SEMINAR

DEMOGRAPHIC, ECONOMIC AND FINANCIAL PERSPECTIVES 2003-2030

IMPACT OF GENETICS ON MORTALITY

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PRESENTATION OUTLINE

- MODES OF GENETIC TRANSMISSION
- MUTATIONS
- HETEROGENEITY OF GENETIC DISEASES
- GENETIC DISEASES AND LIFE EXPECTANCY
- TREATMENT OF GENETIC DISEASES
- LIPID METABOLISM: PREDOMINANT FACTOR IN HEALTH OF INDIVIDUALS
- LESSONS TO BE LEARNED FROM CURRENT KNOWLEDGE AND LONG-TERM PROJECTIONS

HETEROGENEITY OF GENETIC DISEASES

EXAMPLE: *MUCOVISCIDOSIS

(CYSTIC FIBROSIS OF THE PANCREAS)

A VERY LARGE NUMBER OF MUTATIONS OF THIS GENE CAN CAUSE THIS DISEASE

FAMILIAL HYPERCHOLESTEROLEMIA (FH) IS A DOMINANT HEREDITARY DISEASE

*MUTATION OF LDL GENE

(LOW-DENSITY LIPOPROTEIN)

COMMON DISEASES AND TRANSMISSION RISK

- **EXAMPLE: INSULIN-DEPENDENT DIABETES (TYPE I) 5 TO 10%**

SUSCEPTIBILITY

SEGREGATION OF DNA MARKERS WITH THE GENE(S) OF A DISEASE

ENVIRONMENT

JAPANESE AMERICANS HAVE MORE:

COLON AND STOMACH CANCERS AND MORE CORONARY HEART DISEASE AND STROKE

FAMILIES AT RISK

BENEFITS RELATED TO:

*** DIAGNOSTIC TESTS**

*** REPRODUCTION**

***ANNUAL FOLLOW-UP**

MORTALITY DEFERRED

20% OF POPULATION > AGE 65 IN 2020

ONE YEAR OF ACTIVE LIVING GAINED
MEANS 4 YEARS LESS OF UNCERTAIN HEALTH

BRODY AND MILES 1990

MORTALITY AND LIFESTYLE 1962-1990

AGES 45-84

14,786 INDIVIDUALS MONITORED DURING THOSE YEARS

ACTIVITY DELAYS CAUSES OF MORTALITY AND ↑ LONGEVITY

Paffenbarger et al., 1994

TWINS AND LONGEVITY

ENVIRONMENT IS MORE IMPORTANT THAN GEMINATION IN ASSESSING LONGEVITY

KING et al., 2002

GENETIC ASSESSMENT

- LATE-ONSET GENETIC DISEASE
  - SOCIAL PROBLEMS
  - NATURE OF DISEASES
  - ACCESSIBILITY
  - TREATMENT / FOLLOW-UP
  - COST OF TREATMENT

SECONDARY PATHOLOGIES

EFFECTIVE TREATMENT OF A DISEASE DOES NOT RULE OUT CANCER AT A LATER DATE

HIRSCH, 2002

LONGEVITY

- APPROX. 15% OF POPULATION IN 1990 WAS OVER AGE 65
- EXPECTED LONGEVITY 75 YEARS
- INCREASE?
  - * < AGE 12 AS A RESULT OF:
  - * MULTISYSTEMIC PATHOLOGY
  - * ENVIRONMENT
  - – Pushparaj et al., 1983

OBESITY
AGE 65 AND OVER

- INACTIVITY
- REDUCED METABOLISM
- CHANGE IN NUTRITION
  - RISK
- DISABILITY
- DISEASE
- MORTALITY

INELMEN et al., 2003

LATE-ONSET DISEASES

- **SYNDROMES** ***(POLYCYSTIC KIDNEY)***
- **METABOLIC DISEASES** ***(HYPERAMMONEMIA)***
- **CANCERS** ***(INTESTINAL POLYPOSIS)***
- **NEUROLOGICAL DISEASES:** ***ALZHEIMER'S***
- **SKELETAL DISEASES:** ***SPONDYLOLISTHESIS***

