

Abstracts

The following abstracts were presented by investigators at the Eighteenth Annual Samuel Bronfman Department of Medicine Research Day on October 16, 2001 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; and St. Joseph's Hospital and Medical Center, Paterson, NJ. Four papers were presented in the AM plenary session. Only two, identified with an *, are included as abstracts in this publication. The remaining two of these presentations at the plenary session have been published elsewhere. Abstracts from Queens Hospital Center and Jersey City Medical Center were presented as posters on Research Day held at those institutions.

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Alcohol Research

Polyenylphosphatidylcholine (PPC) and Its Main Component Dilinoleoylphosphatidylcholine (DLPC) Attenuate Alcohol-Induced Hepatocyte Apoptosis Through Reduction in Cytosolic Cytochrome C and Caspase-3 Activity. Wen K, Mak KM, Ren C, Lieber CS. Alcohol Research Center and Section of Liver Disease and Nutrition, VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

PPC, a mixture of polyunsaturated phosphatidylcholines extracted from soybeans, attenuates hepatocyte apoptosis induced by alcohol feeding in rats, as determined by TUNEL (terminal transferase dUTPnick end labeling) assay. In the present study, we assessed whether DLPC, the most abundant phosphatidylcholine species of PPC, mediates the antiapoptotic action of PPC and whether this effect is associated with changes of cytosolic cytochrome c and alterations in caspase-3 activity, since it is known that cytochrome c released from mitochondria into the cytosol participates in the activation of caspase-3, which, in turn, triggers the apoptosis. Accordingly, rats were fed Lieber-DeCarli liquid diets containing ethanol (35% of energy) or isocaloric carbohydrate as control for 4 weeks. Another group of rats were fed the ethanol diet supplemented with PPC (3g/L) or DLPC (1.5g/L, equivalent to its content in PPC), or twice that dose. Alcohol feeding increased the incidence of hepatocyte apoptosis 6.5-fold by TUNEL assay ($5.2 \pm 0.4/\text{mm}^2$, $n = 6$ vs 0.8 ± 0.08 , $n = 5$ in controls, $p < 0.01$). The rise was abrogated by PPC or DLPC at 1.5g/L and 3g/L. Cytochrome c in the cytosol, as measured by ELISA, rose 53.5% after alcohol feeding ($64.2 \pm 5.7\text{ng}/\text{mg}$ protein vs 41.8 ± 2.4 in controls, $p < 0.05$). The increase was fully prevented by PPC or DLPC at 1.5g/L and 3g/L. Mitochondrial cytochrome c levels (about 14 times higher than those in the cytosol) did not differ significantly among treatment groups. In alcohol-fed rats, liver caspase-3 activity was 66% higher than in controls (11.5 ± 1.7 pmol AMC (7-amino-4-methylcoumarin)/mg protein/min. vs 6.9 ± 0.7 , $p < 0.05$). The increase was fully prevented by PPC or DLPC (1.5g/L and 3g/L). Caspase-3 activity correlated positively with the incidence of apoptosis ($p < 0.001$). We have shown before that DLPC has a striking antioxidant action, which possibly accounts for its antiapoptotic effect, since oxidative stress is known to exacerbate apoptosis.

Conclusions: DLPC, the main component of PPC, accounts for its protection against the alcohol-induced apoptosis; it acts by reducing the cytosolic cytochrome c level, resulting in decreased caspase-3 activity.

DLPC Protects Against Ethanol-Induced Mitochondrial Injury in Rats. Navder KP, Lieber CS. Alcohol Research Center, and Section of Liver Disease and Nutrition, VAMedical Center, Bronx, NY, and Mount Sinai School of Medicine, New York, NY.

Chronic ethanol consumption depletes phosphatidylcholines (PC) in the membranes and hepatic mitochondria are an early target of this toxicity.

Our previous studies showed that polyenylphosphatidylcholine (PPC), a 94–96% pure mixture of polyunsaturated PC extracted from soybeans, attenuates early manifestations of alcohol toxicity, including the prevention of mitochondrial liver injury. Since the main PC species of PPC (40–52%) is dilinoleoylphosphatidylcholine (DLPC), we wondered whether it is the active compound of PPC. To assess this, 26 male rats were fed the following liquid (Lieber-DeCarli) diets for 28 days: Control; Ethanol-36% of Calories (Cal) without or with PPC (3 g/1000 Cal); DLPC-1.5 (1.5 g/1000 Cal) and DLPC-3 (3g/1000Cal). As expected, ethanol feeding resulted in a 41% ($p < 0.05$) decrease in the activity of mitochondrial cytochrome oxidase; this effect was prevented by PPC and also by DLPC-3 ($P < 0.05$). Furthermore, chronic ethanol feeding decreased the capacity of hepatic mitochondria to oxidize palmitoyl-carnitine, as judged by a 51% decrease in respiratory control (the ratio between the ADP stimulated and non-stimulated O_2 consumption), and a 31% reduction in the ADP:O ratio (a measure of efficiency of coupling between oxidation and ATP production).

Supplementation with either PPC or DLPC-3 prevented the ethanol-induced reduction in the capacity of mitochondria to oxidize palmitoyl-carnitine ($p < 0.05$). Similar effects were observed with glutamate as substrate ($p < 0.05$). In conclusion, DLPC, the main PC species of PPC, fully reproduced PPC's protective effect against ethanol-induced mitochondrial liver injury and thus appears to be PPC's active component. This beneficial effect of DLPC at the initial stages of liver injury may be useful to prevent or delay the development of more severe damage.

CYP2E1 Induced by Ethanol and Its Potentiation by Beta-Carotene. Kessova I, Leo MA, Lieber CS. Alcohol Research Center and Section of Liver Disease and Nutrition, VAMedical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

Hepatotoxicity of ethanol is increased by beta-carotene in both rodents and non-human primates. Furthermore, in smokers who are also drinkers, beta-carotene increases the incidence of pulmonary cancer. The hepatotoxicity was associated with proliferation of the membranes of the smooth endoplasmic reticulum, suggesting the involvement of cytochromes P450. To verify this hypothesis, 24 weanling male Sprague-Dawley rats were paired for 8 weeks liquid diets with and without beta-carotene (56.5 mg/l of diet) and with or without ethanol. As expected, ethanol increased CYP2E1 (measured by Western blots) from 66.8 ± 7.9 to 316.5 ± 26.6 absorbance units ($p < 0.05$). Furthermore, beta-carotene increased the ethanol effect to 442.4 ± 37.7 absorbance units ($p < 0.05$). This rise was confirmed by a corresponding increase in the hydroxylation of p-nitrophenol, a specific substrate for CYP2E1, and by the inhibition with diethyl dithiocarbamate (50 microM). The correlation coefficient between CYP2E1 content and p-nitrophenol hydroxylase activity was very significant ($r = 0.928$, $p < 0.0001$; $n = 24$). Beta-carotene also induced CYP4A1 protein (327.5 ± 49.0 vs 158.0 ± 16.7 absorbance units) with a significant beta-carotene effect

($p < 0.01$; 2 way ANOVA). The corresponding CYP4A1 mRNA (measured by Northern blots) was increased ($p < 0.05$). The combination of ethanol and beta-carotene had no effect on CYP1A1/2, CYP2B1/2, CYP2C11 and CYP3A1/2 content. Since the hepatotoxicity of ethanol has been linked to CYP2E1 induction, the potentiation of this toxicity by beta-carotene may be due, at least in part, to the increase in CYP2E1 by beta-carotene. In view of the possible carcinogenicity of CYP2E1 and CYP4A1, their induction by beta-carotene may also play a role in the greater incidence of pulmonary cancer in smokers who drink and are given beta-carotene.

In conclusion, beta-carotene potentiates CYP2E1 induction by ethanol and it also increases CYP4A1, which may explain, at least in part, the associated increased hepatotoxicity.

Polyenylphosphatidylcholine (PPC) Restores S-Adenosylmethionine (SAME) and Corrects Alcohol-Induced Hepatic Oxidative Stress. Aleynik SI, Leo MA, Aleynik MK, Lieber CS. Alcohol Research Center and Section of Liver Disease and Nutrition, VAMedical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

Alcohol-induced liver injury caused by oxidative stress resulting in glutathione (GSH) depletion and increase of lipid peroxidation. For GSH synthesis, the rate limiting amino acid is cysteine, with S-adenosyl-L-methionine as its ultimate precursor. We showed before that PPC corrects the oxidative stress and the GSH depletion resulting from long-term alcohol consumption in non-human primates. To study whether this occurs already with early liver injury and to elucidate the mechanism involved, 32 Sprague-Dawley rats were pair-fed ethanol (36% of energy) or isocaloric carbohydrates in Lieber-DeCarli liquid diets, with or without PPC. After 2 months, there was a striking depletion of SAME from 68.2 ± 5.1 to 36.2 ± 3.4 nmol/g ($p < 0.001$) associated with a reduction in hepatic GSH from 4.95 ± 0.20 to 4.09 ± 0.08 micromol/g ($p < 0.01$), and an increase from 0.24 ± 0.02 to 0.47 ± 0.07 nmol/g ($p < 0.001$) of 4-hydroxynonenal (4-HNE), a reliable marker of lipid peroxidation. SAME synthetase activity remained unchanged. Feeding PPC corrected all values and, in the absence of ethanol SAME and GSH even exceeded the control values. Neither alcohol nor PPC has an effect on SAME synthetase activity. Phosphatidylcholines (PCs), the backbone of cellular membranes, are produced in the liver via methylation of phosphatidylethanolamine by SAME. PPC, by providing PCs, decreases the utilization of SAME and may thereby contribute to its restoration, with replenishment of GSH and the correction of the alcohol-induced oxidative stress. This hypothesis was corroborated by the observation that hepatic SAME correlated positively with GSH ($r = 0.59$, $p = 0.0005$) and negatively with 4-HNE ($r = -0.64$, $p = 0.0001$).

Conclusion: Already after 8 weeks alcohol caused SAME depletion, which was fully corrected by PPC, thereby explaining, at least in part, how PPC opposes the alcohol-induced oxidative stress and prevents the associated fibrosis.

Cardiology

Evidence for Macrophage Apoptosis as a Mechanism Regulating Tissue-Factor Expression and Plaque Growth Following Arterial Injury in ApoE^{-/-} and C57/BL6 Wild Type Mice: R. Hutter, B.V. Sauter*, J.T. Fallon, V. Fuster, J.J. Badimon. The Cardiovascular Institute and Department of Gene Therapy and Molecular Medicine*, Mount Sinai Medical Center, New York, NY.

Background: Macrophages undergoing apoptosis are considered contributing to progression of atherosclerotic lesions. Tissue factor is a key cell-mediated activator of extrinsic coagulation-cascade and can induce thrombus formation.

Methods: In the present study, we examined the role of macrophage apoptosis on plaque growth by comparing neointima formation in ApoE^{-/-} ($n=10$) and C57/BL6 wild type mice ($n=23$) in a model of femoral arterial denudation injury.

Results: Arterial injury resulted in significantly increased neointima formation in ApoE^{-/-} mice at 4 weeks compared to wild type mice (4.84 ± 1.26 mm² $\times 10^2$ vs. 0.73 ± 0.03 mm² $\times 10^2$; $P < 0.01$). Apoptotic macrophages and foam cells as detected by caspase-3 expression, characteristic morphology and positive staining for MOMA-2 were found only in lesions of ApoE^{-/-} mice and accounted for up to 33 \pm 6 % of intimal cells at 4 weeks after arterial injury compared to less than 0.5 % apoptotic cells in neointima of wild type mice ($P < 0.01$). Importantly, neointima size significantly correlated with the content of apoptotic macrophages in neointima ($r = 0.64$, $P < 0.01$). In addition, apoptotic macrophages were directly associated with increased cellular tissue factor expression as well as reduced alpha-actin expression in neointima of ApoE^{-/-} mice ($r = 0.97$, $P < 0.01$, $r = -0.75$, $P < 0.01$, respectively).

Conclusions: Apoptosis of macrophages and enhanced expression of cellular tissue factor in neointima correlated with increased plaque growth and change of neointima to an unstable plaque-like phenotype. These findings point to an important role of programmed cell death of macrophages in modulating arterial lesion biology and controlling thrombogenic properties of intimal lesions following arterial injury.

Decreased Neointima Formation and Vascular Wall Neovascularization after VEGF-165 Overexpression in a Mouse Model of Arterial Injury. R. Hutter, B. Sauter*, C. Wolinsky, V. Fuster, S.L.C. Woo*, J.J. Badimon. The Cardiovascular Institute, and Department of Gene Therapy and Molecular Medicine*, Mount Sinai Medical Center, New York, NY.

Background: Human VEGF-165 as strong promoter of endothelial cell growth has been contradictorily shown to either decrease or increase neointima formation in different animal models. After arterial denuding injury endothelial cells play a dual role in regulating neointima formation either via re-endothelialization of denuded luminal surface (negative feedback) or via ingrowth of adventitial vasa vasorum (positive feedback). Systemic levels of VEGF-165 might therefore modulate both processes simultaneously.

Methods: Using a mouse model of arterial injury we, therefore, examined in parallel the effects of VEGF-165 overexpression on neointima formation, re-endothelialization and vascular wall neovascularization. C57/BL6 mice underwent femoral arterial denudation and received either recombinant adenovirus expressing VEGF-165 ($n = 14$) at two dosages (10^{10} or 10^9 viral particles) or control adenoviral vector ($n = 17$) by jugular vein injection.

Results: VEGF-165 gene transfer at 10^{10} viral particles (high dose) resulted in significantly elevated VEGF-165 serum levels at 1 week and led to a strong reduction of neointima formation at 4 weeks after arterial injury compared to control vector treatment (2.5 ± 1.4 vs. $8.4 \pm 3.5 \times 10^{-3}$ mm², $P < 0.01$). VEGF-165 gene transfer at 10^9 viral particles (low dose) did not change neointima formation after injury compared to control adenoviral vector. Re-endothelialization was nearly completed at 4 weeks and was not changed by any VEGF-165 treatment compared to control group ($84 \pm 8\%$ vs. $84 \pm 12\%$, $P > 0.05$). However, a more than two-fold reduction of arterial wall neovessel content was found in high dose VEGF-165 treated animals compared to control group (0.6 ± 0.4 vs. $1.6 \pm 0.8\%$, $P < 0.05$). At high dose VEGF-165 treatment an increased mortality during first week was observed.

Conclusions: High dose VEGF-165 gene therapy is effective at inhibiting arterial lesion formation following mechanical endothelial injury. The therapeutic effect of VEGF-165 is probably mediated by accelerated early luminal endothelial regrowth and reduced late arterial wall neovascularization pointing to the luminal endothelium as a strong negative regulator of neointimal and arterial wall neovessel growth. The approach of using VEGF-165 systemically to enhance luminal endothelial cell regeneration is, however, limited by a small therapeutic window. Therefore, to successfully inhibit neovascularization and neointima formation at multiple sites additional, similarly acting molecules with better safety have to be used.

*** Is There a Role for "Limited," Rapid, Bedside Hand-Held Echostethoscope in the Surgical Intensive Care Unit?** Ben Cohen, Medical Student; Thomas Dorantes, Medical Student; Nagaraj Hosakote, M.D. Surgery; Lori B. Croft, M.D. Cardiology; Elie Portnoy, Student*; Anthony Manasia, M.D. Surgery; John Oropello, M.D. Surgery; Ernest Benjamin, M.D. Surgery; Roopa Kohli-Seth, M.D. Surgery; Rosanna DelGiudice, R.N. Surgery; Jerry Hufanda, R.N. Surgery; and Martin E. Goldman, M.D. Cardiology, Mount Sinai Medical Center, New York, NY and *Yeshiva University, New York, NY.

Patients in the Surgical Intensive Care Unit (SICU) are frequently unstable. The clinical exam is frequently not definitive and invasive procedures, such as a pulmonary artery catheter are required to indirectly assess left ventricular filling. Studies have questioned the safety of PAC catheters. Echocardiograms provide a direct, real time assessment of left and right ventricular size and function. Unfortunately, the expertise to perform an echo is limited to specially trained technologists and cardiologists. Recently, small, inexpensive, hand-held echocardiograph systems have been introduced, which may serve as echo-stethoscopes for bedside assessment of LV function.

Hypothesis: A "limited" echo (2-4 views, without Doppler or m-mode) to assess LV size and function, exclude significant valvular disease and pericardial effusions, would provide valuable information in intensive care patients.

Methods: After clinical assessment of the patients in the SICU clinical status, cardiac function and volume status were estimated. Patients then underwent a "limited" echo by surgical intensivists and medical students with a Sonoheart® (Sonosite, WA). After the studies were reviewed and results confirmed by an echocardiologist, the intensivist determined if the echo changed their clinical assessment of the cardiac status (function and volume) or changed therapeutic management.

Results: Diagnostic echo was possible in 59/61 (97%) patients in the SICU. Of the remaining 59 pts, the limited echo changed the cardiac diagnosis in 27/59 (46%) and changed management in 16/59 (27%).

Conclusion: The "limited" echo-stethoscope provided significant new information and changed therapeutic management in a significant number of patients. Studies were performed by non-cardiologists to confirm that this technology can potentially be integrated to the routine bedside examination of patients.

Hand-Held Ultrasound Machines: Are They Ready for Everybody?

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Most recent technological advances in medical imaging have produced huge and expensive equipment (CT, MRI, PET).

However, though hand-held, inexpensive ultrasound systems have been developed but have been evaluated only by physicians and/or technicians with years of experience. The promise of these machines should be to empower all physicians with the skill of performing a limited echo at the bedside, as an "echo-stethoscope."

Hypothesis: Medical students and physicians without prior experience can obtain and interpret diagnostic, "limited" echocardiograms on a hand-held ultrasound device.

Methods: After they had a limited tutorial with practical experience, 2 fellows in Surgical Intensive Care Unit and 2 first year medical students performed a "limited" echo in 61 patients in the Surgical Intensive Care Unit with a new hand-held ultrasound system, the Sonoheart® (Sonosite, WA). Studies were performed and stored on video tape. Each study was reviewed and repeated by an experienced echocardiologist to determine if the intensivists' and students' echo images were adequate to be diagnostic and if they interpreted the images correctly.

	Intensivist	Med Student
Diagnostic Images	83%	97%
Interpreted Correctly	66%	78%

Results: The echocardiologists felt the H-H echo was diagnostic in all but two patients (97%). Of the remaining 59 patients, both intensivists and students were able to obtain diagnostic images in most patients and interpreted them fairly well. Students spent more time in performing and interpreting echo's which may explain the difference with intensivist performance.

Conclusion: Small hand-held, echocardiographic systems enable medical students and non-cardiologists to perform and interpret accurate limited echocardiograms. Implications of this study may support formally educating medical students and physicians to utilize echo-stethoscopes at the bedside.

Atherosclerotic Lesional Macrophage Foam Cell RNA Can Be Selectively Procured by Laser Capture Microdissection for Analysis of Cell-Specific Gene Expression.

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Background: Macrophage lipid-laden foam cells contribute to the formation of atherosclerotic lesions. The ability to selectively measure macrophage foam cell gene expression in atherosclerotic vessels is limited due to the presence of smooth muscle cell, lymphocyte, and endothelial cell derived mRNA transcripts in homogenized samples. To overcome this limitation, we used laser capture microdissection (LCM) to selectively procure RNA from lesional macrophages.

Methods: Frozen serial aortic root tissue sections from 20 week old chow fed apolipoprotein E^{-/-} mice were immunostained for macrophage-specific CD68/Macrosialin by a rapid (~15 min) protocol. Alternating sections from each animal were divided into two groups, with either entire sections processed for RNA isolation (analogous to isolation from whole tissue), or just the CD68-positive areas isolated by LCM. Total RNA was extracted by the guanidinium isothiocyanate and phenol-chloroform method and quantified by a sensitive nucleic acid-dye binding assay (Ribogreen). Using real-time quantitative RT-PCR, mRNA levels of 3 genes were determined; CD68, a macrophage specific marker, *alpha-actin*, a smooth muscle cell marker, and *cyclophilin A*, a normalizing gene.

Results: LCM of the CD68-positive cumulative cross-sectional area (223,662 μm², from 30 sections, each 6 μm thick) yielded 3.6 ng of total RNA. CD68 expression in the LCM-extracted RNA was significantly higher than in that extracted from entire sections when adjusted either to RNA mass or to cyclophilin A levels (fold enrichment: 30.1 ± 4.9 or 37.6 ± 6.2, respectively). In contrast to whole section-extracted RNA, alpha-actin RNA was not detectable in lesional macrophage RNA, demonstrating the high purity of the isolated lesional macrophage RNA. The integrity of the LCM RNA sample was demonstrated by conventional RT-PCR of a 450 bp GAPDH fragment.

Conclusion: LCM provides a means for selectively obtaining macrophage foam cell RNA from lesions and will significantly improve *in vivo* gene expression analysis from heterogeneous atherosclerotic tissue. GCO# 98-221

Human Apolipoprotein AI Suppressed Atherosclerosis without Elevating Plasma HDL Cholesterol in LDL Receptor-Knockout Mice on Western-Diet.

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Background: Expression of human apolipoprotein AI (hAI) transgene has been shown to retard atherosclerosis progression in apoE knockout mice. To test this in another mouse model of atherosclerosis and to compare the relative effects on lesion progression of HDL composed of human vs. mouse apoAI (mAI), studies were performed in LDL receptor knockout (LDLRKO) and hAI/LDLrKO mice.

Methods and Results: At weaning, LDLrKO mice with or without the hAI transgene were fed Western diet, and atherosclerosis was assessed in the aortic root after 10 (n = 4 in each genotype) or 15 (n = 6 in each genotype) weeks. In hAI/LDLrKO mice, mean plasma human apoAI level was 208 ± 30 mg/dL, but mouse apoAI was suppressed compared to that in LDLrKO mice (10 ± 4 vs. 195 ± 70 mg/dL, respectively, P < 0.05). The total apoAI, HDL cholesterol (HDL-C), and total cholesterol were comparable between the two groups. There was also no difference in plasma lipoprotein FPLC profiles. Despite the comparable HDL-C levels, there was significant suppression of lesions in hAI/LDLrKO mice compared to LDLrKO mice after 10 weeks (0.02 ± 0.01 vs. 0.11 ± 0.03, respectively, P < 0.03) and 15 weeks (0.16 ± 0.04 vs. 0.31 ± 0.04 mm², respectively, P < 0.03) on Western diet.

Conclusions: Expression of hAI suppressed diet-induced atherosclerosis in LDLrKO mice without changing plasma levels of apoAI or HDL-C. Therefore, HDL primarily composed of hAI appears to be functionally superior to native mouse HDL as an atheroprotective agent.

F-18 Fluorodeoxyglucose Uptake in Human Thoracic Aortas Assessed *In Vivo* by Positron Emission Tomography.

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Background: Our laboratory (Vallabhajosula et al., Zhang et al., Helft et al) has previously demonstrated increased F-18 fluorodeoxyglucose (FDG) uptake in the thoracic aortas in hypercholesterolemic rabbits *in vivo* and *ex-vivo* as a function of atherosclerotic plaque macrophage burden. FDG uptake in human atherosclerosis has not yet been studied. We set out to determine the prevalence of increased FDG uptake in human thoracic aortas and relate it to age and gender.

Methods: We retrospectively studied 50 consecutive patients undergoing whole body FDG positron emission tomography (PET) imaging for diagnosis and staging of tumors using a GE ADVANCE PET scanner with iterative reconstruction and segmented attenuation correction. The patient population consisted of 32 men and 18 women, mean age 56 years (range 15–82). FDG uptake in the thoracic aortic wall was assessed objectively by measured maximal SUV in the most prominent uptake regions. High uptake (SUV > 2.5) prevalence was related to age and gender using the chi-square test.

Results: 29/50 (58%) patients had foci of increased uptake (SUV > 2.5), two visually very striking, mostly in the aortic arch. Uptake was strongly related to age (p < 0.001) and weakly related to gender (p = 0.09).

Conclusion: The prevalence of increased FDG uptake in human thoracic aortas is common and increases with age and male gender. Noninvasive measurement of FDG uptake in human aortas by PET is a potential tool in the *in vivo* assessment of aortic plaque macrophage activity. It needs to be evaluated for prediction of CAD severity and of future clinical events related to ASHD.

FDG Uptake Gender SUV	Age (yrs)			
	< 55	> 55	Male	Female
SU < 2.5	13	8	10	10
SUV > 2.5	29	18	22	8

F-18 FDG Uptake in Human Thoracic Aortas and Correlation with Clinical Risk Factors.

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Background: Our laboratory (Vallabhajosula et al., Zhang et al., Helft et al.) has previously demonstrated increased F-18 fluorodeoxyglucose (FDG) uptake in the thoracic aortas of hypercholesterolemic rabbits *in vivo* and *ex-vivo* as a function of atherosclerotic plaque macrophage burden. Recently, we found that FDG uptake in human atherosclerosis (AS) is correlated with age. We set out to determine the prevalence of increased FDG uptake in human aortas and relate it to risk factors for CAD.

Methods: We studied 57 patients who were referred to MSSM for routine clinical whole body FDG oncological positron emission tomography (PET) imaging using a GE ADVANCE PET scanner with iterative recon-

struction and segmented attenuation correction. The patients were questioned for risk of CAD. The patient population consisted of 24 men and 33 women, mean age 60.6 years, ranging from 23 to 86. FDG uptake in the thoracic aortic wall was assessed objectively by measured maximal SUV in the most prominent uptake regions. We assessed relationship between high uptake (SUV > median) prevalence and clinical risks using the chi-square test.

Results: The median SUV was 2.0. 28/57 (49%) patients had foci of high uptake (SUV > 2.0), mostly in the aortic arch. Uptake was significantly related to obesity ($p = 0.014$) and hyperlipidemia ($p = 0.043$), and weakly related to diabetes ($p = 0.08$), but not related to gender, smoking, and family history of premature CAD.

Conclusion: Increased FDG uptake in human thoracic aortas is common and the prevalence increases with several risk factors for CAD. Noninvasive measurement of FDG uptake in human aortas by PET is a potential tool for the *in vivo* assessment of aortic plaque macrophage activity. It needs to be evaluated for prediction of CAD severity and of future clinical events related to ASHD.

The Digital Echo Lab Has Arrived: Comparison of Digital vs. Video Review in 100 Patients. Jennifer Pennimpede, RDCS, Cardiology; Lori B. Croft, MD, Cardiology; Eric H. Stern, MD, Cardiology; Tamanna Nahar, MD, Cardiology; Samantha Buckley, RDCS, Cardiology; Robert Shapiro, MD, Cardiology; and Martin E. Goldman, MD, Cardiology. Mount Sinai Medical Center, New York, NY.

Videotape (Video) has been the standard medium for reviewing and archiving echo studies. Recently, digital archiving has been proposed as the new, improved method of echo review and storage. While videotape can record continuously, digital loops must be stored individually throughout the exam (on non-streaming systems). Thus, to determine whether digital reading would be equivalent in quality and review time to video, we acquired and read 100 routine, random patient studies acquired on both video and digital. We used a commercially available system, KinetDx® (Acuson) with 2 cardiac cycles/loop. The video and digital studies were read in alternating sequence (51 digital read first). The time for reading each mode, comparison of quality, missed diagnoses and loops stored by tech and edited down by M.D. were recorded.

Results: The major referring diagnosis was to assess LV function (58%). When read first, the video study took 6.25 ± 1.98 minutes to review, compared to 3.01 ± 1.29 minutes for the digital to be read and edited ($p < .0001$). When read second, the video study took 4.75 ± 1.80 minutes compared to 2.38 ± 1.14 minutes for digital ($p < .0001$). There were 3 major diagnoses missed by video, 6 by digital ($p = N.S.$). Irregular rhythms created gating problems for digital acquisition, even if we defaulted to time acquisition. The average number of loops stored by a technician was 63 ± 20 which was reduced for storage by 28% while the M.D. reviewed the study. Therefore, the total time for digital echo reading and editing for archiving took less than 50% of the time to read video. Study quality was equivalent. Thus, digital acquisition and editing on a commercially available system can significantly speed reading time without loss of quality.

*** The Role of Troponin-I in Chronic Hemodialysis Patients.** Zafar MU^a, Farkouh ME^a, Robbins MJ^{a, b}, Shimbo Da, Davidson K^a, Volate Rb, Halperin JL^a, Epstein EM^b, Patel M^b, Talor Z^b, Chesebro Jh^a. ^aMount Sinai Medical Center (Cardiovascular Institute), NY^b St. John's-Queens Hospital (Department of Medicine), NY.

Purpose: Patients on hemodialysis have a high mortality rate primarily due to cardiovascular events (1, 2). Evidence suggests that troponin-I (cTnI) levels may have a role in predicting these adverse cardiovascular events (3, 4).

Subjects and Methods: All chronic hemodialysis patients at two teaching hospitals in New York were followed prospectively for cardiovascular events after screening for baseline cardiovascular risks and cTnI. Patients who had suffered any acute coronary event within the preceding 30 days were excluded from the study.

Results: A total of one hundred and thirty seven patients were enrolled (mean age 58 years, 52% males). Of these 7.3% (10/137) had elevated cTnI levels when a cutoff of >1.0 ng/ml was used. Controlling for other known cardiovascular risk factors (age, diabetes, hypertension, family history of coronary artery disease, smoking, sex, CPK, homocysteine), at 6 months 40% of patients with cTnI >1.0 ng/ml had an event while 8% of those with normal cTnI levels had an event (OR = 9.7, CI = 1.9–50.6, $p < .01$). At one year the event rate was 60% vs. 16.5% respectively (OR = 4.1, CI = 1.5–11.5, $p < .01$).

Conclusion: Our study of stable chronic hemodialysis patients shows a high incidence of cardiovascular events in all subjects, especially in those with elevated baseline cTnI levels. This finding was found to be significant at both 6 months and at one year. All chronic hemodialysis patients are at a significantly increased risk for future cardiac events and should be managed with aggressive risk factor modification. However, the additional cardiac risk conferred by an elevated cTnI level in this population may warrant an even more aggressive approach and this should be the basis for further studies.

References:

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Clinical Experience with Radiofrequency Catheter Ablation for Atrial Flutter: Is There a Point of Diminishing Return of Energy Delivery? Z. Curillova, C. Irmiere, N.G. Tullo. Dept. of Medicine, St. Joseph's Regional Medical Center, Paterson, NJ.

