Normal tissue tolerance to re-irradiation – from preclinical experiments to clinical applicability

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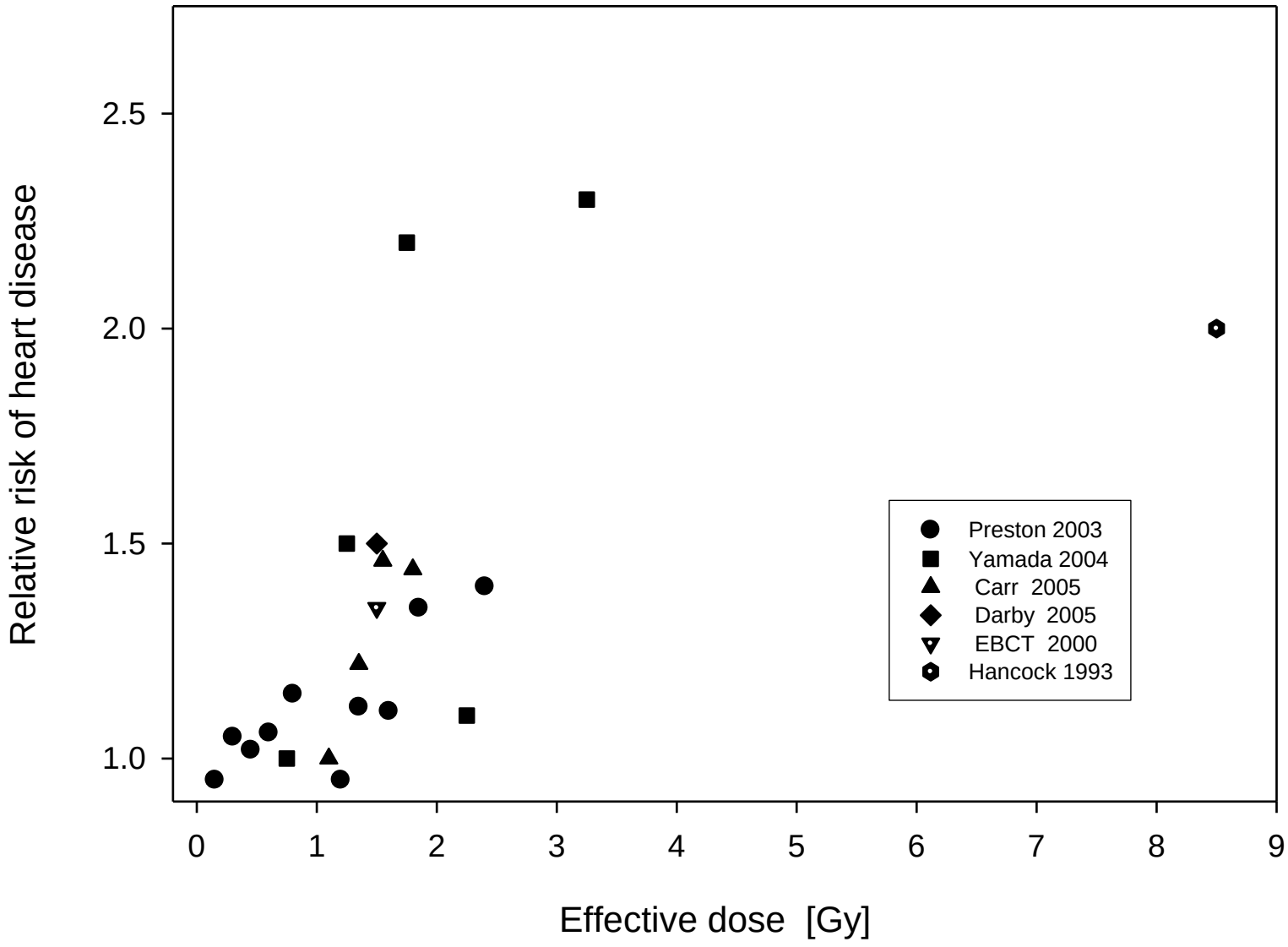
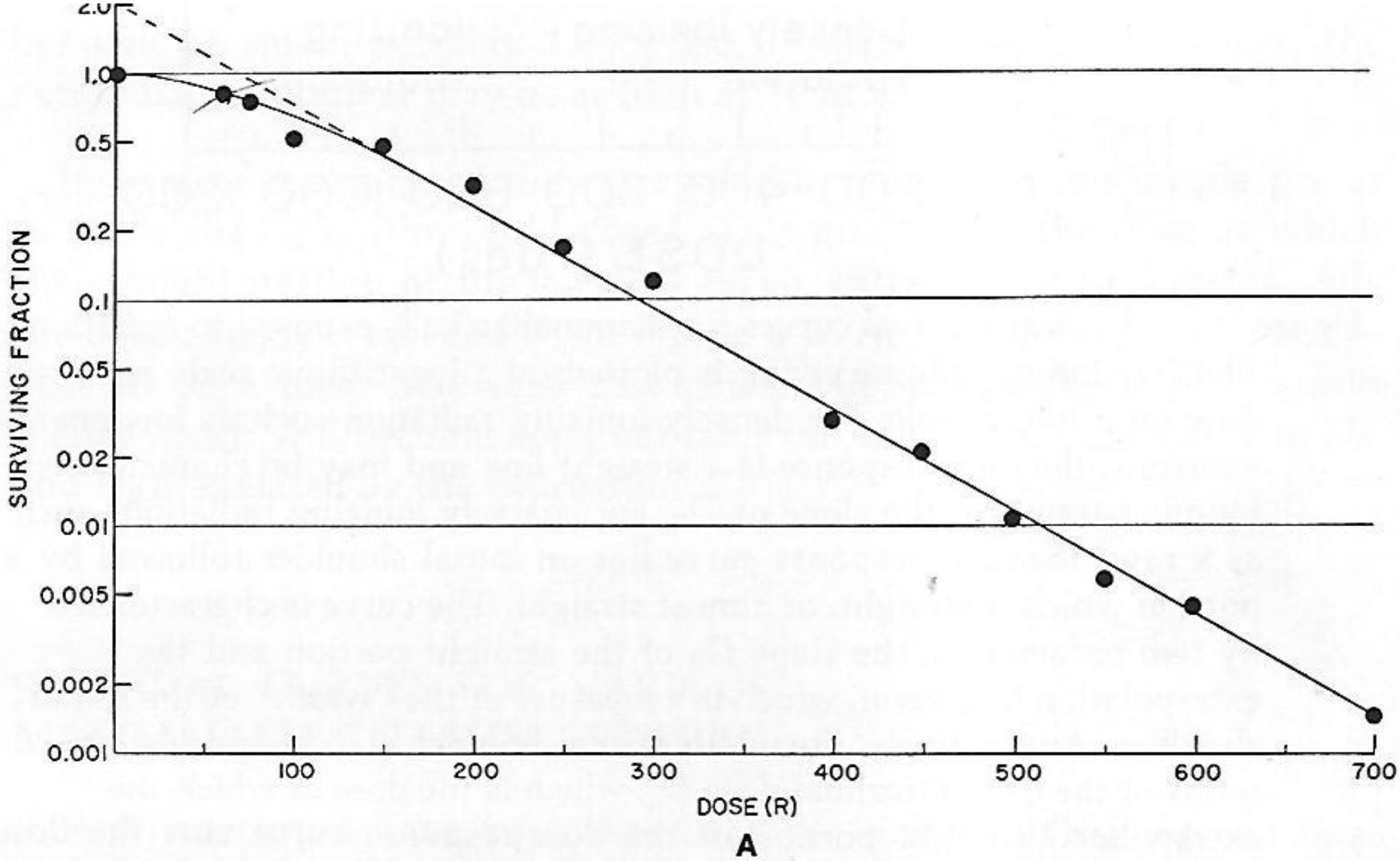
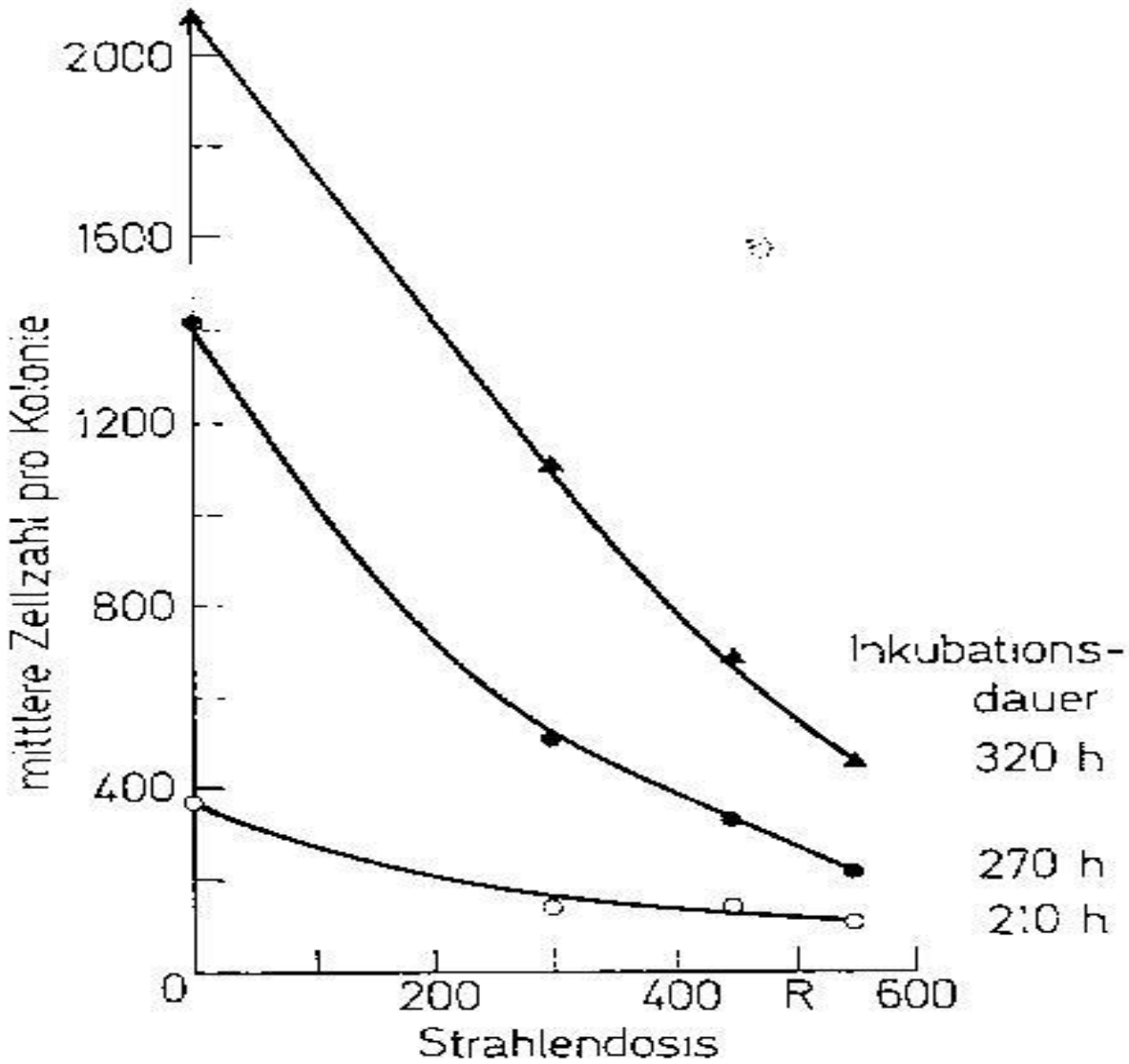
Normal tissue tolerance to re-irradiation – from preclinical experiments to clinical applicability

