ANNUAL REPORT
2007/2008

THE HESS. B AND DIANE FINESTONE LABORATORY IN MEMORY OF JACOB AND JENNY FINESTONE
http://www.mcgill.ca/finestone

Submitted by: Dr. David S. Rosenblatt
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MEMBERSHIP

PHYSICIANS AND SCIENTISTS
Ken Dewar
Eleanor Elstein
William D. Foulkes
T. Mary Fujiwara
Brian M. Gilfix
Tomi Pastinen

Kenneth Morgan
David S. Rosenblatt
Marc Tischkowitz
Patricia N. Tonin
David Watkins

ADMINISTRATION
Maryse Bibeau
Jenny Koulis
Maria Fiorito
Vanessa Flannery
Claire Goguen

Razia Chanda
Morgen Patterson
Danielle Veyre
Anna Wong
Laura Benner

CLINICAL SUPPORT STAFF
Jyoti Chandok
Suzanne Dufrasne
Jennifer Fitzpatrick
Stephanie Fox
Maria Galvez
Lidia Kasprzak

Maria Lalous (mat leave Dec/06)
Jocelyne Lavallée
Laura Palma
Laura Robb
Nora Wong
Sonya Zaor

RESEARCH SUPPORT STAFF
Suzanna Arcand
Joana Dias
Danielle Frappier
Nancy Hamel
Lili Li
I-Ching Lu

Kevin McKee
Carly Pouchet
Nicole Roslin
Nelly Sabbaghian
Zhen Shen, MD
Jessica Wasserscheid

POST-DOCTORAL FELLOWS/CLINICAL FELLOWS
Yohan Bosse
Phillippe Campeau, MD
Luca Cavallone
Long-Qi Chen
Patrick Dion
Nicholas Dupre
Li Fan
Vincenzo Forgetta
Claudia Gaspar
Karen Gambaro

Fabrice Larribe
Richard Le Blanc
Emmanuel Mongin
Laura Oksanen
Matthew Oughton
Michael Quinn
David Serre
André Toulous
Ahmet Yilmaz
GRADUATE STUDENTS
Natascia Anastasio
Faith Au-Yeung
Amanpreet Badhwar
Ashley Birch
Neal Cody
Patrick Cossette
Daniel Darmond
Adrian Diaz
Qingling Duan
Julie Gauthier
Abigail Gradinger
Heidi Howard
Margaret Illson
Tamya Khalil
Kathleen Klein
Peter Lee
Jordan Lerner-Ellis
Junhui Liu
Anastasia Levechenko
Amanda Loewy
Alexandre Marcil
Christiane Messaed
Emily Moras
Emil Nashi
David Novak
Nicole Palmour
Guillaume Pare
Isabelle Racine-Miousse
Vanessa Rossiny
Saravanan Sundararajan
Paulina Wojnarowicz
Lama Yamani

SUMMER STUDENTS
Maeve Bonner

INDEPENDENT STUDIES STUDENTS
Joanna Grater
Carter Li
Fei Li
Emily Brown
Marie Caudrelier
The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone promote the field of medical genetics at McGill University. Dr. David S. Rosenblatt has been Director of the laboratory since its inception. The laboratory was established with the help of an endowment to McGill University and funding is used to advance the academic goals of the Division of Medical Genetics in the Department of Medicine of the McGill University Health Centre (MUHC). As such, this report also serves as the Annual Report of the Division of Medical Genetics of the Department of Medicine of the MUHC. It is available on the Internet (http://www.mcgill.ca/finestone). Since the University Division in Medicine also has included the Division at the Jewish General Hospital, this report also encompasses parts of that activity.

Highlights: Research

Dr. David Rosenblatt and his collaborators have also shown that mutations in the MMADHC gene are responsible for the cblD inborn error of vitamin B12 metabolism. These findings were published in the New England Journal of Medicine.

Dr. William Foulkes and Dr. Marc Tischkowitz have continued to explore the role of PALB2 in breast cancer. They identified and characterized a novel founder mutation, Q775X, in PALB2, that accounts for a small fraction of breast cancer occurring in French Canadian women. The work was published in Breast Cancer Research (doi:10.1186/bcr1828). Studies to understand the function of this and other mutations are underway.

