



Dose-Response of Vitamin D and a Mechanism for Prevention of Cancer

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Disclosures

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose


Dr. Cedric F. Garland



Objectives

Describe the optimal level of serum **25-hydroxyvitamin D** for cancer prevention.

Explain the micro-evolutionary basis of cancer etiology, the dominant role of membranes and **natural selection** in tissue, and ways that vitamin D metabolites reduce incidence and death rates.



Outline:
Dose-response and
mechanisms

Colon

Breast

Ovarian

Kidney

Other cancers

Mechanisms

Model

Recom-

mendations



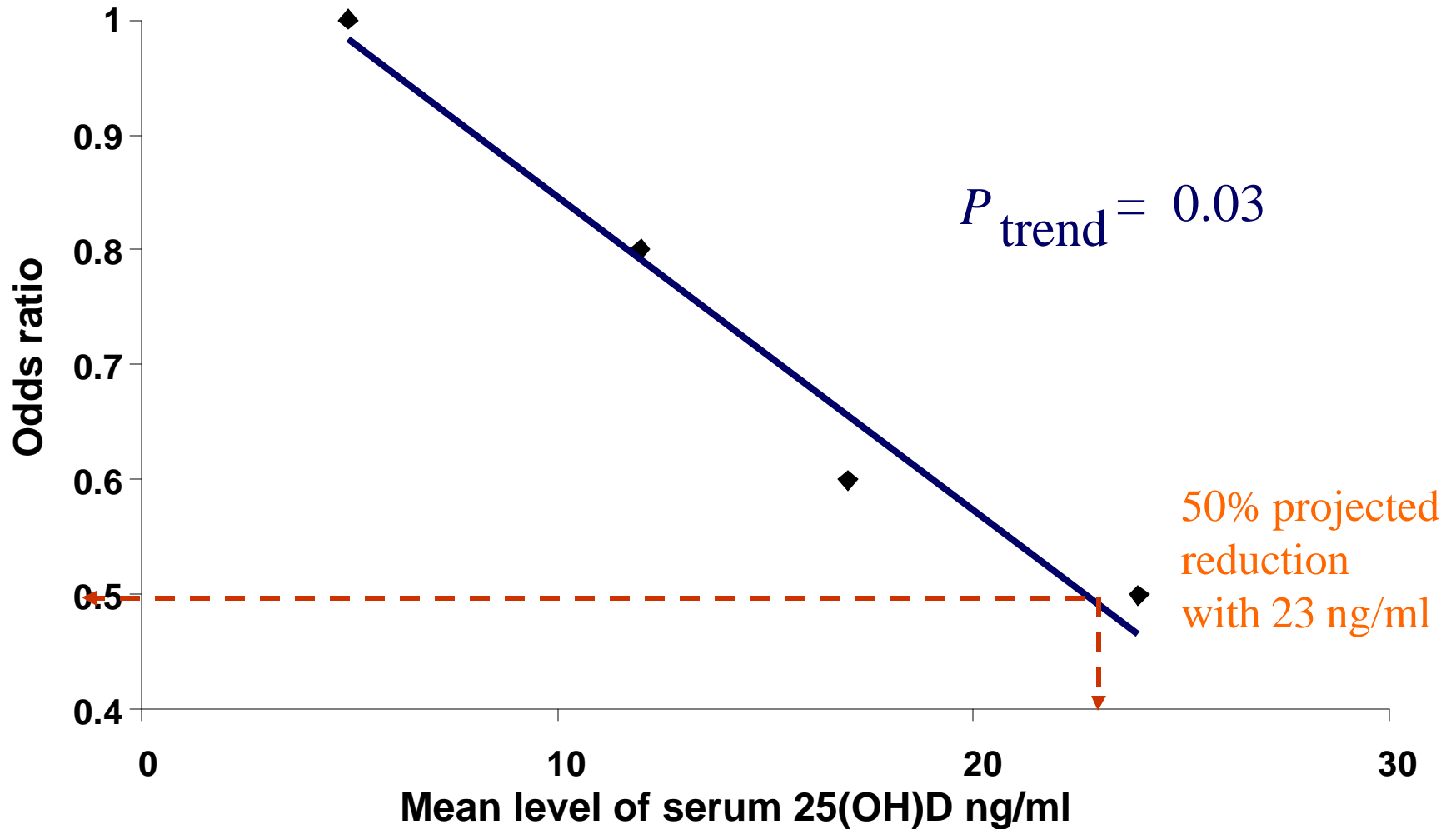
UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER



Serum Levels of 25(OH)D and Colon Cancer



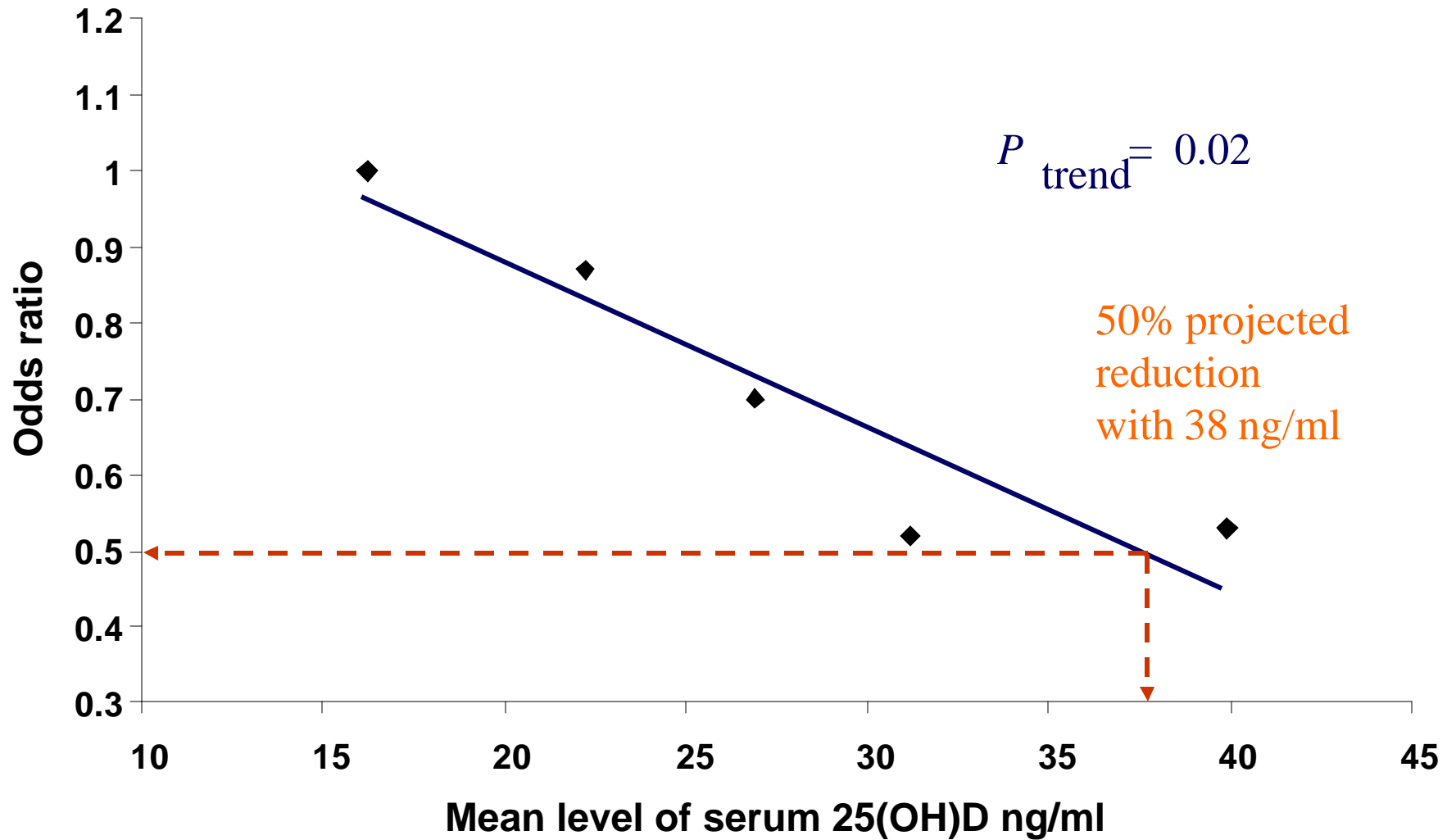
Tangrea et al. 1997



Source: Tangrea J, et al. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control* 1997;8:615–25.
Graphic: S. B. Mohr, M.P.H.



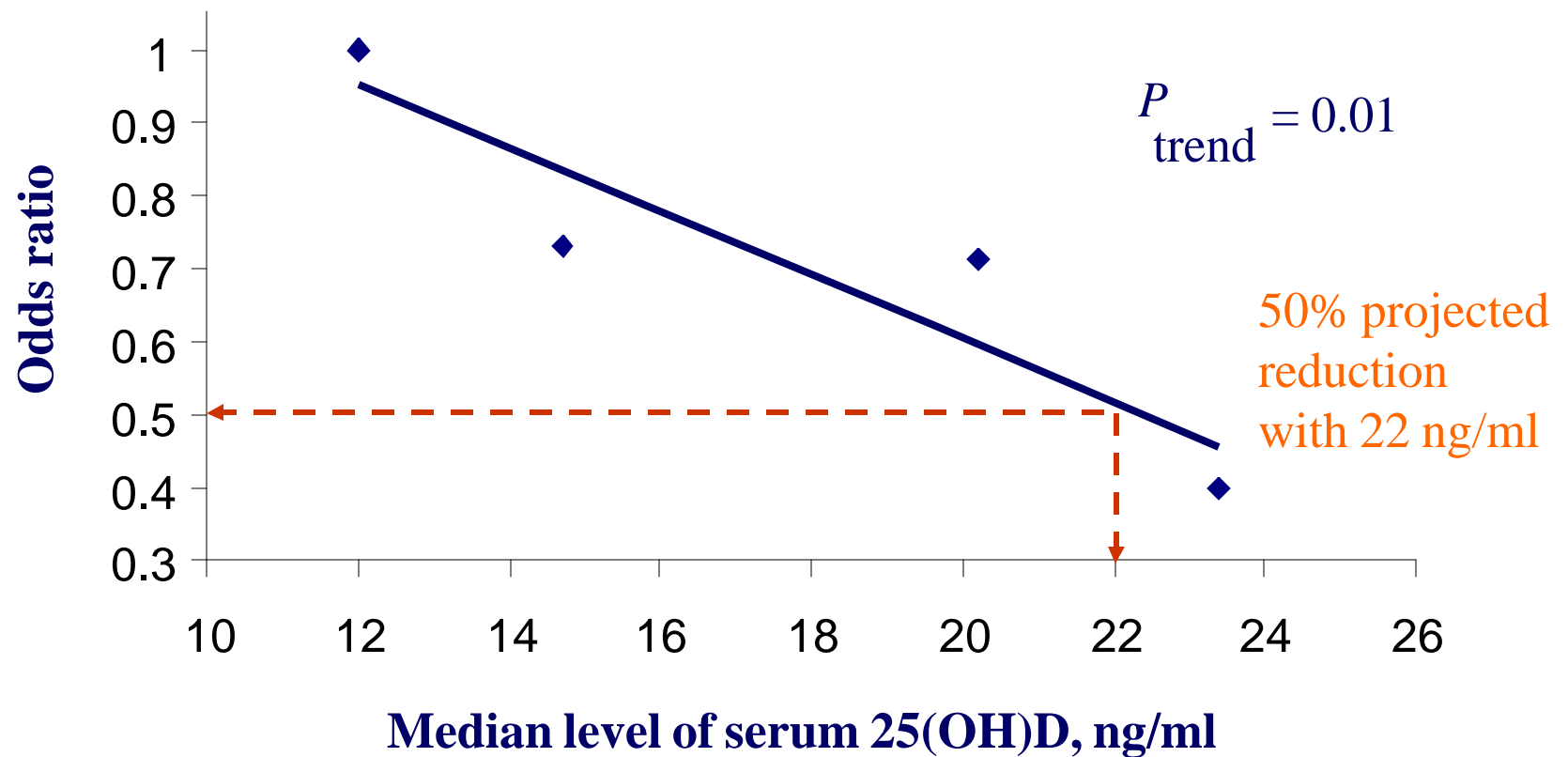
Feskanich et al. 2004



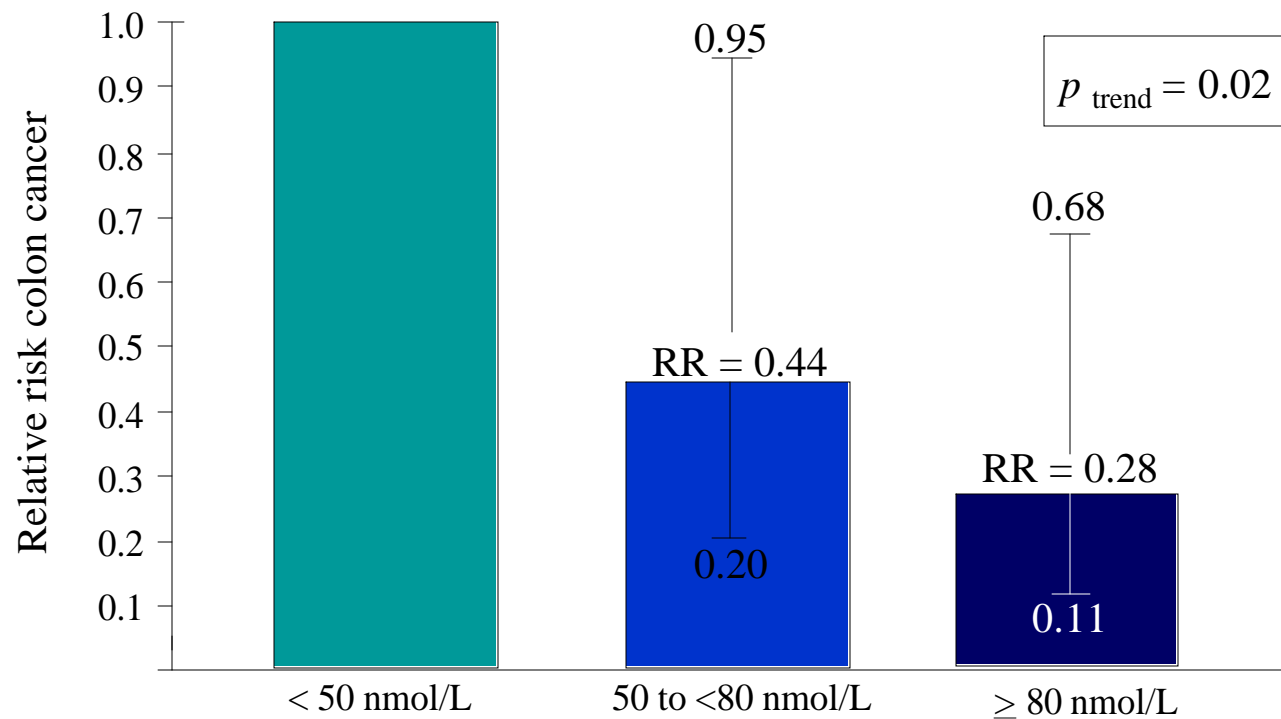
Source: Feskanich D, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2004;13:1502– 8. Graphic: S. B. Mohr, M.P.H.