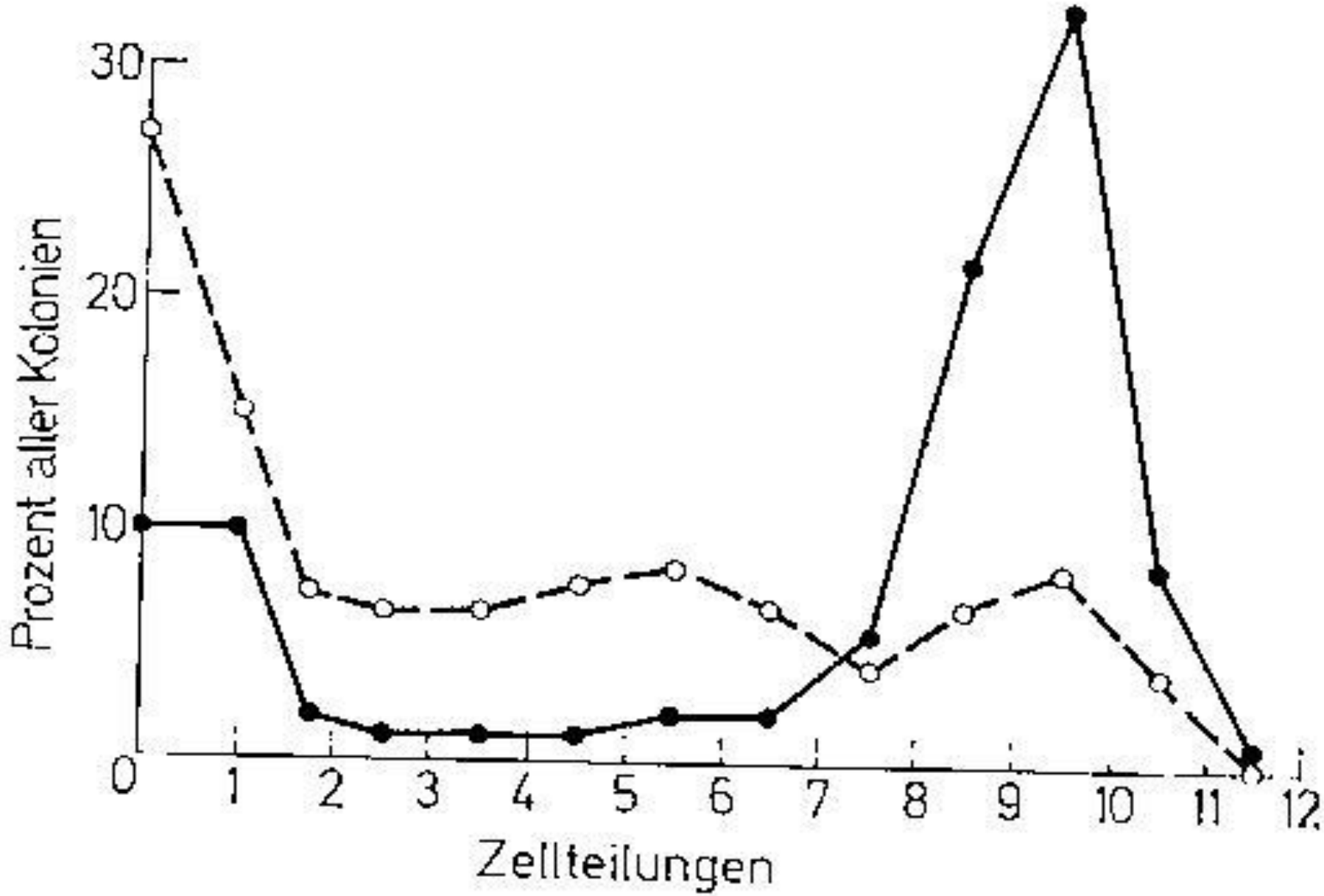
- How long does a cell and its clonal progeny remember the original radiation effects?
- How long can it take until the clinical radiation effects become manifest?
- How does the remembered first radiation effect modulate the effectiveness of a second, independent radiation impact?
- How does this memory work?
- How is this information passed on through generations of cells or stored in non-proliferating stable cells?


