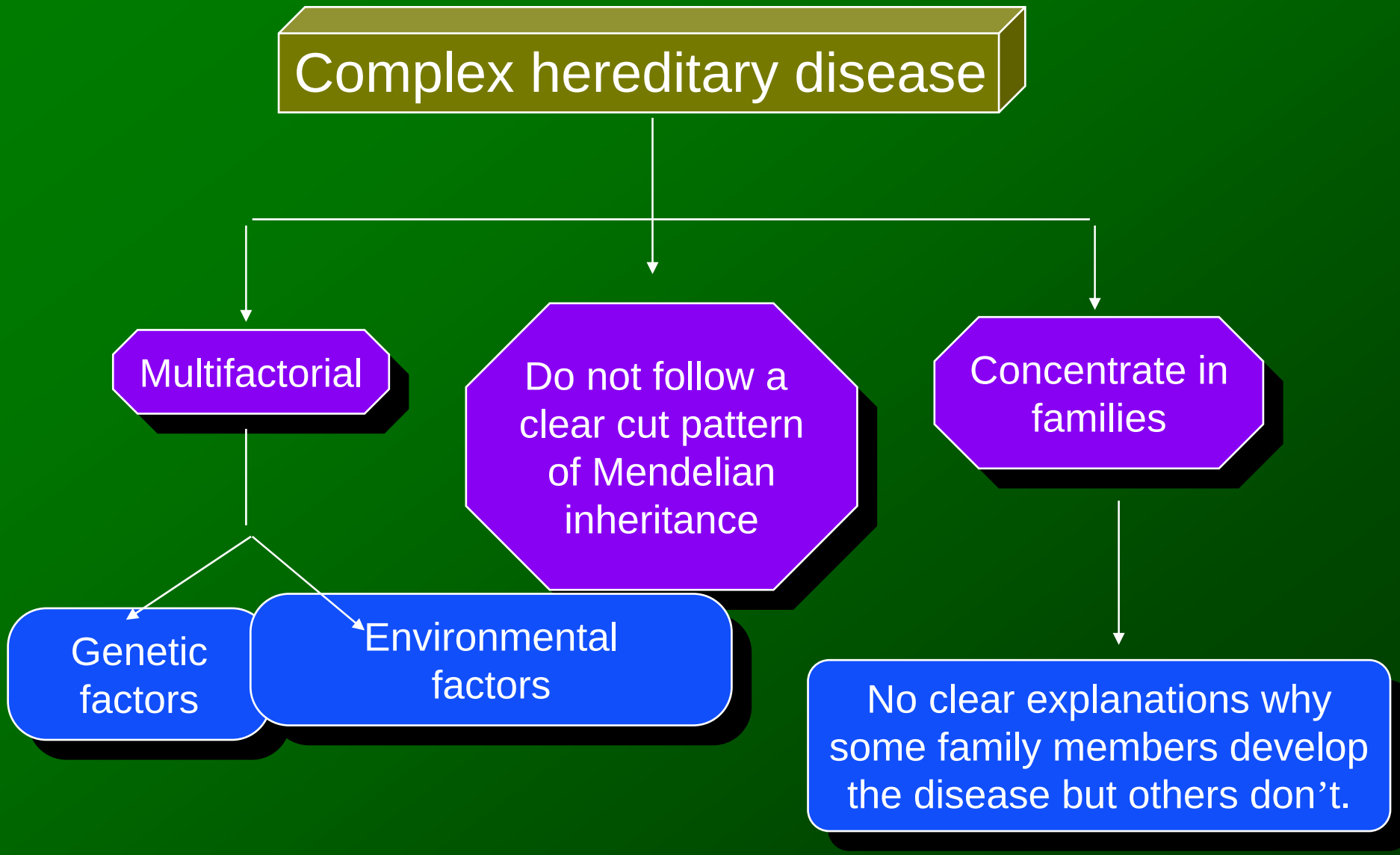
COMPLEX HEREDITARY DISEASES

COMPLEX HEREDITARY DISEASES

- Diverse group of frequently encountered genetic disorders.
- Major cause of morbidity in human populations.
- Polygenic (i.e. complex).

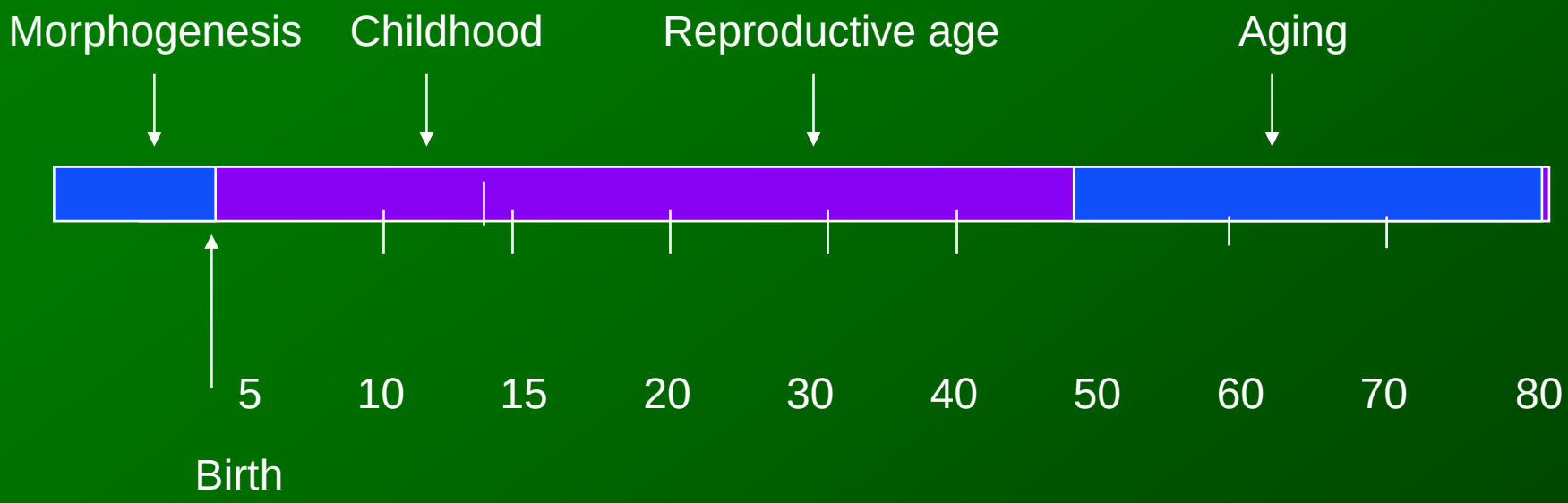

Complex hereditary disease
Multifactorial
Do not follow a clear cut pattern of Mendelian inheritance
Concentrate in families
Genetic factors
Environmental factors
No clear explanations why some family members develop the disease but others don’t.

