

## **A short history of the Endocrine Laboratory at the William Pepper Laboratories, University of Pennsylvania Medical Center, Philadelphia, PA**

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### **The early years and the era of mice, solvents and isotopic labels**

The Endocrine Lab at William Pepper Laboratories was established in 1947 on the 9<sup>th</sup> Floor of the Maloney Building at HUP under the direction of F. Curtis Dohan, MD (1907 – 1991)(1,2). The laboratory at that time was one of only five Clinical Endocrine Laboratories in the United States. Dr. Dohan was Chief of the Endocrine Section until 1966, when Donald McEvoy, a PhD from England, became director, and he was instrumental in the development and introduction of many new endocrine methods.

The first members of the laboratory were Helen Bolashenko (known as Mrs. B), a clinical chemist who earned her MS in Russia, Tamara Kolenchenko (known as Mrs. K), an MD from the Ukraine, and Sonia Levkovich, a medical school student who was forced to leave Russia during the early 1950s.

The Endocrine Lab was moved to 7 Gates West during September, 1967. Soon after, Mary Jo Martin became supervisor of the laboratory and worked with Dr. McEvoy. At that time two additional technicians were hired to perform manual endocrine tests. Examples of the manual methods in use at that time are listed below. None of these methods survive to the current day, all having been replaced by quicker, and more sensitive non-isotopic immunoassays.

## Assays and methods in the Endocrine Laboratory in the 1950s and 1960s

Analyte	Method
plasma cortisol	Radio-assay – cortisol binding globulin (CBG) as binder and a tritium label
vitamin B12	Radio-assay – trans-cobalamin as binder and a Co <sup>57</sup> label
serum folate	Microbiological method
protein bound iodine (PBI)	Wet ash colorimetric technique
urinary estriol	Solvent extraction and colorimetric analysis
urine hCG	Hemagglutination-inhibition slide test
urine aldosterone	Solvent extraction followed by 3 paper chromatography steps with Blue Tetrazolium dye for final qualitative determination
urinary pituitary gonadotropins	Semi-quantitative method based on examination of ovaries of female mice

In 1972, Gerry Knee became supervisor of the laboratory with the departures of Dr. McEvoy and Mary Jo. Dr. Dean Arvan, Director of the Chemistry Laboratory, became interim director until John Pegg, MD, PhD who specialized in Endocrinology, became director for the next several years. During this period many of the endocrine methods were replaced by radioimmunoassay, and this technology offered significant improvement for ligand sensitivity and specificity.

In ~ 1979 the Endocrine Lab took over the estrogen and progesterone receptor assays from the “Proteins” lab, which was part of the Immunology section on 6 Gates. Marilyn Senior, PhD was hired to oversee (and perform) these assays. When the main Endocrine Lab moved to 7 Gates East (1980/1981) the receptor staff moved back into the Lab. Prior to 1979, the Endocrine Lab had started hepatitis testing (this necessitated a flow hood) and when the Endocrine Lab moved to 7 Maloney the small room adjacent to the laboratory was fitted with a hood, and the hepatitis testing finally was co-located with the rest of the Endocrine Lab.

**Directors and Laboratory Managers/Supervisors of the Endocrine Laboratory**

<i>Year</i>	<i>Director</i>	<i>Year</i>	<i>Manager/Supervisor</i>
1947-66	F Curtis Dohan		
1966-72	McEvoy		
1972-	Dean Arvan*	1972-88	Gerry Knee
-	John Pegg		
1981-86	Jerome Strauss, III		
1986	Anthony Jennings		
1987-03	David B P Goodman		
		1988-2012	Marilyn Senior
2003	Donald S Young*		
2003-04	Amin Nanji		
2004	Donald S Young*		
2005-14	Stephen R Master		
		2012-14	David Cardamone
2014-15	Larry J Kricka*		
		2015-	Nichole Rulander

\* *Acting/Interim Director*

The laboratory was moved again to 7 Maloney in ~1981 at which time Jerome Strauss, III, MD, PhD accepted the directorship (3). He had a 30% appointment at the William

Pepper Laboratory and the remainder of his time was with the OB/Gyn department. HUP's IVF Program started shortly afterwards, and the Endocrine Lab played a significant role for the success of the program by offering daily estradiol (E2) to monitor ovarian hyper-stimulation. Dr. Strauss's contributions were important in shaping the future of the laboratory. He was director for ~5 years and stepped-down in order to lead the University of Pennsylvania's MD/PhD Program. Subsequently, he became the Dean of Virginia Commonwealth School of Medicine in 2005.

