no known history of CAD who presented for elective cardiac catheterization were included in the study. These patients were evaluated for the presence (M+) or absence (M−) of the metabolic syndrome using the NCEP-ATP III criteria; CAD was defined as the presence of at least 70% stenosis in one of the three major coronary vessels or one of their significant branches or 50% stenosis in the left main coronary artery. The relationship between the metabolic syndrome and the presence of CAD was assessed by using the Pearson chi-square test. **Results:** Metabolic syndrome was present in 95/174 patients (54.6%), and M+ was significantly more likely to have CAD than M− (43% vs 28%, $p = .036$). There was no significant difference between M+/M− with regard to the mean Framingham risk score or for age, tobacco use, or family history of CAD; there was a significantly increased prevalence of DM (defined as fasting blood sugar > 126 mg/dL or DM Rx) in the M+ group ($p < .01$). Given that DM is a coronary risk equivalent, subgroups with DM and without DM were evaluated separately:

	Diabetic p = *NS*			*Nondiabetics* p = *NS*	
	No CAD	CAD		No CAD	CAD
M−	5	2	M−	52	20
M+	18	23	M+	36	18

Conclusion: Metabolic syndrome, independent of diabetes mellitus, is not a risk factor for obstructive coronary artery disease.

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METFORMIN-DIET AMELIORATES CORONARY HEART DISEASE RISK FACTORS AND FACILITATES RESUMPTION OF REGULAR MENSES IN ADOLESCENTS WITH POLYCYSTIC OVARY SYNDROME. M. Winiarska, D. Aregawi, G. Luo, J. Munjal, L. Sieve, P. Wang, C.J. Glueck, Cholesterol Center, Jewish Hospital, Cincinnati, OH.

In 35 postmenarchal adolescent females (17 ± 2 years, range 14–19) with polycystic ovary syndrome (PCOS), in a case-series prospective description, we assessed effectiveness of metformin-diet for 1 year for reduction of weight, insulin, HOMA insulin resistance (IR), cholesterol, triglycerides, and resumption of regular menses. By selection, all 35 girls met the 2003 consensus criteria for diagnosis of PCOS; all 35 had clinical hyperandrogenism, 37% were amenorrheic, and 60% oligomenorrheic. Pretreatment median weight was 82.7 kg, BMI 30.8 kg/m^2, and 19 (54%) girls had BMI > the CDC age-gender-specific 95th percentile (overweight). Calories (26% protein, 44% carbohydrate) were targeted to 1,500–1,800/day if BMI was < 25 or to 1,200–1,500/day if BMI was ≥ 25, along with 2,550 mg metformin. After 1 year on metformin-diet, median weight fell from 82.7 to 79.1 kg ($p = .009$); the median of the percent change was −5%. In 6 girls (17%) weight loss was ≥ 10 kg, in 8 (23%) was 5–10 kg, and in 11 (31%) was 0–5 kg. After 1 year on metformin-diet, fasting serum insulin 16.7 to 13.3 uU/mL ($p < .0001$), HOMA IR 3.41 to 2.74 ($p = .0004$), total cholesterol 164 to 151 mg/dL ($p = .002$), and triglyceride 103 to 85 mg/dL ($p = .006$). After 1 year on metformin-diet, reduction in insulin was associated with reduction in testosterone, $R^2 = 20\%$, $p = .008$. The percentage of cycles with normal menses rose from a pretreatment median of 8% to 100% after 1 year on metformin-diet, $p < .0001$. In 19/35 girls (54%) serum progesterone was ≥ 2.3 ng/mL (ovulatory range) at ≥ 1 of their follow-up visits. Because we did not randomize to diet-placebo vs diet-metformin, we cannot separate metabolic-endocrine benefits attributable to metformin alone or diet alone. The importance of the diagnosis of PCOS in adolescence lies in primary prevention of adult endocrinopathy, obesity, infertility, hyperinsulinemia, hypertriglyceridemia, type 2 diabetes, and increased cardiovascular morbidity-mortality. In adolescents with PCOS, metformin-diet reduces weight, insulin, IR, cholesterol, and triglycerides and facilitates resumption of regular menses. Successful reversal of endocrine and cardiovascular risks associated with PCOS soon after menarche should save the adolescent from the early and late stigmata of the syndrome and emphasizes the importance of the earliest diagnosis and treatment of PCOS in adolescence.

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GENE EXPRESSION PROFILING CAN DISTINGUISH PHYSIOLOGIC B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA CLONAL EXPANSIONS FROM PRELEUKEMIC AND LEUKEMIC CLONES. B. McCarthy,[1] X.-P. Wang,[2] S. Paul,[1] L. Goodwin,[2] A. Rawstron,[3] N. Chiorazzi,[1] [1]Laboratory of Experimental Immunology, The Feinstein Institute for Medical Research; [2]Molecular Genetics/Core Facility, The Feinstein Institute for Medical Research, Manhasset, NY; [3]Haematological Malignancy Diagnostic Service, Leeds General Infirmary, Leeds, United Kingdom.

