Impacts of Biostatistics on Advancing Human Health in the 20th Century: My Personal View

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Outline

- Impacts of research universities in U.S.
- Statistics as a discipline
- Impacts of biostatistics
  - A bit about history
  - Statistical challenges for dealing with chronic diseases
- Graduation education in biostatistics
- Discussion

Research Universities in U.S.

Compared to traditional colleges starting in 1636, emphasis of research universities is on "creation and dissemination of knowledge" through research rather than "transmission and preservation of knowledge" through teaching

- Model after German system
- Non-existent prior to 1860's in the States
  - First American Doctoral degree conferred in 1861

Cole (2009) The Great American University

Research Universities in U.S. (cont’d)

- Johns Hopkins University, founded in 1876, is the first research university in U.S.
- Strong emphasis on graduate education

“.. There seemed to be a demand for scientific laboratories and professorships, the directors of which should be free to pursue their own researches, stimulating their students to prosecute study with a truly scientific spirit and aim.”

Daniel Gilman, the first president of Hopkins

Impacts of Research Universities

In a short period of time, American research universities have risen to preeminence:

- 17 (40) of the 20 (50) most distinguished research universities are in U.S.
- 60% of all Nobel prizes awarded go to Americans
- Generate new industries (80% from discoveries at American universities)
- Improve public health and medical care
- Create higher standards of living

Impacts of Research Universities (cont'd)

- An interesting question to ask: Are there any roles the field of biostatistics have played in improving public health and medical care?
- After all, we have witnessed increasing number of Department of Biostatistics created in research universities in the States the last century

  From 1 in 1918 to more than 30 currently

- Is this a coincidence?

What is Statistics?

Statistics is the study of the collection, organization, analysis, interpretation and presentation of data

- As a profession, statistics has enjoyed rich history

  Stigler (1986) The History of Statistics: The Measurement of Uncertainty before 1900

- As a discipline, statistics consists of two components
  - Principles
  - Methods

Statistics as a Discipline

- Principles (e.g., likelihood, conditioning, long run frequency, Bayesian, etc.) provide means for statistical reasoning* and interpreting "evidence"

  Cox & Hinkley (1974) Oxford University Press

- Methods (e.g., ANOVA, regression analysis, Cox proportional hazards model) provide tools for analyzing data
- All together, statistics helps to draw valid scientific conclusions

Statistical Reasoning: An example

Back around the 1960's, causal relationship (or association) between smoking and lung cancer between was established

- R. A. Fisher argued that such association can be explained by unmeasured genetic make-up
- W.G. Cochran used Bayes theorem to explain that to do so, the association of the underlying genetic component with smoking and with lung cancer would have to be the same degree, which is unlikely

Biostatistics

It is a sub-discipline of statistics with applications to biological sciences

- It was coined “biometrics” in the beginning of the century with strong attention on agriculture
- It has more commonly been termed “biostatistics” with strong interest in and concern with human health

Some Historical Remarks

- First biostatistics department was founded in 1918 at Johns Hopkins

  Department of Biometry and Vital Statistics

- British Journal in Biometrika, first published in 1902, reflects disease evolution in 20th century
  - Infectious diseases in the 20's
  - Chronic diseases in the 40's and on
  - Back on infectious diseases in the 80's

Issues in Dealing with Chronic Diseases

- Long latent period
  - Taking considerable amount and duration of exposures
  - Relatively rare in incidences
- Complicated disease mechanisms
  - Environmental
  - Genetic
  - Behavioral
  - …..
- Others

Statistical Challenges

I. Assessing efficacy of new treatment(s) for chronic diseases such as cancers

II. Identifying risk factors for prevention and intervention

III. Newly developed (bio-)markers permit more flexible designs for clinical trials

IV. Post-genomic era permits examining genetic associations with complex diseases

Statistical Challenges I

Assessing efficacy of new treatment(s) for chronic diseases such as cancers

- Need randomized clinical trials to minimize bias
- Need sufficiently long period to cumulate enough numbers of “events” (e.g., death, occurrence of AIDS)
- Encounter “censored” data due to loss of follow up or event free at the end
- Two-sample T-test or ANOVA won’t work
- Survival analysis comes to rescue

An Illustrative Example

Treated group: 23, 16+, 18, 20+, 24+

Control group: 15, 18, 19, 19, 20

Time-to-event: duration (in months) from treatment to death among breast cancer patients

16+: surviving for 16 months or longer (censoring)

How does censoring occur?

