Causes and mechanisms of birth defects

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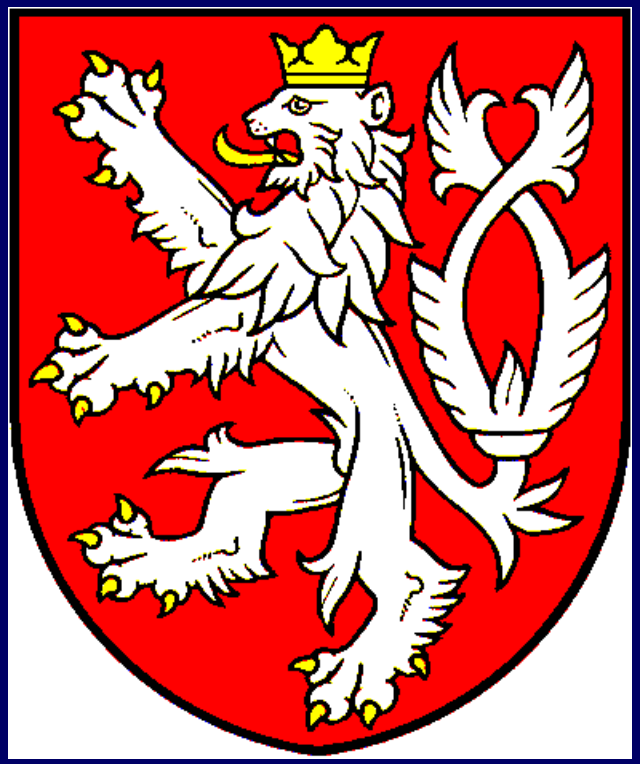
Teratology

- **Teratology** investigates abnormalities of physiological development. It is often thought of as the study of birth defects.

- The term stems from the Greek τέρᾰς (téras, genitive τέρᾰτος- tératos), meaning *monster*, or *marvel* (miracle).

- **Birth defects (congenital malformations)** result from a negative influence of extrinsic or genetic factors on individual prenatal development.



Heraldry documents many examples of serious monstrosities
(often used as national or town emblems)

TERATOLOGY

Prague

Birth defect

Inborn deviation of a structure, function or metabolism.

It originates prenatally and its manifestation exceeds a threshold of normal variability in a species.

- **Major malformation -** a serious structural disturbance, monstrosity
- **Minor malformation** – a mild structural defect manifesting as a disturbance of function.
- **Metabolic defect** – enzymopathy – affection of enzymes – most often it is a decrease of their catabolic activity

Major malformations

Spina bifida and myelo-meningocele

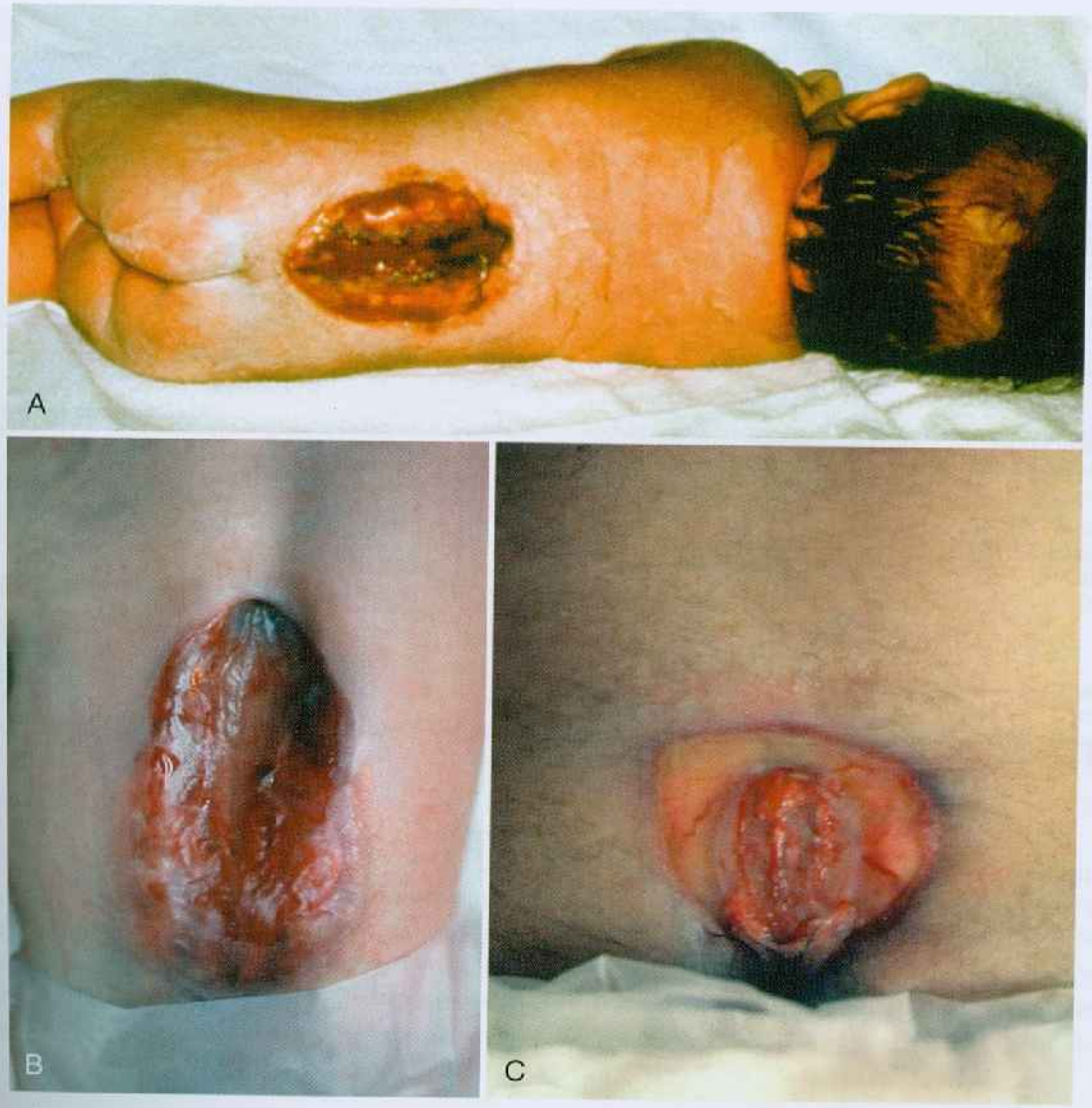


Figure 4-11. Three newborns with myelomenigoceles. *A*, *B*, The myelomenigoceles extend from the thoracic to lumbosacral level. Note the location of the split vertebral elements to the left of the lesion in *B*. *C*, The myelomenigocele is localized to the lumbosacral level. In *B* and *C*, the infant's diapers (bottom of each illustration) are shown for orientation.

Partialy fused eyes (uncomplete cyclopia) and proboscis

FIGURE 8-16. Cyclopia in a newborn. Note the fleshy proboscis above the partially fused eye. (Courtesy M. Barr, Ann Arbor, Mich.)

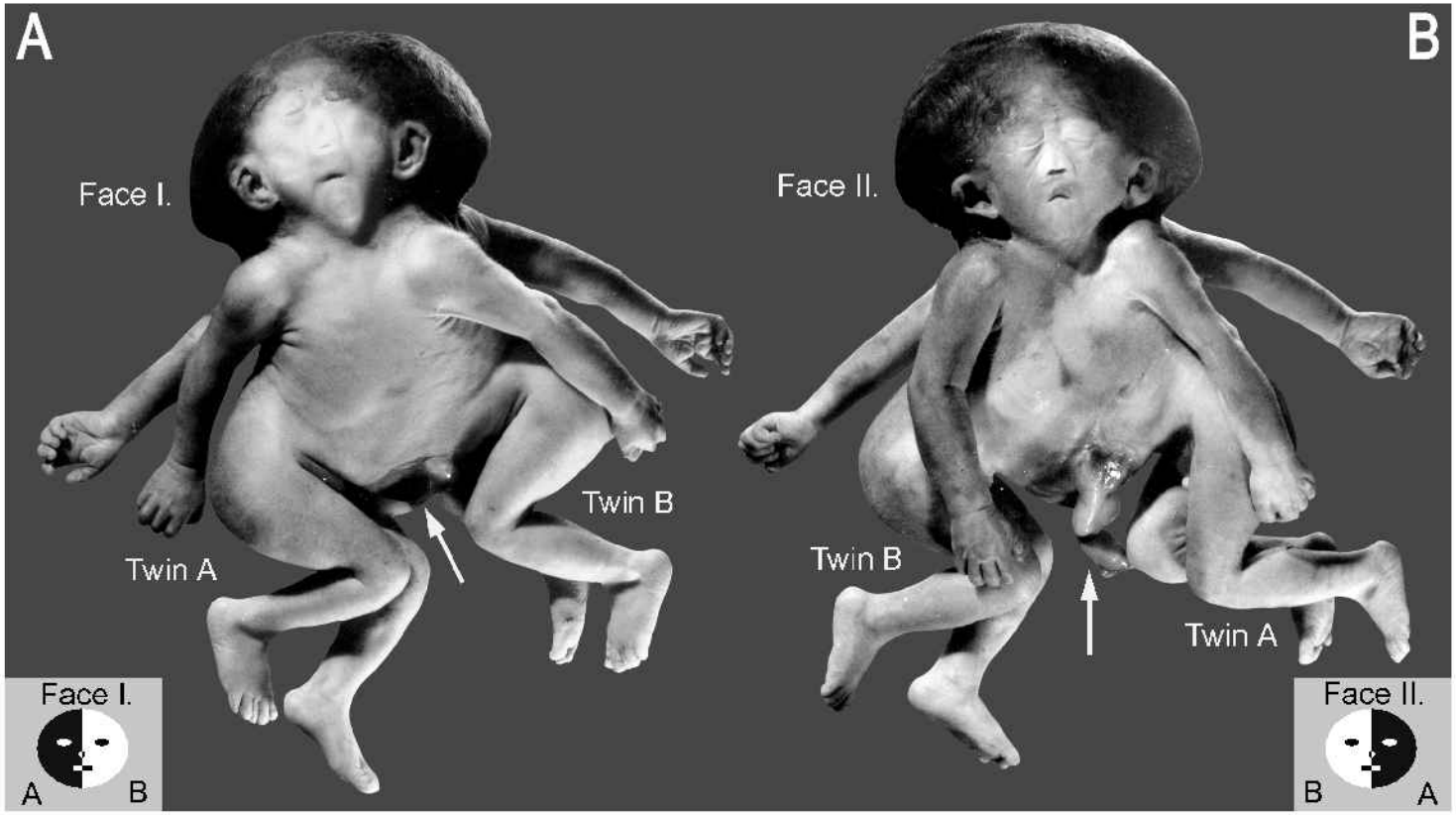
Sirenomelia

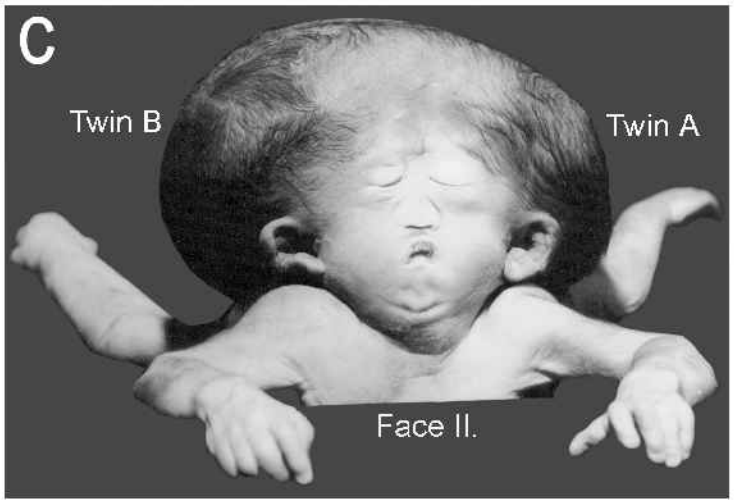
Sirenomelia. Severe reduction of caudal structures has resulted in fusion of the lower limb buds.

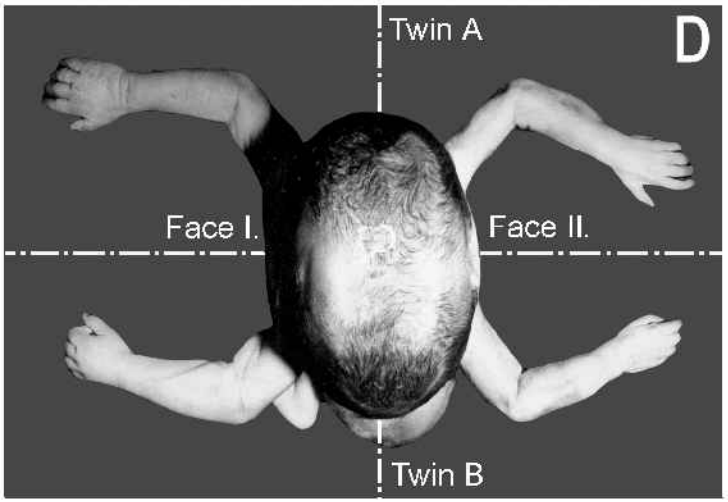
Polydactylia


B

Cephalo-thoraco-pagus


A
Face I.
Twin B
Twin A
Face I.
A
B
B
Face II.
Twin B
Twin A
Face II.
B
A


C
Twin B
Twin A
Face II.


Twin A
D
Face I.
Face II.
Twin B

Thoracopagus


profimedia.cz

Major malformations

originate during **embryonic period**

of prenatal development

Human stages of life cycle

Prenatal period

Embryo	1 - 8 weeks
Fetus	9 weeks – birth

Postnatal period

Newborn	birth - 4 weeks
Suckling, toddler	5 weeks - 2 years
Child	2 years - puberty (11 - 14 years)
Teenage	puberty - adult age (20 years)
Young age	20 - 40 years
Middle age	40 - 65 years
Old age	65 - death

Determination of the beginning pregnancy

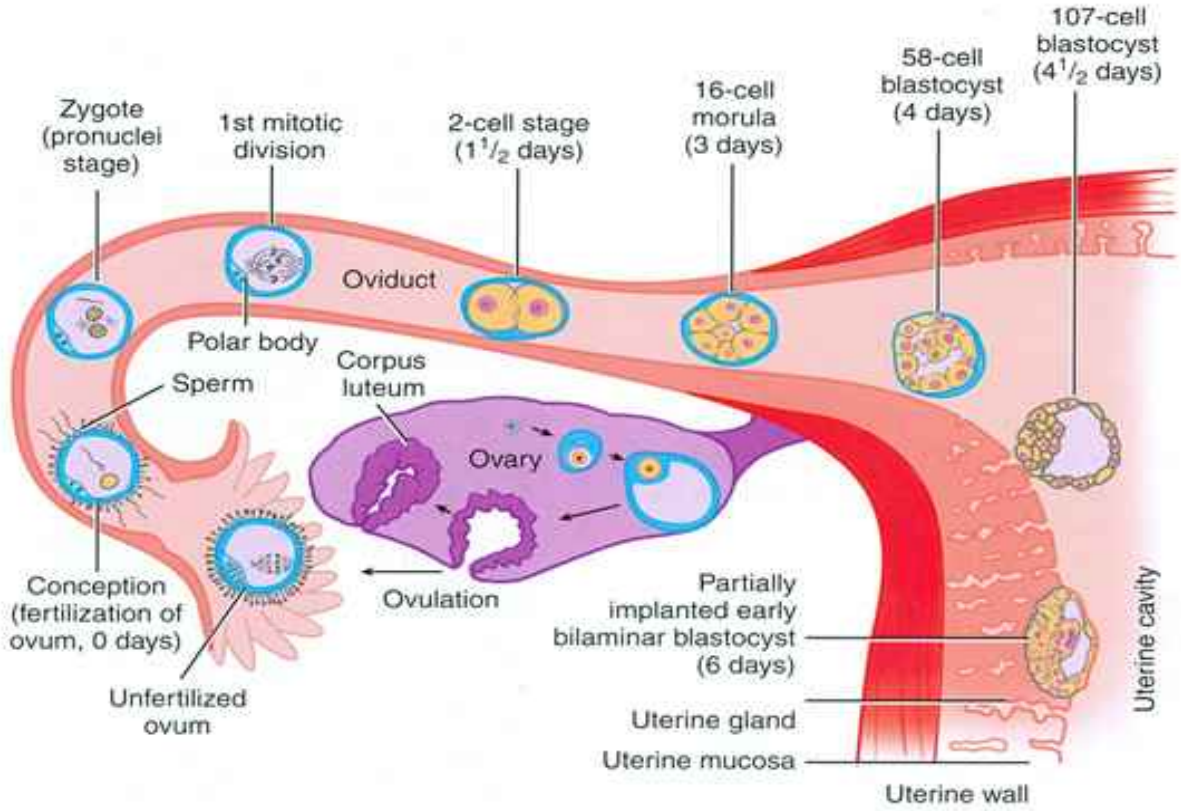


Figure Intro-1. The first week of prenatal development of the human.

Figure 2-5. *Schematic representation of the events taking place during the first week of human development. (1) Oocyte immediately after ovulation. (2) Fertilization approximately 12 to 24 hours after ovulation. (3) Stage of the male and female pronuclei. (4) Spindle of the first mitotic division. (5) Two-cell stage (approximately 30 hours of age). (6) Morula containing 12 to 16 blastomeres (approximately 3 days of age). (7) Advanced morula stage reaching the uterine lumen (approximately 4 days of age). (8) Early blastocyst stage (approximately 4½ days of age). The zona pellucida has now disappeared. (9) Early phase of implantation (blastocyst approximately 6 days of age). The ovary shows the stages of the transformation between a primary follicle and a Graafian follicle as well as a corpus luteum. The uterine endometrium is depicted in the progestational stage.*

Determination of pregnancy

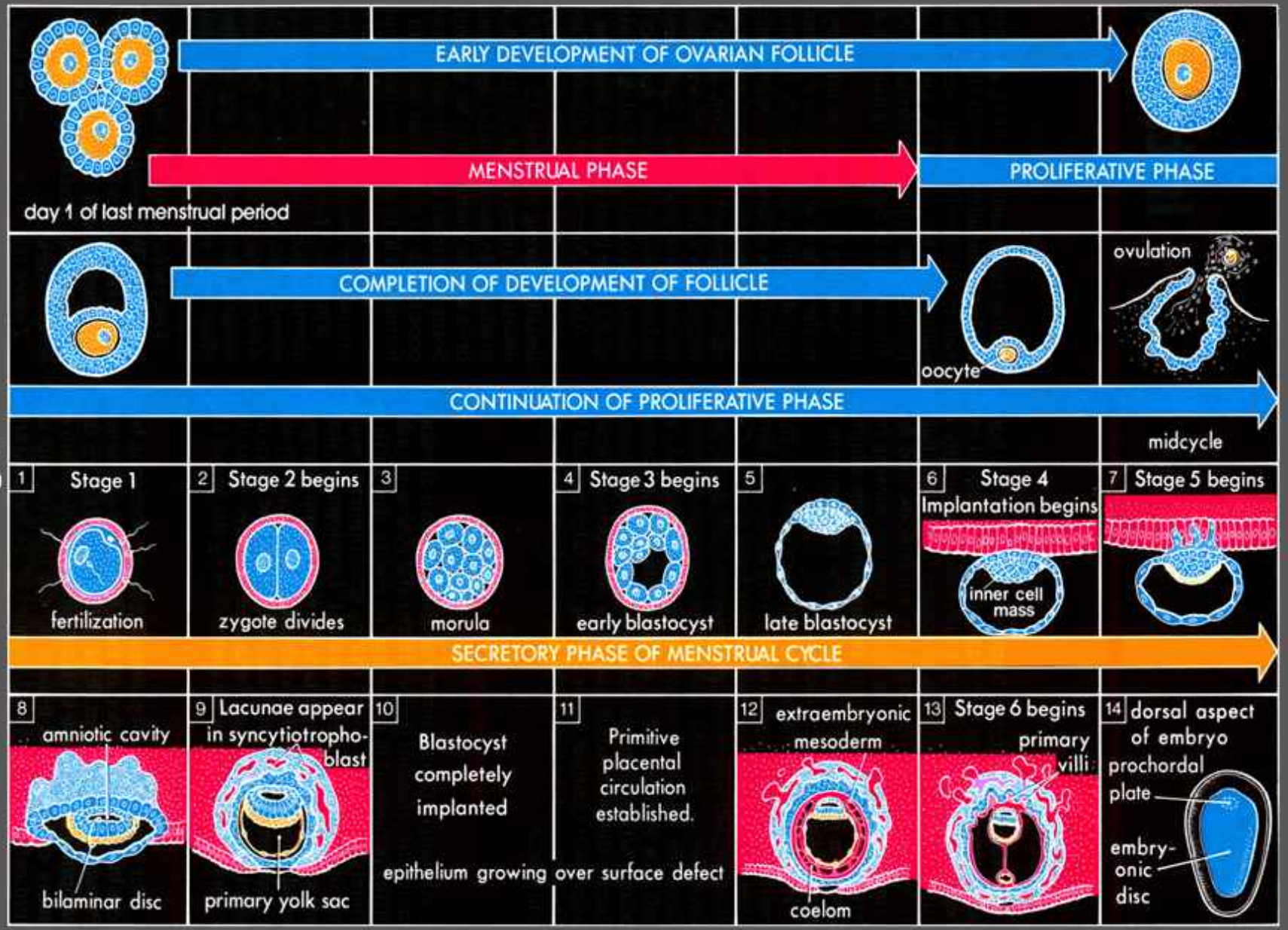
- Positive determination of HCG (human chorionic gonadotropin) from urine (9 – 12 day after fertilization)
- Verification of HCG from blood
- Ultrasound investigation - determination of the place of embryo implantation

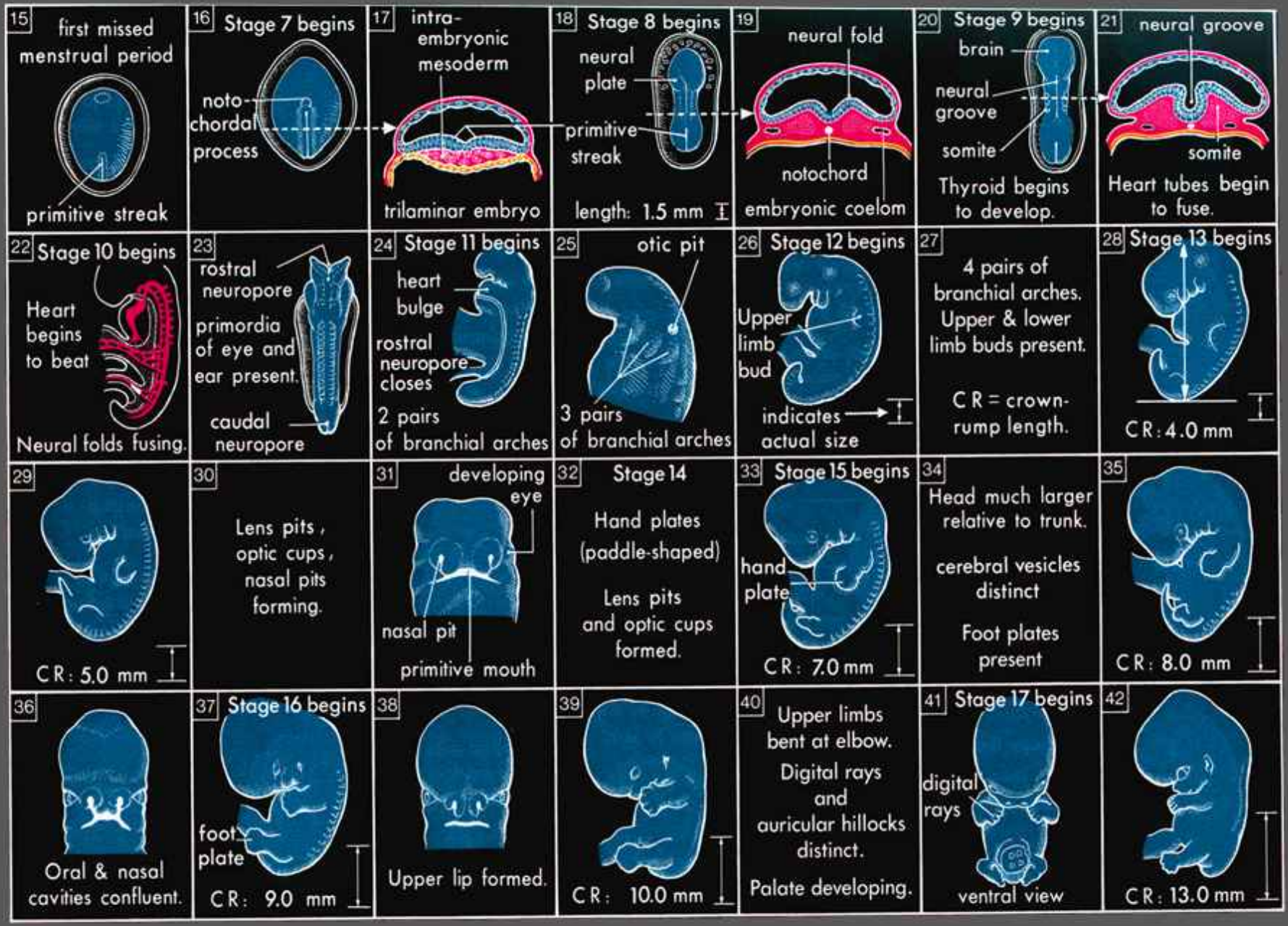
Pregnancy length

- **280 days, 40 weeks** – calculated from the first day of the last menstruation.