Factors differentiating complex hereditary disorders from single gene defects

	Complex hereditary disorders (multifactorial)	Single gene defect
- Age of onset	- Neonatal post-pubertal	- Pre-pubertal
- Frequency	- Common	- Rare
- Latency	- (Overall-15%) long	- (Overall-1%) short
- Sex difference	- Frequent	- Occasional
- Influence of migration	- Yes	- No
- Secular changes	- Yes	- No
- Pedigree	- Non-diagnostic	- Often diagnostic
- Monozygotic twin concordance	- <100% but >sibs	- 100%
- Risk to relatives	- Usually low - moderate	- Often high

Types of Complex Genetic Diseases

CHORONOLOGY OF COMPLEX DISORDERS IN A LIFE SPAN



Congenital malformation

Late onset multifactorial disorders

Examples of some complex hereditary diseases

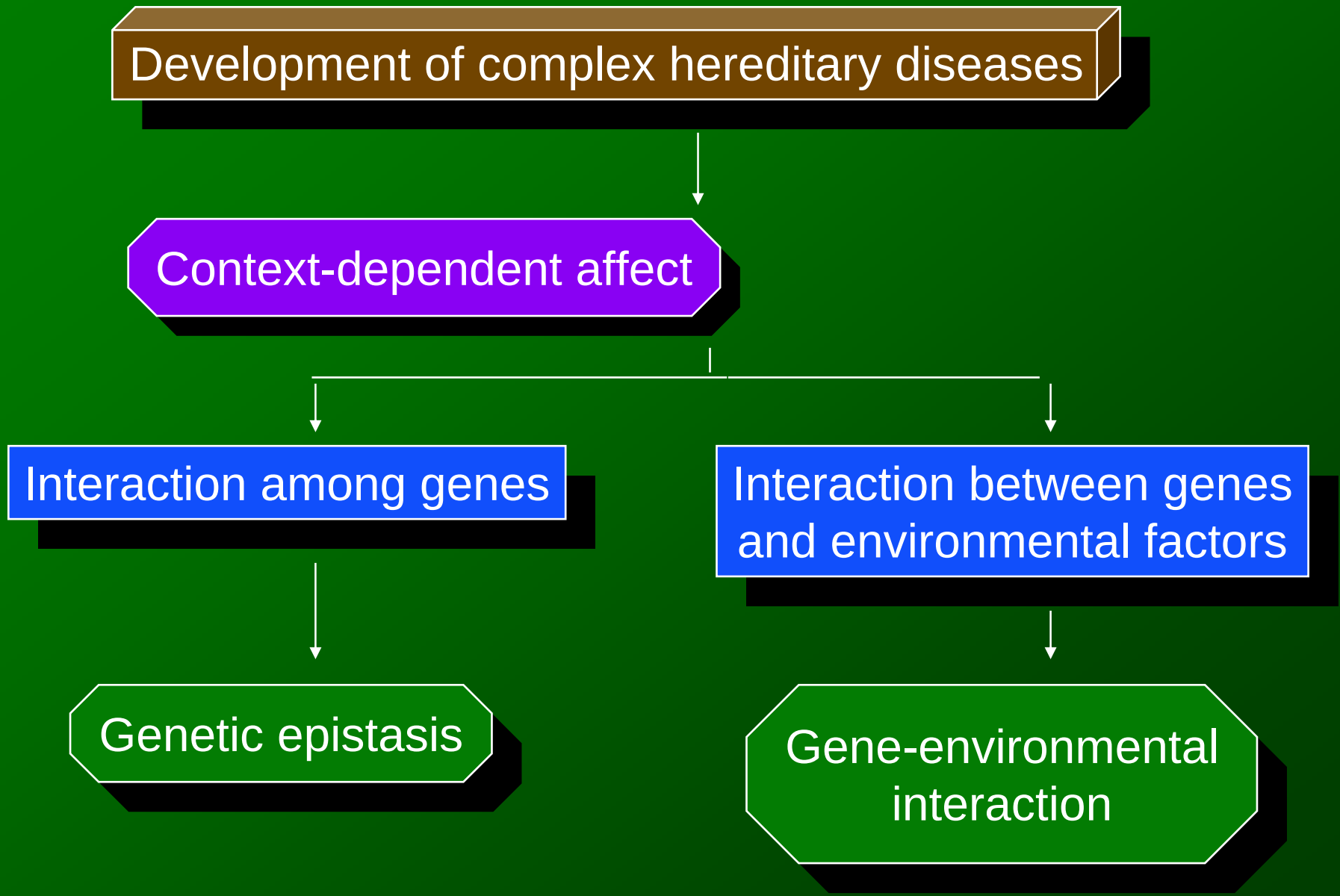
Congenital malformation

- Cleft lip (± cleft palate)
- Club foot
- Neural tube defect
- Congenital dislocation of hip
- Congenital pyloric stenosis
- Anencephaly
- Spina bifida
- Congenital heart disease

Adult onset disorders

- Schizophrenia
- Asthma
- Ankylosing spondylitis
- Coronary heart disease
- Hypertension
- Peptic ulcer
- Diabetes mellitus
- Multiple sclerosis
- Obesity

DEVELOPMENT OF COMPLEX HEREDITARY DISEASES


Development of complex hereditary diseases
Context-dependent affect
Interaction among genes
Interaction between genes and environmental factors
Genetic epistasis
Gene-environmental interaction

CONTRIBUTING GENETIC LOCI FOR COMMON HEREDITARY DISEASES

Contributing Loci

- Diabetes Mellitus (IDDM)
  - HLA-DR3
  - HLA-DR4
  - 14q
  - 11p (nr. insulin gene)
- Coeliac disease
  - HLA-DR3
  - HLA-DR7
  - HLA-DPB 4.2
  - HLA-DPB 3

Contd.....

CONTRIBUTING GENETIC LOCI FOR COMMON HEREDITARY DISEASES

Contributing Loci

.....Contd

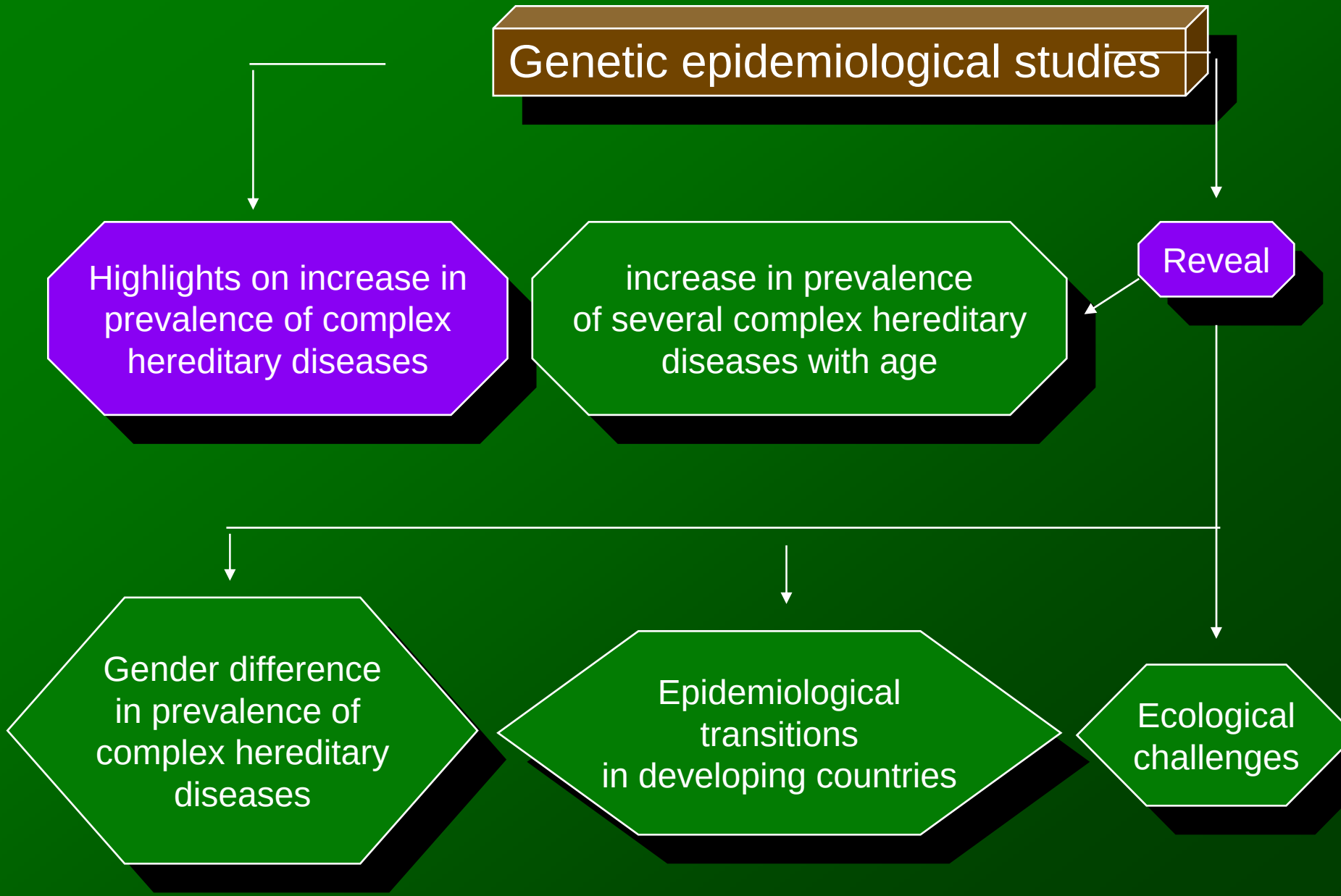
• Rheumatoid arthritis	- HLA-DR4
• Premature vascular disease	- Lipoproteins
• Multiple sclerosis	- HLA-DR2 - HLA-DQ (β–1B) - TCR (β)
• Myasthenia gravis	- HLA-DR3 - HLA-DQ (β)