- Loss to follow up
- Still alive at the end of study

Implication: The traditional two-sample T-test won't work!

Statistical Challenges I (cont'd)

- Survival analysis was the hottest topic for statistical research in the 70-80's

Kaplan & Meier (1958) JASA

Mantel (1966) JASA

Peto & Peto (1972) JRSSB

Cox (1972) JRSSB

Breslow & Crowley (1974) Ann. Statist.

Kalbfleisch & Prentice (1980) John Wiley

Anderson, Borgan, Gill & Keiding (1993) Springer

Lee & Wang (2003) John Wiley

Impacts and Consequences

- Survival analyses have been implemented in major statistical packages (e.g., SAS, SPSSX) and routinely utilized in analyzing data from clinical trials
- Many drugs have been approved by FDA, which in turn benefit health and prolong life of many human beings
- It is also useful for epidemiological studies (e.g., occupational, clinical, etc.)

Breslow & Prentice (1978) Biometrika

Statistical Challenges II

Identifying risk factors for prevention and intervention

- Finding efficacious new drugs has been and continues to be a daunting task (single component won't do it)
- Attention has been turned to searching for risk factors (at community and/or individual levels) for prevention or early detection
- Unethical to conduct experiments to examine, for example, whether smoking causes lung cancer
- Taking too long and too costly to carry out cohort study
- Case-control study comes to rescue

A Case-Control Study of oesophageal cancer

	E	$\bar{E}$	
D	1	0	1
$\bar{D}$	9	106	115

	E	$\bar{E}$	
D	4	5	9
$\bar{D}$	26	164	190

	E	$\bar{E}$	
D	25	21	46
$\bar{D}$	29	138	167

D	42	34	76
$\bar{D}$	27	139	166

19	36	55
18	88	106

5	8	13
0	31	31

D: Oesophageal cancer   E: $\geqq$ 80g/day alcohol consumption

- Hypothesis: risk of oesphageal cancer is associated with alcohol and tobacco consumption
- Age was stratified into six groups (25-34, 35-44, .., 74+) to adjust for confounding

Odds Ratio is Invariant

	D	$\overline{D}$
E		
$\overline{E}$		

Relative Risk (RR) = $\dfrac{P(D|E)}{P(D|\overline{E})}$

Odds Ratio (OR) for disease =

$$\frac{P(D|E) \,/\, P(\overline{D}|E)}{P(D|\overline{E}) \,/\, P(\overline{D}|\overline{E})} = \frac{P(E|D) \,/\, P(\overline{E}|D)}{P(E|\overline{D}) \,/\, P(\overline{E}|\overline{D})} \equiv \text{OR for exposure}$$

- RR $\equiv$ 1 iff OR $\equiv$ 1 no association
- RR $>$ 1 iff OR $>$ 1 positive association

  the larger RR(OR), the greater the association

Cornfield (1951) JNCI

Odds Ratio is Estimable from Case-Control Studies

	E	$\bar{E}$	
D	40	60	100
$\bar{D}$	20	180	200

$\widehat{P}(E|D)=40/100$ $\widehat{P}(\bar{E}|D)=1 – 40/100=60/100$

$\widehat{P}(E|\bar{D})=20/100$ $\widehat{P}(\bar{E}|\bar{D})=1 – 20/100=180/200$

$$\widehat{OR}\text{ for Exposure} = \frac{40/60}{20/180} = 6.0$$

$$\widehat{OR}\text{ for Disease} = \frac{40/20}{60/180} = 6.0$$

$$\text{Var}(\log \widehat{OR})=1/40 + 1/60 + 1/20 + 1/180$$

Is $\widehat{P}(D|\bar{E}) = 60/240 = 0.25$?