- **266 days, 38 weeks** – calculated from the day of fertilization. A child usually borns at about 38 weeks after conception.

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT




3
4
5
6
15 first missed menstrual period
primitive streak
16 Stage 7 begins
noto-chordal process
17 intra-embryonic mesoderm
trilaminar embryo
18 Stage 8 begins
neural plate
primitive streak
length: 1.5 mm
19 neural fold
notochord
embryonic coelom
20 Stage 9 begins
brain
neural groove
somite
Thyroid begins to develop.
21 neural groove
somite
Heart tubes begin to fuse.
22 Stage 10 begins
Heart begins to beat
Neural folds fusing.
23
rostral neuropore
primordia of eye and ear present.
caudal neuropore
24 Stage 11 begins
heart bulge
rostral neuropore closes
2 pairs of branchial arches
25 otic pit
3 pairs of branchial arches
26 Stage 12 begins
Upper limb bud
indicates actual size
27
4 pairs of branchial arches. Upper & lower limb buds present.
CR = crown-rump length.
28 Stage 13 begins
CR: 4.0 mm
29
CR: 5.0 mm
30
Lens pits, optic cups, nasal pits forming.
31 developing eye
nasal pit
primitive mouth
32 Stage 14
Hand plates (paddle-shaped)
Lens pits and optic cups formed.
33 Stage 15 begins
hand plate
CR: 7.0 mm
34
Head much larger relative to trunk.
cerebral vesicles distinct
Foot plates present
35
CR: 8.0 mm
36
Oral & nasal cavities confluent.
37 Stage 16 begins
foot plate
CR: 9.0 mm
38
Upper lip formed.
39
CR: 10.0 mm
40
Upper limbs bent at elbow.
Digital rays and auricular hillocks distinct.
Palate developing.
41 Stage 17 begins
digital rays
ventral view
42
CR: 13.0 mm

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT

7 to 38 weeks

AGE (weeks)

7

43 
CR: 16.0 mm

44 Stage 18 begins

Eyelids beginning

45 Tip of nose distinct.
Digital rays appear in foot plates.

CR: 17.0 mm

46 
Loss of villi
Smooth chorion forms.

47 genital tubercle
urogenital membrane
anal membrane

♀ or ♂

48 Stage 19 begins
Trunk elongating and straightening.

49 
CR: 18 mm

8

50 Upper limbs longer & bent at elbows.
Fingers distinct.

51 Anal membrane perforated
Urogenital membrane degenerating.
Testes and ovaries distinguishable.

52 Stage 21 begins


53 Stage 21
External genitalia still in sexless state but have begun to differentiate.

54 Stage 22 begins
genital tubercle
urethral groove
anus

♀ or ♂

55 Beginnings of all essential external & and internal structures are present.

56 Stage 23

CR: 30 mm

9

57 Beginning of fetal period.

58 

59 Genitalia show some ♀ characteristics but still easily confused with ♂.

60 phallus
urogenital fold
labioscrotal fold
perineum

♀

61 Genitalia show fusion of urethral folds.
Urethral groove extends into phallus.

62 phallus
urogenital fold
labioscrotal fold
perineum

♂

63 
CR: 50 mm

10

64 Face has human profile.
Note growth of chin compared to day 44.

65 

66 
Face has human appearance.

67 clitoris
labium minus
urogenital groove
labium majus

♀

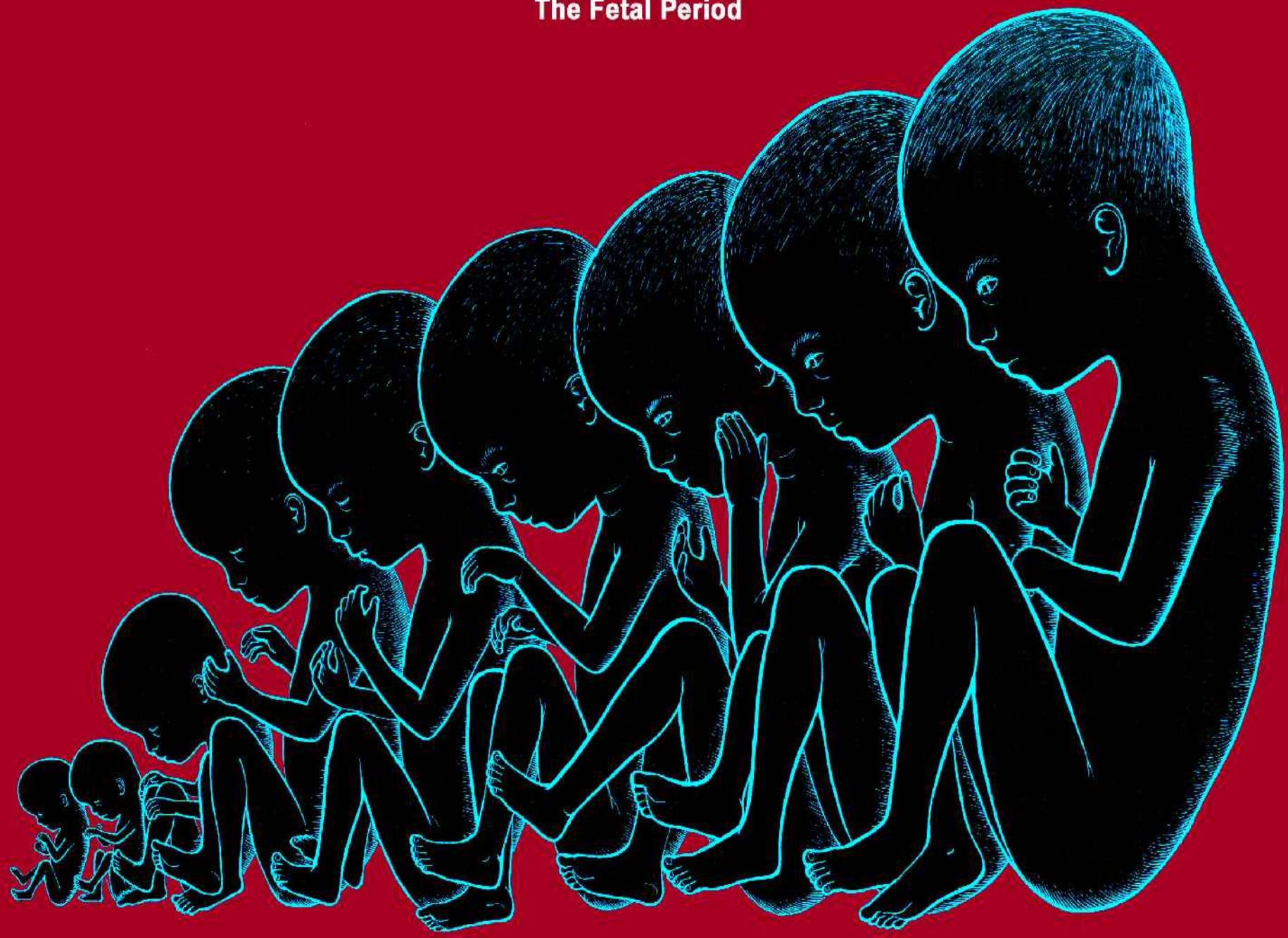
68 Genitalia have ♀ or ♂ characteristics but still not fully formed.

69 glans penis
urethral groove
scrotum

♂

70 
CR: 61 mm

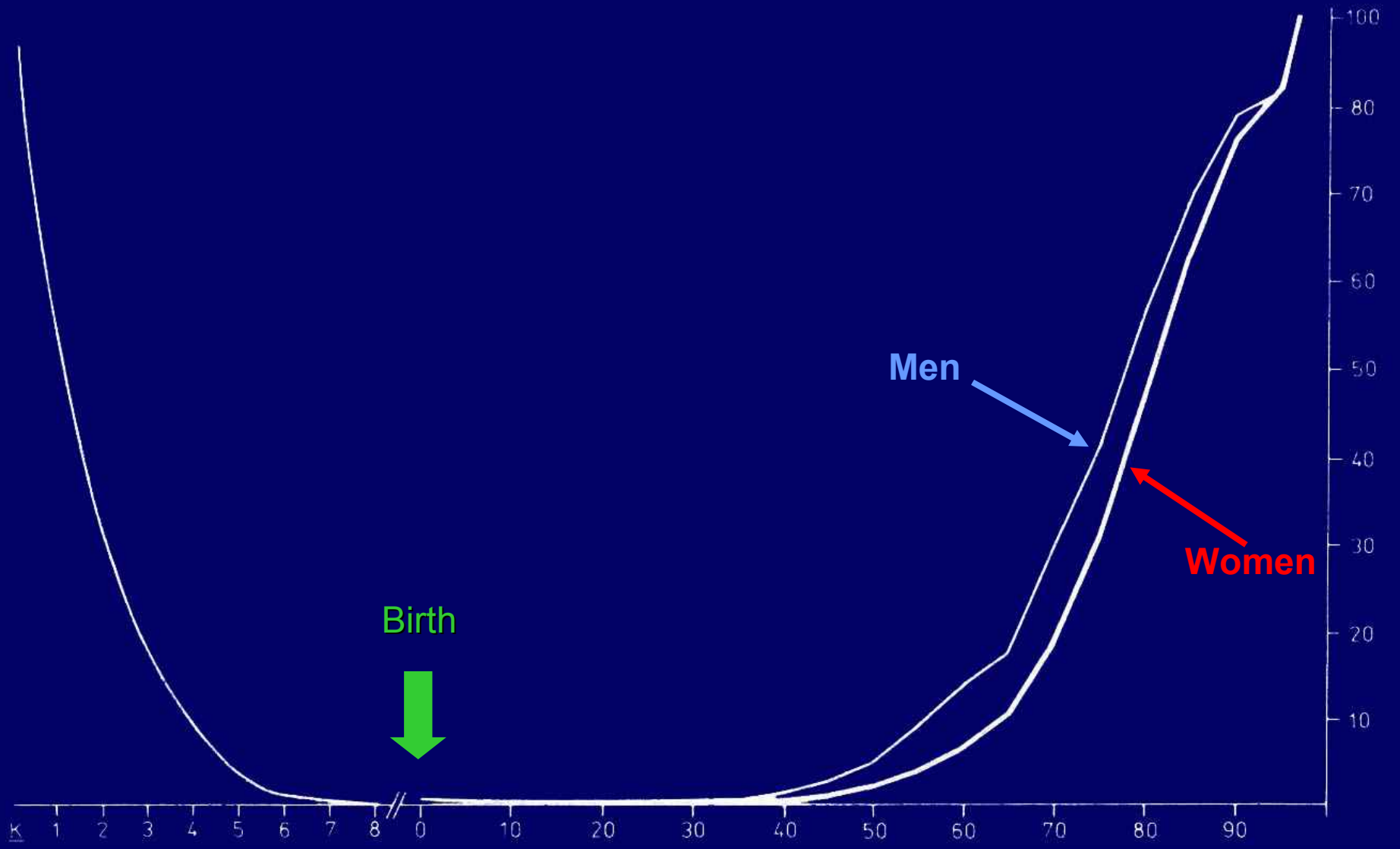
The Fetal Period

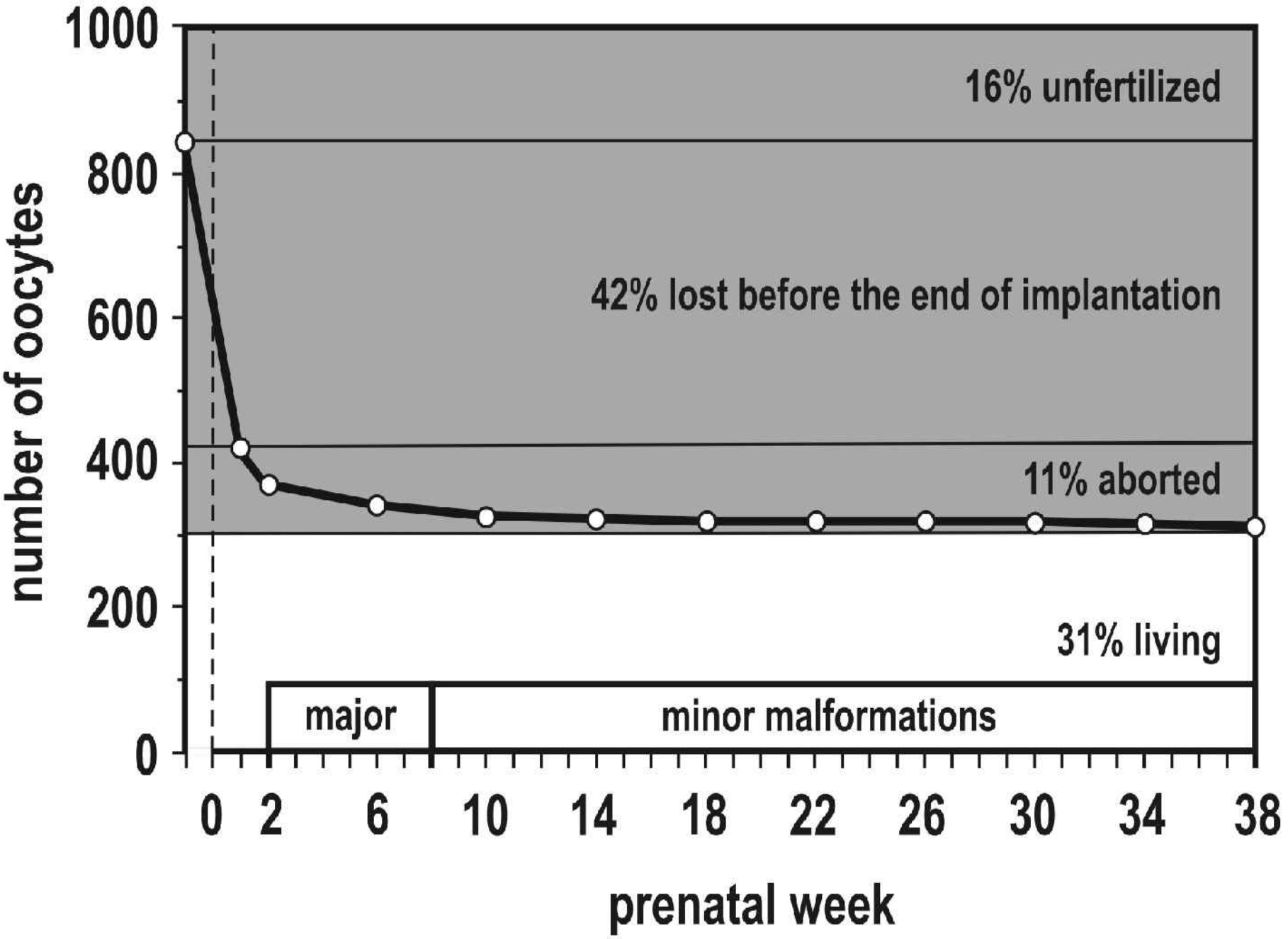


9 12 16 20 24 28 32 36 38 FULL TERM

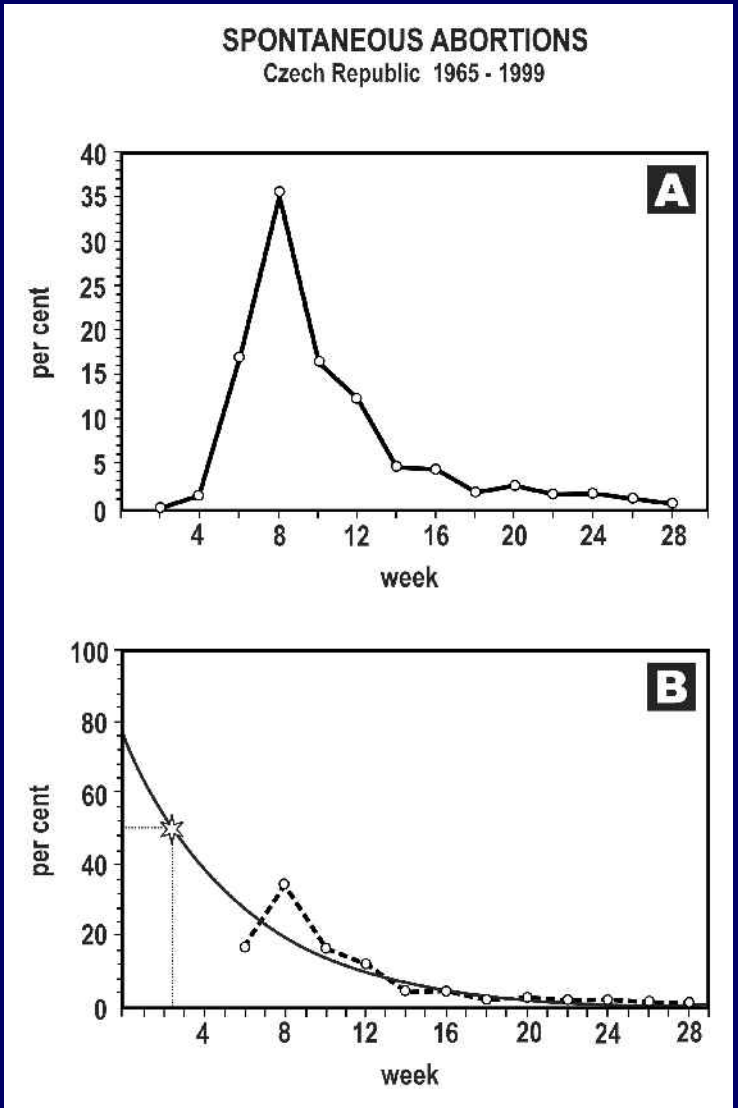
Prenatal and postnatal losses

Death during prenatal and postnatal ontogenesis



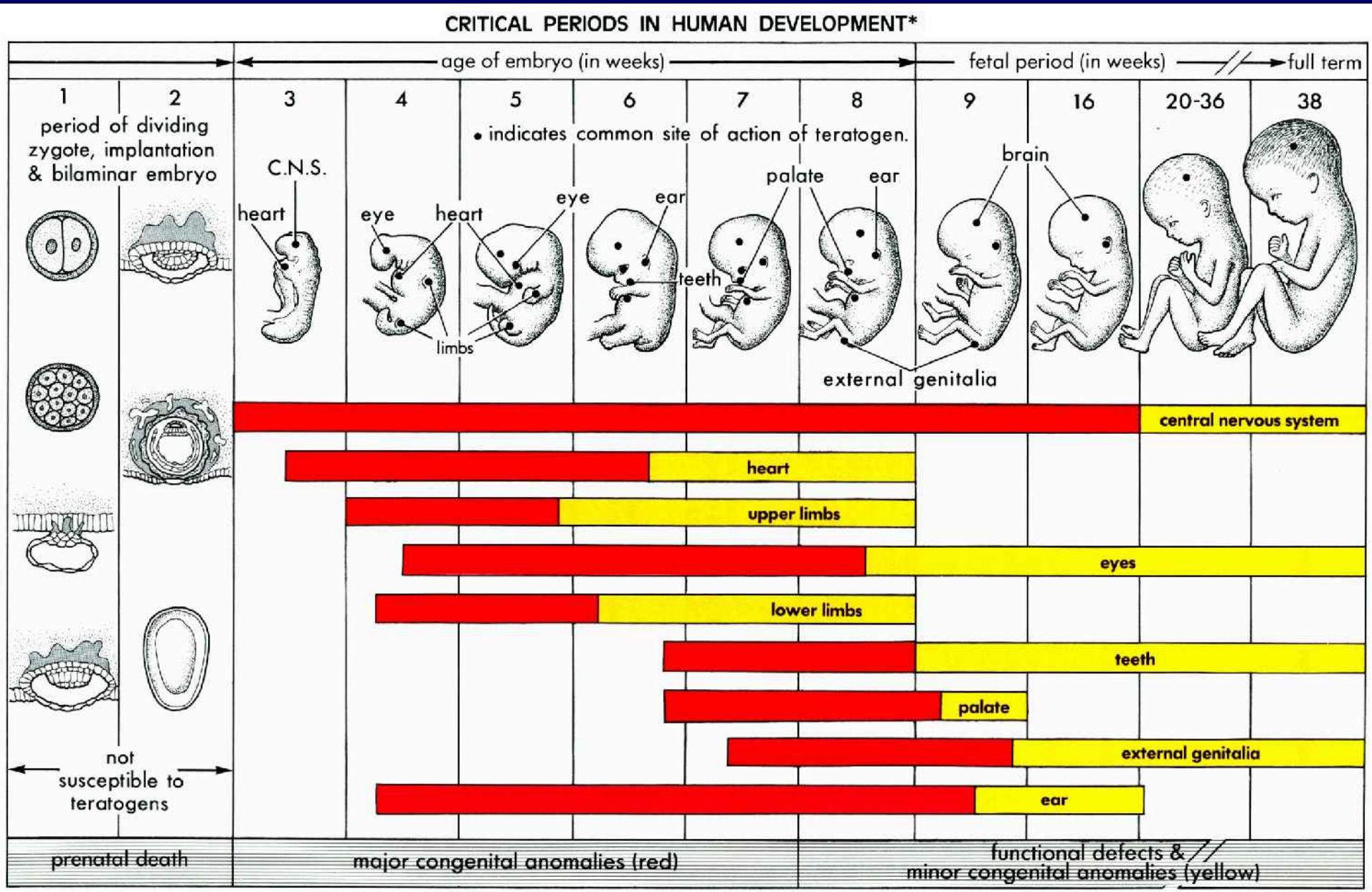

1000
800
600
400
200
0
number of oocytes
16% unfertilized
42% lost before the end of implantation
11% aborted
31% living
major
minor malformations
0
2
6
10
14
18
22
26
30
34
38
prenatal week