Women's Health Initiative Nested Study (N=295)

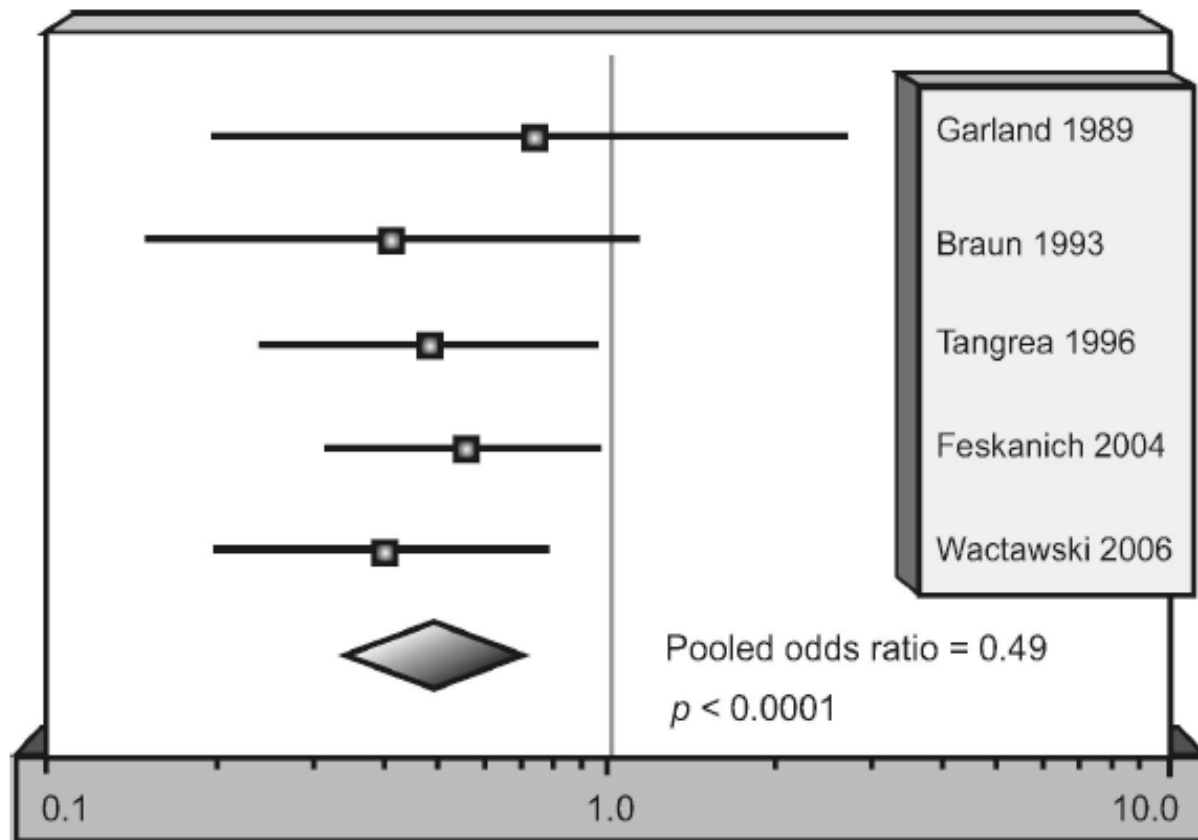


Source: Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *New Engl J Med* 2006; 354:684-96. Graphic: S. B. Mohr, M.P.H.



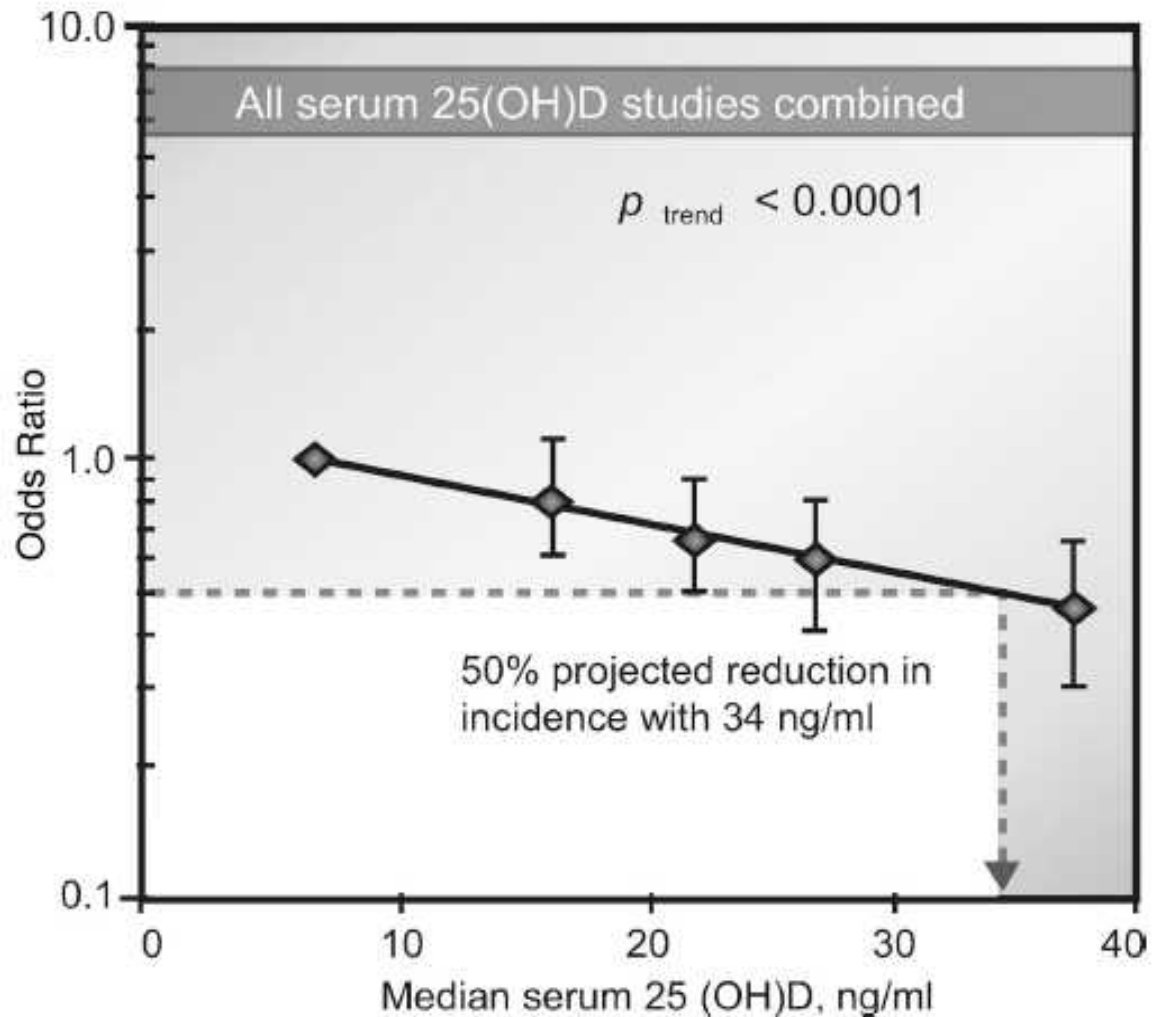
Relative risk of colon cancer mortality, by baseline serum 25-hydroxyvitamin D concentration in tertiles, NHANES III cohort, 1988-2000

Source: Freedman DM, Looker AC, Shih-Chen C, et al. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst* 2007;99:1594-602. Graphic: E. D. Gorham, Ph.D.

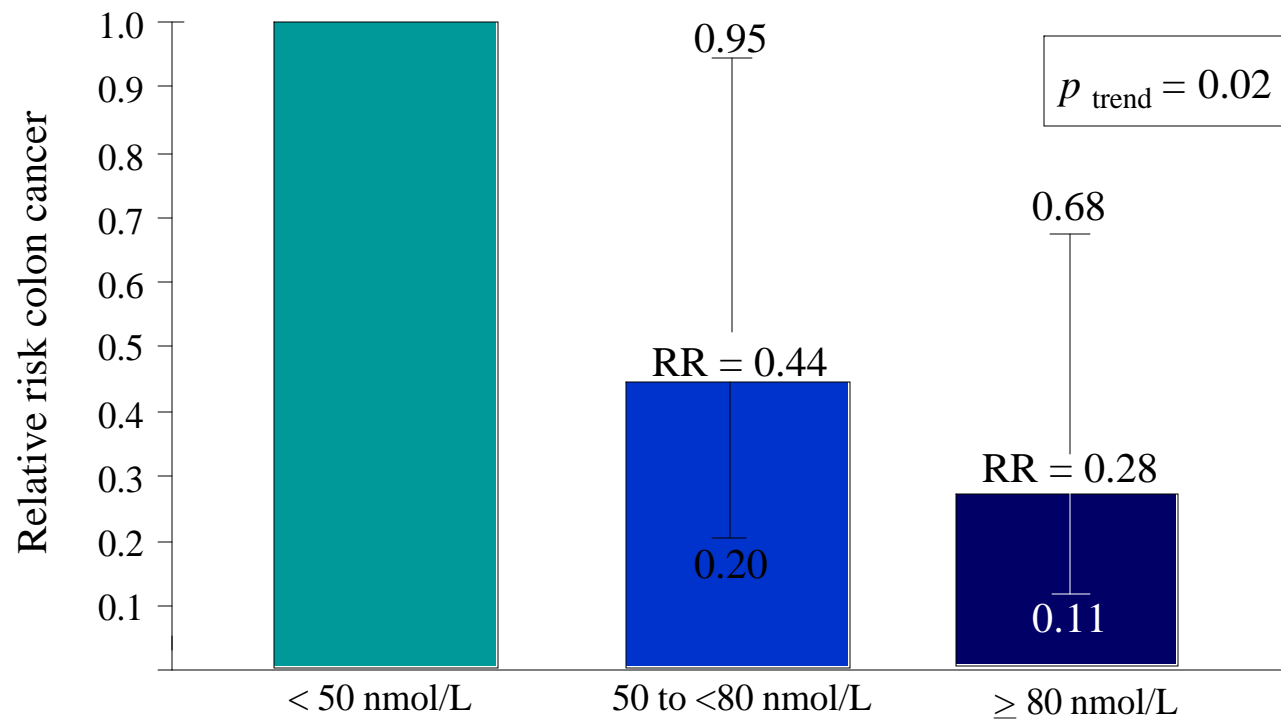


Forest plot of all studies of serum 25(OH)D and risk of colorectal cancer. The upper and lower 95% confidence limits on the odds ratio are denoted by horizontal lines for each study, and the 95% confidence limits for the combined estimate for all studies are denoted by the points of the diamond. The odds ratios compare the highest quintile to the lowest.

Source: Gorham ED, et al. Optimal vitamin D status for colorectal cancer prevention: A Quantitative Meta Analysis. Am J Prev Med March 2007; 32:210-6. Graphic: S. B. Mohr, M.P.H.



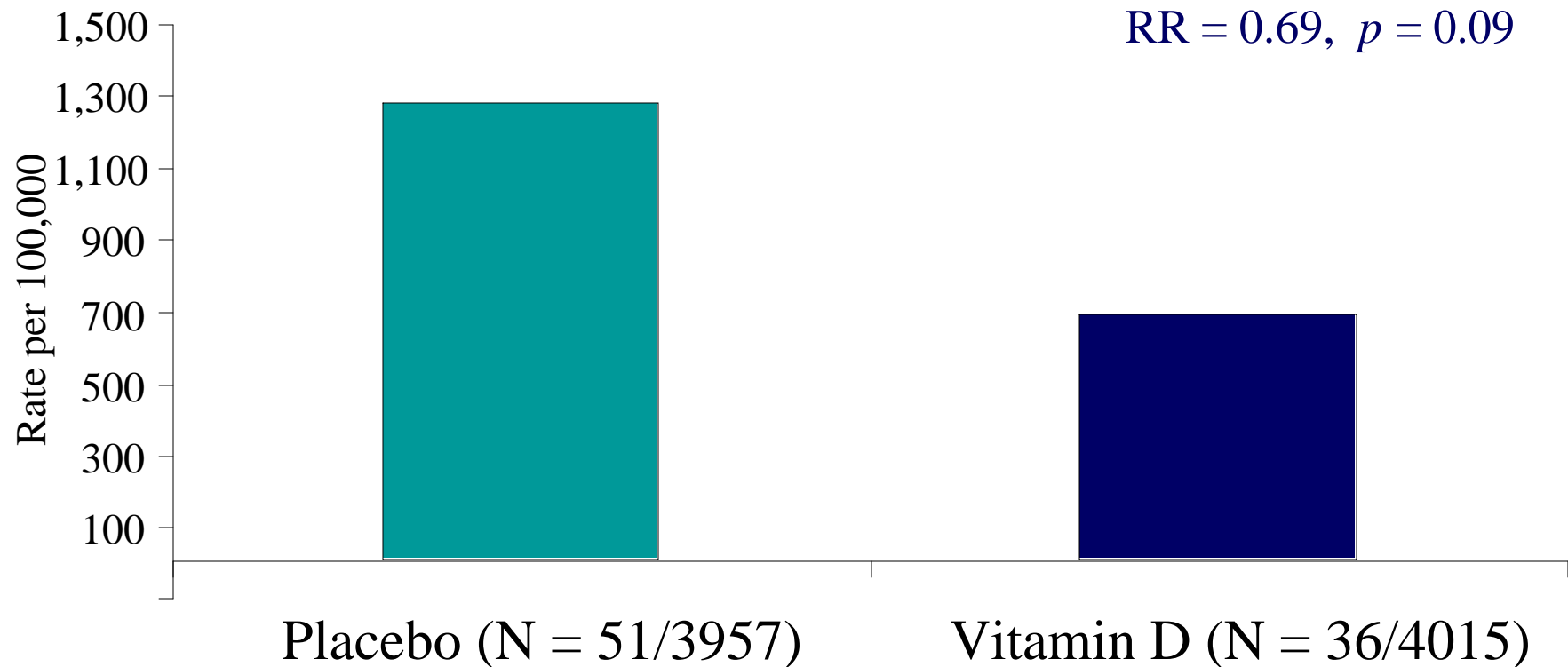
Dose-response gradient for colorectal cancer according to serum 25(OH)D concentration, all five studies combined. — The five points are the odds ratios for each quintile of 25(OH)D based on combined data from the five studies. Source: Gorham ED, et al. Optimal vitamin D status for colorectal cancer prevention: A Quantitative Meta Analysis. Am J Prev Med March 2007; 32:210-6. Graphic: S. B.Mohr, M.P.H.