Dr. Patricia Tonin developed a derivative ovarian cancer cell line though the transfer of chromosome 3 fragments, using a novel modification of an established technique involving whole chromosome transfer. This cell line is being used to identify the underlying chromosome 3p gene(s) involved in tumour suppression.

Highlights: Awards

Dr. Ken Dewar has been appointed Acting Director of the McGill University-Genome Quebec Innovation Centre and promoted to the rank of Associate Professor with tenure at McGill.

Dr. William Foulkes continues to hold a highly competitive Chercheur National Award from the FRSQ.

Dr. Marc Tischkowitz holds a Chercheur Clinicien Award from the FRSQ.

Highlights: Teaching

In the area of professional training, the Department of Human Genetics at McGill has the responsibility for the teaching of Medical Genetics to undergraduate medical students and for residency training in Medical Genetics. McGill has training programs that are certified by the Royal College of Physicians and Surgeons of Canada (RCPSC) and by the Canadian College of Medical Geneticists (CCMG). The M.Sc. program in Genetic Counselling achieved recertification by the American Board of Genetic Counsellors (ABGC). It should be noted that
much of the teaching in the professional programs is done by faculty members, who are primary employees of the teaching hospitals, or by physicians with heavy clinical responsibilities. They give generously of their time and energy to ensure the high quality of these programs.

There are 8 medical genetics residents in the RCPSC training program, 1 in the CCMG molecular training program and 1 in the CCMG clinical genetics-training program (see page 15). In the past year, Dr. Phillipe Campeau has successfully passed the examination in Medical Genetics of the Royal College and Physicians of Canada. In September 2008, he plans to continue fellowship training at Baylor College in Houston. Dr. Nicholas Ah Mew has spent the last academic year in China and will be continuing fellowship training at the National Children’s Hospital in Washington. There are 8 M.Sc. Genetic Counselling students in the ABGC accredited M.Sc. in Genetic Counselling training program.

WILLIAM FOULKES

516 – 614B  Environmental Carcinogenesis
Department: Medicine (Div. Experimental Medicine)
Format: Lecture
Title: Cancer Genetics/Prevention
Role: Lecturer
Level: MSc program
Time (hr/yr): One two-hour session

516–0635D  Experimental and Clinical Oncology
Format: Lecture
Title: Cancer Genetics
Role: Lecturer
Level: MSc program
Time (hr/yr): 1.5-hour seminar

521-690B  Inherited Cancer Syndromes
Department: Department of Human Genetics
Format: Lecture
Title: Cancer Genetics
Role: Lecturer
Level: MSc program
Time (hr/yr): Four two-hour sessions

Unit 8 small group teaching in medical genetics
Role: Lecturer
Level: Medical students
Format: One 2 hour lecture and 4 small groups sessions, 2 hours each
DAVID ROSENBLATT

Biology 575
Department: Biology/Human Genetics
Format: Lecture
Title: *Inborn Errors of Folate and Cobalamin Transport and Metabolism*
Role: Lecturer and Course Co-ordinator
Level: Undergraduate/Graduate
Time: 6 hours

Unit 8
Department: Human Genetics
Format: Lecture and Small Group Teaching
Role: Lecturer-2 sessions; Small Group Leader
Title: *Introduction to Medical Genetics*
Huntington Disease
Level: Medical Students
Time: 2 lectures plus 5 2-hour sessions, twelve hours in total

MARC TISCHKOWITZ

HGEN 690
Department: Human Genetics
Format: Lecture and student presentations
Title: *Cancer Genetics*
Role: Lecturer
Level: MSc program
Time: 2 x three-hour sessions

HGEN 692
Department: Human Genetics
Format: Lecture
Title: *DNA repair and pediatric cancer syndromes*
*Adult cancer predisposition syndromes*
Role: Lecturer
Level: MSc program
Time: 2 x two-hour sessions

516 – 614B Environmental Carcinogenesis
Department: Medicine (Div. Experimental Medicine)
Format: Lecture
Title: *It's a dangerous world out there: DNA repair and environmental toxins*
Role: Lecturer
Level: MSc program
Time: One two-hour session
Highlights: Clinical

The McGill University Health Centre created a hospital Department of Medical Genetics in 2007 and recruited Dr. Teresa Costa to be its first head. It is hoped that the creation of this department will lead to major role for Medical Genetics within the anticipated new MUHC hospital complex. The creation of the MUHC Department was not easy and took many years to accomplish. The first year since its creation has not been an easy one because to date, the MUHC has not clarified the administrative structure, nor infused sufficient resources to assure that it will be a success. Nonetheless, its creation was an important first and necessary step.