RISK FACTORS FOR CARDIOVASCULAR DISEASES

RISK FACTORS

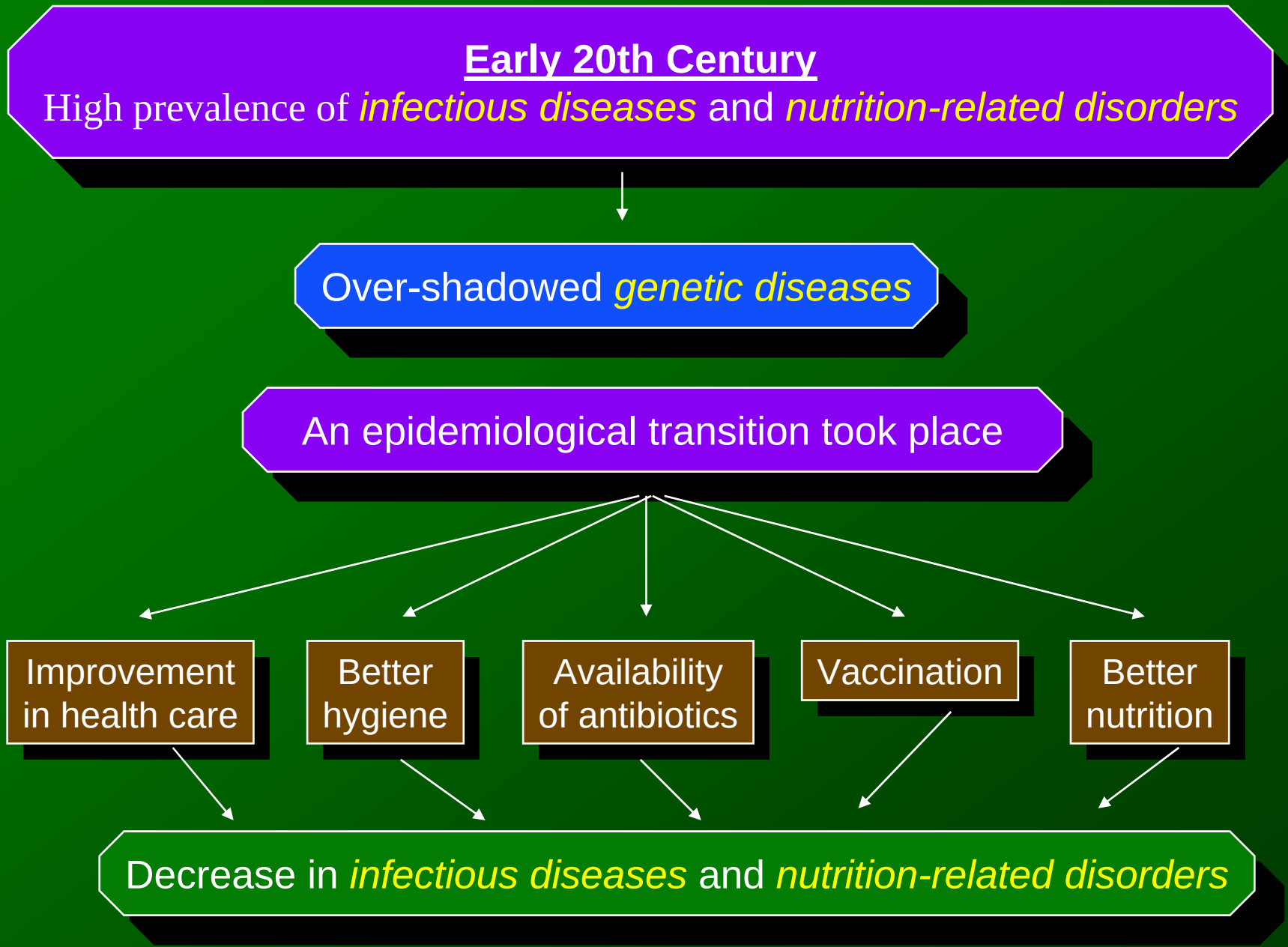
Traditional	Non-Traditional
Age	Endothelial dysfunction
Sex	Homocysteine
Cigarettes	Hemostatic markers
Diabetes	High triglyceride
Family history of CVD	Inflammation
High fat/cholesterol diet	Infectious agents
Hypertension	Lipoprotein a [(Lp(a)]
High LDL cholesterol level	Oxidative stress
High LDL-L/HDL-L ratio	Small, dense LDL particles
Obesity	Others
Physical inactivity	
Stress	

SITUATION ANALYSIS



EPIDEMIOLOGICAL TRANSITION

COMPLEX HEREDITARY DISEASES: EPIDEMIOLOGICAL TRANSITION



EPIDEMIOLOGICAL TRANSITION .....(Contd)

Decrease in *morbidity and mortality* due to infectious disease and nutrition-related disorders

