"The Future of Research in Obstetrics & Gynaecology"
A Personal Assessment

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Acknowledgment and Gratitude to:

• Professor O. S. Miettinen
• Professor K.S. Joseph
• Dr. Jan Christlaw
• Professor John Challis
• Professor David Huntsman
Objectives

"The Future of Research in Obstetrics & Gynaecology".

At the conclusion, you should be able to:

i. Discuss the evolving role of research in medical education and practice.

ii. Reflect on recent trends that will influence future medical research

iii. Identify future opportunities for research in our specialty
The Evolution of Scientific Medicine

**The Flexner Report 1910**
- Assessed medical education in North America
  - Written by Abraham Flexner
  - Commissioned by Carnegie Foundation
- Higher admission and graduation standards
- Strict adherence to protocols of mainstream science in education and research.
Differentiation of basic and clinical research

Basic Biomedical Research

Clinical Science & Knowledge

Translational Continuum
The Evolution of Scientific Medicine

Evidence Based Medicine

• “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research”

Dr. David Sackett
The Evolution of Scientific Medicine

**Evidence Based Medicine**

- Decisions are based on integration of:
  - The best research evidence
    - Assesses strength of evidence
      - Risks and benefits of
        » Diagnostic tests
        » treatment and no treatment
  - Patient values
  - Clinical expertise
    - Depends on physician assimilation
Preterm Birth: A Global Problem

- Preterm birth contributes more to under-five deaths than AIDS, malaria or tuberculosis

- Thirteen (13) million babies are born preterm (before 37 weeks gestation) each year

- Survivors experience long-term problems, including cerebral palsy, visual, hearing and neurological impairment
Preterm Birth is a Complex Problem

Complex endpoint with multi-factorial causes that differ according to gestational age:

- Immunologic
- Cervical insufficiency
- Infection/inflammation
- Bleeding
- Stress (CRH)
- Uterine over-distension

**Early Preterm Birth**

**Late Preterm Birth**

*Usually defined as simple endpoint, regardless of etiology*

- This has led to apparent uniform, largely unsuccessful interventions for preterm labor
Activation of Maternal/Fetal HPA Axis

Inflammation /Infection

Decidual Hemorrhage, Thrombosis

Pathologic Uterine Distension

Decidua & Fetal Membrane Activation

CRH
Placental estrogens

Cytokines

Thrombin

Contraction-associated Proteins
Oxytocin receptors

Matrix metalloproteinases
Proteases

Cervical Ripening
Rupture of Membranes

Prostaglandins

Uterine Contractions

Maternal Oxytocin

Preterm Birth

Pathways to Preterm Birth
Activation of Maternal/Fetal HPA Axis

Inflammation /Infection

Decidual Hemorrhage, Thrombosis

Pathologic Uterine Distension

CRH-Ri

Antibiotics/Probiotics

Anti-inflammatory

Decidua & Fetal Membrane Activation

Matrix metalloproteinases
Proteases

CRH, Placental estrogens

Cervical Ripening
Rupture of Membranes

TIMP’s, LPS-Ag, Toll-R

Progestins

Preterm Birth

Ritodrine

CRH-Ri

Prostaglandins

Uterine Contraction

ORTR-Ag

Antibiotics/Probiotics

Oxytocin receptors

Decidua & Fetal Membrane Activation

Contraction-associated Proteins

Oxytocin

Maternal Oxytocin

PGHS-i

Prostaglandins

PGR-Ag

Progestins

Ritodrine

Preterm Birth

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
The valley in the research continuum
The Translation Triangle

Basic Research

Translation

Innovation Commercialization

Clinical research
Science and the Social Contract

.........as scientists we are in the privileged position of being able to indulge our passion for science, to do so with freedom of enquiry and lack of constraint........  Our research is generally funded, in whole or part, through the public purse, in Canada, provincially or federally. But, ........ we have no entitlement to those funds. We have to justify their receipt and usage and show the return on investment. .......we have a responsibility to offer something back to Society for the trust that has been placed in us.
Scientific Medicine in the Information Age

• Medicine has become a highly technological industry focused on a “culture of improvement”
• Increasingly, the knowledge base is codified in terms of probability functions
• These functions can be embedded into a practice guiding expert system accessible for ad hoc retrievals.