Relative risk of heart disease
2.5
2.0
1.5
1.0
0
1
2
3
4
5
6
7
8
9
Effective dose [Gy]
Preston 2003
Yamada 2004
Carr 2005
Darby 2005
EBCT 2000
Hancock 1993


SURVIVING FRACTION
2.0
1.0
0.5
0.2
0.1
0.05
0.02
0.01
0.005
0.002
0.001
100
200
300
400
500
600
700
DOSE (R)

A


2000
1600
1200
800
400
0
mittlere Zellzahl pro Kolonie
200
400
R
600
Strahlendosis
Inkubations-
dauer
320 h
270 h
210 h


30
20
10
0
Prozent aller Kolonien
1
2
3
4
5
6
7
8
9
10
11
12
i
Zellteilungen

Response to X-irradiation of a Tumour Recurrence after a TCD-95 Radiation dose

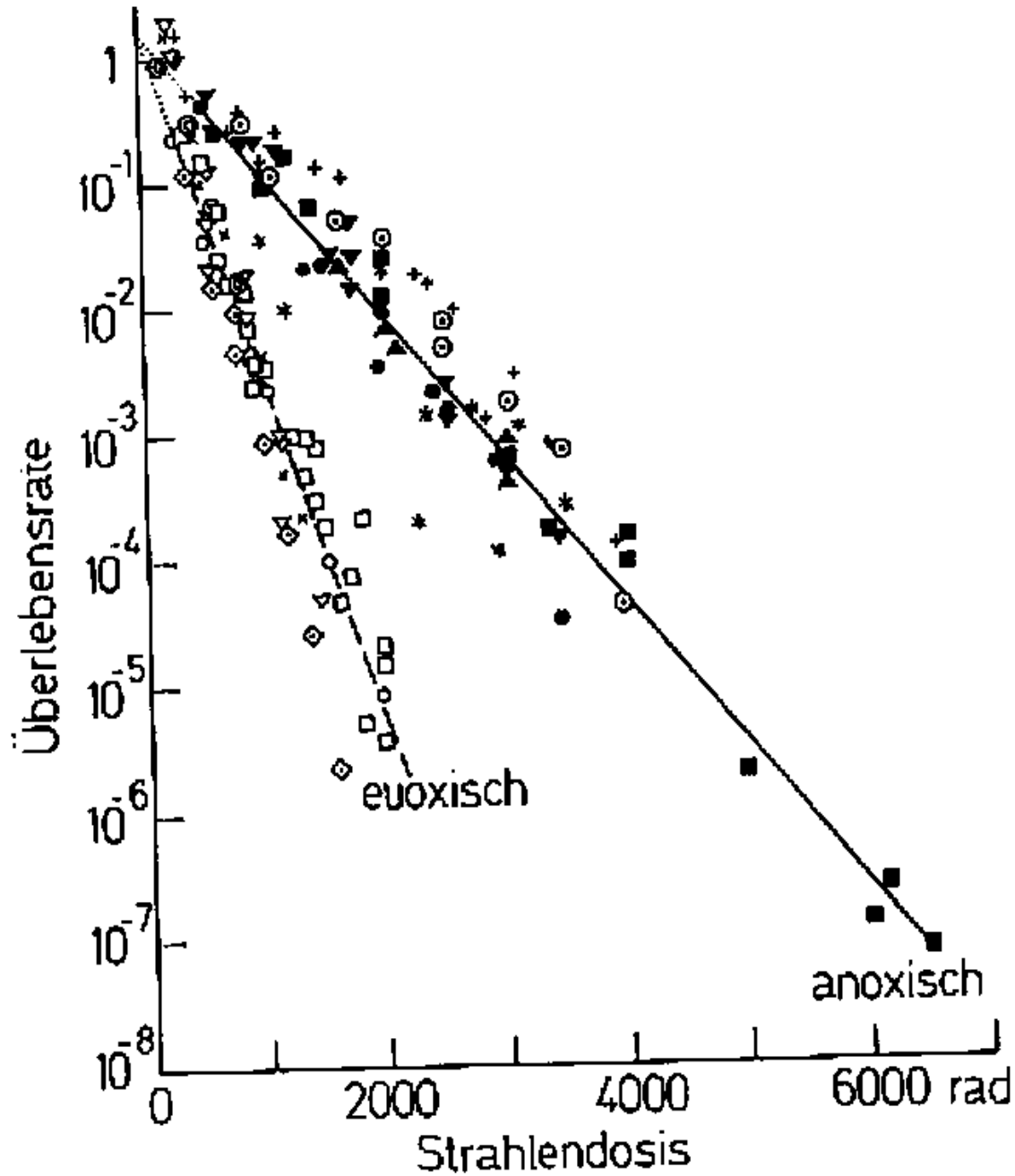
