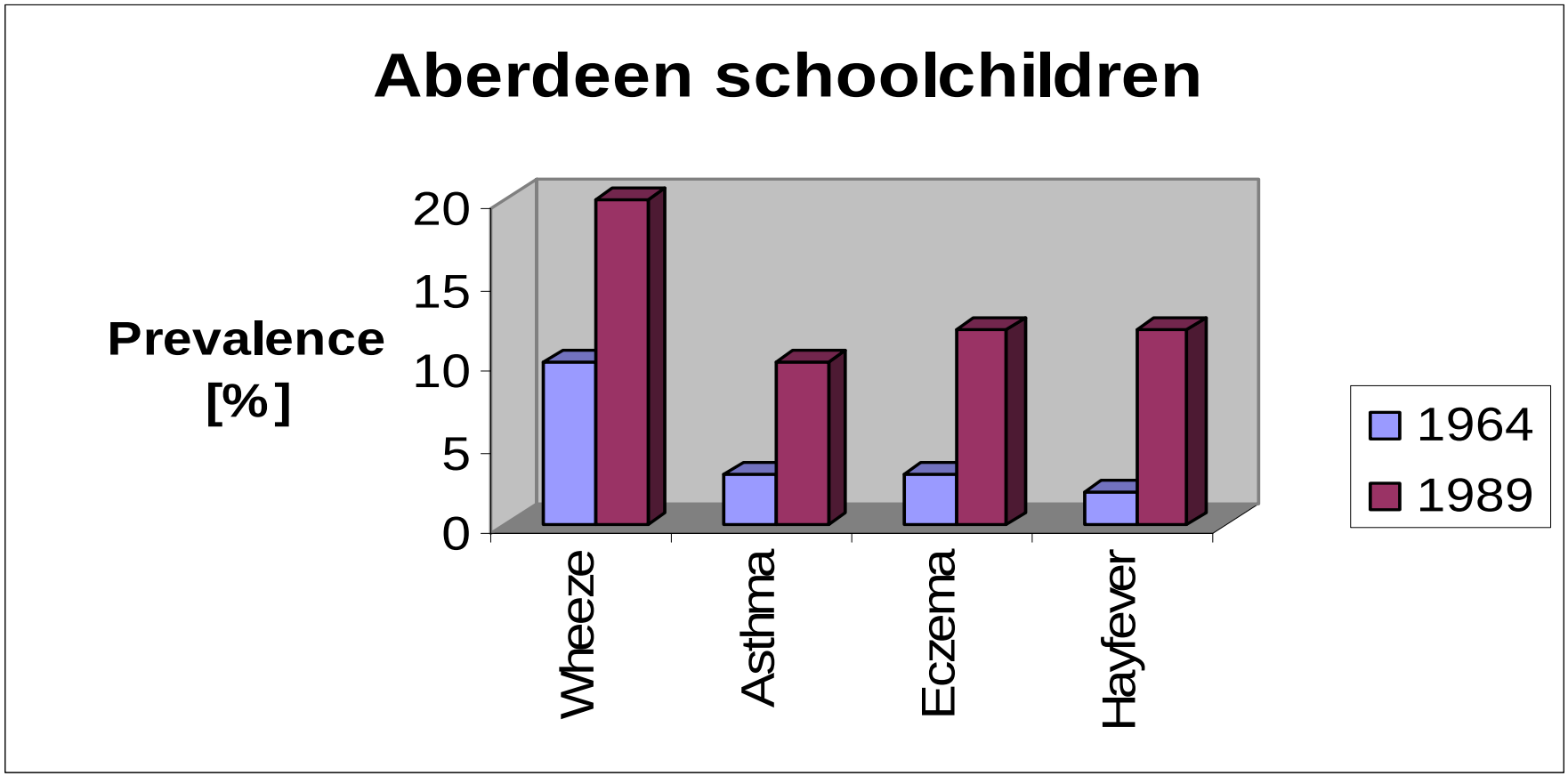
The Hygiene Hypothesis: an analysis based on information theory