The Department of Medical Genetics at the Jewish General Hospital, under the directorship of Dr. David Rosenblatt, has defined its major areas as those of cancer genetics and prenatal diagnosis. In this regard, the Cancer Genetics Program, jointly based at the Jewish General Hospital and the MUHC and also housed jointly in the McGill Departments of Human Genetics and Oncology, received the highest rating by the Quebec Program in the Fight against Cancer - the only cancer genetics program in the province to earn this rating. This program is headed by Dr. William Foulkes and consists of Dr. Marc Tischkowitz, genetic counselors Nora Wong and Sonya Zaor at the JGH, and Lidia Kasprzak and Laura Palma at the MUHC.

In keeping with the new RUIS structure mandated by the Government of Quebec, a provincial committee and a local McGill committee have been established to examine how to best serve the interest of the Quebec population in the area of Medical Genetics. These two committees have begun to address issues such as manpower for health services in genetics, screening for Down Syndrome, newborn screening, and the availability of genetic testing.
Clinical Statistics:

At the MUHC site, the total number of cancer genetics patients seen in 2007-2008 was 482, which is a small increase over the 456 seen the previous year.

Research Interests and Accomplishments of Individual Members:

Dr. Eleanor Elstein evaluates inherited cardiac diseases as well as systemic genetic diseases that have cardiac manifestations.

Dr. Ken Dewar and his laboratory are using genomics and bioinformatics technologies to study genome structure and variation. One focus of the lab is to develop genetic mapping tools for investigating complex trait mapping in a nonhuman primate, the vervet monkey. Using comparative genomics approaches they have leveraged other genome projects (human, chimpanzee, rhesus monkey) to streamline the discovery of markers of genetic variation (SNPs). They have also embarked upon the generation of corresponding genome-wide physical map, entailing the paired-end sequencing and genome alignments for >200,000 BAC clones. The vervet BAC map is being used to delineate chromosomal breakpoints and to identify vervet BAC clones associated with evolutionary recently derived centromeres and pericentromeric regions.

His group is also interested in understanding genome structure and virulence factors in the human bacterial pathogen Clostridium difficile. C. difficile remains a serious health risk in Quebec, North America, and Europe, in part due to an epidemic strain of increased virulence, which has emerged in the last several years. The laboratory has performed the sequencing of the entire 4 Mb genome of a virulent strain from Montreal, and is now generating the genome sequences of other isolates with important clinical phenotypes. Cross-genome comparisons of gene content and organization will be used to identify additional candidate genes involved in pathogenicity.

Dr. William Foulkes and colleagues have been characterizing mutations in the new breast cancer gene PALB2, as indicated above. In addition, he has worked with BRCA1-mutated cell lines to try to develop novel treatments. With George Chong, he has described several novel mutations in families with colorectal cancer. As mentioned above, in recognition of the excellence of his work, he has been awarded a Chercheur Nationaux award from the FRSQ. Please see www.mcgill.ca/cancergenetics for more information about the Program in Cancer Genetics.

Mary Fujiwara is interested in the distribution and maintenance of genetic variability, including deleterious alleles, in human populations. She studies the Hutterite population of North America, an inbred population isolate, to map and further delineate the clinical variability of a Joubert-related cerebello-oculo-renal syndrome. She also collaborates with Daniel Bichet (Hôpital Sacré-Coeur de Montréal) on the genetics of nephrogenic and neurohypophyseal diabetes insipidus. The study of mutations in three different genes has shown that the mode of inheritance can differ based on the particular mutation.
Dr. Brian Gilfix has a large cohort of patients in the Adult Genetics Clinical with homocystinuria. He is exploring new treatments of for homocystinuria and investigating the effect of elevated homocysteine on other risk factors for cardiovascular disease. He also works on developing new laboratory methods in molecular diagnostics in order to decrease net cost and to allow for a faster turn-around-time.