ATHEROSCLEROSIS

CORONARY HEART DISEASE

CEREBROVASCULAR DISEASE

PERIPHERAL ARTERIAL DISEASE

HEREDITARY BREAST AND OVARIAN CANCERS

SPORADIC.....90%

HEREDITARY.,…5-10%

PROTOCOLS

- THERAPY BY BLOCKING THE METABOLIC PATHWAY
- GENE THERAPY
- REPLACEMENT THERAPY
  - ENZYME
  - ORGAN

COMMON DISEASES (US) IN ORDER OF IMPORTANCE

CARDIOVASCULAR (1)

ARTHRITIS (2)

DIABETES (3)

CANCER (4)

ALZHEIMER'S (5)

OSTEOPOROSIS (6)

MULTIPLE SCLEROSIS (7)

SCHIZOPHRENIA (8)

INCIDENCE OF COMMON DISEASES IN CANADA'S POPULATION (IN MILLIONS)

Alzheimer's 0.4

Arthritis 5.0

Cancer 1.0

Cardiovascular 6.0

Diabetes 2.0

Schizophrenia 0.2

Multiple sclerosis 0.04

Osteoporosis 0.1

DISEASES AND AGING-I

ALZHEIMER'S

DEMENTIA

DEPRESSION

PARKINSON'S

NEUROPATHOLOGIES

AGING-II

ATHEROSCLEROSIS

CANCER

TYPE-2 DIABETES

CONGESTIVE HEART FAILURE

LUNG DISEASE

INCIDENCE OF DYSLIPIDEMIA

- **QUEBECOIS** **1/270**
- **QUEBECOIS: CERTAIN REGIONS 1/80**
- **NORTH AMERICAN POPULATION 1/500**

RISK OF DEVELOPING HYPERCHOLESTEROLEMIA IN INDIVIDUALS WHO ARE HETEROZYGOTIC OR CARRYING A MUTATED GENE

- 20% AGE 40
- 45% AGE 50
- 75% AGE 60

RISK OF HYPERCHOLESTEROLEMIA IN WOMEN WHO ARE HETEROZYGOTIC (OR CARRYING A MUTATED GENE)

- 25% AT AGE 50
- 50% AT AGE 60

A NUMBER OF GENES AND OTHER FACTORS AFFECT HDL* CHOLESTEROL

- **OBESITY**
- **ALCOHOL**
- **EXERCISE**
- **TOBACCO**
- ***** ***HIGH-DENSITY LIPOPROTEIN***

173 FH CHILDREN TREATED FOR OVER 48 WEEKS

from *JONGH et al., 2002*

LDL CHOLESTEROL	**↓ 41%**
CHOLESTEROL	**↓ 31%**
TRIGLYCERIDES	**↓ 9%**
HDL CHOLESTEROL	**↑3%**

21 MILLION YEARS OF DISABILITY SAVED THROUGH COLLECTIVE TREATMENTS AROUND THE WORLD *

**MURRAY 2003*

STUDY OF TREATMENT COST

Marang-van de Mheen et al., 2002

COST OF SCREENING LOWER THAN COST OF TREATMENT AMONG 2,229 HYPERCHOLESTEROLEMIC SUBJECTS

CONCLUSION-1 (TREATMENT)

THE CARE OF CHILDREN FROM HIGH-RISK FAMILIES PLAYS A PRIMARY ROLE IN PREVENTION

SIGNIFICANT BUT UNMEASURED INCREASE IN SURVIVAL OF PATIENTS SUFFERING FROM DYSLIPIDEMIA

CONCLUSION-2 (TREATMENT)

