Course Format (3 hours/week, 13 weeks):
70% Didactic lectures
30% Interactive presentation of medically related topics (see appended topic list)

Weighting of Course Metrics:
Midterm: 30%
Assignment 1: 15%
Assignment 2: 15%
Final: 40%

Course Units:
OXYGEN AND THE BIOCHEMISTRY OF CELLULAR STRESS: ECTOPIC MODIFIERS OF OXYGEN TRANSPORT AND DELIVERY (4 hours)
- Review properties of hemoglobin, myoglobin and oxygen delivery
- Erythrocyte development and the biochemistry of heme: genesis, distribution, destruction, re-utilization, clinically useful indicators
- Biochemistry of redox energy metabolism in vascular (and other) systems (sites, synthesis and properties of mammalian redox species, Pentose monophosphate shunt, consequence to erythrocyte function and oxygen delivery)
- Endogenous regulators of redox stress (synthesis, catabolism, and actions of Glutathione, Catalase, SOD1 and Nrf2; direct and indirect actions in drug detoxification - paracetamol)
- Exogenous toxicants / drugs which modify erythrocyte function (ROS-generating drugs; cyanide, carbon monoxide and methemoglobinemia; Favism; drug-induced hemolytic anemia, Malaria biochemistry)
- Genetic modifiers of redox stress / erythrocyte function (G6PD deficiency, Sickle cell anemia, biochemistry, thalassaemias)

IRON HOMEOSTASIS, TRANSPORT AND TOXICITY: TREATMENTS OF ANEMIA (4 hours)
- Biochemistry of iron (uptake, export and homeostatic regulation, intracellular transport and conversion, iron storage, ferroreductases, DcytB, Ferritin, hepcidin, ferroprotin, hephaestin)
- Iron distribution in the body (molecular biology of iron signaling - transferrin, clatherin mediated cycling of the transferrin receptor, reciprocal control of ferritin and transferrin receptor etc.)
- Causes of iron deficiency (dietary and drug induced) and anemias (major classes)
- Medical conditions and drugs which they alter iron uptake / distribution
- Clinical indicators of iron, diagnostic criteria used to identify class and type of iron deficiency
- Iron supplementation (dietary, pharmaceutic, drug interactions)
- Iron overload (environmental, clinical, drug induced, genetic) early indications and mechanisms of iron toxicity. Therapeutic approaches to iron overload.

BIOCHEMISTRY OF ONE CARBON METABOLISM (3 hours)
- Folic acid: sources, synthesis and mechanisms of deficiency and clinical pathology (environmental and drug-based)
-Biochemistry of tetrahydrofolate (THF): absorption, distribution, metabolic isoforms
-THF cycle I: purine biosynthesis and catabolism
-THF: Chemotherapeutic drugs and mechanisms in 1C metabolism
-THF II and III: The remethylation cycle, transport of 1C units from amino acids, critical role of B vitamins in 1C metabolism, S-adenosyl methionine (SAM) cycle
-Regulation of THF cycles (Methionine synthase and the folate trap)
-DNA methylation and cancer, genetic derangements of one carbon metabolism
-Vitamin B12: synthesis, mechanisms of absorption and distribution, clinical pathology of B12 deficiency and its treatment

INTRODUCTION TO IMMUNOLOGY AND IMMUNE DRUGS (4 hours)
Overview of the immune system, organs and cells of immune function, development of immune response (classical studies), innate versus acquired immunity
-Mechanisms and classes of immune function: The T-cell receptor, T cell sub-classes and function; B cells – immunoglobulin function; proliferation, selection, deletion and anergy of immune cells
-Common immunodeficiency syndromes
-Introduction to transplantation, biochemistry of immunosuppressive drugs (calcineurin, cyclosporin, mTOR, steroid-mediated)
-Network derangements (cellular) in autoimmunity