Miettinen, O.S. *Up From Clinical Epidemiology & EBM* 2011
Historical Examples of Clinical Research

Virginia Apgar 1909-1974

The Apgar Score

- 5 predictors scored 0, 1 or 2
- Proposed years before logistic regression was developed by Jerome Cornfield and others.
Historical Examples of Clinical Research

Biophysical profile

- Non-stress test Score 0 or 2
- Fetal breathing Score 0 or 2
- Fetal movement Score 0 or 2
- Fetal tone Score 0 or 2
- Amniotic fluid volume Score 0 or 2

“In order to facilitate comparative analysis of variable combinations, each variable when normal was arbitrarily assigned a score of 2 and when abnormal a score of 0.”

Failure of Study Design?

A scoring system for detection of macrosomia and prediction of shoulder dystocia: a disappointment.

Table I. The macrosomia score.

<table>
<thead>
<tr>
<th></th>
<th>2 points</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biparietal diameter</td>
<td>(\geq 90%) for GA</td>
<td>(&lt; 90%) for GA</td>
</tr>
<tr>
<td>Head circumference</td>
<td>(\geq 90%) for GA</td>
<td>(&lt; 90%) for GA</td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td>(\geq 90%) for GA</td>
<td>(&lt; 90%) for GA</td>
</tr>
<tr>
<td>Femur length</td>
<td>(\geq 90%) for GA</td>
<td>(&lt; 90%) for GA</td>
</tr>
<tr>
<td>Amniotic fluid index</td>
<td>(\geq 24\ cm)</td>
<td>(&lt; 24\ cm)</td>
</tr>
</tbody>
</table>

Macrosomia score does not predict shoulder dystocia

Arbitrary weights

Use of Probability Functions in Prognosis

Prognostic function for neonatal outcomes at 22-25 weeks

The neonatologists have an equation

Probability of Death/Neurodevelopmental Impairment

\[
\frac{1}{1 + e^{-\left(5.0599 - 0.005018 \times \text{Birth Weight (g)} + 1.5181 \text{ (if GA=22)} + 0.9408 \text{ (if GA=23)} + 0.3554 \text{ (if GA=24)} - 0.7407 \text{ (if Female)} - 0.3528 \text{ (if Singleton)} - 0.6402 \text{ (if ANS)} \right)}}
\]

Use of Probability Functions in Prognosis

Adverse maternal outcomes in preeclampsia
Probability expressed as a function of

a) Gestational age
b) Chest pain or dyspnoea
c) Oxygen saturation
d) Platelet count,
e) Creatinine
f) Aspartate transaminase
PIERS Prevalence Function

Probability of adverse maternal outcome

\[
\frac{1}{1 + e^{-\left(2.8 + (-5.1 \times 10^{-2} \times GA) + (1.3 \times \text{chest pain or dyspnoea}) + (-2.1 \times 10^{-2} \times \text{creatinine}) + (2.7 \times 10^{-1} \times \text{platelets}) + (4.0 \times 10^{-5} \times \text{platelets}^2) + (1.1 \times 10^{-2} \times \text{AST}) + (-3.5 \times 10^{-6} \times \text{AST}^2) + (2.50 \times 10^{-4} \times \text{creatinine.} \times \text{platelets}) + (-6.99 \times 10^{-5} \times \text{platelets} \times \text{AST}) + (-2.56 \times 10^{-3} \times \text{platelets} \times \text{SpO2})\right)}}
\]
Pre-eclampsia Integrated Estimate of RiSk (PIERS)

• Multi-centre International study
  – North America (Canada, USA)
  – Africa (Mali, Nigeria, South Africa, Uganda, Zimbabwe)
  – South Asia (Bangladesh, India, Pakistan)
  – Asia/Oceana (China, Fiji)
  – Latin America (Brazil)

• Aims to develop classification system based on the system’s ability to predict adverse maternal and perinatal outcomes
  – fullPIERS model
  – Validation study
  – miniPIERS Model
  – Validation study

• Funded by
  – CIHR
  – WHO
  – UNDP
  – UNFPA
  – World Bank
  – Pre-eclampsia Foundation
  – FIGO
  – MSFHR
  – CFRI

• Principal Investigator
  – Dr. Peter Von Dadelzen

The Realization of Scientific Medicine

• Individual physicians’ practice can now be informed by expert systems that collate evidence to specific clinical scenarios.
  – Knowledge from clinical trials about effectiveness can enhance efficiency and cost effectiveness.

• This vision informs the gaps in scientific evidence and the priorities for research.
The two "Death Valleys" of the clinical translational continuum

- Valley 1: Basic Biomedical Research
- Valley 2: Clinical Practice & Health Decision Making
Taxonomy of Clinical Research

gnos\textipa{sis} |ˈnōsis| knowledge related to

diagnosis |dīəgˈnōsis| knowledge of the distinctive characterization of symptoms

etiagnosis |ētēgˈnōsis| knowledge of the etiology of a disease

prognosis |prägˈnōsəs| knowledge of the likely course of a disease
Examples of Knowledge Gaps in Diagnosis

Assessment of Fetal Health

“Despite widespread use of [fetal assessment] technologies, there is limited evidence to .......demonstrate their effectiveness.......”