Statistical Challenges II (cont'd)

- A good deal of efforts has been made to developing statistical methods to address issues such as confounding, multiple risk factors, etc. in the 70's

Cornfield (1951) JNCI

Mantel & Hanszel (1959) JNCI

Breslow et al. (1976) Am. J. Epidemiology

Prentice & Pyke (1979) Biometrika

Breslow & Day (1981) IARC

Impacts and Consequences

- Newly developed statistical methods have been implemented and routinely applied to analyze data from case-control studies
  - Smoking and lung cancer in 1956
- Many important preventable risk factors for chronic diseases have been identified and intervention procedures through health education have been adopted
  - Incidences and mortalities of major chronic diseases have been dropped
  - Health expenditure has been reduced

Survival Data Revisited

Treated group: 23, 16+, 18, 20+, 24+

Control group: 15, 18, 19, 19, 20

1	0		5
0	1		5
	1		10

0		4
1		4
1		8

0		3
2		3
2		6

0		3
1		1
1		4

0		2
1		0
1		2

- One can re-express the data in 2 x 2 tables
- The celebrated M-H test can be utilized

  Mantel (1966) J. Amer. Statistical Association

Statistical Challenges III

Newly developed (bio-)markers permit more flexible designs for clinical trials

- Traditional clinical trials with "events" such as death and occurrence of AIDS are subject to criticism
  - More interested in quality-of-life for late stage cancer patients
  - It takes too long to get the drug(s) approved by FDA
- Markers such as SF-32, CD4 counts, cholesterol levels, etc. are readily available, which can be measured repeatedly over a <u>shorter</u> period of time
- Traditional regression methods assume statistical "independence" among observations, which is invalid

Pre-Post Design: Diagram

Y_0 | Y_1 Y_2 Y_T

$t_0 = 0$ ↖ t_1 t_2 … t_T Time

randomization

- Subjects are randomized to two (or more) groups
- Randomization is made without regard to baseline measurement, Y_0
- Time intervals between measurements same for all subjects
- Scientific question of interest:

  Rates of change in Y, on average, are the same between groups?
- An issue to keep in mind:

  How to effectively use the baseline measurements?

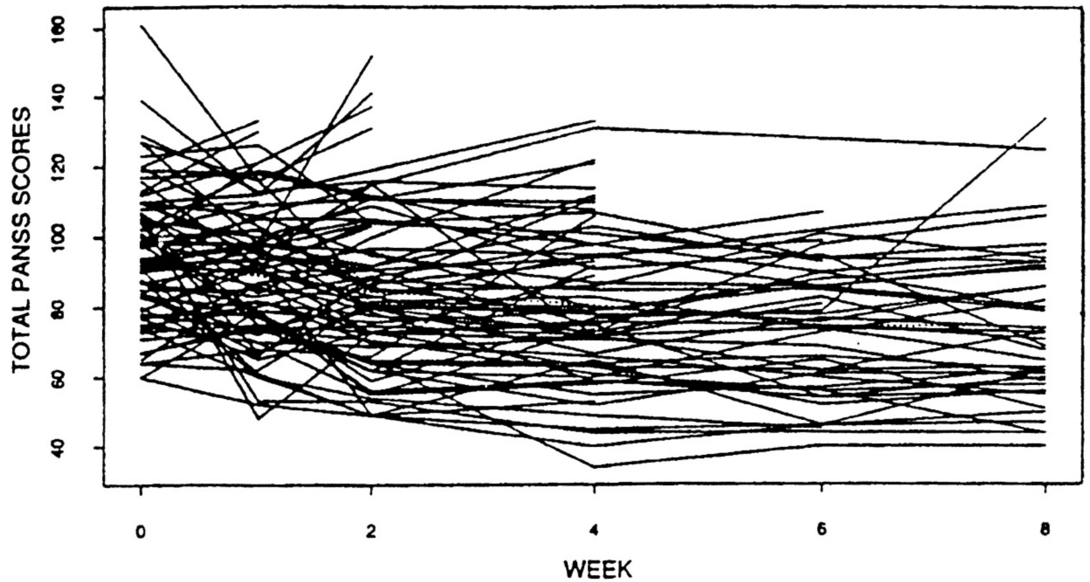
An Illustrative Example

- Back in the 80's, haloperidol was considered the standard treatment for schizophrenia
- A new treatment called risperidone was introduced to improve upon the effectiveness on negative symptoms
- 523 patients were randomized into six arms: placebo, haloperidol (20 mg) and risperidone at four dosage levels: 2, 6, 10 and 16 mg