H.D.Suit, M.D.Anderson Hospital

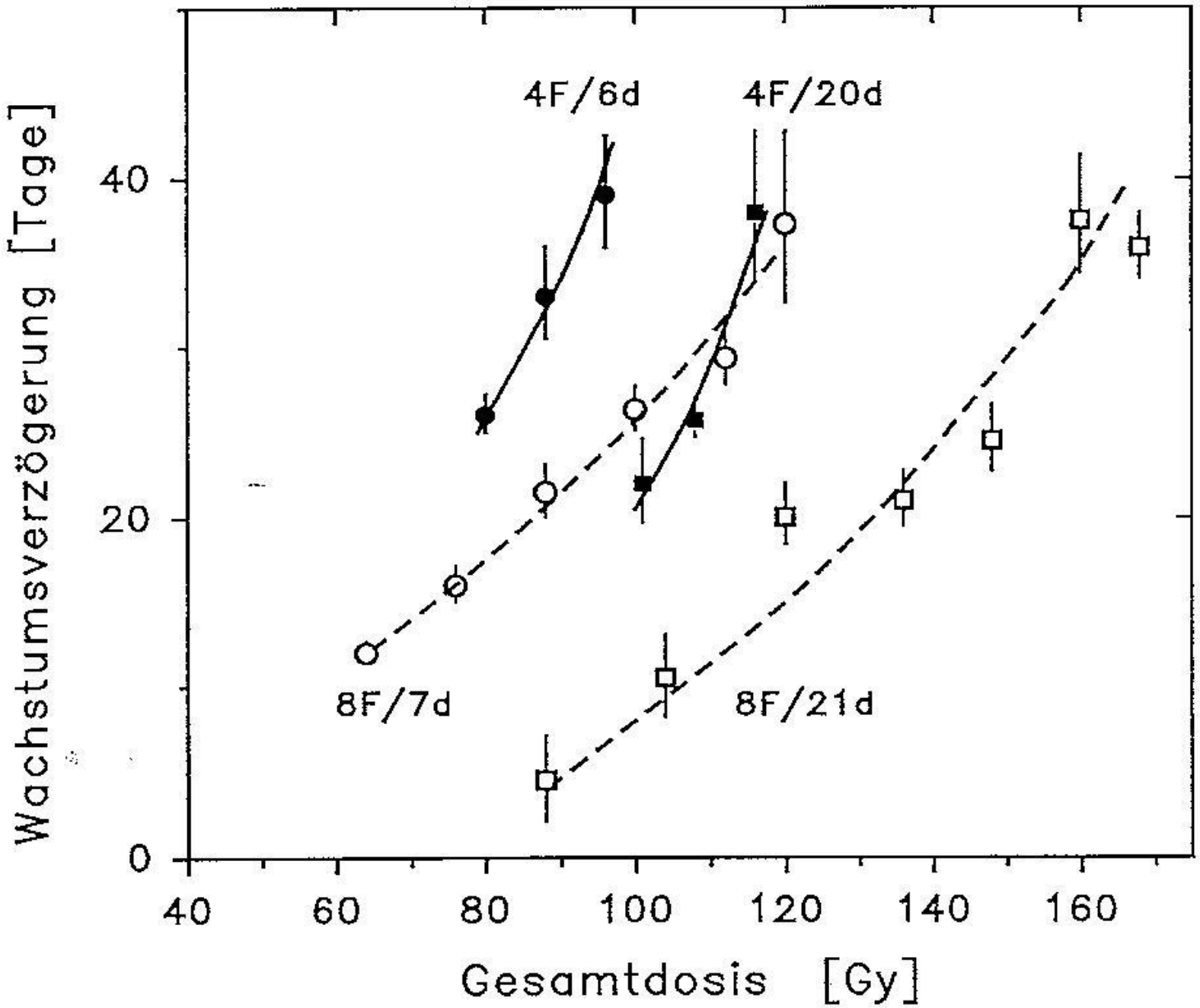
Nature **211** 996-997 (1966)

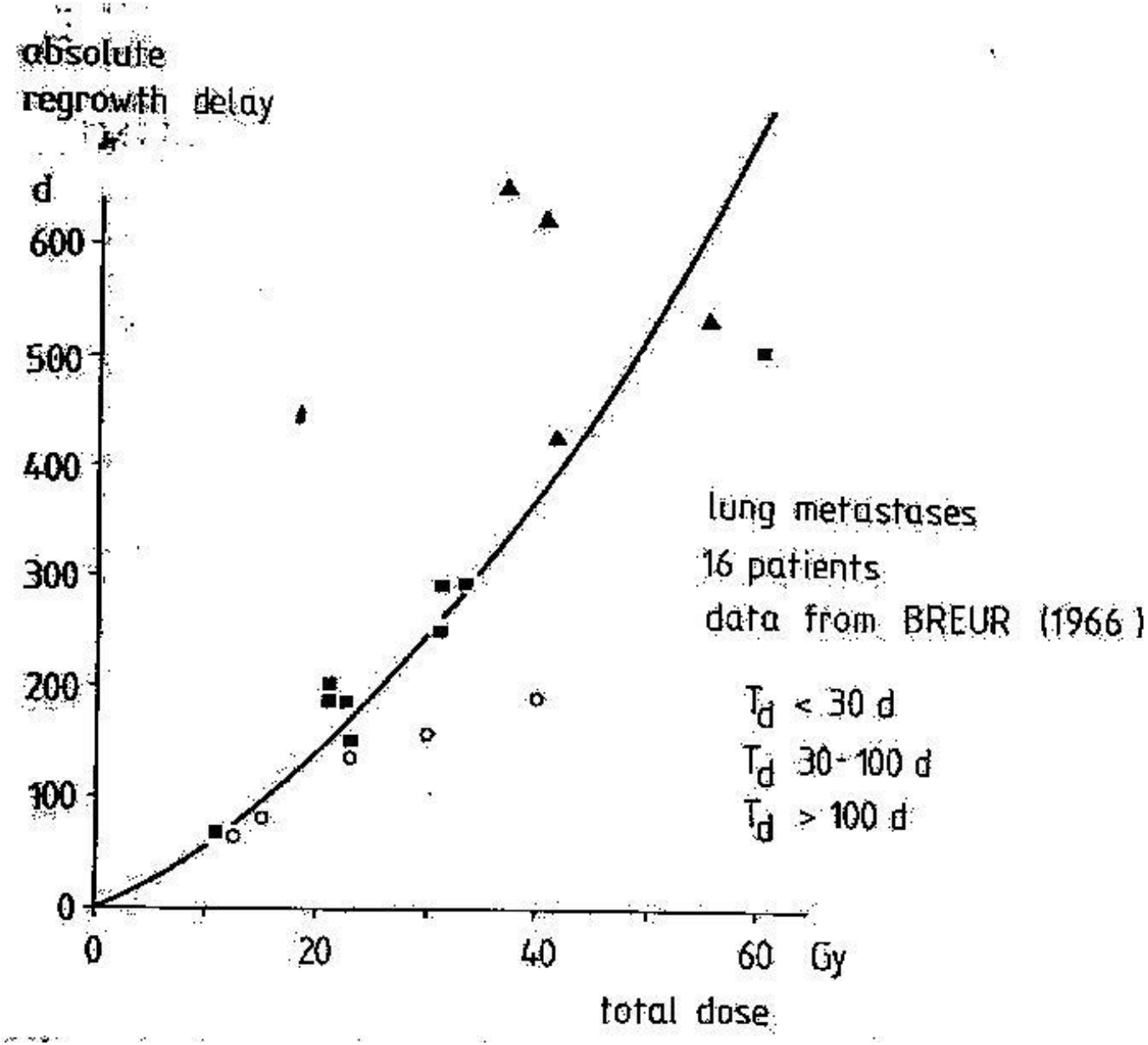
- A recurrence was noted in one of eight animals at 240 days following 66 Gy.
- The recurrent tumour had a volume doubling time of 17 days as compared to 3-4 days for the original unirradiated tumours.
- The recurrent tumour was transplanted into highly inbred mice. It grew slowly reaching a diameter of 15 mm by 6 months. From this tumour, isotransplants were created for determination of the local control dose

