization of platelet counts. The severity of thrombocytopenia was related to respiratory failure with subsequent intubation, the length of ICU stay and subsequent adverse outcome. Three patients had unexplained thrombocytopenia; all three had counts around 75,000/mm³ with no subsequent morbidity, and all recovered soon after discharge from the ICU.

TABLE
Platelet Counts

Lowest Platelet Count per mm ³	No. of Patients
0–10,999	4
11,000–20,999	1
21,000–30,999	6
31,000–40,999	2
41,000–50,999	5
51,000–100,000	24

***Pneumocystis carinii* Pneumonia as the First Presentation of HIV Infection in the Elderly.** V. Jedlovsky and J. Fleischman. Department of Medicine, Mount Sinai Services Queen Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: The number of elderly patients first diagnosed with HIV infection at the time of presentation with an AIDS-related opportunistic infection has increased over the past several years. This increase has been observed in all categories of HIV transmission risk factors. From 1991–1996, a 53% increase in AIDS cases diagnosed in this manner has been reported in injection drug users, with a 94% increase in patients with heterosexual contact risk factors. This suggests a significant delay in the diagnosis of HIV infection and may lead to delayed administration of anti-retroviral therapy as well as prophylactic therapy for opportunistic infection. It is also a missed opportunity for education and behavior modification to decrease the spread of HIV infection.

Method: We retrospectively reviewed records of all elderly patients (>50 years of age) admitted to a municipal New York city hospital over a three-year period with confirmed *Pneumocystis carinii* pneumonia. This age cutoff was utilized as the Centers for Diseases Control (CDC) invokes a minimum of 50 years of age for epidemiological studies on HIV infection in the elderly. The clinical presentation, hospital course and outcome were reviewed and compared with published data for younger age groups.

Results: The mean patient age was 57.9 ± 6.6 years. In 80% (8 of 10 cases), the diagnosis of HIV infection was made at presentation with *Pneumocystis carinii* pneumonia (PCP). The mean CD4 count was 34.2 ± 39.2/mm³ (1–117/mm³), indicating advanced AIDS. The clinical presentation of PCP was similar to that in younger patients. With prompt and appropriate therapy, including initiation of appropriate anti-PCP treatment on day 1 of hospitalization, a 70% survival rate for this hospitalization was achieved, similar to that reported in younger age groups.

Discussion: The diagnosis of HIV infection was not considered until presentation with PCP at an advanced stage of AIDS in 80% of these elderly patients, thus delaying initiation of HIV treatment and counseling. Possible factors contributing to a delay in diagnosis may include: (1) poor access to medical care, (2) a misperception that HIV is a disease of younger age groups, or (3) masking of HIV/AIDS symptoms by comorbid disease which was present in 60% of our patients. Early consideration of HIV infection in the elderly is important because of the increasing number of AIDS cases in this age group. Our study suggests that when the diagnosis of AIDS/PCP is considered in the elderly and appropriate therapy is begun, favorable outcomes can be achieved.

Community-Acquired Native Valve *Staphylococcus epidermidis* Endocarditis in a Patient with Cerebral Palsy. S. Karuvannur and D. Brennessel. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We report a unique 37-year-old male with cerebral palsy who presented with *Staphylococcus epidermidis* native valve endocarditis. Although coagulase negative staphylococci are the most common cause of prosthetic valve endocarditis, native valve endocarditis occurs infrequently (1). Most reported patients had documented valvular abnormalities.

Case Report: A 37-year-old man with cerebral palsy was brought from his nursing home with complaints of lethargy, inability to swallow and poor appetite. The patient had cerebral palsy and a seizure disorder since birth. He had multiple admissions in the past for phenytoin toxicity and aspiration pneumonia, the last admission being in 1992.

There was no history of past surgery, allergies, smoking, alcohol or illicit drug use. He was receiving phenytoin 100 mg three times a day and

clonazepam 1 mg twice a day. His family history was not contributory. Three days prior to hospitalization, the patient had an upper respiratory infection for which he was receiving erythromycin.