MOLECULAR MECHANISMS OF WHITE BLOOD CELLS (3 hours)
-Neutrophils, eosinophils and chemical warfare
NADPH oxidase (Nox) activation, myeloperoxidase, drug induced hepatic neutrophil infiltration, inflammatory liver injury. Inflammatory mediators and inhibitors.
Inflamasosomes, Autoimmunity diagnosis using anti-neutrophil cytoplasmic antibodies (ANCA c,p,x).
-Autoimmunity: Role of Macrophages, Kupffer cells, Lymphocytes
-Autoimmunity problems e.g. penicillamine
-Autoimmune disease treatment :: corticosteroids, alkylating cytostatic drugs, antimetabolites, antimacrophage therapy, anticytokine antibody therapy.
-Idiosyncratic drug toxicity mechanisms
Liver toxicity, skin rash, agranulocytosis, bone marrow toxicity. Immune molecular mechanisms contributing to idiosyncratic drug toxicity. Reactive metabolites, Hapten theory, Danger signals released by immune cells, Animal models for idiosyncratic drug toxicity.
-Leukocytes and leukotriene formation: eosinophils and asthma

INTERMEDIARY METABOLISM OF WHITE BLOOD CELLS (3 hours)
-Leukocytes classes, Macrophages, Eosinophils: Chemical Warfare
-Leukocyte modifiers of migration and inflammation: cytokines and interferons, and pharmaceutical modification
-Molecular mechanisms of leukocyte function
-Genetic diseases e.g., CGD disease
-Cell adhesion molecules in inflammatory disease, drugs and inflammatory disease
-Macrophages: function, growth factors and cytokines:
Multiple organ failure, ARDS, sepsis, Macrophage-induced tissue injury.
- Rheumatoid arthritis and therapeutics
- Endothelial and Smooth Muscle Cells
- Cell death and inflammation signaling
  Cytokines, NFκB and TNF signalling, organ failure

**FATTY ACID OXIDATION AND METABOLISM (3 hours)**
- Arachidonic acid metabolism (platelets, influence of nutrition on AA and PHS,
  Prostaglandins and heart disease; COX inhibitors and NSAIDs.
- Endothelial cells: Prostacyclin formation, Angiotensin
- Biochemistry of clotting (homeostatic and pathologic – stroke)
  Plasminogen activator, vitamin K, anticoagulants
- Pharmacologic management of Ischemic Stroke
- Activation of drugs and carcinogens by prostaglandin synthetase
- Ketogenic diets for epileptic children
- Gluconeogenesis inhibitor drugs, hypoglycemic drugs and the treatment of Type 2
  Diabetes
- Genetic diseases: Mitochondrial myopathies and treatment (mitochondrial medicine)
  Supplement: Carnitine therapy, Drug induced fatty liver, steatohepatitis
  (NASH), alcohol induced hepatitis (ASH).
- Metabolism of monoamines/alcohol/aldehydes
- Genetic diseases: Porphyria, porphyrin toxicity
- Biosynthesis of haem for cytochromes
- Drug induced porphyria
- Hepatic Detoxication of monoamines, alcohols, purines, heme, bilirubin
  Rhabdomyolysis, Kernicterus

**SPECIAL TOPICS IN BIOCHEMISTRY (4 hours)**
**MODULATION OF METABOLISM BY HORMONES AND CALCIUM (1 hour)**
- Role of endothelial cells in regulating blood pressure.
- Biochemistry of smooth muscle contraction, cGMP, Ca^{2+}, cAMP.
- Nitric oxide formation, signaling and toxicity.
- Use of drugs that generate NO.