Dr. Anthony Jennings, an Endocrinologist at HUP, became acting director for a short time before Dr. David Goodman (1943-2003)(4) became director of the Endocrine Lab around 1987 and Dr Marilyn Senior became Technical Manager following Gerry Knee's departure in 1988. Shortly afterwards, the Endocrine Lab moved again (together with the receptors and hepatitis testing) this time to new space on the 7<sup>th</sup> floor of the Founders Pavilion. However, the hepatitis testing was again separated from the main Endocrine Lab - it was located down the hall in the Microbiology research area.

### **Non-isotopic immunoassay and automation**

In the mid-1980s, the Endocrine Lab instituted HIV testing, along with the Western blot confirmation (homemade blots - exciting days! – subsequently replaced by the Bio-Rad commercially available Western Blot, and then in 2012 by the Bio-Rad Multispot HIV1/HIV2 rapid test). The new HIV screen was based on an EIA, not an RIA method, and so the hepatitis testing was also moved to the EIA format. The Endocrine Lab had been attempting to move away from radioactivity, but it was difficult, since the RIA tests performed, for the most part, better than the early EIAs. Of course, at that time no manufacturer wanted to automate RIA, so the introduction of other methods was inevitable.

Although the Endocrine Lab had an automated Tecan pipettor to help with the approximately 80-100 T<sub>4</sub>, T<sub>3</sub>-uptake, and 50-60 TSH assays/day, these were still RIA methods. The Lab's first automated EIA instrument was the Abbott IMx, and this was used to perform hCG assays. Interestingly, the Endocrine Lab was presented with a

plaque by Abbott for helping to introduce the IMx to the Philadelphia market. There was also another IMx in the Stat Laboratory, and it was used for the off-hours stat hCG testing. These instruments were replaced by DPC Immulite-1 after Abbott's hCG problem on the IMx.

Subsequently, a variety of small, automated instruments were introduced for various assays, including a Hybritech analyzer for CEA and PSA and a Tosoh AIA 1200 analyzer for CEA and PSA testing. The Endocrine Lab's first large automated analyzer was the Corning ACS 180 and this was used for thyroid tests, and several other high volume tests. The ACS180 automated the chemiluminescence immunoassays (acridinium ester label) but it was prone to mechanical problems and had reagent inconsistency issues. Consequently, this was replaced with Bayer Immuno 1 analyzers. These instruments automated an EIA with a colorimetric end-point, and the precision for the sandwich assays was far superior to that seen with the ACS-180s, however, the competitive assays were, as usual, problematic.

In the meantime, new and better assays had been developed for the estrogen and progesterone receptors, which could be performed in Anatomic Pathology on tissue that could be verified to be the tumor. The Endocrine Lab gladly relinquished the receptor assays to Anatomic Pathology. Assays for HIV and HCV virus quantitation filled the void left by the departure of the receptor assays.

In ~1997, plans for the new fully automated laboratory on 7 Founders, the "Autolab", were being finalized, and the 7 Founders space occupied by the Endocrine Lab had to be vacated. So, the Endocrine Lab moved again, back home to 7 Gates East. The hepatitis testing remained in 7 Founders and viral quantitation was transferred to the Molecular Pathology Laboratory.

When the Autolab became fully operational, the high volume immunoassays (e.g., thyroid function tests, cortisol, ferritin, PSA) on the Immuno-1 analyzers were moved to the Autolab. This was not entirely successful, since the Immuno-1s required a substantial amount of maintenance and checking of results, and this did not fit into a high volume fully automated Autolab environment. After an extensive search, the

Immuno-1 analyzers were replaced by DPC Immulite 2000 analyzers. These instruments had many more safety nets for the operator, and the precision was good for the most part (except for the competitive assays!). The Endocrine Lab retained an Immuno-1 analyzer for reproductive hormone testing, but at this point replaced it with another Immulite 2000 analyzer in order to meet the projected testing workload. Subsequently, a Roche 2010 analyzer joined the growing ranks of automated analyzers in the Endocrine Lab. Finally, the Endocrine Lab was beguiled by the Ortho 3600 for automating all of the hepatitis tests and the HIV assay. Although the instrument performed adequately, the reagents were very inconsistent in performance. Subsequently, in 2014, the infectious disease testing was transferred from the Ortho 3600 to a free-standing Abbott Architect i2000 located in the Autolab.

In ~2009, the Immulite 2000 analyzers in the Autolab were replaced by Roche E170 analyzers, and subsequently these were attached to the track in the Autolab. At the same time stat testing (CK-MB, BMP, hCG, cardiac troponin T) was transferred to a Roche e411 in the Autolab. This analyzer replaced an Abbott AxSym analyzer which had been used for stat immunoassays in the Autolab.