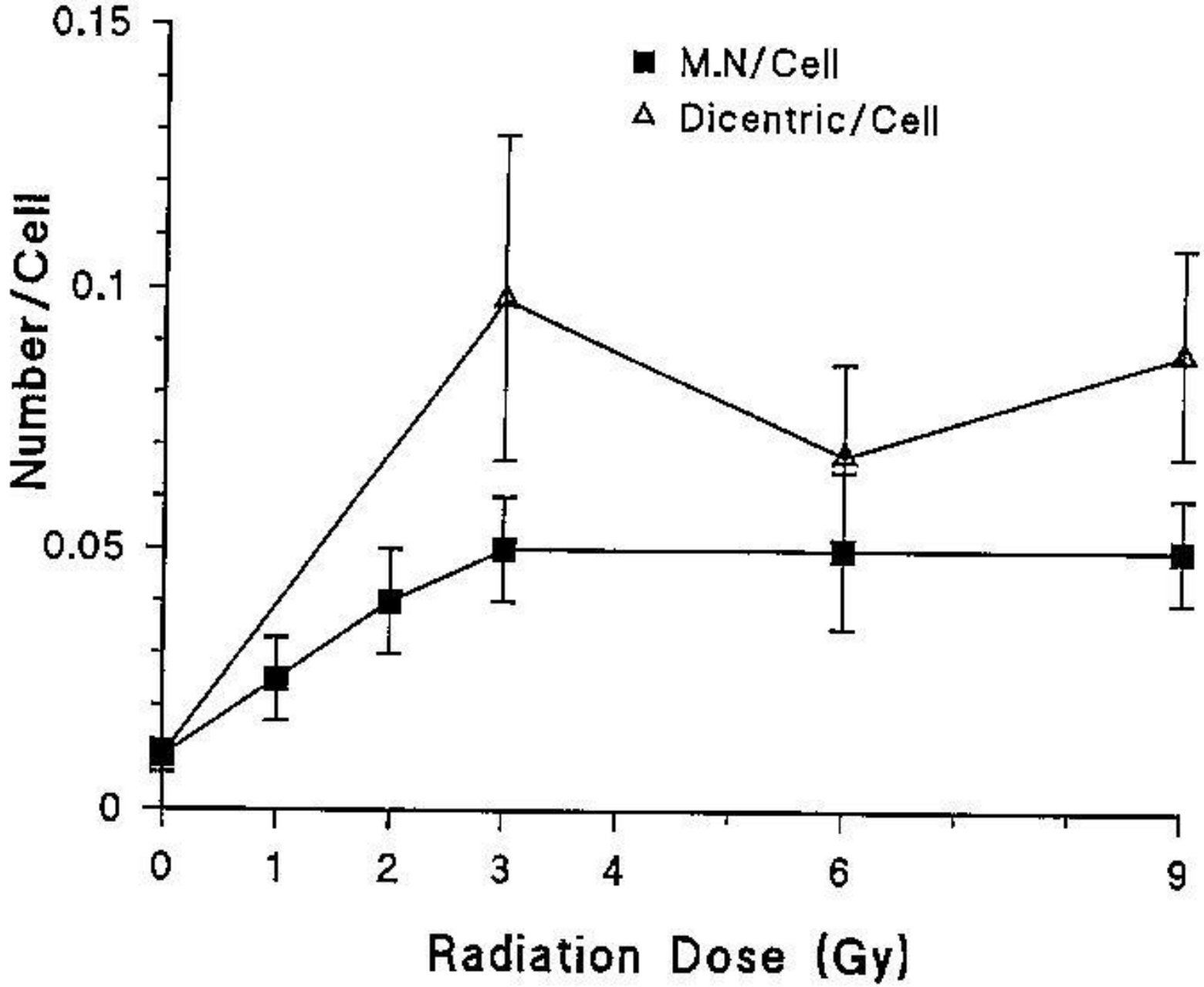
Results: TCD-50

original tumour	**late recurrent tumour**
59.9 Gy	**51.3 Gy**


Überlebensrate
1
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
10^{-8}
euoxisch
anoxisch
0
2000
4000
6000 rad
Strahlendosis


4F/6d
4F/20d
8F/7d
8F/21d
Wachstumsverzögerung [Tage]
0
20
40
40
60
80
100
120
140
160
Gesamtdosis [Gy]


absolute
regrowth delay
d
600
500
400
300
200
100
0
0
20
40
60
Gy
total dose
lung metastases
16 patients
data from BREUR (1966)
T_d < 30 d
T_d 30-100 d
T_d > 100 d


0.15
0.1
0.05
0
Number/Cell
M.N/Cell
Dicentric/Cell
0
1
2
3
4
6
9
Radiation Dose (Gy)

Normal tissue tolerance to re-irradiation – from preclinical experiments to clinical applicability

Pathological hallmarks of radiation-induced normal tissue damage

Hypoplasia, caused by impaired cell production, mostly, but not exclusively seen in „early normal tissue damage“

Atrophy, caused by impaired microvasculature and subsequent starvation of cells, often associated with hyperproliferation and inflammation, characteristic for „late normal tissue damage“

The fundamental question is:

- How does re-irradiation affect the progression of late normal tissue damage from the first radiation exposure
- How does progressive late normal tissue damage from the first radiation exposure affect the development of early normal tissue damage from re-irradiation exposure, e.g. by precipitating so-called consequential late normal tissue damage?

Clinical presentation of radiation-induced heart diseases

- **Pericarditis**
- **Myocardial infarction**
- **Ischaemic heart disease**
- **Valvular disease**
- **Conduction defects**

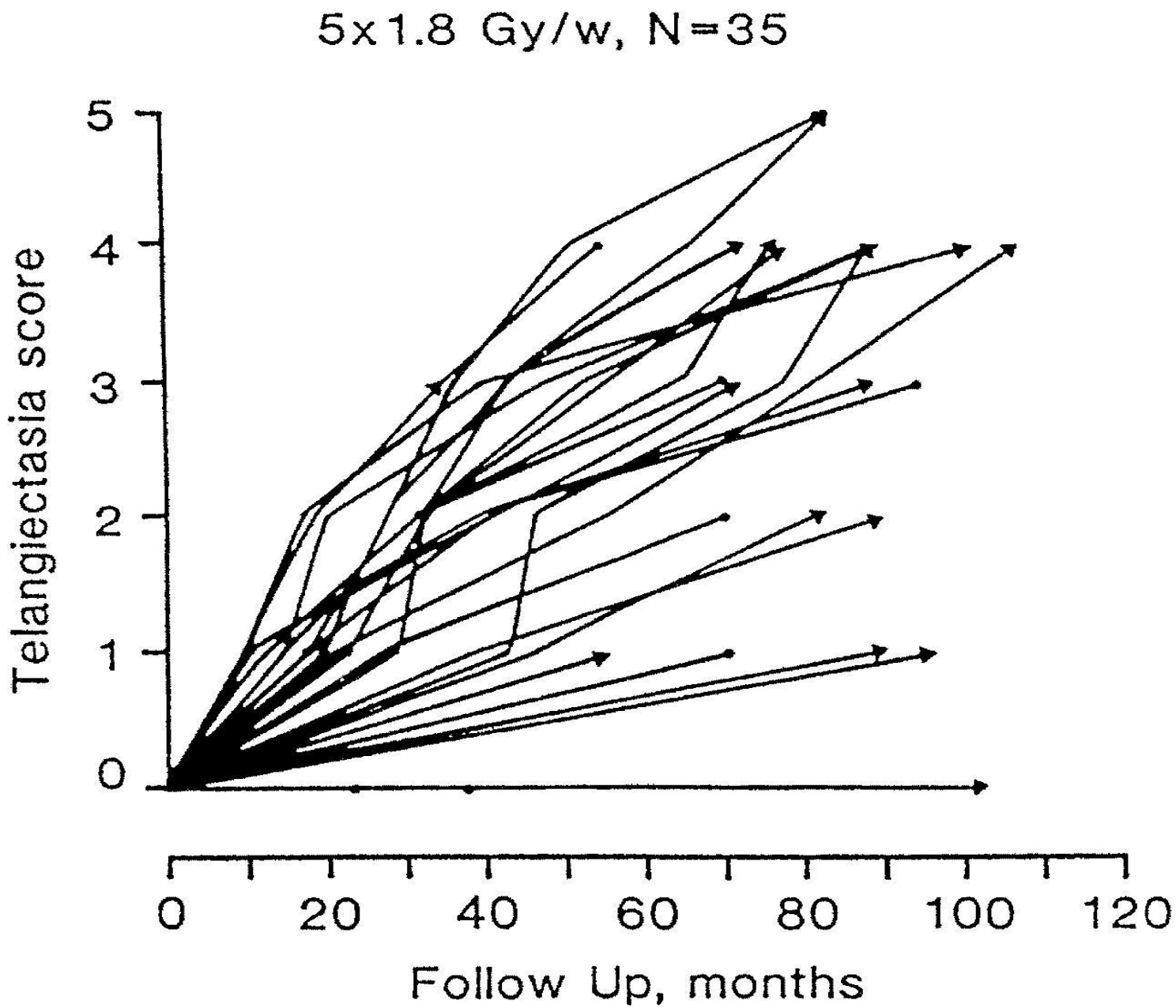
The different heart diseases differ with regard to

- heart sub-volume in which the pathogenic process is triggered,
- threshold dose and shape of dose response relationship,
- the latency to clinical manifestation,
- the dependence on age at exposure
- the radiobiological pathways and mechanisms.