Introduction: Radiofrequency (RF) catheter ablation is an interventional procedure that is effective in eliminating atrial flutter. RF electrical energy is delivered to the tricuspid annulus/inferior vena cava isthmus to create bi-directional conduction block across this critical part of atrial flutter reentry circuit. However, complete block cannot be accomplished in some cases. We attempted to analyze our experience with this procedure, to determine how much energy was sufficient to successfully ablate the tricuspid-caval isthmus (CTI).

Methods: A retrospective analysis of catheter ablations for atrial flutter at St. Joseph's Hospital and Medical Center between 05/96 and 12/00 was performed. Successful and unsuccessful outcomes were analyzed, with respect to demographic characteristics.

The temperature, electrical power, and duration of each RF burn were examined. The total RF energy (in joules) and the number of burns delivered were compared between successful and unsuccessful procedures. Statistical analysis using Student's T-Test was used.

Results: A total of 33 patients (28 male, 5 female), mean age 61.6 ± 13.6 years were included in the analysis. Of these, 22 ablations (67%) resulted in successful CTI block and 11 (33%) were unsuccessful. Over time the success rate improved. There were no significant differences in mean temperature, power, or duration of the burns between successful and unsuccessful ablation. The mean total energy delivered in successful ablation was 25.9 ± 15.3 kJ, while the energy delivered in unsuccessful ablations was 50.8 ± 30.7 kJ ($p = 0.025$). A mean of 24 ± 13.3 burns were made during successful ablations, compared with 50 ± 27 burns in unsuccessful ablations ($p = 0.011$). No successful procedure required more than 50 burns of 60 kJ of energy delivered.

Conclusions: (1) The success rate of RF catheter ablation for common atrial flutter increased over time, which is likely related to the experience of the operators and improvement in mapping/catheter technology. (2) Significantly higher energy delivery and a greater number of burns were seen in unsuccessful cases, reflecting persistent attempts at creating complete CTI block. (3) It appears that delivering more than 50 burns or 60,000 J of energy would be unlikely to result in successful ablation, possibly due to the development of edema in the CTI. In that event a repeat ablation procedure is suggested after the edema has resolved.

Clinical Immunology

Human B Cell Differentiation Factor, 446BCDF, Also Is B Cell and Monocyte Directed Chemokine. Yande Kuang and Lloyd Mayer. Division of Clinical Immunology, Department of Medicine, Mount Sinai Medical Center, New York, NY.

B cell differentiation factor (BCDF), 446BCDF, derived from anti-CD3 mAb (446) stimulated human T cells is a 44KDa cytokine which is a potent inducer of Ig secretion by SAC activated human B cells. We have previously reported that 446BCDF is also chemotactic for B cells and monocytes, but not for T cells and neutrophils. Both the immunoglobulin inductive activity and chemotactic activity were found only in fractions with higher molecular weight (>30 KDa) and were blocked by anti-446BCDF mAb, 929. The chemotactic activity of 446BCDF pre-absorbed with monocytes was significantly reduced for both B cells and monocytes, suggesting that chemotaxis was induced by a single cytokine. Only two of the known chemokine receptors (CCR2 and CXCR4) are expressed on both B cells and monocytes. Monocyte migration induced by 446BCDF was not inhibited by an anti-CXCR4 mAb. Furthermore, human B cells did not respond to MCP-1 (CCR2 ligand) in a chemotaxis assay. Therefore, it appears that both CXCR4 and CCR2 are not involved in 446BCDF induced cell migration. To confirm these data in a competitive assay, we added either optimal concentrations of SDF-1a (CXCR4 ligand), MCP-1 or MIP-1a into the upper chamber along with monocytes and measured chemotactic activity of 446BCDF in the lower chamber. SDF-1a, MCP-1 and to a lesser extent MIP-1a blocked cell migration to the lower well. However when these chemokines were added to both the upper and lower chambers (eliminating the gradient), monocytes migrated towards the lower chamber containing 446BCDF. These data support the contention that 446BCDF binds to a distinct chemokine receptor and is in itself a distinct chemokine.

Endocrinology

More on the Role of HLA Genes in the Susceptibility to Autoimmune Thyroid Disease in 102 Families. Y. Ban, Y. Tomer, ES. Concepcion, DA. Greenberg*, and TF. Davies. Division of Endocrinology, Diabetes, and Bone Diseases, Department of Medicine and *Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The autoimmune thyroid diseases (AITDs), comprising Graves' disease (GD) and Hashimoto's thyroiditis (HT), are complex diseases which result from an interaction between predisposing genes and environmental triggers. Population-based case control studies have shown a consistent association of GD with human leukocyte antigen (HLA)-DR3 in Caucasian populations. HLA association studies in HT have shown different alleles and have not been as consistent as in GD. Linkage studies of HLA with AITD have been mostly negative. Recently, only one study showed weak evidence for linkage with HLA in GD using non-parametric analysis of sib-pairs (Vaidya et al., 1999). The aim of our study was to perform detailed linkage and association analyses of the HLA region in AITD in order to further resolve the previous conflicting data. We studied 102 multiplex, multi-generational, AITD families for linkage with the HLA region. We generated a map of the region as follows: (Inter-marker distances are in centimorgans.) Telomere-D6S276-3.7-D6S464-2.9-HLA-A-1.3-HLA-C-0.05-D6S439-0.15-HLA-B-1.15-HLA-DRB1-0.01-D6S273-0.22-HLA-DQA1-0.24-TNF alpha-1.2-D6S1610-Centromere. The analysis showed negative LOD scores throughout the region. The maximum LOD scores at marker D6S273 (the closest to HLA-DRB1) were -2.4 for GD, -0.4 for HT, and -3.8 for AITD (GD + HT). These results confirmed earlier studies by us, and others, showing no evidence for linkage of HLA to AITD. We then performed case-control association analyses using the 99 Caucasian probands from our families (60 with GD and 39 with HT) and 135 sex- and age-matched Caucasian controls. As previously reported, we found that DR3 was associated with Caucasian GD probands ($P = 0.00032$; $\chi^2 = 12.9$; $RR = 3.42$). We also found that DR4 was associated with Caucasian HT probands ($P = 0.043$; $\chi^2 = 4.09$; $RR = 2.13$). We found no evidence for linkage to the HLA region when analyzing only DR3 positive families ($n = 34$). We concluded that 1) HLA genes made only a small contribution to the overall genetic susceptibility to AITD, because they were not linked; 2) HLA-DR3 conferred an increased risk of developing GD, but it was most likely only a minor modulating gene that may increase susceptibility to GD.

The Thyroglobulin Gene Is a Major Gene for Autoimmune Thyroid Disease. Y. Tomer, DA Greenberg¹, ES Concepcion, and TF Davies. Division of Endocrinology and Metabolism, Department of Medicine, and ¹Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Abundant epidemiological data point to a strong genetic influence on the development of autoimmune thyroid disease (AITD). We have been mapping the susceptibility genes for AITD using whole genome screening. In our first genome scan of 56 families we identified 7 loci which were linked with AITD. In two of these loci there was evidence for putative susceptibility genes (CTLA-4 on chromosome 2q33 and CD40 on 20q11). We have now extended our studies to a larger group of 102 multiplex, multigenerational, families (540 individuals). A whole genome screen using these 102 families showed strong evidence for linkage at chromosome 8q24 with a maximum 2-point LOD score (MLS) of 2.8 (NPL= 2.2). This MLS was obtained with heterogeneity (~45% of the families were linked). Multipoint analysis showed a 12 cM interval giving a maximum heterogeneity LOD score of 3.5 between markers D8S514 and D8S284. This interval contained the thyroglobulin (Tg) gene. In order to analyze whether the Tg gene could be the AITD susceptibility gene on 8q24 we performed BLAST searches through chromosome 8 sequence databases and identified two new microsatellites inside the Tg gene (designated Tgms1 and Tgms2). Tgms1 was located in intron 10 of the Tg gene, and Tgms2 in intron 27. Allelic analysis showed that Tgms2 was much more informative with a heterozygosity index of 0.79, and was, therefore, used for further analyses. The Tgms2 microsatellite showed strong evidence for linkage with AITD (MLS = 2.9, NPL= 2.2), confirming that the Tg gene was linked to AITD. We then used Tgms2 to test whether the Tg gene demonstrated association with AITD in addition to linkage. We compared 190 Caucasian GD patients (64 of them probands from our families) to 134 age and sex-matched Caucasian controls. The analysis showed an association of GD with Tgms2. Allele #3 (336 bp) was present in 30% of the patients and in 22% of the controls ($p = 0.05$, relative risk = 1.4). When we analyzed only the probands from the linked families we found that 40% of them had allele #3 versus 22% in the controls ($p=0.004$). We concluded that the thyroglobulin gene was a major AITD susceptibility gene because it was linked and associated with AITD. Alterations in the Tg gene could theoretically predispose individuals to develop AITD by changing the antigenicity of Tg as demonstrated in many studies.

Cell Biology of the TSH Receptor: Capping and Multimerization within Intact Cells Shown by Fluorescence Resonance Energy Transfer (FRET). R. Latif, P. Graves, and T.F. Davies, Division of Endocrinology, Diabetes and Bone Diseases, Mount Sinai School of Medicine, New York, NY.

We previously showed that human TSHRs, from detergent solubilized thyroid membranes existed as cleaved "alpha and beta" subunits plus some uncleaved holoreceptors. These were present as monomers, dimers, and higher order complexes, some of which were disulfide bonded (Endocrinology 1997; 137:3915-3920). To facilitate such studies, we expressed the human TSHR as a fusion protein linked to amino terminus of Green Fluorescent Protein (GFP). Chinese Hamster Ovary (CHO) cells expressing hTSHR-GFP fusion proteins demonstrated plasma membrane localization observed by plasma membrane labeling with a red lipophilic carbocyanine derivative (CM-DiI) generating a yellow cell surface membrane fluorescence upon co-localization with GFP. Furthermore, the fluorescent receptor was functional as evidenced by TSH-induced generation of cAMP with a maximum stimulation index of >40, suggesting appropriate internal trafficking and correct folding of the recombinant hTSHR-GFP construct. In addition, we observed time- and dose-dependent capping of the receptor following TSH stimulation. We next used FRET to examine the proximity of individual hTSHRs on the CHO plasma membrane. hTSHR linked to GFP variants (red-RFP & yellow-YFP) were used as donor and acceptor molecules. FRET data using single transfectants fused by polyethylene glycol (PEG-1500) showed a transfer of energy from YFP to RFP. This confirmed the close proximity of the tagged receptors and further suggested the existence of functionally relevant dimers and/or multimers on the surface of these transfected cells. To confirm this observation, hTSHR carrying a c-myc epitope tag on its carboxyl end was transfected into TSHR-GFP cells for co-immunoprecipitation experiments. The presence of hTSHR-GFP in anti-myc immunoprecipitates was confirmed by using GFP antibody to probe the immunoblot. A fusion protein of 85 kD, comprising GFP (27KD) fused to a TSHR-S fragment of 58KD, indicated the presence of hTSHR-GFP dimers (and/or higher order complexes) in the co-immunoprecipitates. The absence of TSH holoreceptor in the co-immunoprecipitates further suggested that cleavage was essential for hTSHR complex formation. These data demonstrated that the dynamic life cycle of the TSHR involved expression, capping, and multimerization. However, the function of these higher order complexes remains to be determined.

Gastroenterology

Divergent Effects of Chronic Nicotine Administration on Jejunitis and Colitis in Interleukin 10-Deficient Mice. Eliakim R, Fan Q, Nimmagadda K, Babayatsky MW. Divisions of Gastroenterology, Rambam Medical Center, Haifa, Israel, and Mount Sinai School of Medicine, New York, NY.

Cigarette smoking alters the course of inflammatory bowel disease (IBD). Smoking protects against ulcerative colitis (UC), but aggravates or has no effect on Crohn's disease (CD). While the etiology of this discrepancy remains unclear, differences between location of involvement in UC and CD have not been examined in these studies. We have previously shown that nicotine (12.5mg/ml), a main active ingredient in cigarette smoke, protects against colonic injury but exacerbates jejunal injury induced by iodoacetamide in rats. The aim of the current study is to examine the effects of nicotine administration on the course of jejunitis and colitis in interleukin (IL)-10 deficient (KO) mice. **Methods:** Male C57/Bl6 IL-10 KO and wildtype (WT) mice were given nicotine (12.5mg/ml) in their drinking water at age 12-14 weeks when they had developed clinical signs of IBD. Sex and age-matched control mice received tap water alone. All mice were sacrificed after two weeks of treatment. Whole tissue sections of jejunum, proximal and distal colon were separated and examined by macroscopic and histologic score. RNA was prepared by Trizol reagent purification; Northern blots were examined for somatostatin (SST) and intestinal trefoil factor (ITF) gene expression, two peptides with protective properties in experimental IBD; blots were reprobed with b-actin and MUC2 as RNA/mucin expression controls. **Results:** At sacrifice at 14-16 weeks, IL-10 KO untreated control mice developed both jejunitis (macroscopic score (macro) = 1.4 + 0.5, microscopic score (micro) = 2.0 + 0.2) and colitis (macro = 2.0 + 0.2, micro = 5.9 + 0.9). IL-10 KO mice treated with 2 weeks of nicotine had significantly reduced macro (1.4 + 0.6) and micro (2.2 + 0.15) colonic scores ($p=0.01$). In contrast, the jejunum was more severely damaged with macro scores 2.6 + 0.4 and micro 4.0 + 0.3 ($p = 0.01$). Nicotine significantly increased both SST and ITF mRNA expression in colon but not in jejunum; no effect was noted on MUC2 or b-actin mRNA expression. **Conclusions:** 1. Two weeks of nicotine administration leads to contrasting effects on jejunal and colonic inflammation in IL-10 KO mice. 2. Nicotine ameliorated inflammation in the colon, which was associated with enhanced expression of two protective peptides. 3. Regional effects of nicotine on gut inflammation may, at least partially, explain divergent effects of cigarette smoking seen in UC and CD.

Somatostatin Improves Enterocolitis in IL-10 Deficient Mice. Nimagadda K, Eliakim R, Fan Q, Zhang J, Babyatsky MW. GI Divisions, Rambam Hospital, Haifa, Israel; and Mount Sinai School of Medicine, New York, NY.

We have previously demonstrated that local neural somatostatin (SST) is markedly deficient in interleukin (IL)-10 deficient (KO) mice, even prior to the appearance of enterocolitis (Gastroenterology 1998; 114:A1004). Further, IL-10 administration in IL-10KO mice prevents or ameliorates the enterocolitis and restores SST levels to those seen in wildtype non-inflamed control mice. Aim: to determine if SST treatment alters the IBD phenotype in IL-10 KO mice.

Methods: Male C57Bl/6 IL-10 KO mice from Jackson laboratories were housed in conventional facilities until age 16-18 weeks of age, when they developed evidence of IBD (weight loss, bloody diarrhea, or rectal prolapse). IL-10KO mice or wildtype mice (20 mice/group) were treated with continuous SST (2.5 mg/day) or saline infusion by Alzet miniosmotic pump for 14 days. Mice were weighed every 2 days; no mice expired during the treatment. At sacrifice, serum was obtained for SST radioimmunoassay (RIA). Equivalent whole tissue sections were obtained from jejunum, right colon, and left colon and placed in formaldehyde for tissue sections or Trizol buffer for RNA preparation. RNA was examined by Northern blot analysis for cytokine expression and re-probed with b-actin for RNA loading control by scanning densitometry.

Results: SST infusion resulted in high levels of serum SST by RIA in both the IL-10KO mice and wildtype controls. By the end of two weeks, the wildtype mice treated with SST or saline gained similar amounts of weight (2.12 ± 0.6 vs. 1.98 ± 0.5). IL-10 KO mice treated with SST gained a similar amount of weight to the two groups of wildtype mice (1.78 ± 0.7g). In contrast, IL-10 KO mice treated with saline lost weight (0.25g ± 0.5g; p < 0.001). No wildtype mice demonstrated any signs of enterocolitis, either grossly or microscopically. IL-10 KO mice had significantly higher macroscopic (3.4 ± 0.9) and microscopic (5.0 ± 1.2) colonic scores compared to SST-treated mice (macro: 1.4 ± 0.6) (micro: 2.0 ± 0.9) (p < 0.001). Similar results were seen in the jejunum. Northern blot analysis demonstrated significantly lower levels of IL-8, MCP-1 and TNFα in IL-10 KO mice treated with SST compared to those treated with saline. However, SST did not alter levels of these cytokines in SST-treated or control wildtype mice.

Conclusions: 1. SST significantly ameliorates the enterocolitis seen in IL-10 KO mice. 2. SST reduces pro-inflammatory cytokine mRNA expression in IL-10 KO mice but not in non-inflamed controls. 3. SST acts as an anti-inflammatory mediator in IL-10 KO mice and may play an anti-inflammatory role in IBD.

Dieulafoy Lesion: Successful Treatment of Massive Bleeding with Combination Epinephrine Injection and Band Ligation. Z. Salem, MD, J. Fares, MD, H. Elfarra, MD, W. Baddoura, MD. St. Joseph's Regional Medical Center, Paterson, NJ, and Seton Hall University School of Graduate Medical Education, South Orange, NJ.

Introduction: Dieulafoy lesion is characterized histologically by an aberrant artery coursing beneath the mucosal surface. It can occur anywhere along the gastrointestinal tract with predominance to the proximal stomach. Its incidence as a cause of gastrointestinal bleeding varies between 0.3% and 6.7%. Endoscopic therapy has dramatically improved the management of these lesions. Multiple endoscopic modalities are reported to be effective. These include electrocoagulation, heater probe, injection sclerotherapy, laser photocoagulation, hemoclipping and band ligation.

Case Report: A 54 year-old man with history of hypertension, coronary artery disease, congestive heart failure, antiphospholipid syndrome, and mesangiocapillary nephritis with end-stage renal disease on hemodialysis was hospitalized with decompensated heart failure. His medications included warfarin, steroids and ASA. After responding to initial treatment, he developed a sudden episode of massive hematemesis and subsequently became hypotensive with systolic blood pressure of 60mmHg. Aggressive volume resuscitation was initiated. An emergent gastroscopy was performed which showed an actively spurting fundic vessel with normal surrounding mucosa, consistent with a Dieulafoy lesion. The bleeding site was injected with five mls of epinephrine 1/10,000 followed by band ligation. This provided immediate hemostasis and improved hemodynamics. Repeat endoscopy demonstrated a non-bleeding banded site and no additional pathology. A total of eight units of packed RBC's were required to bring the hemogram back to baseline. Patient remained stable throughout hospitalization with no further evidence of bleeding.

Conclusion: Early diagnosis and prompt endoscopic intervention is critical for successful management of Dieulafoy lesions. Combination therapy with epinephrine injection and band ligation may be an effective modality.

General Internal Medicine

Use of Metformin in the Medical Primary Care (MPC) Clinic at Elmhurst Hospital Center (EHC). A. Maslona, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Metformin has been shown in large randomized controlled trials to be effective in improving glycemic control in type 2 diabetic patients already treated with maximum doses of sulfonylurea agents (DeFronzo et al. Efficacy of metformin in patients with NIDDM. N Engl J Med 1995; 333:541-549). Since 1995, patients at MPC have been prescribed metformin in a similar strategy, yet data are lacking on the effectiveness of this approach in this particular patient population.

Methods: To evaluate the effectiveness of metformin used as an adjunct to sulfonylureas in MPC, we performed a quasi-experimental observational study of type 2 diabetics on maximum doses of glyburide for whom metformin prescriptions were approved by the EHC pharmacy between January 1998 and December 1999. Glycemic control (fasting plasma glucose [FPG] and hemoglobin A1c) was assessed before and after a stable maximum metformin dosage was reached. Secondary outcomes included body weight, fasting lipid levels, and side effects.

Results: During the study period, 110 patients received approval for metformin therapy; 56 patients (51%) met inclusion criteria and 54 (49%) were excluded, largely for lack of sufficient follow-up data. The average absolute improvement in FPG after metformin therapy was 73 mg/dl on an average daily dosage of 1908 mg of metformin. The average absolute improvement in hemoglobin A1c was 2.3%. The average follow-up period was 8.7 months. Univariate analyses showed that the degree of improvement was most closely related to baseline control; poor baseline control predicted enhanced response to metformin (r = 0.600, p < 0.001). Improvement was less closely related to age, with increasing age predicting lesser improvement. Improvement was not related to ethnicity, gender, initial body mass index or change in BMI, history of a dietitian visit, or the dose of metformin. Linear regression analyses showed that improvement in hgbA1c was significantly associated with baseline control and age (accounting for 43% of improvement, p < 0.001). Metformin treatment had no effect on body weight, but had a marginally significant effect of lowering LDL cholesterol levels. No significant adverse effects were seen among the study patients.

Conclusions: Metformin is an effective way to improve glycemic control in type 2 diabetics already on maximum doses of sulfonylurea agents, especially among poorly controlled patients. It is safe in this setting, does not cause weight gain, and may have beneficial effects on lipid levels.

Evaluation of a Managed Care Curriculum in a Primary Care Internal Medicine Residency Program. L.M. Reich, MD, and R.A. David, MD. Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: In its 1998 Program Requirements for Residency Education in Internal Medicine, the ACGME included the recommendation that it is "desirable that each resident receive instruction in the principles of managed care." In order to adhere to the intent of this recommendation, as well as to ensure that our housestaff were adequately prepared to practice in the current medical environment, we developed a Managed Care (MC) curriculum, and integrated it into our Primary Care Internal Medicine Residency Program. One component of this curriculum was a monthly small-group discussion focussing on the practical issues involved in understanding MC. The purpose of the present study was to evaluate the success of this Workshop in terms of its utility to the housestaff and its effectiveness as a teaching modality.

Methods: All 36 residents in our Program as of June 2001 were asked to complete a survey designed to assess their educational experiences in the MC Workshop. They were asked to rank, on a 5-point Likert scale, their comfort level with the use, application, and discussion with patients of 13 concepts central to current MC issues, and to assess to what extent the MC Workshop improved or enhanced this level of comfort. They were then given 10 true/false questions designed to measure their understanding of key MC points. Their performance on this section was evaluated based on their individual experiences with the MC Workshop.

Results: Twenty-two of 36 house officers responded to the survey. Of these, 9 (6 interns and 3 junior and senior residents) never attended the MC Workshop, 8 attended a single Workshop, and 5 attended the Workshop more than once. The 13 house officers who attended the Workshop at least once included 6 senior residents and 7 interns and junior residents. The mean comfort level for all 13 MC topics increased from 2.79 before participation in the Workshop, to 3.51 after participation. The mean comfort level improved for 11 out of the 13 topics (only "Medicaid" and "Medicare" did not show this improvement). The performance on the 10-question test was clearly related to experience in the Workshop.

The mean percent correct score was lowest for those who did not attend the Workshop (60% for interns and 67% for residents), intermediate for those who attended once (78%), and highest for those who attended more than once (84%). Of those who attended at least once, senior residents did not outscore interns and junior residents (78% vs. 81%).

Conclusion: The inclusion of a MC curriculum as described above can be shown to increase Internal Medicine residents understanding of and comfort with important topics in Managed Care.

Screening for Risk Factors for Osteoporosis in Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center. A. Sheikh, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Osteoporotic fractures in aging women are a major health problem in industrialized nations. In the United States, approximately 150,000 hip fractures occur annually in women over the age of 65. Epidemiologic studies have identified major risk factors; early screening for bone loss may allow detection before fracture occurs. A study was conducted at MPC to assess the prevalence of screening for osteoporosis.

Methods: A chart review was conducted of female patients without a prior diagnosis of osteoporosis in the clinic chart's Problem List who were seen at MPC for routine follow-up visits from February-March 2001. A convenience sample of patients scheduled for MPC appointments was selected. Clinic records were reviewed to ascertain documentation of a) daily calcium intake, smoking, alcohol consumption, exercise, family history; b) bone mineral density studies; c) treatment.

Results: Seventy charts were reviewed. Twenty-eight (40.6%) were aged 50-59, 30 (42.8%) were 60-69, 12 (17.1%) were 70-79. Fifty-two (74.3%) were Hispanic; Pakistani and East Asian origin each comprised 5 (7.1%), and Indian and African-American each comprised 4 (5.7%). Sixty-five patients (92.9%) had documentation of at least one screening question having been asked; smoking was assessed in all screened patients; 20 (28.6%) were questioned about daily exercise; daily calcium intake was documented for 4 patients (5.7%). Bone mineral density study was ordered in 14 (21.9%) and performed in 6 of these patients (42.9%). Sixty-three patients (90%) were prescribed calcium supplements; 19 (27.1%) were given hormone replacement therapy. Five patients had evidence in the chart of a diagnosis of osteoporosis; three (60%) received alendronate, one patient (20%) received calcitonin and 1 (20%) was not treated.

Conclusions: Nearly all patients were asked at least one screening question, but excluding the assessment of smoking status substantially decreased the proportion screened. Only a fifth were referred for bone mineral density evaluation. Although calcium supplementation was used in 90% of patients, other preventive measures were uncommon. Further study is needed to assess strategies to increase primary and secondary prevention measures.

Utilization of Pulmonary Function Tests (PFT) in Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center (EHC). R. Suleman, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Aim: To evaluate the utilization of PFTs by primary care physicians at EHC.

Background: PFTs are utilized by primary care physicians in diagnosis, prognosis, treatment evaluation, and perioperative or disability assessment.¹

Methods: A list of all patients referred from MPC from January-June, 2000 was obtained and a convenience sample of 50% was selected for review. Data were collected by chart review on demographic variables, pre-PFT diagnosis, indication for PFT, whether diagnosis was confirmed by PFT, whether change in clinical management resulted, and prognosis. Data were analyzed and graphs constructed using Excel software.

Results: One hundred sixty-eight patients were referred and underwent PFTs; 85 charts (50%) were reviewed. There were 36 males (42%); average age was 51 years; 32 (38%) were smokers. Frequency distribution by race/ethnicity: Hispanic—39 (46%), South Asian—20 (24%), white—12 (14%), East Asian—7 (8%), Black—7 (8%). Eighty per cent of patients were cooperative. Seventy-eight per cent of PFTs were ordered to confirm diagnosis. The pre-PFT clinical diagnoses were: asthma—70 (82%), restrictive disease—8 (10%), other [COPD, upper airway obstruction]—7 (8%); 46 (54%) of PFT results were consistent with pre-PFT clinical diagnosis. Twenty-eight results (33%) were utilized to confirm diagnosis or appropriateness of therapy; 27 (32%) resulted in alteration of treatment plan and 2 (2%) were acknowledged but treatment was not altered. Nine (11%) of results were not acknowledged in the clinic chart notes. Eighteen (21%) of patients failed to return for follow-up. In summary, there were 79 PFTs (93%) that were definitely or possibly helpful in clinical management.

Conclusions: Results of this study suggest that PFTs are most likely to supplement the clinical management of outpatients with pulmonary disease if appropriately used. Further studies are needed to determine how utilization can be improved.

¹Andrews JL. The clinical roles of PFT. *Med Clin of NA* 1979; 63:355-77.

Epidemiology of Hepatitis C at Elmhurst Hospital Center (EHC). K. Mostafizi, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Hepatitis C infection is the most common cause of chronic liver disease in the U.S., comprising 40-60% of cases and resulting in an estimated 8,000-10,000 deaths each year.

Although the number of newly acquired acute HCV infections has decreased from 180,000 in 1984 to 28,000 in 1995 in the U.S., immigration from countries with higher prevalence is occurring. A study was conducted at EHC, a public hospital serving a largely immigrant population, to determine the prevalence of infection among outpatients.

Methods: All patients who were enrolled in adult outpatient clinics and had a positive HCV antibody result (EIA) from 1999-2000 were identified from the data base of Infection Control. Demographic and clinical variables were extracted from the patient record and tabulated by hand. Univariate analyses were performed with EpiInfo software.

Results: The first 60 consecutive patients were selected from a total of 172 patients; ten charts (16%) were unavailable. Of the 50 patients included in the study, thirty-five (70%) were male. Race/ethnicity distribution was: African-American—15 (30%), Hispanic—15 (30%), Caucasian—10 (20%), other—10 (20%). Nineteen males (54%) and 7 females (47%) were injecting drug users [odds ratio (95% confidence interval) for males = 1.36 (0.34, 5.41)]. Four males (11%) and 0 females were hepatitis B surface antigen-positive [OR = undefined, p = .578]. Eight males (22%) and 2 females (13%) had serum transaminase levels > twice normal (results unavailable for 2 patients of each sex). Eight males (23%) and 0 females had cirrhosis [OR = undefined, p = .086]. Of the males, 8 (23%) were HIV+, 6 (17%) were HIV-, and 21 (60%) had no information in the chart; of the females, corresponding figures were 1 (7%), 3 (20%) and 11 (73%) [OR (95% confidence interval) of HIV-positivity for males = 4.95 (0.23, 235)]. Three males (8%) had an elevated (-fetoprotein level, 26 (74%) had a normal result, 6 (17%) were not tested; corresponding values for females were 0, 11 (73%), and 4 (26%). Thirty males (85%) had hepatic sonogram performed; 1 (3%) showed a mass lesion (expired before diagnosis). Nine females (60%) had a sonogram; all were normal.

Conclusions: In this population with a high proportion of substance abusers, better evaluation and follow-up may be indicated to ensure all patients requiring treatment receive it. A substantial proportion of patients were not evaluated for presence of hepatoma. No patients were undergoing interferon/ribavirin therapy. Utilization of a health educator may improve care of these patients.

Control of Hypertension in Elderly Type II Diabetics at Medical Primary Care Clinic at Elmhurst Hospital Center (MPC). S. Kats, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background. The incidence of diabetes is increasing in the United States as the population ages, and hypertension is twice as common in diabetics. JNC-VI recommends prompt pharmacologic therapy and lifestyle modification for the diabetic with even high-normal blood pressure (130-139/85-89 mm Hg). Microalbuminuria is a risk factor for both macrovascular damage and end-stage renal disease. Increased urinary microalbumin excretion is better correlated with systemic blood pressure than with many other variables; e.g., glycemic control, age, duration of diabetes, gender and body mass index. Therefore, a study was conducted to determine blood pressure control in diabetic patients treated in MPC.