Relative risk of colon cancer mortality, by baseline serum 25-hydroxyvitamin D concentration in tertiles, NHANES III cohort, 1988-2000

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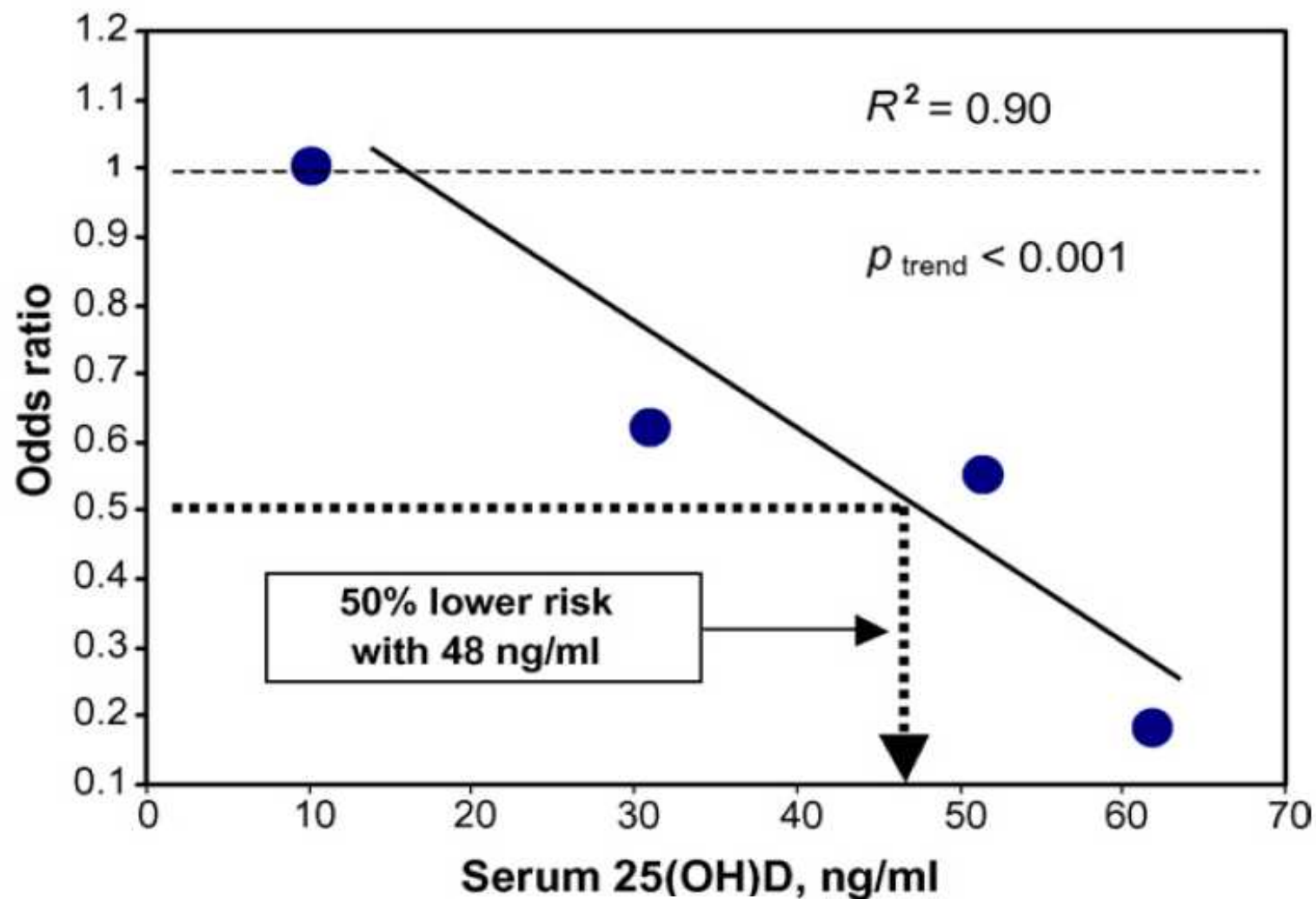
Incidence rate of colorectal cancer by vitamin D in the subgroup of women not assigned to HRT, Women's Health Initiative trial, 7 year follow-up, 1995-2004



Source: Calculated from Wactawski-Wende et al. N Engl J Med 2006;354:684-96.

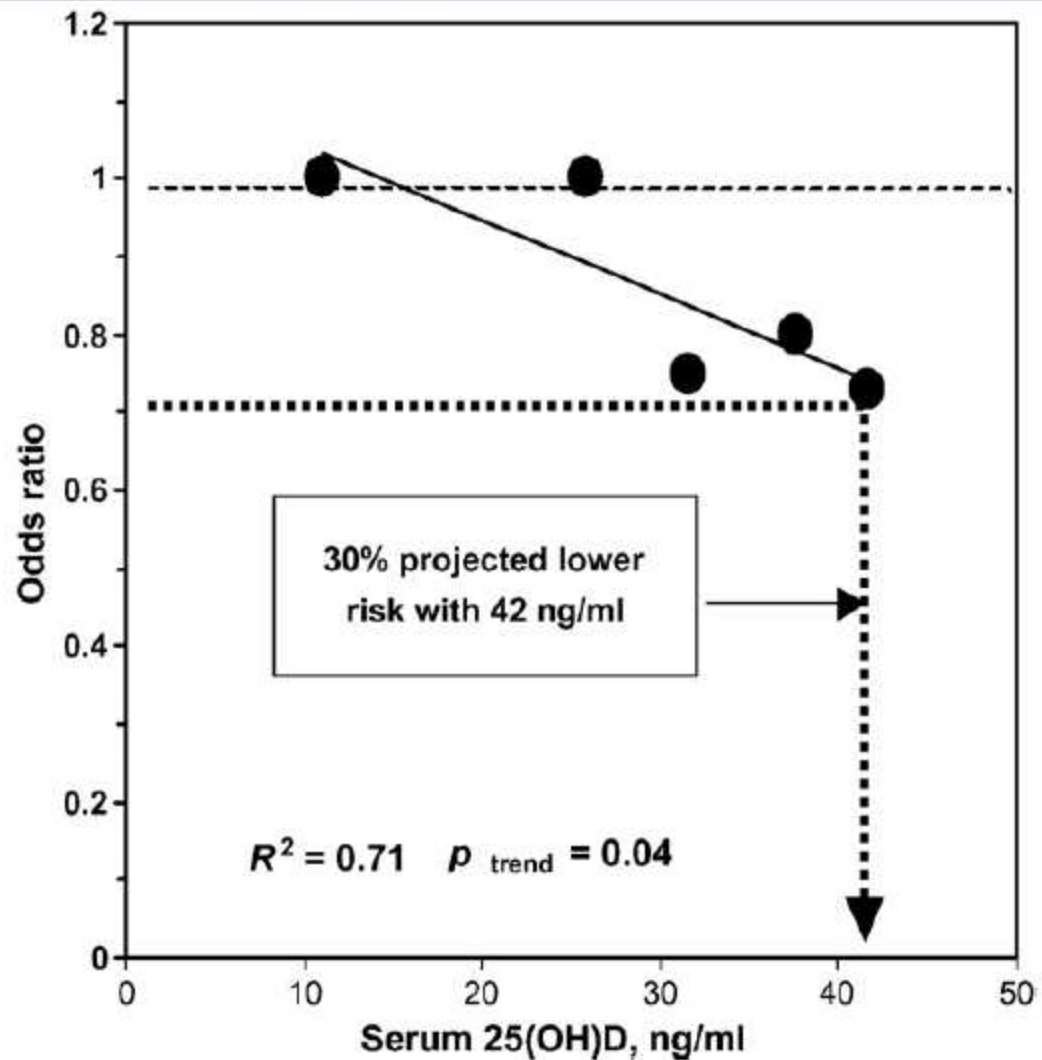


Serum Levels of 25(OH)D and Breast Cancer



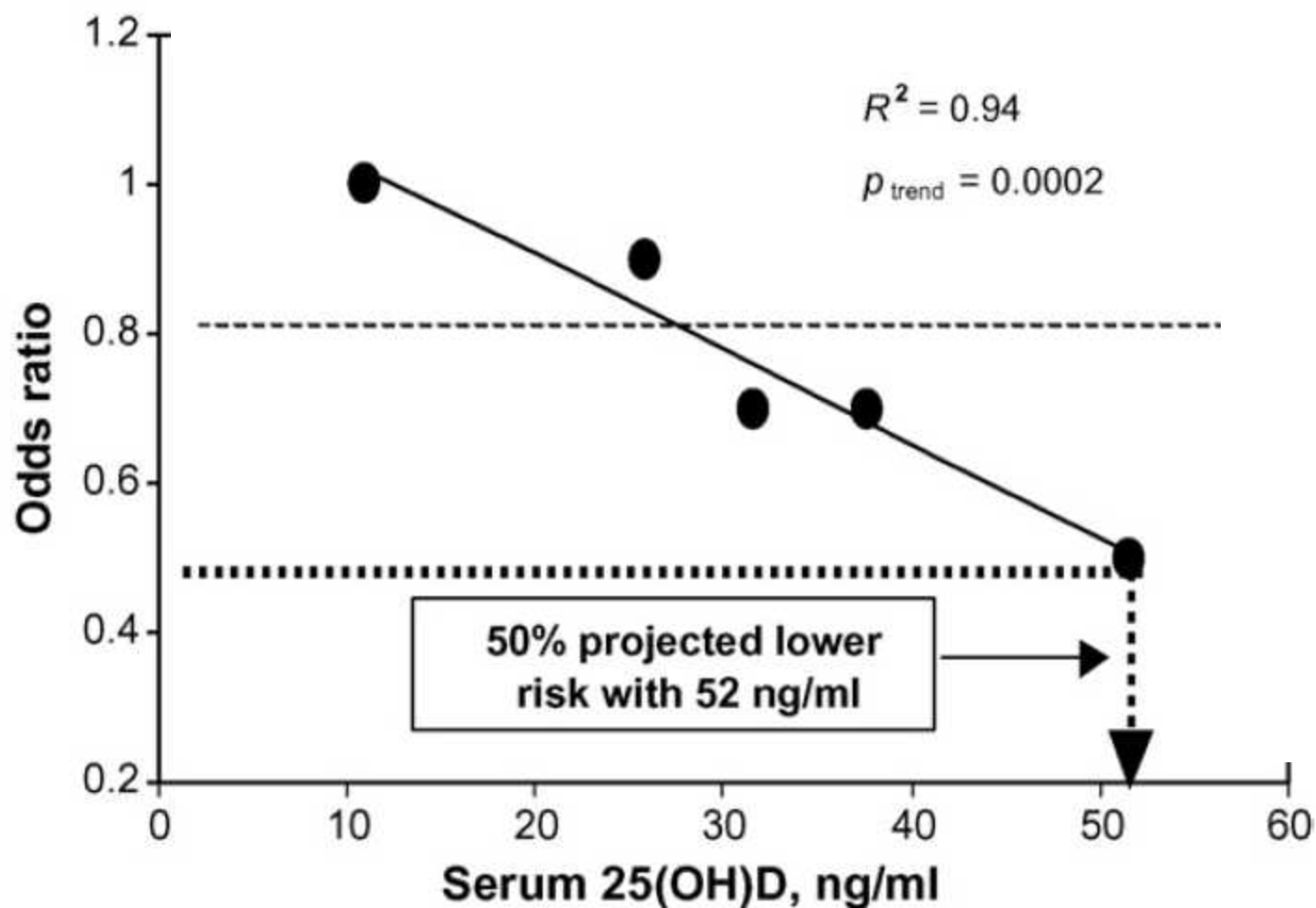
Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, St. George’s Hospital, London

Data from: Lowe LC, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. *Eur J Cancer*. 2005;41:1164-9. Graphic: S. B. Mohr, M.P.H.



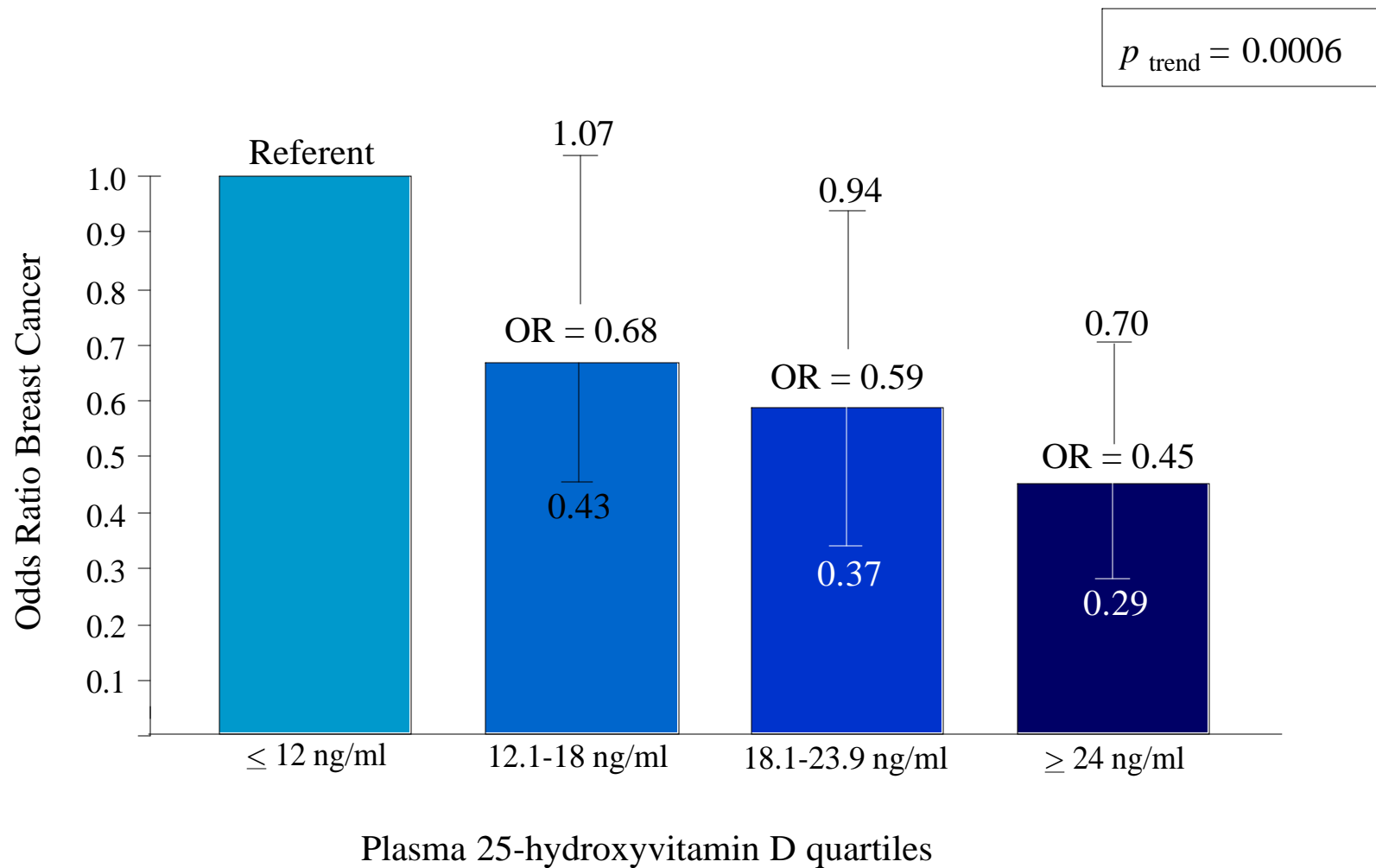
Dose-response gradient of risk of breast cancer according to prediagnostic serum 25-hydroxyvitamin D concentration, Harvard Nurses' Health Study

Data from: Bertone-Johnson, E.R. et al. Plasma 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 2005; 14: 1991-7. Graphic: S. B. Mohr, M.P.H.