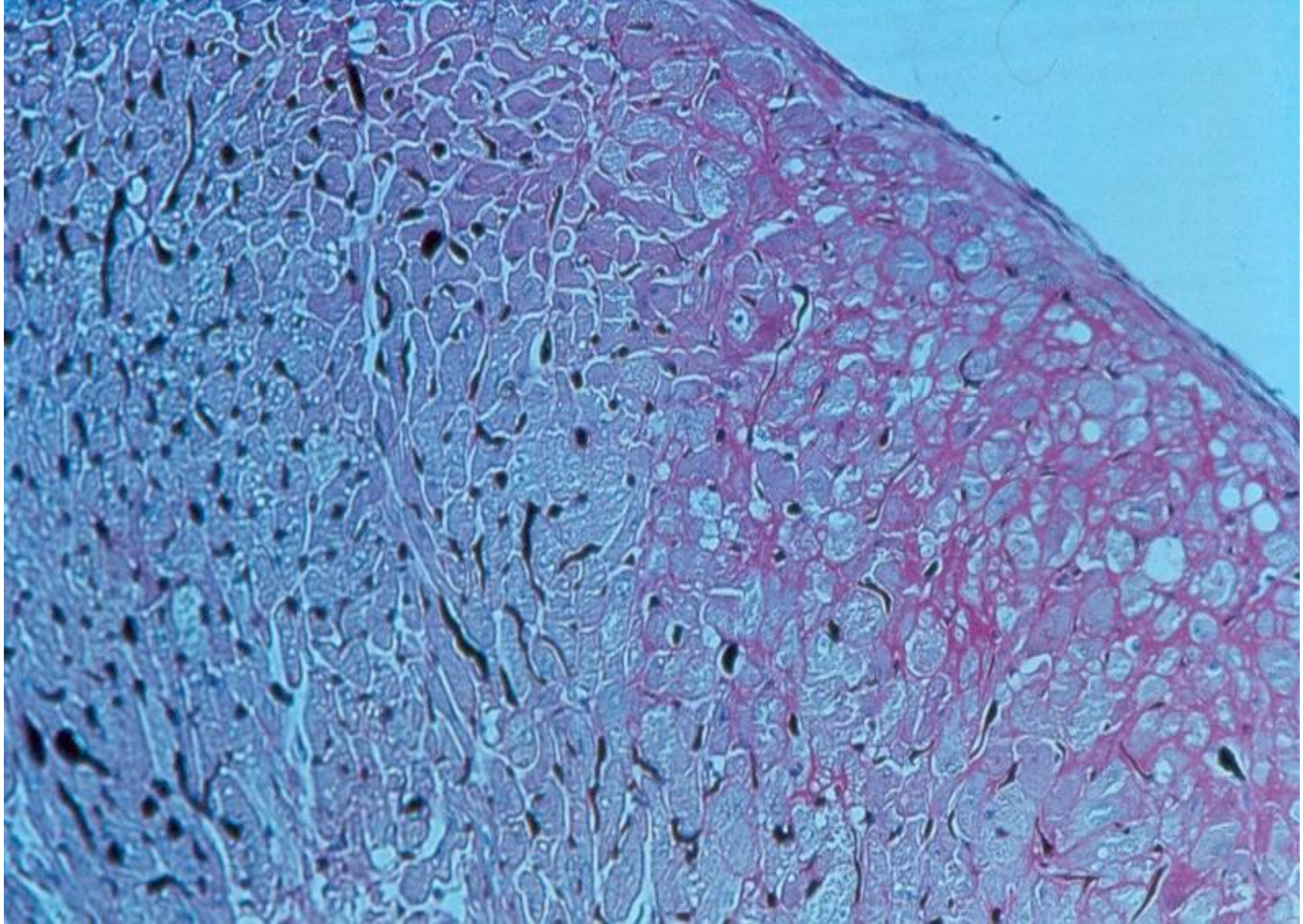
ALLEGRO: Biological mechanisms of normal tissue damage:

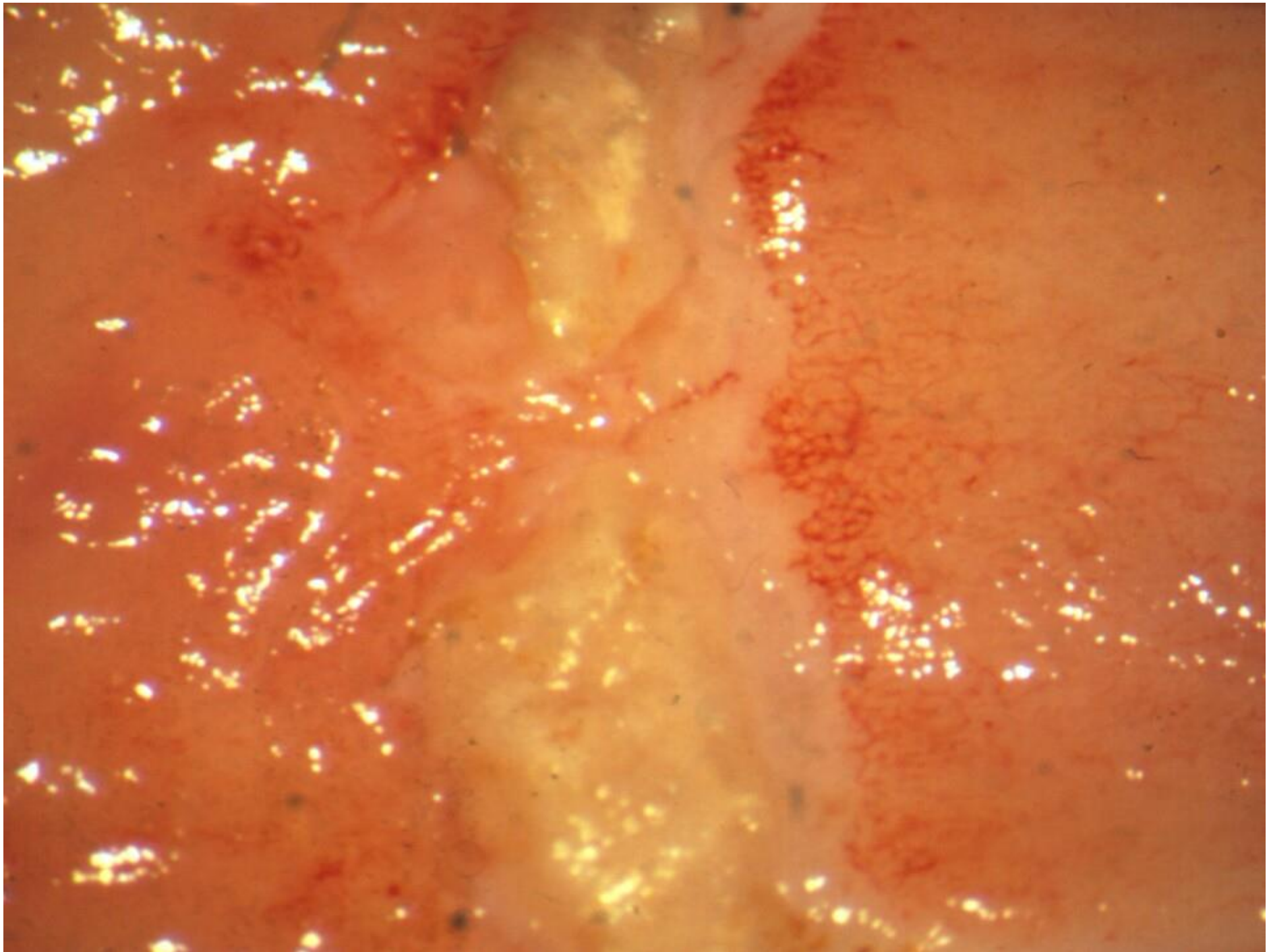
The biological mechanisms which have been identified as potentially involved in the pathogenesis of normal tissue complications of radiotherapy can be classified as either