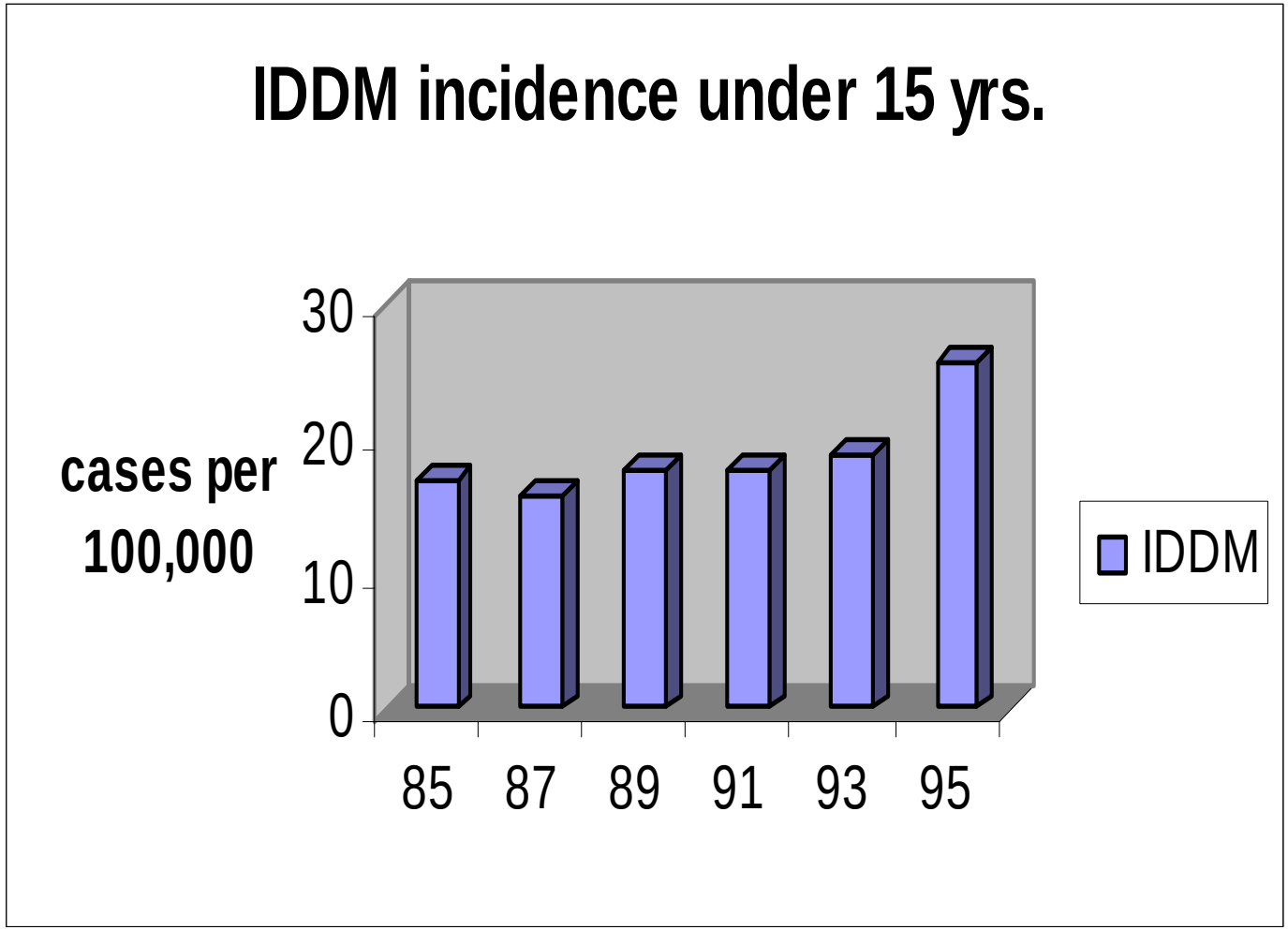
J A Morris: presidential address to Manchester Medical Society

1. Microbial flora

2. Mathematical models

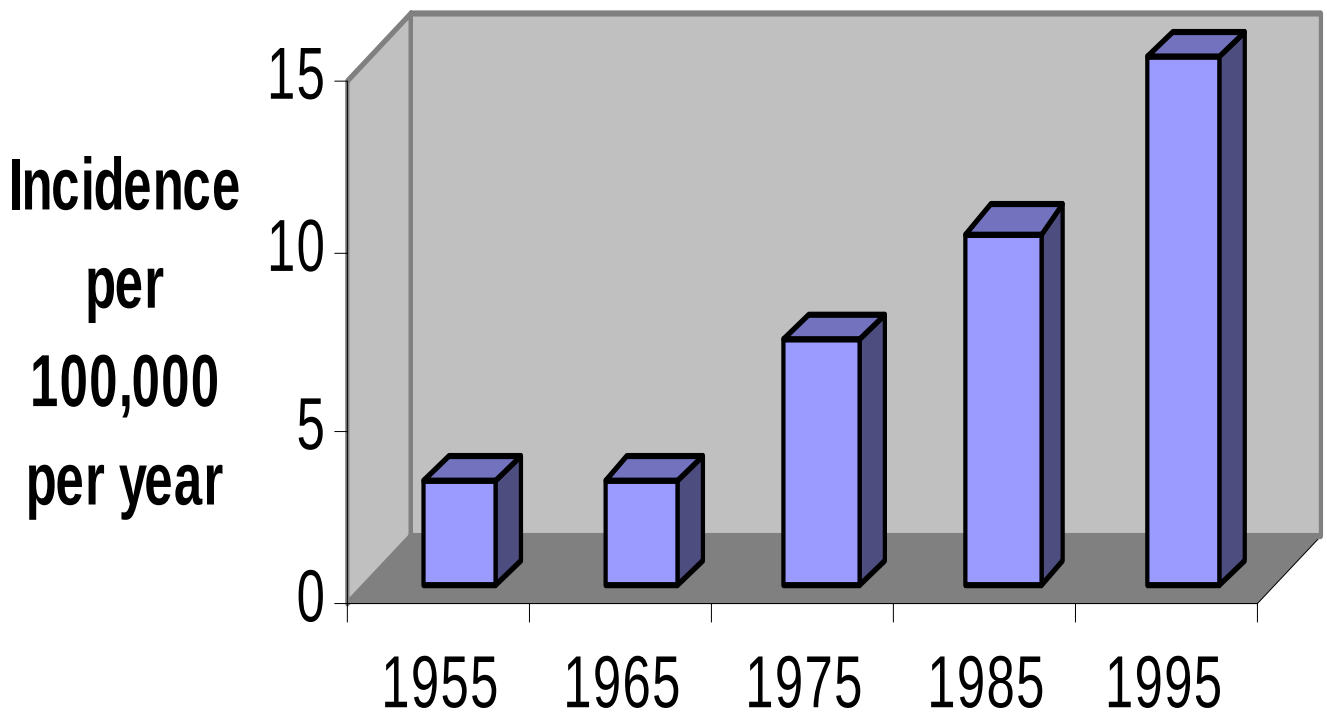
3. Information theory


Aberdeen schoolchildren
Prevalence [%]
20
15
10
5
0
Wheeze
Asthma
Eczema
Hayfever
1964
1989



IDDM in children under 15 years in Oxford, 1985 - 1995

IDDM under 5 yrs. England



Rising Incidence

1Asthma

2.Eczema

3.Hayfever

4.IDDM

5.Crohn`s disease

6.Multiple sclerosis

7.Rheumatoid arthritis

Hygiene hypothesis: the risk of immune mediated disease rises with:

1.improved socio-economic conditions

2. small sibship size

3.first born rather than later born

4.delayed contact with other children

5.rural environment

These are all factors that decrease exposure to micro-organisms and decrease childhood infection.