Methods. A convenience sample of 100 patients seen within one week with dual diagnosis of hypertension and Type II diabetes mellitus was selected. Patients were included if they were aged 65 and older and had been under MPC care for more than 2 years. Electronic charts were reviewed. Mean blood pressure at the previous three visits, age, gender, ethnicity, treatment of hypertension and metabolic parameters (urinary microalbumin excretion, glycemic control, cholesterol and body mass index) were ascertained.

Results. Of the 100 patients included in the study, 41% were women and 53% were of Hispanic origin. The average age of the subjects was 72; 27% were overweight and 23% were obese. Ninety-eight per cent of subjects received pharmacologic treatment of hypertension, of whom 76% were on combination therapy and 74% were on ACE-inhibitors. Mean systolic blood pressure was 146.1 mmHg and mean diastolic blood pressure was 75.3 mmHg; mean glycosylated hemoglobin was 7.3. Nineteen per cent of the participants had blood pressure less than 130/80 mmHg (however, many subjects had isolated systolic hypertension with adequate control). There was no appreciable difference in blood pressure according to gender, race or age. Data on microalbuminuria were available for 26 subjects (28%), of whom 30% had urinary albumin excretion greater than 20 mg/L. Twelve patients (13%) had clinical proteinuria.

Conclusion. Blood pressure control in elderly diabetic patients at MPC is in accordance with JNC-VI guidelines. More aggressive screening for microalbuminuria is recommended. Further study is needed to identify strategies to maximize control of hypertension in these patients.

The Diagnostic Value of Bronchoalveolar Lavage (BAL) in Sputum Smear-Negative Pulmonary Tuberculosis. E. Chang, M.D., M. Venkataraman, M.D., A. Lyman, M.D., MSCM. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: BAL is proven useful and widely used in the diagnosis of opportunistic infections, such as *Pneumocystis carinii*, in immunosuppressed patients with pulmonary infiltrates. However, its role in the diagnosis of sputum smear-negative pulmonary tuberculosis is less well established.

Methods: We conducted a cross-sectional study of all patients at Elmhurst Hospital Center from 1994–2000 who were diagnosed with pulmonary tuberculosis by either 1) positive *Mycobacterium tuberculosis* culture, 2) caseating granuloma(s) on histologic specimen or 3) clinical and radiological improvement following antitubercular therapy, who had undergone bronchoscopy and BAL and had had at least three consecutive AFB smear-negative sputum samples. Hospital records were reviewed for demographic and clinical data, and results were tabulated with Excel software.

Results: Thirty patients met inclusion criteria; 22 charts (73%) were available for review. Sputum cultures were positive for *Mycobacterium tuberculosis* in 17 (77%), compared to BAL cultures, which were positive in 13 (59%). All 5 sputum culture-negative patients were also negative on BAL culture. Four patients (18%) had positive BAL smears; all of these were ultimately sputum culture-positive. No diagnosis was made solely by BAL smear results; however, diagnosis was made sooner in these 4 patients. In addition, 4 patients (18%) underwent transbronchial biopsy; one (25%) had a positive smear of the specimen. This patient had negative smear and culture of both sputum and BAL specimens.

Conclusions: The diagnosis of pulmonary tuberculosis can be made in majority of patients from sputum culture alone. BAL resulted in a more rapid diagnosis in a small percentage (18%). We conclude that BAL should not be the only procedure used when bronchoscopy is performed. If rapid diagnosis is clinically important, efforts should be made to include transbronchial biopsy and polymerase chain reaction analysis, which have been shown in other studies to be helpful to increase diagnostic yield.

Colonoscopy Findings in the Elderly at Elmhurst Hospital Center (EHC). S. Caro, MD, A. Lyman, MD, MSCM; T. Riley, MD, A. Sharma, MD, and V. Gumaste, MD. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Utilizing colonoscopy, the best methodology for colonic imaging, benign or malignant pathology is frequently encountered in the elderly population. The incidence of colorectal cancer (CRC) is positively correlated with age and generally occurs in individuals >50 years. The purpose of this study was to assess the indications and findings of colonoscopies in an elderly, multiethnic population conducted at EHC.

Methods: From the endoscopy suite database, a list of all colonoscopies performed from 7/1/98–1/2001 was obtained and a convenience sample of consecutive eligible patients >60 years old was selected. Endoscopy suite charts and computerized records were reviewed, and age, sex, indication for the study, colonoscopic findings and pathologic findings were extracted. Indications were categorized as 1) bleeding (hematochezia, unexplained iron deficiency anemia, guaiac-positive stool), 2) symptoms (abdominal pain, diarrhea, constipation), 3) surveillance colonoscopy after a previous abnormality, and 4) weight loss.

Results: The first 75 eligible patients were selected. Age: 60–86 (mean = 69). Forty-four percent were male. The most common indication for colonoscopy was GI bleeding (47%), followed by surveillance colonoscopy (23%), GI symptoms (11%), weight loss (4%) and other (3%). The most common colonoscopy finding was hemorrhoids (66%), followed by polyps (31%), diverticuli (27%), cancer (9%), arteriovenous malformations (1%). CRC was found in 7 patients (9%); 6 (86%) were male [odds ratio (95% confidence interval) = 9.11 (.99, 429.04)]. Six (86%) with CRC had GI bleeding as the indication. Three (43%) of the cancers were in the rectum, 3 (43%) — sigmoid colon, and 1 (14%) — ascending colon. Of 29 polyps found (in 22 patients), location was: 14 (48%) — sigmoid colon, 6 (21%) each were in the ascending colon and descending colon, 3 (10%) — cecum, and 2 (7%) — rectum. None of the colonoscopies were completely normal in this study population. There were no complications.

Conclusions: The most common indication for a colonoscopy was GI bleeding and the most common colonoscopy finding was hemorrhoids. CRC was found in 9% of the patients; the proportion of cancers in the rectum was higher than expected. Males comprised 86% of the patients with CRC, consistent with the known higher rate of CRC in men. The low complication rate and high frequency of abnormal findings in this population support the use of colonoscopy for elderly patients with appropriate indications.

Profile of Elmhurst Hospital Center (EHC) Dialysis Patients (1965–1999). V. Kagramanov, MD; A. Lyman, MD, MSCM; and M. Neff, MD. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

End-stage renal disease (ESRD) is a serious medical, economic and public health problem in the US costing \$16.7 billion/year in 1998 with projected costs rising to \$28.3 billion by 2010 (1). EHC, a regional referral center for renal dialysis, was one of the first centers in the US, operating since 1965. A review was undertaken of EHC dialysis database, containing demographic and clinical data on all dialysis patients treated at EHC from 01/01/65–12/31/99, to describe trends in incident dialysis cases at EHC and to characterize EHC patients by demographic and clinical characteristics and indications for dialysis. A comparative analysis of contemporary EHC incident renal dialysis patients with corresponding data from US Renal Data System (USRDS) (2) (data available starting 1990) was undertaken to identify prevention strategies for ESRD in Queens County, NY. Data lacking personal identifiers were extracted from patient records. From 1965–1999, 2805 patients were treated in EHC dialysis center: 932 (32.2%) non-Hispanic whites (NHW), 1219 (43.5%) Blacks (BL), 439 (17.6%) Hispanics (HIS) and 161 (5.7%) Asian/Pacific Islanders (API). Nearly all patients (85.5–94.5%) were Queens residents. The proportion of BL among incident dialysis patients steadily rose from 28.5% (1965–69) to 55.4% (1990–94). HIS comprise the third most populous group among EHC incident dialysis patients (ranged from 12.3 to 20.7% (1995–99)).

API increased (2.3% in 1970–74 and 9.4% in 1995–99). NHW tended to be older than other groups. Number of males > females, especially in NHW (61.6% males) and HIS (59.6% males) vs. BL (52.7% males); except for BL females >50 years. Diabetes (31%), hypertension (22%) and glomerulonephritides (24.7%) were the most frequent indications for dialysis at EHC. Diabetes was more frequent indication (42.2%–EHC vs. 34.1%–USRDS) probably due to higher proportions of BL and HIS in Queens County. BL dialysis patients are also more likely to have hypertension-, IVDU- and HIV-related ESRD. In API, HIS and NHW, glomerulonephritis (all types) is indication in incident cases in 35.8%, 33.5% and 24.7%, respectively. From 1990–2000, the population of Queens increased by 225,000 (11%); ethnic minorities, who have higher rates of ESRD, now comprise 71%. In view of these developments, EHC should expect to manage an increasing number of ESRD cases in the next decade.

- 1 Collins AJ. End-stage renal disease. *Postgraduate Med* 2000; 108(1):13–15.
- 2 2000 Annual Data Report of the U.S. Renal Data System. *Am J Kidney Dis* 2000; 36(6):15–36.

Highly Active Antiretroviral Therapy (HAART) at Elmhurst Hospital Center (EHC) Part II. M. Ciobatea, M.D. and A. Lyman, M.D. MSCM. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: HAART significantly reduces morbidity and mortality in HIV patients. Plasma viral load appears to be the best predictor of long-term clinical outcome. Numerous randomized controlled trials have assessed the effect of HAART on viral load^{1,2}. Astudy at Johns Hopkins Hospital showed that only 37% of patients receiving HAART had undetectable HIV-RNA 1 levels one year after initiation; main risk factors for failure were frequently missed appointments, young age and nonwhite race. Astudy conducted at EHC from 7/97–6/98³ found higher rates of failure in males, Blacks, those aged 35–44, those missing > 10% of appointments, or those with 12 years of education. This study was continued to further examine the relationship of demographic and clinical factors on the viral load.

Methods: Retrospective cohort study utilizing chart review of all new medication-naïve patients placed on a regimen containing protease inhibitors (PI) or non-nucleotide reverse transcriptase inhibitors (NNRTI) from January 1999 to December 2000. Age, sex, marital status, level of education, race/ethnicity, language spoken, and HIV risk factors [intravenous drug user (IVDU), homosexual/bisexual not IVDU, and heterosexual not IVDU] were abstracted from the medical records. Kept appointments (> 50% vs less) was obtained as an indirect indicator of adherence to treatment. Mean and median of all viral loads (VL) obtained at least one month after starting treatment. Results were tabulated and analyzed by hand.

Results: 211 patients were identified; 69 (32.7%) met inclusion criteria; 142 subjects (67.3%) were excluded. Mean VL was highest for those aged 35–44 (27442). Females had better response (953 vs. 12834). People with 12-grade education had lower VL (6248) than people who had < 12-grade (27529). Race/ethnicity: lowest for Caucasians (702) and highest for African-Americans (19677), single subjects had highest results (11401).

Unlike prior study, sample of IVDU was too small to permit reliable estimate of viral load. Heterosexuals (largest category) had the highest results (11812). Spanish-only-speaking had lower results than English-speaking (1593 vs. 8218). Median VL was not appreciably different between various groups; the most frequent value was undetectable. Adherence to clinic appointments was lower for Caucasians and single patients, but showed no appreciable difference according to all other variables.

Conclusions: Mean VL was lowest for patients aged 18–24, females, education < 12 years, Caucasian, widowed, and IVDU as risk factor; median VL were usually in the undetectable range. Adherence to clinic appointments was generally good, as measured by > 50% compliance. Adherence was lower for Caucasians and single subjects. Further studies on a larger sample, permitting meaningful subgroup analyses are indicated.

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Effect of Severity of Withdrawal Symptoms on Smoking Cessation in Subjects Treated with Clonidine or Placebo. A. Lyman, M.D., M.S.C.M.¹ and L. Covey, Ph.D.²

Background: Nicotine withdrawal symptoms may increase risk of failure to quit or of relapse. An analysis was performed on data from a double-blind placebo-controlled randomized trial of clonidine treatment of nicotine dependence³ to determine if severity of withdrawal symptomatology was associated with failure to quit.

Methods: The study has been previously described. Exclusion criteria included major depression (MD) in past six months or antidepressant therapy in past six weeks. SCID and Fagerström Tolerance Questionnaire (FTQ) were administered to evaluate, respectively, history of MD and nicotine dependence. Withdrawal symptoms (craving, irritability, anxiety, depressed mood, restlessness, increased appetite, sleep disturbance, difficulty concentrating) were ascertained by self-rating on a six-point Likert scale one week post-quit date and summed to yield a total withdrawal symptom score (TWSS). Abstinence was assessed at the ten-week visit with confirmation by plasma cotinine. Logistic regression was performed to estimate the odds ratio of cessation for each five point increase in TWSS, using SPSS software.

Results: More than 85% of the sample was Caucasian and of middle or upper income; mean age = 45 years; median daily consumption = 30 cigarettes; mean duration of smoking = 28 years; nearly 80% had high scores on FTQ. Mean TWSS was 16.18 (maximum = 40). In a logistic regression model, only FTQ was significantly associated with cessation [odds ratio (95% confidence interval) = .851 (.735, .986)], TWSS, clonidine, and history of MD were not. Every one-point increase in FTQ score was significantly associated with a 15% decrease in the odds of cessation. A subject on placebo without history of MD with a high TWSS and high FTQ had a predicted probability (95% confidence interval) of cessation of only 18.77% (17.20, 42.11), as compared to 50.53 (39.51, 61.49) for a similar subject with low TWSS and low FTQ.

Conclusions: Withdrawal symptom severity was not significantly associated with cessation in a clinical trial of clonidine (hypothesized to relieve withdrawal symptoms). Failure to identify significant predictors of cessation underscores need for further research to determine which, if any, symptoms are associated with failure or relapse, and to identify pharmacologic and behavioral means to address them.

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- Dept. of Clinical Psychopharmacology, NYS Psychiatric Institute
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Geriatrics

Interns Learning to Care for Dying Patients. Jennifer Rhodes-Kropf, M.D., Mount Sinai Geriatric Department, New York, NY; R. Adelman, M.D., Cornell Geriatric Department, New York, NY; and D. Meier, M.D., Mount Sinai Geriatric Department, New York, NY.

Objectives: To examine intern self-assessment of their care of dying patients. To examine intern assessment of the educational role of attending physicians in the care of dying patients.

Methods: The data was collected at a New York City Teaching Hospital. Interns were identified from death certificates of their patients during six months in the year 2000. Patient deaths were excluded if the deaths were unexpected or if the patients died in the intensive care unit. Intern interviews were scheduled within a few days after their patients' deaths. Fifty half hour structured interviews were completed by one interviewer. The questions were quantitative (Likert scale) and qualitative. The following topic areas were included; intern relationship with the dying patient, intern

relationship with the dying patient's family, and intern relationship with the patient's attending physician.

Results: Fifty-eight percent of interns rated their comfort level in talking to their patient and family about end-of-life issues as good, 4 to 5 on the Likert scale of 1–5. Sixty percent of interns reported minimal emotional impact in terms of making their patient's experience with death emotionally easier, 1 to 2. Minimal time to spend at bedside was cited as the most important influential factor. Seventy-four percent of interns rated their patient's physical comfort level 4 to 5, 26% 1 to 3. Interns rated how well their patient's attending matched the definition of the ideal role model caring for a dying patient: 34% received a 1 to 3, 66% a 4 to 5. Observation of discussions by attendings with patients and families was rated as the most effective method to learn how to care for dying patients (mean 4.45 on the Likert scale).

Conclusions: The majority of interns are comfortable talking to their patients and families about end-of-life issues, but the majority also felt that they had minimal emotional impact. Interns think that observing attending interactions with patients is the most effective way to improve their skills caring for dying patients and their families, however, there is wide variability in attending performance in their capacity as role models caring for dying patients.

Hematology

Generation of Recombinant Adenoviruses for Gene Transfer of Antistathmin Ribozymes in Cancer Cells. Sucharita J. Mistry, Alex Bank, and George F. Atweh, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Stathmin plays an important role in the regulation of the mitotic spindle by promoting microtubule depolymerization. It is highly expressed in a wide variety of human cancers including leukemia, lymphoma, breast carcinoma, prostate carcinoma and ovarian carcinoma. We had previously shown that antisense inhibition of stathmin expression abrogates the malignant phenotype of leukemic cells *in vitro* and *in vivo*. We also showed that combination of antisense stathmin inhibition and drugs that target the mitotic spindle (e.g. Taxol) have synergistic antiproliferative effects. Ribozymes, which have the potential to catalytically cleave more than one molecule of the target RNA, may provide a more efficient approach for downregulating genes like stathmin that are expressed at very high levels in cancer cells. We had previously designed three novel hammerhead ribozymes that efficiently cleave native full length stathmin mRNA in a catalytic manner. We have now cloned two of these antistathmin ribozymes, Rz184 and Rz305, in a bicistronic adenoviral gene transfer vector (pQBI-AdCMV5-IRES-GFP) to coexpress antistathmin ribozyme and GFP. The potential growth inhibitory effects of the cloned antistathmin ribozymes were first analyzed in HeLa cells by a colony suppression assay. HeLa cells were cotransfected with the antistathmin recombinant vector and a neomycin resistance gene expression plasmid. In a control experiment, the cells were cotransfected with a neomycin resistance gene expression plasmid and a control ribozyme (RzC) carrying non-specific sequences that do not target stathmin. The G418 resistant colonies were counted after three weeks. HeLa cells that were cotransfected with pRz184.GFP and pRz305.GFP showed 77.3% and 90% inhibition of colony formation, respectively, compared to cells cotransfected with pRzC.GFP. This demonstrates that the antistathmin ribozymes are biologically active and have growth inhibitory effects *in vivo*. In order to achieve efficient gene transfer of anti-stathmin ribozymes in cancer cells *in vivo*, we generated a recombinant adenovirus construct expressing the antistathmin ribozyme. The adenoviral recombinants were identified by the presence of green fluorescent plaques and screened by PCR analysis. Out of 17 plaques, 8 showed the insertion of anti-stathmin ribozyme and GFP sequence into the Ad genome. We examined the antistathmin ribozyme activity of 5 of these clones by transducing 293 cells. After 48 hours of infection, nearly 100% of the cells were transduced as determined by the appearance of green fluorescence. Northern analyses of RNA isolated from the transduced cells showed 70–86% reduction in the level of stathmin mRNA relative to uninfected cells. This demonstrates that these recombinant adenoviruses are capable of efficient gene transfer of anti-stathmin ribozymes and can inhibit stathmin expression in transduced cells. The ability of these recombinant adenovirus to transduce different cancer cells is currently being investigated. These studies may lead to the development of a novel antistathmin ribozyme based therapeutic approach to cancer therapy.

A Novel Pathway for Activation of Hematopoiesis and Vasculogenesis in the Mouse Embryo. ^{1,2}M.A. Dyer, ²D. Mohn, and ²M.H. Baron. ¹Department of Genetics, Harvard Medical School, Boston, MA, and ²Department of Medicine, Mount Sinai School of Medicine, New York, NY.

During mouse development, the first blood and endothelial cells arise from mesoderm induced and patterned by secreted signaling molecules. We demonstrated previously that specification of these lineages requires a signal(s) secreted from the adjacent visceral endoderm (VE) (Belaousoff et al., 1998 *Develop.* 125:5009). Recently, we have reported (Dyer et al.,

2001, *Develop.* 128:1717) that Indian hedgehog (Ihh) is a VE-secreted signal which alone is sufficient to induce formation of hematopoietic and endothelial cells. As seen with VE, Ihh can also specify prospective neural ectoderm (anterior epiblast) along hematopoietic and endothelial (posterior) lineages. Downstream targets of the Hh signaling pathway (*Ptch1*, *Smo*, *Gli1*) are upregulated in anterior epiblasts cultured in the presence of Ihh protein, reflecting a response by the target tissue to the Hh signal. Dispersed cells from IHH-treated anterior epiblasts form primitive or definitive hematopoietic colonies in secondary cultures in the presence of appropriate cytokines, indicating that functional hematopoietic stem cells are produced. Blocking Ihh function in VE inhibits activation of hematopoiesis and vasculogenesis in the adjacent epiblast, suggesting that Ihh is an endogenous signal that plays a key role in the development of the earliest hemato-vascular system. We have shown that another family member, *Desert hedgehog* (*Dhh*), is activated in the embryo during gastrulation and is expressed in the mature yolk sac mesoderm (Farrington et al., 1997, *Mech. Dev.* 62:197).

In *Ihh* null embryos, *Dhh* might compensate, at least in part, for the function of Ihh and may also stabilize the mesodermal patterning initiated by Ihh during early gastrulation. IHH-N upregulates expression of *Bmp4* in anterior epiblasts. Our recent work has demonstrated that recombinant human BMP4 protein can substitute for IHH-N in explant cultures. Therefore, the hedgehog signaling activities observed in our explant cultures might be mediated, in part, by *Bmp4*. Indeed, the BMP-binding protein noggin inhibits activation of hematopoiesis and vascular development in whole embryo explants as well as in HH-treated anterior epiblasts, indicating that *Bmp* signaling functions downstream from Ihh signaling in this pathway. Interestingly, *Hedgehog* genes and protein are expressed by adult mouse and human bone marrow stromal cells and *Ptch1* and *Smo* are expressed in hematopoietic stem/progenitor as well as endothelial cells. Recently it has been reported that, in postnatal mice, Sonic hedgehog can activate angiogenesis through upregulation of VEGF and angiopoietins. We suggest that Ihh and *Dhh* may also function in vascular development by regulating the expression not only of *Bmp4* but also of vascular cytokines. Therefore, these findings may have important implications for regulating hematopoiesis and vascular development for therapeutic purposes in humans and for the development of new sources of stem cells for transplantation and gene therapy.

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Cross-Talk between Human Vascular Endothelial and Smooth Muscle Cells: An Explanation for the Atherogenicity of Lipoprotein(a). Nasreen Haque, Mark Taubman and Peter Harpel. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Background: Monocyte/macrophage and vascular smooth muscle cells (VSMC) invasion of the intima is a hallmark of atherosclerosis. The lipoprotein Lp(a) is an independent risk factor for atherosclerosis but the mechanisms are not known. We have shown earlier that Lp(a) stimulates human vascular endothelial cells (HUVEC) to produce the CC chemokine I-309, a monocyte chemoattractant (*Circulation*. 2000;102:786-92). We have also reported that HUVEC express CCR8, the I-309 receptor, and that endothelial chemotaxis is induced by I-309 (*Blood* 2001; 97:39-45). We postulated that Lp(a) may induce monocyte chemotaxis into the vessel wall via stimulation of HUVEC I-309 and that this activity of Lp(a) may play a role in its atherogenicity. We now show that VSMC express CCR8 and transmigrate in response to I-309 and to Lp(a) stimulated HUVEC conditioned medium (LCM).

Methods and Results: We have found that I-309 and LCM induce VSMC chemotaxis and that this migration is inhibited by a monoclonal antibody we have produced against CCR8. Further, pertussis toxin inhibited VSMC migration in response to I-309 showing a Gi-coupled receptor response. Northern blot analysis of VSMC documented CCR8 mRNA. These results indicate that VSMC express functional CCR8. We have also found that I-309 stimulates VSMC to secrete metalloproteinase-2 (MMP-2) as assessed by gelatin zymography. MMP-2 activation appears critical for VSMC migration since neutralizing antibody to MMP-2, but not MMP-9, blocks both I-309 and LCM induced migration of VSMC through reconstituted basement membrane.

Conclusion: These results document that I-309 and I-309 induced in the CM of HUVEC by Lp(a), stimulate VSMC migration. I-309 also increases secretion of MMP-2 by VSMC, an activity that appears essential for I-309 induced VSMC migration through matrix. These new data support the concept that Lp(a) may induce molecular cross-talk between HUVEC and VSMC resulting in smooth muscle cell recruitment into the intima of the human atherosclerotic plaque.

New Generation of Retroviral β -globin Vector Capable of Transducing Hematopoietic Cells at High Level. Hassana Fathallah, H-Y. Lung, K. Chirkova, Y. Galperin, R.S. Weinberg, and G.F. Atweh.

One major obstacle to gene therapy of human sickle cell disease and β -thalassemia with retroviral vectors of the Moloney murine leukemia type is inefficient gene transfer into non-dividing hematopoietic stem cells. We have developed a new generation of HS-40 based retroviral vectors that

carry a human beta (or gamma) globin gene as the therapeutic gene and the green fluorescent protein (GFP) gene as a selectable gene. The globin gene in these vectors is under the control of the human beta globin promoter while the GFP gene is under the phosphoglycerate kinase gene promoter. We demonstrate that these retroviruses are genetically stable in producer cell lines and can be produced at high titer. Following a three-day transduction protocol of murine bone marrow cells, gene integration in progenitor cells was determined by culturing cells in methylcellulose followed by a PCR assay for the presence of the viral sequences. Gene expression was analyzed in transduced cells by flow cytometry to determine the % of GFP positive cells. PCR analysis of individual colonies showed 60% of GFP and globin positive colonies while FACS analysis showed 16% of GFP positive cells. These retroviruses were also able to transduce peripheral blood cells from sickle cell patients at a reasonable efficiency (7% of GFP positive cells). High level of transduction and a selection based on GFP expression could potentially ensure the selection of transduced cells which express the transferred gene and eliminate nontransduced cells and transduced cells that don't express the transferred gene. Enrichment of transduced cells and their engraftment in the recipient bone marrow could make effective gene therapy of human beta-globin gene disorders an achievable goal.

Changes in Stathmin Expression during Megakaryocyte Maturation: A Potential Role In Endomitosis. Camelia Iancu and George F. Atweh, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Megakaryopoiesis is characterized by two independently regulated processes, functional maturation and polyploidization. In the process of polyploidization, immature megakaryocytes (megakaryoblasts) increase their DNA content to $2n$ by a poorly understood process named endomitosis. Endomitotic cells are characterized by the presence of complex multipolar mitotic spindles, limited chromosome separation and absence of cytokinesis. The endomitotic cell cycle involves highly dynamic changes in microtubules that are essential components of the cytoskeleton and the mitotic spindle. Stathmin is a major cytosolic phosphoprotein that plays an important role in cell cycle progression by regulating the dynamics of microtubule polymerization and depolymerization both in interphase and mitosis. Inhibition of stathmin expression is associated with abnormalities in cell cycle progression, mitotic spindle formation and mitotic exit. We hypothesized that a regulation of the level of stathmin expression might be critically important for megakaryocyte differentiation and its loss of expression might be responsible for the abortive mitosis in megakaryocytes which is referred to as endomitosis. We first analyzed stathmin expression in two different human erythroleukemia cells cell lines (K562 and HEL cells) that are capable of both maturation and polyploidization following exposure to inducing agents. Upon exposure to phorbol ester or staurosporine stathmin mRNA expression was downregulated in a concentration and time dependent manner in both cell lines. This was associated with the appearance of a characteristic differentiated phenotype and upregulation of megakaryocytic specific markers. In addition, downregulation in stathmin mRNA expression correlated with increased DNA content of differentiated cells. We had previously found that partial stathmin inhibition in K562 cells increased the propensity of these cells to become polyploid upon exposure to staurosporine. Thus, these results in established cell lines strongly suggest that stathmin expression may also play an important role in megakaryocytic maturation of primary cells. Therefore, we derived primary megakaryocytes in culture from murine bone marrow to investigate stathmin expression during megakaryopoiesis. Immature and mature megakaryocytes were separated by density gradient separation. The different fractions were subsequently analyzed for the characteristic megakaryocytic morphology by light microscopy and for CD41 expression and DNA content by flow cytometry. We used a semiquantitative RT-PCR assay to determine stathmin mRNA expression at different stages of megakaryocyte maturation. Megakaryocyte progenitors with low ploidy levels (i.e. $2n$ to $4n$ DNA content) showed significant levels of stathmin mRNA expression. In contrast, mature megakaryocytes had no detectable levels of stathmin mRNA. More importantly, the absence of stathmin mRNA expression in these cells correlated with a high level of ploidy (up to $128n$ DNA content). Thus, these results support the hypothesis that the loss of stathmin expression might be associated with or even responsible for megakaryocyte polyploidization. Our findings are the first evidence for a potential involvement of stathmin in primary megakaryocyte maturation. Further investigations are underway to determine the role of stathmin expression during megakaryopoiesis *in vivo*.

Molecular Mechanism of Action of the BTB Class of Transcriptional Repressors. A. Melnick¹, F. Ahmad², V. Bardwell³, G.G. Prive², and J.D. Licht¹. ¹Derald Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY; ²Department of Medical Biophysics, University of Toronto, Canada; and ³Department of Genetics Cell Biology and Development, University of Minnesota.

The PLZF transcriptional repressor causes a refractory form of acute promyelocytic leukemia when fused to the retinoic acid receptor alpha. Its

highly conserved N-terminal BTB domain plays a critical role in this disease since it is believed to recruit co-repressors that inappropriately silence target genes. The crystal structure of the PLZF BTB domain revealed an obligate homodimer with a highly conserved charged pocket formed by apposition of the two monomers. An extensive structure-function analysis showed that the charged pocket motif plays a major role in transcriptional repression mediated by PLZF. In the current study we wished to determine the mechanism of action of the BTB pocket in transcriptional repression. We found that mutations which neutralize key charged pocket residues without disrupting dimerization abrogated the ability of PLZF to repress transcription. Interestingly, loss of repression correlated with loss of interaction with N-CoR, SMRT and HDACs. We extended these structure function studies to the Bcl-6 protein, which is linked to the pathogenesis of non-Hodgkin's lymphomas. In this case, neutralizing the charged pocket also resulted in loss of repression and loss of co-repressor binding. We identified the BTB binding region of co-repressors and show for the first time a direct interaction between co-repressors, PLZF and Bcl-6. Furthermore, a comparison of the PLZF, Bcl-6 and the FAZF^{ROG} protein shows that variations in the pocket results in differential affinity for co-repressors which predicts the potency of transcriptional repression. Thus, the BTB pocket is a novel molecular mechanism for recruitment of transcriptional repression complexes to target promoters.