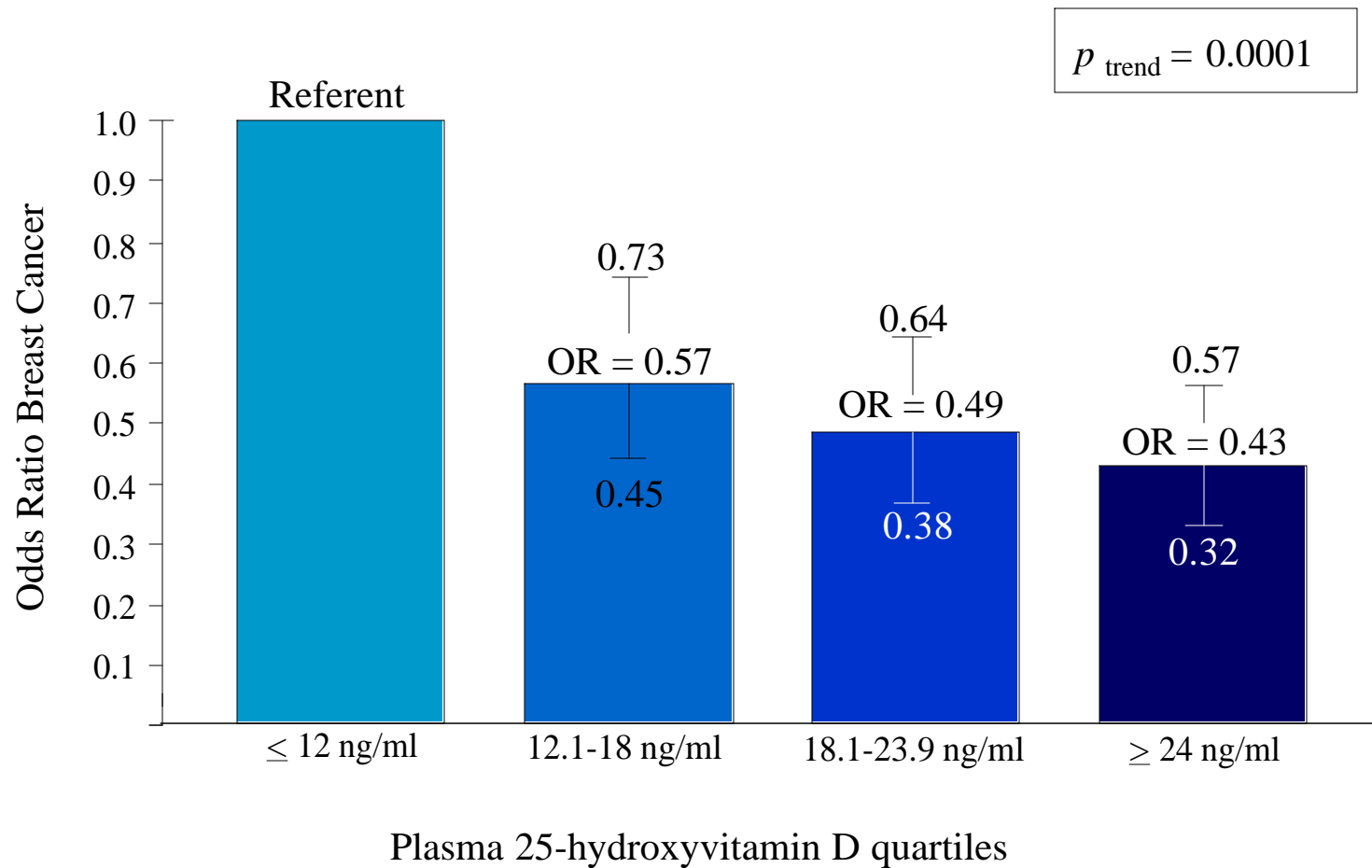
Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.

Source: Garland CF, et al. Vitamin D and prevention of breast cancer: Pooled analysis, *J Steroid Biochem Mol Biol.* 2007;103:708-11 Graphic: S. B. Mohr, M.P.H.



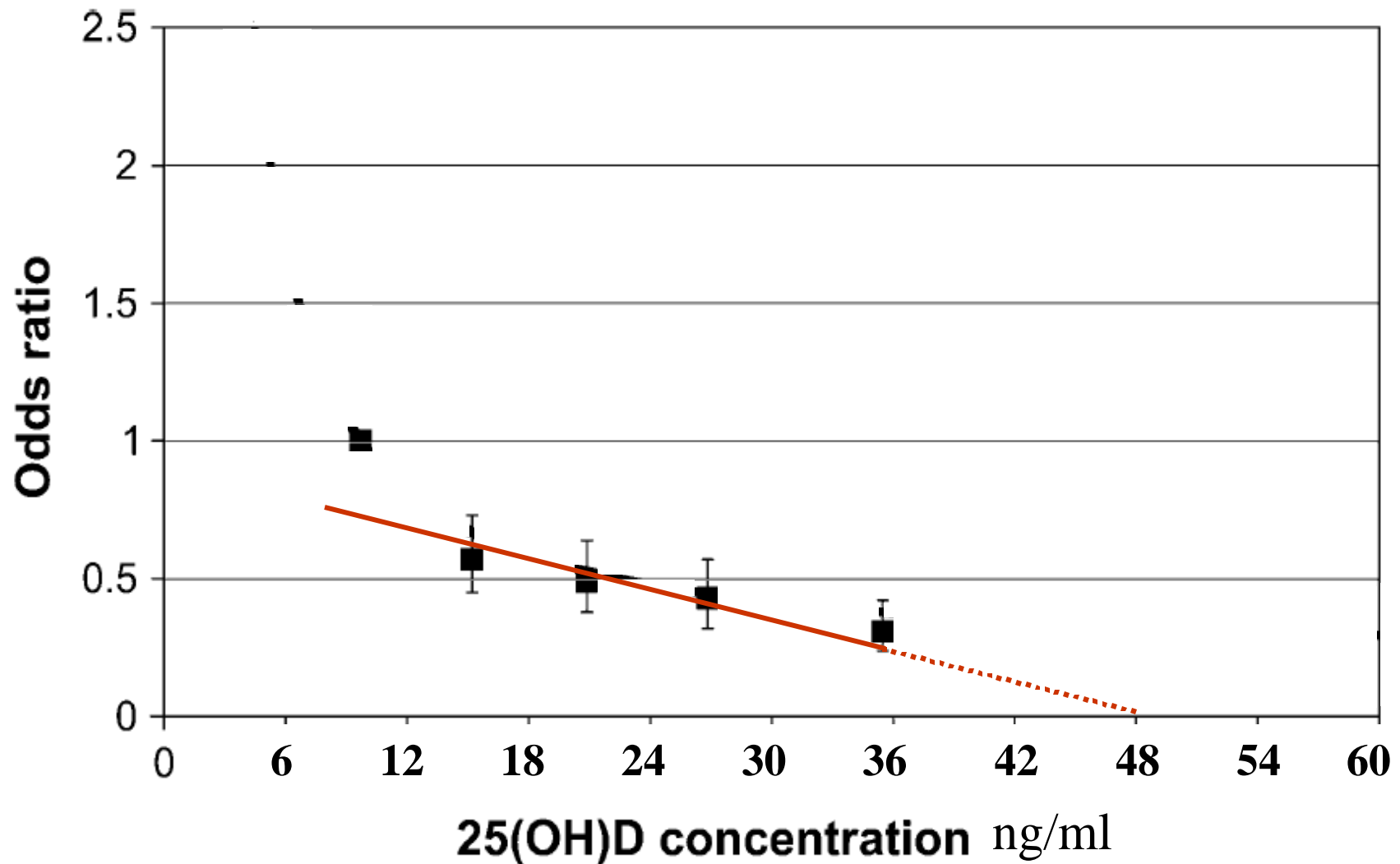
Multivariate-adjusted odds ratios for **pre-menopausal** breast cancer by plasma 25-hydroxyvitamin D concentration by quartiles, 289 cases, 595 matched controls, Heidelberg Germany

Source: Abbas S, Chang-Claude J, Linseisen J. Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study. Int J Cancer. 2008. Graphic: E. D. Gorham, Ph.D.



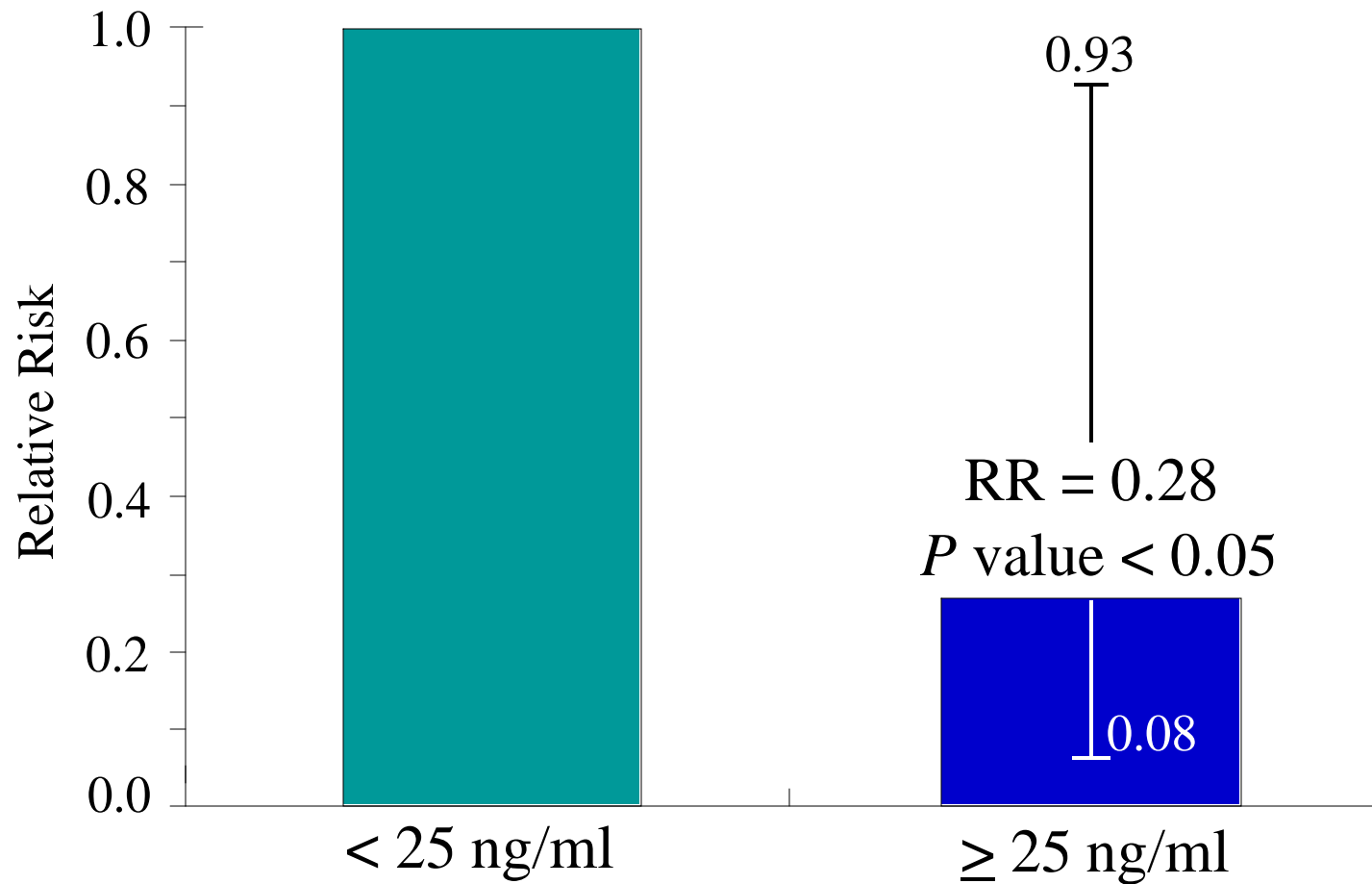
Multivariate-adjusted odds ratios for **post-menopausal** breast cancer by plasma 25-hydroxyvitamin D concentration by quartiles, 1,394 cases, 1,365 matched controls, Heidelberg Germany

Source: Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer--results of a large case-control study. *Carcinogenesis*. 2008 ;29:93-9. Graphic: E. D. Gorham, Ph.D.



Odds ratios for **post-menopausal** breast cancer by 25(OH)D concentrations with a least squares line indicating a linear relationship

Source: Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer--results of a large case-control study. *Carcinogenesis*. 2008 ;29:93-9. Graphic: E. D. Gorham, Ph.D.