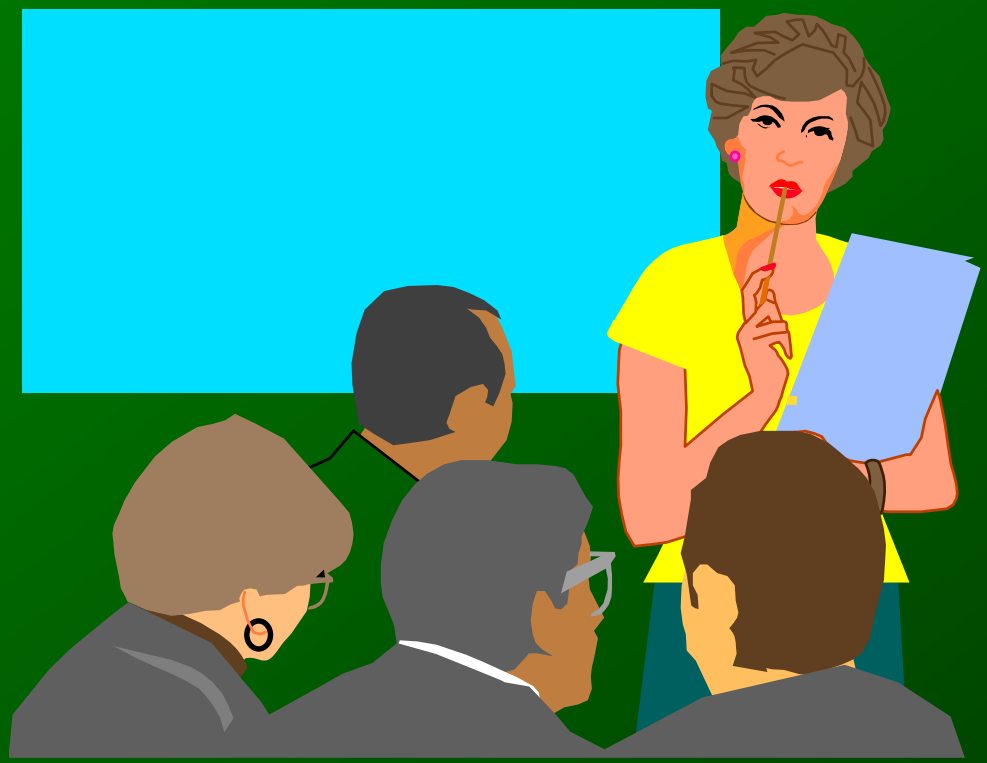
↓

Surfacing of Genetic disease as a major cause of childhood and adult morbidity and mortality in developed and developing countries

↓

Complex hereditary disorders are significantly more prevalent than single gene disorders

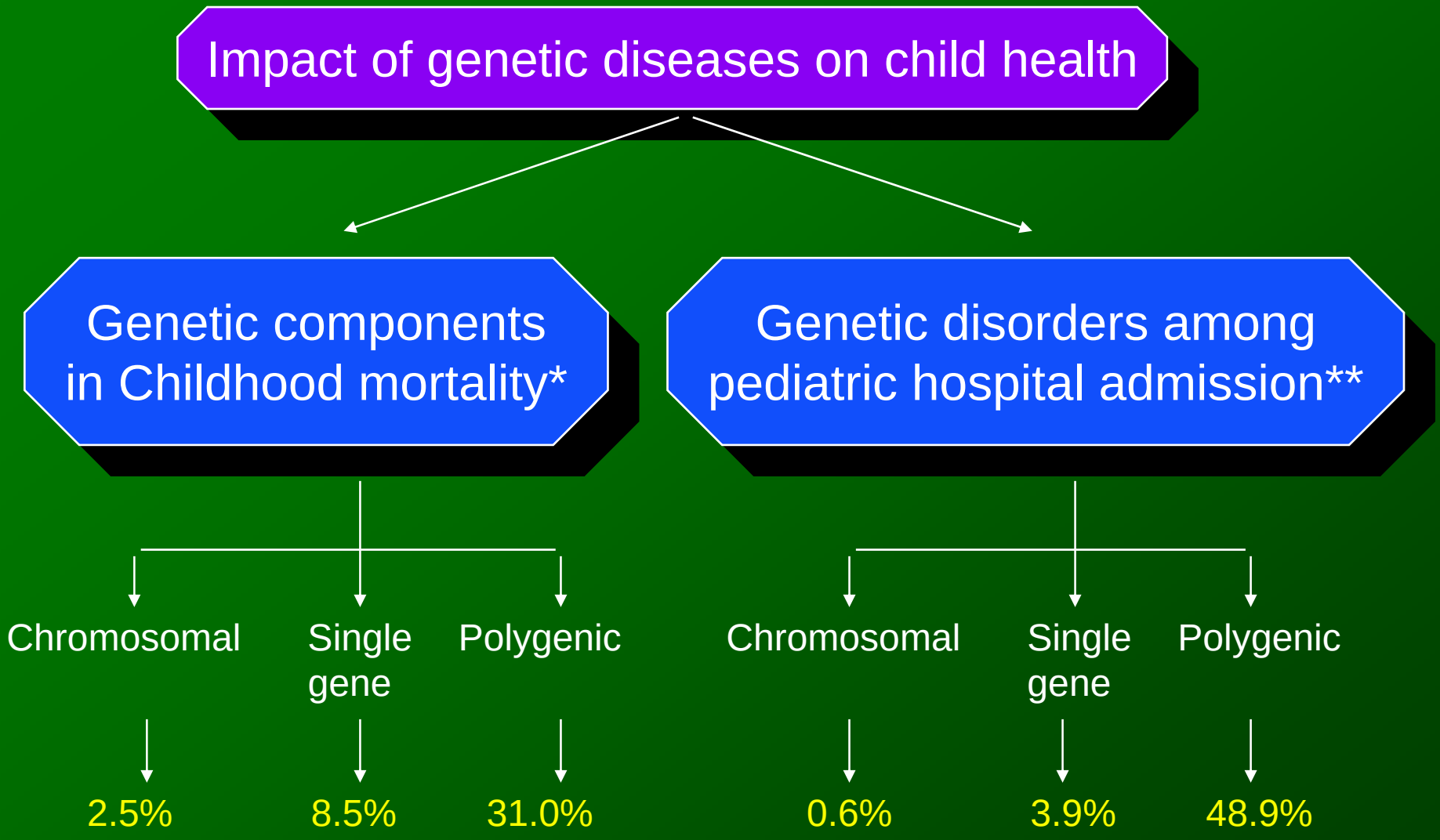
EPIDEMIOLOGY



PREVALENCE OF COMPLEX HEREDITARY DISEASES

- Distributed *world-wide*.
- Prevalence for several disorders estimated in the developed countries and in some developing ones.
- e.g. in the U.S.
  - *~ 50% of all deaths (~ 1 million/year) are due to diseases of heart and circulation.*
  - *~25% of all deaths are due to cancer.*
  - *~16 million Americans suffer from Diabetes.*
  - *~ 4 million Americans suffer from Alzheimer's disease*