Spontaneous abortions

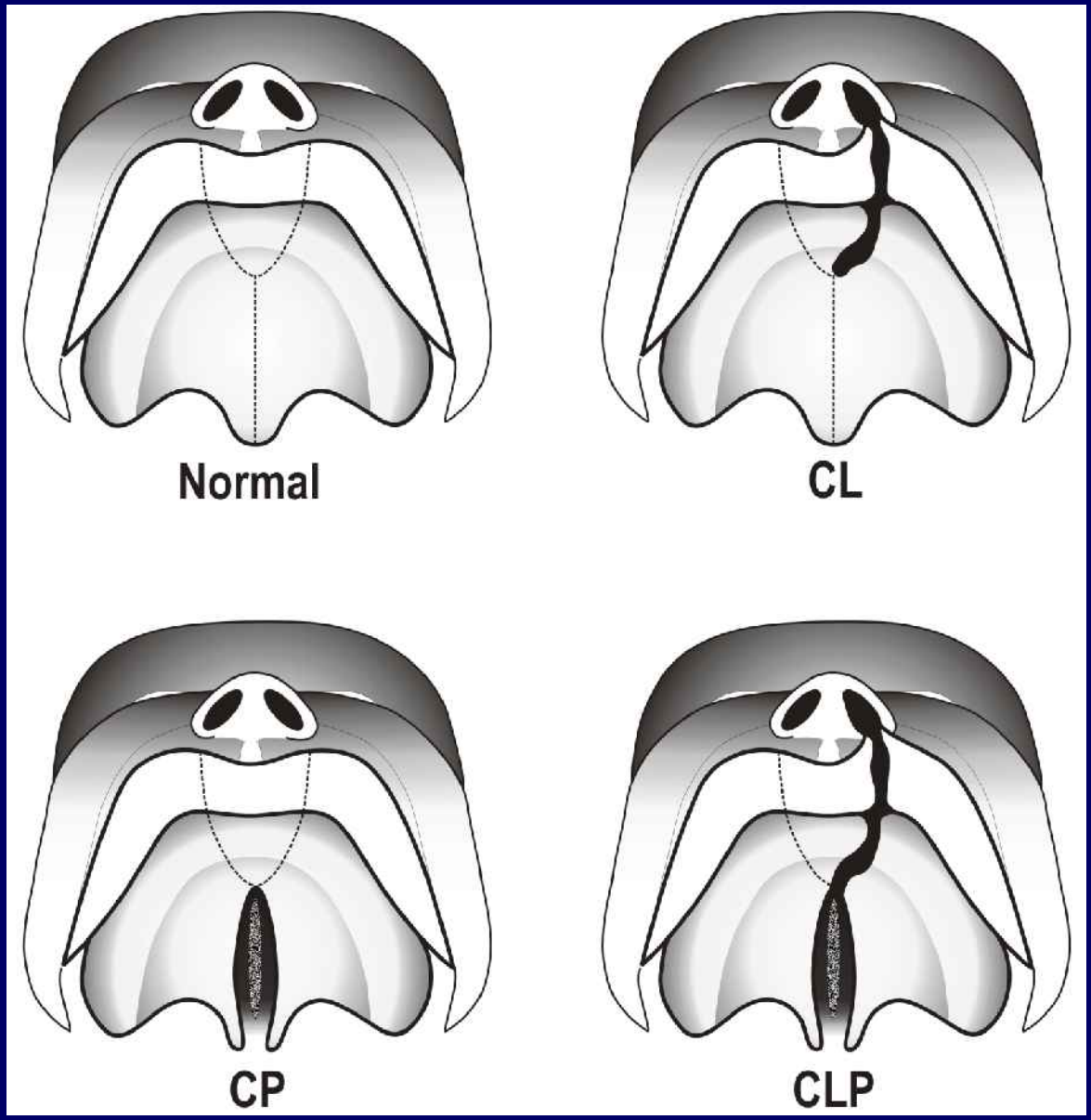


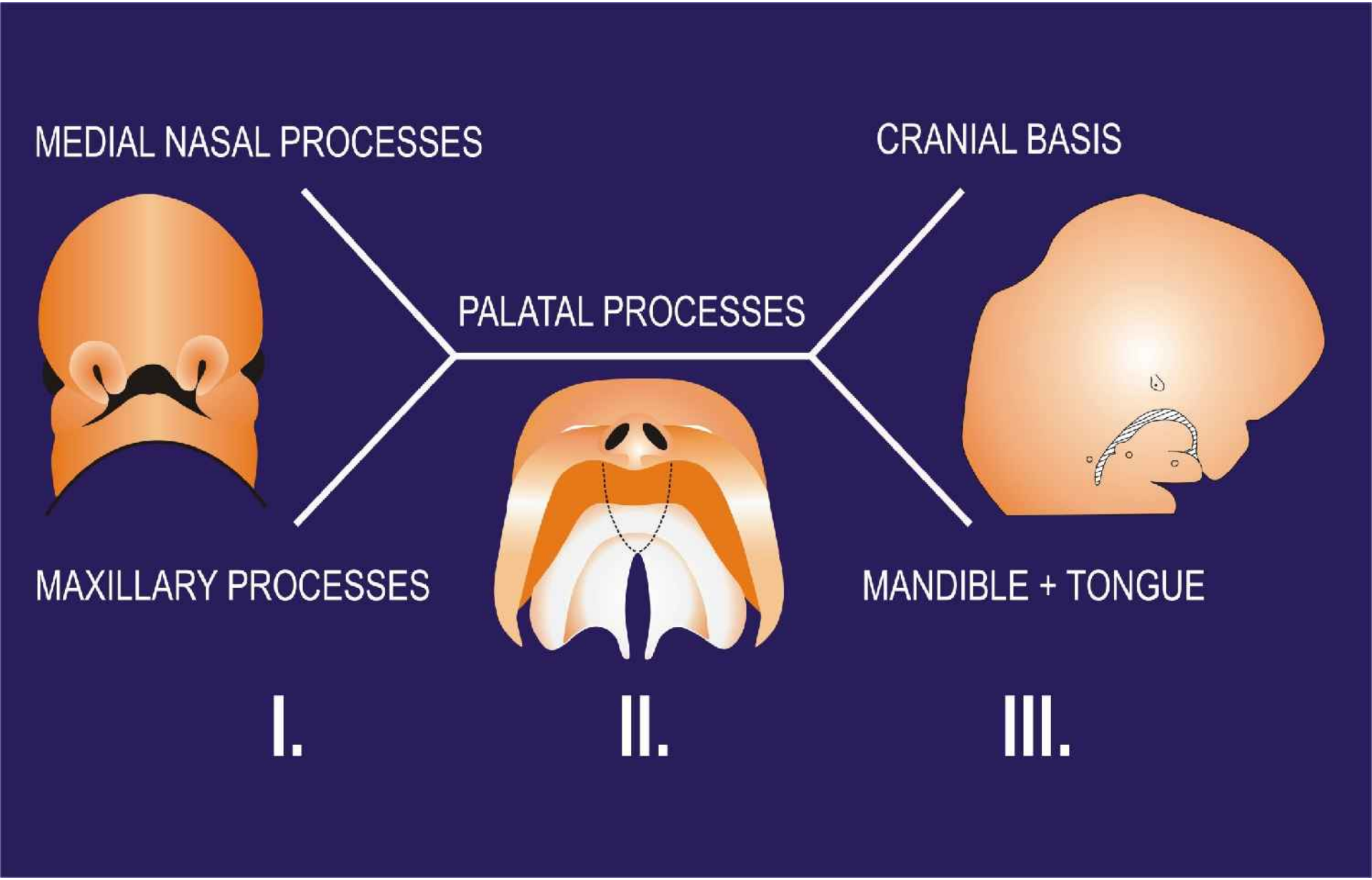
- Czech Republic 1965 – 1999
- **A** – official statistics record no abortions during the first month of pregnancy
- **B** – situation after mathematical extrapolation of data A using an exponential curve

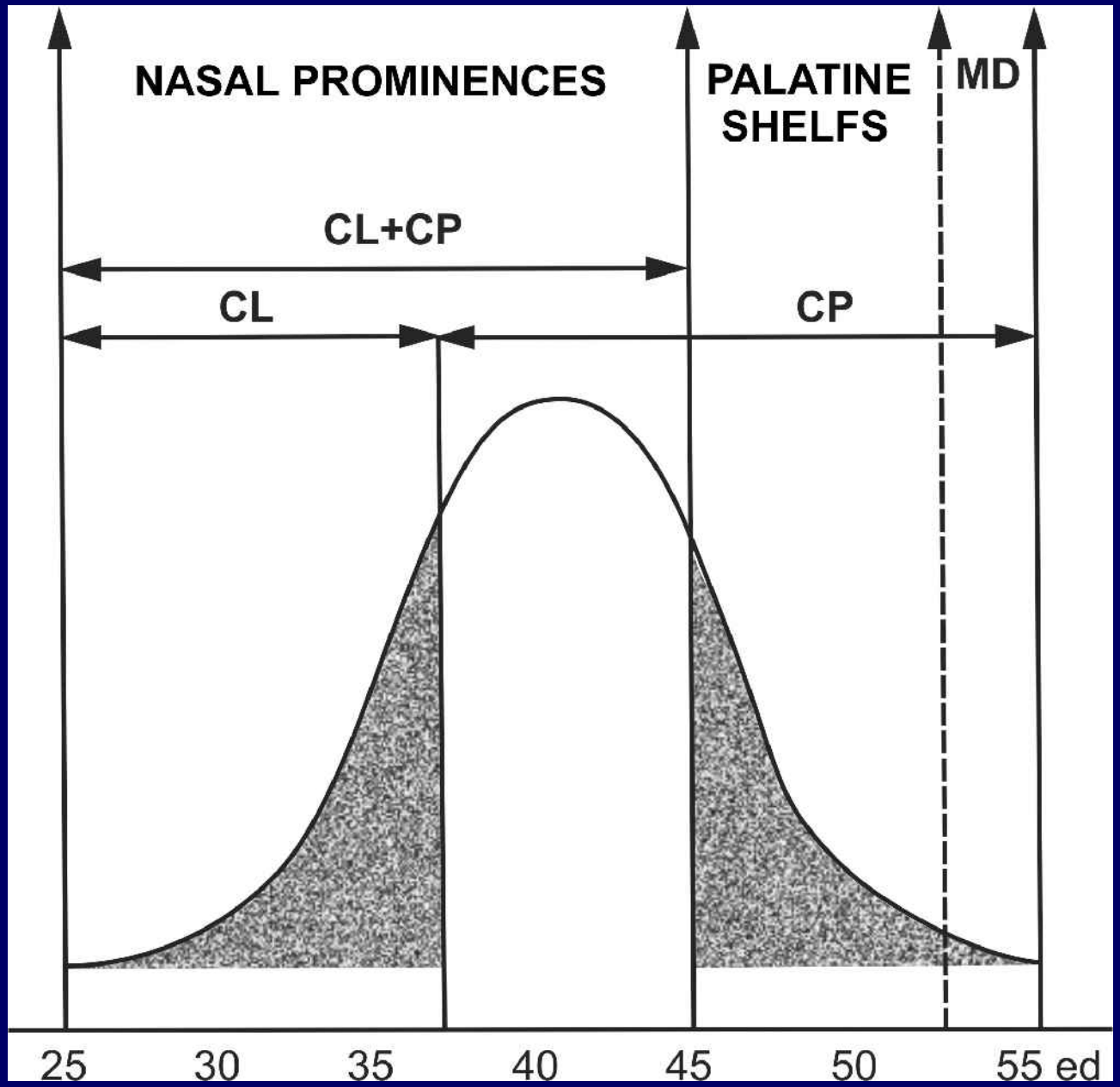
CRITICAL PERIOD



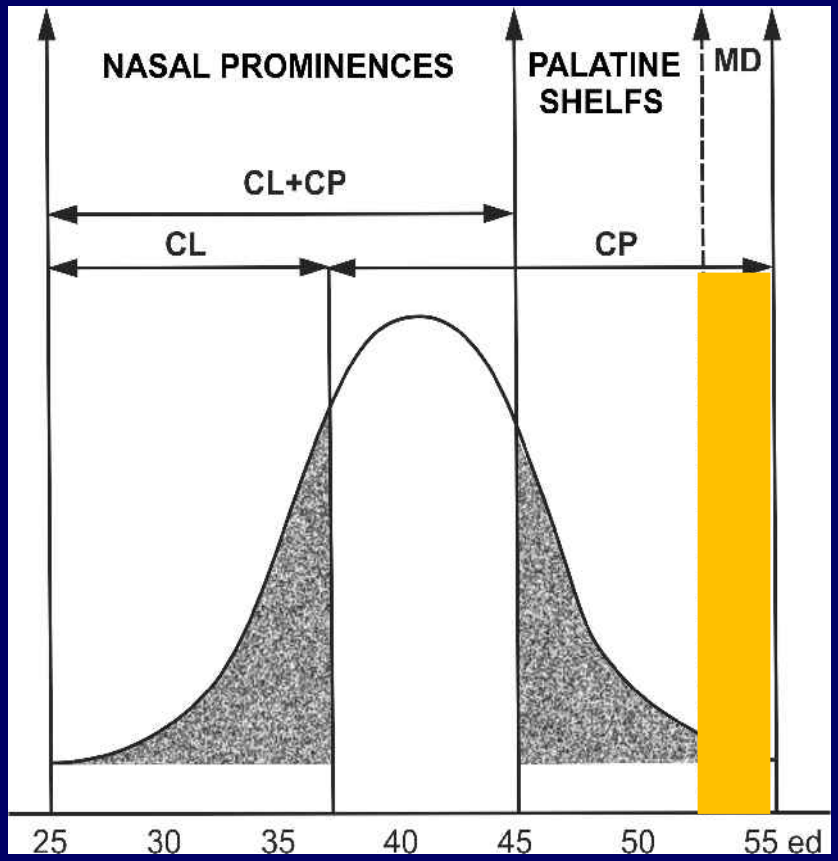
* Red indicates highly sensitive periods when teratogens may induce major anomalies.


Normal
CL
CP
CLP

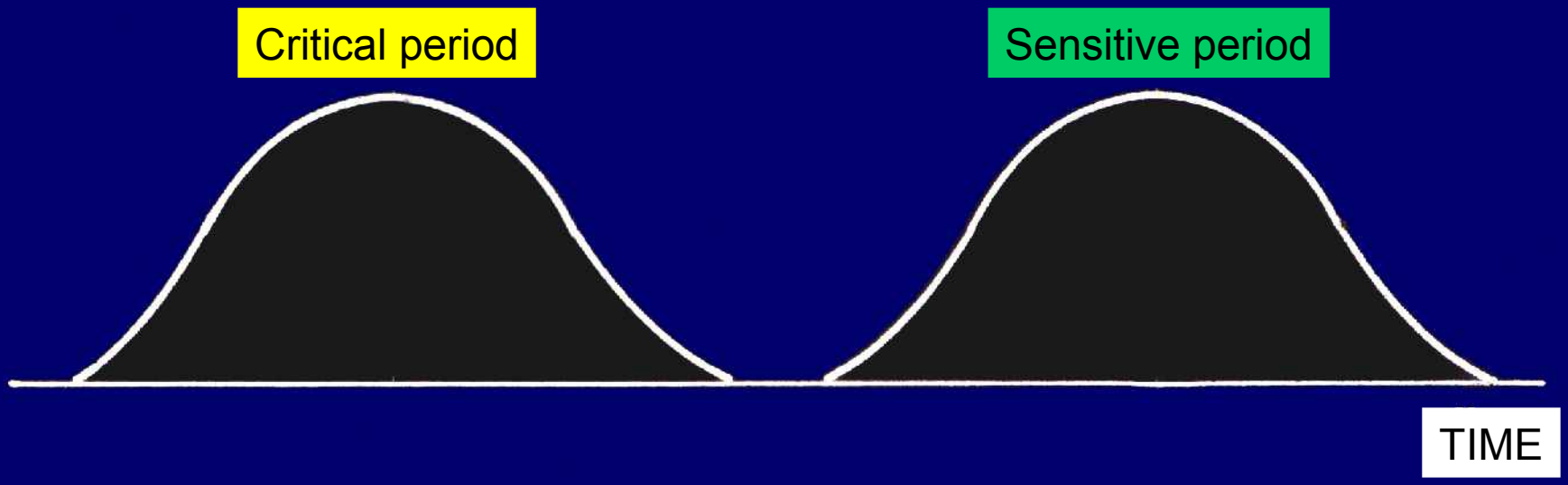

MEDIAL NASAL PROCESSES
CRANIAL BASIS
PALATAL PROCESSES
MAXILLARY PROCESSES
MANDIBLE + TONGUE
I.
II.
III.

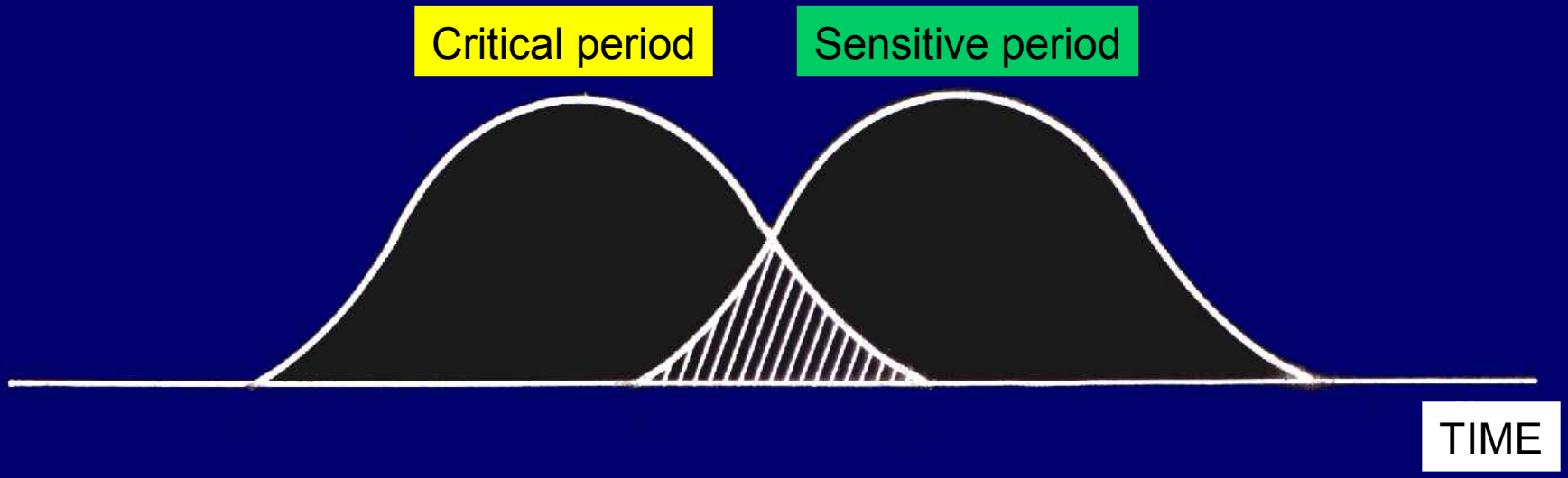

NASAL PROMINENCES
PALATINE SHELFS
MD
CL+CP
CL
CP
25
30
35
40
45
50
55 ed

Pierre Robin Syndrome

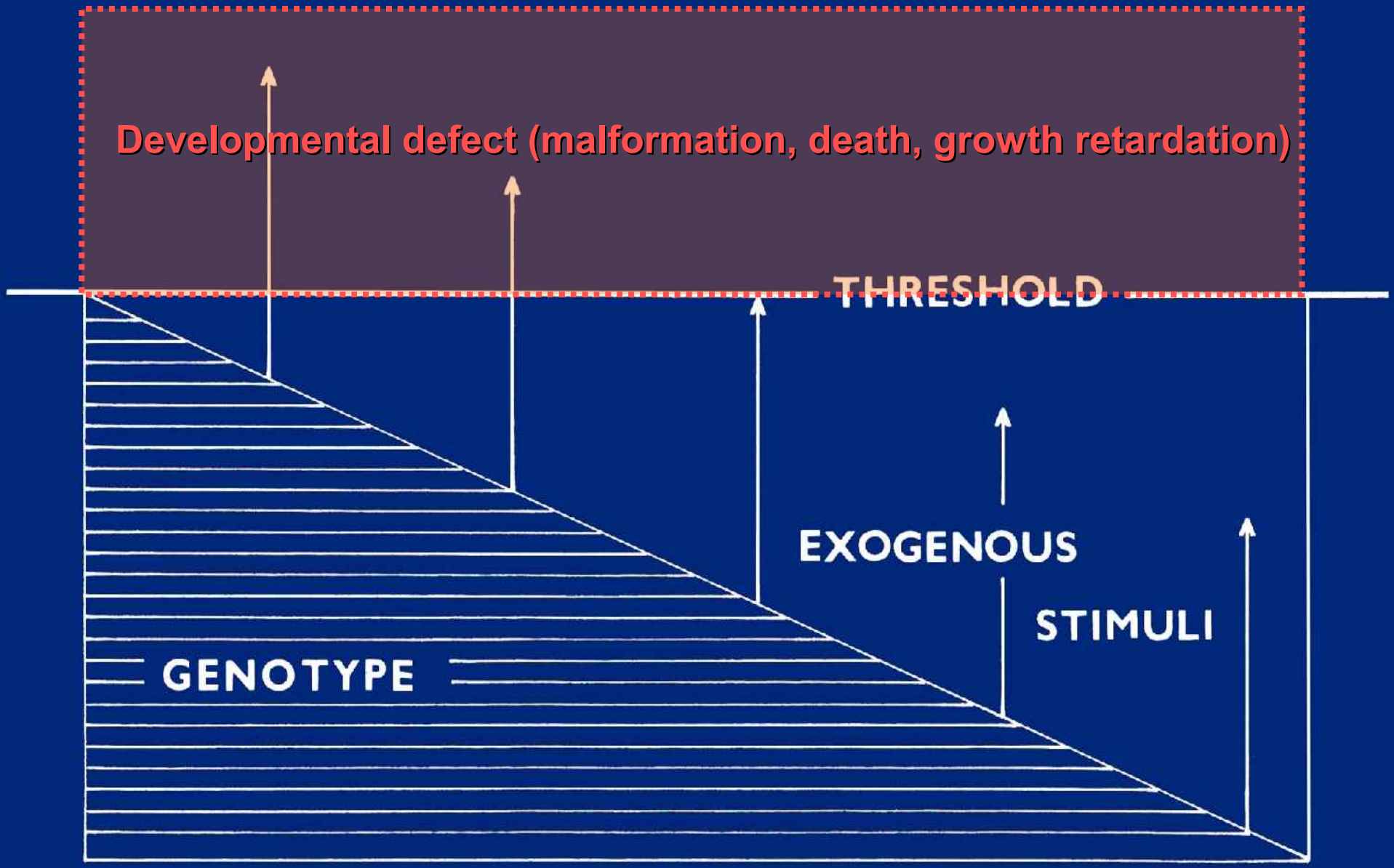


SENSITIVE PERIOD


Critical period
Sensitive period
TIME


Critical period
Sensitive period
TIME

Threshold in TERATOGENESIS

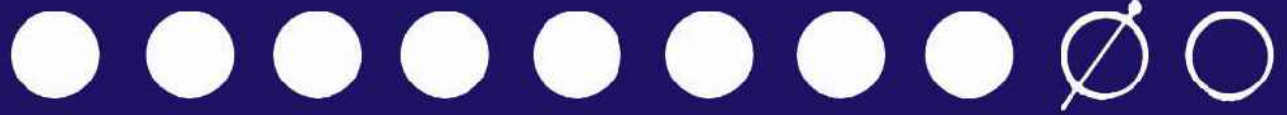
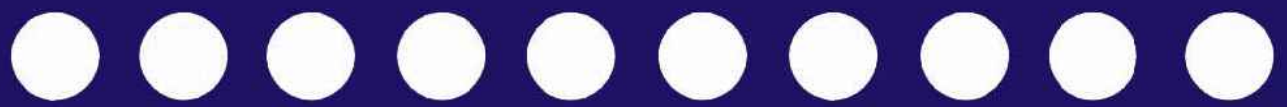

Developmental defect (malformation, death, growth retardation)
THRESHOLD
EXOGENOUS
STIMULI
GENOTYPE