Intra-operative PTH assays were introduced in the late 1990s and the test volume was initially projected to be about 10 per year, a volume that could be easily incorporated into the Endocrine Lab's workload if advanced notice that there would be a surgery was provided. Shortly thereafter, with the arrival of Dr. Fraker, the volume increased to 2-12 per week! Eventually the IO-PTH testing (Immulite 1000 analyzer) was moved to the PCAM lab, so as to be closer to the patients.

In the early 2000s, HBA1c had become a high volume assay. The method in use in the Autolab required a pre-dilution, and this was inconvenient and slowed down the reporting of test results. Consequently, a more efficient method, an ion-exchange HPLC method (BioRad) was introduced and located in the Endocrine Lab. This method was replaced by an affinity HPLC method (Primus) a few years later.

Following Dr Goodman's death, Donald Young, MD took over as acting director until Amin A Nanji, PhD was appointed director, but he departed for a new position at the

Dalhousie University School of Medicine in Canada after ~18 months, and once again, Dr. Young became the acting director. Stephen Master, MD, PhD became Director in 2005 and subsequently left to become the Director, Central Laboratory and Chief, Clinical Chemistry at Cornell Weil Medical College in New York, NY (5). Larry Kricka, DPhil replaced him and served as the interim Director from 2014-2015.

As of 2015, the following analyzers are in use in the Endocrinology Laboratory: *Roche e601* – (electrochemiluminescence immunoassay; ruthenium label); *Immulite 2000* (ELISA, alkaline phosphatase label and chemiluminescent detection with a dioxetane substrate); *Beckman Access II* (ELISA, alkaline phosphatase label and chemiluminescent detection with a dioxetane substrate); *Primus Ultra 2* -(boronate affinity chromatography for HbA1c); *BioRad Multispot* (ImmunoConcentration method on a disposable cartridge for HIV confirmatory testing). A trend in the 2000s has been to move high volume testing from the Endocrinology laboratory to the Autolab (e.g., thyrotropin (TSH), thyroxine, triiodothyronine were moved onto the Roche E170 in the Autolab in ~2009). Subsequently, infectious disease testing was also moved from the Endocrinology laboratory to the Autolab onto the newly acquired Abbott Architect i2000 (chemiluminescent microparticle immunoassay, acridinium ester label).

### **Special clinical services**

Endocrinology Laboratory also provides a number of special clinical services and these include (i) intra-operative-PTH (performed in the PCAM laboratory on an Immulite 1000 analyzer), (ii) intra-operative-cortisol (performed in the Endo Lab on the Roche e601 analyzer), (iii) Quad screening and neural tube defect screening (the Endo Lab performs the Quad screen (AFP, hCG, Inhibin A, unconjugated estriol) and uses the Maciel Multiple Marker Program to assess risk; (iv) Occupational Exposure Profiles to assess occupational exposure to infectious agents (HIV Ag/Ab, Anti-HCV, and HBsAgQu tests plus confirmatory testing) and stat HIV Ag/Ab testing for Labor and Delivery; (v) Customized anti-allergen IgE testing for a panel of antigens based on regional specific flora and fauna.

The next major challenge for the laboratory will be the planned move to 7 Founders in 2015.

In addition to their high competence in their work, diligence, and concern for our patients, the members of the Endo Lab have enjoyed and continue to enjoy a well-deserved reputation for gastronomic discernment. Frequent among their celebratory repasts are gourmet cheeses, cakes, tarts, crisps, summer puddings, cronuts, chocolate-covered bacon, and ethnic food and delicacies of all sorts!

## References

1. [http://articles.philly.com/1991-11-14/news/25769226\\_1\\_medical-researcher-medical-school-medical-college](http://articles.philly.com/1991-11-14/news/25769226_1_medical-researcher-medical-school-medical-college)

2. F. Curtis Dohan. [http://en.wikipedia.org/wiki/F.\\_Curtis\\_Dohan](http://en.wikipedia.org/wiki/F._Curtis_Dohan)

3. Jerome F Strauss III, MD, Ph.D.

<https://endo.confex.com/endo/2015endo/webprogram/Person1472.html>

4. David Goodman, researcher. [http://articles.philly.com/2003-02-20/news/25449736\\_1\\_research-medicine-endocrinology](http://articles.philly.com/2003-02-20/news/25449736_1_research-medicine-endocrinology)

5. Welcome to Stephen Master, MD, PhD, appointed as Director, Central Laboratory and Chief, Clinical Chemistry. <http://cornellpathology.com/about-us/cornell-pathology/news/department-welcomes-stephen-master-md-phd-recently-appointed>