The bipolar TH1/TH2 concept

TH1[T helper cells type 1]:

concerned with protection against intracellular infection

produce interferon gamma and TNF

associated with organ specific autoimmune disease e.g. IDDM

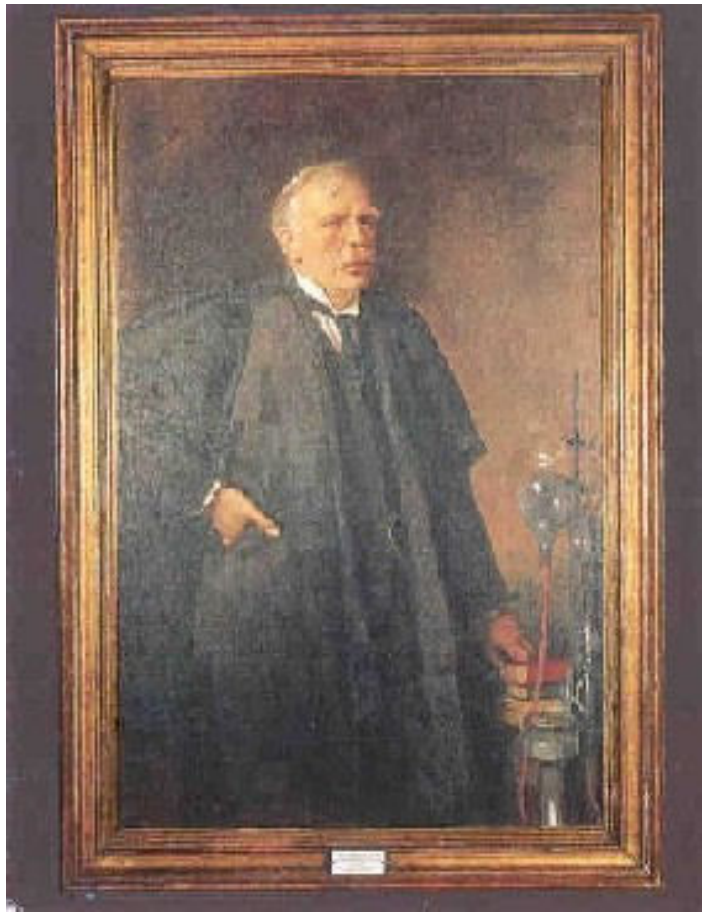
TH2 [T helper cells type 2]

protection against extracellular infection e.g. parasites

increased interleukins 4 to 10, raised serum IgE

associated with type 1 allergy e.g. asthma, eczema.

Hygiene hypothesis is vague and *post hoc*



Ernest Rutherford

Physics

Idea first – express in mathematics – conclusion –test in experiment – modify and develop a model

Theory and experiment

Stamp collecting

Collect data and then ask what does it mean?

- Matter and energy
- $E = mc^2$
- Energy distorts space time hence gravity
- Uncertainty principle
- Energy/uncertainty

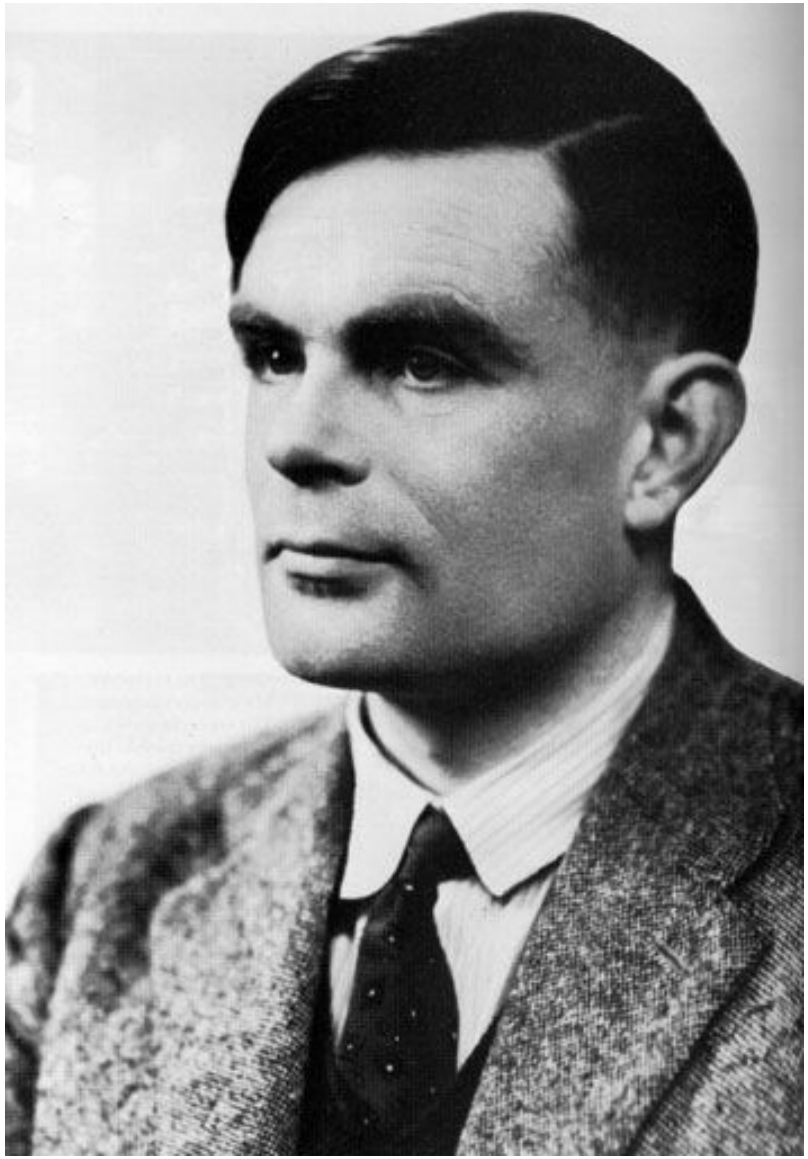
- **Information**
- **Reduction of uncertainty: one bit of information reduces uncertainty by one half.**
- **Energy is a form of information (“it from bit”)**