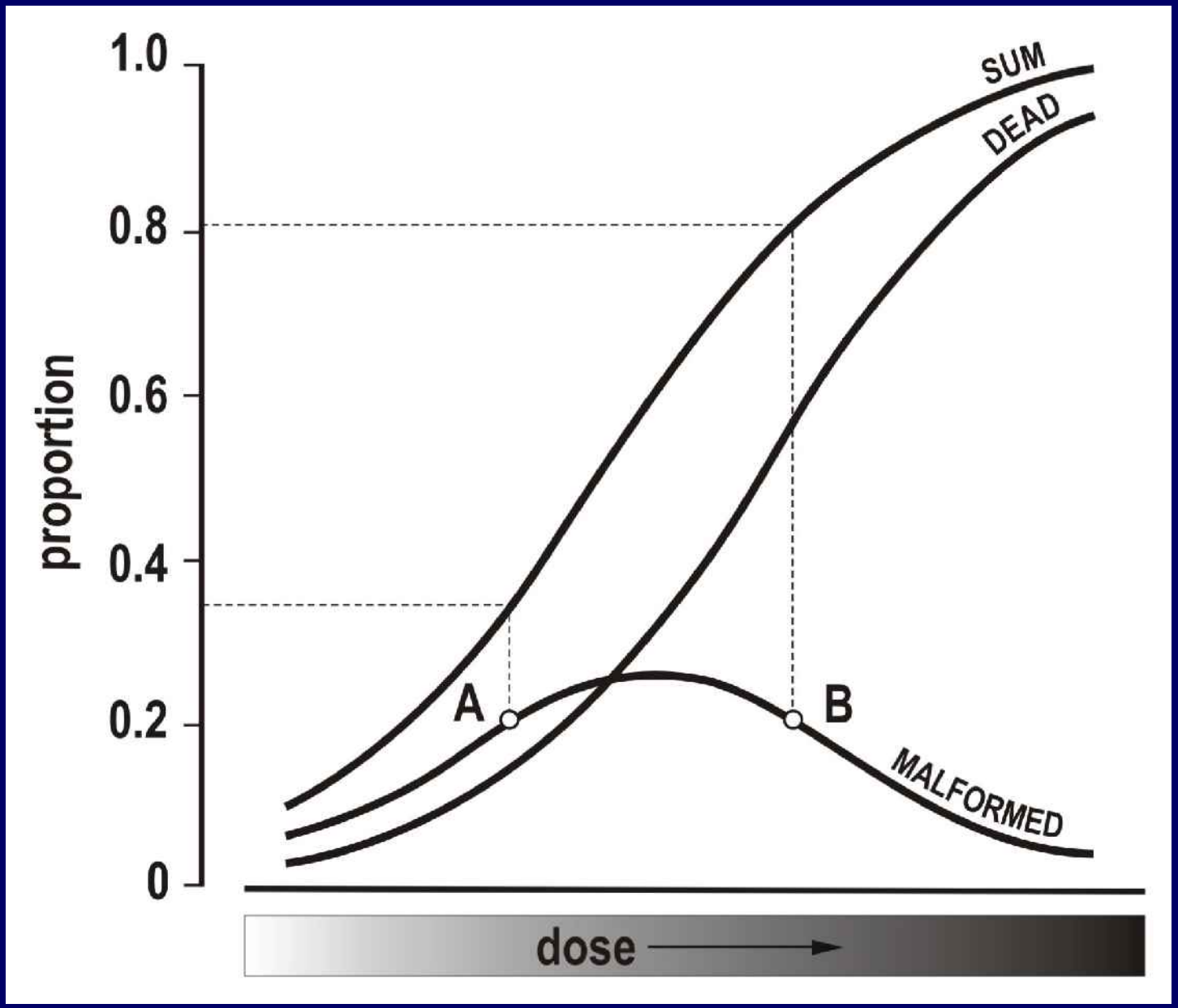
DOSES
and
EMBRYOTOXICITY

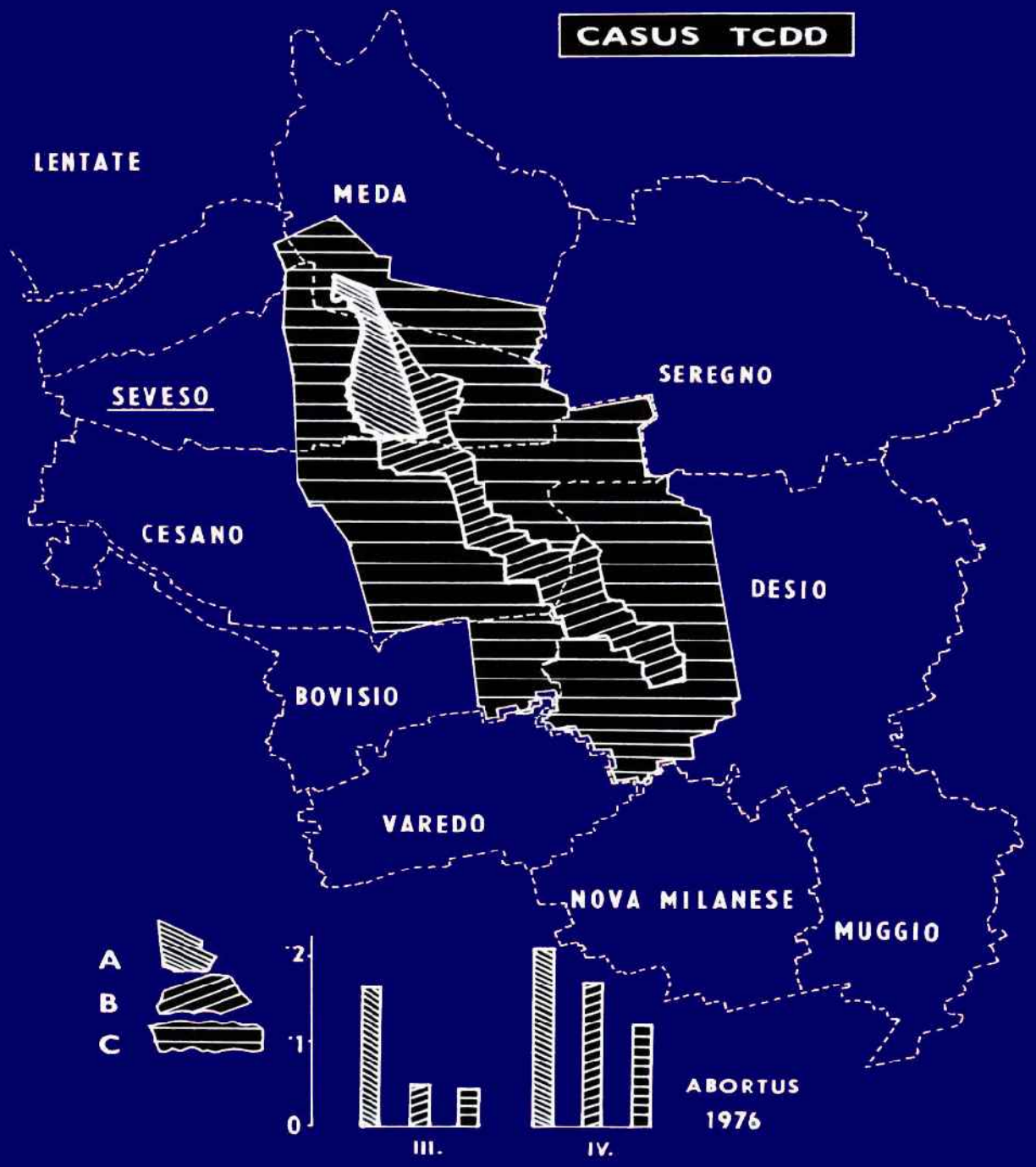
Three components of embryotoxicity

- Developmental defect - teratogenicity
- Death of embryo/fetus - lethality
- Growth retardation

EMBRYOTOXICITY

1. 
2. 
3. 


1.0
0.8
0.6
0.4
0.2
0
proportion
SUM
DEAD
A
B
MALFORMED
dose


CASUS TCDD
LENTATE
MEDA
SEVESO
SEREGNO
CESANO
DESIO
BOVISIO
VAREDO
NOVA MILANESE
MUGGIO
A
B
C
2
1
0
III.
IV.
ABORTUS
1976

Head deformation and protrusion of eyes

Skin defects

Reduction deformity of limbs

CAUSES of BIRTH DEFECTS

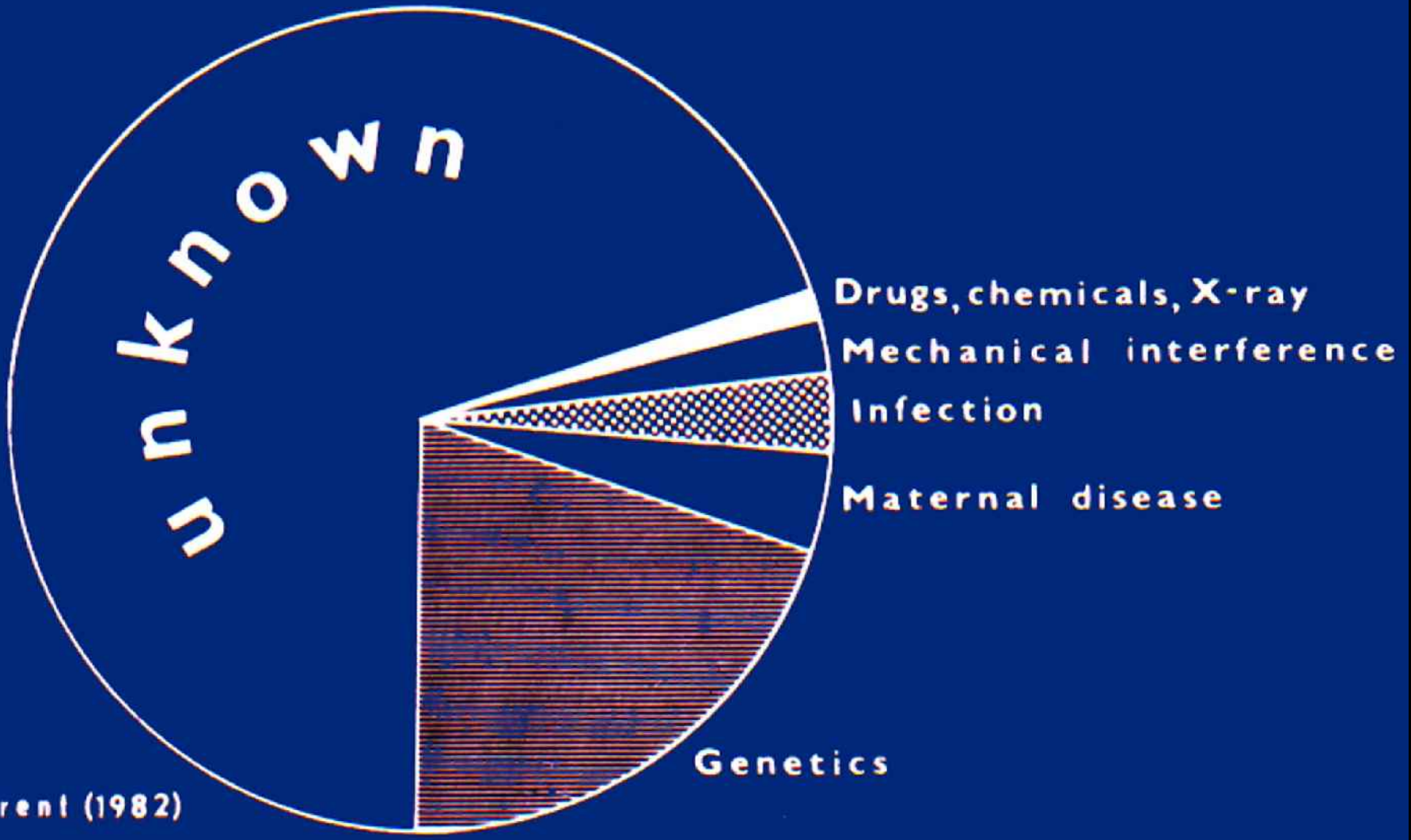
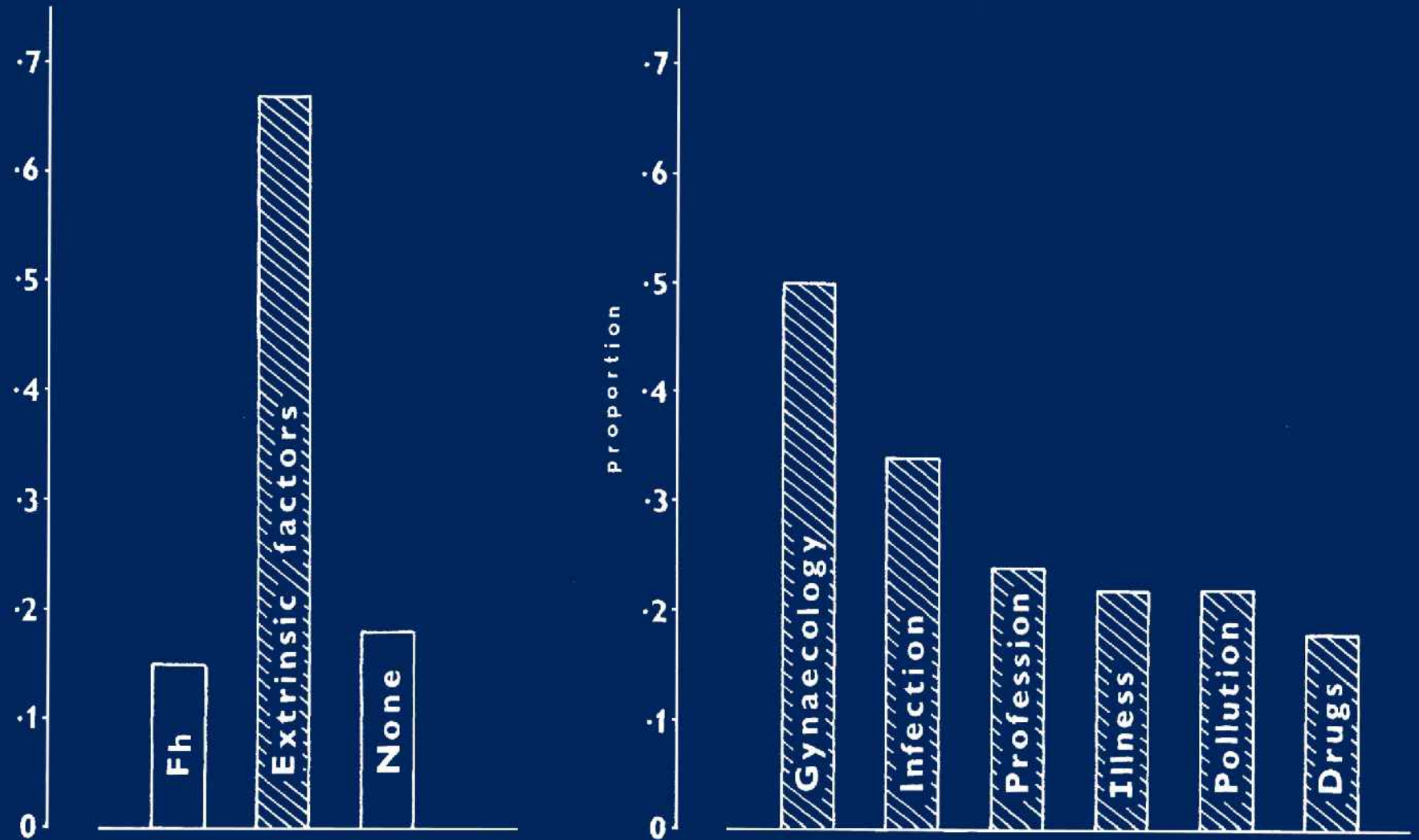

unknown
Drugs, chemicals, X-ray
Mechanical interference
Infection
Maternal disease
Genetics
Brent (1982)

Figure 5-1. Mutations in the *SONIC HEDGEHOG (SHH)* gene have multiple manifestations. *A*, Infant with bilateral cleft lip and facial findings associated with holoprosencephaly. *B*, Foot of an infant with preaxial polydactyly.

CLEFT PATIENTS´ ANAMNESIS



HUMAN TERATOGENES

Harmful environmental factor

A factor present in environment in such a concentration, which, in exposed population, significantly increases incidence of birth defects above their spontaneous frequency in un-exposed population.

Teratogene

- A qualitative definition:

  Environmental factor of chemical, physical or biological nature.

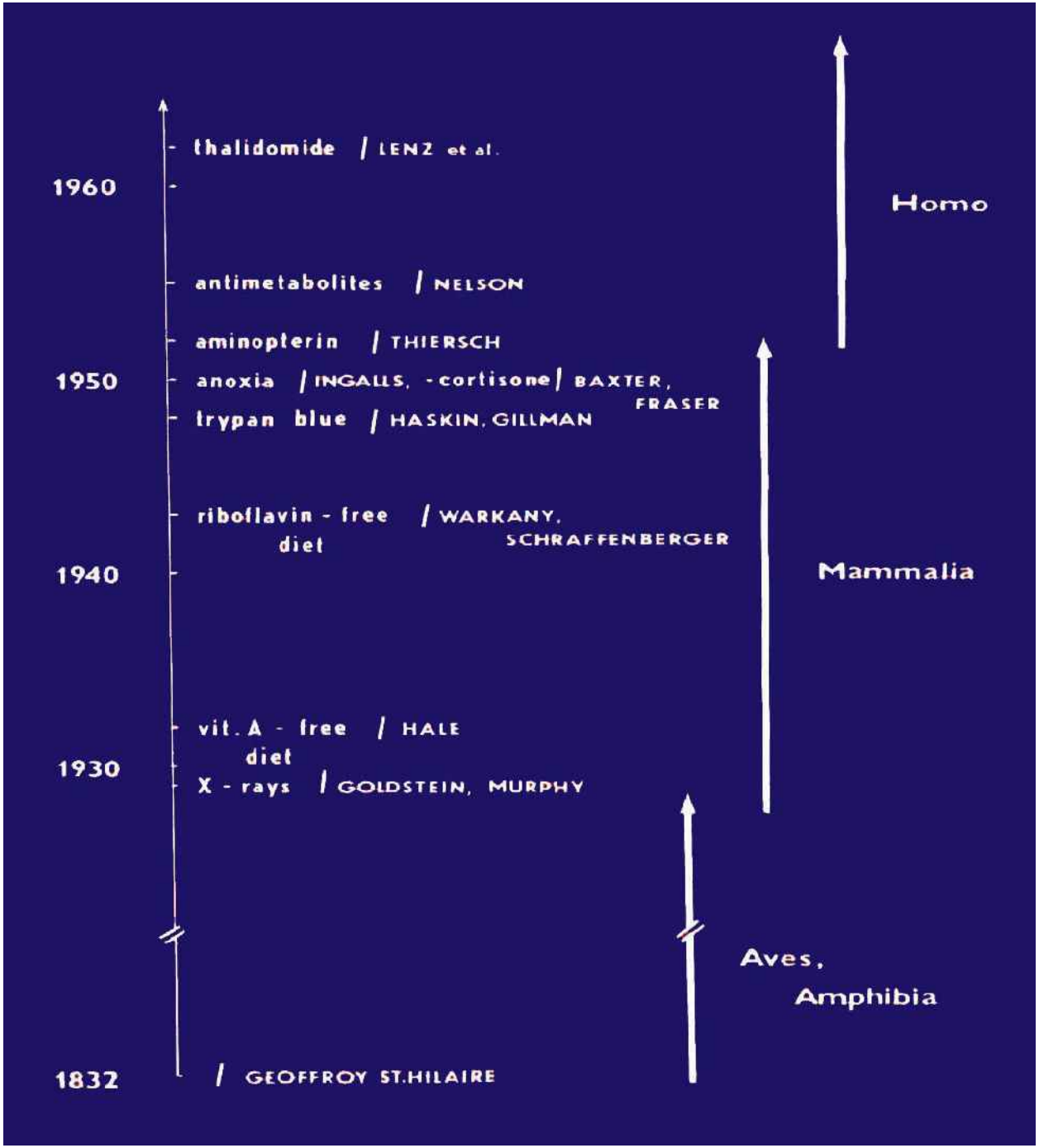
  It can induce a structural birth defect in exposed offspring, which is not hereditary.

Mutagene

- A qualitative definition:

  Environmental factor of chemical or physical nature.

  It can induce DNA damage in exposed offspring. In case it also affects germ cells, the birth defect becomes hereditary.


1960
1950
1940
1930
1832
thalidomide / LENZ et al.
antimetabolites / NELSON
aminopterin / THIERSCH
anoxia / INGALLS, - cortisone / BAXTER, FRASER
trypan blue / HASKIN, GILLMAN
riboflavin - free diet / WARKANY, SCHRAFFENBERGER
vit. A - free diet / HALE
X - rays / GOLDSTEIN, MURPHY
/ GEOFFROY ST. HILAIRE
Homo
Mammalia
Aves,
Amphibia

MODIFIED FROM KHERA 1976

	THALIDOMIDE	AMINOPTERIN	METHOTREXATE	METHYLMERCURY	TESTOSTERONE
HAMSTER	−			+	+
MOUSE	−	+	+	+	+
RAT	−		+	+	+
RABBIT	+		+		+
GUINEA PIG					+
CAT	+	±	+	+	
DOG	+	+		+	
SWINE	+	+		−	
MONKEY	+	−	−	−	+
HUMANS	+	+	+	+	+

Number of newborns with malformation of the limbs (black) and quarterly thalidomide sales (white).

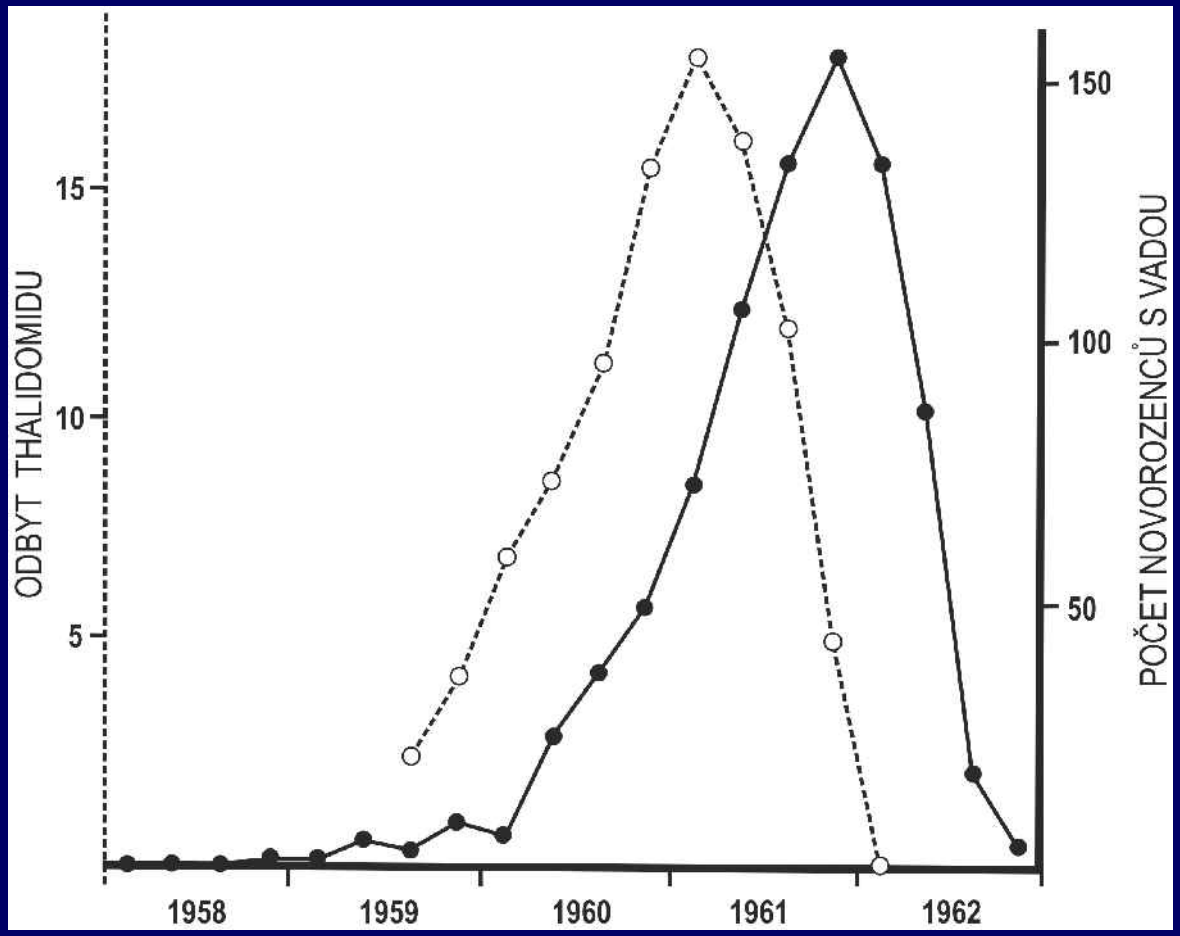


FIGURE 8-2. Phocomelia in all four limbs. This fetus had not been exposed to thalidomide. (Courtesy M. Barr, Ann Arbor, Mich.)