On physical examination, the patient was a young black man, uncommunicative, and lying in a curled fetal position. There was no pallor, icterus, petechia, splinter hemorrhages, Osler's nodes, Roth's spots or Janeway lesions. He had conjunctivitis. The blood pressure was 120/80 mmHg, heart rate 66 beats per minute, respiratory rate 18 per minute and temperature 91°F. Pupils were equal and reactive to light. There was no heart murmur or splenomegaly. Pulmonary, abdominal and rectal exams were unremarkable. Both lower limbs had contractures at the hips and knees, and he had a right wrist drop. He was nonverbal and had no meningeal signs.

The blood leucocyte count was 11,000/mm³ (3.4–10,000/mm³), hemoglobin 14.3 g/dL, hematocrit 43.6% (42–52%) and platelets 239,000/mm³ (150–450,000/mm³). His phenytoin level was 56 µ (10–20 µ/mL). Electrocardiogram showed sinus rhythm with prolonged QT interval (480 ms) and chest roentgenogram was within normal limits.

Because of hypothermia, the patient was treated with intravenous vancomycin and clindamycin pending cultures for presumed sepsis. Four sets of blood cultures drawn over a 24-hour period grew methicillin-resistant *S. epidermidis*. Vancomycin was continued; clindamycin was discontinued. A transthoracic echocardiogram was performed but did not reveal any vegetations. A transesophageal echocardiogram showed a 1.1 cm vegetation on the tricuspid valve, normal valvular anatomy and normal left ventricular function.

The patient received vancomycin for 30 days and remained normothermic since day two of hospitalization. Repeat blood cultures were negative. He remained symptom free thereafter and was discharged to his nursing home on the forty-first day of admission.

Discussion: Previously considered a contaminant, *S. epidermidis* and other coagulase negative staphylococci are nowadays leading causes of nosocomial infection (2). The rise in incidence is attributed to the wide use of medical devices such as vascular catheters, shunts, prosthetic valves and joints in the care of hospitalized and chronically ill patients. *S. epidermidis* infection associated with devices tends to produce "slime," an exopolysaccharide that mediates adherence of the organism to the smooth surface of the prosthetic device. In a biofilm environment, organisms that are highly sensitive *in vitro* become resistant *in vivo*. Our patient with *S. epidermidis* endocarditis of a normal tricuspid valve had no vascular or prosthetic device. He seems to have acquired the infection outside the hospital setting. Community acquired *S. epidermidis* native valve endocarditis has been reported before (2) but it is very rare. Usually the organism is susceptible to methicillin. In contrast, hospital acquired *S. epidermidis* endocarditis is more common on prosthetic valves and more often involves methicillin resistant strains. Combination therapy has been advocated in the presence of methicillin resistance. However, this patient responded well to treatment with vancomycin alone, probably because there was no vascular or valvular prosthesis.

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Review of Infective Endocarditis over an Eleven-Year Period at a Public Hospital. S. Karuvannur, D. Brennessel, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We reviewed the predisposing factors, presenting signs and symptoms, time to diagnosis, bacteriology, echocardiographic

findings, complications and outcome of patients with infective endocarditis. A retrospective analysis of 51 cases of endocarditis as defined by the criteria of Duke (1) was conducted for the period from January 1, 1987 to December 31, 1997.

Materials And Methods: Queens Hospital is a municipal hospital that serves a population of one million people in the Borough of Queens. On an average, there are 16,583 discharges per year, 56% of whom are female and 44% male. Of these patients, 59% are black, 17% Hispanic, 12% white, 5% Asians and others 9%.

Charts of 130 patients were reviewed. Only 51 cases met the Duke criteria for infective endocarditis. Reasons for retrospective disqualification were negative blood cultures with no other evidence of endocarditis, absence of vegetations in patients without other clinical criteria or resolution of symptoms without treatment. The following data were obtained: age, sex, race, pre-hospital duration of illness, coexisting disease, dental history, presenting complaints, complications, results of investigations, treatment and outcome.