Dr. Ken Morgan has a major interest in human population genetics and genetic epidemiology. He is involved in the genetic analysis of Mendelian and complex traits in humans and mice. Ongoing collaborations include segregation and linkage analysis of intermediate phenotypes contributing to calcium kidney stone formation; genetic susceptibility to inflammatory bowel disease in children; and reducing the complexity of pedigrees in founder populations such that statistical analysis is computationally feasible. Accomplishments related to human genetics include mapping rare Mendelian diseases. Ongoing collaborations include segregation and linkage analysis of intermediate phenotypes contributing to calcium kidney stone formation; genetic susceptibility to inflammatory bowel disease in children; and reducing the complexity of pedigrees in founder populations such that statistical analysis is computationally feasible.

Dr. David Rosenblatt and his laboratory continue to be the major international referral source for the diagnosis of patients with inherited disorders of folate and vitamin B₁₂. They are involved in studying the biochemical and molecular bases of these diseases. This year they, along with collaborators in Switzerland and the United Kingdom, have described the gene responsible for the cblD inborn error of cobalamin metabolism. They have also shown that with newborn screening of infants, it is also possible to diagnose non-genetic disease involving vitamin B₁₂ in their mothers. Dr. Rosenblatt continues to serve as Chairman of the Department of Human Genetics at McGill.

Dr. Marc Tischkowitz has established a research program at the Segal Centre, Jewish General Hospital, where he is undertaking innovative and effective research in the field of hereditary predisposition to cancer, with a focus on the genetic links between breast cancer and Fanconi Anemia. Over the past year he has continued to explore the role of the Fanconi Anemia gene PALB2 in breast cancer predisposition. He aims to deliver high-quality patient-focused research results, as shown by several of his recent papers (PMID: 18285836, 17650314). He has also fostered collaborations with researchers working on gastric cancer – this work was published in JAMA (PMID: 17545690). In his capacity of Attending Staff at the Jewish General Hospital, he is responsible for providing services for Cancer Genetics, Prenatal Diagnosis and General Genetics. In addition, he has clinical responsibilities at Hôpital Charles LeMoyne, where he advises and assists the local Genetic Counsellor and holds a genetics clinic once every other month.

Dr. Patricia Tonin works in two principal areas of research; these are described on the web site: www.toninlab.mcgill.ca

A. The Molecular study of Human Epithelial Ovarian Cancer

More than 70% of women diagnosed with ovarian cancer die of the disease. Knowledge of the molecular events associated with the development and progression of epithelial ovarian cancer has been limited by the lack of a suitable model system. Also, since the disease is often diagnosed at a late stage when numerous complex chromosomal changes have already taken
place, the early molecular events remain largely unknown. Research in the lab is focused on the identification of tumour suppressor genes, particularly those physically associated with chromosomes 3p and 17q. Various molecular genetic techniques are used to identify them, which include, allelic content analysis such loss of heterozygosity studies and single nucleotide (SNP) polymorphism analyses, large-scale gene expression assays (Affymetrix platform), and more recently functional approaches based on chromosome transfer fragment and gene complementation. In collaboration with her colleagues at the CHUM-Notre Dame, Dr. Tonin investigates gene expression profiles of ovarian cancer samples with the aim of identifying signature patterns of gene expression in order to elucidate molecular pathways important in ovarian tumourigenesis.

B. Breast and Ovarian Cancer Susceptibility Genes

Hereditary breast and ovarian cancer accounts for approximately 5-10% of all breast and ovarian cancers. A large majority of cancer families are attributed to germline mutations in BRCA1 and BRCA2. However, about 40% of cancer families are negative for mutations in these known genes. Dr. Tonin’s group is also focused on the determining the contribution of known and unknown cancer susceptibility genes to inherited predisposition to breast and ovarian cancer. Recent accomplishments include the analysis of high-risk families for germ line TP53 mutations and further characterization of the contribution of BRCA1/2 to hereditary breast and ovarian cancer families of French Canadian descent.
MEETINGS AND PRESENTATIONS

WILLIAM FOULKES

August 28th, 2007

42nd World Congress of the International Society of Surgery, International Surgical Week
Palais des Congrès
Montreal, Quebec
Title: *Hereditary breast cancers - Guidelines for treatment options to women at high risk: what id the evidence behind?*