Frances Kathleen Oldham Kelsey

(she has prevented the thalidomide catastrophe in USA)

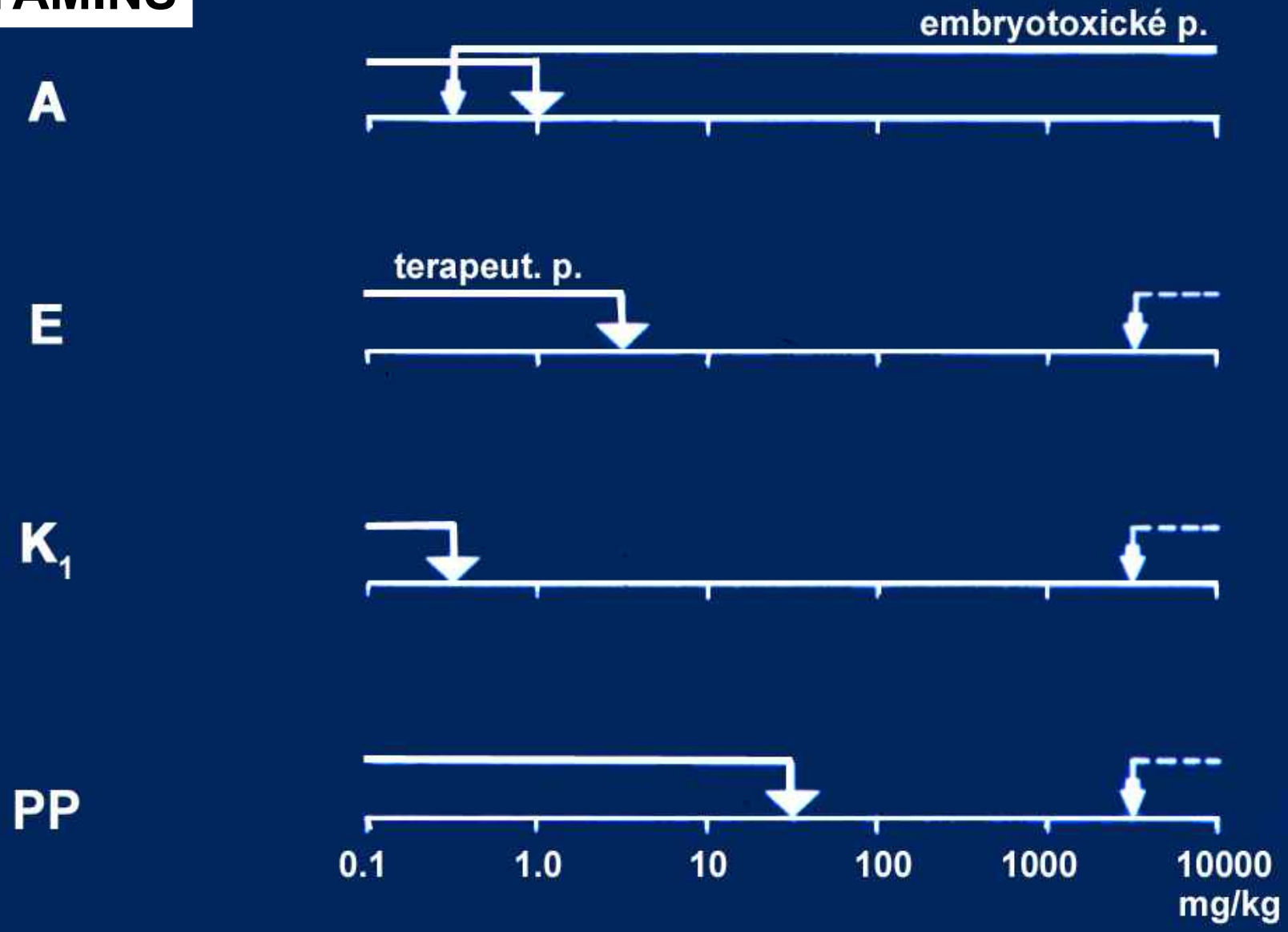
Therapy of leprosy by thalidomide

+

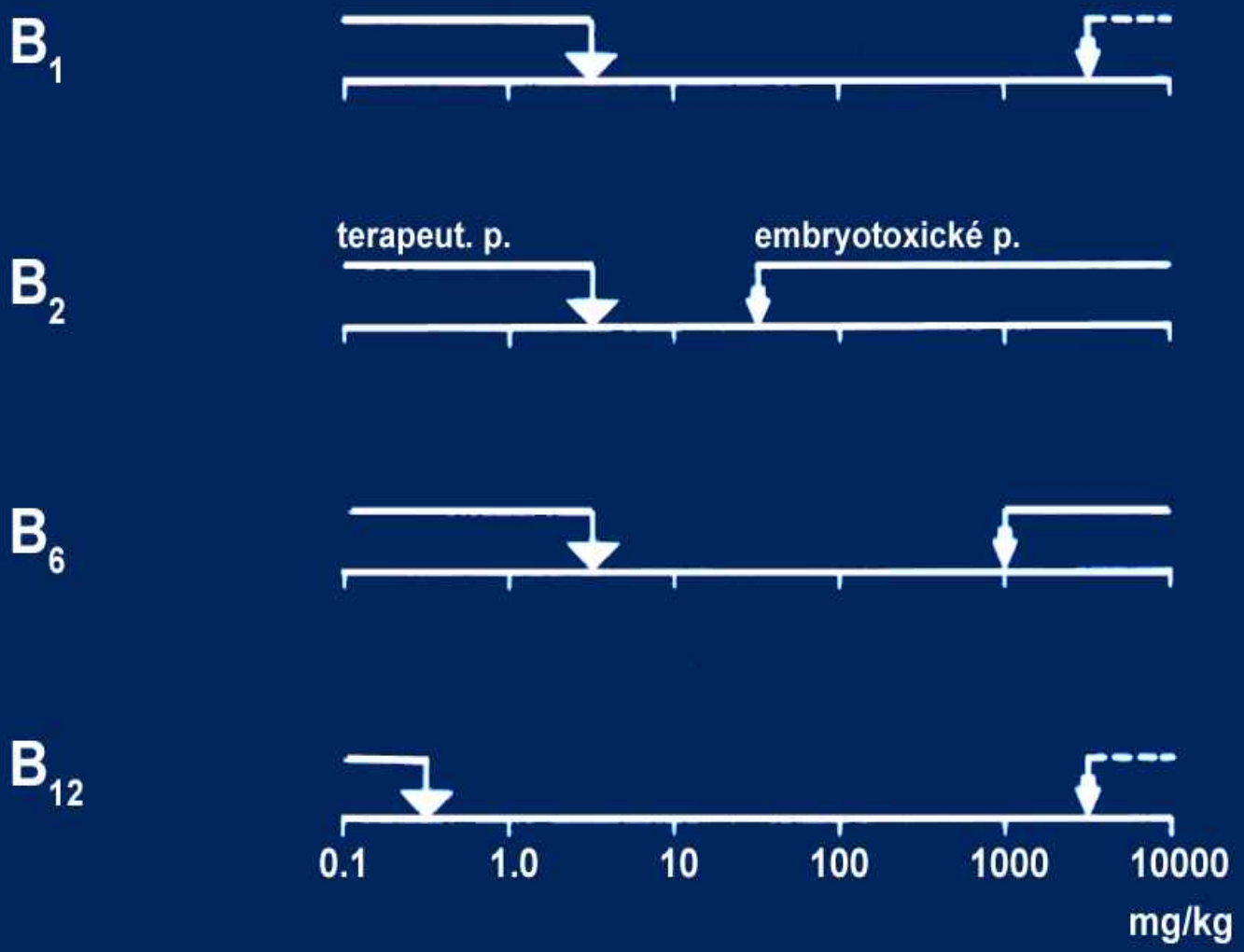
interdict of abortion

(Brazil, 2002)

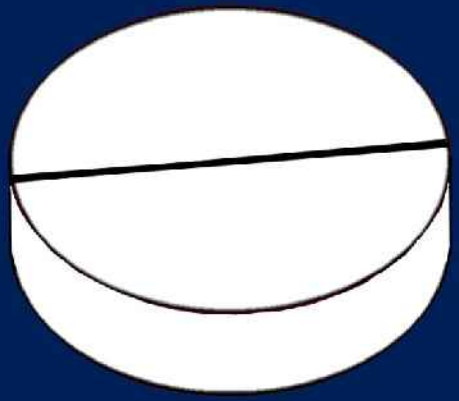
VITAMINS


embryotoxické p.
A
terapeut. p.
E
K1
PP
0.1
1.0
10
100
1000
10000
mg/kg

VITAMINS


B1
B2
terapeut. p.
embryotoxické p.
B6
B12
0.1
1.0
10
100
1000
10000
mg/kg

VITAMIN A

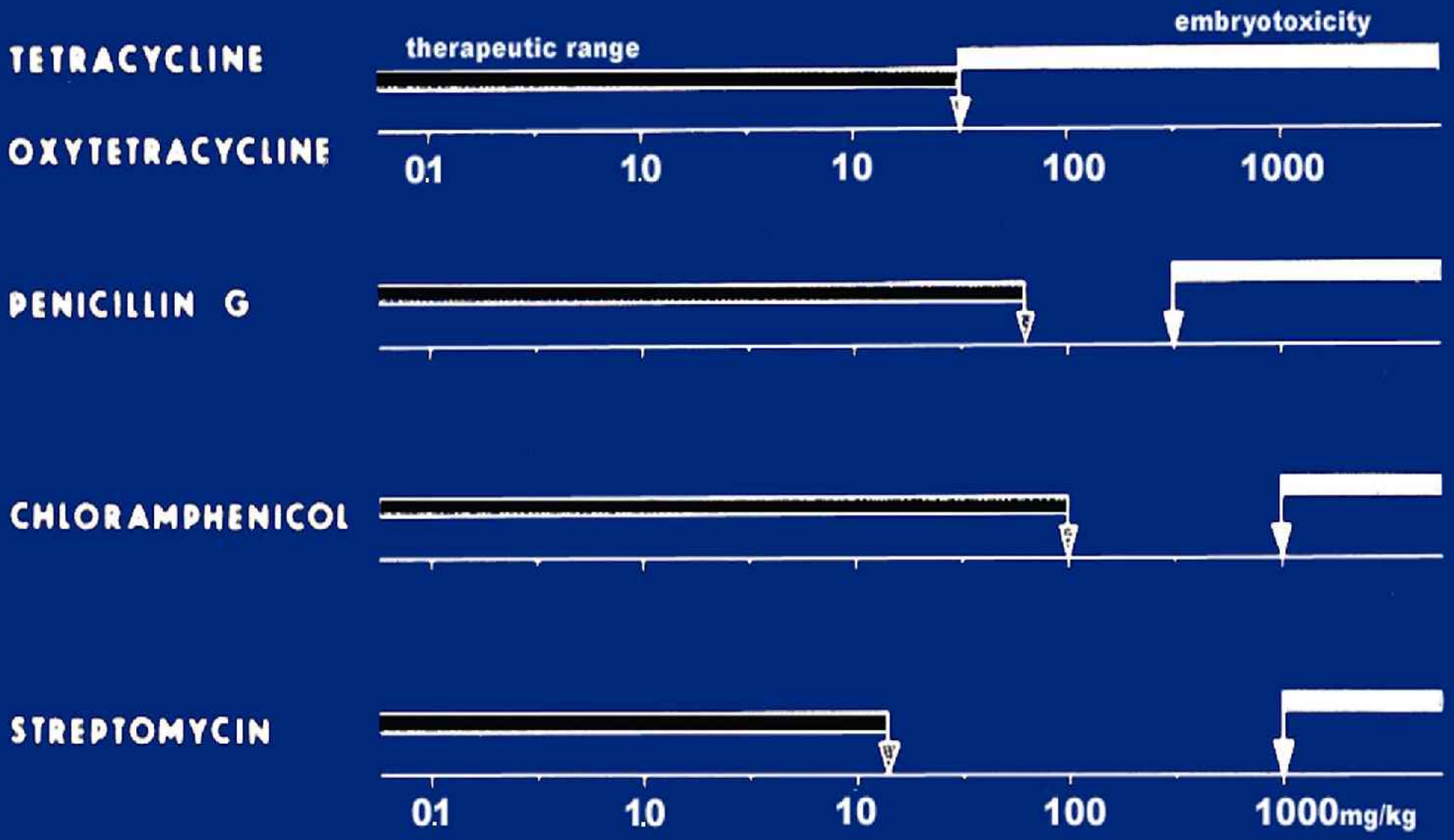


27 l of milk

= 100 peace of eggs

0.37 kg of carrot

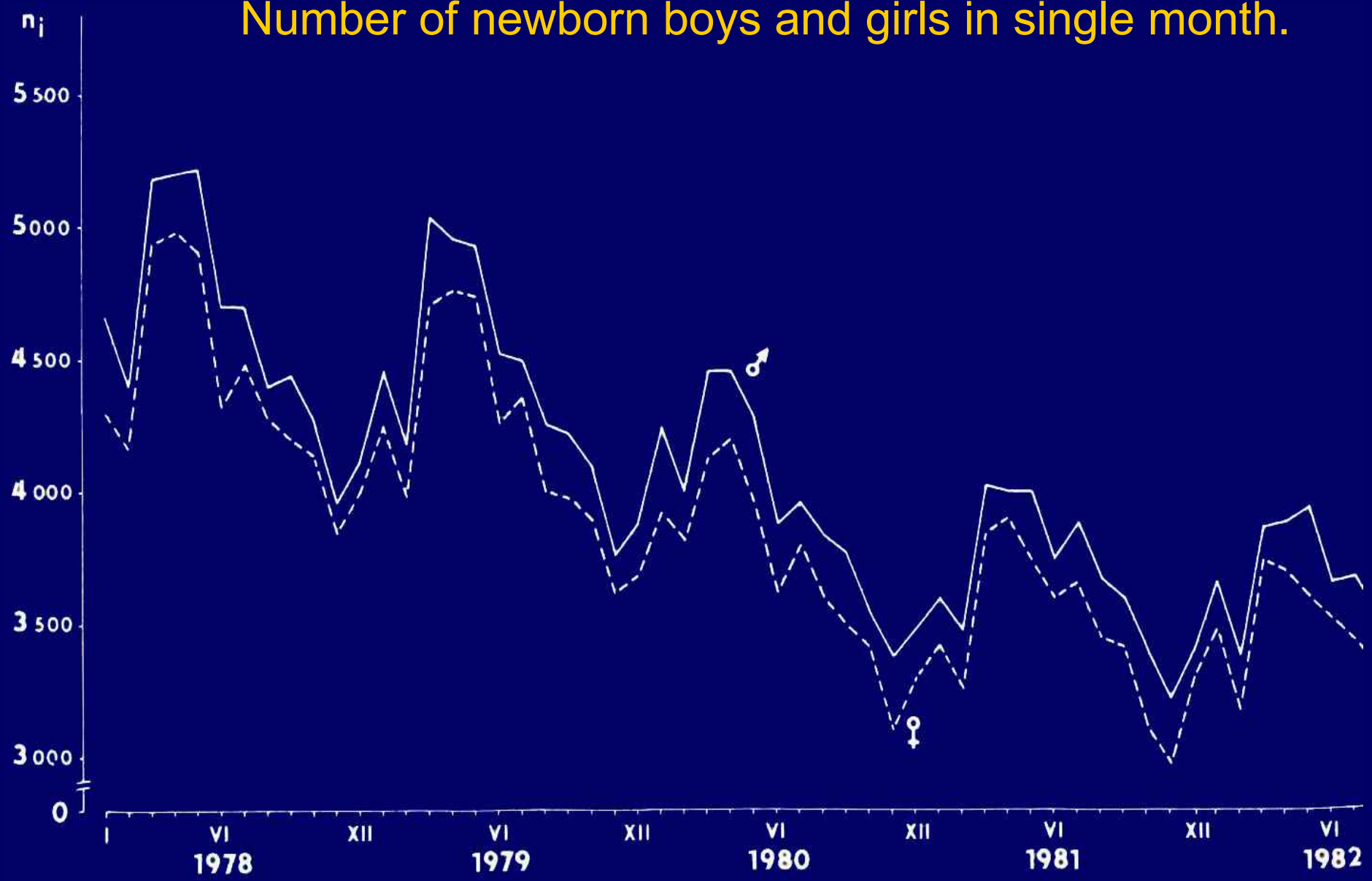
BASIC ANTIBIOTICS

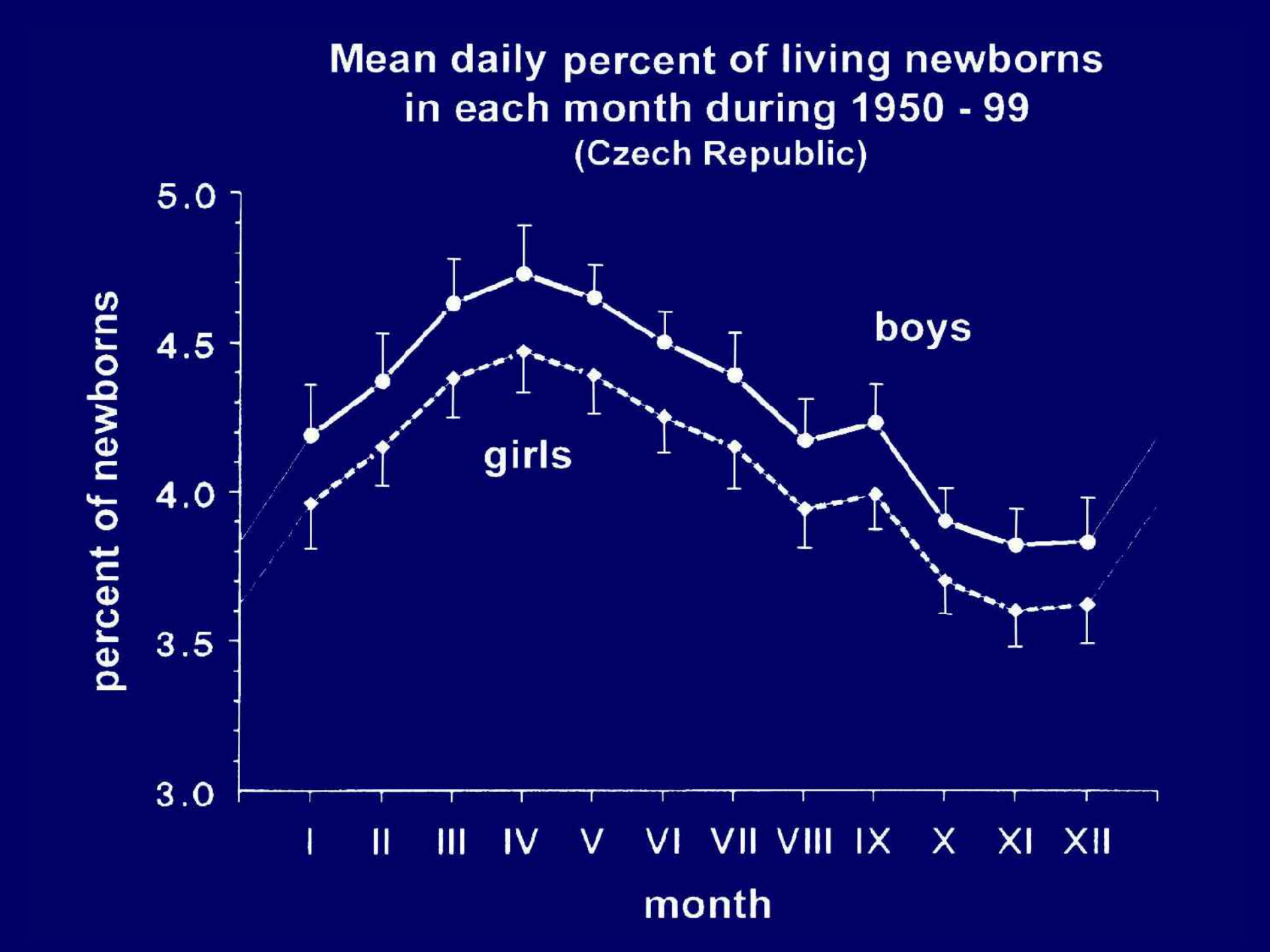


Crash of atomic reactor in CHERNOBYL 1986

Peterka et al., 2004, 2007

Number of newborn boys and girls in single month.




Mean daily percent of living newborns
in each month during 1950 - 99
(Czech Republic)
5.0
4.5
4.0
3.5
3.0
percent of newborns
boys
girls
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
month

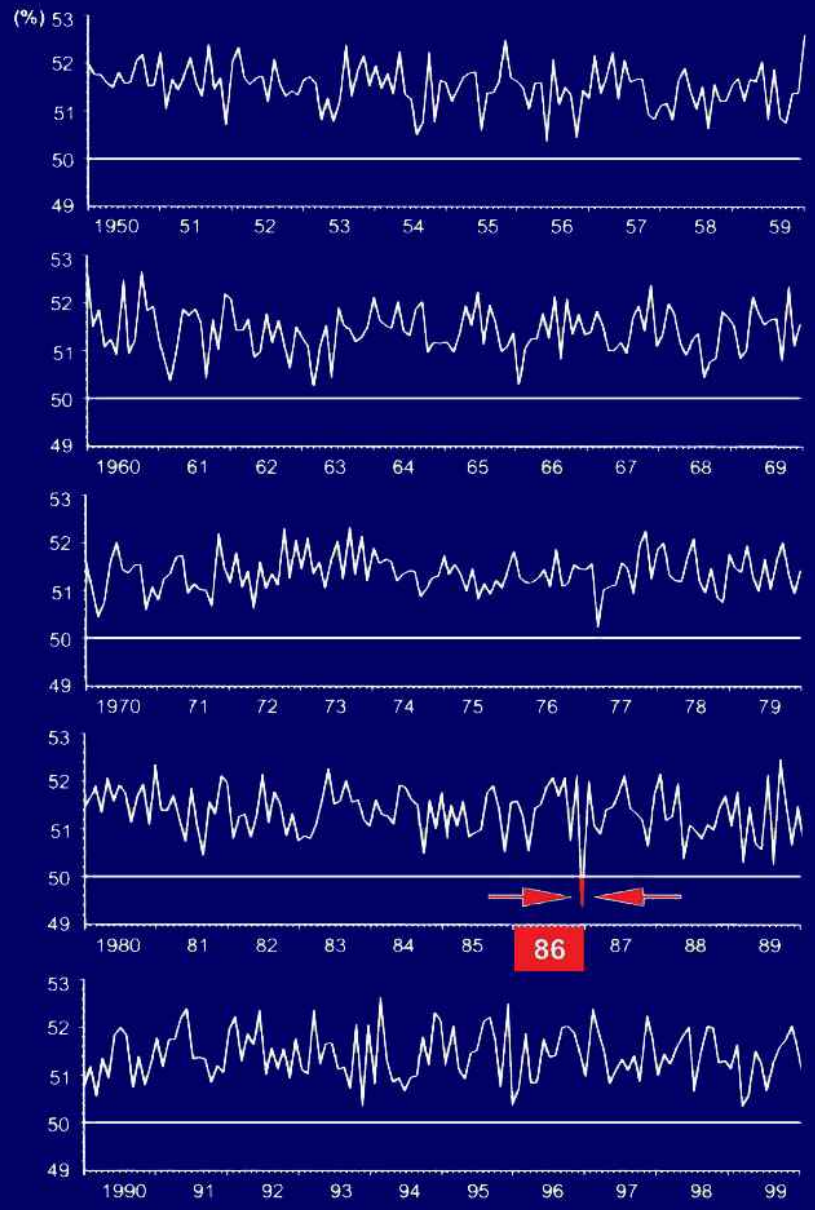
Newborn sex ratio

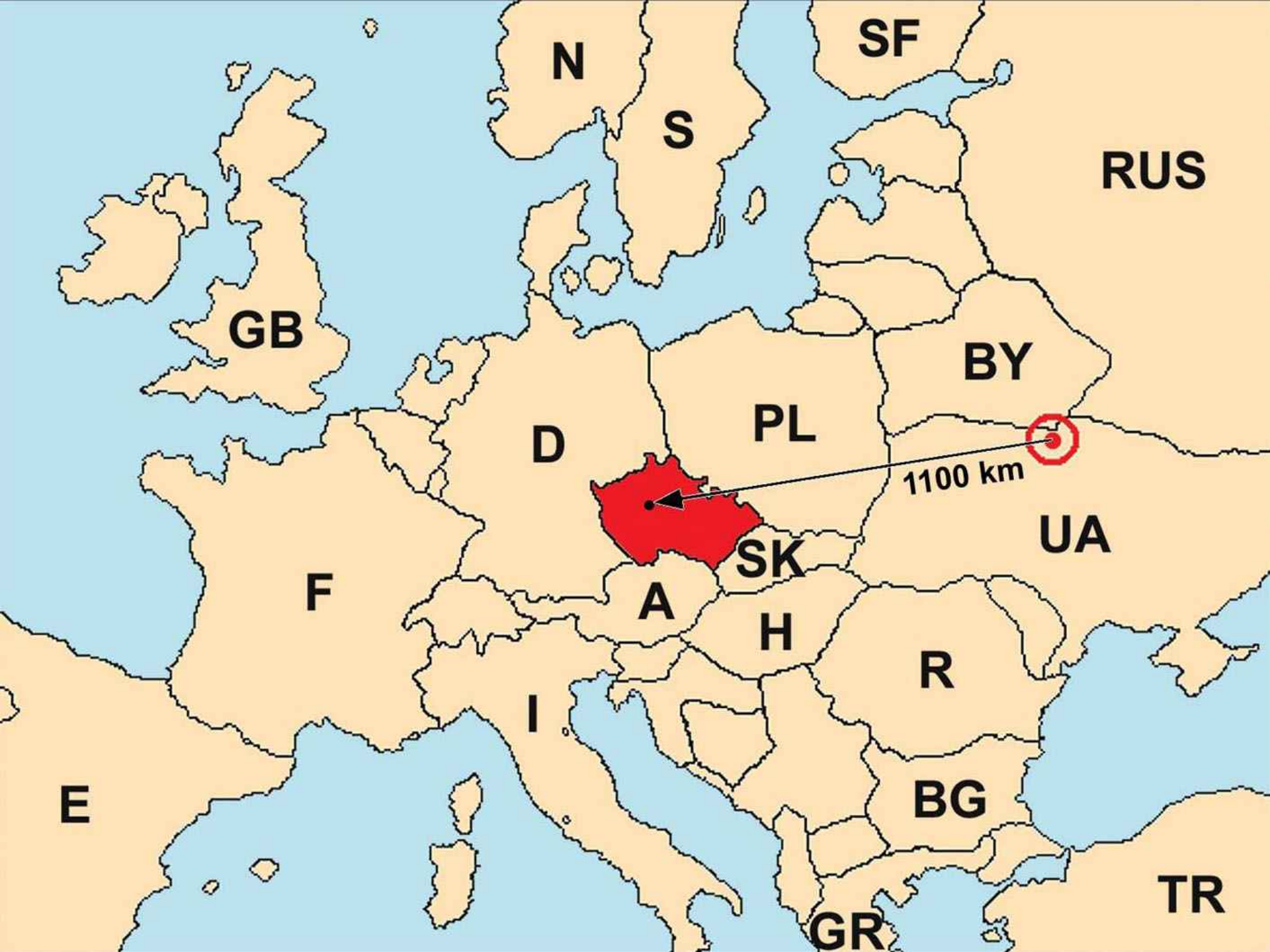
=

proportion of newborn boys and girls

105 : 100

Percent of newborn boys in single month from 1950 to 1999.