Results: The mean age of the 51 cases was 38 with a range from 21–75 years. The incidence was higher in Blacks (82%) and in males, the ratio of males to females being 1.8:1. The mean pre-hospital duration of illness was 2 weeks; the mean time to diagnosis after admission was six days. We noted that patients who died had a shorter pre-hospital duration of illness of 4–7 days.

Fever was the commonest symptom at presentation (59%), followed by pleuritic chest pain (29.4%) and shortness of breath (23.5%). Loss of appetite (13.8%), night sweats (7.8%) and headache (7.8%) ranked next. Lethargy (4%) was less common. Two patients with a history of intravenous drug abuse presented with neck pain, one due to a retropharyngeal abscess and the other due to a cervical epidural abscess. In this series, intravenous drug abuse was the commonest risk factor, followed by valvular heart disease. HIV, although not an independent risk factor, occurred in 17.6% of cases. Interestingly, intravenous drug abuse was more prevalent during 1987–1991 (45%) than during 1992–1997 (13.7%), although the numbers are too small to be statistically significant. A previous history of endocarditis was given by 15.6% of patients. Only one patient had a congenital heart lesion, a univentricular anomaly.

The commonest organism was *Staphylococcus aureus* (43%) followed by alpha hemolytic *Streptococci* (13.7%). *Staphylococcus epidermidis* was seen in 6%, *Pseudomonas aeruginosa* in 6%, *Streptococcus pneumoniae* in 6%, *Streptococcus faecalis* in 6%, *Escherichia coli* in 2% and *Klebsiella pneumoniae* in 2%; 13.7% of cases were culture negative.

Septic emboli occurred in 12 patients (23%); the commonest site was to the lungs (9.8%). Two patients had intracranial mycotic aneurysms complicated by subarachnoid hemorrhage. One had emergency resection. Both however died. One of the patients had emboli to the brain, liver and lungs and died. Emergency aortic valve replacement for vegetation-induced acute aortic incompetence was performed in one patient and another had surgery for cord compression secondary to epidural abscess. In all, 3 patients (5.9%) needed emergent surgery.

No patients in this series gave a history of a recent dental procedure. In our series, the incidence of hematuria was 10% (compared to previous reports of 49% to 70%). Thirty-two patients (62.3%) had valvular vegetations. The tricuspid valve was involved in 46.8%, followed by mitral valve 31.2%.

There was an overall mortality of 13.7% with a decrease in mortality from 15.6% in the first five years to 10.5% in the latter six years of the study. Cause of death was congestive heart failure in four patients (7.8%), subarachnoid hemorrhage secondary to mycotic aneurysm in two patients (3.9%), multiple emboli to brain, liver and lungs with sepsis in one patient (1.9%).

Summary And Conclusions: There was a higher incidence of endocarditis among males, the commonest presenting symptom was fever, the commonest organism *S. aureus* and septic emboli were the most frequent complication. Unlike other studies in which the aortic valve was the most frequently involved (2) in our series the tricuspid valve was more often involved. We had a very low incidence of surgery, low incidence of hematuria and no patients had previous dental procedures. Our overall mortality is significantly lower than any other series (21–35%) (3, 5) and may be explained on the basis of a higher frequency of intravenous drug abusers and right-sided endocarditis which is known to have a better outcome. The lower mortality in the latter half can be accounted for at least in part to earlier diagnosis and treatment and the use of transesophageal echocardiography which was commenced in 1992 at Queens Hospital Center.

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Short-Term Effect of Phentermine and Fenfluramine on Weight and Lipid Profiles in Obese Individuals. I. Sachmechi, K. Kazzawa, A. Srivastava, and L. Rezainadimi. Department of Medicine, Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Objective: To evaluate the short-term effect of the combination of phentermine and fenfluramine on weight and lipid profiles in obese individuals.