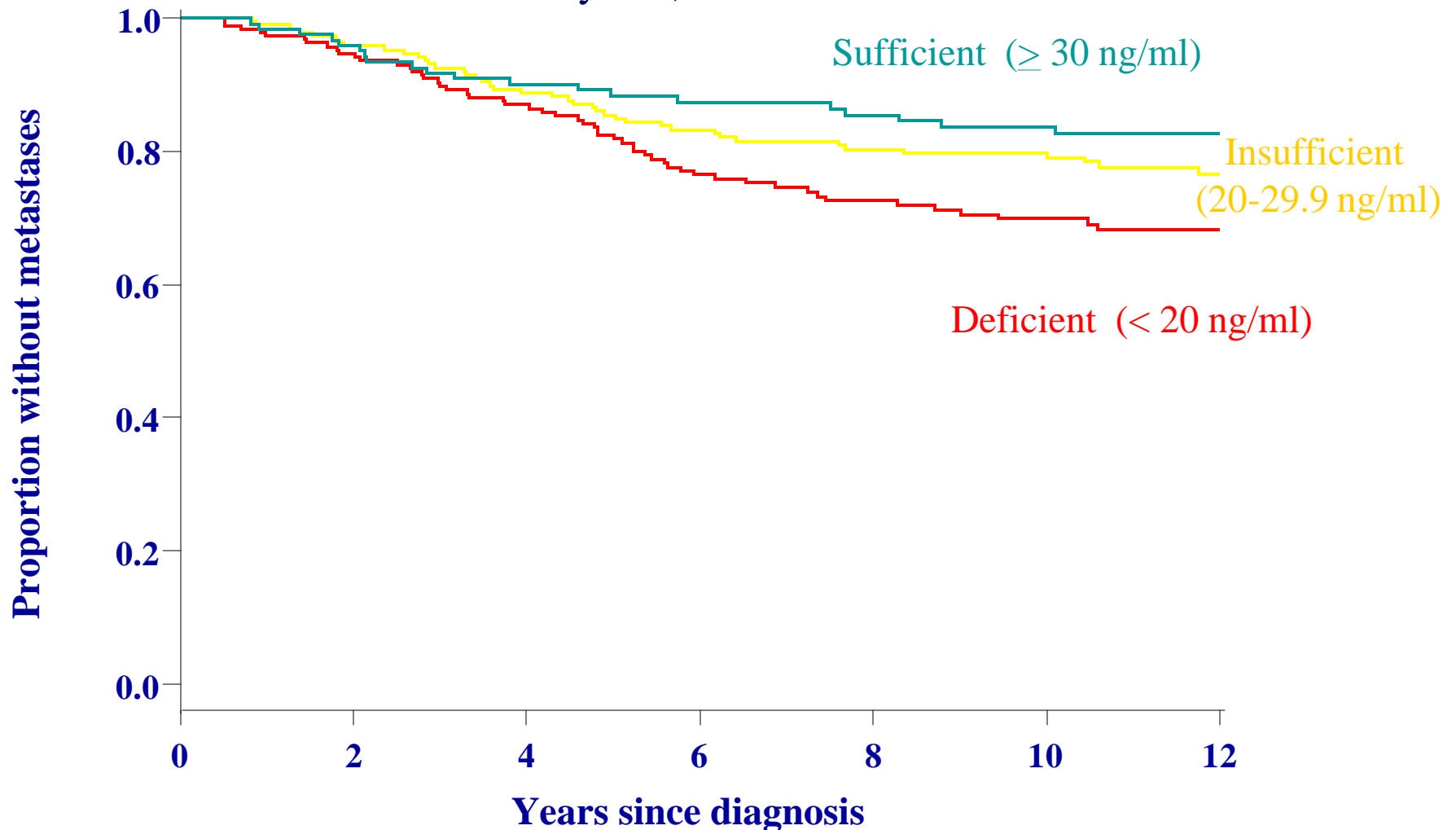
Relative risk of breast cancer **mortality**, by baseline serum 25-hydroxyvitamin D concentration, divided at the median, **NHANES III** cohort, 1988-2000

Source: Freedman DM, Looker AC, Shih-Chen C, et al. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst* 2007;99:1594-602. Graphic: E. D. Gorham, Ph.D.



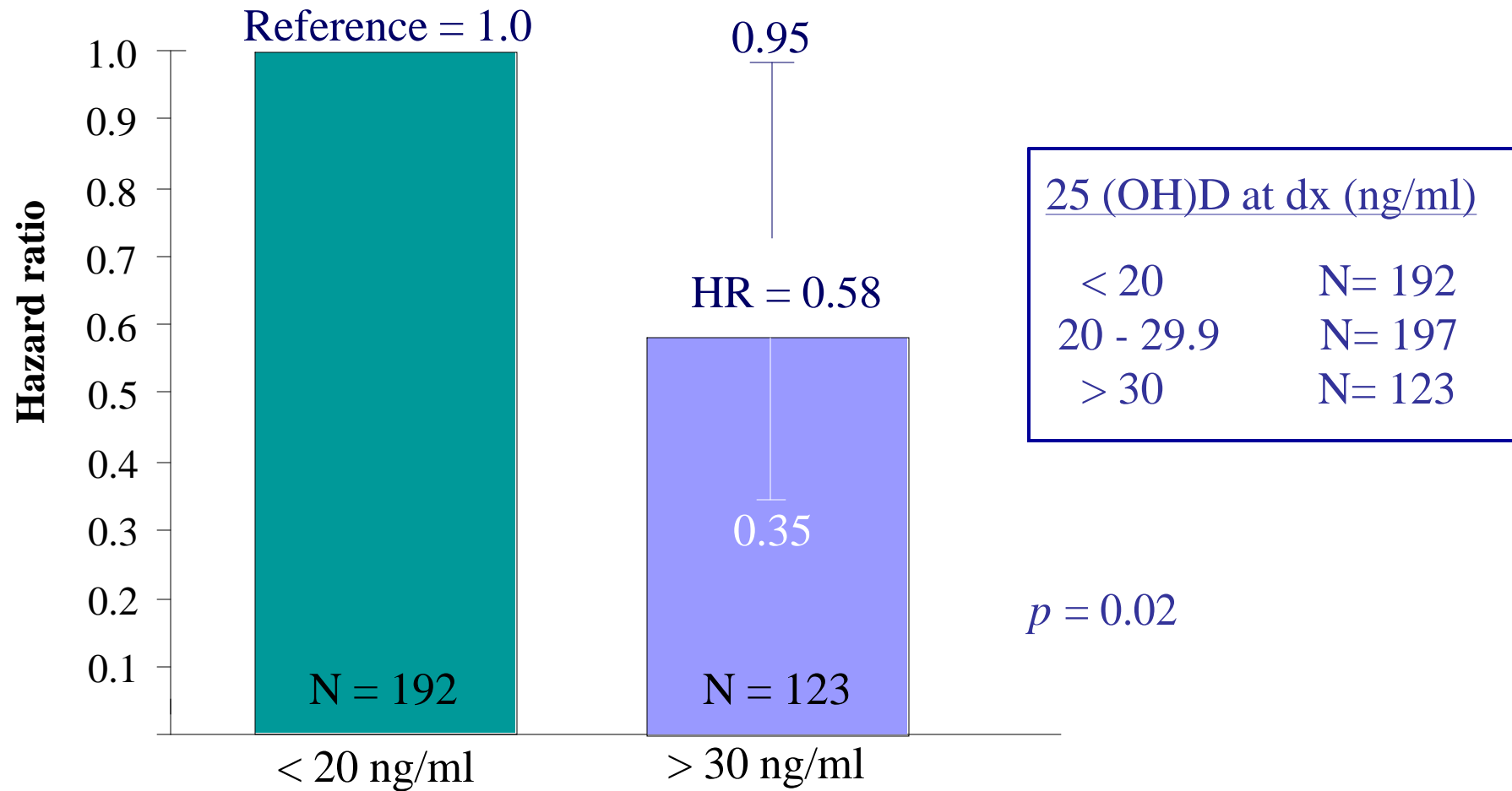
Serum Levels of 25(OH)D and Breast Cancer Survival

Proportion of patients who did not develop distant metastases, 512 women with early stage breast cancer, by serum 25(OH)D at diagnosis, median follow-up 12 years, Toronto



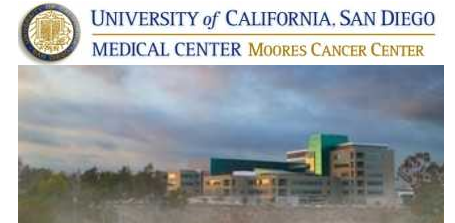
Source: P J Goodwin, et al. Vitamin D deficiency is common at breast cancer diagnosis and is associated with a significantly higher risk of distant recurrence and death in a prospective cohort study. American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, May 30-June 3, 2008. Abstract number: 08-AB-31397-ASCOAM.

Hazard of dying , 512 women with early stage breast cancer by serum 25(OH)D level at diagnosis, median follow-up 11.6 years, Toronto, Canada



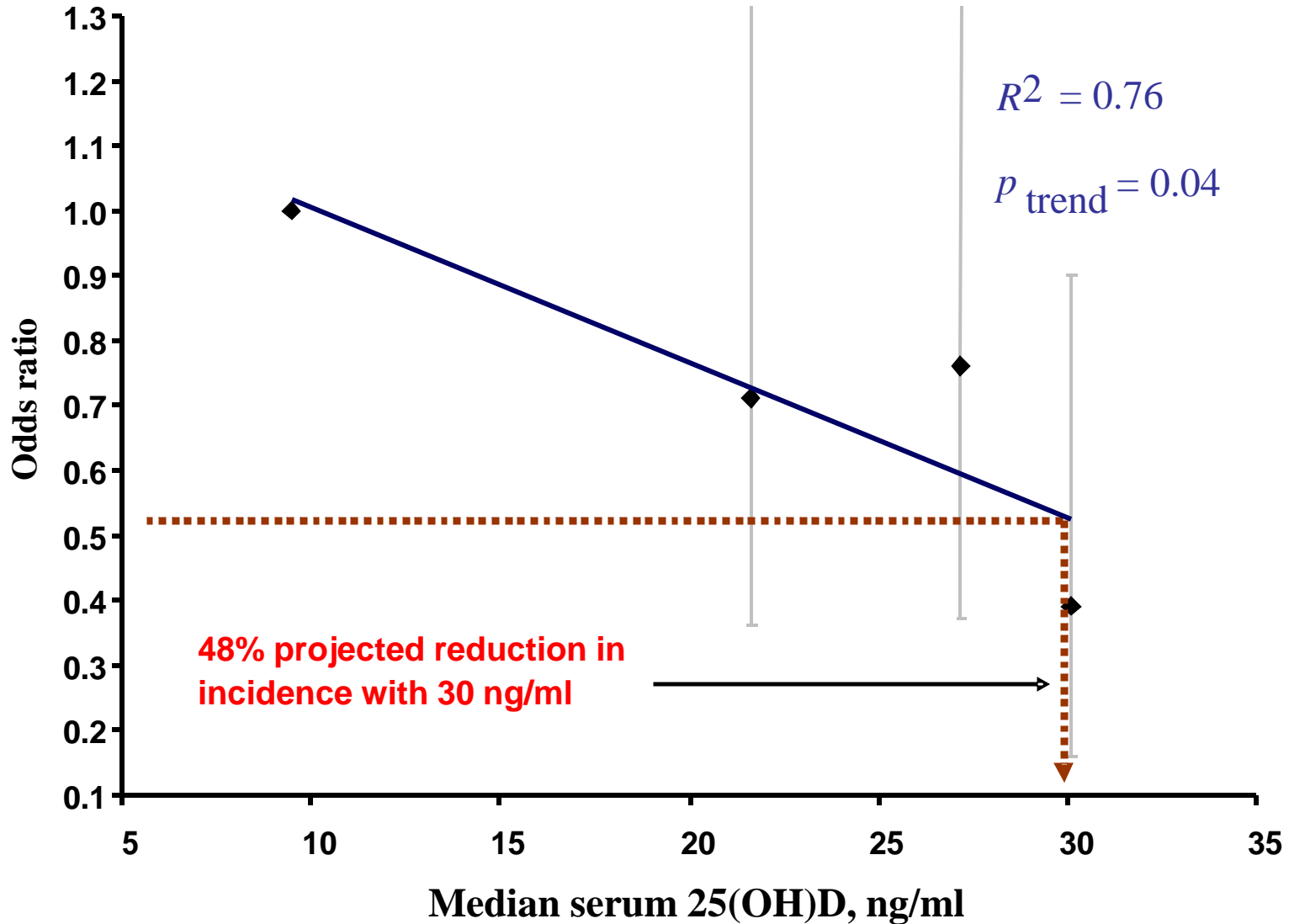
Hazard ratio for **death**, breast cancer patients, with 95% confidence interval, by serum 25(OH)D at diagnosis, Toronto (latitude 43° 40'N)

Source: P J Goodwin, et al. Vitamin D deficiency is common at breast cancer diagnosis and is associated with a significantly higher risk of distant recurrence and death in a prospective cohort study. American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, May 30-June 3, 2008. Abstract number: 08-AB-31397-ASCOAM. Graphic: E. D. Gorham, Ph.D.



Vitamin D and Other Cancers

25(OH)D and Ovarian cancer



Dose-response gradient of ovarian cancer according to prediagnostic serum 25-hydroxyvitamin concentration, subgroup of women with Body Mass Index > 25. Graphic: E. D. Gorham

Source: Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16:783-8.

Harvard Health Professionals Follow-Up Study: determinants of plasma 25-hydroxy-vitamin D were examined in relation to cancer risk in 47,800 men

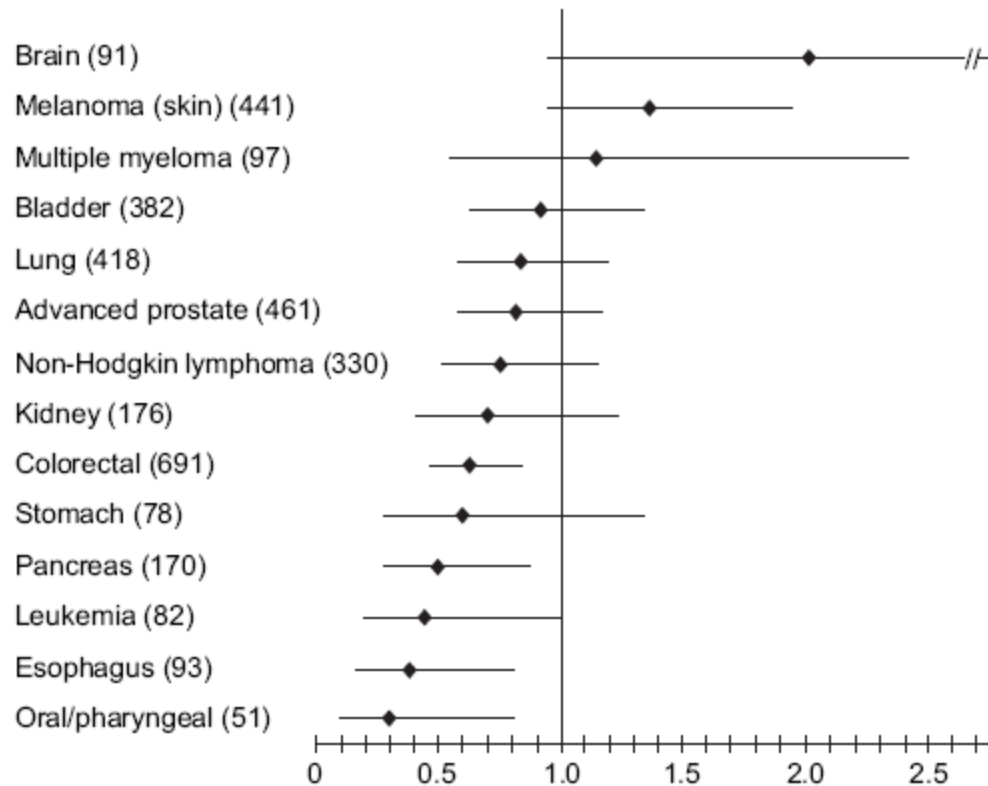


Fig. 1. Multivariable relative risks and 95% confidence intervals for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D level for individual cancers in the Health Professionals Follow-up Study (1986–2000). Number in parentheses = number of cases. Covariables included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

Source: Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst.* 2006;98:451-9.