NICHD review

Examples of Knowledge Gaps in Etiognosis

Given some outcome, what is the probability that a specific antecedent was causal?

e.g., Erb’s palsy following shoulder dystocia
Probability that fundal pressure was causal?
Examples of Knowledge Gaps in Prognosis

Shoulder Dystocia

“Most cases of shoulder dystocia cannot be predicted or prevented.”
“...risk factors can be identified but their predictive value is not high enough to be useful in a clinical setting.”

All references more than 15 years old

ACOG Guideline 2002
Examples of Knowledge Gaps in Prognosis

Third or fourth degree perineal laceration (or resultant fecal incontinence)

Many studies on determinants of severe perineal lacerations but no prognostic equation

Cannot use postnatal information such as birth weight, only estimated fetal weight
Community gnosis

Planning for Maternity Services

The Acute Perinatal Program, BCWH, attempted to project maternity needs for 2017 and 2035

Number of deliveries?
Number of deliveries $\geq$ 35 years?

- BMI $> 30$ kg/m$^2$
- Hypertension?
- Diabetes mellitus?
- PPH with blood transfusion?
MILLENNIUM DEVELOPMENT GOALS - TARGETS FOR 2015

Goal 1 – Eradicate extreme poverty and hunger
Goal 2 – Achieve universal primary education
Goal 3 – promote gender equality and empower women
Goal 4 – Reduce child mortality
Goal 5 – Improve maternal health
Goal 6 – Combat HIV/AIDS, malaria and other diseases
Goal 7 – Ensure environmental sustainability
Goal 8 – Develop a global partnership for development

All 189 state members of UN signed Millennium Declaration in 2000
The Global Picture...

• Over 400 000 women die each year - one every minute - from complications of pregnancy and childbirth

• 99% of these deaths occur in developing countries

• Girls aged 15 - 19 are twice as likely to die from childbirth as women in their twenties. Those under 15 are 5 times as likely to die from childbirth
Maternal mortality is highest in countries of sub-Saharan Africa and South Asia

Maternal mortality ratios (MMR) per 100,000 live births (2005)


Note: This map and all maps in this publication are stylized and not to scale. They do not reflect a position by UNICEF on the legal status of any country or territory or the delimitation of any frontiers. The dotted line represents approximately the Line of Control in Jammu and Kashmir agreed upon by India and Pakistan. The final status of Jammu and Kashmir has not yet been agreed upon by the parties.
Etiognosis of Maternal Mortality

Causes of maternal deaths, developing regions, 1997/2007 (Percentage)

- 35 Haemorrhage
- 18 Indirect causes
- 18 Hypertension
- 11 Other direct causes
- 8 Sepsis
- 9 Abortion and miscarriage
- 1 Embolism

Vital statistics registration critical need

WHO 2007
Maternal Mortality: A Social Justice Issue

- Maternal Mortality remains one of the statistics with the greatest gap between countries.

- This is rooted not just in availability of care, but in social systems and the reproductive rights of women.

Maternal Mortality

- Canada 4/100,000
- South Africa 300/100,000
- Uganda 650/100,000
- Afghanistan >2000/100,000
HUMAN HEALTH RESOURCE CRISIS

Africa:

• has 25% of global disease burden
• 50% global Maternal Mortality

• and 1.3% of the global Human Health Resources
Maternal mortality: a matter of political will

“Women are not dying of diseases that we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving.”

-- Dr. Mahmoud Fathalla
The two "Death Valleys" of the clinical translational continuum

Includes the provision of cost effective care
“By harnessing the world’s capacity for scientific innovation, I believe we can transform health in the developing world and save millions of lives.”

BILL GATES
UBC receives $21M grant from Bill & Melinda Gates Foundation for PRE-EMPT Project
Catching the momentum of a Research Team

• Professor Von Dadelzen has combined his model for diagnosing pre-eclampsia with mobile technology developed by Dr. Mark Ansermino, an Associate Professor in Anesthesia...