Methods: Thirty-seven patients (35 female, 2 male) were enrolled with eligibility criteria including: age 20–59 years; 20% over desirable body weight or body mass index ≥ 28 , no serious medical or psychiatric disease, and no contraindications to drug therapy. Patients were instructed on diet, exercise, and behavior modification techniques and received phentermine (15 mg/day) and fenfluramine (60 mg/day) continuously for 6 months. Nine patients dropped out of the study (3 for significant increase in blood pressure, 2 for gastrointestinal upset, 2 for complaints of memory clouding, one for chest pain, and one with new onset diabetes).

Results: Mean average weight reduction in the 28 patients who completed the study was 29.53 lbs. ($p=0.0153$), or 12.84% of initial body weight. Mean body mass index decreased by 4.607 ($p=0.0046$). The total cholesterol decreased from a mean of 237.14 ± 34.03 (mg/dL) to 204.61 ± 27.345 (mg/dL) for a mean reduction of 32.53 or 13.7% ($p=0.0002$). The total serum triglycerides decreased from a mean of 203.32 ± 96.62 (mg/dL) to 156.93 ± 65.55 mean reduction of 46.39 or 22.81%. The LDL cholesterol decreased from the mean of 153.04 ± 37.25 (mg/dL) to 127.93 ± 25.84 (mg/dL) for a mean reduction of 25.10 or 16.4%. Total mean serum HDL cholesterol increased from 40.96 ± 16.41 (mg/dL) to 47.00 ± 16.96 (mg/dL) for a mean increase of 6.03 or 14.72%.

Conclusion: Diet therapy with the combination of phentermine and fenfluramine significantly reduces weight and improves the lipid profile in obese patients. The improvement in lipid profile was much more than expected due to weight reduction alone, suggesting the possibility that phentermine and/or fenfluramine may have a direct effect on the production or clearance of lipoproteins. This study was done in 1995 when phen/fen was approved by the FDA.

Hepatic Nodular Sarcoidosis Mimicking Disseminated Cancer. G. Shidham, M. Sharma, A. Briones, T. Otrok, D. Sondhi, S. Chokhavatia, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Most patients with sarcoidosis are diagnosed between 20 and 40 years of age. The disease is very rare among Southeast Asians. Thoracic sarcoidosis commonly presents with characteristic radiographic and computed tomographic (CT) findings of interstitial lung disease and mediastinal/hilar lymphadenopathy. In contrast, CT findings of abdominal sarcoidosis are less characteristic and are commonly reported as nonspecific hepatosplenomegaly, retroperitoneal lymphadenopathy and, least commonly, hepatosplenic nodules. These nodules may occur in one of five patterns of which hepatic predominance is the least common presentation. The hepatosplenic nodular appearance can be mistaken for lymphoma, metastatic cancer or infection.

Case Study: A 58-year-old Asian Indian woman had a 6-month history of abdominal pain, nonproductive cough, loss of appetite, low grade

fever and weight loss. On physical examination, the liver was enlarged (17 cm), as was the spleen (5 cm below the costal margin). No lymphadenopathy was noted. Laboratory data showed aspartate transaminase of 114 IU/L (normal: 2–40), alanine transaminase of 75 IU/L (normal: 2–50), alkaline phosphatase of 690 IU/L (normal: 30–115) and angiotensin converting enzyme of 86.7 units/L (normal: 8–52). Bilateral interstitial infiltrates were seen on chest X-ray. CT of the abdomen demonstrated hepatosplenomegaly with a nodular contour of the liver and

multiple hepatosplenic nodular lesions with hepatic predominance. Initial diagnostic considerations were lymphoproliferative disorder, metastatic cancer and chronic granulomatous infection. Sputum, transbronchial biopsy and liver biopsy were negative for acid-fast bacilli (AFB)/fungus stains and cultures. Multiple noncaseating granulomas consistent with sarcoidosis were seen on liver and transbronchial biopsy. This elderly Asian Indian woman represents a very rare case of sarcoidosis in view of her ethnicity and hepatosplenic nodular appearance mimicking metastatic cancer.