August 30th, 2007

42nd World Congress of the International Society of Surgery, International Surgical Week
Palais des Congrès
Montreal, Quebec
Title: *Is breast cancer the same disease in Asia as in the west? – Analysis and summary*

October 11th, 2007

Découvrir de nouveaux sommets, 28ème Congrès Annuel de la société québécoise de biologie clinique
Mont-Tremblant, QC
Title: *Les aspects génétiques du cancer du sein*

October 17th, 2007

**BRCA: New Frontiers in Research and Practice**
Second International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes
Hotel Delta, Montreal, QC
Title: *BRCA1/2 mutations: helping you and your loved ones deal with the hand you are dealt*

December 11th, 2007

Triple Negative Breast Cancer Conference
San Antonio, TX, USA
Title: *BRCA1 and sporadic basal-like breast cancers: similarities and differences*

December 12th, 2007

BCFR Scientific Conference
San Antonio, TX, USA
Title: *How should we study special populations-Ashkenazim, Minorities?*
March 13th 2008

Breakthrough Breast Cancer Research Centre Seminar
London, UK
Title: From the bedside to the bench and back again: short stories that end up as novels

April 10th, 2008

1st Annual Canadian Human Genetics Conference
Manoir St-Sauveur, St-Sauveur, QC
Title: From the bedside to the bench and back again: translating cancer genetics

April 1st, 2008

MUHC Urology seminar
MUHC
Title: It is a short walk from the clinic to the laboratory, but sometimes you get lost on the way

May 12th, 2008

The 2008 CLIMOA Annual Scientific Meeting
Sofitel Montreal, Montreal, QC
Title: Improving breast cancer mortality: have genetic markers helped?

BRIAN GILFIX

March 19, 2008

MUHC Division of Hematology Inter-Hospital Rounds
Montreal General Hospital
Montreal, QC
Title: Molecular Diagnostics – Ongoing Projects and Future Directions

KENNETH MORGAN

April 15-17, 2007

Second Annual Canadian Genetic Epidemiology & Statistical Genetics Meeting
Toronto, Ontario
Title: Population structure and genetics of the Hutterites in North America.

MARC TISCHKOWITZ

October 19th, 2007

BRCA : Today & Tomorrow conference
Montreal, QC
Title: **PALB2/FANCN – Another link between Fanconi Anemia and breast cancer**

**PATRICIA N. TONIN**

May 21-24, 2007

Human Genome Meeting - HUGO: The Human Genome Organization
Montreal, Quebec

**Title:** *Heterogeneity of BRCA1/2 mutations in hereditary breast and/or ovarian cancer in French Canadian families from Quebec Canada*

October 17-19, 2007

The 2nd International Symposium on Hereditary Breast and Ovarian Cancer - Hereditary Breast and Ovarian Cancer Foundation, Montreal, Quebec

**Title:** *BRCA1, BRCA2, and TP53 mutations in French Canadian Breast and ovarian cancer families*

October 28-28, 2007

Pan-Canadian Biomarker Workshop, Ontario
Terry Fox Research Institute, MaRS Centre
Toronto, CA

**Role:** Representing ovarian cancer researchers

December 5-6, 2007

7ième Réunion Scientifique Annuelle,
Association des Médecins Génétiens du Québec

**Role:** Session Chair: From Breast to Leukemia

March 26, 2008

Place Samuel Lunenfield Research Institute, Mount Sinai Hospital,
Toronto, CA

**Title:** *Integrating genomic, gene expression and functional complementation strategies to identify chromosome 3p genes implicated in ovarian cancer*

March 31, 2008

Centre for Cancer Therapeutics, Ottawa Health Research Institute,
Ottawa, Ontario

**Title:** *The identification of chromosome 3 genes important in ovarian cancer through integration of genomic, gene expression and functional complementation strategies.*
May 3, 2008

Trainee Session for a Pre-Meeting of the The 4th Canadian Conference on Ovarian Cancer Research, Montreal Quebec
Role: Lecture for Trainee session
Title: Genetics of Hereditary Ovarian Cancer