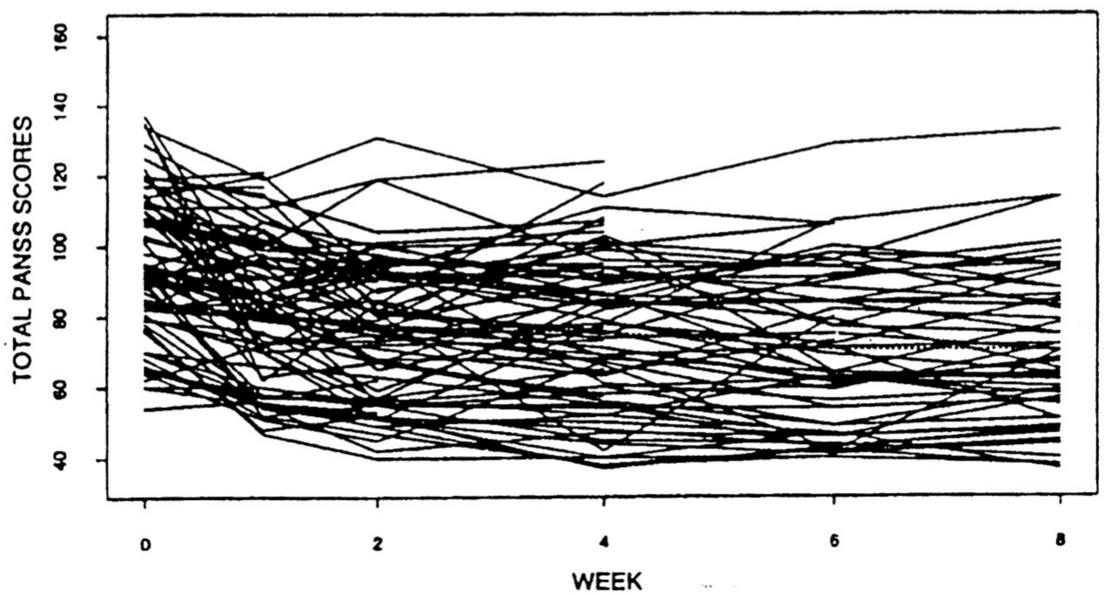
An Illustrative Example (cont'd)

- Primary outcome variable was the Positive and Negative Score Scale (PANSS)
  - Measuring the severity of schizophrenia
  - The higher the value, the more severe the condition
- PANSS was measured once prior to the randomization and at 1, 2, 4, 6 and 8 weeks after randomization
  - $T = 5$
  - $t_0 = 0$, $t_1 = 1$, $t_2 = 2$, …, $t_5 = 8$ (in weeks)