N
SF
S
RUS
GB
BY
PL
D
1100 km
UA
SK
F
A
H
R
I
BG
E
TR
GR

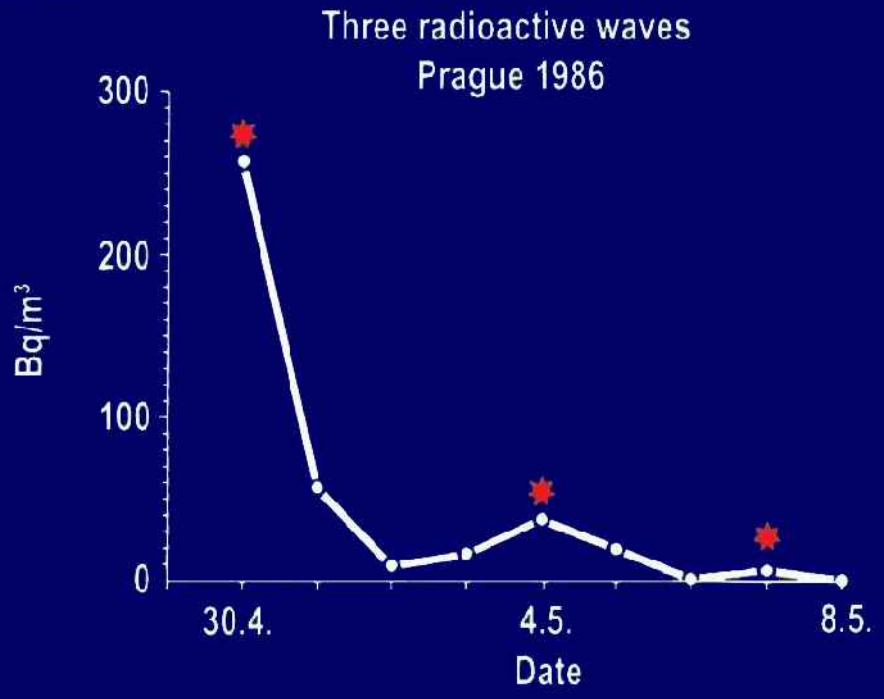
Chernobyl - history

- **26.04.1986** – explosion in 01:23:44 hours.
- **28.04.1986** – detection of a radioactive cloud in Sweden (mainly ^{131}I, ^{132}Te, ^{103}Ru, ^{134}Cs, ^{137}Cs)
- **30.04.1986** – detection of radioactivity in Czech Republic (mainly ^{131}I, ^{132}Te, ^{103}Ru, ^{134}Cs, ^{137}Cs)

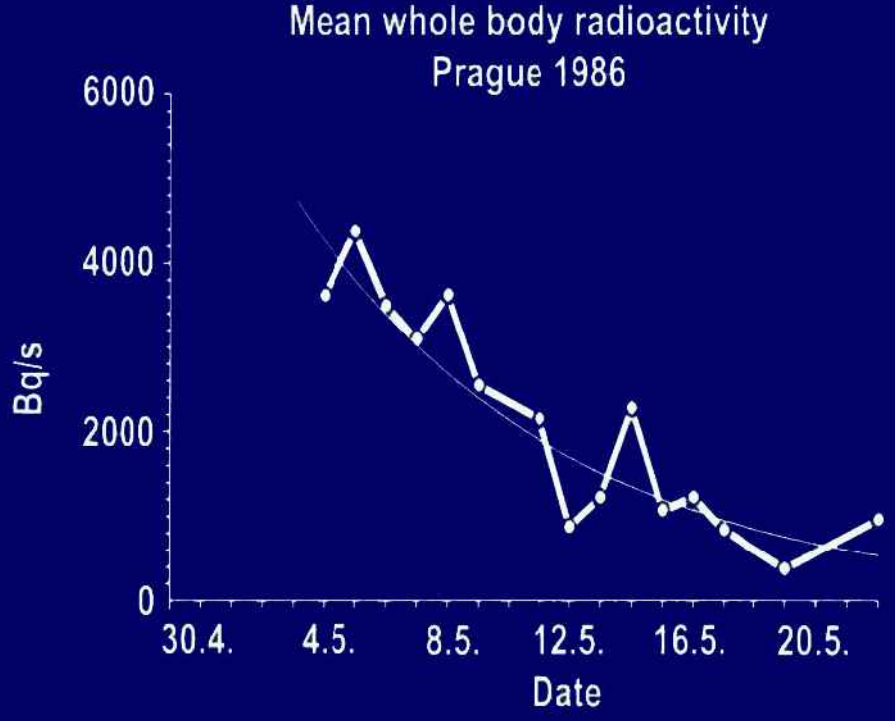
Černobyl - historie

- **26.04.1986** – exploze v 01:23:44 hod.
- **28.04.1986** – detekce radioaktivního mraku ve Švédsku (hlavně ^{131}I, ^{132}Te, ^{103}Ru, ^{134}Cs, ^{137}Cs)
- **01.05.1986** – západní státy zakazují dovoz potravin z ČSSR (přítomnost ^{134}Cs a ^{137}Cs)
- První týden v květnu 1986 – Rakousko nepřijímá naše kamiony a železniční vagony (kontaminace radioaktivním prachem)
- 05.05.1986 – ČTK oznamuje mírné zvýšení radioaktivity
- 06.05.1986 – hl. hygienik ČSR vyzývá k zachování zásad osobní hygieny a umývání ovoce a zeleniny

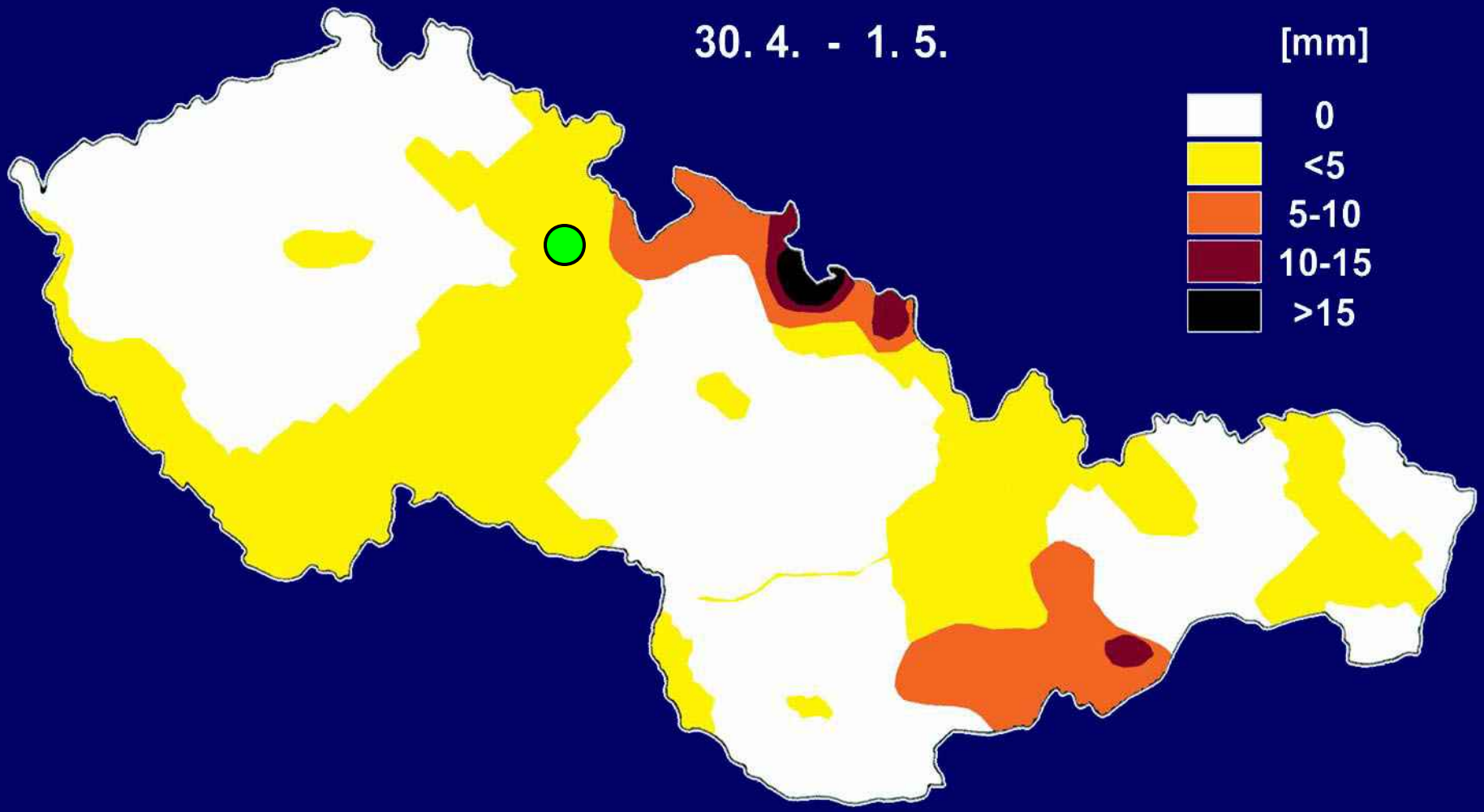
A


Three radioactive waves
Prague 1986
300
200
100
0
Bq/m³
30.4.
4.5.
8.5.
Date

B


Mean whole body radioactivity
Prague 1986
6000
4000
2000
0
Bq/s
30.4.
4.5.
8.5.
12.5.
16.5.
20.5.
Date

Raining during the 1st radioactivity wave



Radioactivity (Bq/m^2)

Raining

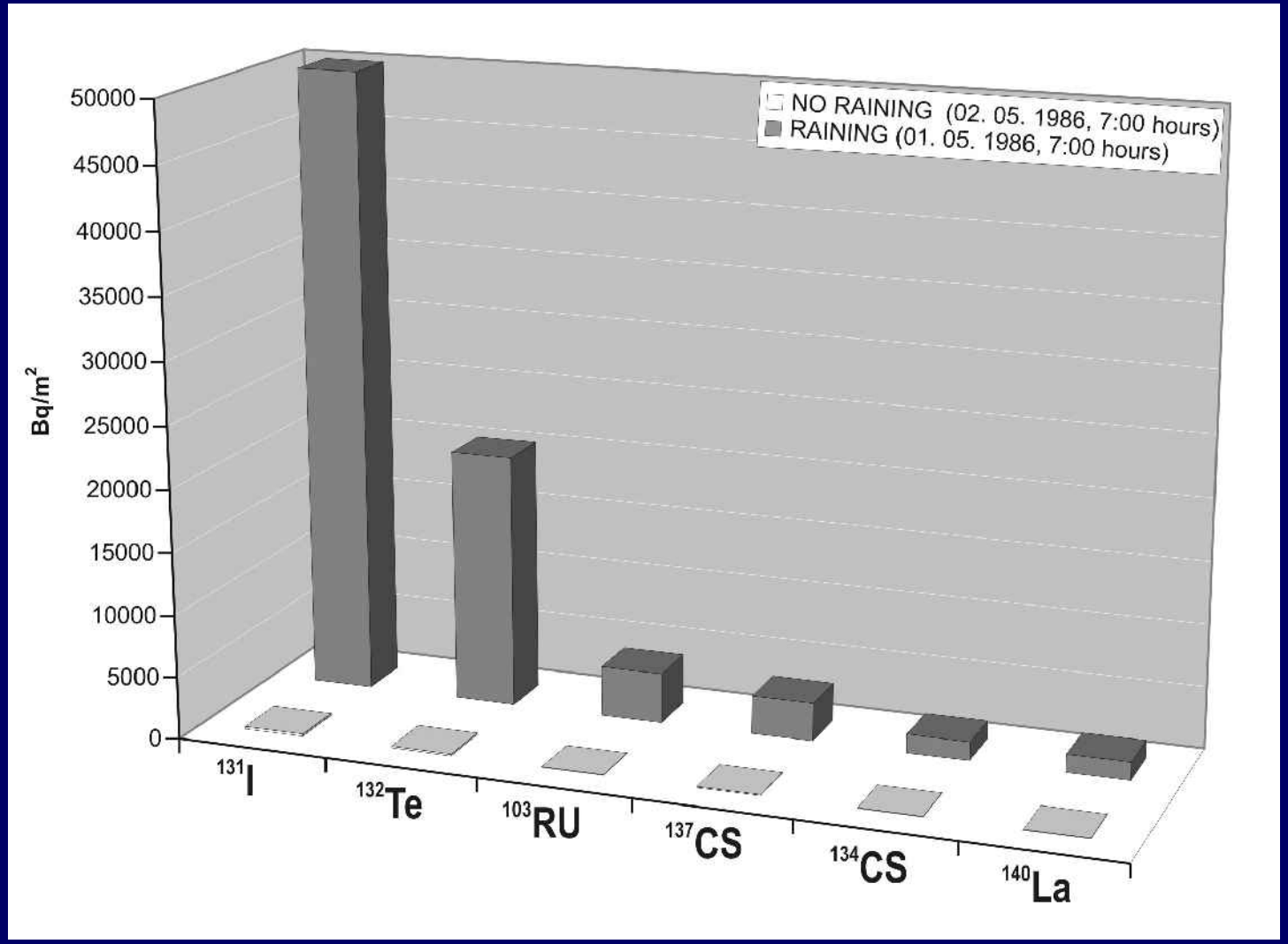
1.5.1986, 7:00 hours

- ^{103}RU 4 000,0
- ^{131}I 50 000,0
- ^{132}Te 20 300,0
- ^{137}Cs 3 100,0
- ^{134}Cs 1 500,0
- ^{140}La 1 470,0
- Total **80 370,0**

No raining

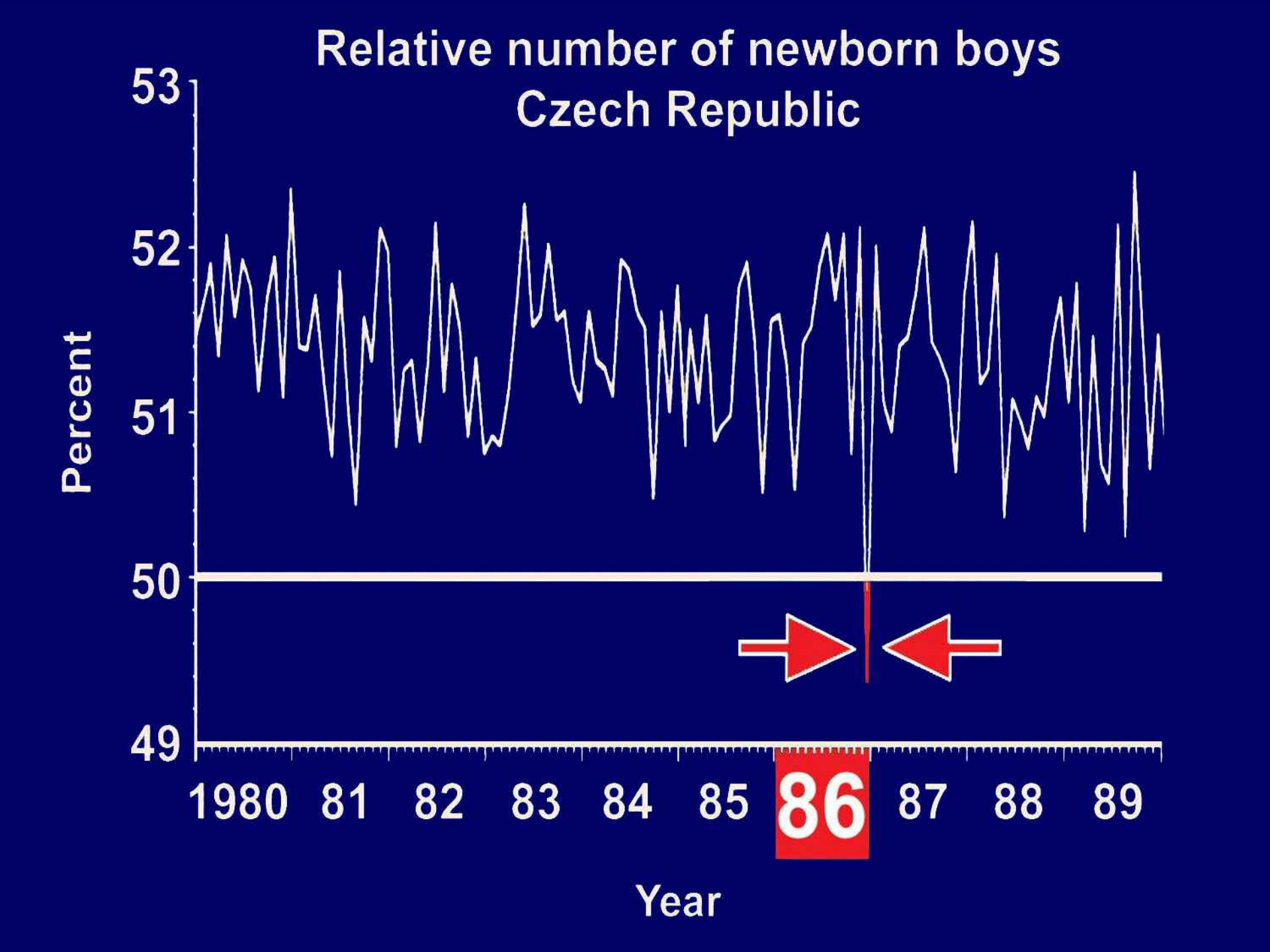
2.5.1986, 7:00 hours

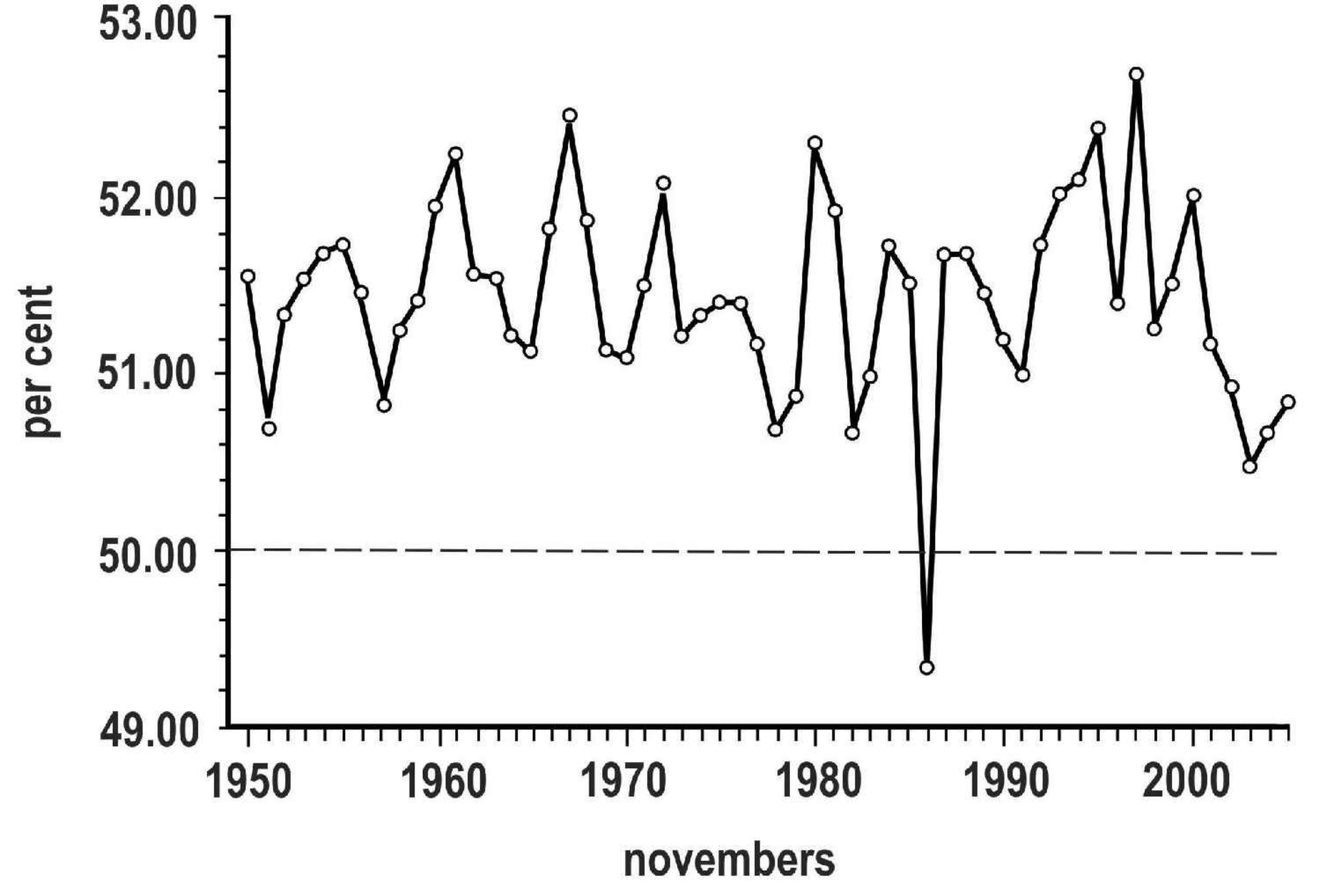
- ^{103}RU 40,0
- ^{131}I 196,0
- ^{132}Te 130,0
- ^{137}Cs 86,0
- ^{134}Cs 46,0
- ^{140}La 41,0
- Total **539,0**


NO RAINING (02. 05. 1986, 7:00 hours)
RAINING (01. 05. 1986, 7:00 hours)
Bq/m²
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
131I
132Te
103RU
137CS
134CS
140La