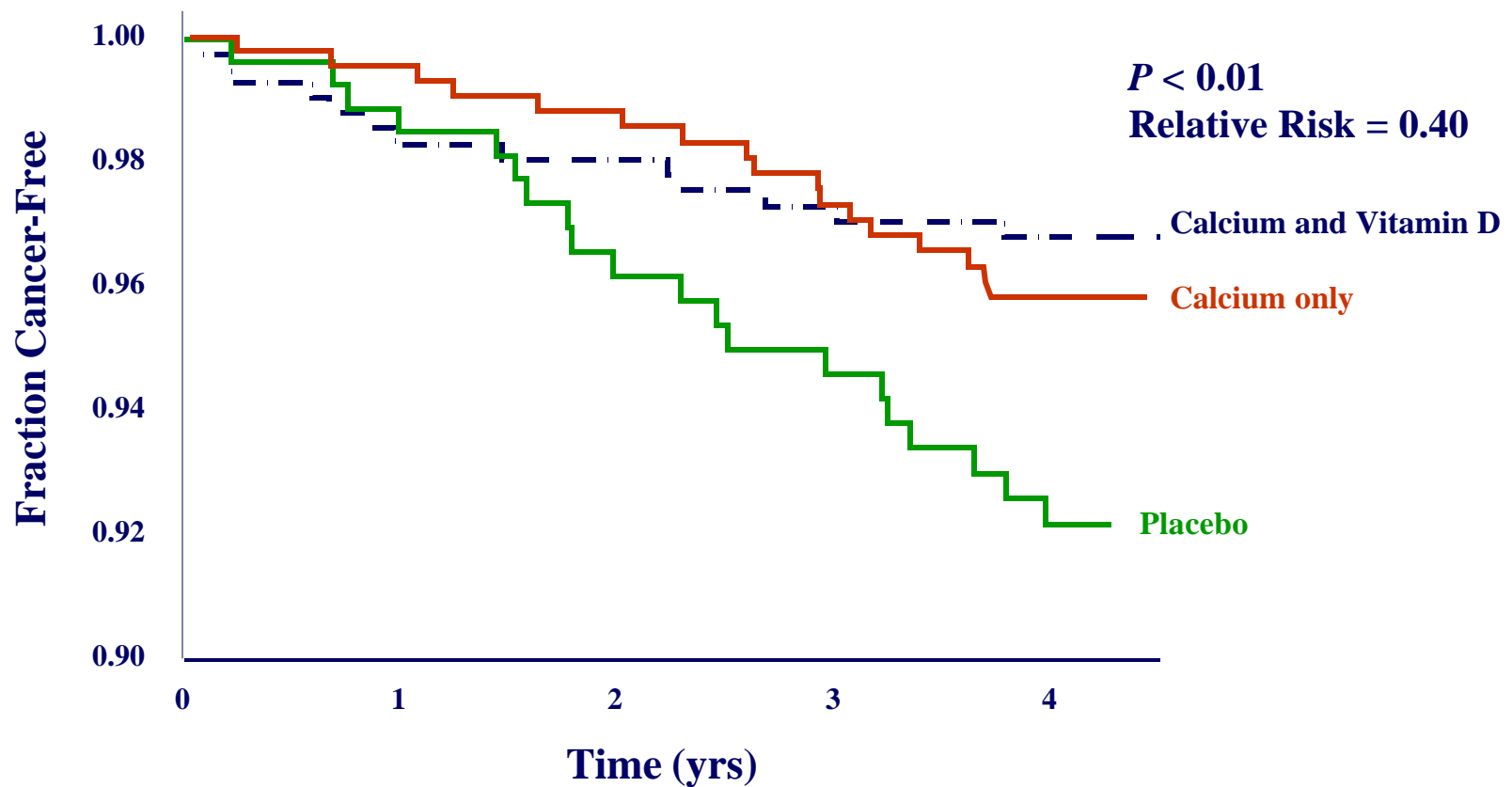
Randomized Controlled Trial of Vitamin D and Calcium

- Four years, N = 1,179 healthy women in Omaha NE
- Mean age 66.7 ± 7.3 years
- N = 1,032 finished trial (87.5%)
- Baseline serum 25(OH)D: 29 ± 8 ng/ml (72 ± 20 nmol/L)
- Three treatment groups:
 - Vitamin D₃ (1,100 IU/day) and calcium (1450 mg/day)
 - Calcium (1,450 mg/day)
 - Placebo
- Outcome: All cancers (mainly breast, lung and colon)

Source: Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr.* 2007;85:1586-91.



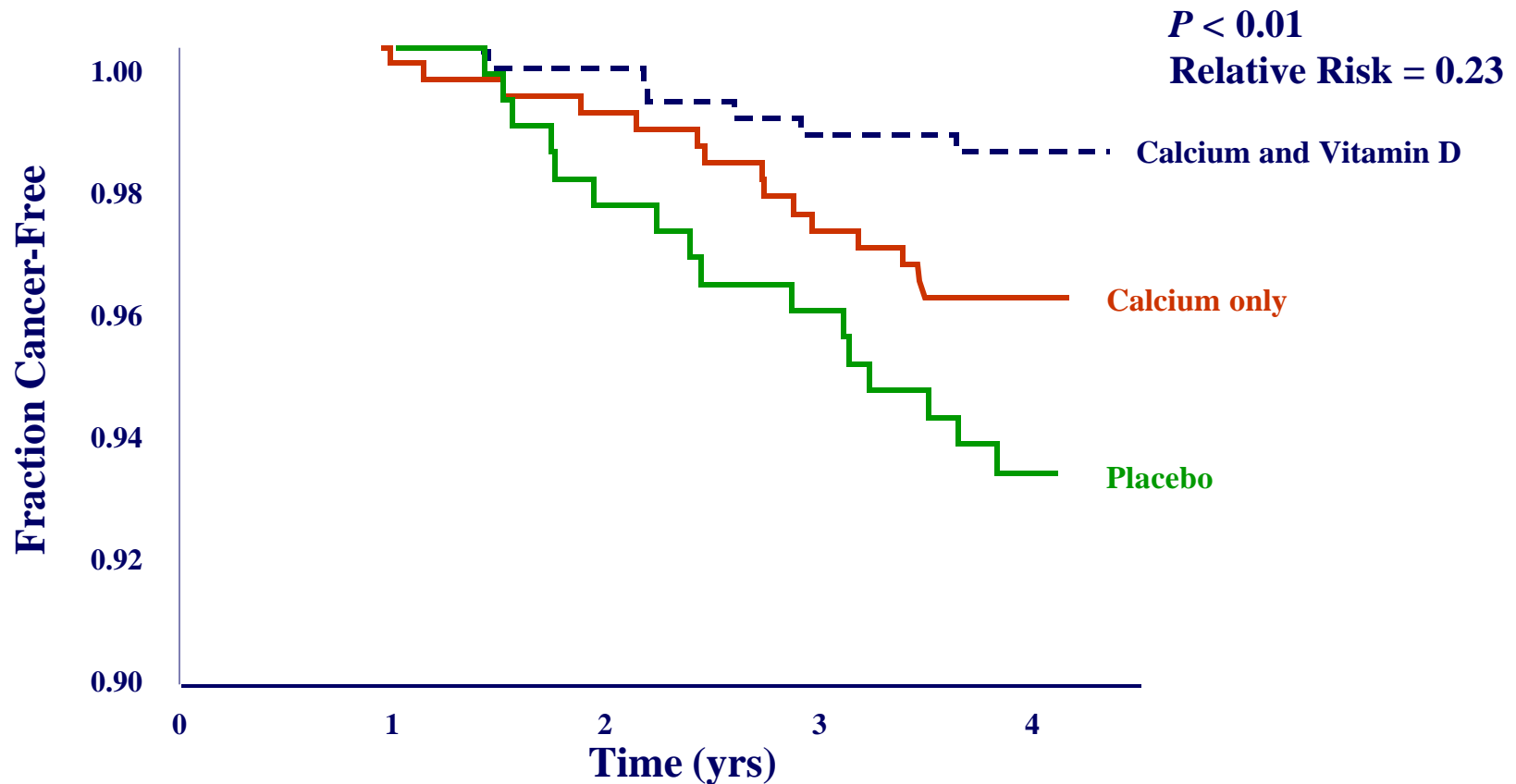
Randomized Controlled Trial



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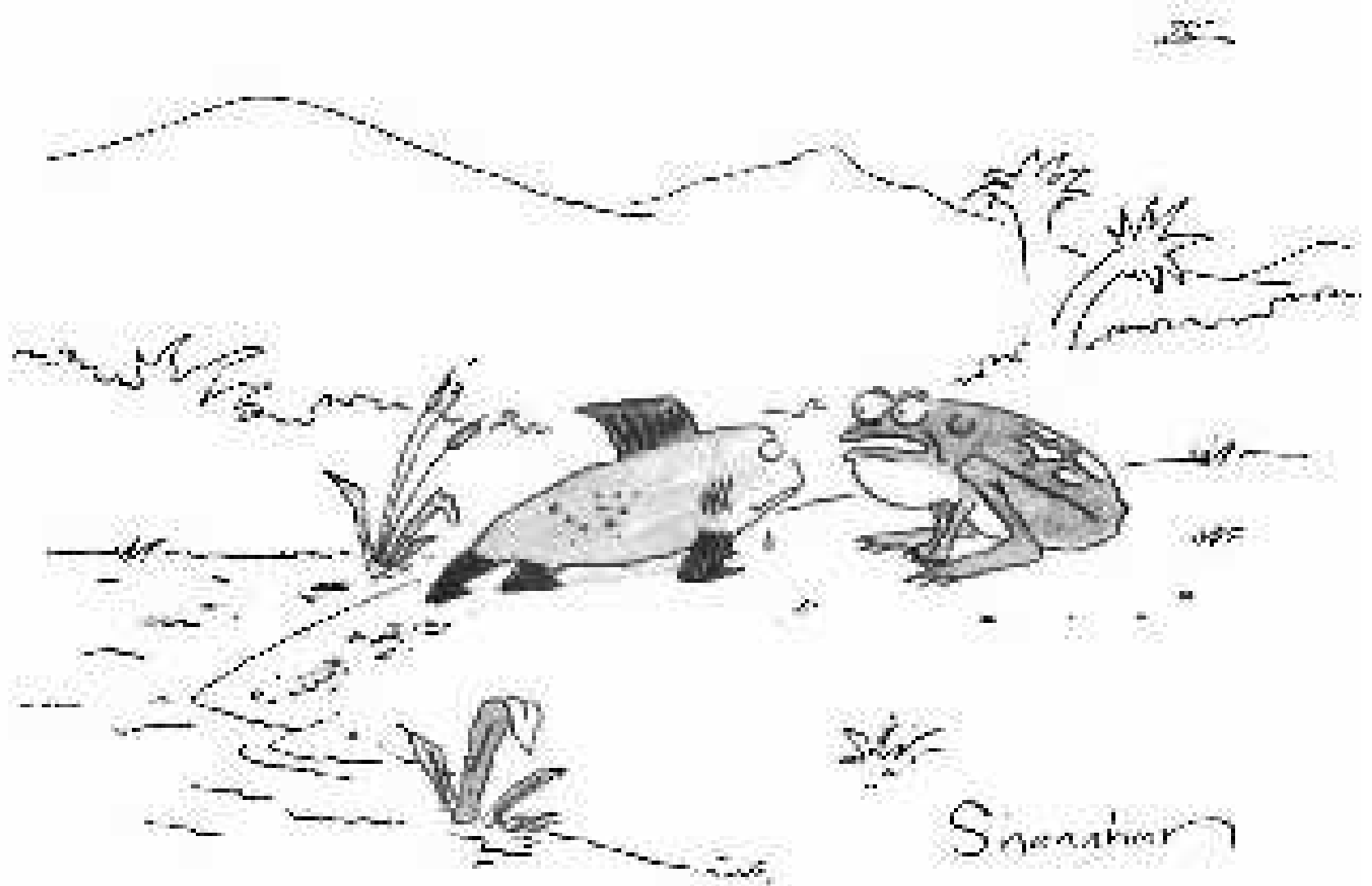