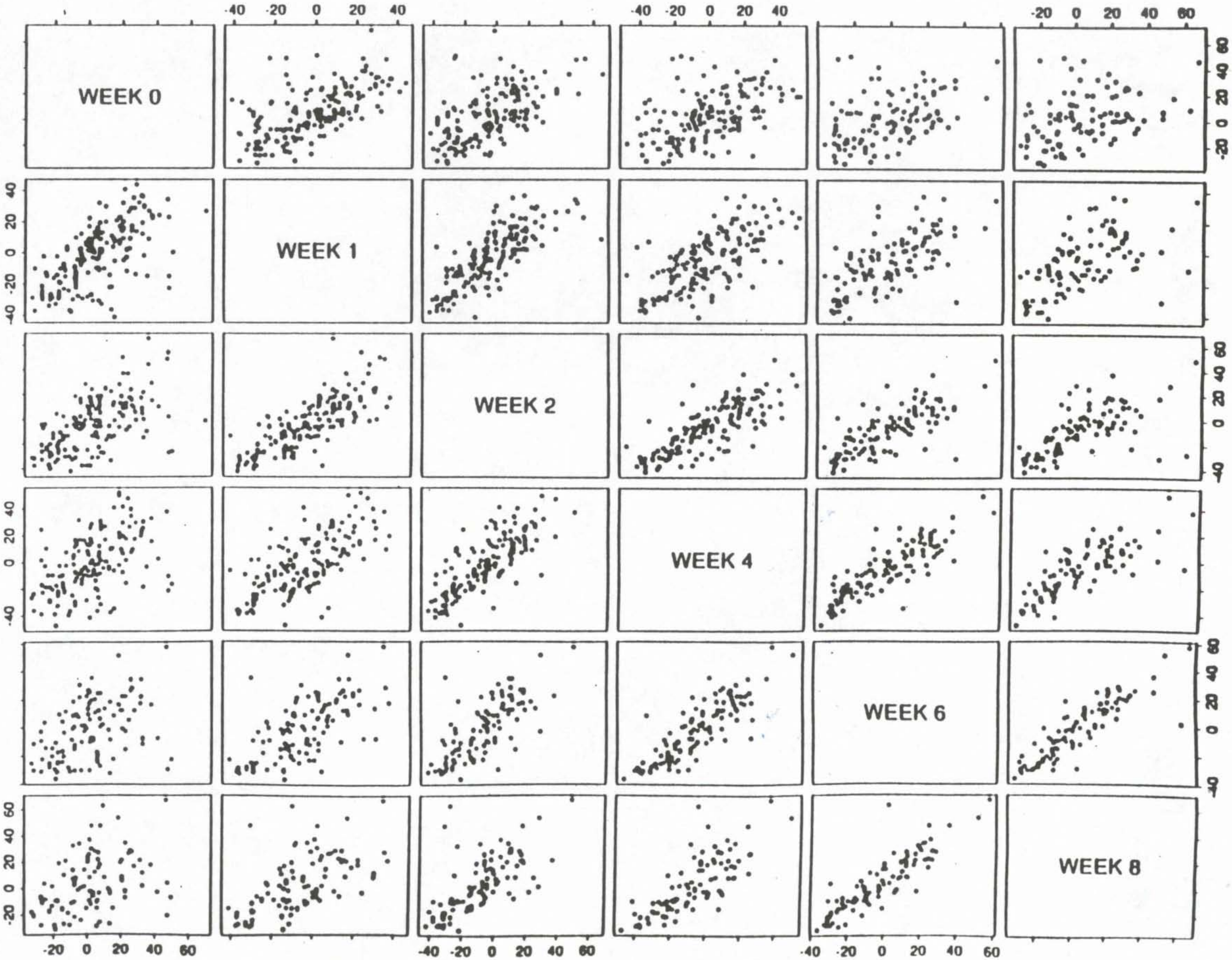
Haloperidol (20mg)



Risperidone (6 mg)



Empirical correlation matrix plot based on PANSS score correcting for treatment, time, and treatment by time interactiom.



Statistical Challenges III (cont'd)

- Such pre- and post-design along with statistical methods for analyzing longitudinal data have been actively developed in the 80-90's

Grizzle, Starmer & Koch (1967) Biometrics

Laird & Wares (1982) Biometrics

Liang & Zeger (1986) Biometrika

Liang & Zeger (1990) Sankya

Breslow & Clayton (1993) JASA

Diggle, Heagerty, Liang & Zeger (2002) Oxford University Press

Impacts and Consequences

- Longitudinal design has long been adopted in public health to address important questions
  - Growth of children
  - Changes in risk factors
- Availability of (bio-)markers provides further flexibility to conduct clinical trials more efficiently
- Timely statistical methods to take into account of correlation of repeated observations meet the demands and challenges (without having to “sweep under the rug”)

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Some Historical Remarks (cont'd)

- The field of biostatistics has drawn a good deal of attention in medical and public health community in the 50's and ever since
  - Many biostatistics departments were established
  - Biostatisticians as co-investigators for NIH grant applications in clinical and public health research
  - Signatures from both clinicians and biostatisticians in protocols and final reports for clinical trials by pharmaceutical industry

What prompt the Recognition?

- Valid scientific conclusions are essential to advance human health
- Such validity relies on <u>sound</u> statistical methods and reasoning to draw proper conclusions while acknowledging (or dealing with) “statistical uncertainty”
  - Understanding subject matters
  - Solid fundamental training in statistics

Statistical Uncertainty

Such uncertainty could be due to

- Insufficient sample size (sampling variation)
  - Budgetary consideration
  - Time constraint
  - Ethical consideration
- Measurement errors
  - Quality of instruments
  - Limitation of instruments
- Insufficient scientific knowledge

How to Deal with Statistical Uncertainty?

Appealing to the concept of probability, which forms the basis for statistical inference

Statistics versus mathematics

- While statistics deals with uncertainty, it is the opposite in mathematics
- Another way of saying:
  - Induction for statistics
  - Deduction for mathematics
- Just like statistics is a powerful tool for scientific pursuit, mathematics is important for statistics (reasoning, logical and analytical thinking, technical capability, etc.)