Information is to biology what energy is to physics

Can create a theoretical biology based on information theory

History of information

1. Telecommunications
2. Heisenberg's uncertainty principle
3. Alan Turing – Cambridge 1930s
4. World War 2 – enigma
5. Digital computer – Turing in Manchester
6. Shannon – mathematical theory of information -1948
7. Crick and Watson – DNA is the molecule of information



Information processing systems:

- Finite capacity
- Information processed in noise: errors will occur
- Systems subject to law of entropy –deteriorate with time – error rate rises with time
- Redundancy: complex systems need high level of redundancy to reduce error rate

Information processing systems

- Brain
- Digital computer
- Neural networks
- Immune system
- Physiology

Immune system / microbial flora

- 30,000 protein coding genes in human genome
- Code for over 250,000 proteins
- Bacteria have 3000 to 5000 genes coding for 3000 to 5000 proteins
- Microbial flora: 400 species with 40 at any one time.
- Code is linear sequence of amino acids – perhaps 10, therefore ten thousand billion possibilities.

Immune system / microbial flora

- Self –must recognise and avoid attack
- Not self / important – attack
- Not self / unimportant - ignore

INFORMATION THEORY [Shannon 1948]

1.All systems that transmit information have a finite capacity.

2.Information is transmitted in a background of noise and there is always a possibility of error.

3.Systems decay with time according to the laws of entropy and the error rate will rise.

4.Redundancy reduces error in complex information processing systems.

Probability of error in a single system:

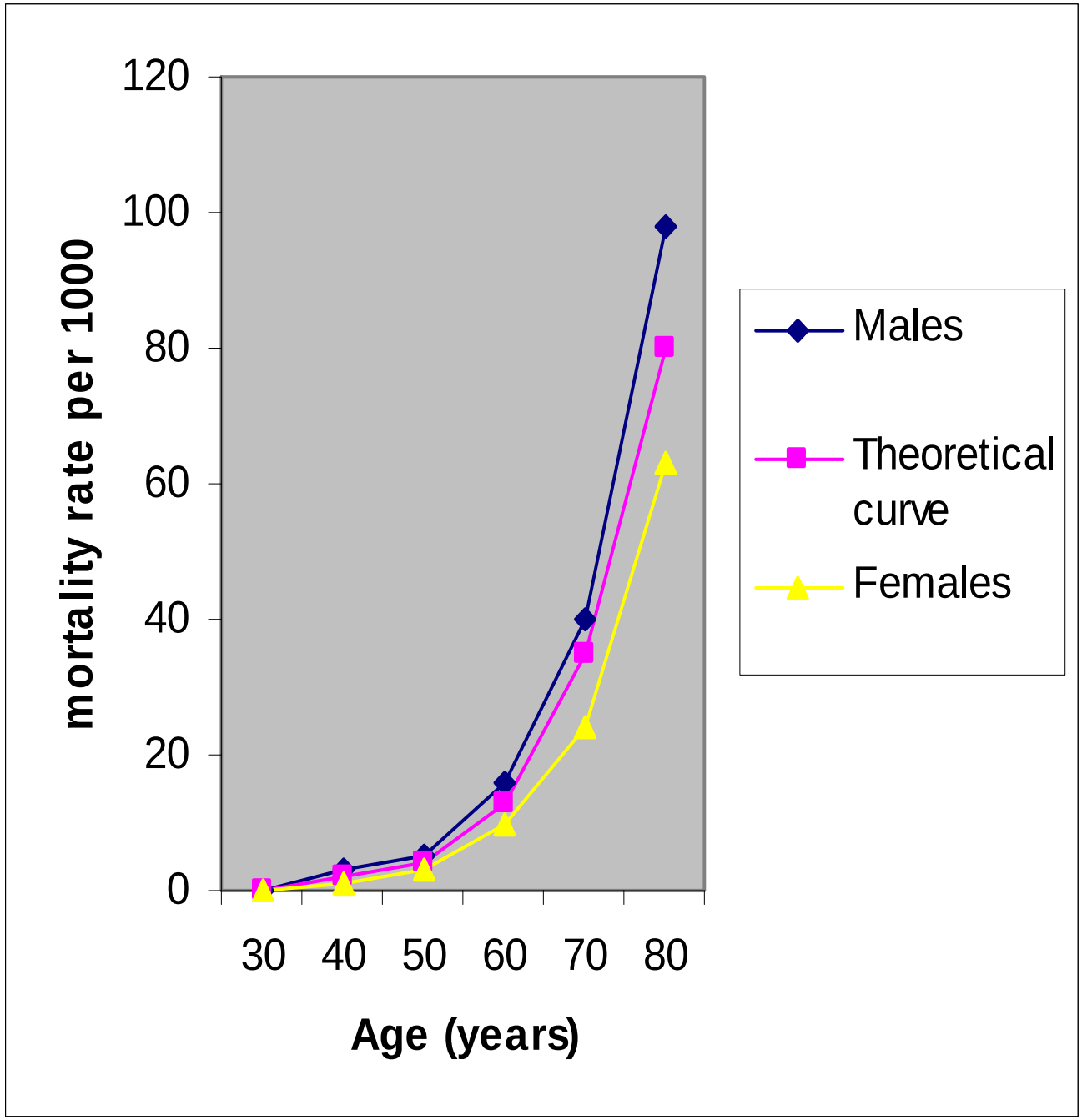
$$1 - R$$

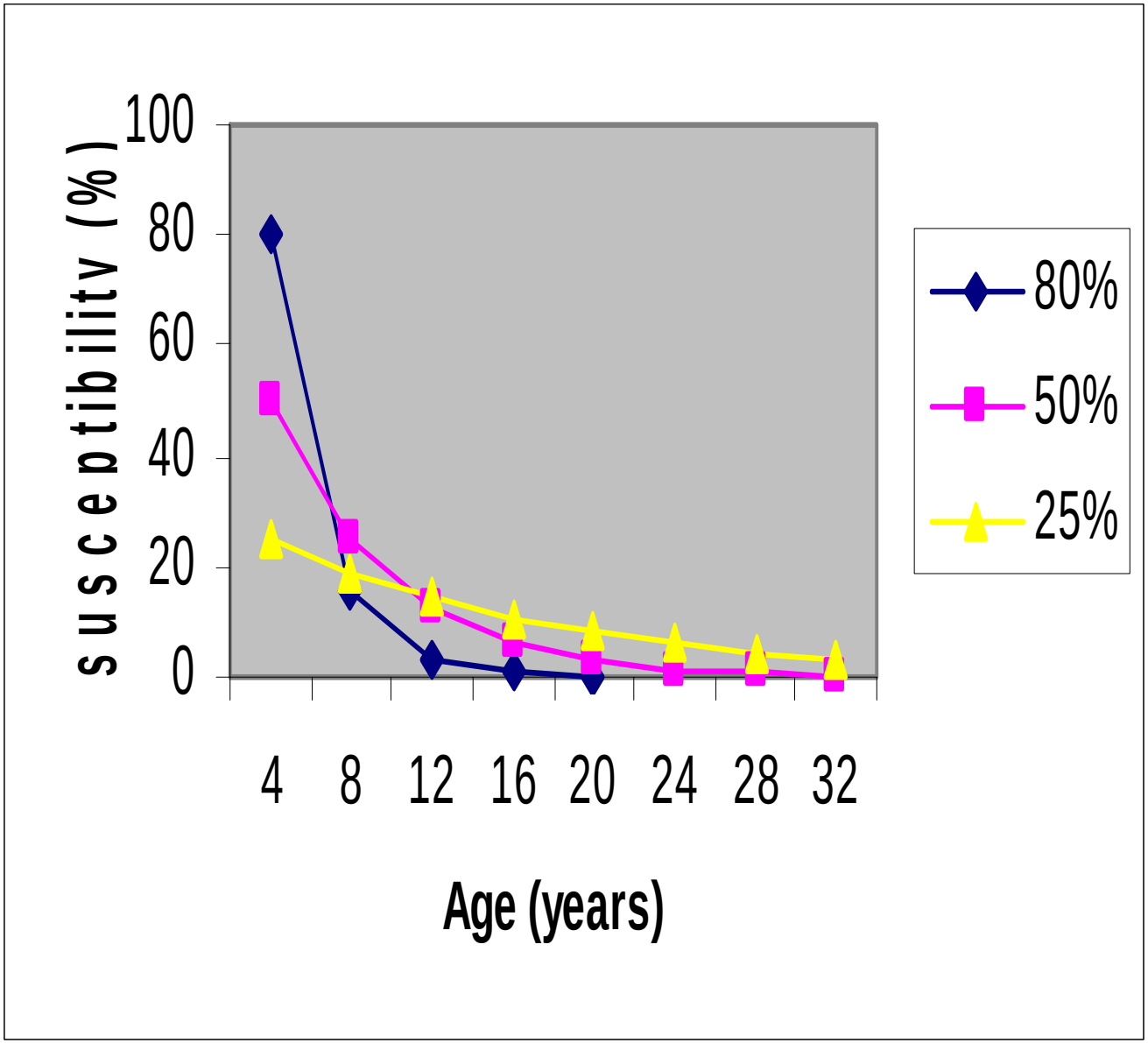
Probability of error when the system decays with time:

$$1 - Re^{-kt}$$

Probability of error in a redundant system [n-fold]

$$[1 - Re^{-kt}]^{n}$$


120
100
80
60
40
20
0
mortality rate per 1000
30
40
50
60
70
80
Age (years)
Males
Theoretical curve
Females


susceptibility (%)
100
80
60
40
20
0
4
8
12
16
20
24
28
32
Age (years)
80%
50%
25%

Disease caused by first exposure to a specific microbe:

TYPE ONE. Fail to recognise a key epitope as foreign,this increases the chance of infection.