May 4-7, 2008

The 4th Canadian Conference on Ovarian Cancer Research, Montreal, Quebec
Role: Member of the organizing committee

DAVID ROSENBLATT

July 1-6, 2007

Gordon Research Conference: Vitamin B\textsubscript{12} & Corphins
University of New England
Biddeford, ME
Title: Combined homocystinuria and methylmalonic aciduria; lessons from MMACHC

September 17-19, 2007

Canadian Academy of Health Sciences
3rd Annual Meeting
Montreal, Quebec

October 23-27, 2007

The American Society of Human Genetics
San Diego, California
Four posters presented by graduate students

April 2-12, 2008

1st Annual Canadian Human Genetics Conference
St-Sauveur, Quebec
Four posters presented by graduate students

May 14-16, 2008

7éme Journée génétique: RMGA
Quebec, Qc
One poster presented by graduate student
SONYA ZAOR

October 17-19, 2007

BRCA: NEW FRONTIERS IN RESEARCH AND PRACTICE
Second International Symposium on Hereditary Breast and Ovarian Cancer
Montreal, Quebec
Title: Workshop A: *Genetic Counseling for BRCA1/2 Variants of Uncertain Significance: A Case-Based Approach*


**Foulkes WD.** BRCA1-sowing the seeds crooked in the furrow. *Nat Genet.*, 40:8-9, 2008.


**Gilfix B. M.** (and others) Patient’s and Doctor’s Guide to Medication in Acute Prophyria


Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA*, 297:2360-72, 2007


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RESEARCH OPERATING FUNDS

WILLIAM FOULKES
US ARMY - Synergistic - 2008-2010 (PI)
CBCRA – IDEÂ – 2006-2007 (PI)
CBCRA – Operating – 2006-2009 (PI)
CBCRA – Operating – 2005-2008 (PI)
CIHR – Operating – 2003-2006, extended 2007 (PI as of 12/18/06)
Susan G Komen BrCa Found. 2008-2011 (Co-I)
Susan G Komen BrCa Found. 2007-2010 (Co-I)
Susan G Komen BrCa Found. –2006-2009 (Co-I)
NIH – Group Grant – 2002-2006, extended 2007 (Co-I)
CIHR –Group Grant – 2003-2007 (Co-I)
PCRFC – Operating – 2005-2007 (Co-I)
CBCRI – Operating – 2004-2009 (Co-I)

BRIAN GILFIX
Gustuv Levinschi Foundation Award, PI - 2007, Transfer of Clinical Tests to the LightCycler

KENNETH MORGAN
Networks of Centres of Excellence, MITACS Team Member - 2000-2009
CIHR, Strategic Training Program Grant, Co-investigator - 2002-2008
CIHR, Operating Grant, Co-principal applicant - 2006-2009
CIHR, Operating Grant, Co-applicant - 2007-2010

DAVID ROSENBLATT
CIHR, Operating Grant, PI – 2006-2009
CIHR, Group Grant, Co-Investigator – 1975-2009
Canadian Gene Cure Foundation, PI-2007-2008

MARC TISCHOWITZ
FRSQ Chercheur-bousier clinicien Junior 1 - July 2007
Susan G. Komen for the Cure Career Catalyst Research Project Title: PALB2 - A new hereditary cancer gene: implications for treatment March 2008 (PI)
Weekend to End Breast Cancer Operating (PI)
Komen Career Catalyst (PI)
Rethink Breast Cancer - Operating 2006-2008

PATRICIA TONIN
Terry Fox Research Institute (Montreal Node), Group - (3 years) start date pending
Cancer Research Society, Inc, Strategic Grant - September 1, 2007 – August 31, 2009 (renewal)
Fonds de la Recherche en Santé du Québec: Réseau cancérologie, Group Infrastructure - April 1, 2007 – March 31, 2012 (renewal)
Canadian Institutes of Health Research, Operating - October 2006 – September 2009
Cancer Research Society, Inc, Strategic Grant - September 1, 2005 – August 31, 2007
Canadian Institutes of Health Research, Operating - Oct 1, 2005– Sept 30, 2008
Quebec Breast Cancer Foundation, Group Operating - July 1, 2004– June 30, 2007
[Extended to June 2009]
## FINANCIAL REPORT – 2007/2008

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*Balance was Capitalized*