B-cell chronic lymphocytic leukemia (B-CLL), the most common adult leukemia, is a clonal disease manifested by an absolute lymphocytosis. However, not all clonal lymphocytoses are B-CLL since monoclonal B-cell subpopulations can be detected in apparently healthy individuals using flow cytometry. This phenomenon is termed monoclonal B-cell lymphocytosis (MBL) or clonal lymphocytosis of uncertain significance (CLUS). CLUS has been identified in healthy volunteers with normal lymphocyte counts at a frequency of 3.5% and among first-degree relatives of B-CLL patients at a higher frequency (13.5%).* These findings suggest a transition from a B-CLL progenitor cell to overt B-CLL that occurs over time. Therefore, it would be useful, both therapeutically and mechanistically, to identify genes involved in this transition and to determine which cell population is vulnerable to leukemic progression. Using gene expression profiling, we and others have identified genes transcribed at significantly different levels between B-CLL patients and normal subjects. From these genes, a select panel was chosen, and the expression of these genes was quantified by rtQ-PCR from mRNA of patients with B-CLL as well as from normal subjects, with and without CLUS. Since the numbers of cells within the expanded clones from normal individuals with CLUS was limiting, in these instances we amplified mRNA using the Nugen OVATION RNA Amplification System. Using this rtQ-PCR approach, we accurately distinguished the clonal expansions of normal healthy subjects from those with CLUS and B-CLL. Therefore, expression of this gene panel may provide a novel way to identify genetic patterns that change during the transition from B-cell clonal expansions that occur physiologically from those that occur among preleukemic and leukemic B-cell populations.

*Rawstron et al. Blood 2002;100:635–9.

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PHENOTYPIC AND GENETIC CHARACTERIZATION OF A COMMON DENTOFACIAL DEFORMITY: MANDIBULAR PROGNATHISM. S.A. Frazier-Bowers,[1] C. Bui,[1] T.M. King,[2] W.R. Proffit,[1] [1]Department of Orthodontics, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Department of Pediatrics, University of Texas Health Science Center, Houston TX.

Although substantial evidence has supported the role of heredity in Class III dentofacial deformity (mandibular prognathism), the relative contribution of genetic and environmental factors that led to this dentofacial problem, however, continues to be debated. The objective of this study is to elucidate the role of genetics in the development of the Class III trait. We therefore performed a detailed phenotypic characterization of both isolated and familial cases of Class III dentofacial deformity to address the fundamental hypothesis that the Class III trait is an inherited trait with distinctly segregating subphenotypes. We further propose to categorize individuals based on these subphenotypes that can ultimately be correlated with specific haplotypes. It should be possible to eventually understand the contribution of genetic factors in the various expressions of Class III dentofacial problems and to apply this knowledge to improved treatment approaches. To date 15 families with multiple affected individuals have been identified within the existing database of the Dentofacial Clinic at the University of North Carolina through which surgical patients are followed and through the records of the graduate orthodontic clinic and faculty practice. Cluster and principal components analyses were performed using cephalometric variables to compare familial and isolated Class III individuals. Finally, a genome-wide scan followed by linkage analysis was conducted to identify the chromosomal locus of the Class III trait for four families with significant power. The results indicated that there are five clusters, from 309 individuals, representing clinically distinct phenotypes. A pedigree "analysis by inspection" revealed that the broad Class III phenotype is inherited as an autosomal dominant trait in 15 families analyzed. Linkage analysis reveals a locus suggestive of linkage with the Class III trait. We therefore conclude that the Class III dentofacial deformity is largely under strict genetic control and is made up of distinct subphenotypes.

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EPIDEMIOLOGY OF PEDIATRIC MASTOIDITIS IN THE PRE– AND POST–PNEUMOCOCCAL VACCINE ERAS. M.G. Roddy, S. Glazier, D. Agrawal, Children's National Medical Center, Washington, DC.