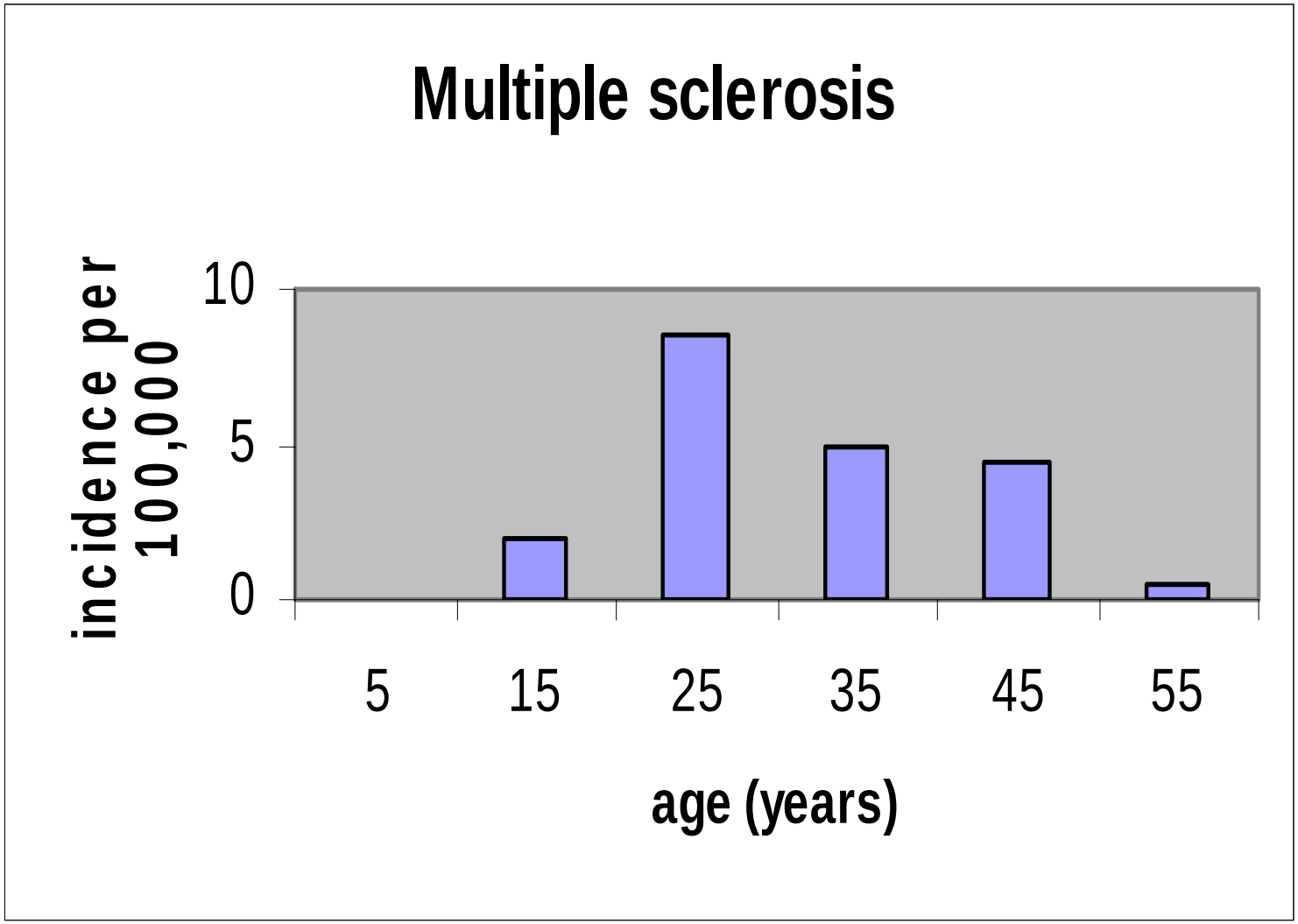
TYPE TWO. Fail to recognise that a microbial epitope is the same as a self epitope, this increases risk of autoimmune disease.

TYPE THREE. Fail to ignore that which should be ignored, increases risk of atopic disease

2. The age incidence curve of disease is the product of:

Ce^{-mt} and $(1 - Re^{-kt})^{n}$. The curve rises to a peak in early or middle life and then falls

3. For common microbes the peak is early and the incidence is low, for less common microbes the peak is later and the incidence higher.



Acheson E D, 1985, data from Rochester.

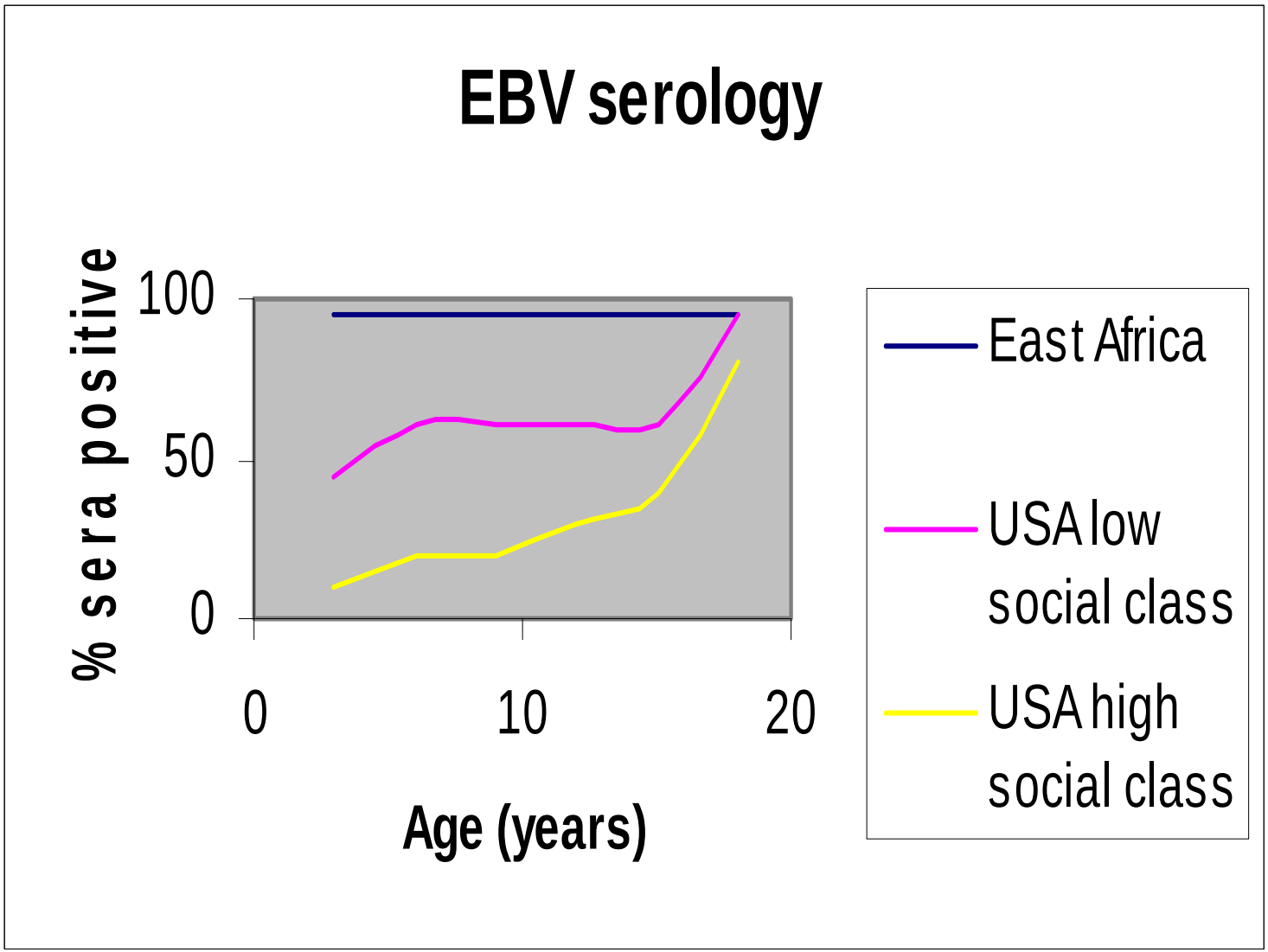
Multiple Sclerosis:

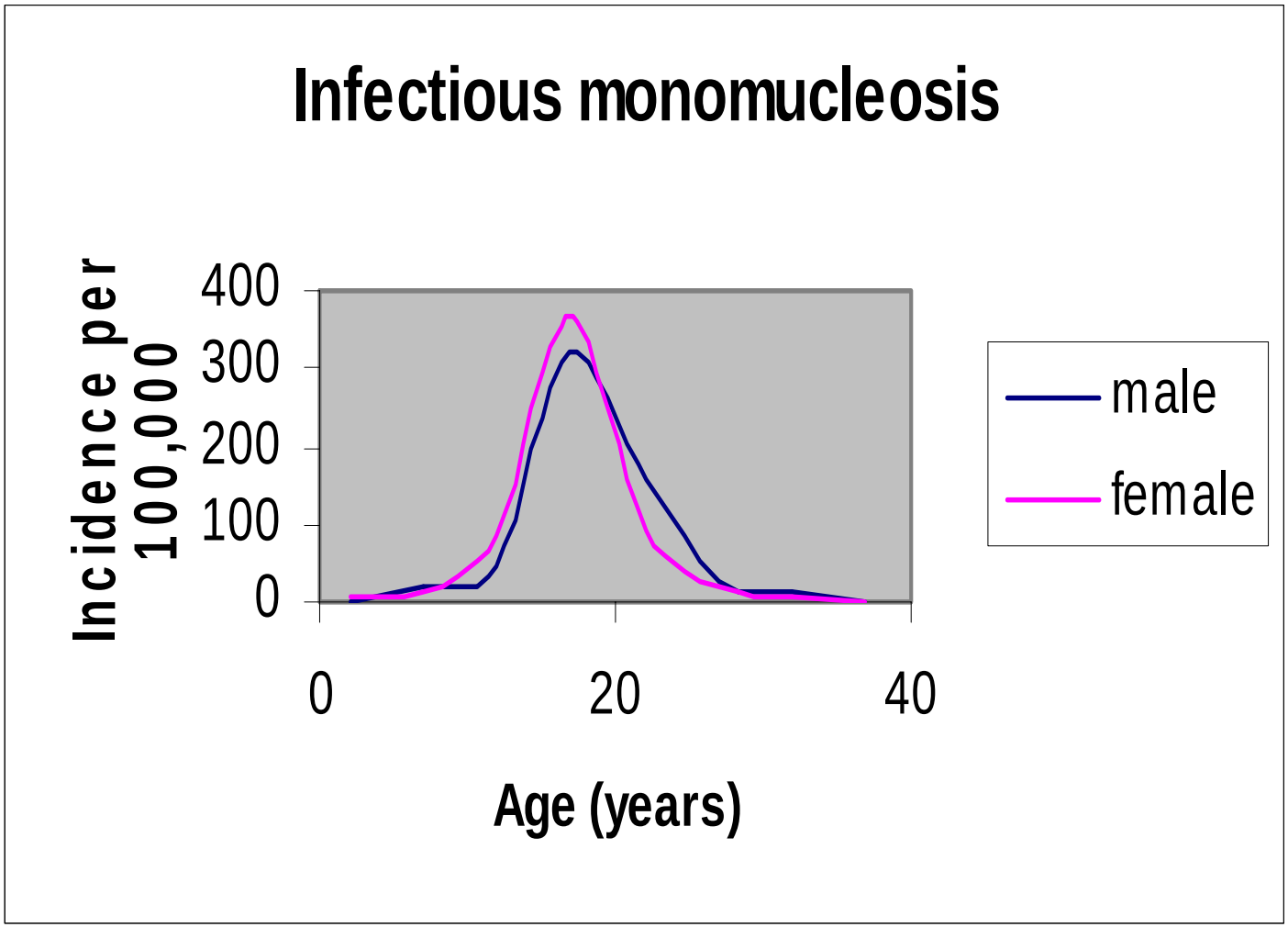
1.Geography - colder climates, technically advanced, slower circulation, more disease.