• “... the idea so compelling that it won a seed grant of $250,000 from the Bill & Melinda Gates Foundation...”
Changing Paradigms for Cancer Care

Generic Cancer Care 1990

Stratified Cancer Care 2010

Individualized Cancer Care 2020

Breast cancer
Lymphoma
Ovarian cancer
Pancreatic cancer
The Move Towards Individualized Control is a Result of the Explosion of Genomics

- This is a biomarker driven process, but how to discover and validate the biomarkers we require
  - One gene at a time biological approach: yielded Her2, ER, PR, BRCA1 and BRCA2 etc.
  - Looking at everything at once
The First Sequences of Human Genomes: Biology’s Leap Forward

- Initial sequencing and analysis of the human genome.

The sequence of the human genome.
*Science.* 2001 Feb 16;291(5507):1304-51
The Illumina HiSeq 2000 is state-of-the-art technology for genomics. The GSC has 12 units in production, allowing for one human genome sequence every 8 minutes.

To date, GSC has generated 100,094,105,402,927 bp of DNA sequence.
Diagnostic Gene Sequencing

- **Ion Proton™ Sequencer**
- As big as a bread maker
- 1000$ genomes promised
- Quality not yet assured
Yesterday’s Impossible Research Becomes Today’s Diagnostic Test

- In 2014 the cost to sequence an entire genome will be under $1000

- Within a few years whole genome sequencing of BC’s population will be commonplace

The Sequencing Explosion

![Graph showing the decrease in cost of sequencing and computing over time.](image)
The Move Towards Individualized Cancer Care: What is needed

- Ability to decode cancer and host genome
- Ability to study intra-tumoural heterogeneity
- Ability to study the emergence of drug resistance
Approach to Cancer Genomics: Three flavors of cancer

High grade cancers
- High grade serous cancer
- Pathognomonic mutations unlikely

Moderate grade cancers
- Clear cell cancer
- Mutations in specific pathways that will be important in other cancers

Unusual tumours with pathognomonic features
- Granulosa cell tumor of the ovary
- Pathognomonic mutations
Low grade Endometrioid Carcinoma of the Ovary versus Uterus

- Same (or similar) tissue of origin - abnormal endometrium versus endometriosis
- Same risk factors
- Same biomarker profile
- Same mutational profile
- Similar clinical behaviour

Beyond inertia what evidence supports keeping LG endometrioid with other ovarian cancers in clinical trials?
Mutation Based Classification of Gynaecological Cancers

- Clear Cell Ca.
- Endometrioid Ca.
- High Grade Serous Ca.

- ARID1A
- PIK3CA
- PTEN
- KRAS
- PPP2R1a
- CTNNB1
- MSI
- PTEN
- ARID1A
- PPP2R1a
- TP53
- BRCA1
- chromosomal instability
- genetic chaos

Endometriosis
Uterine Cavity
Fallopian tubes
Endosalpingiosis
OvCaRe is a multidisciplinary research team in BC spanning basic to clinical science.

Scientific Director: David Huntsman
Clinical Director: Dianne Miller

Core Research Resources

- Genomics & Bioinformatics led by S. Shah
- Tumour Bank led by B. Gilks (also COEUR)
- Tissue Microarray led by B. Gilks (also OTTA and COSMOS)
- Xenografts led by Y.Z. Wang
- Cheryl Brown Ovarian Cancer Outcomes Unit led by K. Swenerton & A. Tinker
- Clinical Trials led by A. Tinker & J. McAlpine

Research Projects (funded or under consideration)

- CCSRI Multisector Team Grant: Prevention From Precursors to Prevention: A Population-Based Risk Reduction Strategy for Ovarian Cancer
  - PIs: D. Huntsman, D. Miller
- CIHR Operating Grant: ARID1A Mutations in the SWI/SNF Chromatin Remodeling Complex Genes: An Alternative Mechanism for Ovarian Carcinogenesis
  - PI: D. Huntsman
- CIHR Operating Grant: FOXL2 Clinical and Functional Significance of a Pathogenic FOXL2 Mutation in Francois Cell Tumours of the Ovary
  - PI: D. Huntsman
- NSERC-CHRP Grant: Intratumoural Heterogeneity: The evolutionary history of high-grade serous ovarian cancer
  - PI: S. Shah
- CIHR Operating Grant: Intratumoural Heterogeneity Genomic Disruption in High-Grade Serous Ovarian Carcinoma: Steady State or Continuous Drift?
  - PI: S. Shah, J. McAlpine
- TFRI New Frontiers Grant: Classifier for Ovarian Carcinomas
  - PI: D. Huntsman
- CHIR POP grant: Bioinformatic Models for Drivers
  - PI: D. Huntsman
- CCSRI Innovation Grant: siRNA-based Nanomedicines Regenerative Medicine and Personalized Nanomedicines
  - PI: P. Cullis
- CIHR Emerging Team Grant: siRNA-based Nano-medicines
  - PI: A. Tinker, J. McAlpine
- TFRI Grant: Clinical Trials for Rare Tumours
  - PI: P. Cullis
The BC-PMI is an Inclusive Initiative That Brings Together BC’s Technological and Health Care Communities

