Research in Biomedicine and Health – I

Day 4 seminar
Research design and planning
Medical Discoveries

- 2600 BC Imhotep describes 200 illnesses
- 420 BC Hippocrates Oath
- 1249 Glasses to correct eye vision
- 1736 Operation of appendix
- 1796 Vaccination against smallpox - 1976 eradication of smallpox
- 1895 Röntgen
- 1928 Penicillin
- 1954 First kidney transplant
- 1965 Ultrasound
- 1971 CT
Medical Discoveries

- 1981 Discovery of HIV
- 1987 Separation of conjoined twins
- 2000 Human Genome sequenced
- 2003 SARS
- 2006 HPV vaccine
- 2007 Stem cells created from skin cells
- 2012 HIV Pre-exposure prophylaxis
- 2013 First artificially created kidney transplanted in mice
Why research?

- describe new things
- determine causes of diseases
- determine which medication is better for treatment
Original research article

new knowledge

for the first time
Study design

- Observational studies
  - Descriptive
    - Case report
    - Case series
  - Analytical
    - Cross-sectional
    - Case-control
    - Cohort

- Experimental studies
  - (randomized) Controlled clinical trials
Study design

Did investigator assign exposures?

- Yes
  - Experimental study
    - Random allocation?
      - Yes
        - Randomised controlled trial
      - No
        - Non-randomised controlled trial
  - No
    - Observational study
      - Comparison group?
        - Yes
          - Analytical study
        - No
          - Descriptive study

Exposure → Outcome

Exposure and outcome at the same time

- Yes
  - Cohort study
- No
  - Case-control study
  - Cross-sectional study
Types of study design according to the time-frame

- Cross-sectional study
- Case control study
- Historical cohort study
- Experimental research
- Cohort study

Time of study group formation:
- Past
- Present
- Future

Time of data collection:
- Past
- Present
- Future
Case-control study

**Cases**
- Exposed
- Non-exposed
- Sick

**Controls**
- Non-exposed
- Healthy

**Time**
- Past
- Present

- Time of group formation
- Time of dana collection
Cohort study

- **Exposed**
  - Healthy
  - Sick

- **Non-exposed**
  - Healthy
  - Sick

**Time**
- Past
- Present

**Legend**
- Red Circle: Time of group formation
- Blue Circle: Time of dana collection
Examples of observational studies
A 42-year-old male electrician presented to the eye clinic with decreasing vision 4 weeks after an electrical burn of 14,000 V to the left shoulder. His vision in both eyes was limited to perception of hand motions, with an intraocular pressure of 14 mm Hg in each eye. Slit-lamp examination showed bilateral stellate anterior subcapsular opacities of the lens (top panels, right and left).
Four months after the injury, the patient underwent cataract extraction and implantation of an intraocular lens, which was followed by improvement in visual acuity to 20/70 in the right eye and 20/400 in the left eye. Two years after the injury, a retinal detachment developed in the left eye, and the patient underwent repair. At a 10-year follow-up visit, the patient's visual acuity was 20/100 in the right eye, but in the left eye he could only count fingers.

Although the patient was legally blind, he was able to read with the use of low-vision aids and was able to independently commute on public transportation. When lenticular opacities are the sole manifestations of electrical injury, cataract extraction is expected to produce a functional outcome. However, with concurrent damage to the optic nerve and retina, complete visual rehabilitation may be limited.
A strike of lightning left Winston Kemp, a 24-year-old electrician, with a skin discoloration. Known as a "Lichtenberg figure," for the German physicist who first described seeing a similar pattern while experimenting with static electricity, these reddish fern-leaf patterns are a skin reaction to a lightning strike. They are sometimes referred to as "lightning flowers" or "lightning trees." and tend to occur on the arms, back, neck, chest, or shoulders of lightning strike victims.
Case series

**Pneumocystis pneumonia – Los Angeles**

In the period October 1980-May 1981, 5 young men were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. The patients did not know each other and had no known common contacts or knowledge of sexual partners who had had similar illnesses. Two of the 5 reported having frequent homosexual contacts with various partners. All 5 reported using inhalant drugs, and 1 reported parenteral drug abuse. Patients had profoundly depressed *in vitro* proliferative responses to mitogens and antigens.
Pneumocystis pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients (1). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and Pneumocystis pneumonia in this population. It also suggests the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis.
Cross sectional studies
Stress and depression among medical students: a cross-sectional study

Students at the Karolinska Institute Medical University, Stockholm, Sweden were asked to complete a Higher Education Stress Inventory (HESI) and the Major Depression Inventory (MDI).