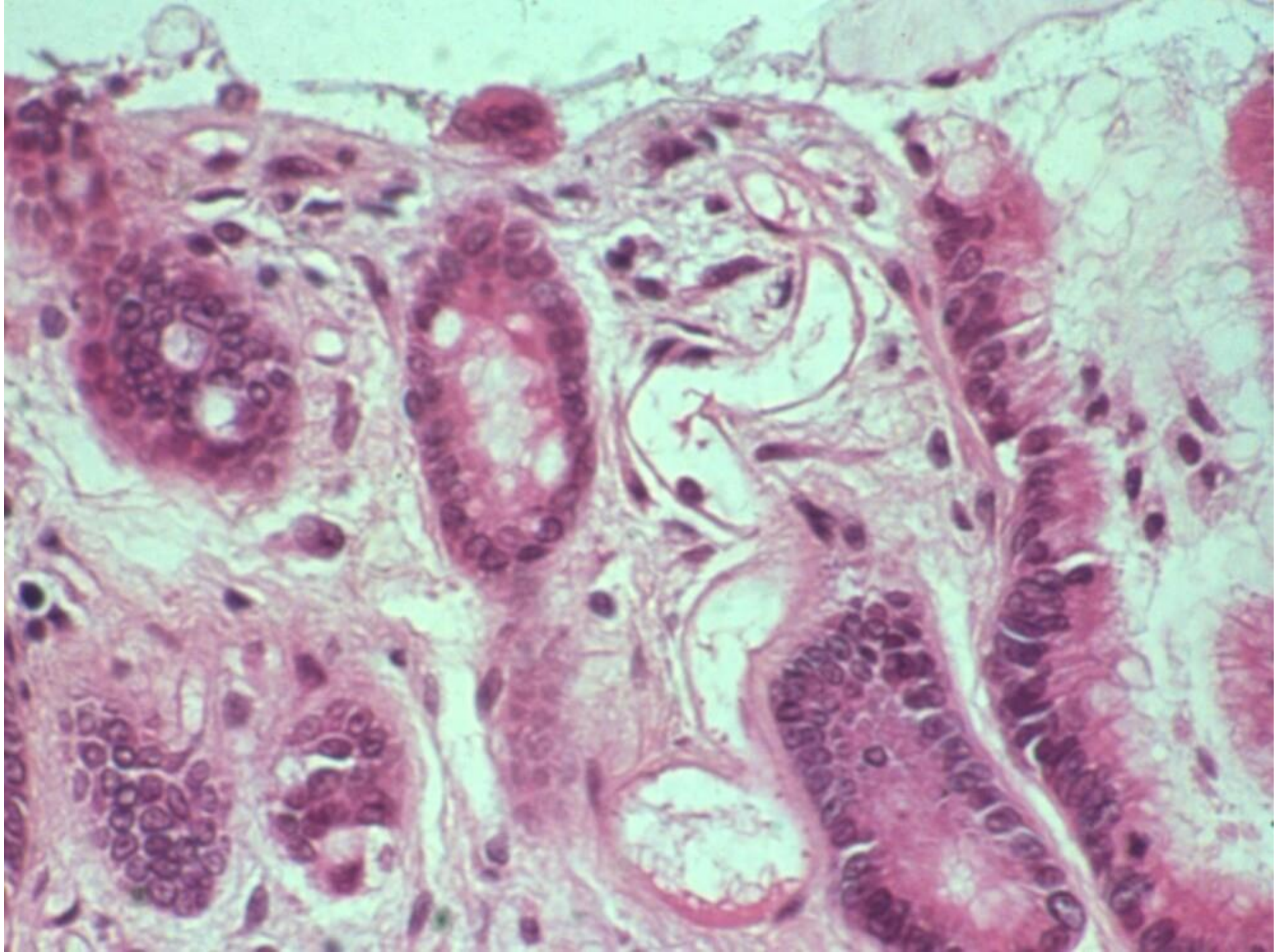
- Single cell effects such as “cell death”, sterilisation of stem cells, inhibition of proliferation
- Tissue effects which depend on the interaction between different cells and cell populations within organs or between organs such as inflammation or differentiation
- Effects which result from alterations of tissue structure such as vascular injury or fibrosis
- Other, less well defined functional changes such as alterations in neuromuscular function or immunological responses