Construction, Characterization, and Expression Analysis of Lentiviral Vectors That Carry the Human Beta and Gamma Globin Genes. Abdallah Nihrane and George Atweh. Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Retroviral-based transfer of a functional human globin gene and its integration in the genome of hematopoietic stem cells could provide a cure for Sickle Cell disease. Earlier generations of retroviral globin gene transfer vectors suffered from genetic instability, low titers and low levels of expression of globin genes in transduced cells. HIV- or FIV-based Lentiviral vectors can be produced by transient transfections of three constructs (packaging construct, envelope construct and transfer vector) into 293T human kidney cells. The resulting lentiviral vectors are capable of infection, integration and stable expression in non-dividing target cells such as hematopoietic stem cells, hepatocytes, neurons and retinal cells. We have generated several HIV-based lentiviral vectors that express human globin genes under the enhancing activity of HS-40 element. The first vector carries the human beta-globin gene driven by its own promoter and modified by deleting recombinogenic IVS-2 sequence. The second vector carries a human gamma globin gene under the control of the beta-globin promoter. Lentiviral particles were prepared from concentrated or non-concentrated supernatants recovered from transiently transfected 293T cells and used to transduce Mouse Erythroleukemia (MEL) cells. Human globin gene expression in transduced MEL cells was assessed by S1 nuclease assays. In the absence of selection, the level of human beta-globin gene expression was greater than 10% of the expression of a single endogenous murine beta-globin gene. This suggests that the lentiviral vectors are giving rise to efficient gene transfer and a relatively high level of expression of the transduced human beta-globin gene. The gamma globin vector also expressed well in MEL cells. Further analysis is being conducted to accurately assess the efficiency of globin gene transfer and the level of human globin expression relative to that of the murine endogenous globin gene. We also generated similar globin vectors that include the GFP reporter gene. This modification should allow for more accurate estimation of viral titers and tracking of transduced cells both *in vitro* and *in vivo*. In the case of FIV-based vectors, four constructs were generated. A first vector carries eGFP gene driven by the CMV promoter. Two vectors carry either human beta- or gamma-globin genes linked to HS-40 regulatory element. The two remaining vectors carry eGFP reporter gene, together with either human beta- or gamma-globin genes linked to HS-40 regulatory element. These vectors were characterized and are being analyzed for the efficiency of transduction and expression of human globin genes *in vitro* and *in vivo*.

Infectious Diseases

Follow-up of Inadvertent Occupational Exposure to Resistant Tuberculosis via a Computerized Record System. D.A. Finch*, J. Williams*, A. Roveal*. *Bronx Veterans Affairs Medical Center, Infectious Disease Section, Bronx, NY.

Introduction: On November 11, 1999 the infection control service was notified by the microbiology lab that a patient on the acute care ward had a positive AFB smear of the sputum. The patient was subsequently diagnosed with military tuberculosis involving the brain, lungs, spleen, liver and kidneys. At the request of the NYC Department of Health, a contact investigation was initiated for all potentially exposed health care workers on duty for three months prior to the positive smear.

Methods: Hospital contacts were identified using hospital duty rosters and via a computerized patient record system (CPRS). At the Bronx VAMC, health care providers use the CPRS to write electronic progress notes and orders. Providers are identified via unique electronic signatures. Electronic progress notes were reviewed in full to identify any contact that may not have been identified via duty rosters.

Results: Six of 164 potentially exposed health care workers were not on any duty roster file. Based on CPRS notes, 49 of 164 employees were determined to have had close contact with the patient. Baseline tuberculin skin testing (TST) and repeat TST at three months post-exposure were recommended for all those who were TST negative. Eleven had previously positive TST. Three did not comply with TST. One new conversion was identified at annual follow-up. No secondary cases of active TB were identified.

Discussion: We conclude that electronic patient record systems can assist in contact investigations through clear documentation of health care provider contacts.

HIV Genotype Reports without Evidence of Significant Resistance Mutations: Incidence and Physician Interpretation of Medication Adherence at a Veterans Affairs Medical Center. D.A. Finch, MD*, A. Shahidi, PhD*, S. Brown, MD*. *Bronx Veterans Affairs Medical Center, Infectious Disease Section, Bronx, NY.

Introduction: It has been previously reported that HIV wild-type virus can re-emerge when anti-retroviral therapy is interrupted (Deeks. *NEJM* 2001; 344(7): 472-80). A recent study of electronic surveillance of adherence to anti-retroviral therapy found that physicians misjudge the degree of adherence in 41% of their patients (Patterson. *Ann Intern Med* 2000; 133: 21-30).

Methods: The results of HIV genotyping performed at the Bronx Veterans Affairs Medical Center between May, 2000-May, 2001 were reviewed to determine the incidence of reports without evidence of significant resistance mutations. Physician interpretation of these results as a measure of adherence was assessed by reviewing physician encounter notes documented in a computerized patient record system.

Results: The microbiology lab at the Bronx Veterans Affairs Medical Center has performed 181 HIV genotype tests in the past twelve months. Ten genotypes (5.5%) did not reveal any significant resistance mutations. Physician interpretations were unavailable for one of ten results. Four of ten of these patients were thought to be adherent at the time the test was drawn; four of the four patients were subsequently considered non-adherent. Five of ten patients were known to have interrupted therapy at the time genotype testing was performed.

Discussion: This study confirms that physicians are willing to accept the presence of wild-type HIV virus as evidence of treatment interruption. This implies that large studies of clinical and virologic failure to respond to HIV anti-retroviral therapy will find that some failures are due to treatment interruption rather than HIV resistance.

Integrating Hepatitis C Screening and Counseling into an Existing Infectious Disease Clinic. E. Recher, C.S.W-R, J. Saporito, C.S.Wand, D.A. Finch, M.D. Bronx VAMedical Center, Infectious Disease Section, Bronx, NY.

Introduction: Hepatitis C virus (HCV) is recognized as serious national public health problem. Limited surveys of Hepatitis C infection in the VA system have shown that the prevalence may be as high as 20% of all veterans. In the period from October 1, 1995 to March 31, 2001, the Bronx VAMC tested 14,800 veterans for the HCV antibody, 3,650 (25%) tested HCV positive. As per VA policy, HCV antibody testing and post-test counseling is offered to all veterans with past or present risk factors for HCV infection. At the Bronx VAMC, integration of HCV counseling and treatment into the I.D. Clinic evolved out of the existing HIV practice model.

Methods: We applied a multidisciplinary team approach because of the similarities in psychological responses of HCV diagnosis and HIV diagnosis. All Bronx VAMC primary care providers are reminded to screen their patients for high risk for HCV infection via a computerized reminder. HCV elisa positive patients are referred to a newly created viral hepatitis clinic. Additionally, HCV testing is offered to veterans requesting HIV testing by the HIV social workers. Social workers trained in HIV test counseling give the results of HIV and HCV tests to patients during the post-test counseling session. These social workers took on the additional task of providing comprehensive initial HCV counseling to newly referred patients before they were evaluated by the physician. Veterans are first seen by one of the clinical social workers for HIV and/or HCV counseling, which includes a biopsychosocial assessment. Baseline lab work and HCV confirmatory testing is drawn at this visit. Veterans are referred for medical specialist evaluation and other programs, i.e. psychiatry, substance abuse, as needed. Additionally, a new Hepatitis C educational and peer support group, co-facilitated by a social worker and nurse practitioner was formed.

Results: In the period from September 8, 1999-March 31, 2001, 418 veterans received comprehensive counseling regarding Hepatitis C.

Discussion: Integration of HCV counseling into an existing HIV counseling model is a method to address patient's biopsychosocial needs and the evaluation and management of an emerging epidemic.

HIV-1 Envelope Is a Neutral Antagonist to CXCR4 in T-Cells and Does Not Induce Interactions with G-Proteins. R. Staudinger*, X. Wang† and J.C. Bandrés‡. Departments of Neurology* and Pathology†, New York University School of Medicine; Department of Medicine, Mount Sinai School of Medicine‡ and Bronx VAMedical Center, ID Section, Bronx, NY‡

Background. The chemokine receptor CXCR4 is the principal coreceptor for X4 (T-tropic) HIV-1. HIV-envelope (gp120) interacts first with surface CD4 and then with CXCR4, a G-protein coupled receptor (GPCR). We analyzed the biochemical interaction between gp120 and CXCR4 and compared it with the one between CXCR4 and natural ligand stromal derivative factor-1 (SDF-1).

Results. Interaction with G-proteins. By using membrane extracts from CXCR4-rich T-cell line CEM we found that SDF-1 stimulated [³⁵S]-GTP-gamma-S binding to 210%, over control. Also, SDF-1 (20 nM) stimulated GTPase activity to 205 ± 5%. Alternatively, gp120_{LA1} (300 nM), combined to 300 nM of sCD4, did not affect [³⁵S]-GTP-gamma-S binding to CEM membranes and left the basal level of GTPase unaltered. Still, gp120_{LA1}/sCD4 (300 nM) reduced SDF-1 stimulation of [³⁵S]-GTP-gamma-S binding to CEM membranes to 120 ± 14%. GTPase stimulation by SDF-1 was reduced to 108 ± 10%. In conclusion, HIV-gp120 does not induce interaction between CXCR4 and G-protein, but antagonizes the agonist effect of SDF-1.

Gp120 binding to CXCR4. Scatchard analysis of the homologous competition curve showed a single binding site, $K_D = 71.6 \pm 17.14$ nM and $B_{max} = 3.77 \pm 0.55$ pmol/mg. Binding of gp120 was neither regulated by guanine nucleotides, nor affected by divalent cations and was temperature independent.

The affinity of gp120_{LA1} for CXCR4 was 10 times lower than for CD4 (KD of 8.2 ± 0.3 nM). This suggests a substantial role for CD4 to facilitate binding of gp120 to CXCR4.

SDF-1 binding to CXCR4. Similar analysis revealed two binding sites of CXCR4 for SDF-1. 13–20% of binding sites were of high affinity ($K_D = 0.48 \pm 0.1$ nM), and the remaining of lower affinity ($K_D = 9.6 \pm 2.1$ nM). [¹²⁵I]-SDF-1 binding was highly temperature dependent. Inclusion of GTP-gamma-S converted the higher affinity-binding site to the lower affinity site. Scatchard analysis revealed a homogeneous receptor population, $K_D = 5.75 \pm 2.3$ nM and $B_{max} = 3.16 \pm 0.1$ pmol/mg.

In conclusion, gp120 acts as an antagonist to a GPCR and the interaction of CXCR4 with HIV-1 viral envelope and chemokine exhibits fundamental differences that might help us devise new therapeutic approaches.

Allosteric Regulation of CCR5 by Guanine Nucleotides and HIV-1 Envelope. R. Staudinger*, X. Wang†, and J.C. Bandrés‡. Departments of Neurology* and Pathology†, New York University School of Medicine; Department of Medicine, Mount Sinai School of Medicine‡ and Bronx VA Medical Center, ID Section, Bronx, NY‡.

Background: The chemokine receptor CCR5 is the principal coreceptor for R5 (macrophage-tropic) strains of HIV-1. Chemokine receptors belong to the super-family of GTP-binding protein coupled receptors (GPCR). Here, we report the biochemical consequences of the interaction between CCR5 and G-proteins and how HIV-1 envelope affects this interaction.

Results: Binding studies using [¹²⁵I]-macrophage inflammatory protein (MIP)-1beta and membrane extracts from HOS-CCR5 cells showed that MIP-1beta binding to CCR5 was potent and specifically inhibited by guanine nucleotides. GTP inhibited MIP-1beta binding with an IC50 of 115 nM. The effects of GTP on the equilibrium binding properties of MIP-1beta were determined by using pre-incubation with increasing concentrations of GTP. GTP caused a concentration-dependent decrease in the computed number of binding sites (B_{max}), but had no effect on the affinity of the residual receptor sites. This indicated that the molecular mechanism of this inhibitory effect was a dose-dependent reduction in MIP-1beta receptors. We did not observe the appearance of a low affinity state.

Studies with HIV-envelope. In the absence of sCD4 the R5 tropic gp120W61D had no effect on MIP-1beta binding, indicating that binding of HIV-1 viral envelope to CCR5 is absolutely dependent on CD4. In the presence of sCD4, 100 nM gp120W61D inhibited [¹²⁵I]-MIP-1beta binding to CCR5 by 56 ± 9%. Equilibrium binding data revealed that 100 nM gp120-sCD4 decreases the affinity of CCR5 for MIP-1beta ($K_D = 425 \pm 72$ pM) with only a slight decrease in receptor density ($B_{max} = 1.08 \pm 0.21$ pmol/mg). Gp120-sCD4 had mostly a K_D effect on MIP-1beta binding to CCR5, so we examined this effect using kinetic studies. Gp120W61D-sCD4 accelerated the decay of the MIP-1beta-CCR5 complex, indicating that gp120W61D-CD4 is not a competitive ligand for the MIP-1beta binding site. Gp120W61D-sCD4 also decelerated the association reaction of MIP-1beta to CCR5. The dissociation constants were as follows: 112 pM in the absence and 340 pM in the presence of 100 nM gp120W61D-sCD4. All of this proves that HIV-1 envelope glycoprotein decreases the affinity of CCR5 for MIP-1beta, but also alters the kinetics of MIP-1beta binding to CCR5, indicating that it interacts with a distinct, but allosterically-coupled binding site.

Once Daily Dosing of Aminoglycosides (ODA) at the Bronx VA Medical Center. B.Ojofeitimi, D. Finch, and H.Fung. Bronx Veteran Affairs Medical Center, Bronx, NY.

The Aminoglycosides continue to be the mainstay therapy for the treatment of severe enterococcal and gram negative infections even though newer, less toxic antibiotics have gained FDA approval for clinical use. Aminoglycosides are usually used in combination with beta-lactams to provide synergistic effects although it can be used as a single entity for clinical conditions such as urinary tract infections. Studies have shown that pharmacodynamic, administrative and cost benefits do exist with the use of aminoglycosides once daily compared to multiple times daily. However, there are exceptions to the use of once daily dosing of aminoglycoside especially in certain patient populations and disease states, therefore its use should be carefully evaluated. This review will evaluate the use of once daily aminoglycoside dosing in our patient population with emphasis on side effects most importantly, changes in renal function.

Methods: Electronic charts of all patients who received once daily aminoglycoside dosing for the period 1998–2001 were reviewed retrospectively. Baseline renal function, gentamicin serum concentration and renal function parameters post aminoglycoside dosing will be analyzed.

Results: Only 5 patients (all male) were identified. Average age was 71 years. Three patients received ODA in Intensive Care Unit (ICU) and two in the medicine floor. All patients were on concomitant antibiotics including Zosyn, Kefzol and Flagyl. Only 1 patient was on Vancomycin, which could potentiate the nephrotoxic effect of aminoglycosides. Average duration of therapy was 7 days. Four patients had recently undergone surgical procedures (small bowel resection, aortic bifemoral bypass and tumor resection) complicated by infection or post-operative decompensation. One patient was treated for urosepsis.

Three patients (average age 80 years, average estimated creatinine clearance = 45 ml/min) with normal baseline renal parameters had an increase in BUN/Scr from baseline (50% increase serum creatinine).

Gentamicin trough concentrations in 3 patients were greater than 2 mcg/ml. Two patients (average age 57, average estimated creatinine clearance = 70 ml/min) had no change in renal function from baseline.

Conclusion: Once daily dosing of aminoglycosides is rarely used at our institution. The incidence of nephrotoxicity is high (3/5) probably due to decreased clearance of aminoglycosides in the elderly with impaired renal function.

Evaluation of a Safety IV Catheter (IVC) (Becton Dickinson, Insyte Autoguard): Final Report. *Meryl H. Mendelson, MD, B.Y. Lin-Chen, MPH, L. Finkelstein-Blond, RN, MA, E. Bailey, RN, MPH, G. Kogan, MS. Mount Sinai Medical Center and School of Medicine, New York, NY.

Asafety IVC (BD, Insyte Autoguard) was evaluated at an 1,100 bed university affiliated medical center to determine efficacy in reducing needlestick injuries (NIs). NI rate during a baseline period I (non-safety; 6/93–8/96, 39 months) was compared to the study period II (2/99–7/00, 18 months). The study period included a two-month training (2–3/99) and a three-month pilot (4–6/99). Protectiv[®] Plus Catheter (Johnson and Johnson) was evaluated during the interim time between Period I and II. NI data was analyzed utilizing the CDC NaSH database. Two sharp disposal surveys were performed to assess usage and activation rates in 6/99 and 7/00; and two product evaluation surveys were conducted in 12/99 and 7/00. A 95% reduction in IV stylet related NIs was demonstrated comparing the baseline period I NI rate of 6.6/100,000 IV stylets (56 injuries/848,958 IV stylets) to the study period II NI rate of 0.3/100,000 IV stylets (1 injury/331,516 safety IV stylets) ($p < 0.001$). The Period II NI occurred while the stylet was being withdrawn from the patient and the HCW failed to activate the safety mechanism. When comparing the two sharps disposal surveys, the 2nd survey activation rate was 91% vs. 85% (1st). The 2nd product evaluation showed 98% of HCWs answering the safety IVC catheter was very easy/easy to use compared to 78% (1st). 95% (2nd) vs. 76% (1st) felt there was either no change/a slight change in technique needed to use this safety device. 99% of HCWs during both surveys answered the safety IV catheter provided effective protection against needlesticks. In conclusion, the Insyte Autoguard resulted in a marked and significant reduction in IV stylet-related injuries during the study period. Although this safety IVC requires activation by the user, the simplicity of the activation process promotes user compliance and therefore reduction in injuries. In that IV stylet-related injuries are high risk (hollow-bore needle, inserted directly into vein or artery), usage of this safety device should result in decreased blood-borne pathogen transmission to HCWs. GCO#98-1046 ME*

Post C-Section Endometritis: Impact of Usage and Timing of Surgical Prophylaxis. M.H. Mendelson, MD, E. Santos-Cruz, BS, S. Gaddipati, MD, A. Adeyeye, RN, G. Kogan, MS, and J. Goldbold, PhD. Mount Sinai Medical Center and School of Medicine, New York, NY.

Prospective surveillance of post-partum endometritis following C-section (PPE) was performed to determine the role of antimicrobial prophylaxis

and the impact of timing of prophylaxis for patients undergoing clean (not in labor with intact membranes prior to incision) and clean-contaminated (rupture of membranes, or intact membranes and in labor prior to incision) procedures. This surveillance was performed at the Mount Sinai Medical Center, a 1000 bed university affiliated hospital which performs approximately 5000 deliveries per year, 23% C-sections. From 8–10/99, there were 25 cases of PPE (CDC NNIS definition) following 286 C-sections (8.7%). The PPE rate was 4.0% for clean and 11.8% for clean-contaminated cases. When PPE rates were analyzed by prophylactic antibiotic usage and timing for clean cases: 0/25 (0)- pre-op (< 60 min prior to incision), 1/15 (6.6%)- intra-op(after cord clamping), and 3/59 (5.1%)- not meeting criteria (NMC) for pre or intra-op. For clean-contaminated cases PPE rates were: 3/35 (8.6%) pre-op, 6/35 (17.1%)-intra-op, and 9/83 (10.8%)-NMC. In conclusion, antibiotic prophylaxis when administered within 60 minutes prior to incision appears to be associated with a decrease in PPE following C-sections for both clean and clean-contaminated cases. Additional data is currently being collected to assess whether these findings will be statistically significant. If so, this data supports other analyses that have supported the effectiveness of antimicrobial prophylaxis for clean C-sections. Furthermore, the standard practice of administering antimicrobial prophylaxis after cord clamping will need to be re-evaluated.

Migraine Headaches during Treatment with Oral Ribavirin in Combination Therapy for Chronic Hepatitis. C. Norbert Bräu^{1,2}, Edmund J. Bini^{3,4}, Ayse Aytaman^{5,6}, Douglas A. Finch^{1,2}, Saray Stancic^{7,8} Mount Sinai School of Medicine, Dept. of Medicine, I.D. Division (1), Bronx VA Medical Center (2), NYU School of Medicine (3), VAnew York Harbor HCS, Manhattan Campus (4), SUNYDownstate Health Science Center (5), VA New York Harbor HCS, Brooklyn Campus (6), New York Medical College (7), VAHudson Valley HCS.

Background: Headaches have been associated with oral ribavirin (RBV) in early trials of RBV monotherapy for chronic hepatitis C. In treatment

trials of RBV + interferon alfa-2b (IFN) for hepatitis C, headaches are described equally frequently in IFN monotherapy and in combination of IFN + RBV (63–68%). Specific links between migraine headaches and ribavirin therapy have not been reported to date.

Method: During May 1998 and December 2000, 452 patients were treated with IFN + RBV for chronic hepatitis C in four medical centers. All patients who developed new migraine headaches (confirmed by a neurologist) or had worsening of existing migraine during treatment were evaluated for a possible causal relationship with either IFN or RBV.

Result: A total of 9 of 452 patients (2.0%, 95% CI 1.1% to 3.7%) developed migraines during treatment with IFN 3 MU TIW + RBV 1000–1200 mg/d, 8 with a new diagnosis and 1 with worsening of existing migraine headaches. In 8 of 9 cases, a causal link with RBV treatment could be established: in 5 patients, migraine symptoms improved significantly when RBV dose was reduced or stopped and symptoms resumed with full RBV dose. In 3 patients there were no headaches with prior IFN monotherapy. In one patient, a temporal relationship with RBV was made because headaches occurred daily, even on days off IFN doses. All nine patients had severe migraine headaches that required opioid analgesics. In all 6 patients where the RBV dose was reduced, migraine symptoms became less severe. In 7 of 8 patients with new onset migraine headaches, the headaches resolved completely upon discontinuation of RBV. One patient with prior diagnosis of migraine ceased having severe headaches after RBV was discontinued and only had rare migraine attacks in a similar way as before RBV treatment. The one patient with a new diagnosis of migraine headaches who continued to have symptoms had had chronic headaches since adolescence, which in retrospect were judged by the neurologist as undiagnosed migraine-style headaches. Table 1 describes the nine patients.

Conclusion: Migraine headaches (usually new onset) may occur as a consequence of ribavirin therapy in about 2% of cases. They are typically severe and require opioid analgesics. Dose reduction of ribavirin therapy usually leads to improvement of migraine symptoms, and discontinuation leads to resolution in most cases.

TABLE 1
Characteristics of 9 Patients with Migraine Headaches on Ribavirin Treatment

No.	Age	Sex	HCV risk factor	Daily RBV dose [mg]	Migraine new/worse	Onset of migraine on RBV Rx	Link RBV migraine	Outcome of migraine after RBV/D/C
1	43	M	IDU	1000	new	1 day	causal	continued
2	44	M	IDU	1200	worse	1 day	causal	mild, rare
3	37	M	IDU	1200	new	1 day	causal	resolved
4	46	M	IDU	1200	new	21 days	causal	resolved
5	51	M	IDU	1000	new	4.5 mo	causal	resolved
6	52	M	IDU	1200	new	4.0 mo	causal	resolved
7	40	M	Tattoo, cocaine, sex	1200	new	2.0 mo	temporal	resolved
8	40	M	IDU	1200	new	41 days	causal	resolved
9	45	M	IDU	1200	new	30 days	causal	resolved

Interferon Dose Increase for Early (Week 12) Non-Responders to Interferon Alfa-2b + Ribavirin Therapy for Chronic Hepatitis C Does Not Lead to a Viral Response at 48 Weeks. Norbert Bräu^{1,2}, Peiyong Xiao², Douglas A. Finch^{1,2}, Charles S. Lieber^{1,2} From the Mount Sinai School of Medicine, Dept. of Medicine (1) and Bronx VAMedical Center (2).

Background: At the end of treatment with interferon alfa-2b (IFN) and ribavirin (RBV) for chronic hepatitis C, the viral response rate (HCV RNA <100 copies/ml) is only 50%. Patients who have a poor response at treatment week 12 typically have a low treatment response. This study examined whether in such patients a dose increase of interferon can lead to a better outcome.

Methods: An open-label non-randomized parallel-group dose increase study was conducted in which patients with chronic hepatitis C (HCV RNA +) were begun on standard dose combination therapy (IFN 3MU TIW + RBV 1000 mg QD) for a total of 48 weeks. Patients were either treatment naive or had prior unsuccessful treatment with IFN monotherapy. Patients were considered early non-responders, if at treatment week 12 HCV RNA was reduced by less than 50% from baseline or ALT was elevated. These early non-responders were continued at treatment week 16 with an increased IFN dose of 5 MU TIW. Early responders were continued at the same IFN dose of 3 MU TIW. RBV dose remained unchanged in both groups. Primary endpoint was sustained viral response (SVR), i.e. HCV RNA < 100 copies/ml at post-treatment week 24.

Secondary endpoints were viral response at end of treatment (EOT) and post-treatment week 48. Analysis was by intention-to-treat.

Results: Fifty-five patients were enrolled in the study, of whom 8 discontinued from the study before week 16. The remaining 47 patients continued at week 16 with an IFN dose of either 3 MU (n = 37) or 5 MU TIW (n = 11) and are used for this analysis. Both groups were similar in HCV genotype (1 = 87.5% 2 + 3 = 12.5%), baseline HCV viral load (median 3.4 M copies/ml), prior treatment vs. naive, and demographics. Among the 47 subjects, 3 were lost to follow-up and were considered end of treatment non-responders. One patient in the 5 MU group had HCV RNA <100 copies/ml at weeks 12, 48, 72, and 96 with abnormal ALT throughout due to Parkinson medication rather than hepatitis C. He was reclassified as early responder. The results of viral response and early discontinuation in each group are displayed in table 1. No early non-responder had a response to treatment with increased IFN dose of 5 MU TIW + RBV 1000 mg/d. By contrast, early responders had a significantly higher rate of EOT viral response of 35.1% (p = 0.025) and SVR of 29.7% (p = 0.049). All 11 sustained viral responders remained HCV RNA negative at follow-up week 48.

Conclusion: Increasing the IFN dose from 3MU TIW at week 16 for early non-responders to IFN 5 MU TIW + RBV 1000 mg/d does not lead to a viral response at the end of 48 weeks of treatment. It may lead to more treatment discontinuation due to side effects. A sustained viral response at follow-up week 24 remains sustained at week 48.

TABLE 1
Viral response and early discontinuation

Treatment group	N	Viral response end Rx (EOT)	Viral resp. post-Rx wk 24 (SVR)	Viral resp. post-Rx wk 48	SVR genotype 1	SVR genotypes 2+3	Early D/C
Early responders	37	35.1%	29.7%	29.7%	21.9% (n = 32)	80.0% (n = 5)	16.2%
Early non-responders	10	0.0%	0.0%	0.0%	0.0%	0.0%	30.0%
p value (Fisher's exact test)		0.025	0.049	0.049	0.15	0.33	0.29

Liver Diseases

KLF6 Upregulates p21 Expression Through Recruitment of Histone Acetyltransferases CBP and PCAF. Dan Li¹, Steven Yeah¹, Goutham Narla¹, Francis J. Eng¹, Martin J. Walsh² and Scott Friedman¹. ¹ Division of Liver Diseases, Department of Medicine, ² Division of Pediatrics, Mount Sinai School of Medicine, New York, NY.

KLF6 is a ubiquitously expressed "Kruppel-like" transcription factor whose mRNA is upregulated in a biphasic manner following partial hepatectomy. We have previously shown that KLF6 induces growth arrest *in vivo* by transcriptional upregulation of p21 independent of p53. Histone acetyltransferases (HATs) are chromatin-remodeling proteins critical for regulating gene transcription. Recent evidence suggested that acetylation of non-histone proteins by HATs play an important role in modulating the functions of these proteins, many of which are transcription factors. The aims of this study were to investigate whether KLF6 is a substrate for acetylation by histone acetyltransferases CBP and PCAF, and whether the acetylation of KLF6 is critical for its transcriptional upregulation of p21.

Methods: Chromatin-immunoprecipitation (ChIP) assay was performed to examine whether KLF6 physically binds to endogenous p21 promoter. Co-immunoprecipitation/Western analyses were carried out in 293T cells transfected with KLF6 and CBP, KLF6 and PCAF, respectively. Luciferase reporter assays were used to study whether CBP and PCAF synergize with KLF6 in transactivating p21.

In vitro HAT assays were performed to examine whether KLF6 can be acetylated by CBP and PCAF.

Results: ChIP assay revealed that KLF6 physically binds to the endogenous p21 promoter, confirming p21 as a direct target of KLF6. The physical interactions between KLF6 and both CBP and PCAF were demonstrated by co-immunoprecipitation/Western analysis. Co-transfection/luciferase reporter assays showed that CBP increases by 6-fold the transactivation of p21 promoter by KLF6, with 5-fold further increase when 100nM histone deacetylase (HDAC) inhibitor trichostatin A (TSA) was added. PCAF increased the KLF6's transactivating p21 by 10-fold, which was also further increased by the addition of TSA. *In vitro* HAT assays revealed that KLF6 can be heavily acetylated by CBP and modestly acetylated by PCAF. In order to determine acetylation of which lysine residue(s) may be important in p21 upregulation, 10 lysine to arginine point mutants were constructed and their abilities to transactivate endogenous p21 gene characterized. Western blots showed that K(74, 80)R, K124R, K280R have marked reduced ability to transactivate endogenous p21 genes, suggesting the acetylation on these residues may be important for the upregulation of p21 by KLF6.

Conclusions: Our results demonstrated that KLF6 transactivates p21 gene through recruitment of histone acetyltransferases CBP and PCAF. KLF6 is a substrate for acetylation by both CBP and PCAF, and abolishing the acetylation on certain residues will markedly reduce KLF6's ability to transactivate p21, suggesting acetylation on these residues is important for the antiproliferative effects of KLF6. This provides new insights into the gene regulation during liver regeneration following parenchymal liver injuries.

Medical Oncology

Isolation and Characterization of Retroviral Particles from Human Breast Cancer. S.M. Melana¹, S. Dales², J.F. Holland¹, B. G-T. Pogo¹, ¹Division of Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; ²The Rockefeller University, New York, NY.

We have previously reported sequences homologous to the *env* gene of the mouse mammary tumor virus (MMTV) but not to the human endogenous retrovirus K-10 in 38% of American women's breast cancers. The sequences were absent from other human tumors and tissues; they were

expressed in most of the positive breast specimens. The complete 9.9 kb proviral structure of an MMTV-like agent has now been amplified and sequenced in two breast cancers. Structural features of this provirus indicate that it could be functional. The presence of viral particles and viral genes have now been investigated in primary cultures of *env* positive tumors.