Impact of genetic diseases on child health



* Roberts et al. Arch. Dis. Child 1970; 48: 33-38

** Hall et al. Am J Med. Genet 1978; 1: 417-438

BURDEN OF SOME ADULT ONSET DISEASES

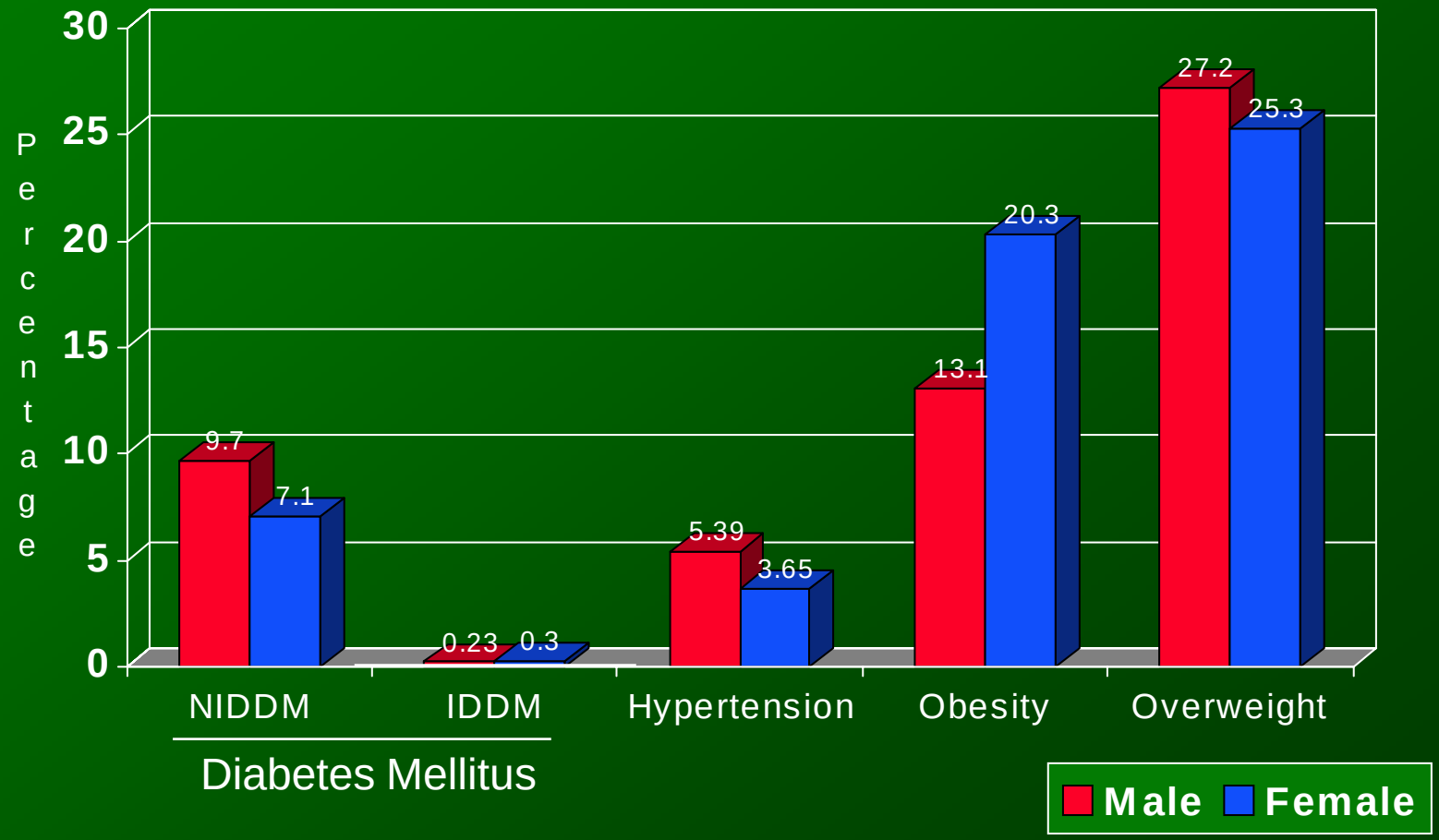
Disease	Incidence per 1000	Risk for 1st degree relative
Diabetes Mellitus		
IDDM	2	2-5 fold
NIDDM	20-70	10 fold
Hypertension	30-100	10 fold-
Inflammatory bowel disease		
Crohn's disease	0.2	13 fold
Ulcerative colitis	0.3	8-10 fold
Atherosclerosis	17 (male)	2 fold
	11 (female)	2 fold
Epilepsy	20	8
Manic-depressive psychosis	4-10	-
Peptic ulcer disease	40-50	10

Contd.....

BURDEN OF SOME ADULT ONSET DISEASES

Disease	Incidence per 1000	Risk for 1st degree relative
.....Contd		
Psoriasis	10-20	10
Rheumatoid arthritis	20	-
Schizophrenia	10	10
Leprosy	Various	-
Ankylosing spondylitis	0.2 - 2 (male)	-
Autism	0.5	-
Glaucoma	5	20
Myasthenia gravis	0.1	-
Multiple sclerosis	0.5	-
Parkinson's disease	10-30	-

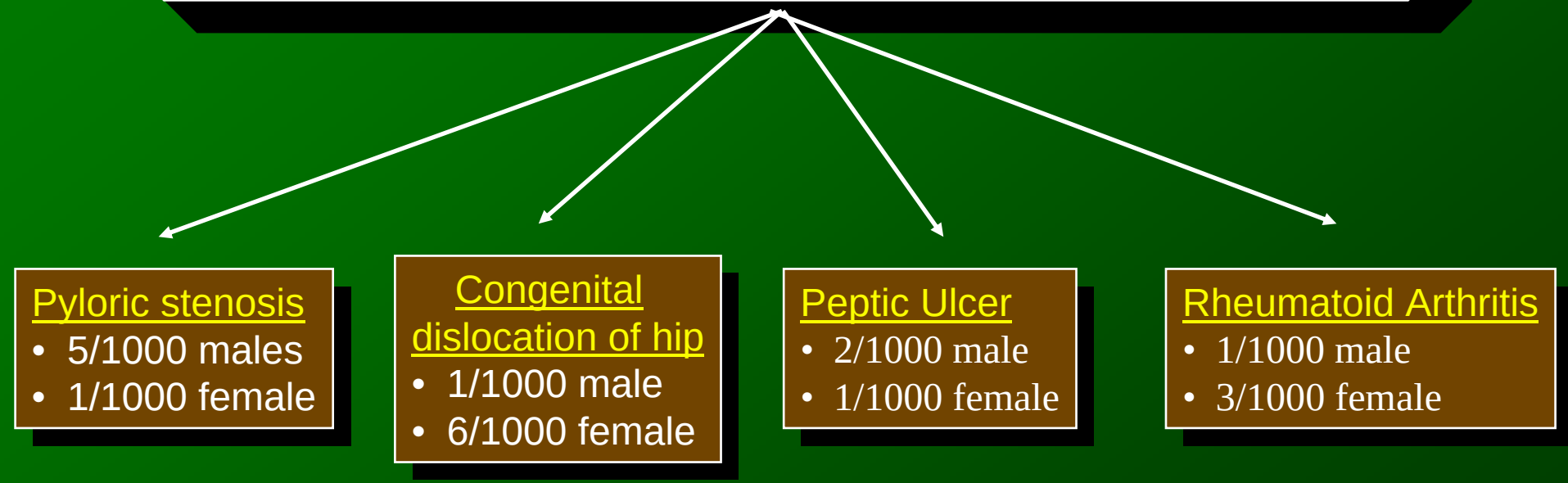
PREVALENCE OF SOME COMPLEX HEREDITARY DISEASE IN ADULT SAUDI POPULATION



GENDER DIFFERENCES

COMPLEX HEREDITARY DISEASES: GENDER DIFFERENCES AND DEMOGRAPHY

Several hereditary diseases show a unequal sex ratio



The incidence is increased in the relatives of the affected individuals i.e. "***Heritability***" (proportion of the etiology ascribed to genetic factors as opposed to environmental factors)

RISK OF COMPLEX HEREDITARY DISEASES

- If a disorder is frequent in males, then the relatives of an affected female have higher recurrence risk than the relatives of an affected male.
- Risk to relatives of an affected person :
  - *increases if the prevalence in general population decreases;*
  - *if the severity of the disease increases;*
  - *if the number of affected relatives is higher;*

HERETABILITY

HERITABILITY OF SOME COMPLEX HEREDITARY DISEASES

Disease	Freq. in general population(%)	Heritability
(a) Common congenital malformation		
- Cleft lip (± cleft palate)	0.1	76
- Club foot	0.1	68
- Neural tube defect	0.2	-
- Congenital dislocation of the hip (female only)	0.2	60
- Congenital pyloric stenosis (males only)	0.5	75
- Anencephaly and spine bifida	0.5	60
- Congenital heart disease	0.5	35
(b) Adult onset disorders		
- Schizophrenia	1.0	85
- Asthma	4.0	80
- Ankylosing spondylitis	0.2	70
- Coronary heart disease	3.0	65
- Hypertension	5.0	62
- Peptic ulcer	4.0	37
- Diabetes mellitus	4.0	62

TWIN CONCORDANCE FOR SOME DISCONTINUOUS TRAITS

Trait	Concordance	
	Monozygotic (%)	Dizygotic (%)
• Cancer	17	11
• Cleft lip ± cleft palate	35	5
• Congenital dislocation of the hip	41	3
• Diabetes mellitus (IDDM)	30-40	6
• Diabetes mellitus (NIDDM)	100	10
• Hypertension	30	10
• Ischaemic heart disease	19	8
• Manic depression	70	15
• Multiple sclerosis	20	30
• Pyloric stenosis	15	2
• Rheumatoid arthritis	30	5
• Schizophrenia	45	12
• Spine bifida	6	3