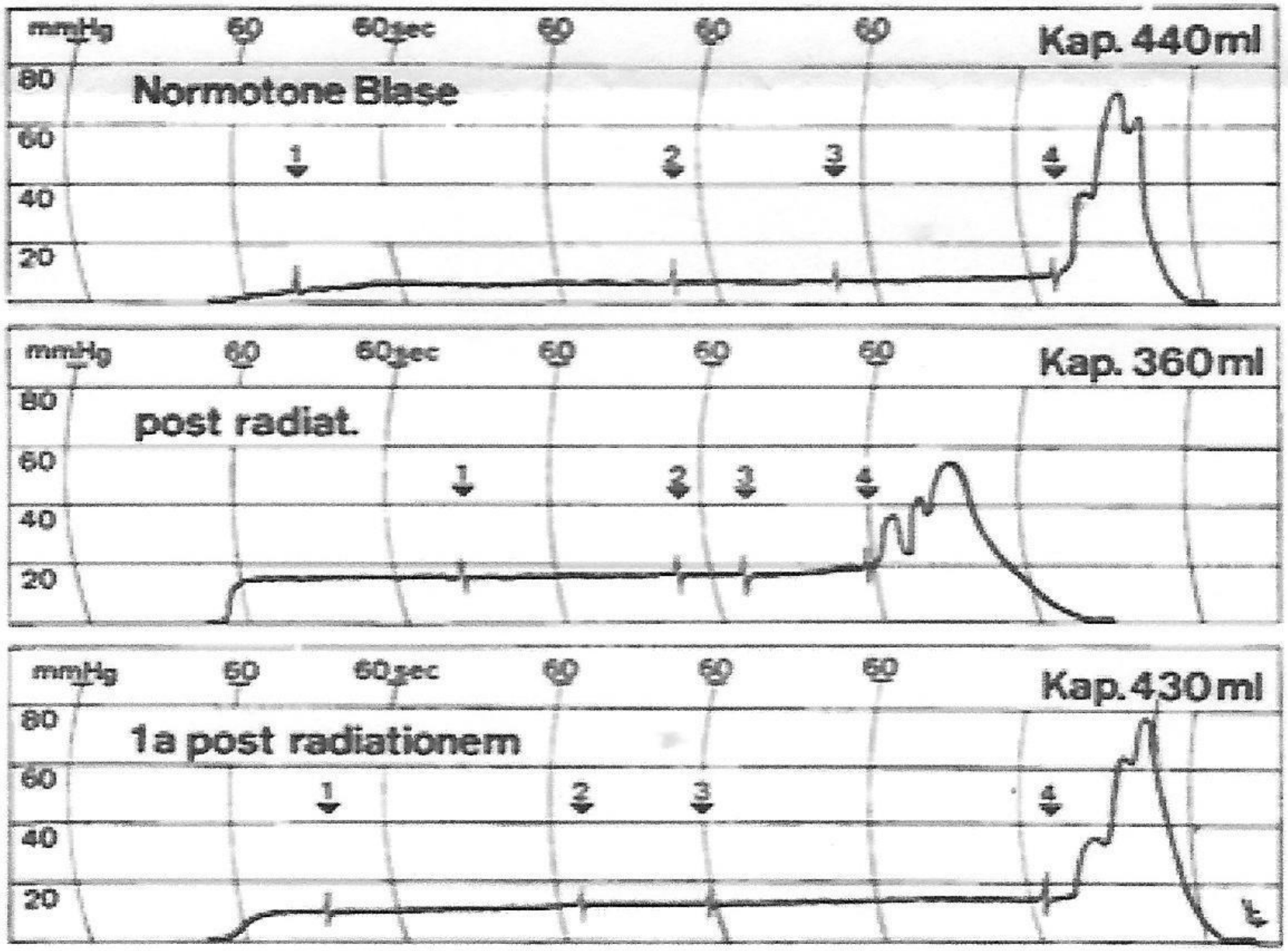

5x1.8 Gy/w, N=35
Telangiectasia score
0
1
2
3
4
5
0
20
40
60
80
100
120
Follow Up, months

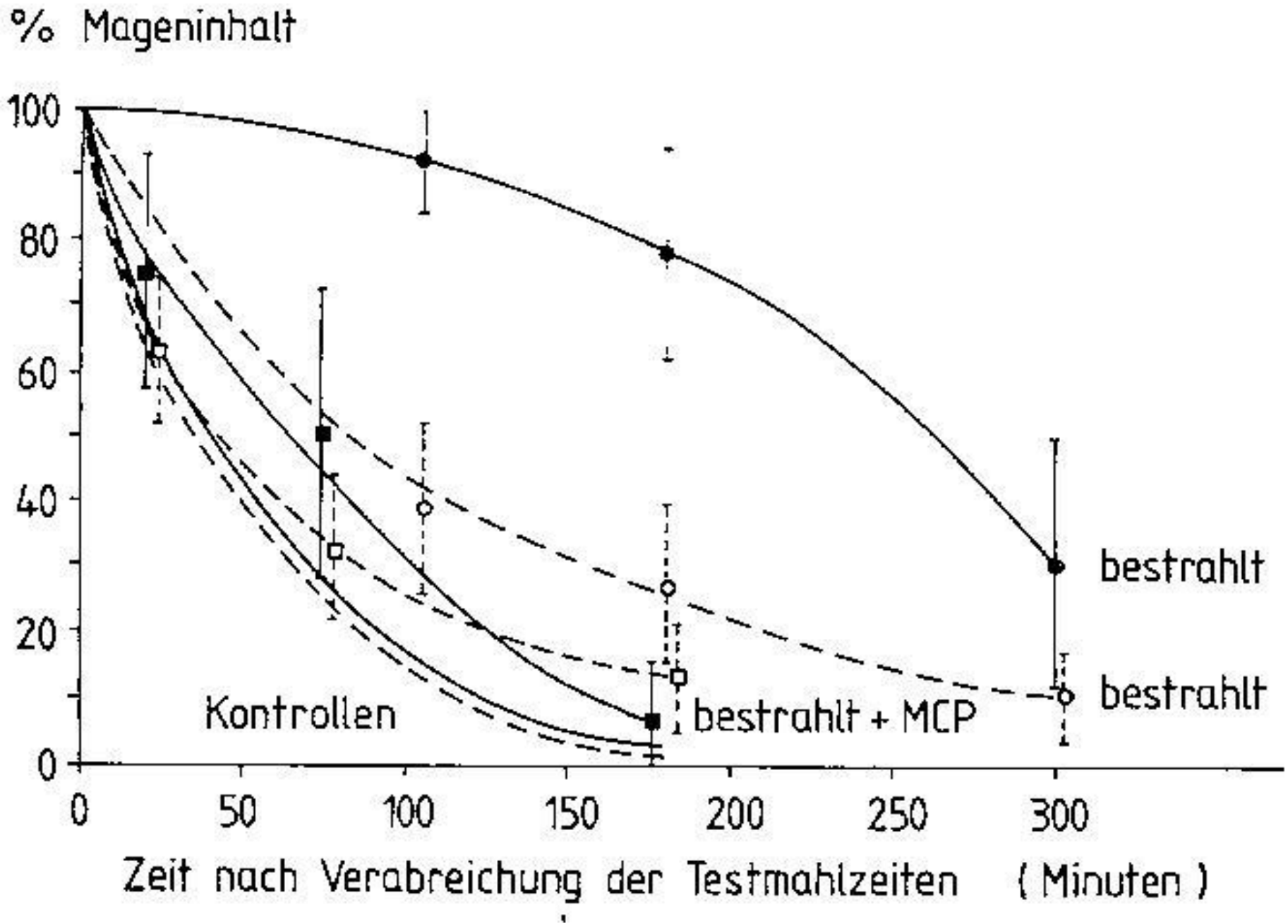

length density of capillaries
mm/mm³
4000
3500
3000
2500
2000
1500
1000
0
5
10
15
20
25
30
35
40
45
50
days after irradiation








mmHg
60
60sec
Kap. 440ml
Normotone Blase
80
60
40
20
1
2
3
4
mmHg
Kap. 360ml
post radiat.
mmHg
Kap. 430ml
1a post radiationem
E


% Mageninhalt
100
80
60
40
20
0
0
50
100
150
200
250
300
Kontrollen
bestrahlt + MCP
bestrahlt
bestrahlt
Zeit nach Verabreichung der Testmahlzeiten (Minuten)

Limitations inherent in preclinical experiment

- How does mouse time relate to human time?
- How does anatomical dose inhomogeneity which is characteristic for normal tissues exposures in radiation oncology affect re-irradiation tolerance?
- How do the experimental endpoints used for effect quantification relate to the signs and symptoms from which patients suffer?

Final conclusion

Animal experiments are useful for studying specific mechanisms involved in the pathogenesis of various signs and symptoms of clinical late normal tissue damage. Yet animal experiments are not useful for testing or even optimizing clinical protocols. This can only be achieved by careful clinical studies which permit quantitative reconstruction of individual dose distributions as well as quantification of specific signs and symptoms of critical normal tissue damage such as those re-commended in the ***dictionary of normal tissue morbidity*** by the late Stan Dische.