All Except First Year Cases

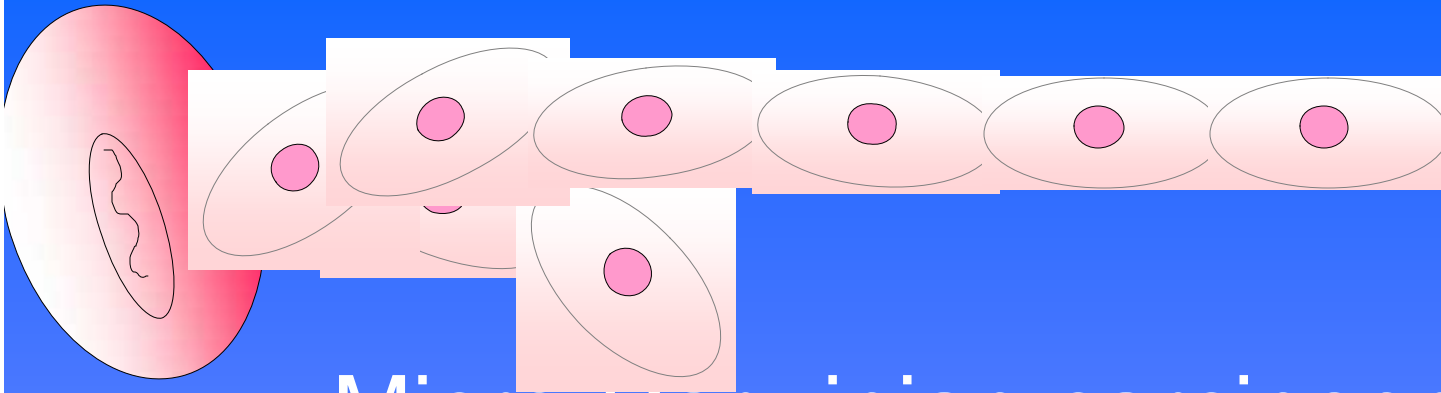


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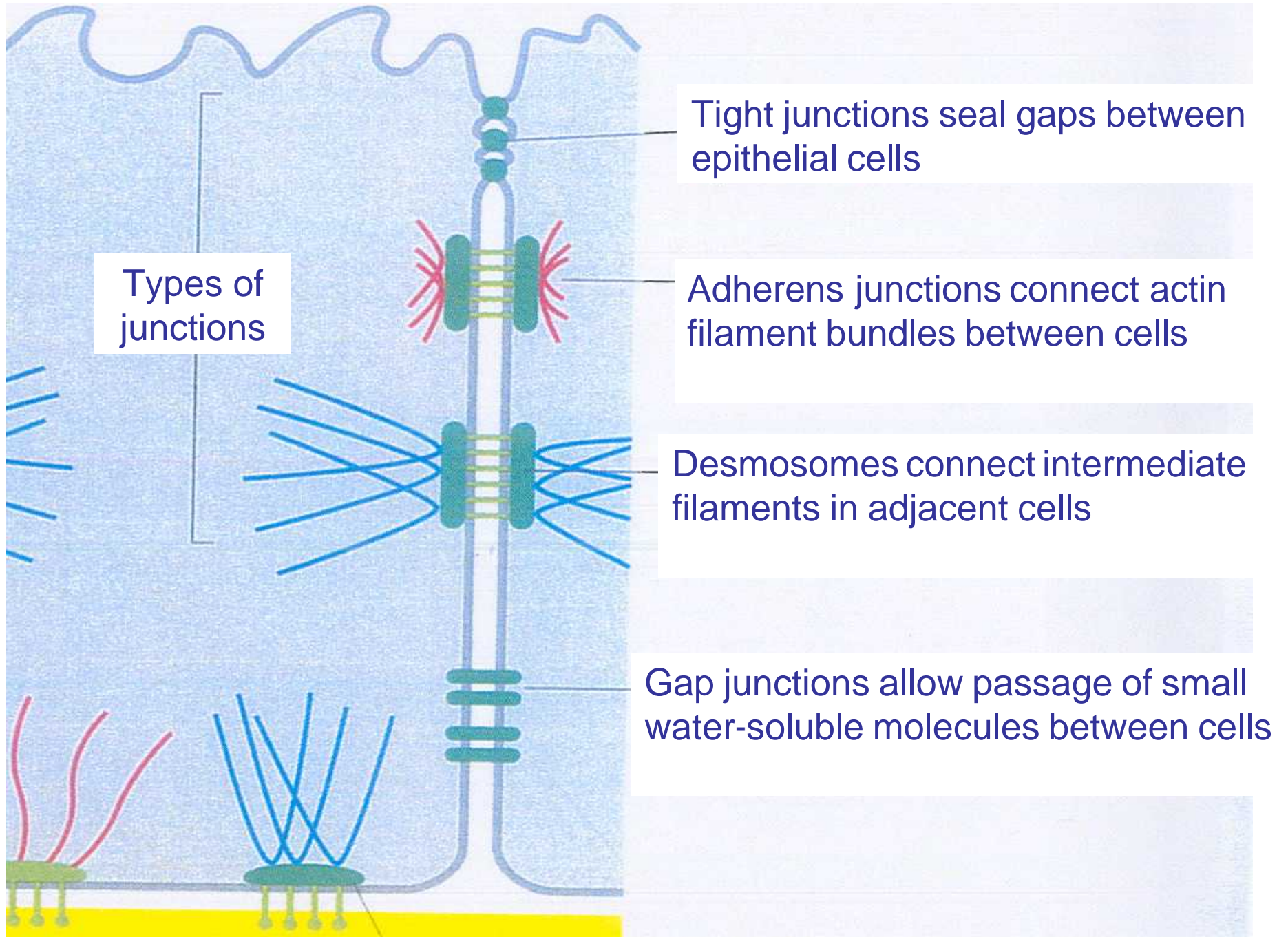


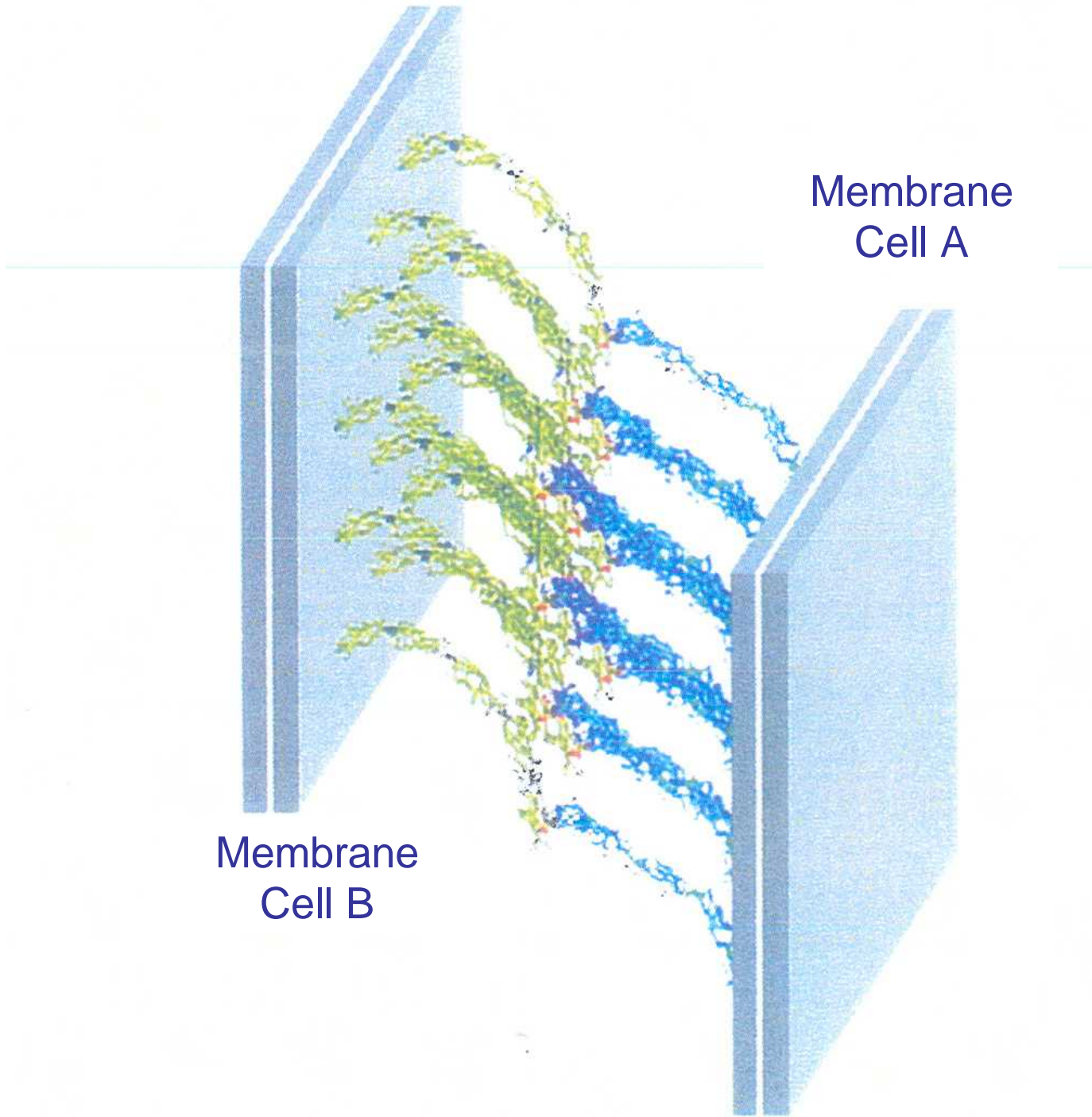
The first thing you need to do is update your CV



Micro-Darwinian carcinogenesis and Vitamin D deficiency induced D-volution

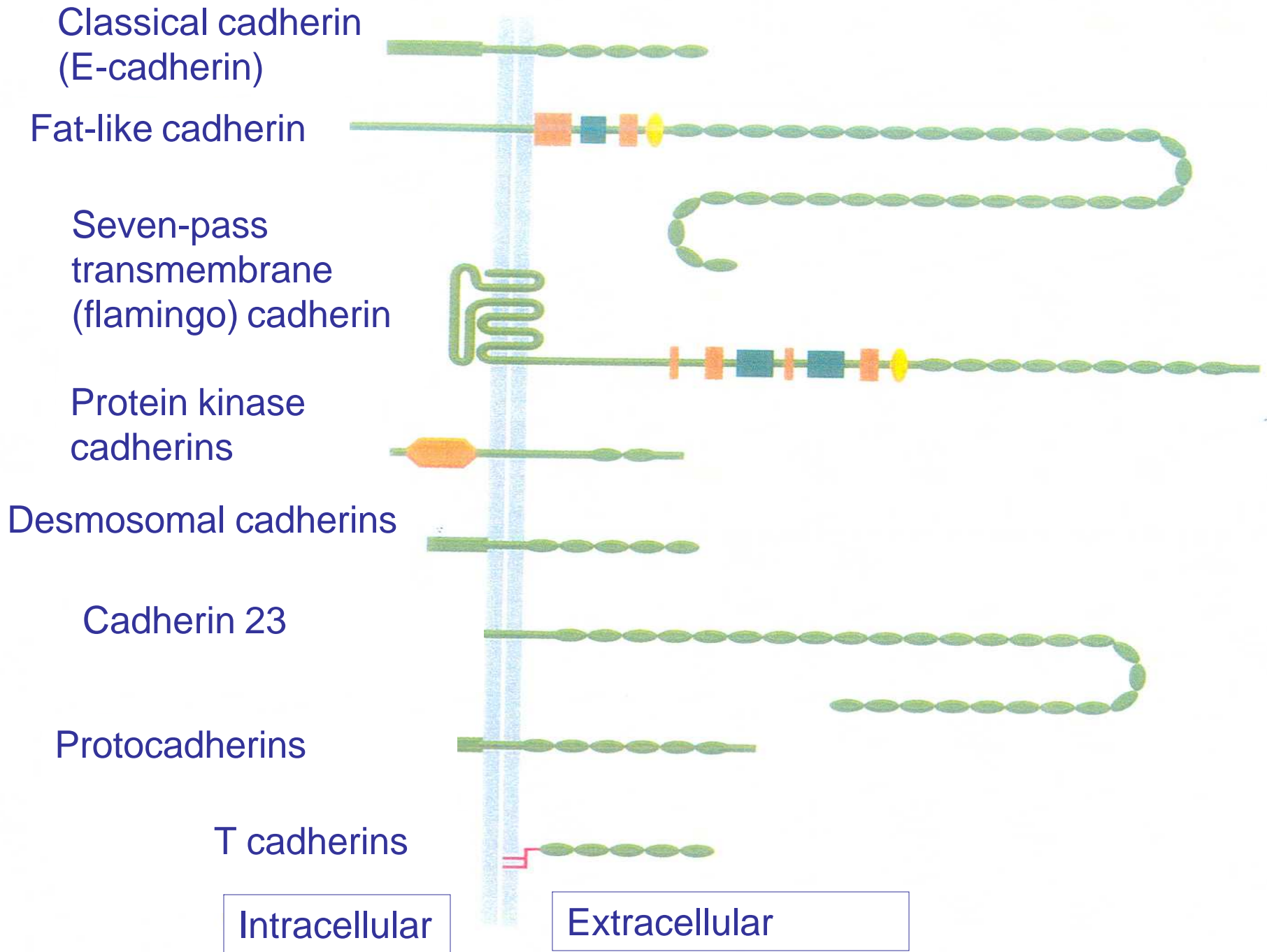
- In vitamin D deficiency, the first lesion is harm to the cellular **membrane**, specifically, the intercellular junction.
- This unleashes **natural selection**.
- **Natural selection is the engine of growth of the cancer**



