Chemical Pathology (Clinical Chemistry): *Rotation Director: Neil S. Harris, M.D., Associate Professor*

1. Description: This rotation consists of one-on-one meetings between the resident and the clinical chemistry attending staff. Usually the resident meets with 2 different staff per day. Each session is ~60 minutes. The purpose of these sessions is to discuss pertinent cases, methodologies, disease states, test ordering and test interpretation. The resident is expected to take part in the consultative activities of the service (e.g., SPE, UPE, IFE). The remainder of the day is dedicated to independent study part of which can be dedicated to a research project or a project oriented towards solving a laboratory problem. As appropriate to the individual case or consultation under review, the ethical, socioeconomic, medicolegal, and cost-containment issues are reviewed and discussed. As well, research design, statistics and critical review of the literature are discussed.

2. Goals: Residents will become familiar with sample procurement, processing, and handling (**pre-analytical** phase of testing); with **analytical** sections (automated general chemistry, urinalysis, electrophoresis, immunoassay, special chemistry); with the **specific tests** performed in each section (basic chemistries, enzymes, proteins, drugs for therapeutic drug monitoring/toxicology, fetal lung maturity tests, amniotic scans, hormones and peptides, hepatitis and HIV, urinalysis, etc); with **regulatory guidelines** including QC/QA, procedure manuals, safety; and management (residents attend regularly scheduled section meetings) and result reporting through MISYS™ (the **post-analytical** phase of testing). The residents are supervised by technical staff and the medical directors. By use of the literature, MEDLINE, and textbooks, the resident is trained to become a lifelong learner.

3. Duration of the rotation: 4 weeks; subsequent exposure to chemistry occurs during the general laboratory rotation.

4. Duties and responsibilities: Residents are assigned a paper (QA, management issues) to review at the clinical chemistry seminar/journal club during the rotation. *Graduated responsibilities:* PGY-1 residents are expected to begin interpreting data and problem solving (interference, drug interactions, etc) under the guidance of technologists, medical directors. PGY-2 residents, under the supervision of the medical directors, participate in the consult services for serum, urine, and CSF electrophoresis, hepatitis testing, HIV testing, that culminates in the generation of a written *report* that directly enters the patient's electronic record.

5. Teaching staff: Neil S. Harris, M.D.; Glen Hortin, M.D.; William E. Winter, M.D.

6. i. **Resident Supervision:** Attendance at Monday morning's CP conference is required. The faculty interacts with the residents during their one-on-one sessions. Any consultative reports that are generated are produced in concert with the attending faculty and signed out by the attending faculty. Calls are discussed and reviewed.

ii. **Resident Evaluation: *Written monthly evaluation***. Evaluation criteria include attendance, degree of preparedness and participation.

Chemical Pathology (Clinical Chemistry) Core Curriculum Subjects

Analytical principles: PGY-1, 2

- Spectrophotometric techniques
  - Spectrophotometer design - light sources, cuvettes, wavelength selection, photomultiplier tubes
  - Dye binding techniques: total protein, albumin, Ca++, Mg++
  - Use of enzymes to measure analytes, e.g., glucose, urea, creatinine, uric acid, cholesterol, triglycerides, etc.
  - Chemical reactions: bilirubin (total and direct)
  - Enzyme measurements: CK, AST, ALT, LD, alkaline phosphatase, amylase, lipase

- Enzyme kinetics
- Direct spectroscopy: Hemoglobin saturation, BU, BC (neonatal bili)
- Fluorometry: FPA
- Atomic absorption and flame photometry

Electrochemistry
- Blood gases: pO2, pCO2, pH
- Electrolytes: Na+, K+, Cl-, CO2, Li++, iCa++, iMg++

Immunoassays
- Precipitin curves
- Ouchterlony double diffusion
- Radial immunodiffusion
- Rocket electrophoresis
- Counter immunoelectrophoresis
- IEP, IFE, western blots
- Nephelometry, turbidimetry
- RIA (competition assays), Immunometric (double antibody) assays (IRMA, ICMA), CEDIA, EMIT, FPIA, FPA, chemiluminescence, electrochemiluminesence

Radioactivity and radiomeasurements
Electrophoresis - serum, urine, CSF
Chromatography (L/S ratio, TLC, HPLC, GC)
Mass spectroscopy applications, tandem mass spectroscopy and GC-MS, LC-MS
Laboratory automation in chemistry: review of all major systems (including dry-slide technology)
Verification of results
Method validation: reproducibility, accuracy, linearity, carry-over, etc.