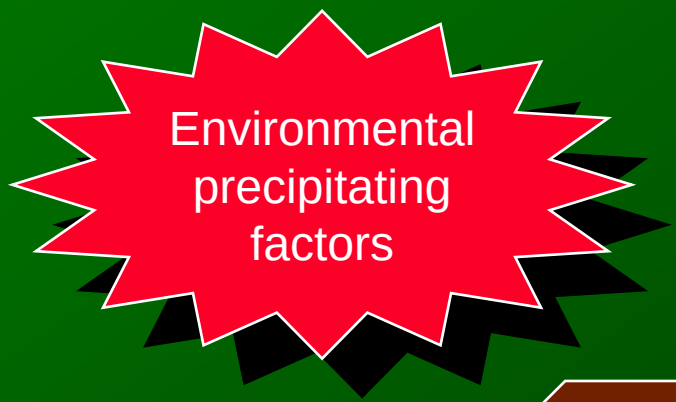
ECOLOGICAL CHALLENGE

COMPLEX HEREDITARY DISEASES
ECOLOGICAL CHALLENGES

Ecology plays an essential role in the development of complex diseases

e.g.

Genetically susceptible individuals
(with several predisposing alleles) each with small, additive effect



Increasing age

DISEASE

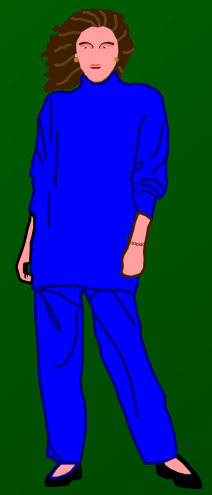
MULTIPLE SCLEROSIS

5-10 years old

≥ 35 years old

Viral infection

≥ 30 years later

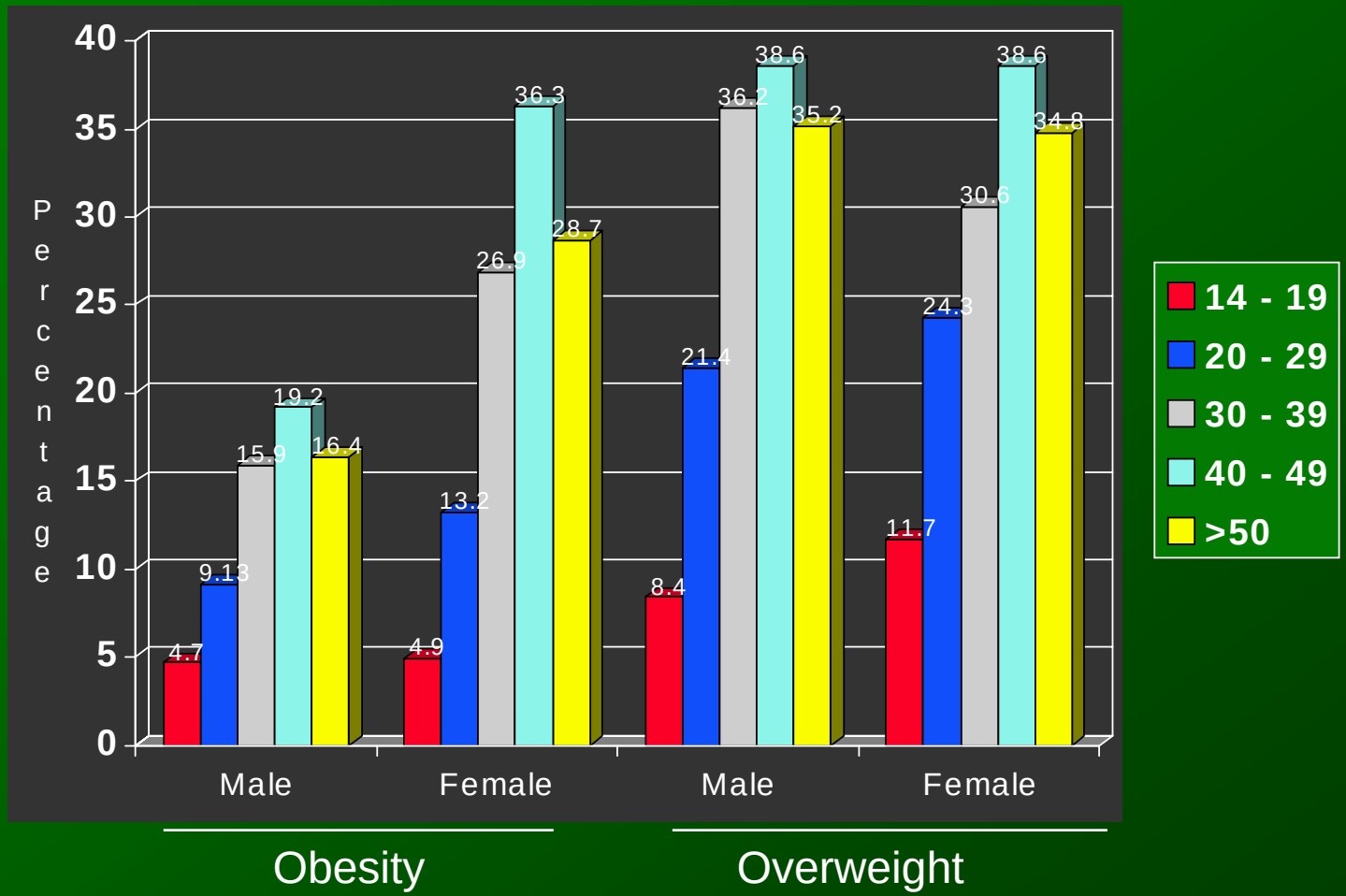


Genetically susceptible child

Other environmental factors

Multiple sclerosis

INCREASE IN THE PREVALENCE OF OBESITY AND OVERWEIGHT WITH AGE IN SAUDIS



IDENTIFICATION OF SUSCEPTIBLE INDIVIDUALS

GENES AND MARKERS LINKED TO COMPLEX HEREDITARY DISEASES

EXAMPLES OF GENES AND MARKERS LINKED TO DIABETES MELLITUS, HYPERTENSION, OBESITY & CARDIOVASCULAR

Diseases	Linked genes/markers
• NIDDM	- Glucokinase
	- Glucose transporter
	- Glycogen receptor
	- Insulin (11p15)
	- Insulin receptor (19p13.3-p 13.2)
	- Insulin HVR (11p15)
	- Apo A1 (11q13-qter)
• IDDM	- HLA DQ (6p21.3)
	- HLA-DR4 (6p21.3)
	- HLA-DR3 (6p21.3)
	- Insulin HVR (11p15)

Contd.....

EXAMPLES OF GENES AND MARKERS LINKED TO DIABETES MELLITUS, HYPERTENSION, OBESITY & CARDIOVASCULAR

Diseases	Linked genes/markers
• CHD	- Apo B
	- Apo E
	- Lipoprotein(a)
	- Apo-A-1 (Pst-1)
	- ApoA-1/CIII (Sst-1)
	- Homocysteine
• Hyperlipidaemia	- Apo-II (Mspl)
	- Apo B (Taq I)
	- Apo B (Puv II)
	- Apo B (EcoR 1)
	- Apo B (Xba I)
	- Apo C-II (Taq I)

Contd.....