**UREA CYCLE AND NITROGEN CATABOLISM (1 hour)**
- The Urea Cycle, nitrogen catabolism of amino acids, detoxification of ammonia

**INTERMEDIARY/DRUG METABOLISM: HEPATOCYTES (1 hour)**

**INTERMEDIARY METABOLISM: PEROXISOMES VERSUS CYTOSOL (3 hours)**
- Role of peroxisomes in intermediary metabolism
- Inborn errors of metabolism
- Synthesis and export of uric acid, proteins, cholesterol, steroids
- Nitrogen Catabolism of Nucleic Acids (uric acid excretion)
  a. Role in Ischemic Reperfusion Injury (also heart)
  b. Biochemistry of Gout, Lesch-Nyhan syndrome: Drug treatment
  c. Purine Nucleotide Biosynthesis and N-catabolism to endogenous toxins.
- Drug / Steroid metabolism
- Steroid Synthesis and Metabolism
- Detoxification of Drugs, Steroids and other Physiological Substrates
- Cytochrome P450 Isozymes and polymorphism (Dr. D.H. Grant)
- Pharmacogenomics, Protein Synthesis and Targeting.
- Export of Albumin Transport Proteins and Proteins Involved in Blood Clotting (Fibrinogens, Prothrombin, Factors)
- Biochemistry of antithrombotic drugs

**CHOLESTEROL AND CHOLESTEROL LOWERING DRUGS (2 hours)**
- Synthesis and Export of Cholesterol
- Utilization of cholesterol and fatty acids by extra-hepatic tissues for membrane biosynthesis
- Molecular diseases of cholesterol and lipoproteins
- Mechanism of LDL oxidation in foam cell mediated plaque formation
- Biochemistry of Cholesterol lowering drugs (statins and non-statins)
- Synthesis and function of coenzyme Q

**ENOCRINE BIOCHEMISTRY, DISORDERS OF THE THYROID AND TREATMENTS (3 hours)**
- The thyroid, its interactions and control of metabolism, the biochemistry of iodide
- Biochemistry of the hypothalamic-pituitary axis, actions and regulation
- Thyroid hormones: synthesis, activation and inactivation
- Pharmaceutics and dietary agents which alter thyroid function (adverse)
- Clinical indicators of thyroid function, biochemistry of thyroid pharmaceutics
- Thyroid syndromes: Hyperthyroidism (Graves disease, thyroid cancer, thyroid storm)
- Thyroid syndromes: Hypothyroidism (Hashimoto’s thyroiditis, cretinism)

**BIOCHEMISTRY OF THE CNS: NEUROTRANSMITTERS, MODIFIERS AND MIMICS (3 hours)**
- CNS structure and function, principles of neural processing and neurotransmission, roles of excitation and inhibition (Glutamate, GABA and epilepsy)
- Biochemistry of mood altering substances: CNS stimulants
  - Psychomotor: caffeine, nicotine, cocaine, amphetamine
  - Psychomimetics: LSD, PCP, THC
- Structure function relationships between neurotransmitters and drugs of abuse
- Mechanisms of Anxiolytics (benzodiazepines and non-barbiturate sedatives)
- Mechanisms of Antidepressants (Tricyclics, SSRI’s, MAO inhibitors)
APPENDIX:
Grand rounds group presentation subjects augment specific lecture components. In any given year 48 such presentations are performed. Topic examples follow