Graduate Education in Biostatistics

Qualifier: Serving as

- Faculty members (1982-2010)
- Founding Graduate Program Director (1996-2003)
- Co-Director (2006-2010)

for Department of Biostatistics, Johns Hopkins School of Public Health

Biostatistics Graduate Programs in U.S.

- Most of the Biostatistics Departments in the States are located within School of Public Health
- Graduate programs cover
  - Core courses in theory and methods
  - Elected courses in survival, longitudinal, statistical consulting, etc.
  - Seminars, “grand rounds”, etc.
  - “Exposures” to biomedicine, public health in particular, through courses (e.g., epidemiology), participation in research projects, etc.

Biostatistics Graduate Programs in U.S.A. (cont'd)

- There are intangible aspects which are just as important
  - Peer influence & competition (良性競爭)
  - Journal clubs
  - Participating in conferences, symposia
  - Extra-curriculum activities
  - Eager to engage in conversations (academic or not)

    Frank yet polite

Qualification as Graduate Students

- Strong quantitatively with interest in sciences
  - Calculus and linear algebra for Master degree
  - Real analysis for Ph.D.
  - Not necessary in biomedical sciences
- Connecting the dots (觸類旁通): broad yet focus
  - Generalized linear models

    Nelder & Wedderburn (1972) JRSSA
  - Correlated data

    Liang & Zeger (1993) Ann. Review of Public Health

Qualification as Graduate Students (cont'd)

- Strong communication skills
  - Can we explain the concept and limitations of "P-value" in words?
- English proficiency
- Internal drive
  - Self motivated
  - Setting priority straight
  - Not afraid to fail

Job Markets in Biostatistics

- It has been and continues to be excellent in the States, both in academics and industries
  - One of the hottest fields
  - Reflecting the appreciations by the scientific communities and by the publics in general
- In Taiwan, there are ways to go
  - There are positive signs (國衛院）
  - But more work is needed

Discussion

- Biostatistics as a field has made a big stride in the past century regarding as a
  - Discipline developing its own principles (how to interpret scientific evidence) and methods
  - “Tool” to help scientists, policy makers and industrial leaders to unmask phenomena so as to advance human health

Discussion (cont'd)

- The last century demonstrated that research universities in U.S. have been instrumental for advancing science and technologies, which in turn improving standards of living
- (Bio)statistical profession has contributed through training high quality graduates and engaging in collaborative and methodological research
  - Injecting concept of randomization into clinical trials
  - Searching for preventable risk factors of chronic diseases
  - Developing new designs and methods for drug approval

Discussion (cont'd)

- It has come a long way for medical community, health officials and (pharmaceutical) industry to recognize what biostatistics could offer
  - It is more than providing "p-values" once the data were collected or "quick fix-ups" when the manuscripts were rejected by the medical journals
  - It takes collaborations from the onset
  - There are difference between consultation and collaboration

Discussion (cont'd)

- It is important to recognize that (bio)statistics is NOT a penicillin as it has its own limitations
  - It is essential that such limitations be recognized by scientists and biostatisticians so as not to abuse its utility
  - To do so, it goes back to the fundamentals, i.e., statistical reasoning
    - What are the scientific questions?
    - Do the statistical methods (tools) help to address those questions in a meaningful way?

Discussion (cont’d)

Meanwhile, one needs to be

- Politically savvy as, for example, political climates for dealing with infectious diseases are vastly different between the 20’s ad the 80’s
- Conscientious to engage in debates/discussions when scientific findings have the potential to be implemented for policy making
- After all, we are part of the society, not ivy tower

Discussion (cont'd)

There are many challenges ahead:

- Both scientific pursuit and technological development are advancing simultaneously
  - At risk that science is dictated by technology
  - Hypothesis driven versus exploring data/generating hypothesis
  - Education as well, for that matter
- Aging is becoming a serious societal issue
  - Fewer new births
  - Higher health expenditure among elderly
  - Long term health care (長期照顧) especially for demented individuals

Discussion (cont'd)

Can our profession continue to live up with the expectation and anticipation from the society to help tackling these important issues?

- We need to understand the subject matters first before formulating these issues statistically so as to tackle
  - Service management, finance and work force to integrate acute, post-acute, long-term and community cares
- We need more young, energetic and committed researchers to join the battles