When examined by electron microscopy, the cells show budding retroviral particles. Particulate fractions from culture media show reverse transcriptase (RT) activity, and the presence of viral genes as detected by RT-PCR. The RT activity peaked at densities characteristic of retroviruses in sucrose gradients. Furthermore, viral sequences have been detected in the particulate fractions. None of these properties were observed in similar studies with putatively normal breast cell lines. Taken together, these findings support the conclusion that a human mammary tumor virus, HMTV, similar to MMTV, has been identified. GCO#: [77-107](#)

Effects of Ribozyme (Rz) Targeted against Deletion-Mutant (d) EGFR mRNA on Growth of Human Glioblastoma Multiforme (GBM) Tumor Implanted in Mice. C.F. Qu, M-E. Halatsch, J. F. Holland, T. Ohnuma. Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

In GBM, amplification of the *EGFR* gene is frequently present. Approximately half of the amplified genes are rearranged to delete a DNA fragment containing exons 2 to 7 (*EGFR* VIII). As a result of the (d), the fusion junction of the gene is created directly upstream of a Rz target codon (GUA). Previously, we have reported construction of a hairpin Rz directed against (d)*EGFR* mRNA (anti-(d)*EGFR*-Rz). When the specific Rz was transferred via a retroviral vector (N2A-(d)*EGFR*-Rz) into GBM cell line U-87MG which over-expressed (d)*EGFR* (U-87MG.(d)*EGFR*), the Rz was capable of specifically inhibiting (d)*EGFR* expression and was able to markedly reduce the clonogenic property of tumor cells in soft agar (J Neurosurg 2000; 92:297).

Aims: In the present study, we evaluated whether anti-(d)*EGFR*-Rz could render U-87MG. *EGFR* cells less malignant *in vivo*.

Methods: U-87MG. *EGFR* cells were infected with N2A-(d)*EGFR*-Rz and Rz-expressing cells were selected by limited dilution method (U-87MG.(d)*EGFR*-Rz). In culture medium containing 10% FBS, the cell growth rate of U-87MG.(d)*EGFR* and U-87MG.(d)*EGFR*-Rz was identical. 5×10^5 U-87MG.(d)*EGFR*-Rz cells were inoculated subcutaneously in male SCID mice and tumor appearance and tumor size were compared with those of U-87MG.(d)*EGFR*. In a therapeutic experiment, large amounts of N2A-(d)*EGFR*-Rz were produced by micro-ping-pong method (Bunnell and Morgan), cross-infecting amphotropic GP+*env*AM 12 packaging cells and ecotropic GP+E86 packaging cells alternatively, followed by centrifugation (final product 7×10^7 CFU/ml). For the Rz treatment of mice implanted s.c. with 5×10^5 U-87MG.(d)*EGFR* cells, the concentrated retrovirus-containing anti-(d)*EGFR*-Rz was injected at the implant site (MOI 30 CFU/cell/day) on days 2-8. Notation of the tumor appearance and measurement of tumor size was made.

Results: U-87MG.(d)*EGFR* tumor nodules appeared by day 10 and grew with a volume doubling time of 2 days; by day 20 the tumor size exceeded 1 cm³. In contrast, when U-87MG.(d)*EGFR*-Rz cells were implanted, the appearance of a tumor nodule was delayed until day 19. Likewise, retroviral treatment with Rz resulted in similar delays in the appearance of U-87MG.(d)*EGFR* tumors.

Conclusion: Our observations show that the anti-(d)*EGFR*-Rz is capable of decreasing (d)*EGFR*-mediated high tumorigenicity in mice. This phenomenon was seen both after transduction of Rz *in vitro* or local injection of retrovirus expressing Rz at the U-87MG. (d)*EGFR* tumor implant site. The delayed tumor growth may be due to contamination with cells that had low or no expression of the Rz and/or expression of other oncogenes present in the parent U-87MG cells. GCO#: [77-107ME](#)

Construction of a Multitargeted Multiribozyme System Targeted against Both *MDR1* and *MRP1*, and its Cleavage Activity. D.P. Xu, T. Ohnuma, F.-S. Wang, J.F. Holland, Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Previous work from our laboratory showed that stem II-modified hammerhead ribozymes (Rzs) targeted against the codon 196 of *MDR1* mRNA (196*MDR1*-Rz) were able to completely reverse the multidrug resistance (MDR) phenotype of human lymphoma cells overexpressing P-glycoprotein (Human Gene Ther 1999; 10:1185). Combined overexpression of *MDR1* and *MRP1* has been reported in clinical tumor samples including AML, cells, prostate and GI cancers. Simultaneous expression of *MDR1* and *MRP1* was shown to have a strong negative impact on response and survival of patients with AML.

Aims: We set out to develop a multitargeted multiribozyme system expressing both anti-196*MDR1*-Rz and anti-210*MRP1*-Rz.

Methods and Results: To construct this system, first we synthesized Rzs targeted against GUC sites of different codons of *MRP1* mRNA. After having shown that a Rz targeted against the GUC site of codon 210 of *MRP1* mRNA (210*MRP1*-Rz) had high cleavage activity, we designed a shotgun type multiribozyme structure containing 4 cis-Rzs and 2 potential trans-Rz cloning sites (Coat-Rz) with computer-assisted assessment of secondary structure. We initiated construction of an upstream half-Coat (Coat' A) containing two cis-Rz sequences, GUC cleavage sites and one trans-Rz cloning sites (BamHI, XbaI and Sall) through PCR elongation using synthetic oligonucleotides as template and primers. The Coat' A was inserted into a cloning vector pGEM3Zf(-) (Coat' A-pGEM). Previously constructed 196*MDR1*-Rz and 210*MRP1*-Rz were individually cloned into the Coat' A-pGEM (196Coat' A-pGEM and 210Coat' A-pGEM). The downstream half-Coat (Coat' B) was obtained from Coat' A-pGEM by PCR using primers containing HindIII ligation sites at the both ends. Empty Coat' B, Coat' B containing 210*MRP1*-Rz and 196*MDR1*-Rz were then individually ligated downstream in tandem to create empty full Coat-pGEM, 196/210Coat-pGEM and 210/196Coat-pGEM, respectively. Orientation of downstream Rz was confirmed by DNase sequence analysis. After transcription, excellent self-cleavages with liberation of both 196*MDR1*-Rz and 210*MRP1*-Rz from Coat-Rz by cis-ribozymes were recognized after one hr at 37°C and 5mM Mg²⁺ concentration. The *MDR1* and *MRP1* target gene fragments were obtained through RT-PCR using total RNAs isolated from human laryngeal carcinoma KBv200 cells, which overexpressed both *MDR1* and *MRP1*. The two ribozyme system expressing both 196*MDR1*-Rz and 210*MRP1*-Rz effectively cleaved *MDR1* and *MRP1* target mRNAs. Cleavage activity was not influenced whether the position of Rz was upstream or downstream in tandem structure and whether the Coat-Rz contained single or double trans-acting Rz(s).

Conclusion: We developed a double-functional double-ribozyme system targeted against *MRP1* and *MRP1* mRNAs. Adenovirus expressing this ribozyme system is being developed for transduction into target tumor cells. This versatile Coat-Rz system can be utilized for creation of multifunctional systems by adding tandem additional Rzs and for liberation of any other therapeutic genes (Rzs/antisense). GCO# 77-107ME

Effects of Transduction of Anti-*MDR1*-Ribozyme on Drug Sensitivity of Multidrug Resistant Human Lymphoma Growing in SCID Mice. LY Liu, T. Ohnuma, DPXu, CF Qu, FS Wang, JF Holland, Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

We have previously reported that infection with Moloney murine leukemia-derived retrovirus N2A which expressed stem II modified hammerhead ribozyme (Rz) against GUC sequence at codon 196 of *MDR1* mRNA (196*MDR1*-Rz) resulted in complete reversal of the multidrug-resistance (MDR) phenotype of P-glycoprotein-positive Daudi human Burkitt lymphoma cells, Daudi/*MDR*₂₀ (Daudi cells which were 20-fold resistant to vincristine (VCR) *in vitro* (Hum Gene Ther 1999; 10:1185).

Aims: In the present study we have extended our *in vitro* observations to a mouse model using both Daudi/*MDR*₂₀ cells previously transduced *in vitro*, and Daudi/*MDR*₂₀ cells transduced *in vivo* after transplantation.

Methods: SCID mice were implanted i.v. with Daudi/*MDR*₂₀-196*MDR1*-Rz (196*MDR1*-Rz transduced Daudi/*MDR*₂₀ cells) on day 1, and treated with VCR i.p. for 5 days (days 2–5). Survival was observed. Daudi/wt and Daudi/*MDR*₂₀-mut-196*MDR1*-sRz (Daudi/*MDR*₂₀ cells transduced with 196*MDR1*-sRz in which stem II had been mutated and thus disabled) served as controls. In order to test therapeutic activity of the Rz, a recombinant adenovirus (Ad-5) expressing 196*MDR1*-Rz was developed through cotransfection of 196*MDR1*-Rz containing adenoviral vector pCA14 and rescue vector pJM17 into a packaging cell line (human embryonic kidney cell line 293). After 14–20 days the plaques formed were picked up and subcultured in new culture plates containing the packaging cells. When cytopathic effects were observed 3–5 days later, cells were frozen and thawed, and the supernatant containing Ad5 particles was harvested by centrifugation (Ad5-196*MDR1*-Rz).

After confirmation of the presence of Rz by PCR, virus was further amplified and purified by CsCl gradient centrifugation, followed by dialysis. The mice were implanted s.c. with Daudi/*MDR*₂₀ and then treated immediately or 5, 12 or 19 days later with Ad5-196*MDR1*-Rz (MOI 400) x 3 days (days 1–3), followed by 5 days of i.p. VCR treatment (days 2–6). Time of tumor appearance was observed.

Results: VCR chemotherapy resulted in 80% of mice bearing Daudi/*MDR*₂₀-196*MDR1*-Rz cells (3 x 10⁶ cells) with long-term survival (>120 days), exactly overlapping with that of wild-type Daudi cells treated with VCR. All the mice who were treated with PBS died in 19–25 days, as was true for VCR treated mice bearing Daudi/*MDR*₂₀ cells or mutated Rz-transduced Daudi/*MDR*₂₀ cells. For the therapeutic experiments, immediate administration of Ad5-196*MDR1*-Rz at the site of the Daudi/*MDR*₂₀ implant resulted in increased VCR sensitivity manifested by approximately a 3-fold delay in tumor occurrence (day 77) as compared to virus untreated group or delayed virus injection groups (days 26–39).

Conclusion: Retrovirus-mediated transduction of anti-*MDR1*-Rz reversed chemoresistance of MDR human lymphoma cells when transplanted in mice. Likewise, immediate local injections of Ad5-196*MDR1*-Rz substantially decreased chemoresistance of mice bearing human MDR lymphoma cells.

With further improvements in *in vivo* transduction methodology, anti-*MDR1*-Rz may serve as an adjuvant in the chemotherapy of human MDR tumor. GCO# 77-107ME

Orthopedics

Transforming Growth Factor Beta (TGF-β) in Synovial Fluid. B.M. Mehling, L.B. Keil, V.A. DeBari. Departments of Medicine and Orthopedics, St. Joseph's Regional Medical Center, Paterson, NJ.

Background: The transforming growth factors beta (TGF-), TGF- 1 and TGF- 2, are believed to play a role in cell development relevant to wound healing. This notwithstanding, there are few data on the issue of TGF- in synovial fluid.

Purpose: The purpose of this study was to determine if detectable levels of TGF- could be found in synovial fluid and if TGF- existed free or as a pre-procytokine associated with latency-associated protein (LAP).

Methods: Patients undergoing knee surgery, both arthroscopic and open, consented (protocol approved by human subjects committee) to the donation of synovial fluid for analysis. Specimens were stored at -70°C until analyzed using an enzyme-linked immunosorbent assay (R & D Systems, Inc.) with TGF- receptor as the capture protein and peroxidase-tagged anti-TGF- as the probe. The activation procedure utilized HCl followed by neutralization.

Results: Negligible TGF- was detected in synovial fluid in which the TGF- was not activated. Levels of TGF- in activated specimens were found to be 332 ± 382 pg/ml for TGF- 1 and 274 ± 203 pg/ml for TGF- 2. These were significantly higher (p<0.0001) than levels detected in the unactivated specimens.

Conclusions: TGF- exists in synovial fluid as a pre-pro-growth factor and is detectable when LAP is cleaved. It is unclear at this point whether the levels of synovial fluid growth factors in healthy patients vary from those in patients with knee pathology.

Reproducibility of Bone Measurements by Dual Energy X-Ray Absorptiometry. Brett A. Sears, MPT; Ann M. Spungen, EdD; Roberta Modeste-Duncan, BA; Joana C. Lessey; and William A. Bauman, MD.

Introduction: Bone mass is rapidly lost during the acute phase of spinal cord injury (SCI) and continues to be lost during the chronic phase at a rate that exceeds the average loss associated with aging in the able-bodied population. Dual energy x-ray absorptiometry (DXA) is a method of measuring bone tissue mass and density.

Aim: The purpose of this study is to determine the reproducibility of total body and regional bone mineral content (BMC) and density (BMD) measurements using DXA in persons with SCI compared with that in able-bodied individuals. Design: A prospective, two-group, repeated measures study was performed.

Methods: DXA measurements (LUNAR DPX-IQ) were obtained in 15 individuals (5 female able bodied [AB], 4 male AB, and 6 males with chronic SCI) on 4 occasions within a 7-day period. BMC and BMD measurements were determined for the total body and regionally for the arms, legs and trunk.

Results: For total body BMC measurements, coefficients of variation ranged from 0.88 ± 0.40% in able-bodied males to 2.44 ± 1.74% in paraplegic males. Total body BMD measurements varied even less, from 0.63 ± 0.06% in paraplegic males to 0.90 ± 0.48% in able-bodied males. Regional bone measurements for BMC and BMD of the arm, leg, and trunk also had acceptable coefficients of variation. Coefficients of variation (%) for each group by region and total body are reported in the table.

	Arm BMC	BMD	Leg BMC	BMD	Trunk BMC	BMD	Total BMC	BMD
AB Female (n = 5)	2.92 ± 1.26	0.88 ± 0.53	1.12 ± 0.51	1.08 ± 0.70	3.62 ± 2.17	1.48 ± 0.98	1.10 ± 0.63	0.78 ± 0.25
AB Male (n = 4)	1.50 ± 0.78	1.23 ± 1.01	1.18 ± 0.36	1.83 ± 0.91	2.48 ± 1.51	0.65 ± 0.24	0.88 ± 0.40	0.90 ± 0.48
Para Male (n = 3)	4.57 ± 4.14	2.03 ± 1.64	1.73 ± 0.61	1.43 ± 0.70	6.10 ± 2.65	2.70 ± 0.458	2.44 ± 1.74	0.63 ± 0.06
Tetra Male (n = 3)	1.73 ± 0.35	1.47 ± 0.23	1.33 ± 0.98	1.50 ± 1.22	37 ± 1.05	0.90 ± 0.27	1.90 ± 1.32	0.80 ± 0.36

Conclusion: BMD and BMC measurements obtained by DXA are highly reproducible in able-bodied and SCI individuals. Thus, regardless of the degree of osteoporosis and dramatic soft tissue compositional changes in persons with SCI, DXA remains a highly reproducible means to assess bone mass.

Pulmonary

Estrogen Receptors Alpha and Beta Expression and the Effects of Estrogen and Tamoxifen in Human Lung Cancer Cell Lines. C. F. Caracta¹, C.A. Powell², L. Wei³, J. S. Brody³, Q. Yu³ ¹Mount Sinai School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care, New York, NY; ²College of Physicians and Surgeons, Columbia University, Division of Pulmonary, Allergy, and Critical Care Medicine, New York, NY; and ³Boston University School of Medicine, The Pulmonary Center, Department of Pulmonary and Critical Care, MA.

Epidemiologic and experimental evidence suggest that sex hormones may play a role in the incidence and progression of lung cancer. We surveyed, by RT-PCR and sequencing, twenty-three human lung cancer cell lines for expression of estrogen receptors: Estrogen alpha receptor (ER alpha) and estrogen receptor beta (ER beta) and its isoforms. Seven of the nine adenocarcinomas (78%) expressed ER alpha, vs. three of fourteen (23%) other cell types ($p < 0.03$). Adenocarcinomas tended to express both receptors vs. other cell types (55% vs. 23%). To study functional consequences of ER expression, we assayed in low serum, hormone-free media, cell proliferation by BrdU incorporation and apoptosis with a propidium iodide assay in response to various concentrations of estradiol and tamoxifen, using MCF-7 breast cancer cell lines as a positive control. MCF-7 increased proliferation in response to estradiol and tamoxifen induced MCF-7 apoptosis that was blocked by addition of estradiol. None of the six lung cancer cell lines increased proliferation in response to estradiol. We compared the effects of tamoxifen in three lung cancer cell lines, one expressing ER alpha, one expressing ER beta, and the third expressing neither of the receptors. Tamoxifen decreased proliferation and induced apoptosis which was blocked by exogenous estradiol only in the ER beta+ line. Our results suggest that proliferation of lung cancer cell lines is estrogen-independent, but that tamoxifen decreases cell growth and induces cell death by both ER-dependent and independent pathways.

Pharmacological Characterization of an Extract of Wheat Grain. E.N. Schachter, E. Zuskin, N. Rienzi, S. Goswami, V. Castranova, P. Stiegel, M. Whitmer, G. Skloot, E. Chung. Mount Sinai School of Medicine, New York, NY.

The harvesting and processing of wheat is associated with acute and chronic respiratory disease. A water soluble extract from wheat grain (WGE) collected on a farm near Zagreb, Croatia, was prepared as a 1:10 w/v solution. The dust contained 337 g of protein/mg of dust and 1101 EU of endotoxin/mg of dust. Dose related contractions of nonsensitized, guinea pig trachea (GPT) were demonstrated using these extracts. WGE was added to the GPTs 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 WGE over the entire range of doses tested. Pyrilamine, Acivicin, NDGA, and BPB (a phospholipase A2 inhibitor) moderately reduced WGE-induced constriction. Capsaicin depleted irritant nerves of bronchoconstricting mediators, and also resulted in a modest reduction of WGE-induced constriction as did TMB8 and captopril. Indomethacin had no effect on contraction induced by WGE. We conclude that WGE exerts a non-immunologic constrictor effect on guinea pig tracheal muscle. The mechanism of this effect is complex and capable of being modulated by

many mediator modifying agents. Anticholinergic agents in particular exert a profound blocking effect on this extract. GCO# 88-250ME

The Effect of Indomethacin and Pyrilamine on Airway Smooth Muscle Stretch-Induced Relaxation. K. Mrejen, G.S. Skloot, D.H. Tishler, Jourdy, I. Shpak, H. Singh, 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 healthy guinea pig trachea (GPT) (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 on SIR and its modulation by indomethacin (I) and pyrilamine (P).

Guinea pigs were sensitized using 3 repeated intraperitoneal injections [0.5ml of a 6mg/ml solution of ovalbumin (OA)] given over a one week period. On day 21, the guinea pigs (n = 10) were challenged with an aerosol of 2.5% OA. A control group of unsensitized animals (n = 10), followed concurrently, received a sham challenge of double distilled water. Both groups were sacrificed 24 hours after challenge. Guinea pig tracheal rings were prepared (in equal numbers) with (ep+) and without (ep-) epithelium. The rings were then suspended in physiologic buffer and maintained at a baseline tension of 2g. Individual rings were then stretched by applying a tension of 10g. After equilibration, the tissues were washed and reset to 2g tension. I (10^{-6} M), or P (10^{-5} M), or buffer was added and the response to stretch again studied. 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). In **uninflamed tissue ep+**, SIR was significantly increased following the addition of P ($p < 0.5$).

In **inflamed tissue ep+**, SIR was significantly decreased following the addition of P ($p < 0.5$). By contrast in both inflamed and uninflamed tissue ep-, SIR remained unchanged following the addition of P. In **inflamed tissue ep+**, SIR was significantly increased following the addition of I ($p < 0.5$). In contrast, in **inflamed tissue ep-**, SIR remained unchanged following the addition of I ($p < 0.5$). In uninflamed tissue ep+ and ep-, SIR remained unchanged following the addition of I. These results suggest that both histamine and prostaglandins are released during SIR, by the epithelium, but they cause different responses in inflamed and uninflamed tissue.

Salmeterol Improves Static Respiratory Pressures Among Subjects with Tetraplegia. Gregory J. Schilero, MD; David R. Grimm, EdD; Ann Spungen, EdD; Erwin J. Oei, MD; Roberta Lenner, MD; William A. Bauman, MD; Marvin Lesser, MD.

Introduction: It was previously demonstrated that a beta-2 adrenergic agonist improved arm muscle strength and size among subjects with muscular atrophy secondary to spinal cord injury. It has not been determined if a beta-2 adrenergic agonist similarly improves respiratory muscle.

Design: A randomized double blind, placebo-controlled, crossover study was performed.

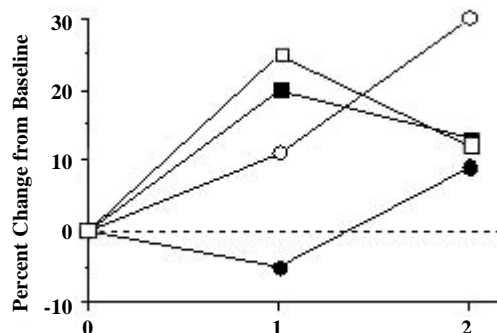
Methods: Salmeterol (50mcg powder: BID), a long-acting beta-2 adrenergic agonist, or placebo were administered by inhalation for 4 weeks with a 3-week washout period in-between. Maximum static inspiratory mouth pressure (PI_{max} , cmH₂O), measured at residual volume, and maximum static expiratory mouth pressure (PE_{max} , cmH₂O), measured at total lung capacity (TLC), were determined at baseline and during the 4th week of administration of salmeterol or placebo.

Results: Eleven healthy outpatients with tetraplegia completed the study. Mean (\pm SE) values for PI_{max} , PE_{max} , expiratory reserve volume (ERV), and TLC for the 11 subjects are shown in the table. Seven subjects received placebo first and 4 subjects received salmeterol first. Percent change from baseline for PI_{max} and PE_{max} for these two groups are shown in the figure.

	Baseline	Placebo	Severe
PI _{max}	73 ± 6	74 ± 6	81 ± 6 *
PE _{max}	41 ± 5	46 ± 6	51 ± 6 *
ERV (L)	0.51 ± 0.06	0.55 ± 0.05	0.60 ± 0.06 **
TLC (L)	5.20 ± 0.16	5.11 ± 0.16	5.32 ± 0.10

*p<0.05 vs. baseline and placebo

**p<0.05 vs. baseline



● = PI_{max} (placebo 1st); ■ = PI_{max} (Drug 1st); ○ = PE_{max} (placebo 1st); □ = PE_{max} (drug 1st)

Interpretations: Increases in PI_{max}, PE_{max}, and ERV during the salmeterol phase suggest that contractile forces generated by innervated but atrophic inspiratory and expiratory muscles improved significantly in response to the drug. Presumably, this was due to systemic absorption and the effect of the agent. Higher PE_{max} values were not due to increases in TLC, because TLC values were not significantly different during the 3 different study periods. The persistence of an elevated PI_{max} among subjects who received drug first indicates that salmeterol may have a prolonged effect on inspiratory muscle strength.

Conclusion: The generation of higher intrathoracic pressures with long-term administration of a beta-2 adrenergic agonist among subjects with tetraplegia is likely a consequence of increased respiratory muscle strength, which may improve effectiveness of airway clearance and decrease the prevalence of bronchopulmonary complications.

Rheumatology

Autoimmune Phenomena and Disease Complicating Antiviral Therapy for Hepatitis C Virus (HCV) Infection. Leslie Wilson¹, Richard Widman, Steven Dikman² and Peter D. Gorevic¹. Departments of Medicine¹ and Pathology², Mount Sinai School of Medicine, New York, NY.

Autoimmunity is prevalent in HCV infection and may complicate combination therapy with interferon-alpha (IFN α) and ribavirin. In particular, IFN α associated autoAbs may target organ-specific antigens (eg. 21OH, GAD65, TG), although only some patients develop organ dysfunction. AutoAbs (eg. RF, ACL) may be directly linked to chronic HCV, or may be uncovered by IFN α . Occasional patients have developed systemic disease, including systemic lupus erythematosus (SLE), rheumatoid-like polyarthritis, glomerulonephritis (GN), coeliac disease, or polymyositis. We describe two cases, both men, found to have HCV Ab and RNA (0.5–1M copies/ml) as part of evaluations for abnormal LFTs, and liver biopsies c/w chronic HCV. Both were started on antiviral therapy, one receiving a year of IFN α before ribavirin was added because of lack of virologic response. While on combination therapy, at 16 and 24 weeks respectively, each developed severe joint pains, myalgias, fever, rash and proteinuria. Renal biopsies done to evaluate for HCV-associated renal diseases revealed instead a severe pauci-immune severe crescentic GN in one, and diffuse mesangial/focal segmental endocapillary proliferative/exudative GN (c/w lupus nephritis) in the other. Both had antineutrophil cytoplasmic antibodies, one to proteinase 3 and the other to myeloperoxidase; in addition, the second was found to have anti-Ro, RNP, dsDNA, and histone antibodies, and striking classical pathway complement activation, with depression of C2-4 and elevated levels of C3a/SC5b-9. Both had type 3 cryoglobulins (0.1 and 0.28 mg/ml respectively); however, serum and isolated cryoglobulin were consistently negative for HCV RNA by RT-PCR. Skin biopsies showed vasculitis and DE junction pathology respectively. Both patients were treated with high-dose corticosteroids, one for Wegeners granulomatosis (sinusitis, neuropathy) and the other for SLE, with gradual clinical and biochemical improvement but without recurrence of viremia, even on cytotoxic therapy. Autoimmune disease complicating therapy for HCV needs to be carefully considered in the evaluation of an expanding spectrum of extrahepatic manifestations of this infection and the use of antiviral/immunomodulatory therapy for HCV; careful virologic and serological studies, biopsy, and analysis of cryoglobulins, may elucidate the differential diagnosis in this setting, and suggest alternative treatment strategies. GCO# pending.

Spinal Cord Research

Colonic Motility during Sleep: Effect of Spinal Cord Injury. Fajardo N.R.¹, Duncan R.², Bauman W.A.², Korsten M.A.^{1,3} Medicine¹ and GI³ Programs, Bronx VAMC; Spinal Cord Damage Research Center², Bronx VAMC, Bronx, NY.

Background: Colonic motor activity during sleep is relatively quiescent but bursts of activity are observed during periods of arousal^{1,3}. However, it is not known how sleep alters the colonic motility of persons with SCI. We thus studied the effect of sleep on the colonic motility of individuals with SCI and compared it with normal subjects.

Methodology: The study was conducted on 8 subjects with SCI (mean age 59 yrs., mean duration of injury 17 years, 4 paraplegics, 4 quadriplegics), and 6 normal subjects (mean age 57 yrs.). SCI subjects all complained of difficulty with evacuation (DWE) at least once in 6 months preceding the study; all received bowel care at least three times per week. After routine bowel preparation, colonoscopy was performed (all subjects had normal examinations). After colonoscopy, the proximal end of a solid-state pressure transducer catheter (4 sensors each separated by 10 cms.) was tethered to the splenic flexure using endoclips (Olympus Corp.) as previously described by Fajardo et. al.⁴. The subjects were then allowed to carry out their usual daily activities, including sleep. Data from the catheter was recorded on a Gaeltec portable recorder. After completion of the study (which lasted for 24 hours), the data was uploaded to a computer for analysis.

Results: The motility index of subjects with SCI was significantly lower than controls during pre-sleep, sleep, and post-sleep (3.5 vs. 8.7, p < 0.0005; 1.4 vs. 8.8, p < 0.005; and 4.5 vs. 17.8, p < 0.001, respectively). Likewise, the motility index from pre-sleep to sleep phase was significantly decreased in the SCI group (p < 0.008). Both groups exhibited significant increase in motility index from sleep to post sleep (p < 0.03 in the control group; p < 0.0003 in the SCI group).

Conclusions: Colonic motility decreases during sleep both in persons with and persons without SCI. However, this decrease was found to be of greater degree in subjects with SCI. To the extent that sleep-induced depression of colonic motility slows colonic transit, our results, in part, may explain DWE seen after SCI.

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Colonic Motility in Spinal Cord Injury. Fajardo N.R.¹, Duncan R.², Bauman W.A.², Korsten M.A.^{1,3}, Medicine¹ and GI³ Programs, Bronx VAMC; Spinal Cord Damage Research Center², Bronx VAMC, Bronx, NY.

Background: Neurogenic bowel dysfunction is an invariable sequela of spinal cord injury (SCI)¹ and is mainly associated with difficulty with evacuation (DWE) of the bowels². It has been ranked as one of the major life-limiting problems by persons with SCI³, and its effects on quality of life after the injury is unquestionably significant. Several studies have

shown that in SCI, large bowel transit is decreased at the level of the left colon and rectum², and that postprandial colonic response to food is absent². Through the use of a solid state manometry catheter, colonic motility and the effect of food is compared in persons with SCI and the spinally intact (SI).

Methodology: The study was conducted on 8 subjects with SCI (mean age of 59 yrs., mean duration of injury of 17 yrs., 4 paraplegics and 4 quadriplegics), and 6 SI subjects (mean age 57 yrs.). SCI subjects all complained of DWE at least once in 6 months preceding the study; all received bowel care at least thrice/week. After routine bowel preparation, colonoscopy was performed (all subjects had normal examinations). After colonoscopy, the proximal end of a solid-state pressure transducer catheter (4 sensors each separated by 10 cms.) was tethered to the splenic flexure using endoclips (Olympus Corp.). The subjects were then allowed to carry out their usual daily activities. Data from the catheter was recorded on a Gaeltec (Medical Measurements Inc.) portable recorder.

After the completion of the study (which lasted for more than 24 hours/subject), the data was uploaded to a computer for analysis. The following 5 phases were compared: 1 hour pre-breakfast, breakfast (which lasted for 1 hour), 1 hour, 2 hours, and 3 hours post-breakfast. The significance of the differences was evaluated by Student's t-test.

Results: The results of the study showed that in all the phases included, the SCI group had significantly lower motility index, mean amplitude, and number of high amplitude waves. Likewise, during meals, the activity index, and number of waves was significantly lower in the SCI group. It was also found that in both the SI and SCI group, there is a postprandial colonic response. However, in the SCI group, the response was only seen in the descending colon and not in the rectosigmoid region.