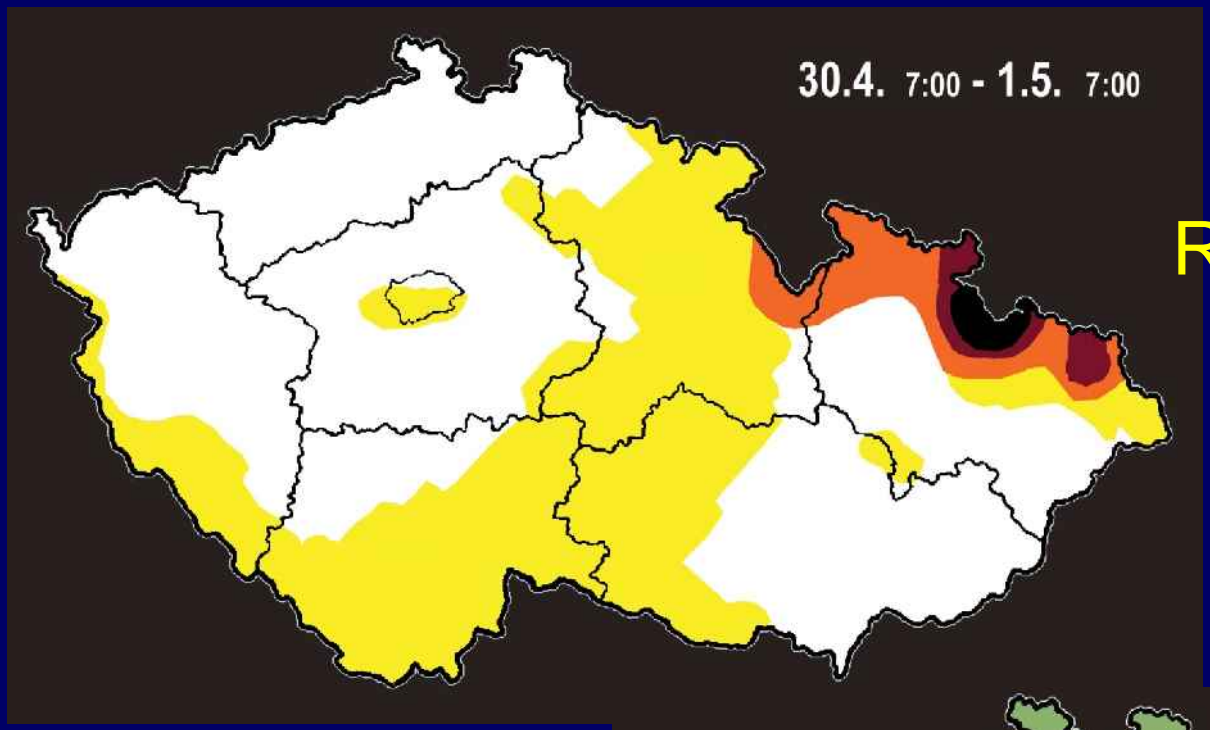
Radioactive half-time of radionuclides

- ^{140}La - 1.7 days
- ^{132}Te - 3.3 days
- ^{131}I - 8 days
- ^{103}Ru - 1 year
- ^{134}Cs - 2 years
- ^{137}Cs - 30 years
- ^{90}Sr - 30 years

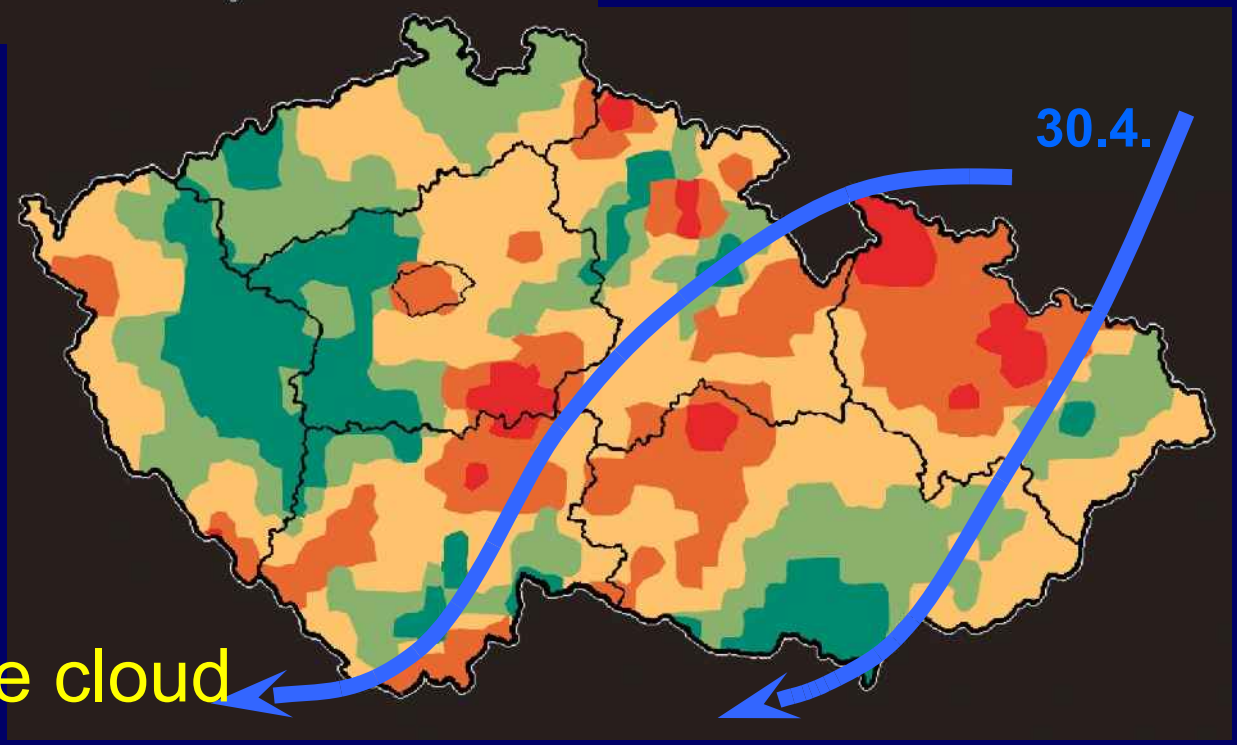

Relative number of newborn boys
Czech Republic
53
52
51
50
49
Percent
1980
81
82
83
84
85
86
87
88
89
Year


53.00
52.00
51.00
50.00
49.00
per cent
1950
1960
1970
1980
1990
2000
novembers

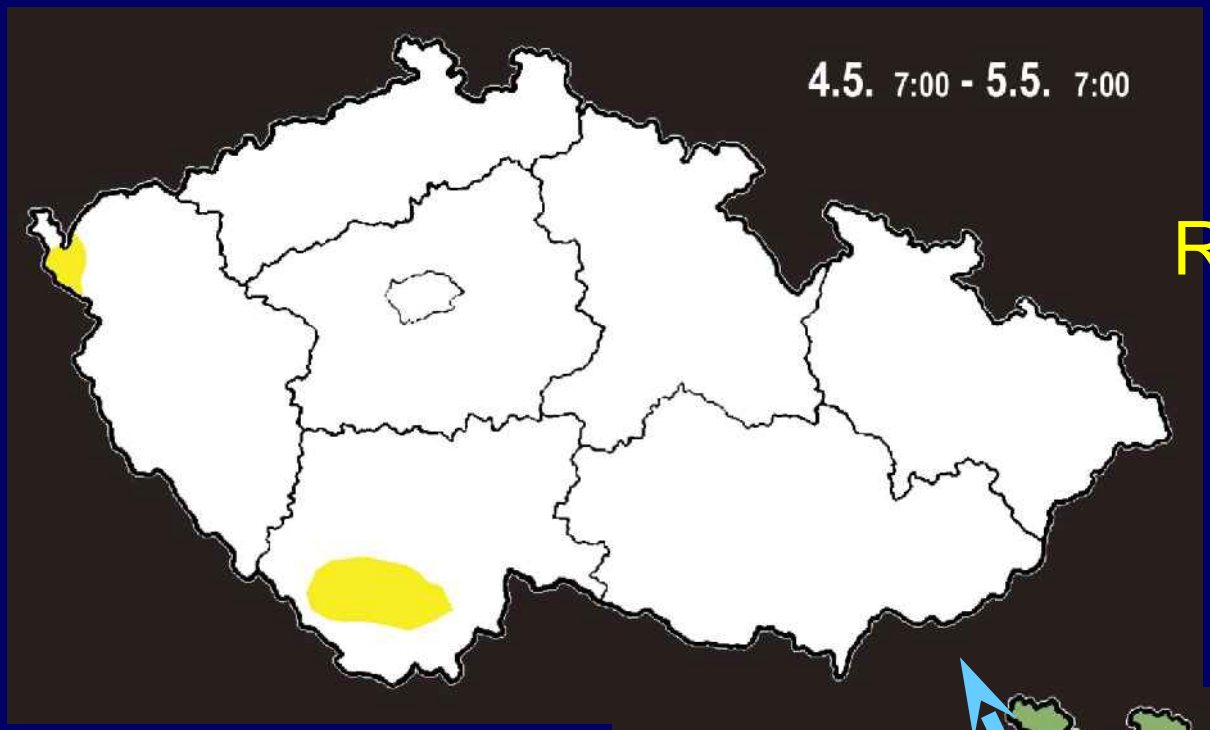
Number of non newborn boys in November 1986 corelate with meteorological situation (wind and rain)