2.Migration - migrants have the risk of the place in which they spend their childhood

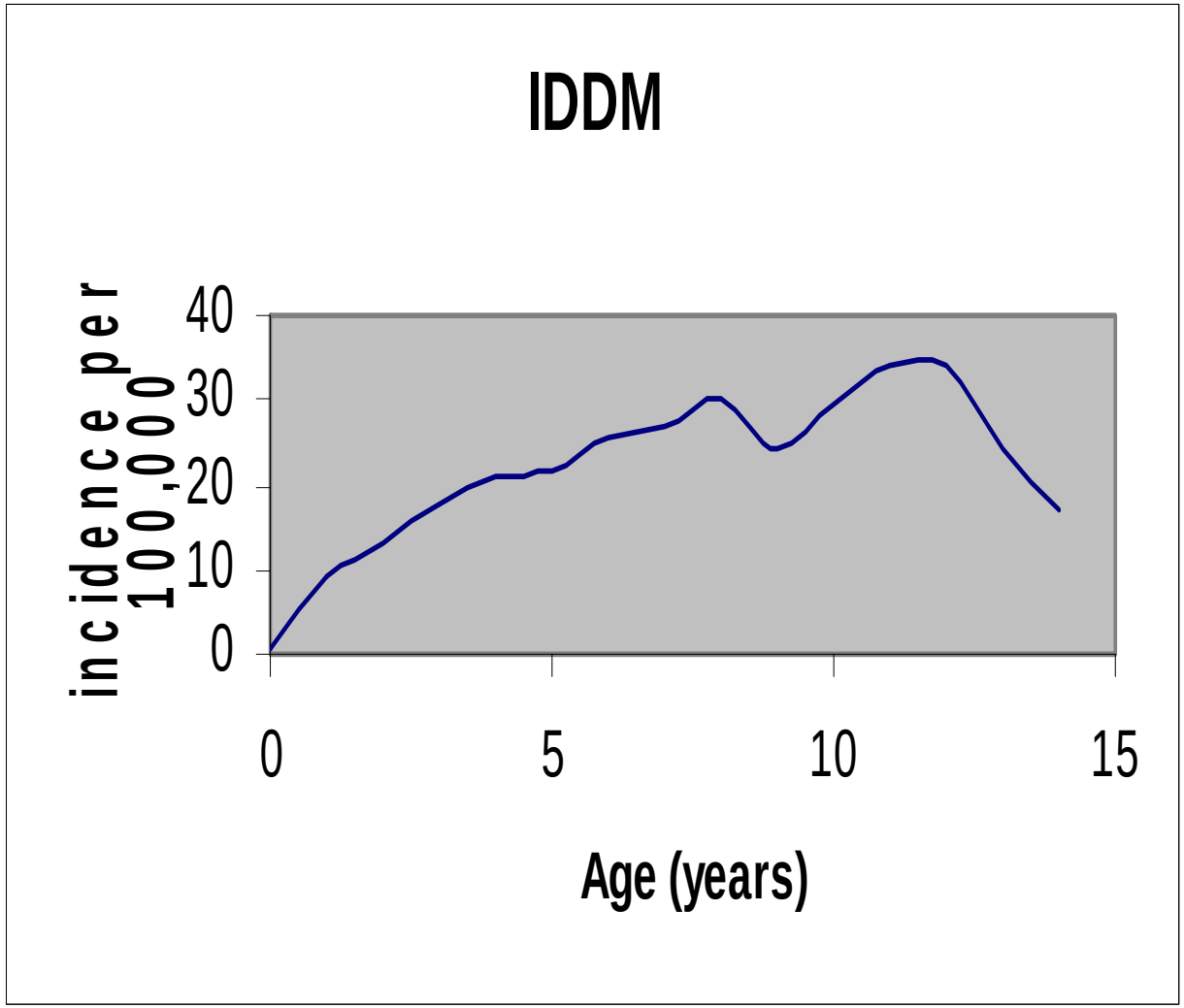
3.The clinical course is one of exacerbation and remission.

4.Genetics - increased risk in families, HLA association, consistent with microbial pathogenesis.


EBV serology
% sera positive
100
50
0
0
10
20
Age (years)
East Africa
USA low social class
USA high social class



Cases of Infectious mononucleosis, Atlanta 1968.



Epidemiology of IDDM in Swedish children 1977 - 1983

IDDM.

1.GENETICS - 50% concordance in monozygotic twins, 10% in dizygotic twins

- association with HLA DR3 and DR4.

2.GEOGRAPHY- incidence of IDDM in Finland is 36 times that in Japan

- eightfold variation in Europe

3.MIGRANTS - acquire the risk of the country to which they move.

IDDM in Lancashire and Cumbria.

Anna Marshall, PhD thesis, Lancaster University.

Case control study, cases 196, controls 381

Barrow, Kendal, Lancaster, Blackburn, Burnley.

Multivariate analysis

Results: 1. Room shared with sibling, OR 0.3[0.15 - 0.58], p = 0.0003

2. Social contact between 6 and 11 months, OR 0.44 [0.25 - 0.75], p = 0.0024

Low dose, early, mucosal exposure

meet under protection of maternal IgG or breast milk IgA

High dose, late and parenteral.

Summary 1

- We need a theoretical biology to guide data acquisition and experiment
- Employ mathematical methods
- Based on information theory

Summary 2

- Central role of microbial flora in disease
- Explains age incidence
- Low dose, early mucosal exposure
- Map microbial flora and learn to control exposure.