Conclusion: Efforts to understand the effects of SCI on colonic motility are meant to address the issues that may improve DWE, thus improving the quality of life. This study is significant as it has shown that DWE is related to decreased colonic motility, and that post prandial colonic response in SCI is phasic and mainly present in the descending colon.

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Preparation for Colonoscopy in Individuals with Spinal Cord Injury. Fajardo N.R.¹, Duncan R.², Bauman W.A.², Korsten M.A.^{1,3} Medicine¹ and GI³ Programs, Bronx VAMC; Spinal Cord Damage Research Center², Bronx VAMC, Bronx, NY.

Background: Better management of complications and improved preventive measures have prolonged the life expectancy of persons with spinal cord injury (SCI)^{1,2}. It has been shown that colonoscopy improves the likelihood of early detection of colon cancer, and screening colonoscopy in individuals over the age of 50 is increasingly advocated³. Individuals with SCI should also benefit from this procedure but standard bowel cleansing regimen is more challenging in this group. The present study was undertaken to better define the optimal colonoscopic preparations of these individuals.

Methodology: This is a single blind prospective study on 15 patients. 3 individuals received oral sodium phosphate 45 ml. in two divided doses; 4 patients received polyethylene glycol electrolyte 4 liters solution; 8 patients were administered a combination of both. The endpoint was a satisfactory colonoscopic examination defined as visualizing the cecum without significant fecal matter. The adequacy of the colonoscopy was determined by the colonoscopist, who was unaware of the bowel preparation regimen.

Results: Patients receiving oral sodium phosphate or electrolyte lavage solution alone had poor bowel preparation which resulted in inadequate bowel visualization. Patients who received a combination of the two agents all had successful colonoscopy due to better bowel preparation.

Conclusion: In individuals with spinal cord injury, the combination of osmotic purgatives and lavage solution results in superior colonic cleansing and improved colonoscopic visualization.

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Effect of Neuromuscular Abdominal Muscle Stimulation on Defecation after Spinal Cord Injury (SCI). Fajardo N.R.¹, Duncan R.², Bauman W.A.², Korsten M.A.^{1,3} Medicine¹ and GI³ Programs, Bronx VAMC; Spinal Cord Damage Research Center², Bronx VAMC, Bronx, NY.

Background: Abdominal muscle contraction contributes to bowel evacuation by increasing abdominal pressure¹. After SCI, defecatory dysfunction significantly impairs quality of life², in part due to impairment of abdominal muscle contraction³. Neuromuscular stimulators produce muscle contraction through the delivery of percutaneous electrical impulses. We studied the effect of the stimulation of the abdominal wall muscles on bowel evacuation of persons with SCI.

Method: This is a single blind randomized trial on 8 participants with SCI (6 quadriplegics, 2 paraplegics), all have lesions greater than T7, and all have 2 or less spontaneous bowel movements per week. The abdominal belt with implanted electrodes (Bioflex Garments, Bioflex Inc.) was fastened around the participant at the level of the umbilicus. Subjects were not informed whether or not stimulation was being applied during their bowel training, which itself was randomized. Parameters measured were time to first stool (TFS) and total bowel care time (TBC). TFS and TBC were compared in the presence and absence of neurostimulation. Statistical significance was analyzed by Student's paired t test.

Results: We found that the TFS for all subjects was significantly less with stimulation (29 mins. vs. 52 mins., $p < 0.005$). Likewise, the TBC for all subjects was significantly less with stimulation (88 mins. vs. 117 mins., $p < 0.01$).

Conclusion: The stimulation of the abdominal wall muscles significantly reduces bowel care time of individuals with SCI. If confirmed in a larger population, the use of the abdominal belt device may serve as an adjunct to the currently available methods needed for bowel care.

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Impaired Insulin-Induced Nitric Oxide Synthesis in Platelets from Spinal Cord Injury Subjects. William A. Bauman, M.D., Asru K. Sinha, D.Sc., Nighat N. Kahn, Ph.D., Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Accelerated coronary artery disease (CAD) is one of the leading causes of death in individuals with spinal cord injury (SCI). Although a cluster of risk factors for atherosclerosis are known to develop in these subjects the identity of the pathologic mediators leading to the development of CAD in SCI is poorly understood. SCI individuals also demonstrate increased incidence of impaired glucose tolerance and diabetes mellitus, which suggests that insulin regulation in SCI subjects is also impaired. Recently, nitric oxide (NO) has been established to be the second messenger of insulin action (Kahn et al., 2000).

Aims: Since insulin-induced NO production might have an important role in the prevention of CAD, through the inhibition of platelet aggregation we investigated the role of insulin-induced NO synthesis in platelets from SCI subjects.

Methods: Blood was collected in sodium citrate (0.013 M final) and washed platelets were prepared in Krebs buffer, pH 7.4, and incubated with insulin (200 μ M/ml) at 23°C for 30 min. NO synthesis that was determined by the nitrate/nitrite colorimetric assay kit (Cayman Chemical).

Results: Incubation of platelets with insulin stimulated the insulin-induced NO synthesis in the control platelets (0.533 ± 0.29 vs. 0.062 ± 0.02 μ M over the basal level) but the SCI platelets demonstrated markedly impaired insulin-induced NO synthesis (0.044 ± 0.010 μ M, $p < 0.001$). As the insulin-induced NO synthesis is dependent on the binding of insulin to its receptors on the platelet surface, ¹²⁵I-insulin binding to control and SCI platelets was analyzed by Scatchard plot. Equilibrium binding of insulin to platelets demonstrated a curvilinear plot. Although the dissociation constants K_d (1.9 nM vs. 2.3 nM) were similar, the receptor numbers (n₁) were significantly reduced in SCI as compared with control (210 ± 34 vs. 452 ± 56). These results suggest that platelets may be an additional site for insulin resistance. While insulin-induced NO production has been reported to be an obligatory step in the hypoglycemic effect, the impaired NO synthesis by SCI platelets may partly explain the observed disorders of the carbohydrate metabolism in SCI. In addition, impaired NO would predispose the SCI subjects to reduced vasodilation and reduced responsiveness to inhibitors of platelet aggregation. It may be postulated that the defective insulin receptors of platelets, and as a consequence, the impaired NO synthesis are probably pathophysiologically important in the pathogenesis of vascular disease in SCI.

Body Composition Analysis in Persons with Chronic Spinal Cord Injury. Ann M. Spungen, EdD; Richard N. Pierson, Jr, MD; Jack Wang, MS; Joana C. Lessey, and William A. Bauman, MD.

Background: Following the immobilization of spinal cord injury (SCI), body composition undergoes drastic remodeling. Losses in lean and gains in fat tissue mass continue during the chronic phase of SCI.

Design: A three group cross-sectional comparative design was used.

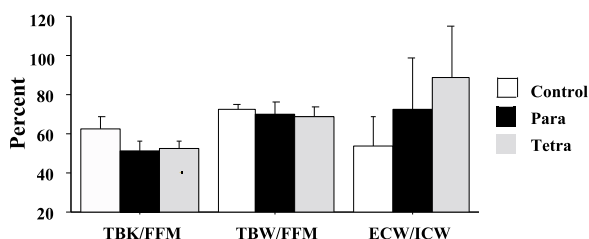
Methods: Body composition was measured by three methods: fat free mass and fat mass (FFM and FM) by dual energy x-ray absorptiometry, total body potassium (TBK) using a 4-Pi whole body counter, total body water (TBW) using tritiated water and radiolabeled sulfate (S^{35}) for segregation of extracellular water (ECW) and calculated intracellular water (ICW).

We compared a height-, weight-, age-, gender- and ethnic-matched control group (n = 19) with healthy subjects with either paraplegia (n = 32) or tetraplegia (n = 29) for differences in FFM, FM, TBK, and TBW.

Results: The group with paraplegia was older, on average, than either the tetraplegia or control groups (43 ± 13 vs. 35 ± 12 or 36 ± 10 , $p < 0.05$, respectively). There were no significant differences for height, weight or body mass index (BMI, kg/m^2) among the three groups. The body composition results are reported in the table and figure below.

	Control (n = 19)	Para (n = 32)	Tetra (n = 29)
FFM (kg)	$61.7 \pm 12^*$	52.2 ± 10	51.8 ± 7
FM (kg)	$15.9 \pm 9^*$	24.9 ± 11	21.5 ± 11
TBK (mEq)	$3826 \pm 929^\ddagger$	2611 ± 635	2702 ± 418
TBW (L)	$44.3 \pm 8^*$	33.8 ± 6	36.4 ± 6
ECW (L)	15.4 ± 4	$13.6 \pm 3^\ddagger$	16.4 ± 4
ICW (L)	$28.7 \pm 5^*$	20.2 ± 5	19.7 ± 5

* $p < 0.005$ for Control vs. Para and Tetra, $^\ddagger p < 0.0001$ for Control vs. Para and Tetra, $^\ddagger p < 0.05$ for Para vs. Tetra.



FFM, TBK and TBW were lower and FM significantly higher in the two SCI groups compared with the Control group. ECW was significantly different for only the Para vs. Tetra group. The ratio of TBK/FFM was significantly greater in the Control compared to the Para or Tetra groups (62 ± 6 vs. 50 ± 5 or 52 ± 4 , $p < 0.0001$). No significant differences were found for TBW/FFM. The Control group had a significantly lower ECW/ICW ratio than the Para and Tetra groups (54 ± 1 vs. 73 ± 3 , $p < 0.01$ and 90 ± 3 , $p < 0.0001$, respectively). In those with SCI, duration of injury, but not age, was significantly associated with a decline in TBK/FFM ($R = -0.42$, $p < 0.05$). **Conclusions:** The reduced TBK per unit FFM may indicate a disproportionate loss of skeletal muscle lean tissue to visceral lean tissue. The normal TBW per unit FFM predominantly represents visceral and skeletal muscle water, which would be expected to remain unchanged. The extreme ECW/ICW fluid shift in the Tetra group is similar to that found in persons with malnutrition or low endogenous anabolic hormones.

Insulin-Induced Nitric Oxide Synthesis Is Impaired in Platelets from SCI Subjects. Nighat N. Kahn, PhD; Asru K. Sinha, PhD; and William A. Bauman, MD.

Coronary artery disease is a leading cause of death in individuals with spinal cord injury (SCI). Individuals with SCI have been reported to have a far greater prevalence of impaired glucose tolerance and diabetes mellitus. Recently, nitric oxide (NO) has been reported to be the second messenger of insulin action (Kahn, N et al., 2000). It has been recently appreciated that one of the insulin-induced platelet anti-aggregating effects is attributable to NO synthesis.

Aims: To quantitate the binding of insulin to platelets in persons with SCI. To assess whether insulin stimulated NO synthesis by platelets is reduced in persons with SCI compared to able-bodied controls.

Methods: Platelets were harvested for study from 7 subjects with SCI and 4 ambulatory controls. The determination of the specific binding of ^{125}I -insulin to platelets used the membrane filtration technique (Kahn N, et al. 1990). To stimulate production of NO, platelets were incubated with

insulin at a concentration of 200 $\mu U/ml$. NO was quantitated kit assay.

Results: The specific binding of ^{125}I -insulin in platelets from subjects with SCI was significantly decreased (85%; $p < 0.001$) compared with binding to normal platelets. Platelets from able-bodied controls had an insulin-induced increase of NO production (0.048 ± 0.024 to $0.525 \pm 0.015 \mu M$), whereas no effect of insulin incubation was observed in platelets from subjects with SCI (0.036 ± 0.023 to 0.047 ± 0.021).

Conclusion: These results suggest that platelets may be an additional site of insulin resistance. Absent or reduced NO production by platelets in subjects with SCI may reduce their ability to resist aggregation. In addition, diminished NO production to insulin by platelets may decrease their potential to induce a vasodilatory response. It may be postulated that reduced platelet production of NO may be another factor in the pathogenesis of vascular disease in persons with SCI.

Soft Tissue Changes in Acute Spinal Cord Injury. Jill M. Wecht, Ed.D., Ann M. Spungen, Ed.D., Steven Kirshblum, M.D. and William A. Bauman, M.D.

Introduction: There have been few studies to date reporting soft tissue changes in individuals with acute spinal cord injury (SCI) (Wilmot, et al. 1995 & Rossier, et al. 1991). Our laboratory is currently investigating the effects of a bisphosphonate on bone mass in persons with acute SCI. There is no evidence to suggest that bisphosphonate administration will affect soft tissue.

Aim: To determine soft tissue changes in acutely injured subjects.

Methods: Seven individuals who incurred a traumatic, complete (ASIA A) transection of the spinal column at levels ranging from cervical vertebrae 4 through thoracic vertebrae 12 were studied at several time points. Data will be presented from baseline (34 ± 17 ; range 12–60 days post-injury) and four months (127 ± 23 ; range 80–147 days post-injury) after enrollment in the study protocol. The data were collected using a LUNAR DPX-IQ (LUNAR Corp. Madison, WI) and analyzed for both total body and regional soft tissue. All data are reported as mean \pm SD.

	Baseline Kilogram	Percent	Month Four Kilogram	Percent
Total Body Weight	68.0 ± 11.4		66.9 ± 10.7	
Total Body Lean	52.5 ± 14.7	81 ± 15	47.1 ± 10.4	74 ± 13
Total Body Fat	12.2 ± 10.0	19 ± 15	16.8 ± 9.2	26 ± 13
Trunk Lean	24.7 ± 6.3	79 ± 14	24.1 ± 5.0	77 ± 12
Trunk Fat	5.5 ± 4.6	17 ± 14	7.4 ± 4.0	23 ± 12
Leg Lean	17.6 ± 7.6	78 ± 16	14.1 ± 3.7	69 ± 13
Leg Fat	4.5 ± 3.4	22 ± 16	6.3 ± 2.9	31 ± 13
Arm Lean	5.7 ± 1.8	77 ± 20	5.6 ± 2.0	73 ± 19
Arm Fat	1.8 ± 1.8	24 ± 22	2.2 ± 2.3	17 ± 19

Summary: Mean total body lean tissue was reduced by 5.4 kilograms, a 6.7% reduction from baseline to 4 months after enrollment. This reduction in lean tissue was primarily found in the leg, which constituted a 3.4 kg loss in lean tissue (8.6%). Mean total body fat increased by 4.52 kg, (trunk = 1.94 kg and legs = 1.75 kg). Of note, percent loss in lean tissue was strongly dependent on the number of days from injury that the baseline data were obtained ($r = 0.861$, $p < 0.013$), indicating a rapid loss of lean tissue within the first 4 weeks of injury with a plateau of loss thereafter.

Serum Total Testosterone Declines with Advancing Age in SCI. Run-Lin Zhang, MD; AM Spungen, EdD; RH Adkins, PhD; RL Waters, MD; and WA Bauman, MD.

In an epidemiological study, serum total testosterone (total T) declined at a rate of 0.4% per year (Gray, 1991). The effect of advancing age on levels of total T has not been reported in a large sample of individuals with SCI. We determined the total T concentrations in a large sample of men with chronic SCI (n = 172). The group was subdivided into those with paraplegia (Para; n = 93) and tetraplegia (Tetra; n = 79), complete (n = 117) and incomplete (n = 54) lesions, or by ethnicity (African-American = 22, Caucasian = 48, Latino = 98, Asian = 3). Chi square analysis was employed to assess whether a significant difference was found in the percent of younger compared with older subjects (≤ 40 versus > 40 y) who had low total T concentrations (total T < 3.0 ng/ml). This analysis also was used to determine if a difference existed in the mean age of subjects with low levels as compared with those with levels within normal limits. Linear regression analysis was used to determine the effect of age, duration of injury, level and completeness of lesion on the total T concentration. The average age of the total group was 39 ± 1 y (Par = 40 ± 1 and Tetra = 38 ± 1 y), duration of injury was 25 ± 1 y (Par = 25 ± 1 and Tetra = 25 ± 1 y), and BMI was 26 ± 1 kg/m^2 (Par = 26 ± 1 and Tetra = 25 ± 1 kg/m^2). For the entire group, the total T concentration was 4.4 ± 0.15 ng/ml (Par = 4.7 ± 0.19 and Tetra = 4.1 ± 0.24 ng/ml). Comparing the younger and older subjects, 15.2

versus 30.1%, respectively, had low total T concentrations ($p < 0.02$). The mean age of persons with low total T concentrations was older than it was in those with normal levels (42.6 ± 1.7 versus 37.8 ± 0.9 , ($p < 0.02$). A significant decline in total T of 0.04 ng/ml per year ($0.7\%/y$) was found ($r = -0.21$; $p = 0.006$). There were no significant effects of ethnicity, duration of injury, level or completeness of lesion on the total T concentrations. In summary, levels of total T declined with age, in persons with SCI at a rate that appears to be increased compared with the reported decline in the general population. In this group of relatively young men with SCI, the fall in levels of total T was independent of duration of injury, ethnicity or degree of neurological impairment.

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Methotrexate-Maintained Remission in a Young Man with Polyarteritis Nodosa. M. Alam, M. Tabriz, A. Opran, and F. Rosner. Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Polyarteritis nodosa (PAN) is a rare cause of systemic vasculitis, histologically characterized by necrotizing inflammation of medium-sized or small arteries which may lead to multiple organ system disease. We describe a 22-year-old man with a large leg ulcer and flu-like symptoms who rapidly progressed to full-blown polyarteritis nodosa (PAN).

Case Report: A 22-year-old African-American man was hospitalized with a large ulcer of the right foot for debridement and possible skin grafting. The patient had root canal work and a tooth extraction four weeks earlier and was treated with ampicillin for a week. One week later he developed generalized arthralgia and myalgias without any joint swelling partially relieved with ibuprofen. He then developed a blister on his right foot, which became enlarged and ulcerated without antecedent trauma. He denied fever, chills, and cardiovascular, respiratory, gastrointestinal or genitourinary symptoms. He lost about 5 kilograms of weight.

Physical examination was remarkable for a 4×9 cm ulcer with clean edges, mild exudate, good granulation tissue and exposed underlying tendons and soft tissue on the dorsolateral aspect of the right foot. Another 1×1 cm blister was present on the dorsolateral aspect of the left foot. The remainder of the physical examination was normal.

The ulcer was debrided. The next day he developed high fever. Multiple sets of blood cultures were negative and both transthoracic and transesophageal echocardiography were normal. By the ninth hospital day the patient was still febrile. The following day multiple small palpable purpuric lesions were noted on the soles of both feet. On the 12th day the distal portion of the right first, left second and third fingers and the left second toe were found cool and cyanotic. Several 2–3 mm soft, mildly tender, subcutaneous nodules were felt on the extensor surface of the forearms. Two days later, the patient developed left-sided wrist drop and weakness of varying degrees in the radial, ulnar and peroneal nerves bilaterally, consistent with mononeuritis multiplex.

Serologic tests were negative for HTLV-1, HTLV-2, parvovirus B-19, syphilis, toxoplasma, and hepatitis A, B, C and D. There was evidence of prior exposure to cytomegalovirus. The antinuclear antibody test was positive at a titer of 1:160 with a homogenous pattern. Total CD4 lymphocyte count was 197 with a ratio of CD4:CD8 of 0.37, but both Human Immunodeficiency Virus (HIV) 1 and 2 antibodies were not detected in the patient's serum. Urinalysis was normal on several occasions. Tests for rheumatoid factor, cryptococcal antigen, cryoglobulins and lupus anticoagulant were negative. Multiple blood and urine cultures were negative. Urine and serum toxicology screens were negative. Assays for antibodies to cardiolipin, double stranded DNA, Smith, SS-A, SS-B, c-ANCA, p-ANCA, ribonucleoprotein were also negative. Complement levels (CH50, C3 and C4) were normal. Biopsy of the sural nerve was normal. Computed tomography (CT) of the abdomen and pelvis showed multiple areas of low attenuation in both kidneys, consistent with multiple microinfarcts. Selective renal angiography revealed innumerable aneurysms involving segmental, lobar and interlobar arteries of both kidneys. Diffuse irregularity with multiple stenoses and occlusions were present in the hepatic arteries, as well as in branches of the splenic artery and other arteries supplying the stomach. The diagnosis of PAN was made based on the clinical presentation of weight loss, myalgias, weakness, fever, palpable purpuric skin rash, mononeuritis multiplex, diastolic BP > 100 and classic angiographic findings of multiple aneurysms and stenoses in renal, hepatic, and splenic arteries. The patient was treated with pulse methylprednisolone IV 1 gm daily for 3 days and one dose of 1 gm IV cyclophosphamide (CYC) with marked clinical improvement and resolution of ischemia. After induction of remission, prednisone was slowly tapered by 5 mg every 2 weeks and daily cyclophosphamide 150 mg orally was continued. Because of concerns about the persistently low CD4 count and the known long-term side effects of CYC, the patient was switched to methotrexate 10 mg weekly, subsequently decreased to 7.5 mg per week. The patient remains asymptomatic with a low erythrocyte sedimentation rate and normal clinical and laboratory parameters. One year later, receiving only methotrexate 7.5 mg per week, the patient's repeat renal angiogram showed resolution of the microaneurysms.

Conclusion: Early identification of PAN and initiation of appropriate treatment are important to avoid severe morbidity and even mortality. Low-dose methotrexate therapy may be an effective alternative treatment strategy for maintaining remission in PAN.

Choriocarcinoma in a Patient with Human Immunodeficiency Virus: Case Presentation and Review of the Literature. I. Ashley. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and the Mount Sinai School of Medicine, New York, NY.

A 26-year-old woman with choriocarcinoma and AIDS presented with hydatidiform mole and was treated with dilation and curettage. Because of persistent elevation of serum beta human chorionic gonadotropin (β -HCG), the patient was treated with combination chemotherapy for high risk gestational trophoblastic tumor. The patient did well for 14 months when her β -HCG again increased. The patient was treated with uterine curettage followed by vaginal hysterectomy. The patient was noncompliant with her chemotherapy, and later developed metastatic disease to the brain and died.

Only three other cases of human immunodeficiency virus (HIV) infection with choriocarcinoma have been reported. There is no evidence to date that gestational trophoblastic disease is more prevalent in AIDS patients. HIV infection and other immunodeficiency states, however, can lead to extensive metastatic choriocarcinoma and can influence the course of treatment in these patients. Perhaps HIV infection should be considered a poor prognostic risk factor for choriocarcinoma.

Myasthenia Gravis and Chronic Lymphocytic Leukemia. A.S. Bawa 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: Myasthenia gravis is an autoimmune disease with a prevalence of 50–150 cases per million population, or approximately 25,000 persons affected in the United States. Chronic lymphocytic leukemia is the most frequent form of leukemia in adults in Western countries. The simultaneous occurrence of myasthenia gravis and chronic lymphocytic leukemia in the same person is very rare. Only ten such cases have been previously reported. We present a patient with myasthenia gravis who developed chronic lymphocytic leukemia fifteen years later.

Case Report: An 81-year-old white man with myasthenia gravis taking pyridostigmine for fifteen years presented with complaints of swellings in the neck, weight loss and malaise over the past year. No thymectomy had been done in the past. On examination, he was obese but with significant loss of subcutaneous tissue, right partial ptosis, pallor, diffuse lymphadenopathy involving cervical, axillary and inguinal regions, marked hepatomegaly, massive splenomegaly and bilateral lower limb cellulitis. His white blood cell count was 104,000 per dL with 90% lymphocytes, 6% neutrophils, 2% monocytes, 1% eosinophils, and 1% blasts. The hemoglobin was 8.8 gm per dL, hematocrit 26.3%, MCV 122 fl and platelets 154,000 per dL. Reticulocyte count was 4%, serum lactate dehydrogenase 523 U/L, and unconjugated bilirubin 1.4 mg per dL. The urine analysis was normal as were routine serum chemistry results. Chest radiography did not reveal any infiltrate, effusion, lymphadenopathy or mediastinal widening. Computed tomography of the abdomen and pelvis confirmed marked splenomegaly, moderate hepatomegaly, diffuse lymphadenopathy and cholelithiasis. Bone marrow aspiration with biopsy showed a hypercellular marrow with diffuse infiltration by small and medium sized lymphoid cells.

Discussion: Myasthenia gravis and chronic lymphocytic leukemia are diseases which involve B-lymphocytes. Both are associated with other autoimmune disorders and malignancies but they rarely occur together in the same patient. The incidence of chronic lymphocytic leukemia is higher in myasthenia gravis patients with an intact thymus compared to thymectomized patients. The same is true in rodents. The occurrence of both diseases in the same patient may represent part of the wide spectrum of B cell differentiation with both conditions having a common pathogenesis involving a defect in immune regulation or a certain genetic constitution. Alternatively, the two diseases in the same patient may be purely coincidental.

Massive Hemorrhage Following Endoscopic Resection of a Brunner's Gland Hamartoma. C. Chang and S. Chokhavatia. Department of Medicine, Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine, New York, NY.

Introduction: Benign tumors of the duodenum are rare (0.008%). Brunner's gland hamartomas, the benign polypoid proliferation of Brunner's glands, account for 11% of the tumors. Small lesions are asymptomatic whereas patients who present with large polyps complain of abdominal pain, dyspepsia and/or partial gastric outlet obstruction. Brunner's gland hamartomas are not premalignant lesions, and asymptomatic lesions need not be removed. Endoscopic removal is associated with post-polypectomy bleeding in 8.3% of the patients.

Case Report: A 30-year-old Chinese man was evaluated for dyspeptic symptoms. His only medication was an unknown Chinese capsule for the

treatment of hypertension. Physical examination was unremarkable. Complete blood count, routine chemistry and coagulation tests were all within normal limits. A 2 cm pedunculated, polypoid lesion was seen prolapsing from the bulb into the descending duodenum. Apolypectomy snare removal was performed using a blended current. Immediate post polypectomy bleeding occurred. Hemostasis was successfully achieved with 4 cc injection of 1/10,000 units of epinephrine around the base of the stalk. The patient maintained hemodynamic stability. Twenty-four hours later, he noticed a large maroon colored stool and felt lightheaded. Emergent endoscopy showed a clear stomach and fresh blood refluxing from the pylorus. Active bleeding from the polypectomy site was seen and endoscopic hemostasis was attempted, but without success. At exploratory laparotomy, marked oozing from multiple incision sites was noted. The polypectomy site was identified via duodenotomy and was cauterized along with the other bleeding sites. Postoperatively, an extensive hematological work up, including protein C, protein S, antithrombin factor Vand ANA, for a disorder of hemostasis was negative. Histologically, the polyp was described as a hyperplastic Brunner's gland. The patient's dyspeptic symptoms were controlled with a proton pump inhibitor and the hypertension was treated with a β -blocking agent.

Discussion: Asian patients frequently ingest herbal supplements. *Dan-shen (Salvia miltiorhiza)*, Devil's claw (*Harpagophytum procumbens*), Dong quai (*Angelica sinensis*) and excessive garlic (*Allium sativum*) are herbs that may cause platelet dysfunction and interact with warfarin. We suspect that the diffuse oozing from multiple wound sites and the post-polypectomy bleeding in our patient was related to his ingestion of an unknown herbal medication. Physicians should inquire about herbal supplements and be cognizant of their side effects and interactions with other medications. Patients undergoing invasive interventions should discontinue herbal medications prior to their procedure.

Perioperative Dislodgement of a Dental Prosthesis. C. Chang and S. Chokhavatia. Department of Medicine, Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine, New York, NY.

Introduction: Foreign body ingestion may be accidental (children and elderly with impaired mental status and/or incoordination) or intentional (attention-seeking psychiatric patients). Perioperative ingestion of a dental prosthesis is rare due to strict adherence to preoperative protocols (dental history and oral examination).

Case Report: A 33-year-old multiparous Pakistani woman was hospitalized at 40 weeks and 4 days of intrauterine pregnancy for induction of labor. Three hours after admission, signs of cord prolapse were noted. The patient underwent emergent cesarian section under general anesthesia and a macrosomic baby boy was uneventfully delivered. Postoperatively, the patient could not communicate with the staff due to a language barrier. In the recovery area, she informed her husband of her missing denture, and he relayed this information to the nursing staff. The patient was still under the effect of general anesthesia but denied any respiratory distress or chest discomfort. X-rays showed the presence of a radioopaque partly metallic object overlying the gastric region. Adental consultant determined that the missing retainer bridge over tooth #6 was consistent with the x-ray findings. Informed consent was obtained from the husband and endoscopic removal of the retainer bridge from the gastric fundus was successfully accomplished utilizing a polypectomy snare. The retainer bridge consisted of a false tooth and two metallic flanges.

Conclusion: The adherence to standard preoperative protocols (dental history and oral examination) ordinarily prevents accidental dislodgment of loose teeth and dental prosthesis. This case highlights the importance of observing standard preoperative protocols even during emergencies.

Plasma Exchange in Wegener's Granulomatosis: A Case Report and Review of the Literature. H. Dhingra, A. Opran, O. Fagbami, N. Agrawal, and F. Rosner. Mount Sinai Services, Queens Hospital Center and Mount Sinai School of Medicine, Jamaica, NY.

We describe a patient with Wegener's Granulomatosis (WG) who, despite therapy with intravenous pulse methylprednisolone and cyclophosphamide, developed acute renal failure. Renal histopathologic examination demonstrated crescentic glomerulonephritis. Treatment with plasmapheresis produced dramatic clinical improvement and significant recovery of renal function.

Wegener's Granulomatosis is a systemic disease characterized by necrotizing, pauci-immune vasculitis predominantly affecting small blood vessels. WG mainly involves the upper and lower respiratory tracts and the kidneys. Before introduction of the "standard therapy" ("Fauci regimen") the prognosis of patients with WG was generally poor. The one year mortality was 80%. Renal and respiratory failure due to necrotizing glomerulonephritis and pulmonary hemorrhage were the main causes of death. However, later studies emphasize that the natural course of WG may be extremely variable, ranging from years of local disease to fulminant vasculitis with death in a matter of weeks. Thus treatment has to be adapted to the stage and activity of WG, the early aggressive therapy being mandatory when life or organ-threatening disease occurs. Our review focuses on therapeutic approaches in seriously ill patients.

Hand-Foot-Mouth Disease in an Adult. O. Fagbami, I. Tan, 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.

Background: Hand-foot-mouth disease (HFMD) is an illness commonly described in children and rare in adults. It is a febrile illness characterized by an eruptive rash involving the hands, feet and mouth. Common etiologic agents include Cocksackie viruses A16, A5, A10, B2 or B4 and Echovirus 71. A review of the literature of HFMD in adults revealed only three reported cases.