CTAG
Technology
• Nanomedicines
• Instrumentation
• Imaging
• Biomarkers

Clinical
• Clinical Assessment
• Patient treatment
• Imaging
• Diagnostics

Business Development
NanoMedicines Research Group
UBC Physics
ICICS
MiNa
Materials Sciences
UVic Genome BC PROTEOIMICS CENTRE

PMI

Technology Development
• Diagnostics
• Drugs
• Devices
• Informatics

Clinical Testing
• Clinical Trials
• New approaches
• Clinical Informatics

Population Delivery
• Economic issues
• Education/ training
• Ethical Issues
• Societal Issues
• Knowledge transfer

Improved Preventative Care; Improved Outcomes; Potential Cost Savings; Commercial Opportunities
The PMI will select and conduct priority PM projects identified from a broad spectrum of disease and preventative care opportunities in consultation with primary/specialist physicians and health economists/payers.
The British Columbia Personalized Medicine Initiative (BC-PMI)

Operations Group: Pieter Cullis, David Huntsman, Michael Hayden, Bruce McManus, Michael Burgess
Operations Officer: Rob Fraser

Better health for all from individualized health solutions
Prognosis

“"We will continue to make key investments in science and technology necessary to sustain a modern competitive economy. But we believe that Canada’s less than optimal results for these investments is a significant problem for our country”"
CIHR’s 13 Institutes

Population and Public Health
Gender and Health
Nutrition, Metabolism and Diabetes
Musculoskeletal Health and Arthritis
Aboriginal Peoples' Health
Genetics
Cancer Research
Circulatory and Respiratory Health
Health Services and Policy Research
Infection and Immunity
Neurosciences, Mental Health and Addiction
Human Development, Child and Youth Health
Healthy Aging
Strategy on Patient-Oriented Research

Goal: Improving health outcomes through clinical research.

Aims:

• to enhance clinical applications and economic impact of health innovations.
• to provide health professionals and decision-makers with information on how to deliver high-quality care and services in a cost-effective manner.

Implies a continuum from:

• “first in patients” studies to
• how new and older drugs, devices and procedures are integrated into health systems and population health as it influences health systems research and the application of best clinical practices in Canada.
CIHR Patient Oriented Research

Strategy has 4 components:
1. Research environment and infrastructure
2. Training and mentor health professionals and non clinicians
3. Improve organizational, regulatory and financial support for multi site studies
4. Support best practices in health care
CIHR Patient Oriented Research

- SUPPORT units linked by *networks* across thematic areas; mental health, primary health care, chronic disease management
- Link *multidisciplinary expertise* along a theme
- Develop *multicentre projects*
- Offer *mentorship*
- Assist in *oversight* of research
CIHR Patient Oriented Research

- **Continuum** from initial human studies to implementation of interventions in the health care system
- **Evaluation** of new and current diagnostic approaches, treatments, devices and practices (comparative effectiveness)
- **Synthesis, dissemination and transfer of knowledge into the health care system**
In 2008, the Burroughs Wellcome Fund launched an institutional award program for five-year institutional training awards providing $500,000 a year to bridge the gap between the population and computational sciences and the laboratory-based biological sciences.

The award supports the training of researchers between existing concentrations of research strength in population approaches to human health and in basic biological sciences.

The goal is to establish training programs by partnering researchers working in schools of medicine and schools (or academic divisions) of public health. The second round was funded in 2012.
Conclusions

• Research should provide benefit to patients and society
  – Investigators have a moral duty to seek knowledge with social value

• The Information Age has provided unprecedented tools for improving Health Care by
  – Facilitating research advances
    • Genomics
    • Epidemiology
  – Providing systems for practicing physicians and health care teams to access and synthesize evidence.
Conclusions

• These technological advances significantly increase the complexity of research
  – Multi-disciplinary research teams are most successful in this environment
  – Funding agencies recognize the value of multi-disciplinary teams
Conclusions

• There remain significant research gaps:
  – Basic science that will redefine health & disease
  – Clinical investigations to define diagnosis, etiognosis, and prognosis in terms of probability functions.
  – Global health (limited resources) and cost effective health care
  – Informatics that will enable evidence guided medicine and personalized medicine