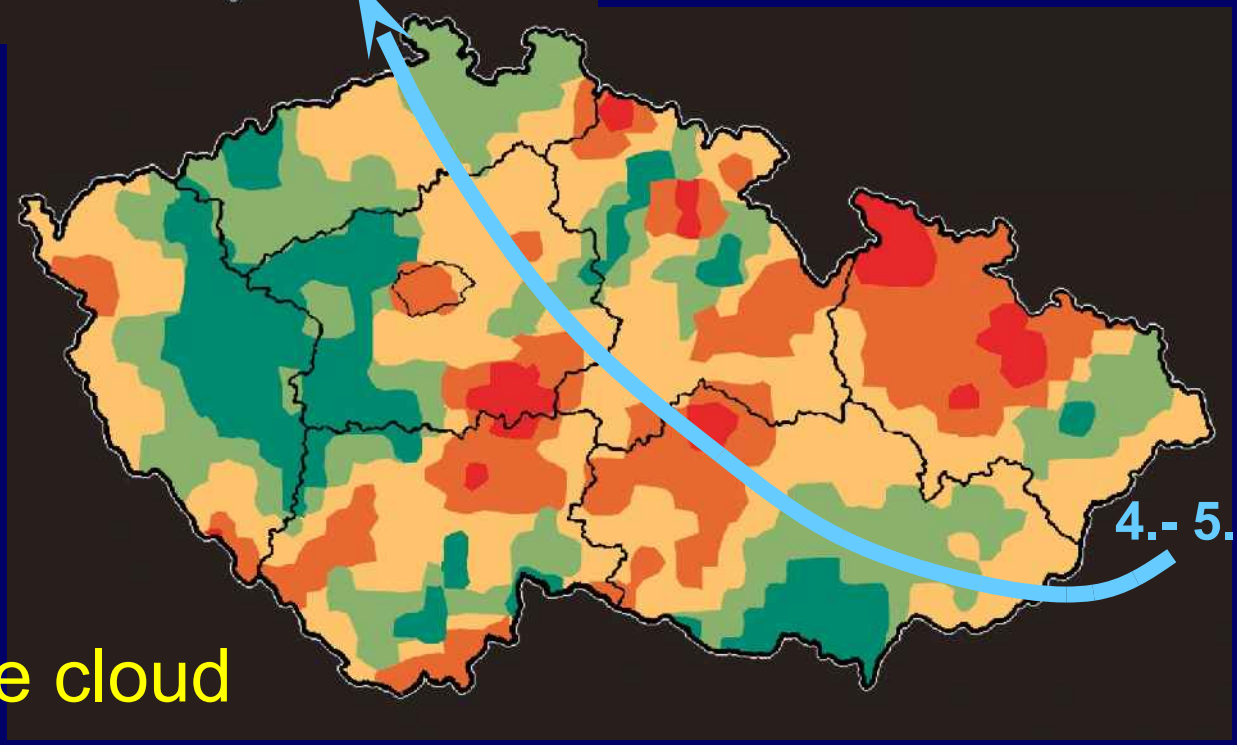
Raining



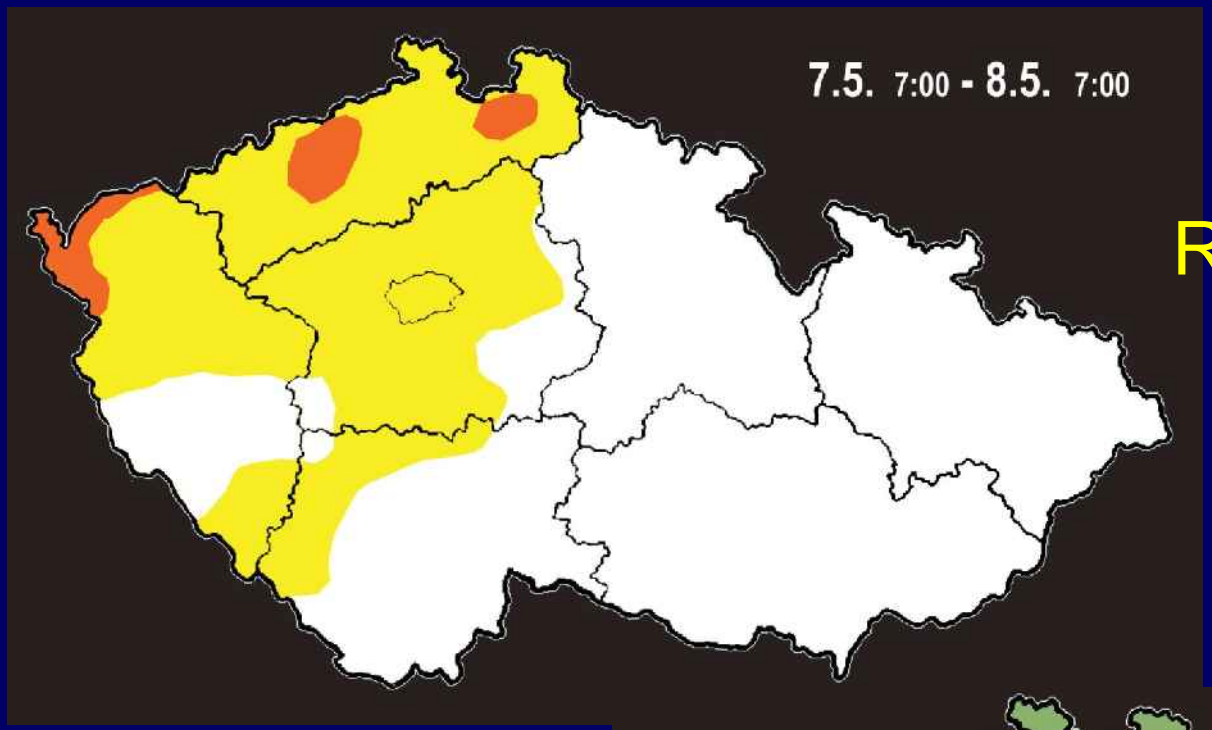
Wind + radioactive cloud



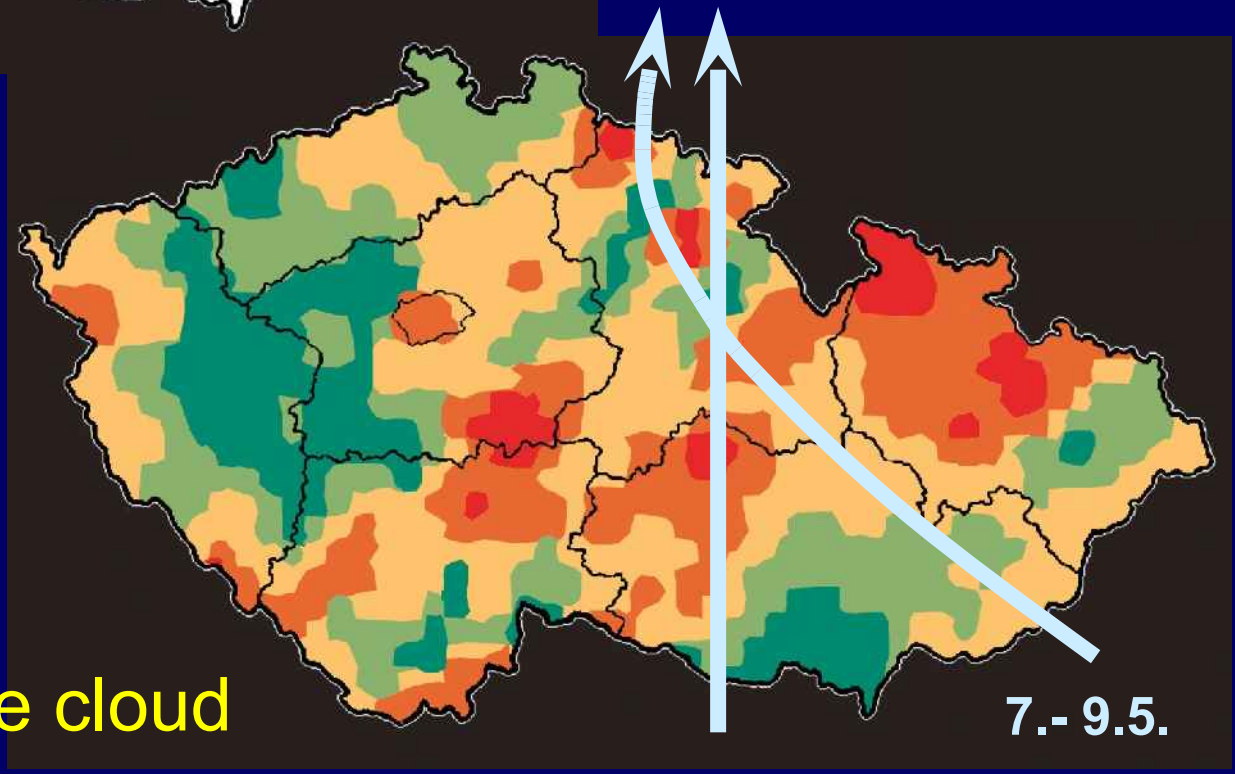
Raining



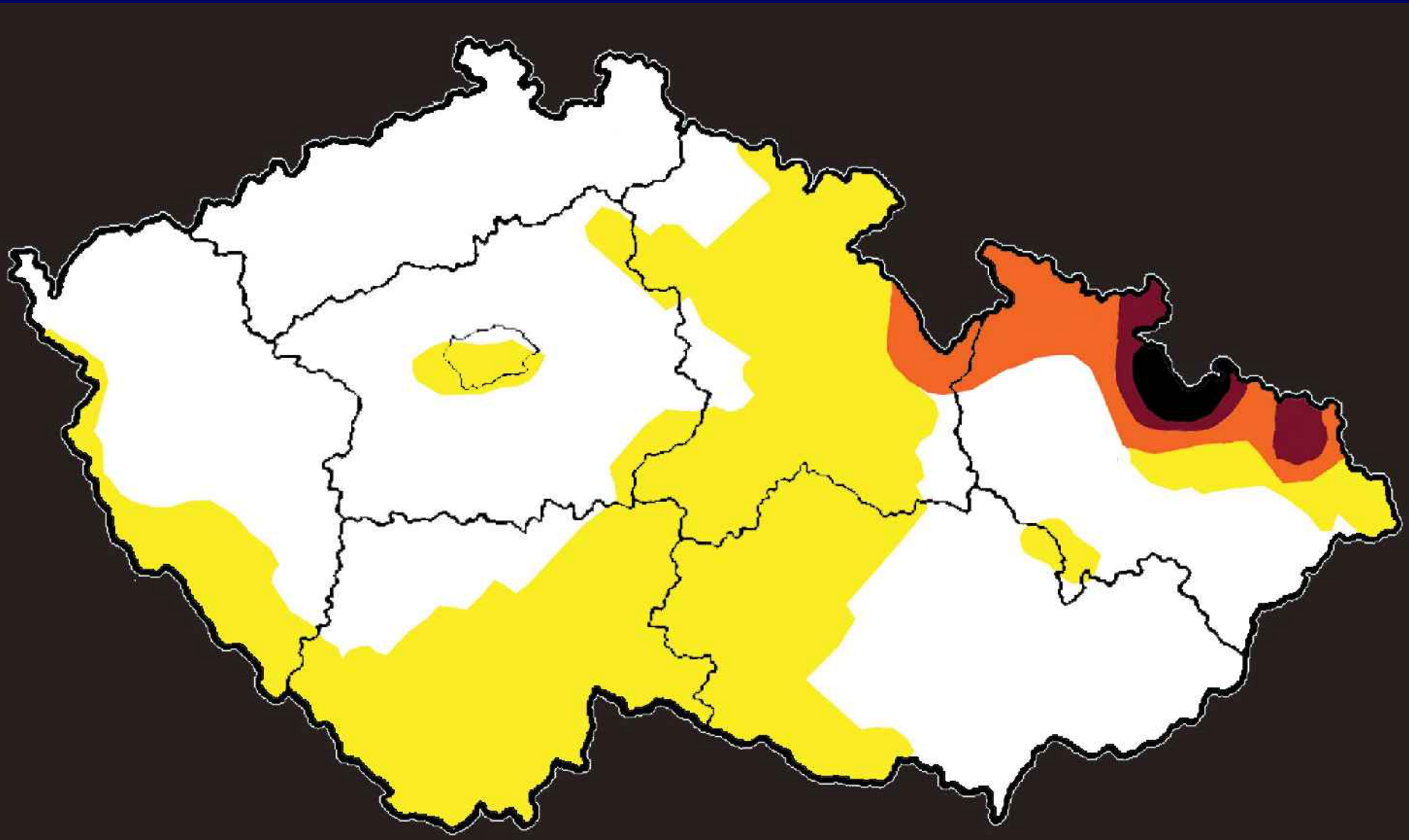
Wind + radioactive cloud

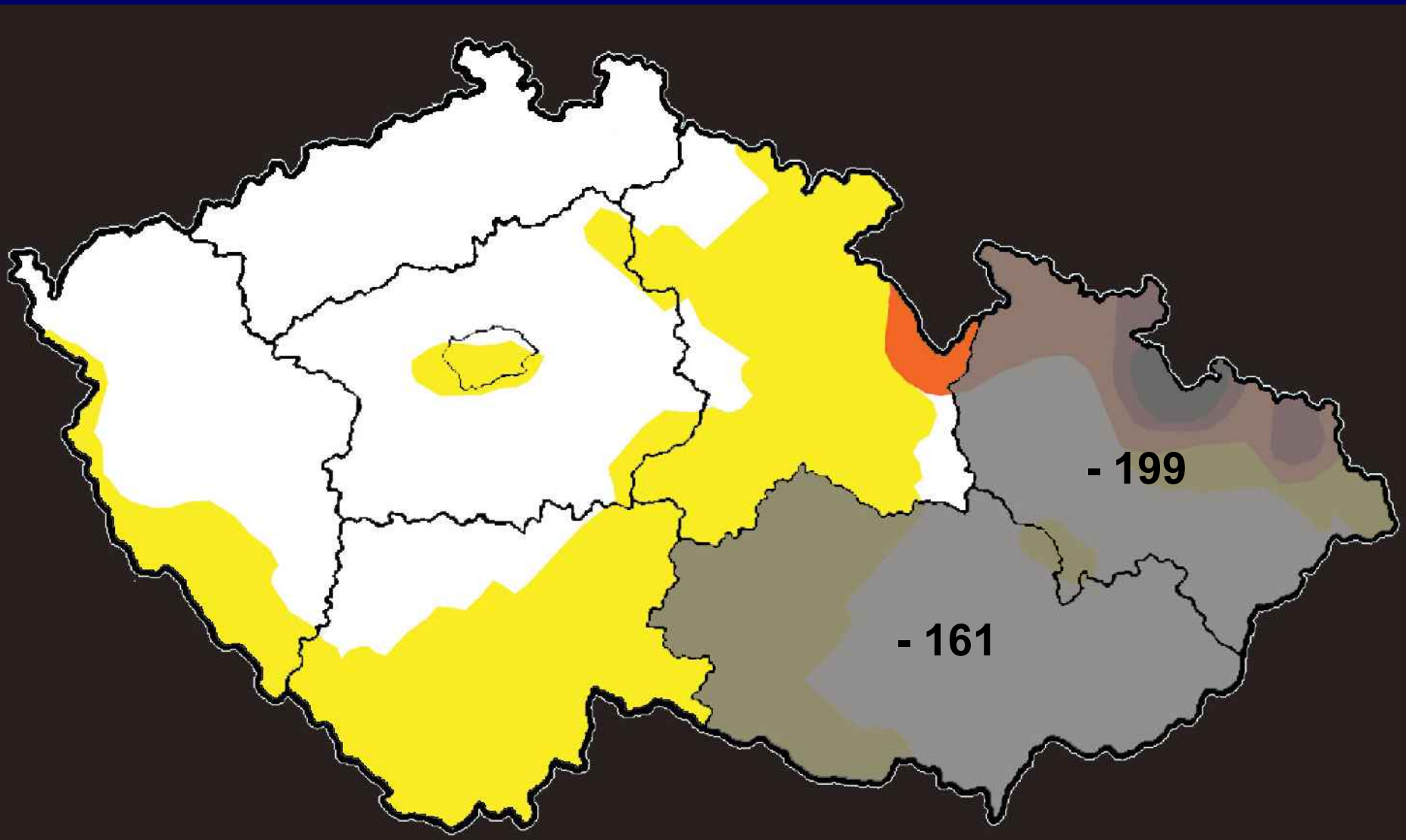


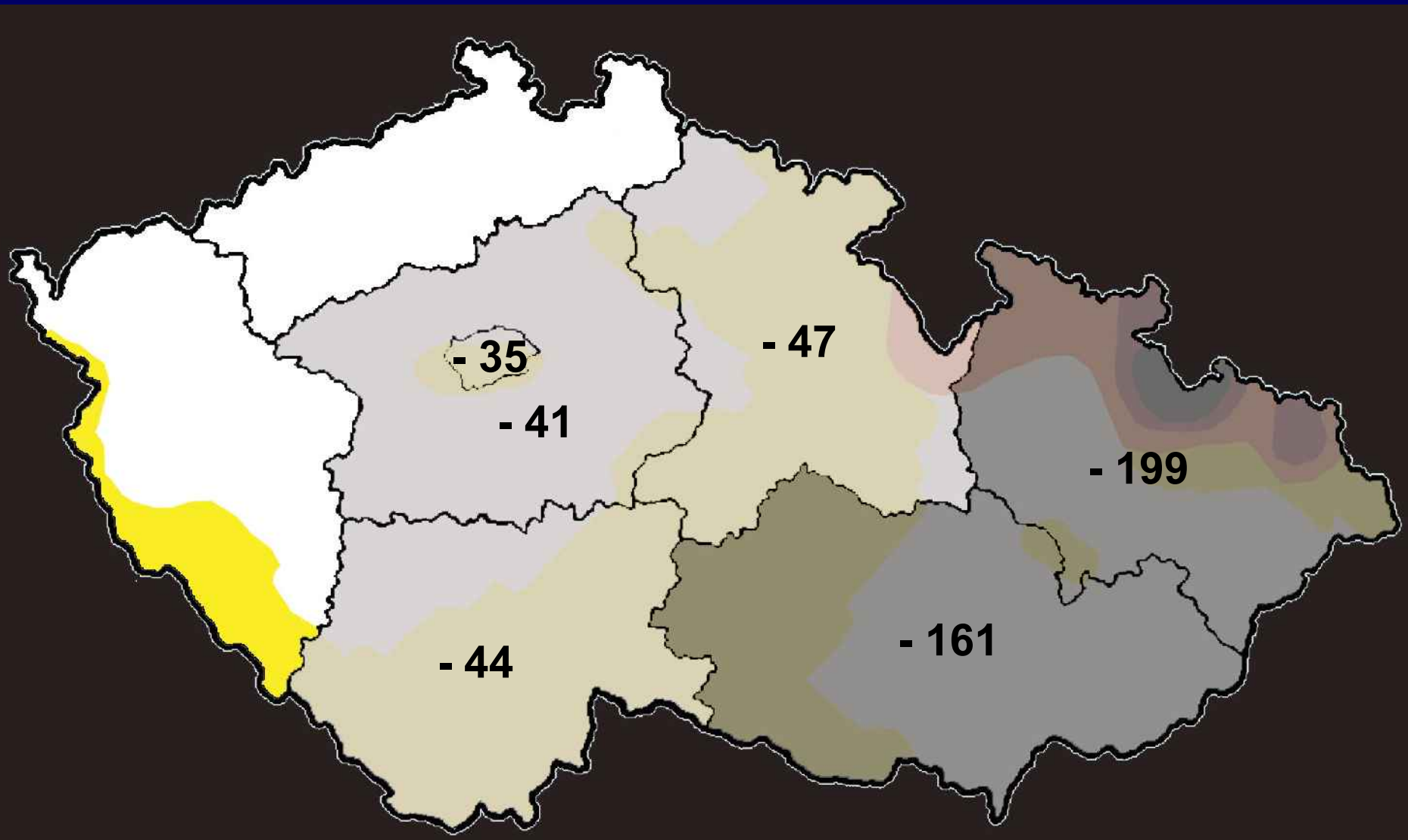
Raining

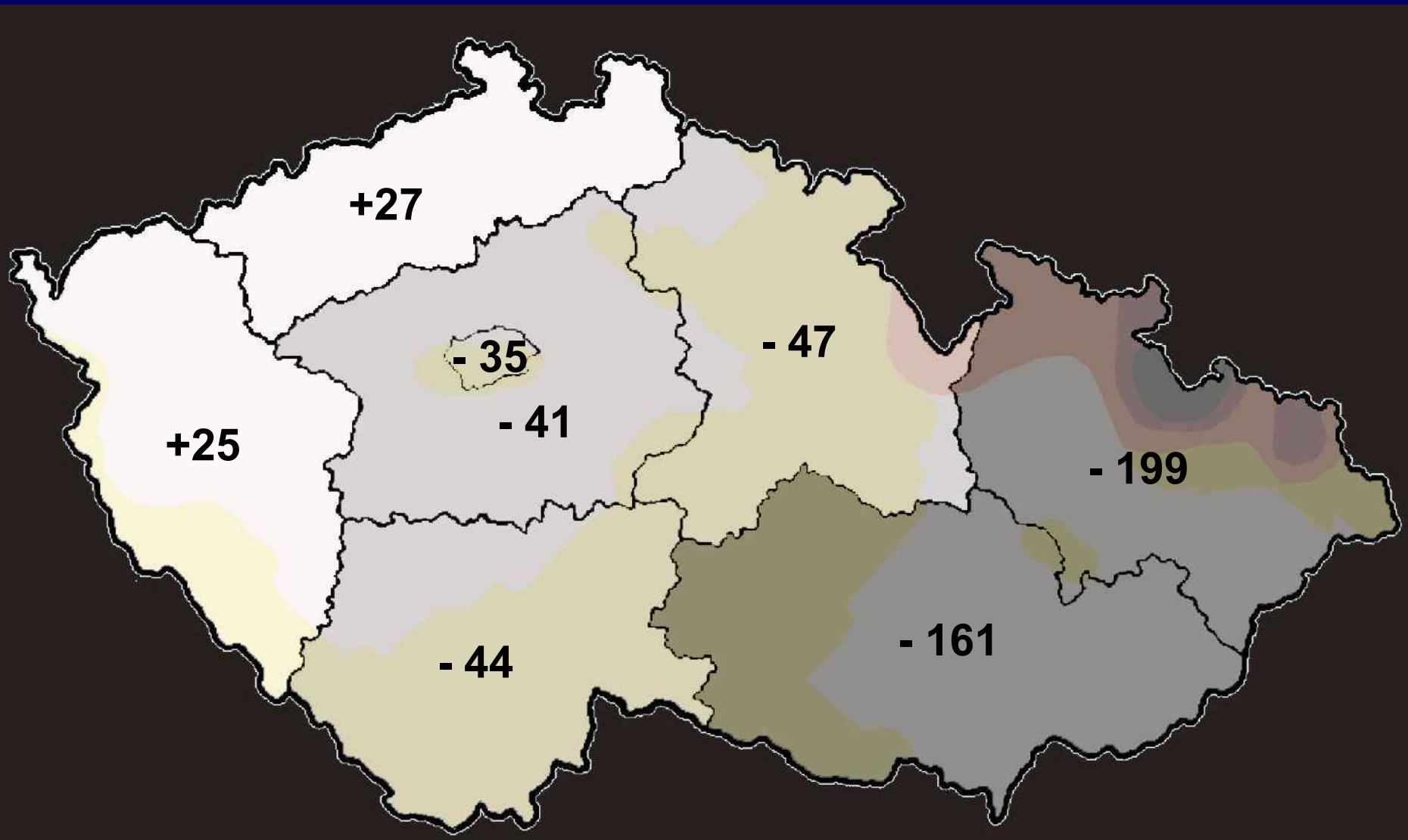


Wind + radioactive cloud

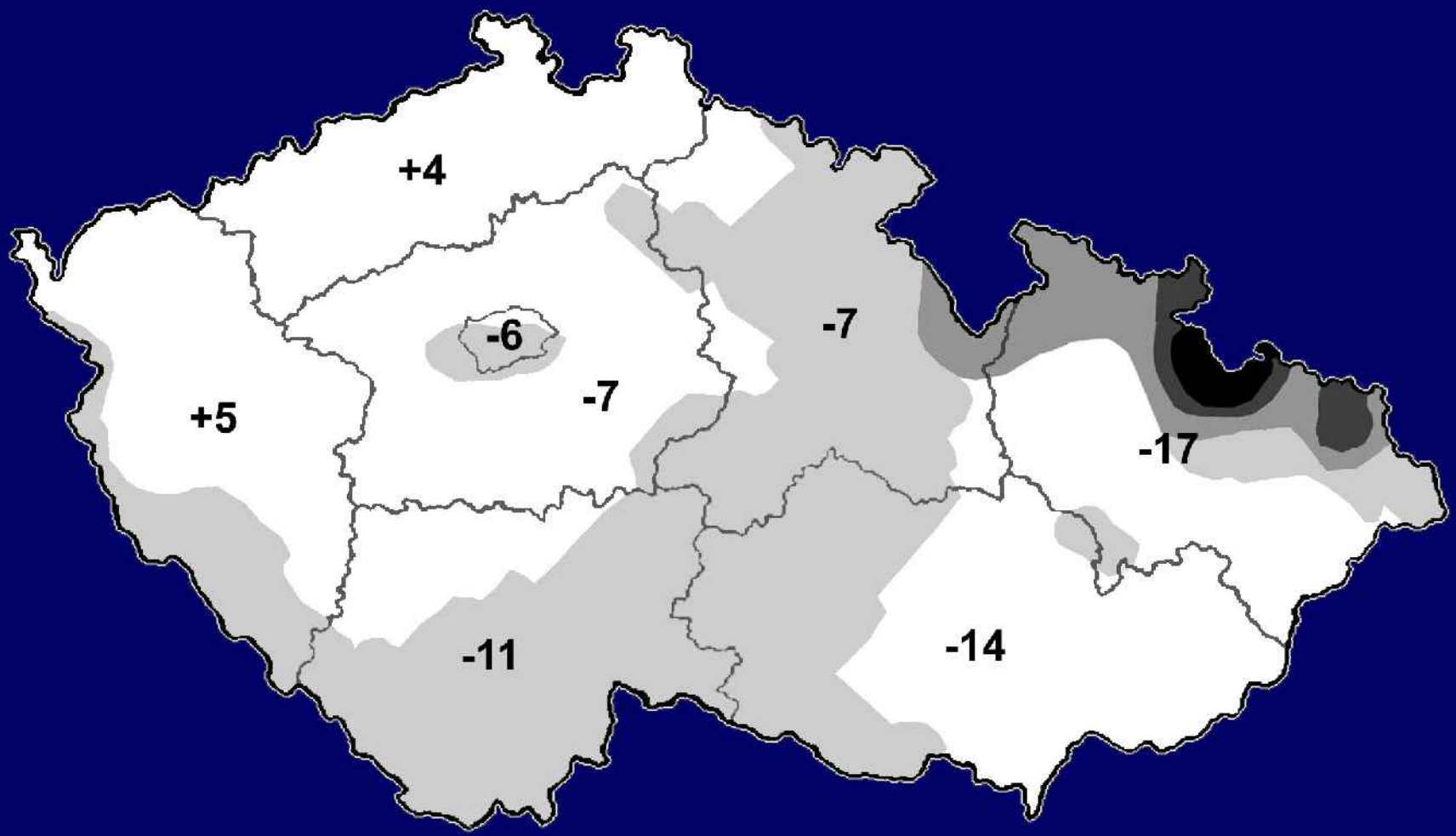


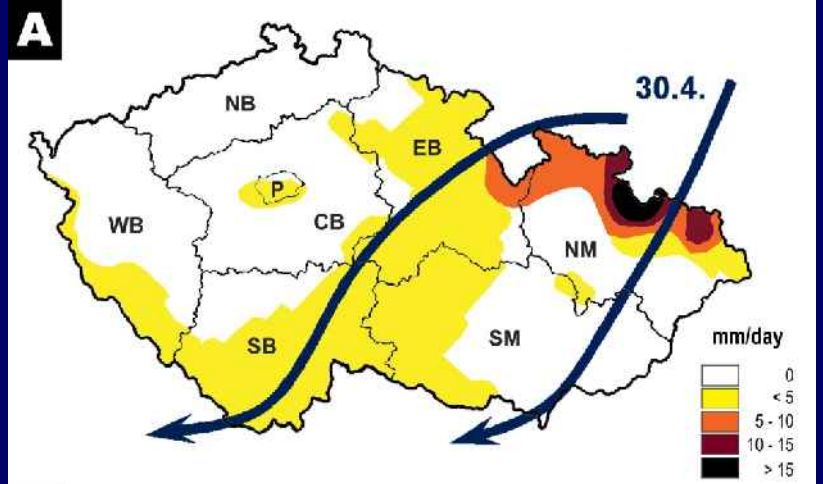

- 199
- 161

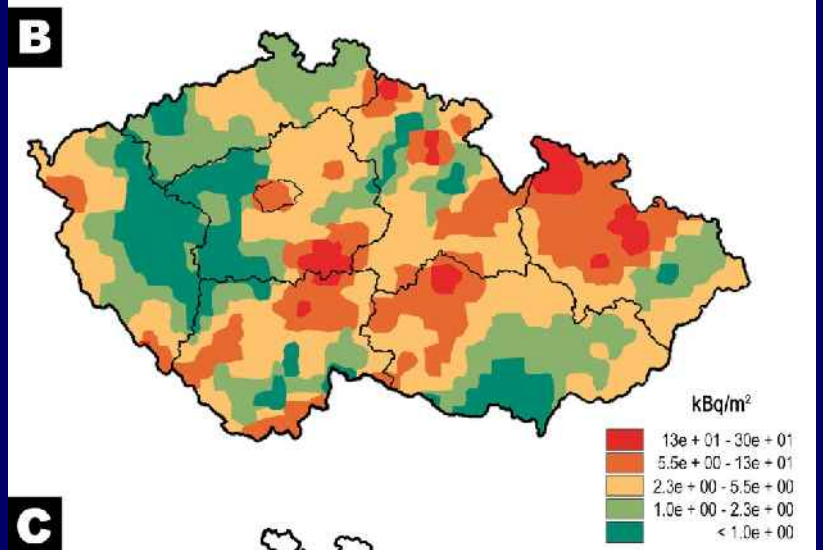

- 35
- 41
- 47
- 199
- 44
- 161

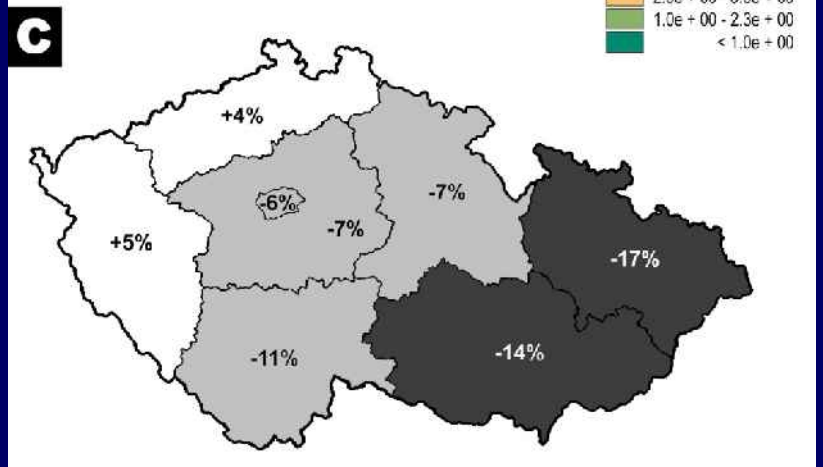

+27
+25
- 35
- 41
- 47
- 199
- 44
- 161

Percent of non newborn boys – November 1986



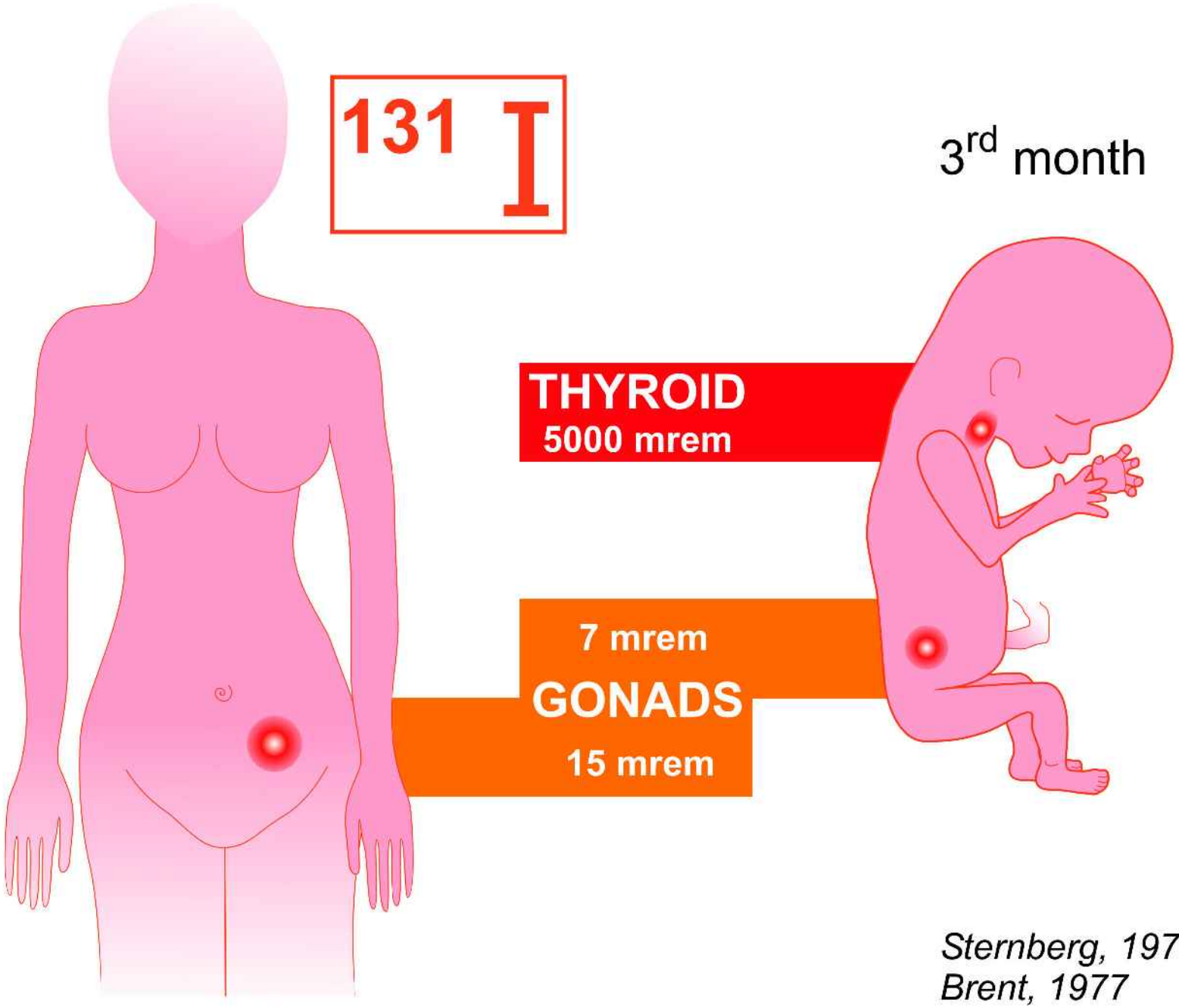

A
30.4.
NB
EB
P
WB
CB
NM
SB
SM
mm/day
0
< 5
5 - 10
10 - 15
> 15


B
kBq/m²
13e + 01 - 30e + 01
5.5e + 00 - 13e + 01
2.3e + 00 - 5.5e + 00
1.0e + 00 - 2.3e + 00
< 1.0e + 00

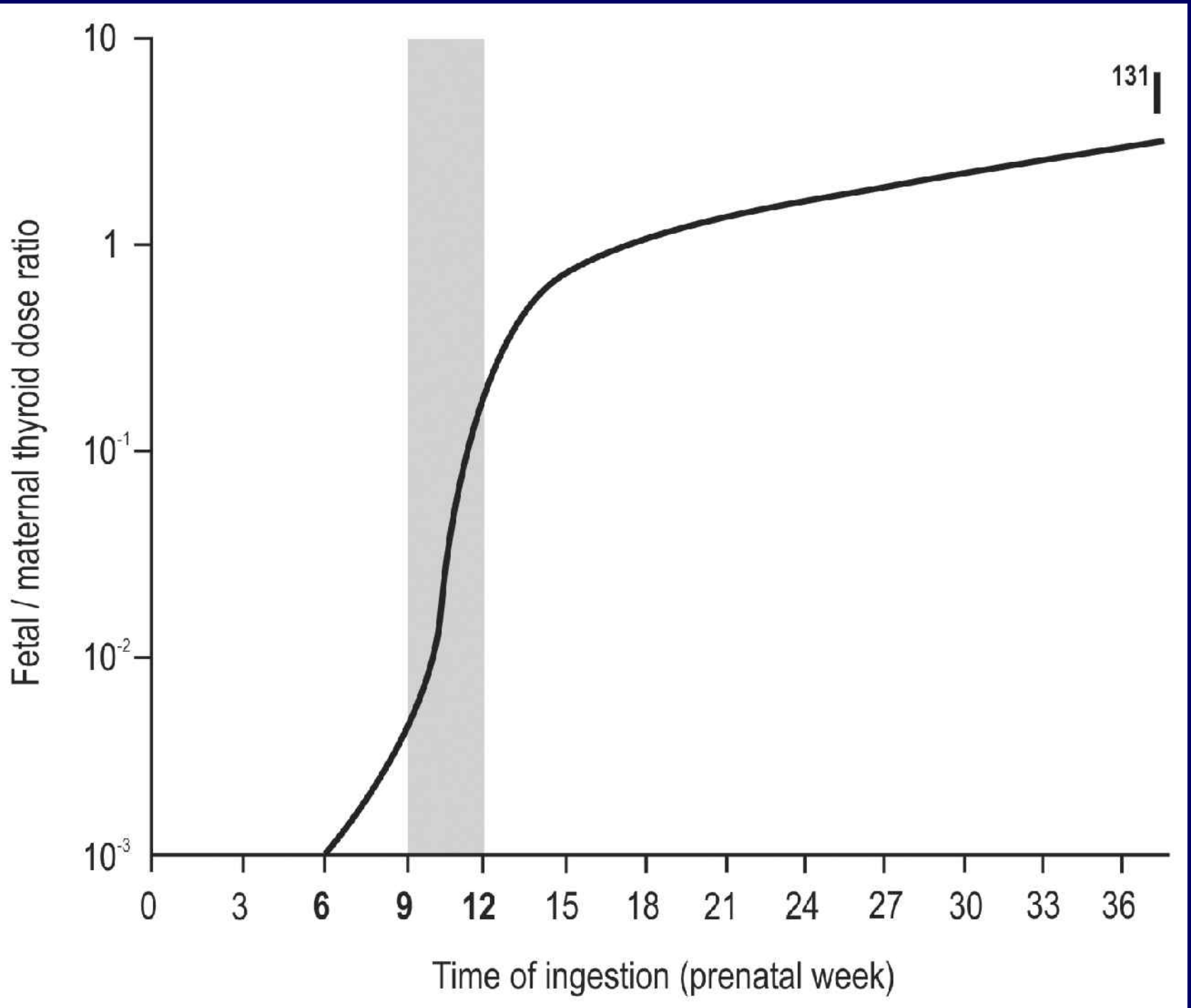

C
+4%
-6%
-7%
+5%
-7%
-17%
-11%
-14%

Probable mechanisms of radiation effect on fetuses

- Environmental radiation can cause thyroid disease (Eheman et al., 2003).
- Thyroid disease in pregnant woman can lead to abortion or neonatal death. ^{131}I is absolutely contra-indicated during pregnancy (Bishnoi and Sachmechi, 1996; Ogris, 1997).
- ^{131}I induces hypothyreosis in mothers and increases the risk of premature delivery or spontaneous abortion (Tatham et al., 2002).
- Brain development is sensitive to increased radiation during the 3rd prenatal month (Yamazaki et al., 1990).



Sternberg, 1970
Brent, 1977


10
1
10^{-1}
10^{-2}
10^{-3}
Fetal / maternal thyroid dose ratio
131
0
3
6
9
12
15
18
21
24
27
30
33
36
Time of ingestion (prenatal week)

Selective accumulation of radioiodine in the thyroid gland was the most probable cause of the death of the male fetuses