Case Report: We describe a 25-year-old woman who presented with a 4-day history of fever and maculo-papular rash involving the face, hands and feet. Her palms and soles were erythematous and very tender. Apart from a slightly increased white blood cell count, her laboratory tests were within normal limits. She received only antipyretics and gradually improved. Serology later showed increased Cocksackie A4 titers.

Conclusion: HFMD is usually associated with Cocksackie virus serotype A16 or enterovirus 71 infection. HFMD due to Cocksackie virus A4 as was proven in our patient is rare in children and even rarer in adults.

Fungal Endocarditis Presenting as a Massive Stroke. Y. Faktorova, C. Galea, A. Rozin, J. Goldstein*, and I. Sachmechi. Departments of Medicine and Radiology*, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Native valve fungal endocarditis occurs in up to 12–20% of intravenous drug abusers. More than half of patients with fungal endocarditis suffer from neurological complications secondary to cerebral emboli with typical abrupt onset of neurological deficit. We report a 40-year-old man with a history of intravenous drug abuse who presented with gradually progressing right side hemiparesis, aphasia and fluctuating changes of mental status.

Case Report: A 40-year-old man with a history of intravenous drug abuse was hospitalized with gradually progressive right sided weakness involving both upper and lower extremities, slurred speech and jerky movements of the right arm for one day. Patient had a fever of 101.4° F. He was able to follow simple verbal commands, but was drowsy with a fluctuating level of consciousness, confused and disoriented to time and place. He had Broca's aphasia, an upper motor neuron lesion of the right facial nerve, right-sided deviation of the tongue and decreased motor function of his right upper and lower extremities, which progressed to total right hemiparalysis within 24 hours. There was no pain perception on the right side of the body. The complete blood count and routine chemistry tests were within normal limits, as was his spinal fluid analysis. Head computerized tomographic (CT) scan on admission and again 36 hours later were unremarkable. Electroencephalogram revealed left hemispheric slowing consistent with left hemispheric dysfunction. Magnetic resonance imaging (MRI) of the brain showed a left-sided middle cerebral artery (MCA) infarct involving the left opercular region, left frontal and left parietal cortexes as well as lacunar infarcts in the left basal ganglia. Magnetic resonance angiography (MRA) revealed marked diminution of flow along the course of the left common carotid artery and proximal left internal carotid artery and no flow in the circle of Willis. Blood cultures grew yeast, *Candida parapsilosis*. Echocardiogram demonstrated vegetations on the aortic valve. The patient was treated with amphotericin B and had his aortic valve surgically replaced with a bioprosthetic one. Antifungal therapy with amphotericin B was continued for 5 weeks followed by fluconazole for one year. The patient remained medically stable and was transferred to an inpatient rehabilitation unit for intensive physical and speech therapy, with gradual but steady improvement.

Conclusion: The diagnosis of fungal endocarditis can be difficult and delayed because of its relative rarity and nonspecific signs and symptoms, often distant and local secondary to early embolization. Awareness of this condition, especially in high-risk groups such as intravenous drug abusers, may lead to an early diagnosis and prompt, effective management.

Intramuscular Bleeding as a Complication of Anticoagulation Treatment in a Patient with Systemic Lupus Erythematosus and Antiphospholipid Syndrome. R. Kucinsky and I. Tan. Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine, Jamaica, NY.

Introduction: Arterial and venous thrombotic events are responsible for significant morbidity and mortality among patients with antiphospholipid syndrome (APS). Treatment commonly consists of heparin, followed by long-term warfarin therapy (INR between 2.5–3.5). The advantage of anticoagulation therapy must be weighed against the risk of bleeding. We present the case of a patient with Systemic Lupus Erythematosus (SLE) and APS with intramuscular hemorrhage as a complication of anticoagulation treatment.

Case Report: A 27-year-old woman from Guyana presented with a one-day history of right calf swelling and pain that developed while she was sitting and watching TV. Pain gradually increased in severity, interfered with her ability to walk, was relieved by rest and leg elevation. There were no other associated symptoms. Patient had been diagnosed with SLE 18 months earlier when she presented with severe polyarthritis of both

shoulders, proximal interphalangeal and wrist joints followed by discoid lesions of the face. Soon after the initial presentation the patient was hospitalized because of the sudden onset of severe headache, photophobia, lethargy, neck pain and stiffness, nausea and vomiting. She had a positive test for antinuclear antibodies (ANA 1:1280), anti DNA, anti Sm, anti histone and anticardiolipin antibodies. CT and MRI examination of the brain were consistent with central nervous system SLE vasculitis. Her medications consist of prednisone 20 mg, azathioprine 125 mg and alternating Coumadin 5 mg and 7.5 mg dose.

Physical examination revealed residual malar rash, right calf swelling and warmth with slight erythema and tenderness on palpation on the anterior tibial aspect and lateral part of the midcalf and a positive Homans' sign. Right calf circumference was 1.5 cm greater than the left. The stool Hemocult test was positive. Blood biochemistry values on admission were within the normal range. Hemocoagulation tests were abnormal: aPTT >100 seconds (11.5–13.1), INR 7.42, PT 39.4 seconds (24.6–35.4). Chest X ray showed no evidence of infiltration or pleural reaction and no cardiomegaly. Doppler study of the right lower extremity was negative for deep venous thrombosis. CT and MRI of the lower extremities showed a focal collection of fluid beneath the medial head of the gastrocnemius muscle between muscle planes, a finding consistent with intramuscular hemorrhage. Coumadin was withheld for 48 hours with daily INR monitoring and again restarted on a lower maintenance dose. The patient did not require surgical intervention, blood or fresh-frozen plasma transfusion, or vitamin K supplementation. By the third hospital day the edema and pain had diminished, and the patient was discharged home. Several months later the patient was still receiving anticoagulation treatment with Coumadin. There was no further bleeding or thrombotic complications during a one-year follow-up.

Discussion: In patients with APS and SLE receiving anticoagulation therapy, the most frequent sites of severe bleeding are in the central nervous and gastrointestinal systems. Hemoperitoneum originating from ovarian bleeding is also described. It is possible that early detection of supratherapeutic INR and intervention in the anticoagulation management could decrease the short term risk and prevent bleeding complications.

Tropical Pulmonary Eosinophilia: All That Wheezes Is Not Asthma. R.A. Lopez, M. Sameen, J.K. Fleischman, and F. Rosner. Division of Pulmonary and Critical Care Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

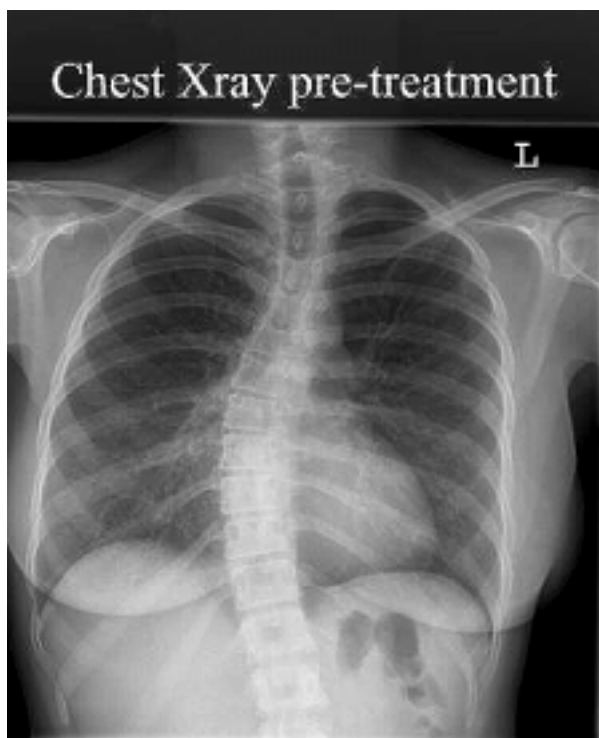
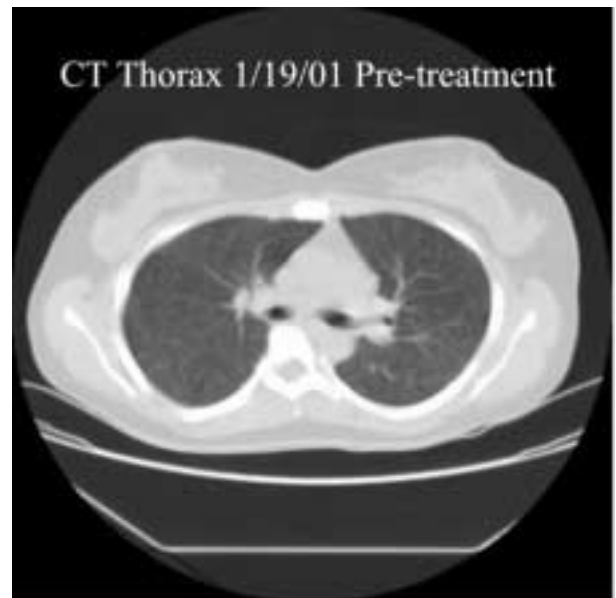
Introduction: Bronchospasm, the hallmark feature of asthma, may occur in many other conditions such as upper airway obstruction (foreign body, tumor), vocal cord dysfunction, congestive heart failure, vasculitis and eosinophilic lung disease.

A poor response to treatment for asthma often prompts referral to a pulmonary physician. We report a case of a patient with tropical pul-

monary eosinophilia (TPE) masquerading as refractory asthma for many months prior to an ultimate diagnosis after referral to our hospital.

Case Report: A 32-year-old woman was referred for evaluation of chronic cough. She had emigrated from Guyana 4 years previously and had not traveled outside the US since that time. She was otherwise healthy and took no medications. The patient's symptoms were uncontrolled for 5 months despite treatment with oral and nasal steroids and albuterol for a presumptive diagnosis of asthma. She also received multiple courses of antibiotics without improvement. Because of a poor clinical response to treatment for asthma, the patient was referred to our pulmonary medicine subspecialty clinic. Additional history of wheezing, dyspnea and a 15 lbs. weight loss over the past 6 months was obtained in the pulmonary clinic.

Physical examination revealed erythematous nasal and pharyngeal mucosa along with wheezing on forced expiration. The erythrocyte sedimentation rate was 37 mm/hr and the peripheral blood leukocyte count was 27.8 cu/mm, with eosinophils comprising 58% of the differential neutrophil count. Her pulmonary function tests revealed a mixed obstructive and restrictive ventilatory defect with reversibility after the administration of bronchodilator therapy and a decreased diffusion capacity. Although her chest x-ray was repeatedly normal (Fig. 1), computed tomography of the chest revealed a fine nodular pattern and mediastinal lymphadenopathy (Fig. 2). To further evaluate the patient's profound eosinophilia (out of proportion to the patient's asthma) anti-filarial IgG4 subclass antibody testing was performed and it was markedly positive, the normal value being <1, our patient's value >4. The patient is currently undergoing therapy with diethylcarbamazine obtained from the Centers for Disease Control and is doing well (Fig. 3).



Conclusion: Tropical pulmonary eosinophilia results from hypersensitivity to lymphatic filarial parasites found in endemic regions. Pulmonary manifestations include cough, wheezing and dyspnea and are often associated with systemic symptoms such as weight loss, fevers, and lymphadenopathy. A peripheral eosinophilia out of proportion to that which occurs in asthma is often an important laboratory clue to the diagnosis. Early diagnosis and treatment are important to prevent long-term sequelae such as pulmonary fibrosis or chronic bronchitis with chronic respiratory failure.

Retroperitoneal Leiomyosarcoma Secreting Beta-Human Chorionic Gonadotropin. I.A. Mansi, V. Glezerov, and I. Ashley. Mount Sinai Services at the Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Hormone production by non-endocrine tumors may result in a variety of paraneoplastic syndromes. Ectopic beta-human chorionic gonadotropin hormone (β -HCG) production from leiomyosarcoma is rarely reported. We describe a patient with a β -HCG producing retroperitoneal leiomyosarcoma.

Case Report: A 57-year-old man presented with progressive abdominal pain and weight loss. A palpable, non-pulsatile, firm abdominal mass was felt below the xiphisternum down to the pelvis. Testicular examination and testicular ultrasound were normal. Computerized Tomography (CT) scan of the abdomen revealed a retroperitoneal mass measuring 30 x 21 x 13 cm. The mass had areas of heterogeneous attenuation, necrosis and scattered calcification. Serum beta-human chorionic gonadotropin (β -HCG) was increased (22.71 mIU/mL). On exploratory laparotomy, a large mass arising from retroperitoneal tissue was found, with a small amount of serosanguinous ascitic fluid. Histopathology confirmed the diagnosis of leiomyosarcoma. The patient was treated with doxorubicin, dacarbazine and ifosfamide. Repeat CT of the abdomen showed more cystic changes in the mass with multiple areas of low attenuation and septation. The level of serum β -HCG decreased to <0.2 mIU/mL after chemotherapy. The patient died two months later from neutropenic fever and septicemia.

Conclusion: We report a case of retroperitoneal leiomyosarcoma secreting beta-human chorionic gonadotropin. Three other cases of β -HCG secreting leiomyosarcoma (intestine, transverse colon, and spermatocord origin) are reported in the literature. The incidence of increased serum levels of β -HCG in sarcomas is not known. The potential role of β -HCG as a tumor marker and/or in the assessment of response to therapy needs further study.

Is Laparoscopic Cholecystectomy Changing the Epidemiology of Gallbladder Disease? L. Miranda, B. Morel, and B. Pace. Department of Surgery, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Background: For more than a century, cholecystectomy had been the gold standard for the management of symptomatic gallstone disease. The first totally laparoscopic cholecystectomy (LC) was performed in 1985. Since its introduction in the US, there has been an apparent change in demographics of the patients that undergo cholecystectomy, one of the most common surgical procedures performed. Our hypothesis was that both genders are undergoing cholecystectomies at an earlier age by laparoscopy compared to laparotomy and that the learning curve influenced the patients' demographics.

Materials and Methods: This retrospective study was performed at Queens Hospital Center (QHC) in Jamaica, NY. The charts of the patients that underwent cholecystectomy between January 1992 to December 2000 were reviewed (n = 761 cases). Patients who underwent cholecystectomy during three years from the pre-laparoscopic decade, 1981, 1986 and 1991 (n = 181 cases) were randomly selected as controls. The charts of incidental cholecystectomies or those with missing codes for age and/or sex were excluded. The age and the sex of the patients were analyzed and the trend was established. The type of procedure (open, LC or conversion) was also considered for analysis.

Results: With the exception of one of the control years (1996), male patients are older than females. This tendency continues throughout the study years. The youngest patient was 12 years old (female), the oldest was 92 (female).

This chart reflects the learning curve that starts in 1992 which was the first year LC was performed at QHC. The peak of the conversions occurred in 1994 (23.7% of the cases). At the end of the study period, the percentage of conversions is 9.5 ± 1.25 .

Conclusions: Despite the conventional wisdom that younger patients undergo gallbladder surgery, our study shows that the age of patients has not changed significantly in the last 20 years. The absolute number of cases has increased 130% in this population during the study period, which probably follows the national trend in the United States.

Average age distribution by gender

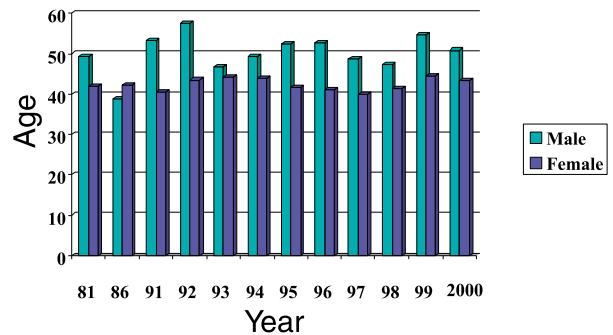
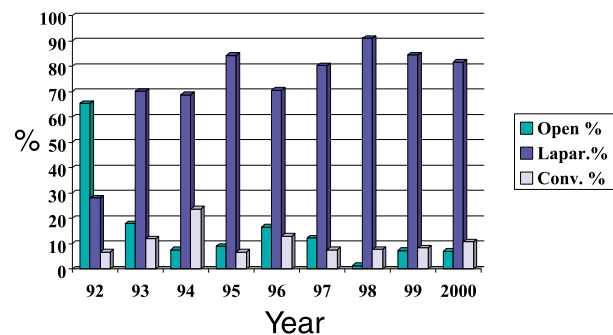


TABLE
Distribution of Average Ages from Both Genders During Control and Study Periods.

Year	Years	Total number of cases n = 942**
1981*	43.1	37
1986*	41.7	62
1991*	43.7	82
1992	45.7	75
1993	44.6	84
1994	44.9	93
1995	43.6	90
1996	44.1	85
1997	42.2	66
1998	43.3	78
1999	45.5	97
2000	44.8	93

* Control year, **Total control cases = 181

Type of procedure performed



Variable AV Nodal Conduction Defect In An Adult With Systemic Lupus Erythematosus. S. Nalamasu, A. Khan, S. Liautaud, A. Onwuanyi, and I. Tan. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Systemic lupus erythematosus (SLE) may involve the cardiovascular system in up to 50% of cases. Patients with SLE may have pericarditis, myocarditis or endocarditis and, less frequently, diverse conduction defects. Most common among the infrequently observed conduction abnormalities is first degree AV block. A few cases of high degree AV block have been reported in infants, but are extremely rare in adults with SLE. We report a case of variable AV nodal conduction defect in a patient with SLE.

Case Report: A 45-year-old Nigerian woman with SLE had AV block of variable degree quickly switching between no AV block, first-degree AV block and Wenckebach phenomenon, which spontaneously changed back to

first degree AVblock. The patient was seen in the emergency room (ER) after being called in from home for a low platelet count. The patient was asymptomatic. During a routine clinic visit one day earlier, the platelet count was $12,000/\text{mm}^3$, which prompted the call in to the ER. Electrocardiogram (EKG) showed first degree AV block with a prolonged PR interval of 0.44 second. When compared to the EKG recorded the day before, the PR interval had tripled in a 24-hour period. A repeat EKG in the ER one hour later showed Mobitz type II second degree AV block with 3:1 ventricular response. Another EKG just before her admission to the CCU again showed first degree AV block with a very prolonged PR interval. She was treated with intravenous corticosteroid. The Wenckebach phenomenon did not recur. The following morning, the EKG showed first degree AVblock, which resolved the following day. Thereafter, no block was observed during the follow-up visit 4 weeks later, before the patient returned to Nigeria.

Four years earlier, SLE was diagnosed in this patient because of polyarthralgia, myalgia, bruises and thrombocytopenia. The ANA test was positive (1:320 speckled pattern), as were Anti-RNP, Ro-SSA, and anti-Smith antibodies. Serum C3 and C4 levels were 61 mg/dL and 13 mg/dL respectively. At that time serial EKGs showed a pattern of normal sinus rhythm converting back and forth from first degree A-V block (with very long PR interval) to quickly resolving AV dissociation and one episode of junctional rhythm.

During the present hospitalization, the patient had no evidence of myocarditis, clinically or by laboratory values other than an increased erythrocyte sedimentation rate (with absence of fever, tachycardia, chest pain, diffuse ST-T wave abnormalities, or positive creatine kinase—MB fraction). The serum Lyme disease titer was negative. Echocardiogram did not show any organic lesion.

Discussion: The mechanism of conduction defects in patients with SLE is not understood. Some authors attribute a pathologic role to anti Ro/La antibodies, which may block the calcium channels. Other studies report conduction defects following myocarditis. More recent studies mention autonomic dysfunction in patients with SLE. There is no consensus regarding the treatment of high degree AVblock. Some patients including our patient received corticosteroids and responded very well, while other patients benefited from a permanent pacemaker.

Conclusion: Conduction defects can be an isolated manifestation of cardiac involvement in SLE and may be the cause of serious morbidity. More studies are needed to determine the role of certain antibodies and to identify possible risk factors.

Interrelationship Between Thyroid Nodularity and TSH Level. S. Nalamasu¹, R. Vuppalanchi², and I. Sachmechi¹. ¹Department of Medicine, Mount Sinai Services/Queens Hospital Center, Jamaica, NY, and ²Department of Medicine, Long Island College Hospital, Brooklyn, NY.

Introduction: Several publications studying the role of Thyroid Stimulating Hormone (TSH) in goitrogenesis report conflicting results. Some studies found high TSH levels in patients with multinodular goiter, some found no difference, and yet other studies describe TSH levels to be low compared to normal controls.

Objectives: In this study, we examined the relationship between thyroid nodularity and TSH levels in patients with multinodular goiter who are clinically and biochemically euthyroid.

Methods and Materials: A survey of forty-four patients with multinodular goiter being followed in endocrine clinic was performed. Nineteen patients were chosen for the study by excluding patients with suppressed TSH (Group 1). These subjects were compared to nineteen age matched controls without any thyroid disease (Group 2). TSH levels in both the groups were obtained by review of their medical records.

Results: In group 1, TSH ranged from 0.29–4.65 $\mu\text{IU}/\text{mL}$ with a mean of 1.45 ± 0.29 . In group 2, TSH ranged from 0.38–1.88 $\mu\text{IU}/\text{mL}$ with a mean of 1.08 ± 0.1 . These values were analyzed using paired t test. The difference was not found to be statistically significant (p value of 0.22).

Conclusions: These data indicate that TSH levels in multinodular goiter are not significantly different from normal controls. More studies are needed to confirm this finding and also to investigate other possible reasons for nodularity in multinodular goiter.

Thrombotic Thrombocytopenic Purpura Associated with Clopidogrel Administration. W. Nara, I. Ashley, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Thrombotic thrombocytopenic purpura (TTP) occurs in 1 of 5,000 patients treated with ticlopidine. TTP was not observed in 20,000

patients treated with clopidogrel in clinical trials. We describe a case of TTP associated with the use of clopidogrel in a middle-aged man.

Case Presentation: A 59-year-old man complained of productive cough with white to yellow sputum for two weeks associated with pleuritic chest pain, shortness of breath and epigastric pain. His past medical history was significant for hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular accidents with complete resolution of left-sided hemiparesis and four episodes of myocardial infarctions. He had acquired immunodeficiency syndrome through sexual promiscuity with a CD_4 count of $146/\mu\text{L}$ and a viral load of 17,585 copies/ μL . He did not use illicit drugs. His medications included aspirin, amlodipine, dapsone, quinapril, metformin, gemfibrozil, multivitamins, stavudine, didanosine, efavirenz, hydroxyurea, digoxin, and isosorbide mononitrate extended release.

Two weeks earlier the patient underwent percutaneous transluminal coronary angioplasty (PTCA) with stent placement for unstable angina. After intracoronary stent placement, the patient was treated with a daily oral clopidogrel (75 mg). Prior to treatment with clopidogrel, the patient's platelet count was $163,000/\mu\text{L}$, his hemoglobin was 10.7 g/dL, and his hematocrit 31.6%.

The patient was afebrile with stable vital signs. His physical examination was remarkable for left lung basal crepitation, normal cardiovascular, abdominal and neurological examinations. His skin had no purpura or petechiae. His chest radiograph showed left basal atelectasis. Normal sinus rhythm at 84 beats/minute, left axis deviation at -51° , septal and inferolateral changes were seen on an electrocardiogram.

The white blood cell count was $4,700/\mu\text{L}$, hemoglobin 6.7 g/dL, hematocrit of 20%, red blood cell count of $1,430,000/\mu\text{L}$, and platelet count of $93,000/\mu\text{L}$ with a mean platelet volume of 8.1 fL. Reticulocyte count was 4.1%. Peripheral blood smear showed thrombocytopenia and fragmented, helmet shaped and schistocytic red blood cells consistent with microangiopathic hemolysis.

Coombs direct and indirect tests were negative. Serum lactate dehydrogenase (LDH) was 475 units/L, total bilirubin 1.1 mg/dL and haptoglobin $< 6 \text{ mg}/\text{dL}$. Prothrombin time (PT) was 13.1 seconds, activated partial thromboplastin (PTT) time 31.6 seconds, and the international normalization ratio was 1.13. Blood urea nitrogen was 25 mg/dL and creatinine was 1.1 mg/dL. The rest of the electrolytes were within normal limits.

The diagnosis of thrombotic thrombocytopenic purpura was made. Clopidogrel and hydroxyurea were discontinued. The patient was treated with transfusion of seventeen units of cryodepleted plasma over a period of eleven days, during which the platelet count reached a nadir of $44,000/\mu\text{L}$. There was gradual improvement. The patient was discharged with a platelet count of $202,000/\mu\text{L}$. Two months later the platelet count was $230,000/\mu\text{L}$ while the patient was receiving all his medications except clopidogrel.

Discussion: Clopidogrel-associated TTP has recently been described. The greatest risk occurs within two weeks of initiating therapy. The pentad of fever, renal failure, change of mental status, thrombocytopenia and microangiopathic hemolytic anemia do not all have to be present to make the diagnosis of TTP.

Other causes of TTP were less likely in this patient. The TTP resolved with discontinuation of clopidogrel. Clinicians treating patients with clopidogrel should be aware of this adverse effect.

Effect of a Troglitazone-Containing Regimen on the HbA_{1c} and Body Weight of Diabetic Patients. I. Sachmechi, and B. Mattam, MD. Department of Medicine, Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Objective: To retrospectively study the effects of troglitazone-containing regimens in Type 2 diabetic patients on HbA_{1c} and body weight.

Study Design: The medical records of 29 type 2 diabetes mellitus patients between the ages of 30 and 70 receiving troglitazone-containing treatment regimens were reviewed. Patients were assigned to 4 categories based on the treatment they were receiving. Four patients were on troglitazone only, seven were on troglitazone plus glyburide and metformin, eight on troglitazone plus insulin and ten on troglitazone plus glyburide. The HbA_{1c} and body weights were obtained from the charts at the start of treatment and again six months later.

Results: The mean HbA_{1c} and body weights at initiation of therapy and after six months of therapy and mean changes in HbA_{1c} and body weights in the four groups of patients are shown in the table.

Conclusions: Troglitazone-containing treatment regimens did not show a significant benefit in the reduction of HbA_{1c} in patients with type 2 diabetes. There was a slight weight gain (statistically not significant) in these patients after six months of follow-up.

TABLE

Groups		1 Troglitazone	2 Troglitazone Glyburide and Metformin	3 Troglitazone and Insulin	4 Troglitazone and Glyburide
HbA ₁ C	Initial	8.6 ± 0.81	8.4 ± 0.42	10.5 ± 1.04	10.98 ± 0.57
	Final	8.7 ± 1.37	8.0 ± 0.34	9.5 ± 1.01	9.8 ± 1.01
	Delta	0.10 ± 0.62	0.40 ± 0.41	0.92 ± 0.66	1.16 ± 0.71
	P Value	0.88	0.37	0.20	0.13
Body Weight	Initial	195.5 ± 24.09	204.86 ± 27.44	148.63 ± 7.25	164.90 ± 9.87
	Final	195.5 ± 26.33	214 ± 32.56	154.13 ± 9.46	169.80 ± 9.58
	Delta	0.25 ± 5.34	9.14 ± 5.25	5.50 ± 2.98	4.90 ± 2.24
	P Value	0.96	0.13	0.10	0.05

Atorvastatin Efficacy and Safety in Patients with Type II Diabetes Mellitus and Hyperlipidemia. I. Sachmechi, A. Rozin, and Y. Faktorova. Department of Medicine, Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Background: Atorvastatin is a synthetic HMG-CoA reductase inhibitor which decreases cholesterol synthesis.

Objective: We examined the efficacy and safety of 10 mg atorvastatin daily in reducing total cholesterol, triglyceride, and low density lipoproteins (LDL) levels and in increasing high density lipoproteins (HDL) levels in type II diabetes mellitus patients with hyperlipidemia.

Materials and Methods: Thirteen men and 9 women (age range 43–72 years) who were taking 10 mg of atorvastatin daily for 6 months were studied. Lipid profile, liver function tests, creatine phosphokinase (CPK) level, and hemoglobin A1c were determined before and 6 months after initiation of treatment.

Results: Of the 22 patients, 20 completed the study. Two of our patients were not compliant with the medication and are not included in the study. The baseline and post-therapy values are shown in the Table.

Conclusion: Therapy with 10 mg atorvastatin daily in patients with type II diabetes mellitus and hyperlipidemia is safe and effective in reducing total cholesterol, triglycerides and especially LDL (37.16 %) with no significant effect on the HDL level.

TABLE

	Initial	After 6 Months of Therapy	Mean Reduction	% Reduction	p* Value
Total Cholesterol (mg/dL)	205 ± 8.9	149 ± 6.3	56.50 ± 8.7	27.5%	<0.0001
Triglyceride (mg/dL)	139.3 ± 19.4	121.55 ± 17.5	17.75 ± 10.6	12.7%	0.1097
LDL(mg/dL)	133.75 ± 7.1	84.05 ± 8.2	49.7 ± 8.2	37.2%	<0.0001
HDL(mg/dL)	43.85 ± 2.5	41.45 ± 2.6	2.4 ± 1.3	5.5%	<0.0427

p* = value by paired T-test

No elevation of CPK or abnormality of liver function tests were noted.

Prostate Cancer Presenting as Paraplegia and Widespread Osteolytic Bony Metastases. S.K. Shekawat, M. Vahedi, I. Ashley, 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: Carcinoma of the prostate is the most common cancer in men. Metastases to the vertebrae occur in about 6.7% of patients and can severely affect their quality of life and longevity in this otherwise relatively indolent neoplasm by causing epidural spinal cord compression (ESCC). Bony metastases are mostly osteoblastic (in 97% of patients). We describe a patient with prostate cancer with multiple osteolytic metastatic lesions and complete paraplegia caused by ESCC as a presenting symptom. He also developed acute renal failure which resolved after urinary obstruction was relieved.

Case Report: A 71-year-old African-American man presented with inability to walk for two days and incontinence of urine for one day. He experienced backache and pain in his lower limbs for three months; two weeks earlier he started feeling as if walking on a sponge and, two days prior to admission, felt extreme weakness in both lower extremities and became unable to walk. In the past, the patient abused alcohol but quit following gastric ulcer bleeding twenty years earlier for which he was treated medically. His physical examination was benign except that he had an enlarged, hard but non-tender prostate gland. The stool guaiac was positive. Tendon reflexes were bilaterally absent and the patient had complete flaccid paraplegia. The examination of sensory function, mental function, speech, cerebellar function and upper limbs was normal.