EXAMPLES OF GENES AND MARKERS LINKED TO DIABETES MELLITUS, HYPERTENSION, OBESITY & CARDIOVASCULAR

Diseases	Linked genes/markers
• Hypertension	- Erythrocyte Li-Na countertransport - SA - ACE - Angiotensinogen - Rennin
• Obesity	- Leptin - Leptin receptor - Pro-opiomelonocortin - Melanocortin-4-receptor gene - Carboxypeptidase E - Agoate signaling protein - Tumor necrosis factor

MOLECULAR DIAGNOSIS SERVICES FOR COMPLEX HEREDITARY DISEASES

Prior to provision of molecular diagnosis services for pre-symptomatic diagnosis

All gene alterations associated with the complex trait have to be identified

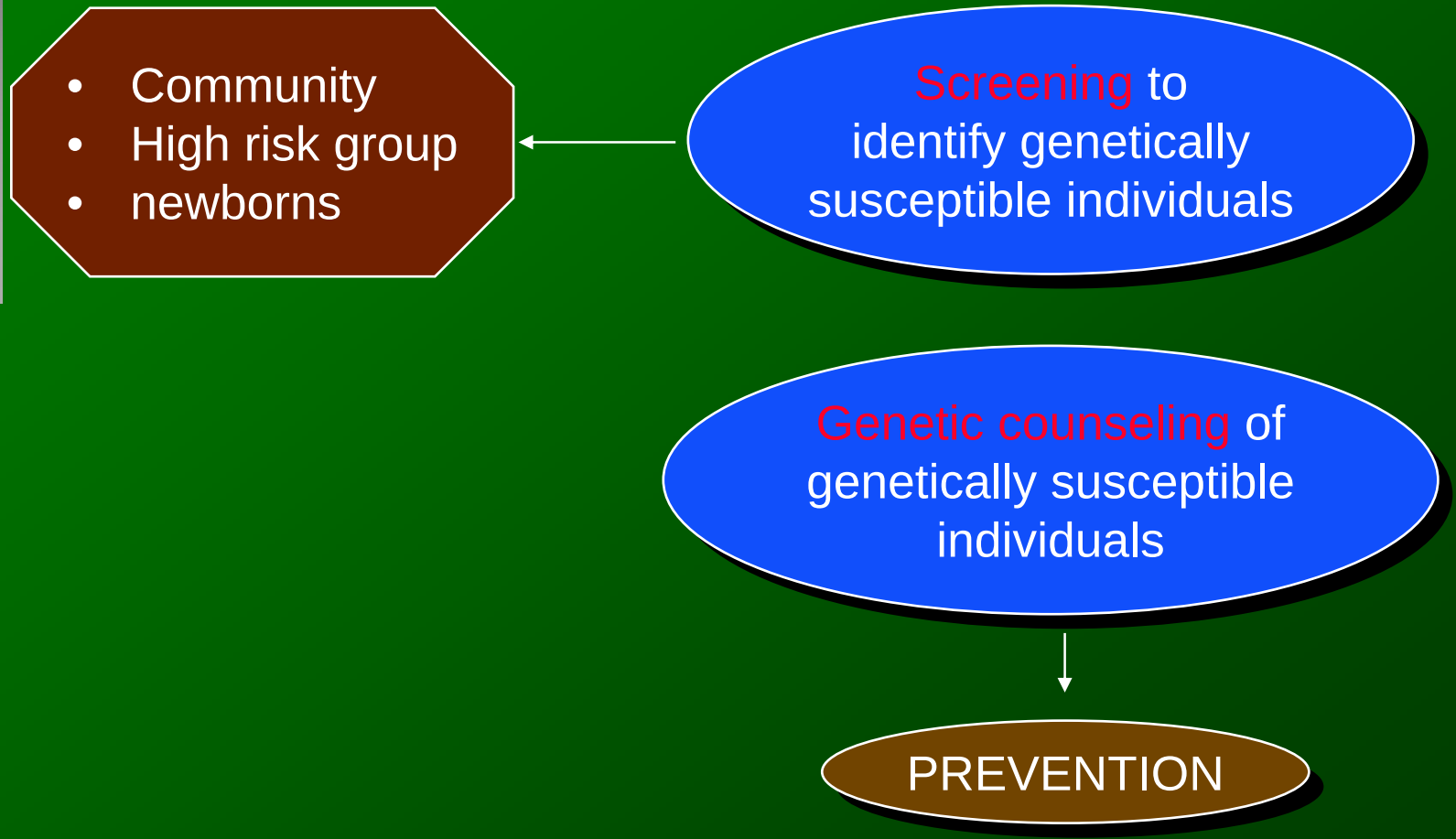
This is an *enormous undertaking* as the genes involved are many and mutations in these genes are numerous

WHERE DO WE GO?

- Complex hereditary diseases affect a high percentage of the population.
- With epidemiological transition, the prevalence is increasing.
- With age the prevalence increases.
- There is a major burden on health care services.

What to do??????

CONTROL AND PREVENTION OF COMPLEX DISEASES - "PRIMARY PREVENTION"



Screening and counseling are important components of control and prevention programs