Background: Studies have shown that the epidemiology, clinical course, and bacterial pathogens for acute otitis media (AOM) have changed in the seven-valent conjugate pneumococcal vaccine (CPV) era. We hypothesize similar changes with mastoiditis, which may require an adjustment of empiric antibiotic therapy. **Objectives:** To describe the epidemiology, etiology, and clinical course of mastoiditis in the pre-CPV (1/95–12/00) and post-CPV (1/01–4/05) eras. **Methods:** We performed a retrospective chart review of patients admitted to a tertiary care pediatric hospital with a discharge diagnosis of mastoiditis from 1/95–4/05. Etiological agents were determined by culture results from mastoid fluid, middle ear fluid, and/or blood. **Results:** 139 charts were reviewed, with 78 pre-CPV and 61 post-CPV. Patient age ranged from 30 days to 18.2 years (median 4.4 years). Myringotomy tubes were placed in 60 (43%), and mastoidectomy was performed in 59 (42%). Etiological agents were determined in 68 (49%). The most common bacterial isolates from the 34 pre-CPV cases were *S. pneumoniae* (15), *P. aeruginosa* (10), *S. aureus* (6), and *S. pyogenes* (1) and from the 34 post-CPV cases were *S. pneumoniae* (12), *S. pyogenes* (8), *P. aeruginosa* (5), and *S. aureus* (5). *S. pneumoniae* was implicated in 15/34 (44%) of pre-CPV cases versus 12/34 (35%) of post-CPV cases ($p = .46$). Acute mastoiditis was diagnosed in 106/139 (76%), and chronic mastoidits (defined as ≥ 3 weeks of symptoms) was diagnosed in 33/139 (24%). *S. pneumoniae* was more likely to be implicated in acute vs chronic mastoiditis (30% vs 7%, $p = .06$), and *P. aeruginosa* was more likely to be implicated in chronic vs acute mastoiditis (40% vs 10%, $p = .003$). Sixty-seven percent of pre-CPV *S. pneumoniae* isolates were pansensitive compared to 33% in the post-CPV era ($p = .09$). Seven percent of pre-CPV *S. pneumoniae* isolates were resistant to ceftriaxone compared to 25% in the post-CPV era ($p = .18$). In the post-CPV era vs pre-CPV era, treating clinicians were more likely to choose empiric parenteral combination therapy with ceftriaxone (38% vs 6%, $p < .0001$). **Conclusion:** In this post-CPV era and in chronic mastoiditis, clinicians must consider choosing broader-spectrum initial antibiotic coverage than ceftriaxone alone.

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INHIBITING GLUCONEOGENESIS PREVENTS THE EFFECTS OF FREE FATTY ACIDS ON GLUCOSE EFFECTIVENESS. S. Koppaka, D.E. Lee, P. Kishore, J. Tonelli, M. Hawkins, Albert Einstein College of Medicine, Bronx, NY.

Glucose effectiveness, the ability of hyperglycemia to suppress endogenous glucose production (EGP), is lost in type 2 diabetes mellitus (T2DM). Free fatty acids (FFA) modulate the effectiveness of glucose to suppress EGP, and increased FFA contribute importantly to the loss of glucose effectiveness in T2DM. Elevating FFA levels in nondiabetic subjects increases gluconeogenesis (GNG) and impairs glucose effectiveness. However, inhibiting GNG alone does not decrease EGP under normoglycemic conditions because of compensatory increases in glycogenolysis (autoregulation). Since hyperglycemia inhibits glycogenolysis, we hypothesized that inhibiting GNG in the presence of hyperglycemia would decrease EGP and prevent the negative impact of FFA on glucose effectiveness. To determine the impact of inhibiting GNG in the presence of elevated FFA, EGP ([3–3H]-glucose) was measured during three separate 7h normoglycemic/hyperglycemic 'pancreatic clamp' studies in $n = 7$ nondiabetic subjects (1F/6M; age = 45 6 5 years; BMI = 28 6 3.0 kg/m^2). Following an initial 210-minute interval of euglycemia (5 mM), blood glucose levels were raised to hyperglycemic levels (10 mM) from $t = 210$–420 minutes. The first pancreatic clamp study was a baseline study with saline infusions (Lip2/Et2) in which hyperglycemia suppressed EGP by 61%. Lipid emulsion (Liposyn 20%) was infused throughout the second and third study types (Lip+ and Lip+/Et+) to increase FFA to T2DM levels (≈500 mM). After raising plasma FFA to T2DM levels, suppression of EGP by hyperglycemia was impaired in Lip+ (34% suppression) and rates of GNG increased by 67% to 1.49 6 0.14 mg/kg.min ($p = .03$). In addition to Liposyn, ethanol (Et) was infused during hyperglycemia in the third study type (Lip+/Et+) to rapidly inhibit GNG (measured by deuterated water) by {223}80%. GNG inhibition significantly enhanced suppression of EGP by hyperglycemia (65.8% decrease, $p = .004$ vs Lip+) and thus restored glucose effectiveness ($p = .6$ vs Lip2/Et2). We conclude that increased FFA impair the ability of glucose to suppress EGP in large part due to FFA-induced stimulation of GNG. Inhibiting GNG with ethanol restored glucose effectiveness despite increases in FFA up to T2DM levels. Thus, inhibiting GNG is a potential approach to regulate glucose production in T2DM.