- **FINDINGS OF STUDIES UNDER WAY ON FOOD RESTRICTIONS FOR CHILDREN FROM FAMILIES SUFFERING FROM FAMILIAL HYPERCHOLESTEROLEMIA WILL NOT BE KNOWN FOR A FEW YEARS.**

HEREDITARY METABOLIC DISEASES

- OVER A 10-YEAR PERIOD
  - 12% OF DISEASES HAVE THE SAME SYMPTOMS
  - 31% OF DISEASES NOT IMPROVED IN 1993 COMPARED TO 48% IN 1983
  - 40% OF DISEASES IMPROVED IN 1983 VERSUS 50% IN 1993

Treacy et al., 1995

HEREDITARY METABOLIC DISEASES

- **TREATMENT NOT YET OPTIMUM, DESPITE:**
  - ***TRANSPLANTS**
  - ***PHARMACOTHERAPY**
  - ***CLINICAL SUPPORT**

RESEARCHES-1

- IN MAMMALS, GENES THAT REDUCE LONGEVITY ACT ON DISEASES
- FRUIT FLIES AND SMALL RODENTS DISPLAY BEHAVIOUR SIMILAR TO THAT OF HUMANS WITH REGARD TO LONGEVITY

RESEARCHES-2

- PENETRANCE OF CERTAIN GENES INFLUENCES LONGEVITY IN RODENTS AND HUMANS
- CERTAIN GENES PROVIDE MICE WITH RESISTANCE TO DIETS THAT MAY ALTER LIPID METABOLISM

RESEARCHES-3

- THERE IS NO EVIDENCE THAT ONE OR MORE GENES SPECIFICALLY CONTROLS THE LENGTH OF ADULT LIFE

LESSONS TO BE LEARNED FROM CURRENT KNOWLEDGE

- THERE IS NO PERMANENT CURE FOR GENETIC DISEASES
- THE ENVIRONMENT AND THE GENOME HAVE A DIRECT INFLUENCE ON LONGEVITY

EPILOGUE (1)

Is there a limit to improved life expectancy?

- **Since the last century, the spectacular development of medicine has increased the probability of survival. Progress in anesthesia and surgery, infectious disease prevention (*vaccination*), medical imaging (*X-rays, computed tomography, ultrasound, magnetic resonance imaging*), obstetrical and neonatal care, metabolic disease screening, tissue and organ transplants, not to mention the discovery of antibiotics, have resulted in observed changes in increased life expectancy.**

EPILOGUE (2)

- **In a transplant (*if there is no rejection*), the new organ (*heart, kidney, liver*) retains its properties unless it is affected by the environment (*alcoholism, hypercholesterolemia, tobacco abuse or any serious disease from which the patient may suffer*).**
- **Cultured skin cells multiply and ultimately produce large quantities of tissue. This is one of the techniques used to care for burn victims. But there is a limit to cell growth in a laboratory setting, and cells eventually stop dividing, an irreversible phenomenon that is responsible for aging.**

EPILOGUE (3)

- **Briefly stated, life expectancy has increased by 10 years or more in recent years as a result of new technologies, but it does not follow that this increased survival will continue or that it will continue at a particular rate. New technologies will be accessible to the entire population, which raises very serious ethical problems for care teams which will very often have to choose between introducing new and very costly therapies and continuing the day-to-day care required for the population as a whole.**

EPILOGUE (4)

- At both ends of the curve are individuals who, as a result of their genetic background, show signs of early aging and die prematurely. At the other extreme, some families have a genetic constitution that promotes good health and a distinctly higher average age at death than the general population. There are even cases of centenarian families.

EPILOGUE (5)

- We all experience a certain number of genetic changes or mutations that act directly on development and metabolism. The molecular approach or the study of genes (DNA) on viability and longevity shows that long-term projections based on the beneficial effects of new therapies are of only limited predictive value.

- In other words, the perfect genetic recipe for longevity has not yet been found.

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