Laboratory Mathematics and assay assessment: PGY-1, 2

Basic statistics
- Mean, median, mode, SD, parametric distributions, nonparametric distributions

Assay performance
- Sensitivity, specificity, positive predictive value, negative predictive value, efficiency (accuracy)

Linearity: defining the upper linear limit
Defining the lower limit of detection
Determining reference intervals
ROC curves
Run-to-run carry -over

Quality assurance PGY-1, 2

Quality assurance
Quality control: Precision, Accuracy, Westgard rules
Proficiency testing

Management principles PGY-1, 2

Lab licensing
CLIA
Lab certification
Lab billing

Preanalytic variation PGY-1, 2

tubes, fasting v. nonfasting, body position, illness v. health, cyclic variations (AM v. PM, monthly, yearly, light dark)

Principles of therapeutic drug monitoring: PGY-3 , 4

indications for therapeutic drug monitoring, peak, trough, half-life, steady state, therapeutic index

Analytes: understand measurement, preanalytic confounders (e.g., hemolysis and K+), causes of depressed concentrations, causes of elevated concentrations, and diseases where the analyte displays an abnormal concentration or is measured for diagnostic or management purposes

PGY-1 ,2:

Blood gases: pH, pO2, pCO2 (base excess), HCO3-, carboxyhemoglobin, methgb

Electrolytes: Na+, K+, Cl-, CO2 (anion gap), plasma osmolality (*see*: www.osmolality.com)

Energy homeostasis: glucose, lactate, pyruvate, beta-hydroxybutyrate, fructose, galactose, hemoglobin A1c, fructosamine, insulin antibodies and insulin autoantibodies, islet autoantibodies (ICA< GADA, IA-2A, IAA)

Minerals: Ca++ (iCa++), PO4---, Mg++ (iMg++), vitamin D and metabolites

Renal function: Cr, BUN, BUN/Cr ratio, CrCl, eGFR, Fractional excretion of Na+, urinalysis, urine microscopy, urine electrolytes, microalbumin measurement, UPE, urinary nitrogen excretion

Metabolic intermediaries: bilirubin (total and direct), phenylalanine, tyrosine, ammonia, bile acids, uric acid, porphyrins (delta-amino levulonic acid, porphobilinogen, urine porphyrins, free erythrocyte porphyrins, etc.), free fatty acids, 5-hydroxy indoleacetic acid (5-HIAA),

Enzymes (clinical enzymology): AST, ALT, LD (LD isoenzymes), alkaline phosphatase (isoenzymes), GGT, acid phosphatase (PAP), CK, aldolase, lipase, amylase, pseudocholinesterase

Cardiac markers: CK, CK-MB, CK isoforms, myoglobin (nonspecific), troponin I, troponin T, BNP, NT-proBNP

Iron status: serum iron, transferrin/TIBC, ferritin, serum transferrin receptor; biology: ferroportin, DMT-1, hepcidin, hephaestin, etc.

Proteins: SPE, prealbumin, retinol-binding protein, albumin, A-1-AT, TBG, CBG, orosomucoid (a1-acid-glycoprotein), A-2-macroglobulin, haptoglobin, ceruloplasmin, transferrin, hemopexin, immunoglobulins
Other proteins: C-reactive protein, fibrinogen, beta-2-microglobulin, serum amyloid A (SAA)

Immunologic procedures: IFE, IEP, IEF, 2-D gel electrophoresis

Immunoproteins: C3, C4, complement cascade, IgG, IgM, IgA, IgD, IgE, IgG subclasses

Lipids: cholesterol, triglycerides, apolipoproteins (apo A1, apo B, apo CII, apo E), HDL, LDL, VLDL, IDL, chylomicrons, Lp(a), Lp(X), LPE, ultracentrifugation, Friedewald equation, Frederickson classification, NCEP cutpoints, hsCRP, homocysteine

Hormones and binding proteins:

Beta cell: insulin, C-peptide, proinsulin, IAPP (amylin)
Alpha cell: glucagon
Delta cell: somatostatin
PP cell: pancreatic polypeptide
Parathyroid gland: intact PTH (Ca++, PO4---, Mg++) versus true-intact, bio-active, cyclase-activating PTH
C-cells: calcitonin
Thyroid: T4, unbound T4, T3, unbound T3, rT3, TSH, TBG, TBPA (transthyretin), T-uptake, T3-resin uptake, albumin, thyroglobulin, thyroid microsomal autoantibodies, thyroperoxidase autoantibodies, thyroglobulin autoantibodies, thyroglobulin, calcitonin

Adrenal cortex: cortisol, transcortin (CBG), aldosterone, DHEA and androstenedione, ACTH, CRH, 17-ketosteroids, 17-ketogenic steroids, 17-hydroxycorticosteroids (adrenal hypo and hyper function and endocrine hypertension)
Mineralocorticoid control: renin, angiotensinogen, angiotensin I, angiotensin II
Adrenal medulla: dopamine, HVA, norepinephrine, epinephrine, metanephrines, VMA, urine v. plasma assays, plasma free metanephrine
GH axis: GH, IGF-1, ALS, GHRH, somatostatin
Prolactin
Gonads: GnRH, LH, FSH, sex steroids (estrone, estradiol, estriol, testosterone, unbound testosterone, loosely-bound testosterone, dihydrotestosterone, inhibins)
Other hormones and hormone systems
Anti-diuretic hormone (ADH) and water balance
Oxytocin
hCG and pregnancy
Gastrin
VIP (vasoactive intestinal polypeptide)
Note: understand all common hormone stimulation and suppression tests, e.g., ACTH stimulation test (1 hour and variations), overnight dexamethasone suppression test, low dose/high dose dexamethasone suppression test, metyrapone test, insulin tolerance test, arginine tolerance test, GH stimulation and suppression tests, calcitonin stimulation testing, GnRH test, IPSS testing, OGTT

Body fluids:
Transudate v. exudate
Chylous effusions
CSF: electrophoresis, glucose, protein, cell counts, myelin basic protein, oligoclonal bands, CSF-transferrin
Fecal fatty (24 hour)
Fetal lung maturity testing: FLM, PG, L/S ratio, lamellar body counts

PGY-3, 4

Amino acids: inborn errors of metabolism: plasma/serum amino acids, urine organic acids, carnitine, long chain fatty acids

Bone markers: bone-specific alkaline phosphatase, osteocalcin, urinary hydroxyproline, N-telopeptides, C-telopeptides, pyridinium crosslinks: pyridinoline, deoxypyridinoline

Tumor markers
PSA, free PSA, CEA, AFP, hCG, beta-hCG, CA125, CA19-9, CA15-3, estrogen and progesterone receptor measurements

Therapeutic drug monitoring

Acetaminophen, salicylates, Theophylline, dilantin, phenobarbital, primidone, carbamazepine (Tegritol), clonazepam, ethosuximide, valproic acid, Li++, cyclosporin A, FK506 (tacrolimus), digoxin, quinidine, procainamide, NAPA, lidocaine, amikacin, gentamicin, kanamycin, tobramycin, vancomycin, methotrexate

Toxicology testing

Cocaine, opiates (natural: codeine, morphine), synthetic and semi-synthetic opiates, barbiturates, benzodiazepines, alcohol, non-ethanol alcohols (osmolal gap), phencyclidine (PCP), LSD, GHB, hallucinogens, amphetamines, meperidine, methadone, EMITS, tox-lab TLC testing,
Heavy metals: aluminum, cadmium, lead, arsenic, chromium, cobalt, copper, nickel, mercury, thallium

Viral serologies:

HAVAb, HACAb-IGM, HBsAg, HBsAb, HBeAg, HBcAb-IgM, HBcAb, HBeAb, HCV Ab, HDV Ab, HDV Ab-IgM, RIBA, HIV EIA, HIB WB.

Vitamins: 25-hydroxyvitamin D, vitamin B12, folate, RBC folate, vitamin C, carotene, vitamin A

REFERENCES

1. *Quick Compendium of Clinical Pathology* 2nd Edition 2008. Mais DD. American Society for Clinical Pathology
2. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 21st Edition 2007 McPherson RA, Pincus MR.(Eds) Saunders/Elsevier
3. *Tietz Textbook Of Clinical Chemistry and Molecular Diagnostics*. 4th Edition 2005. Burtis CA, Ashwood ER and Bruns DE. (Eds) Saunders/Elsevier