Threat of Complex Diseases to mankind is enormous

FUTURE PROSPECTUS

Control, Prevention
and
Treatment of Complex
Hereditary Disease

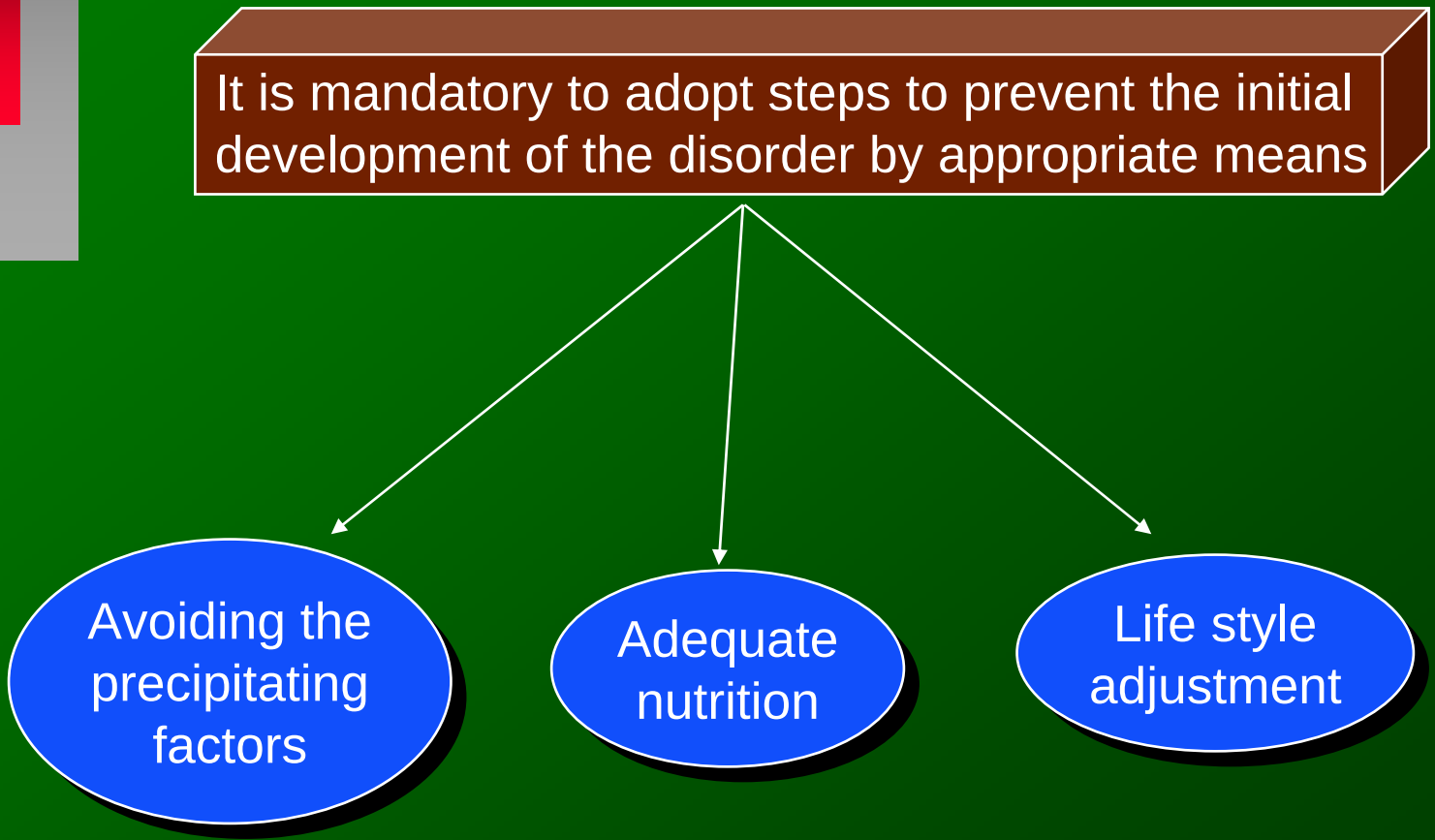
AVOIDANCE OF ECOLOGICAL CHALLENGES

- For genetically susceptible individuals an ecological challenge always persists.
- Avoidance of these ecological factors, even in the presence of of genetic susceptibility leads to:

Delay or inhibition of development of disease state

CONTROL AND PREVENTION

COMPLEX HEREDITARY DISEASES - CONTROL AND PREVENTION



EXAMPLES OF STEPS ADOPTED TO AVOID THE DEVELOPMENT OF CONGENITAL MALFORMATION AND ADULT ONSET DISEASES

PREVENTIVE MEASURES FOR SOME COMPLEX DISORDERS

Diseases	Preventive Measure
• Congenital Malformation	- Folate supplementation prior to and during pregnancy - Control of maternal diabetes mellitus - Vaccination against rubella infection - Adequate vitamins, iron and iodine pior to and during pregnancy

Contd.....

PREVENTIVE MEASURES FOR SOME COMPLEX DISORDERS

Disorder	Preventive Measure
• Adult onset disorders e.g. (Diabetes mellitus Coronary heart disease Hypertension Obesity Hyperlipidaemia)	- Control of plasma lipids (cholesterol/triglycerides) - Control of LDL-C/HDL-C ratio - Body weight control (BMI <25) - Physical exercise (aerobic) - Stop cigarette smoking - Stop alcohol intake - Healthier food choices - Control of B.P. Systolic: < 140 mmHg Diastolic: < 95 mmHg - Optimal glycaemic control - Aspirin

THE HUMAN GENOME PROJECT

MONDAY, 26 JUNE, 2000

Human Genome Project

"The entire human genetic code has been assembled

Dr. Francis Collins stated "In a few years it will be possible to identify individuals susceptible to heart disease, schizophrenia or high blood pressure and it may be possible to cure these diseases"

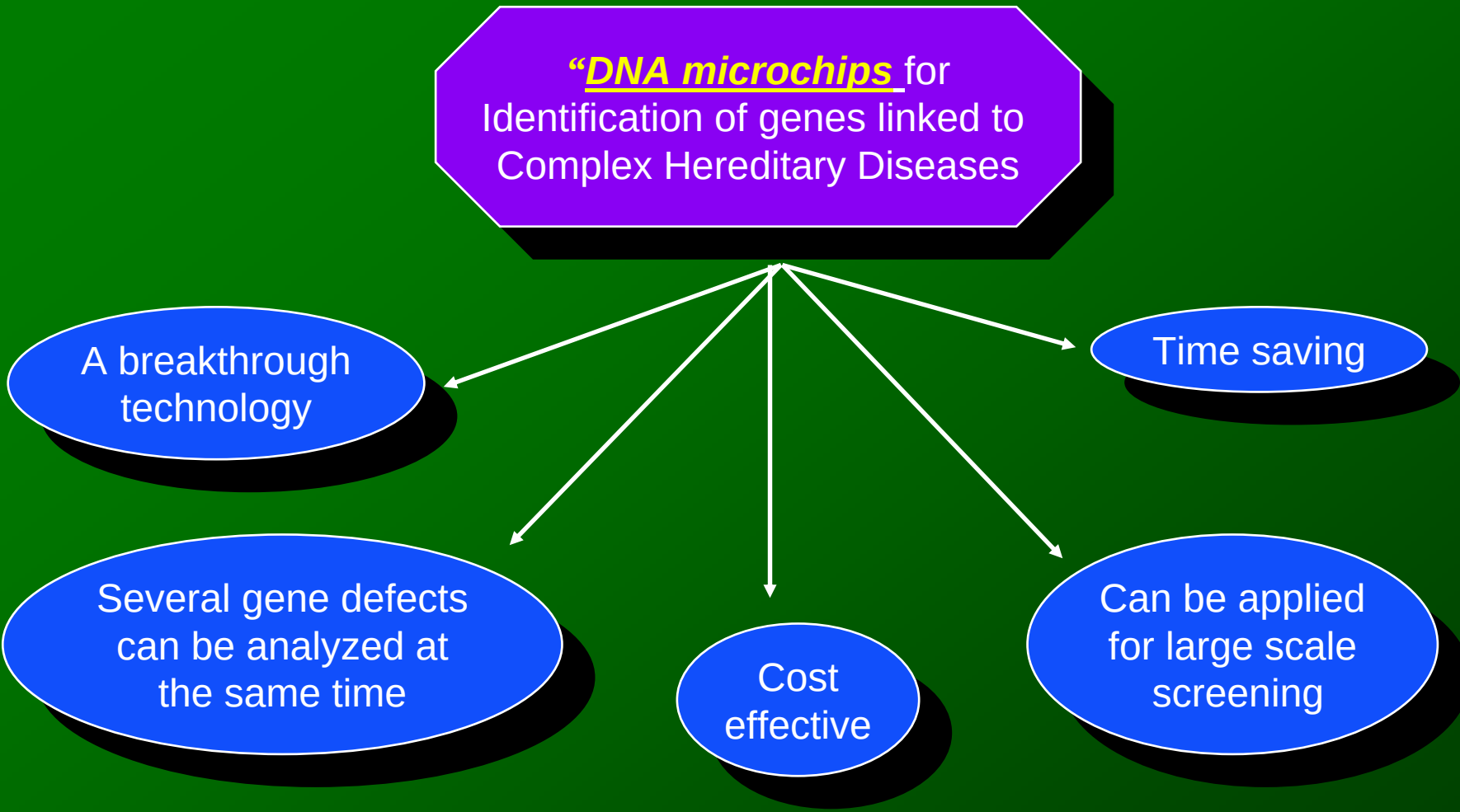
THE HUMAN GENOME PROJECT

- "The time is not far when each newborn will have his/her DNA sequence soon after birth".
- This will reveal any gene defect present and will be used to correct gene defect if possible.

A NEW ERA OF GENETIC MEDICINE

Decoding the human genome will lead to new ways to prevent, diagnose, treat and cure diseases. This information will be able to:

- Alert individuals that they are at risk for certain diseases.
- Reliably predict the course of disease.
- Precisely diagnose disease and ensure the most effective treatment.
- Help to develop new treatment, at the molecular level.


"DNA microchips for
Identification of genes linked to
Complex Hereditary Diseases
A breakthrough technology
Time saving
Several gene defects can be analyzed at the same time
Cost effective
Can be applied for large scale screening

THE WORLD HEALTH ORGANIZATION

"HEALTH FOR ALL IN THE TWENTY-FIRST CENTURY"