Multiple x-rays of the bony skeleton showed numerous lytic lesions in the axial and proximal appendicular skeleton. Magnetic resonance imaging with T1 and T2 weighted spin echo sequences showed multiple rounded areas of abnormal signals in the vertebral bodies. A large focus of enhancement was noted within the T7 vertebral body as well as cord compression at T7 secondary to a large expansile mass. The serum prostate specific antigen (PSA) was 2615 ng/mL (normal: 0–4 ng/mL). The diagnostic impression was diffuse spinal metastases from prostate cancer.

Widespread osteolytic lesions also suggested the possibility of multiple myeloma, which was ruled out. Serum electrophoresis was normal and Bence Jones protein testing of the urine was negative.

The patient was treated with intravenous decadron and also received 3000 cgy of telecobalt therapy covering spines T3–T11. Blood urea nitrogen /creatinine serially increased but corrected after continuous bladder catheterization. The patient underwent prostatic biopsy of the right and left lobe which confirmed the diagnosis of prostatic adenocarcinoma-Gleason's grade 3 and 4. Several months later, some strength returned to both lower limbs. The patient has good appetite with no weight loss and is pain free. PSA three months after treatment was 0.16 ng/mL. Renal function also normalized.

Discussion: Although most prostate cancer patients have osteoblastic metastases, osteolytic lesions can occur. The onset of paraplegia usually shortens survival, but isolated case reports show prolonged survival. Recent trends in the management of patients with vertebral metastases in prostate carcinoma patients show emphasis on early detection, aggressive treatment of subclinical lesions and minimal delay in starting therapy. Moderate doses of corticosteroids are equally effective as high doses and have fewer side effects. The added modalities of radiotherapy and physiotherapy form the mainstay of management, surgery being reserved for selected cases.

Jersey City Medical Center

Radiographic Differentiation of Intraocular Glass—Evaluation of Imaging Techniques, Glass Types, Size and Effects of Intraocular Hemorrhage. J.S. Leen, R. Turbin, D. Gor, C. Kirsch, and S. Von Hagen. Jersey City Medical Center, Jersey City, NJ.

Introduction: The accurate detection of intraocular foreign bodies (IOFBs) is critically important in managing ocular trauma. The purpose of this study was to evaluate the efficacy of computed tomography (CT),

magnetic resonance imaging (MRI), and ultrasonography (US) in detecting seven types of glass, varying in size, placed within three locations in the globe, and the effect of intraocular hemorrhage.

Methods: Glass pieces were cut in 1.5 mm, 1.0 mm and 0.5 mm and implanted on the corneal surface, anterior and posterior chambers of 42 fresh porcine eyes. Twenty-one eyes were scanned comparing axial CT, helical CT and MRI. The remaining 21 eyes were scanned by helical CT and US after implantation in a human cadaver skull before and after placement of blood in the anterior chamber (hyphema).

Results: Detection rates were 57.1% for helical CT, 41.3% for axial CT and 11.1% for T1 MRI. Results were significant with $P < 0.0001$ ($n = 504$). US detected 43% of glass fragments in the posterior chamber and 24% in the anterior chamber. Detectability was greatest for green beer bottle glass (90.3%) and least for spectacle glass (43.1%, P significant at $P < 0.0001$). Detection rates for six ranged from 91.7% at 1.5 mm to 48.3% at 0.5 mm, significant at $P < 0.0001$. On helical CT anterior chamber glass was easiest to detect (91.7%) and corneal surface glass the most difficult (64.9%). Hyphema made no statistical difference ($P < 0.0001$).

Conclusion: Helical CT was the most sensitive imaging modality for the detection of intraocular glass. The sensitivity of detection was unaffected by hyphema and determined by the glass, size and location.

The Outcome of Cardiopulmonary Resuscitation in HIV Patients in an Inner City Hospital. A. Chadha, S. Vasudevan, K. Saluja, M. Bautista, V. Thirumavalavan, and G. Cable. Jersey City Medical Center, Jersey City, NJ.

Background and Aims: The outcome of cardiopulmonary resuscitation (CPR) in HIV patients in inner city hospitals has not been well reported in literature. We aim to study the above and report our findings.

Methodology: Medical records of all patients subjected to CPR from 1996 to 1999 were studied retrospectively. The patients were divided into HIV vs. non-HIV groups. Initial success of CPR (establishment of stable rhythm with cardiac output) and final success of CPR (discharged out of hospital) were the endpoints studied. Multivariate analyses of pre-arrest and intra-arrest variables (CD4 count, duration of code, type of code, diabetes, albumin, electrolyte imbalance, functional status, sepsis and others) were done to predict final outcome and factors affecting outcome.

Results: There were total of 510 codes of which 89 were HIV infected patients. In the HIV group, 61 codes had data complete for analysis. The mean age for HIV patients were 43.3 (median 43, range 26 to 72), and in non-HIV patients was 66.9 (median 68, range 28 to 97). Mortality was 97% (65/67) in HIV patients and 94% in non-HIV patients. Nature of code was cardiac in 70% of HIV patients and 69.5% of non-HIV patients and respiratory in 10% of HIV patients vs. 5.6% in non-HIV patients. Cardiac cause of code was associated with a 78% less chance of survival as compared to respiratory cause of code in HIV patients ($0 = 0.01$). CD4 cell counts ranged from 2 to 730. For every CD4 cell count more than 10 there was a 6% greater chance of survival ($p = 0.004$). For every additional minute in duration of code there was a 6% less chance of survival. Average duration of code was 18.7 minutes in HIV patients vs. 24.2 in non-HIV patients ($p = 0.18$).

Conclusion: Contrary to published data a decade ago, we found that the CD4 count did make a difference in CPR survival. But, the overall outcome of CPR being dismal, more so for HIV patients, the increased survival associated with higher CD4 cell count, although significant in statistical terms, did not improve the overall outcome. Respiratory cause of code was more common in HIV patients and was associated with better outcome as compared to cardiac cause of code. The average HIV patient was coded 6 minutes less than his/her non-HIV counterpart, this could be a reflection of the physician's reluctance not to be persistent with resuscitation efforts in HIV patients.

Should the Pathologic Diagnosis of Chorioamnionitis Impact Maternal Care? A. Yousry, L. Applewhite, C. Strand, A. Khan, and C. Gagliardi. Jersey City Medical Center, Jersey City, NJ.

Chorioamnionitis, occurring in 1–5% of term and up to 25% of pre-term pregnancies, is associated with serious medical complications in both mother and newborn. Maternal complications include bacteremia (3–12%), wound infection (8%), and pelvic abscess (1%). Chorioamnionitis is usually diagnosed on the basis of the following clinical findings: (1) maternal fever, (2) fundal tenderness, (3) sustained fetal tachycardia > 160 bpm. The maternal significance of chorioamnionitis diagnosed solely on pathological examination of the placenta has not been fully assessed.

To determine the association between the pathological and clinical diagnosis of chorioamnionitis, the placentas of 85 consecutive patients delivered by the author were examined by the Pathology Department and the patients were assessed for clinical signs of chorioamnionitis/endometritis.

Of the 85 placentas examined, 48 (56%) were noted to have chorioamnionitis present, and 37 (44%) showed no signs of chorioamnionitis. Clinically, only 3 of 85, or 3.5% of patients exhibited signs of chorioamnionitis. The relative risk (RR) of a patient developing clinical chorioamnionitis with a positive pathology report was 1.5. The predictive value positive of pathologically diagnosed chorioamnionitis was 4%. The low predictive value positive precludes use of this as an additional modality to modify clinical practice for maternal care.

The Benefits of Imaging Studies in Alcohol Induced Acute Pancreatitis. T. Kassis, K. Ghosh, and P. Chikezi. Jersey City Medical Center, Jersey City, NJ.

Alcohol is the second most common cause of acute pancreatitis in the United States. The diagnosis usually is based on history, physical exam, serum pancreatic enzymes and imaging studies (usually abdominal ultrasound or abdominal CT scan).

It is a common practice in many hospitals to order one of these imaging studies within the first 24 hours of admission for all patients with clinically diagnosed acute pancreatitis and elevated lipase level, looking for etiology or complications, regardless of suspected etiology.

Our aim is to determine the benefit of these imaging studies during the initial 24 hours of presentation in acute pancreatitis among patients with active history of alcohol abuse. In retrospective review of the charts of emergency admission patients with acute pancreatitis, diagnoses on the basis of elevated serum amylase and lipase and clinical presentation, we identified 10 cases with an active history of alcohol abuse in which an abdominal ultrasound or CT scan (in some cases both) was done with 24 hours of admission. All patients were hemodynamically stable. None of the patients had surgical abdomen, abnormal bilirubin level or history of gallstones. The mean age of the patients (33% female and 67% male) was 42.1 years. The imaging modality was ultrasound for 79%, CT for 13% and both for 8% of the patients. Fifty-six percent of the imaging studies were reported as showing unremarkable pancreas, 41% were suggestive of pancreatitis. Three percent of the patients had gallstones with no signs of inflammation or obstruction of the pancreatic or common bile duct. None of the patients had pseudocyst or necrotizing pancreatitis. All patients were treated conservatively. No complications were reported.

In summary, our study suggested that abdominal ultrasound and CT scan are not beneficial in the initial evaluation of acute pancreatitis in hemodynamically stable active alcohol abusers.

There is a need for a prospective randomized clinical study to further evaluate these findings.

Kaposi's Sarcoma: Another Cause of Middle Lobe Syndrome. M. Bautista, D. Flores, R. Rojas, and A. Chadha. Jersey City Medical Center, Jersey City, NJ.

A 29-year-old homosexual man, a smoker, with a past medical history of HIV/AIDS, CD4 110, with disseminated Kaposi's Sarcoma (KS) was admitted for a second attempt of chemotherapy, after a frustrated first attempt with vincristine. Patient denied any recent episodes of cough, fever, dyspnea, sore throat, hemoptysis or chest pain. Physical exam was only remarkable for multiple flat and raised purple-brownish cutaneous lesions over the patient's head, trunk and extremities; and marked facial and periorbital lymphedema, with a normal lung auscultation. Chest x-ray showed prominent consolidation in the lateral segment of the right middle lobe suggestive of pneumonia, similar findings were confirmed by CT scan. Diagnostic fiberoptic bronchoscopy was performed, flat brightly red and violaceous vascular appearing lesions involving the trachea and main bronchi were observed, with increased narrowing of lateral segment of the right middle lobe bronchus. Lavage samples were obtained; no microorganism was isolated after staining and culture. Chemotherapy was started with doxorubicin and patient tolerated well. Six weeks later patient was re-evaluated, showing a significant clinical improvement of cutaneous and lymphatic lesions as well as radiographic findings, with total disappearance of previous described consolidation.

Discussion: Middle Lobe Syndrome (MLS) is an uncommon lung disorder involving the right middle lobe and/or lingula and is defined as recurrent or chronic collapse of such areas. It occurs in all age groups and is characterized by a spectrum of clinical and pathological lesions ranging from recurrent inflammatory bronchiectasis to malignant tumors. Kaposi's Sarcoma is one of the most common malignancies in the HIV/AIDS population, the lung involvement has been broadly documented by clinical and autopsy reports, but its manifestation as a solely right MLS has not been well described. KS should be considered together with lymphoma and mycobacterium infection as an etiology of MLS in the HIV population. It is also important to differentiate this entity from an active infectious process as bacterial pneumonia, since the presence of MLS secondary to neoplastic process is likely to respond to chemotherapy and the presence of bacterial pneumonia may worsen.

Port-A-Cath Device in a Patient with HIV: A Cause of Massive Pulmonary Thromboembolism. M. Bautista, A. Rameshbabu, L. Tacsá, E. Osama, M.D., and A. Ameen. Jersey City Medical Center, Jersey City, NJ.

Indwelling central venous catheters are generally well accepted in those patients requiring frequent intravascular access to deliver parenteral medication, nutrition and for blood sampling. This popularity is due to lower cost of patient care and an acceptably low complication rate. Complications are of two types: infection and mechanical. We report a case of subtle presentation of massive pulmonary embolism (PE) mediated by a central venous catheter in a young woman with HIV.

A 27-year-old female, HIV positive with a port-a-cath placed two years previously for IV antibiotic administration, presented to the ER with sudden onset of pleuritic left side chest pain and mild shortness of breath for several hours. When initially evaluated she was asymptomatic, hemodynamically stable and the physical exam unremarkable. Chest x-ray showed normal appearance of the lungs, arterial blood gases were within normal limits, and an EKG revealed normal sinus rhythm, but rightward Axis. VQ scan showed totally absent perfusion of left lung suggestive of PE. Chest CT and echocardiogram demonstrated a 3 x 5 x 4 cm mass with soft tissue echogenicity freely mobile in the right atrium and a 2 x 3 x 4 cm similar mass occluding the left pulmonary artery. Venous Doppler ruled out deep venous thrombosis of lower limbs. IV-Heparin was started while patient remained asymptomatic and hemodynamically stable. Next day, open heart surgery was performed for the removal of the two masses, which were confirmed by pathology to be two large thrombi, and removal of the port-a-cath. Five days post-surgery the patient was able to be discharged.

Discussion: The intrusion of the catheter tip into the right atrium has been suggested as a possible mechanical complication causing intracavitary thrombogenesis, therefore increasing the risk of PE. The incidence of mural thrombi due to central venous catheter is as high as 29% in autopsy rounds, but its clinical significance as a cause of infection or embolization appear to be low. Chronic embolization with physiological adaptation is a possible phenomenon to explain the low incidence of acute fatal episodes and the subjectivity of clinical manifestation like in this case.

Malrotation and Midgut Volvulus in Childhood Period: Two Case Reports and Literature Review. P. Lianthanasarn, L. Gelvez, S. Puvabanditsin, and E. Garrow. Jersey City Medical Center, Jersey City, NJ.

The incidence of midgut malrotation is unknown. The clinical manifestations of the disease are highly variable from one patient to the other and not characteristic. Some remain symptom free throughout their whole life, some present with vomiting, some with failure to thrive and some with acute obstruction secondary to volvulus. More than 75% of children with midgut volvulus present within the first month of life or soon afterwards with vomiting, often bilious, due to intestinal obstruction. Of the remaining 25% most present with a similar clinical picture within the first two years of life and some will be erroneously diagnosed as cases of cyclical vomiting following intermittent episodes of high intestinal obstruction. These children with midgut volvulus can develop intestinal ischemia due to compression of superior mesenteric artery. This development necessitates major bowel resection and carries a poor prognosis. We present two case reports of malrotation and midgut volvulus in the early and late childhood period.

Transient Cortical Blindness Following Carotid Angiography: Evaluation by Diffusion-Weighted Magnetic Resonance Imaging. N. Khodadi, B. Maltzman, and R. Turbin. Jersey City Medical Center, Jersey City, NJ.

Introduction: Transient cortical blindness (TCB) is rare but known complication of contrast media angiography. The incidence of TCB ranges from 0.05 to 1% with highest incidence noted in cerebral angiography. Although the breakdown of blood brain barrier with direct neurotoxicity of the contrast media has been implicated, the exact mechanism remains unknown. To our knowledge, this case reports the first use of diffusion-weighted magnetic resonance imaging in evaluation of angiography contrast dye induced transient cortical blindness.

Case Report: A 63-year-old woman with high grade stenosis of left internal carotid artery underwent carotid angiography with contrast dye, Iodixanol. Immediately post angiography, the patient was found with cortical blindness. Diffusion-weighted magnetic resonance imaging obtained five hours post-angiography did not show signs of ischemia. The patient regained her baseline vision seventeen hours post-angiography.

Conclusion: By showing no evidence of acute ischemia in the occipital lobes, diffusion-weighted magnetic resonance imaging adds evidence against ischemia as a mechanism for transient cortical blindness following angiography.

Successful Treatment and Counseling of Patient with Female Genital Mutilation. A. Yousry, C. Gagliardi, and D. Campbell. Jersey City Medical Center, Jersey City, NJ.

Introduction: Female genital mutilation (FGM), a practice based on cultural and traditional patterns, has been done for the past 2,000 years. According to the World Health Organization (WHO), 80 million women have undergone this procedure. FGM is still widespread in Africa, the Middle East and Southeast Asia.

Case: A 19-year-old gravida 0 para 0 (not previously pregnant) complained of dyspareunia (since her recent marriage), dysuria and repeated urinary tract infections. She underwent FGM at the age of three. On examination, the clitoris, labia minora or the urethral orifice could not be visualized and the vaginal opening was occluded. Defibrillation was done in the OR under general anesthesia. The labia majora were surgically separated and running absorbable sutures were placed. Estrogen cream was applied for 2 weeks. Check-up revealed complete healing and, by 10 weeks, the dysmenorrhea,

dyspareunia, dysuria, had resolved and her urinary stream was restored.

Discussion: FGM takes many forms including (1) removal of clitoral prepuce, (2) excision of clitoris, and (3) removal of clitoris and labia minora and occasionally much of the labia majora, suturing sides together to occlude the vagina. Complications can be both immediate (hemorrhage, shock, infection osteitis pubis) and long-term (dyspareunia, TUI, infertility, pelvic inflammatory disease [PID], psychological trauma). FGM is usually performed prior to adolescence by untrained individuals without benefit of sterile conditions or anesthesia. Patient counseling is vital to successful repair and prevention.

Hepatic Failure as the Presenting Symptom of Childhood Systemic Lupus Erythematosus: A Case Report and Review of the Literature. K. Denev and F. Pelliccia. Jersey City Medical Center, Jersey City, NJ.

A 14-year-old African-American female has been transferred from regular pediatric floor to PICU because of persistent vomiting, marked drowsiness, prostration and progressive deterioration of mental status. Physical findings revealed altered mental status (stuporose), significant jaundice, asterixis, ascites and hepatomegaly in moderately obese female. The past medical history was positive for fatigue, weight loss and anorexia for the last 2-3 months. The teenager has also been treated for PMD for arthritis with NSAID. She denies using any other medications or illicit substances. Laboratory results demonstrated increased ammonia, transaminases and bilirubin levels, hypoalbuminemia, prolonged PT and PTT, anemia and hyponatremia with elevated protein. The patient also has positive test for ds-DNA (speckled pattern), positive AMA and ANA antibodies, antiphospholipid test. All hepatitis screening tests was well as CMV serology were negative. During the hospital stay patient sustained increase in the BUN and creatinine levels, but liver enzymes with bilirubin returned to normal. The patient was treated with lactulose, steroids (for autoimmune hepatitis), vitamin K, furosemide, multiple albumin infusions and transfusions. Several paracentesis were done suggestive of exudate and peritoneal fluid yield negative culture results. The patient underwent flexible esophago-gastroduodenoscopy which revealed candidial esophagitis but no varices. The patient was transferred to St. Joseph Hospital for liver and renal biopsy. The liver biopsy demonstrated autoimmune hepatitis, renal biopsy suggestive of ATN with nephritis. 6-mercaptopurine was added to the therapy. Later on she developed seizures controlled with anticonvulsant, hypocalcaemia—symptomatically treated with Ca. Cardiac echocardiography was positive for minimal pericardiac effusion that resolved with normal LV function and normal heart anatomy. One week after discharge from St. Joseph Hospital, the patient was readmitted to Jersey City Medical Center with generalized seizures, hyperglycemia and hyperkalemia.

The final diagnosis in this case was systemic lupus erythematosus (SLE), lupus hepatitis, nephritis and cerebritis that presented initially as liver failure. This presentation of SLE is rare, unusual and particularly difficult to treat and usually has an ominous prognosis.

Transient Cortical Blindness and Retrograde Amnesia Following Cerebral Angiography: A Case Report. M. Bautista, A. Chadha, A. Mandal, T. Brannan, and S. Malik. Jersey City Medical Center, Jersey City, NJ.

Case Report: A 63-year-old Hispanic female was referred for a carotid arteriogram prior to endarterectomy due to 80-90% stenosis of the left internal carotid artery found on MRI and carotid Doppler. Past medical history was significant for hypertension, hypercholesterolemia and 2 months history of amaurosis fugax. Medications included baby aspirin. Selective carotid arteriogram was done by right femoral approach and during procedure the patient had transient elevation of blood pressure (BP) to 201/101. Half an hour into the procedure patient developed sudden onset of complete loss of vision, frontal headache and confusion. After vital signs stabilization, patient was transferred to critical care unit with a BP of 160/70. Ophthalmology evaluation was unremarkable for any focal lesion and neurology exam did not show any other focal deficit. EKG revealed no new change and MRI with diffusion scan as well as CT of head were normal not showing any finding of ischemia, hemorrhage or focal accumulation of contrast media. Patient was monitored regularly and 24 hours after the event, she fully recovered vision and the headache was relieved. Amnesia was present including events up to 24 hours prior and 12 hours following the angiogram. Patient was discharged 4 days after the procedure.

Discussion: Transient cortical blindness is a rare complication after vertebral and coronary angiography. This event is usually accompanied with altered mental status, headache and/or seizures. Intravenous contrast used for the procedure has been postulated to be the causative agent. Osmotic disruption of the blood brain barrier with leakage of contrast and direct neurotoxicity is the most popular theory because of reports of accumulation of contrast in the occipital cortex. Another theory considered is vasospasm of the posterior circulation due to the neurotoxic effect of the dye. The latter seems to be the possible mechanism in our patient due to absence of abnormal findings on imaging studies, which would have supported disruption of the blood brain barrier. Spontaneous recover is usually the rule with complete resolution of symptoms unless the symptoms are due to occipital lobe embolism.

Botryomycosis—A Bacterial Pseudomycosis. A. Chadha, S. Thamban, M. Bautista, J. Zamora, and A. Khan. Jersey City Medical Center, Jersey City, NJ.

Case Report: A 43-year-old Afro-American female presented to us with complaints of night sweats, neck mass, fever and sore throat for 3 weeks. She was diagnosed with HIV infection 5 years ago and had a CD4 count of 12 and viral load 527,000. She had opportunistic infections in past like *Pneumocystis carinii* pneumonia (PCP) and oral thrush and had been non-compliant to her anti-retroviral medications. Upon examinations, she was found to have anemia and leukopenia with significant cervical adenopathy. With a presumptive diagnosis of lymphoma she underwent lymph node biopsy. The biopsy showed abscesses with surrounding granulomatous inflammation with giant-cell reaction and clusters of bacterial organisms consistent with botryomycosis. Special stain for acid-fast bacilli (AFB) fungus and bacteria were negative. Microbiology cultures were positive for methicillin sensitive *Staphylococcus aureus*. Patient was started on anti staph treatment and on last follow-up showed improvement with resolution of symptoms and adenopathy.

Discussion: Botryomycosis has been defined as a chronic localized and progressive pseudomycosis caused by certain nonfilamentous bacteria. The bacterium most commonly isolated has been *S. aureus* although pseudomonas, *E. coli*, neisseria and other bacillus species have also been involved. In infected tissue, the bacteria characteristically form large aggregates of soft, yellow or white, spherical to lobulated grains, that are actually organized bacterial aggregates in micro colonies, which is the hallmark of botryomycosis. The integumentary form is more common, visceral rare, with isolated case reports of the nodal variety. Defective host resistance or bacteria with attenuated virulence may be key factors in persistence and aggregation of bacteria with the result the bacteria are not killed in tissue by host defenses. Commonly seen in immunocompromised patients. Histopathologic or cytologic evaluation and culture are needed to distinguish from mycetoma or actinomycosis. Usually surgery combined with prolonged IV antibiotics is needed to eradicate the infection although selected antibiotics can sometimes be used effectively.

Community-Acquired Widely Metastatic Fatal Staphylococcal Infection in Absence of Intravenous Focus: A Case Report. A. Chadha, O. El-Sayed, N. Ahmad, J. Matta, and A. Greenberg. Jersey City Medical Center, Jersey City, NJ.

Case Report: A 32-year-old African-American female was brought to the emergency department intubated due to respiratory arrest. For the last 4 months, she had been having pustules in both her axillae that came and subsided with mild temperature elevations. Three days prior to admission she developed upper respiratory symptoms with nasal stuffiness, arthralgia and myalgia that progressed and on the date of admission she became lethargic and unresponsive. In the emergency department she was in shock with fixed dilated pupils and had a burst abscess on her right chest wall. Chest x-rays showed a left middle lobe infiltrate and CT head showed a large bleed in the left parietal lobe with small bleeds in the occipital lobes with intraventricular extension. Echo showed pericardial effusion with no endocarditis. Despite pericardial window and aggressive management of shock, patient expired 18 hours after admission. The next day, two sets of blood cultures and pericardial fluid grew methicillin sensitive staph aureus, the CD4 count was 137 with HIV test negative. Autopsy showed multiple abscesses in the brain, kidneys, liver, lungs, myocardium and pericardium with no endocarditis.

Discussion: Staphylococcal septicemia with widespread metastatic seeding in the absence of endocarditis or IV focus is infrequently reported. Skin, subcutaneous tissue and surgical wound infections account for almost 50% of primary staph bacteremia that may seed peripheral organs causing secondary lesions. Gram-positive organisms can lead to a similar shock picture as in gram-negative endotoxin shock due to cell wall peptidoglycan or teichoic acid complex that triggers the release of mediators. Intra-cerebral bleed has been described as a rare complication of septicemia and is associated with adverse outcomes. It could be caused by septic arteritis or ruptured mycotic aneurysm. Direct seeding of the myocardium can lead to myocarditis with elevated cardiac enzymes mimicking myocardial infarction, as in our case, and contribute to shock. In absence of obvious focus, it can pose a diagnostic dilemma. The immune suppression observed as probably a consequence of overwhelming sepsis rather than a cause of it, although some inherent leukocyte adhesion defect or chemotactic disorder, leading to unchecked bacterial multiplication, cannot be ruled out.

Could Telangiectasias Be the Tip of the Visceral Neoplasm Iceberg? S. Prabhakar and V.S. Thirumavalavan. Jersey City Medical Center, Jersey City, NJ.

Telangiectasias are permanently dilated small blood vessels with a maximum diameter of 1 mm. They have been associated with both cutaneous

and systemic conditions such as pregnancy, ataxia-telangiectasia, systemic lupus erythematosus (SLE), scleroderma and cirrhosis. The following two case histories and the accompanying photographs highlight instances where the appearance of extensive dilated and tortuous intracutaneous telangiectasias preceded other symptoms suggestive of a malignancy.

A 41-year-old white male with a 15-pack year history of smoking presented with cough, hemoptysis, weight loss and shortness of breath for 2 months. Dilated blood vessels had been noticed on the anterior chest wall for more than 6 months. Physical examination revealed a superior mediastinal syndrome. Transbronchial biopsies confirmed adenocarcinoma lung of the non-small-cell type and poorly differentiated non small cell carcinoma in the supraclavicular nodes.

A 31-year-old Hispanic male with a 10-pack year history of smoking presented with right shoulder pain and anisocoria. He had noticed dilated blood vessels on the anterior chest wall for a year. CT-guided biopsy of an anterior thoracic mass confirmed non Hodgkin's lymphoma of the B cell type.

The sudden appearance of telangiectasias may thus predate other clinical symptoms of internal malignancies by several months and should prompt an active and thorough search for occult neoplasia.

Editor's Note: Pack-year = total number of years of smoking x average number of cigarettes smoked/day ÷ 20.

Association between Two Uncommon Findings in Gynecology, Endometrial Cancer and Granulosa Cell Tumor. A. Olanescu, E. Fagbongbe, G. Woroch, and J. Hutchinson. Jersey City Medical Center, Jersey City, NJ.

Introduction: Continuous unopposed estrogen (E), in either exogenous or endogenous form, is associated with an increased risk of endometrial hyperplasia and endometrial cancer (CA). Exposure to exogenous E is commonly associated with E replacement therapy without benefit of progestins. Exposure to endogenous E can be associated with either hormonal disorders or E secreting neoplasms such as Granulosa Cell Tumor (GCT).

Case: A 43-year-old G5P4 (postmenopausal for 5 years) presented with a 2-month history of vaginal bleeding. PE—normal. Ultrasound exam—endometrial thickness of 16 mm and a 3-cm simple ovarian cyst. Endometrial biopsy—complex atypical hyperplasia with foci suggestive of well differentiated adenocarcinoma. CT abdomen/pelvis and CA-125—normal. Atotal abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH-BSO); uterus mildly enlarged with intact serosa, right ovarian solid mass with intact capsule, multiple pelvic adhesions, no evidence of metastasis. Frozen section of ovary disclosed GCT, (6 x 5 x 4 cm), confined to capsule. Call Exner bodies and 2–3 mitosis/10 high-power field (HPF) were seen. Well differentiated CA of the endometrium was also present.

Discussion: Although endometrial CA occurs in less than 5% of patients with GCT, a high index of suspicion for this tumor should be present when the diagnosis of endometrial CA is made in a woman with postmenopausal bleeding and an ovarian cyst who has no other risk factors for endometrial CA. Epithelial tumor markers are not helpful, however a serum E level may help the pre-operative diagnosis of GCT.

ALive Birth with Triploidy Syndrome (69XXY). P. Lianthanasarn, R. Myers, M. Gomez, and S. Puvabanditsin. Jersey City Medical Center, Jersey City, NJ.

The Triploidy Syndrome is a well-recognized clinical entity that occurs in approximately 2% of all conceptuses. The vast majority of triploid conceptuses are aborted spontaneously before 24 weeks of gestation; thus, the syndrome is rarely seen in the neonatal period. This case report describes a live-born infant with the characteristic clinical cytogenetic findings of triploidy syndrome.

Median Cleft Face Syndrome with Lipomas of Corpus Callosum Region: A Case Report. M. Quizon, D. Akpalu, S. Puvabanditsin, and E. Garrow. Jersey City Medical Center, Jersey City, NJ.

Lipomas of the brain are rare, with 50% being situated in the corpus callosum; they are frequently associated with other developmental anomalies. Although intracranial lipomas are usually asymptomatic, they might present with epilepsy, dementia, or headache. Median cleft face syndrome is a rare form of dysraphism that affects the midface. The syndrome has been widely referred to as frontonasal dysplasia. The types of facial clefting seen in this syndrome has been classified differently by different authors. We report a case of median cleft face syndrome that is also associated with Lipomas of the corpus callosum region. Literatures are reviewed.