Acetaminophen mechanisms
Acyl CoA dehydrogenase
Agranulocytosis (2 drugs)
Alcohol induced hepatitis
Amyloidosis
Amylopectinosis
Angelman syndrome
Anti-malarials (2 drugs)
Arsenic poisoning (mechanism)
Artificial hemoglobins
Aspirin biochemistry
Asthma (2 drug mechanisms)
Autoimmunity: Lupus Erythromatosis
Autoimmunity: macrophages
Autoimmunity: T cells
Autoimmunity: transplantation drugs
B Vitamins (2)
Barbituates, mechanisms of action
Basis of diagnostic blood tests
Basis of Eliza’s
Bilirubin metabolism
Biochemical derangements in hemodialysis
Biochemistry of ABO blood groups
Biochemistry of aging
Biochemistry of hypertensive drugs
Biochemistry of pantothenate
Biochemistry of sulfa Drugs
Bone in acid base homeostasis
Cancer: Two hit hypotheses
Cannabinoids, endogenous and exogenous
Carbohydrate/fat metabolism and weight
Carcinogen formation during high temp. food preparation
Chemically induced autoimmunity
Chemo-preventatives
Coagulation inhibitors
Colon cancer
Coumarin drugs
COX-2 inhibitors
Creatine supplementation
Cyanide poisoning
Diabetes mellitus
Diabetic neuropathy (mechanisms)
Disorders of folate metabolism
Disorders of the Urea cycle
Dopamine and Parkinson's disease
Drug induced anemia (2 mechanisms)
Drug induced Porphyria
Dry beriberi
Duchenne/Becker's muscular dystrophy
Effects of high/low vitamin D
Endogenous Opioids
Endotoxemia and disease
Epilepsy (2 drugs)
Epilepsy and red ragged fibers
Errors of metabolism (glycolysis and TCA cycle)
Estrogen and breast cancer
Erythropoietin and renal disease
Fatty liver and therapy
Folic acid supplementation and interactions
Fructoaldolase deficiency
Fructose intolerance (immunity)
Fructose metabolism (genetic errors)
Fumarase deficiency
Galactosemia
Genetic diseases of mitochondria
Genetics differences in drug metabolism
Glucocorticoids (2 drug modifiers)
Glycation end products
Grapefruit - CYP interactions
Green tea and antioxidants
Hemoglobin adducts
Hemoglobin substitutes
Hemolytic anemia
Hemophilia (2 forms)
Hemophilia A
Hyperbilirubinemia
Hypercholesterolemia
Hyperhomocysteinemia
Hyperlipidemia
Hyperoxaluria type 1 & 2
Hyperuricemia
Infant hypoglycemia
Iron deficiency and pregnancy
Iron loading and liver cancer
Isoniazid biochemistry
Leber's hereditary optic neuropathy
Lesch-Nyhan syndrome
Lipop polysaccharide derangement (Tay Sach's)
Lipid oxidation end products
Lithium biochemistry
Macrophages derangement and atherosclerosis
Malignant hyperthermia
Marrow transplantation (2 drugs)
Mechanisms of drug resistance
Menke’s disease
Metabolic derangements in colorectal cancer
Metabolic disease and NASH
Metabolic syndromes: Blood pressure
Metabolic syndromes: Diabetes
Metabolic syndromes: Obesity
Metabolic syndromes: Stroke
Methemoglobinemia
Methotrexate Therapy
Methoxyestradiol
Methylglyoxal diseases
MPTP and Parkinson’s
Myasthenia gravis
Neimann-Pick disease
Nonketotic hyperglycinemia
NSAIDS and GI toxicity
Nuts and carbonylation
Nuts and cholesterol
Opioids (2 drugs)
Oxidative stress and the environment
Parkinson's Disease (2 drug mechanisms)
Pathogenesis of hepatitis
Pellagra
Pendred syndrome
Peroxisomal errors of metabolism
Phenylketonuria
Pickled pigs
Porphyria (2 isoforms)
Porphyria and hepatotoxicity
Prostagladins
Psoriasis (2 drugs)
Pyruvate kinase mutations
Quinolinic acid
Rhabdomyolitis
Rheumatoid arthritis (2 drugs)
Schizophrenia (2 drugs)
Somogi effect
Statin biochemistry
Steatohepatitis NASH
Stevens Johnson syndrome
Stone disease
Thalassemias
Thalassemia treatment
Thiamine and neuritis
Toxic necrolysis
TPI deficiency
Type-2 diabetes
Tyrosinemia
Uric acid and metabolic disease
Vascular biochemistry of nitric oxide
Vitamin C and the CNS
Vitamin K biochemistry
Wernike-Korsakoff syndrome
Wilson's Disease