The prevalence of depressive symptoms among students was 12.9%, significantly higher than in the general population, and was 16.1% among female students versus 8.1% among males. A total of 2.7% of students had made suicide attempts, but none during the previous year. A gender difference regarding stress levels was also seen, where women reported higher levels of stress than men.
Case control studies

Risk Factors for Pancreatic Neuroendocrine Tumors

B: Pancreatic neuroendocrine tumors (PNETs) are uncommon, and little is known about their risk factors and association with other cancers. We evaluated whether the following risk factors known to be associated with pancreatic adenocarcinoma are also associated with PNETs: smoking, alcohol use, family history of PNET, other cancers, and personal history of diabetes.

M: Patients with PNETs seen at Mayo Clinic Rochester between 2000 and 2011 were compared with controls seen for a general medical evaluation. Patients and controls completed the same questionnaires, 309 patients were matched to 602 controls (2:1) on age, sex, and region of residence.
RESULTS:
Personal smoking history was not associated with PNETs. Alcohol use was less common among cases (54% vs 67%, P < 0.001). Cases were more likely to report a family member with sarcoma (P = 0.02), PNET (P = 0.02), gallbladder cancer (P = 0.02), ovarian cancer (P = 0.04), and gastric cancer (P = 0.01). There was no association with other cancers in family members. Diabetes was more commonly reported by cases than controls (19% vs 11%, P < 0.001).

CONCLUSIONS:
With the exception of diabetes, risk factors that are associated with pancreatic adenocarcinoma are not risk factors for PNETs.
The researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts, and began the first round of extensive physical examinations and lifestyle interviews that they would later analyze for common patterns related to cardiovascular diseases.

1961: Cholesterol level, blood pressure, and electrocardiogram abnormalities found to increase the risk of heart disease

1967: Physical activity found to reduce the risk of heart disease and obesity to increase the risk of heart disease

1988: High levels of HDL cholesterol found to reduce risk of death

1999: Lifetime risk at age 40 years of developing coronary heart disease is one in two for men and one in three for women

2002: Lifetime risk of developing high blood pressure in middle-aged adults is 9 in 10.

2005: Lifetime risk of becoming overweight exceeds 70 percent, that for obesity approximates 1 in 2
Antibiotic streptomycin had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli in vitro, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.
By September, 1947, 109 patients had been accepted, and no more were admitted to this trial. Two patients had died within the Preliminary observation week; these are excluded from the analysis. Of the remaining 107 patients 55 had been allocated to the streptomycin group and 52 to the control group.

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill.
Four of the 55 S patients (7%) and 14 of the 52 C patients (27%) died before the end of six months. The difference between the two series is statistically significant; the probability of it occurring by chance is less than one in a hundred.

At four months after admission the general condition had improved in 40 (73%) of the 55 S patients, compared with 26 (50%) of 52 C patients.
Analysis of the results at the end of the first six-month period has shown that the course of bilateral acute progressive disease can be halted by streptomycin therapy; 51% of the streptomycin-treated patients showed considerable improvement radiologically when comparison was made with their chest radiographs taken on admission. That streptomycin was the agent responsible for this result is attested by the presence in this trial of the control group of patients, among whom considerable improvement was noted in only four (8%), and two of these four patients had improved only after collapse therapy. In other words streptomycin therapy was effecting what the patient's tissues alone could not do—checking the spread of the tubercle bacillus in one of its most favourable milieieux.
# Characteristics of study designs

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<th>Cross-sectional study</th>
<th>Case-control</th>
<th>Cohort</th>
<th>Experimental</th>
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<td><strong>Incidence/Prevalence</strong></td>
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<td>-</td>
<td>incidence</td>
<td>incidence</td>
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<td><strong>Outcome</strong></td>
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<td>1</td>
<td>&gt;1</td>
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<td><strong>Causality</strong></td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Sample (N)</strong></td>
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<td>small</td>
<td>big</td>
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<tr>
<td><strong>Duration</strong></td>
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<td><strong>Price</strong></td>
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Hierarchy of evidence

1. N of 1 randomized control trial
2. Systematic reviews of randomized control trials
3. Single randomized control trial
4. Systematic review of observational (cross-sectional, cohort, or case-control) studies
5. Single observational (cross-sectional, cohort, or case-control) study
6. Physiologic studies (studies of blood pressure, cardiac output, exercise capacity, bone density, etc)
7. Unsystematic clinical observations (case series, case report)