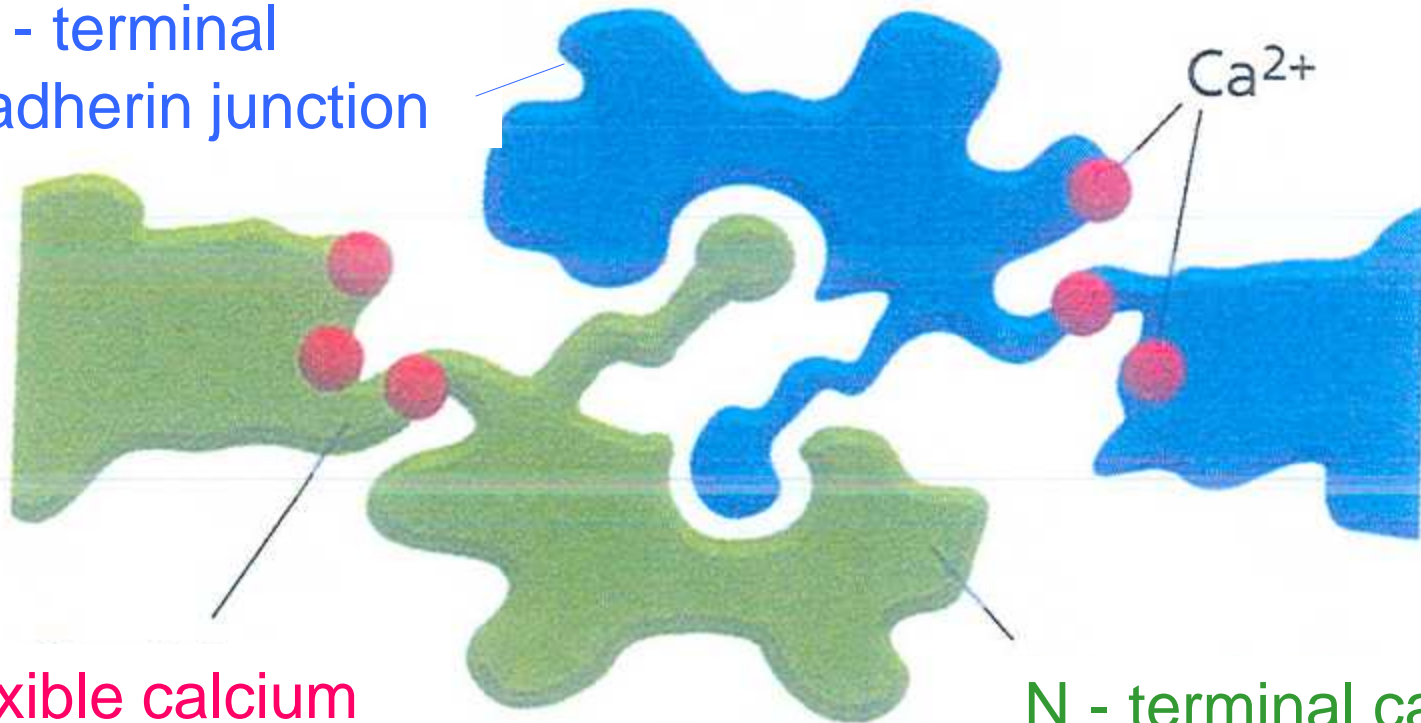


Membrane
Cell A

Membrane
Cell B



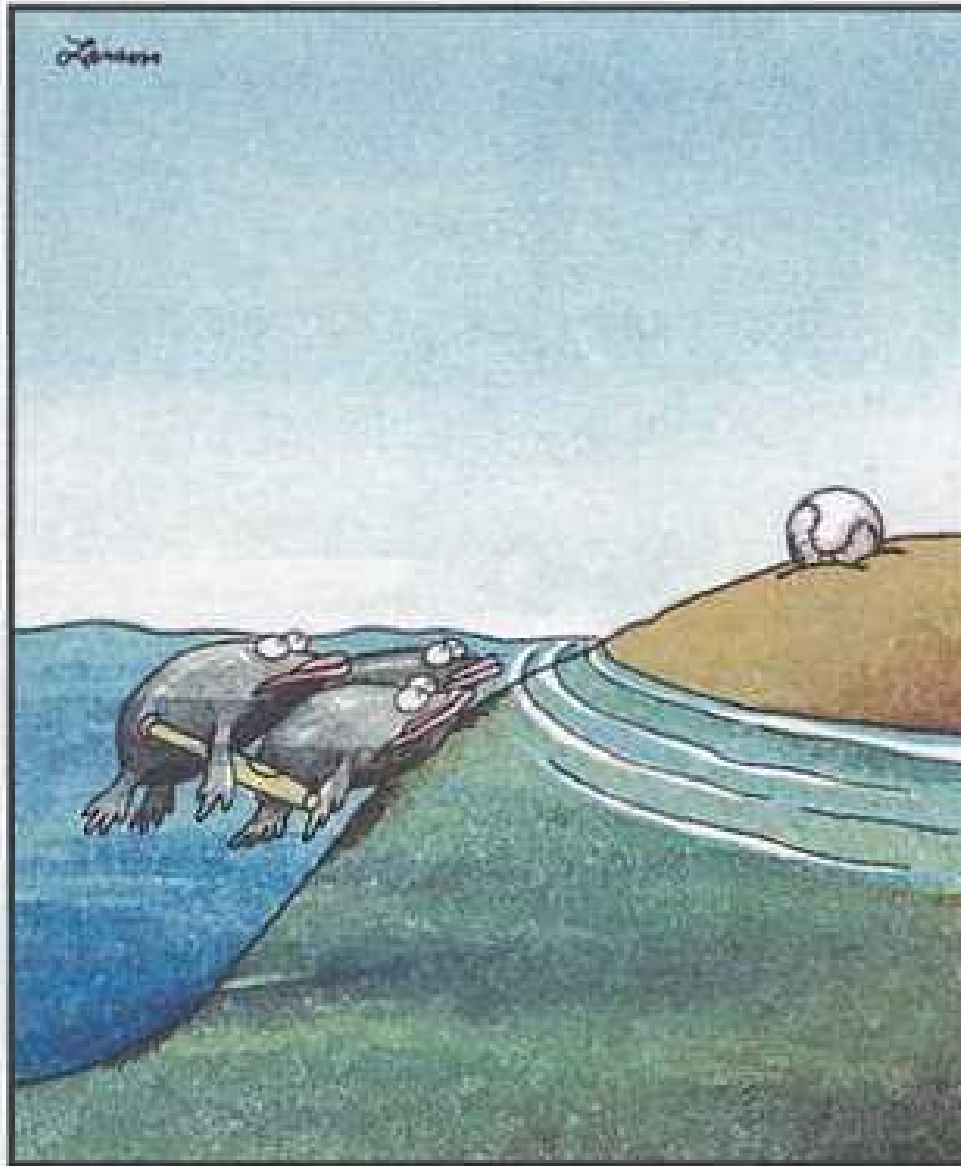
N - terminal
cadherin junction



Flexible calcium
dependent hinges

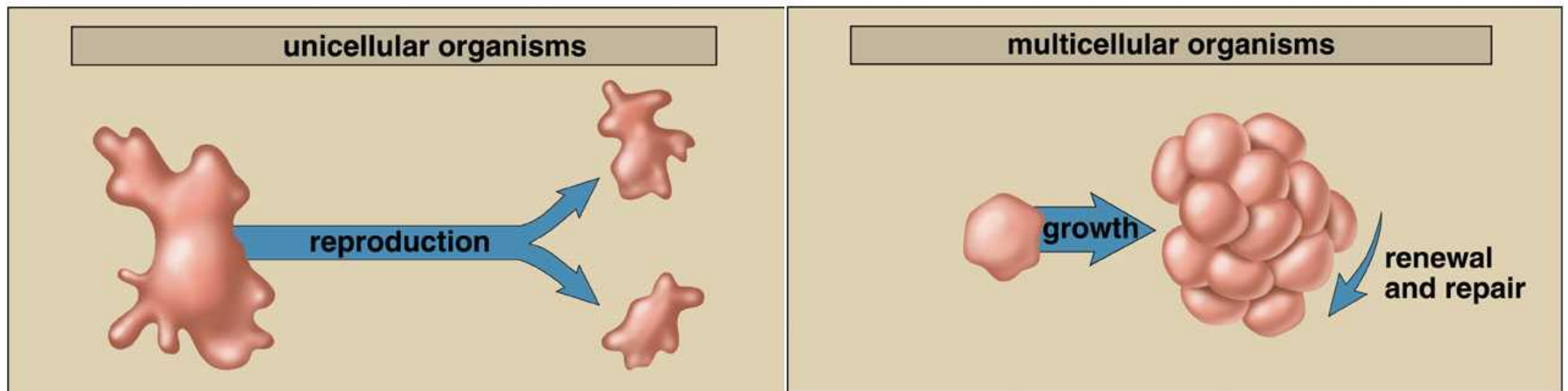
N - terminal cadherin
junction

Coupling between cadherins from two cells



Great moments in evolution

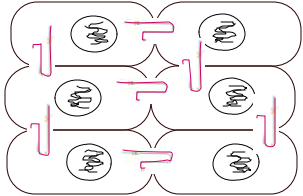
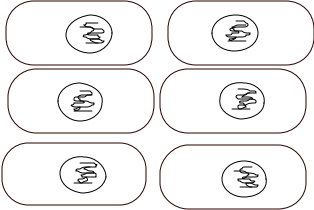
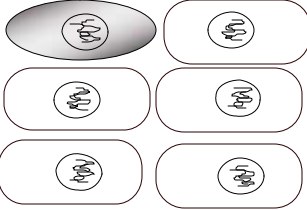
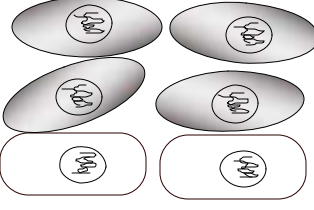
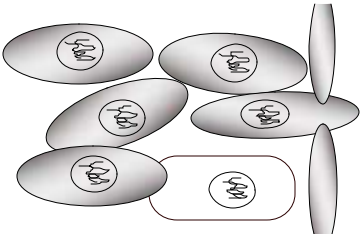
Cell division in unicellular vs. multicellular organisms: role of adherins



No adherins present
(no role of
 $1,25(\text{OH})_2\text{D}$)

Adherins present
($1,25(\text{OH})_2\text{D}$ upregulates)

Vitamin D-volution Theory of Cancer

<u>Phase</u>	<u>Diagram</u>	<u>Process</u>	<u>Preventive or therapeutic Action</u>
Vitamin D Replete (Normal)		Tight junctions intact Intercellular communication, growth inhibition and cell cycle normal non-mitotic	Maintain 25(OH) D level of 40-60 ng/ml
1. Vitamin D Insufficiency Disjunction		Cells separate slightly. Tight junctions and cadherins are downregulated, intercellular communication is reduced, contact inhibition is lost.	Upregulation of tight junctions and cadherins by vitamin D metabolites
2. Natural Selection		Natural selection favors reproduction of fastest dividing, most aggressive cells. These appear as new stem cells (Wicha et al., 2008)	Vitamin D maintains tight junctions, contact inhibition, and normal growth and cell cycle
3. Clonal Expansion		Rapidly dividing, most aggressive progeny predominate, a 1% advantage will fill compartment in 9000 generations	Vitamin D favors apoptosis and normal cell cycle
4. Lysis and Penetration of Basement Membrane		Most aggressive cells compete for nutrients and blood supply, penetrate membrane	Vitamin D inhibits lysis of basement membrane, Promotes sharing of micronutrients; Maintains intercellular junctions and desmosomes

Vitamin D-volution Theory of Cancer

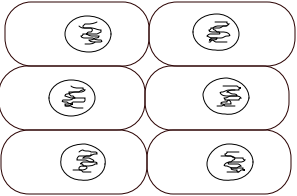
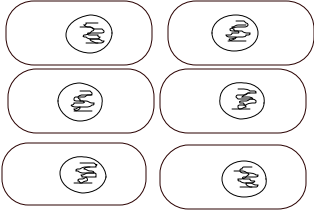
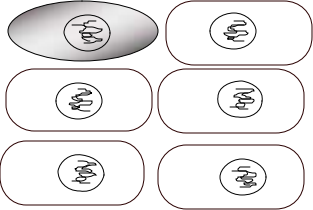
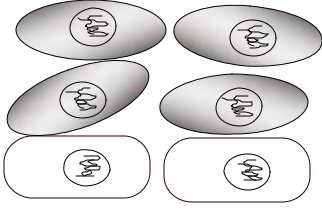
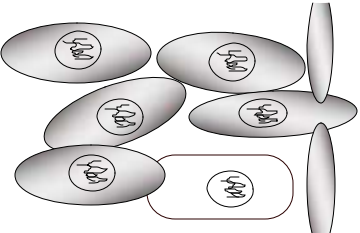
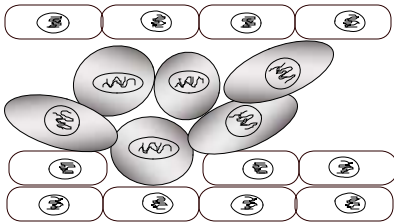
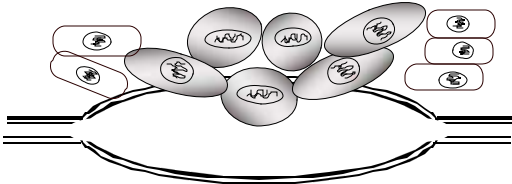
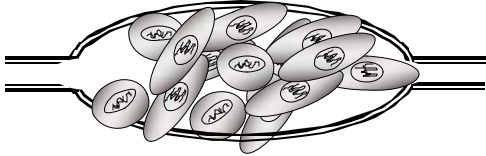
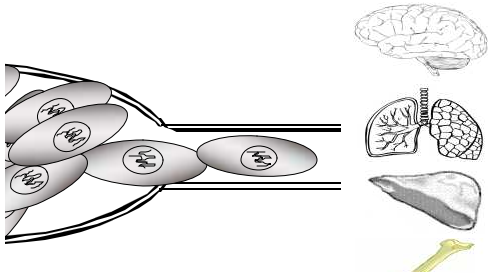
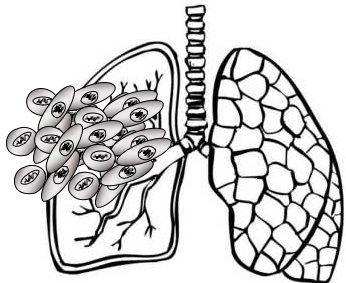
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Figure Vitamin D-evolution Theory of Cancer

<u>Phase</u>	<u>Diagram</u>	<u>Description</u>	<u>Prevention or Therapeutic Action</u>
5. Stromal Phase	 A diagram showing a layer of normal epithelial cells at the top and bottom. In the middle, several cancer cells (represented as larger, more rounded cells with internal structures) are shown invading the space between the normal layers, representing the stroma.	Invasion of Stroma	Re-establish tight junctions between cancer cells
6. Lymphatic Entry Phase	 A diagram showing a lymphatic vessel (represented by two parallel lines) with a gap. Cancer cells are shown entering the vessel through this gap.	Lymph vessel invasion	Re-establish tight junctions Prevent lymphatic entry
7. Lymphatic Growth Phase	 A diagram showing a lymphatic vessel filled with cancer cells, representing colonization and growth within the vessel.	Lymph node colonization	Re-establish tight junctions Confine malignancy to lymph nodes
8. Lymphatic Transport Phase	 A diagram showing cancer cells being transported from a lymphatic vessel to various organs: a brain, a lung, a liver, and a bone.	Lymphatic transport to brain, lung, liver, bone	None
9. Metastasis (colonization) Phase	 A diagram showing a lung with a cluster of cancer cells growing in one of the lobes, representing metastasis to a remote host site.	Malignant cells colonize remote host site	If VDR still present, re- establish tight junctions, downregulate VEGF, reduce growth rate, restore contact inhibition



You raised it from a mutant seed, you whack it!

Gene-fold changes in a human colon cancer cell line (SW480-ADH)
after 48 hours exposure to 1,25(OH)₂ vitamin D₃ (10⁻⁷ M)

Cytoskeleton/adhesion

+ 39	Type II keratin (hHKb1)
+ 14	Gravin
+ 12	E-cadherin
+ 7	Keratin 15
- 4	Calgizzarin

GTPases and related

+ 42	RAB2
+ 21	RA1BP1-interacting protein
+ 4	Breast cancer anti-estrogen resistance protein (BCAR3)

Channels and transporters

+30	Putative monocarboxylate transporter (MCT)
+15	3- <i>beta</i> -hydroxysteriod dehydrogenase (3- <i>beta</i> -HSD)

Apoptosis related

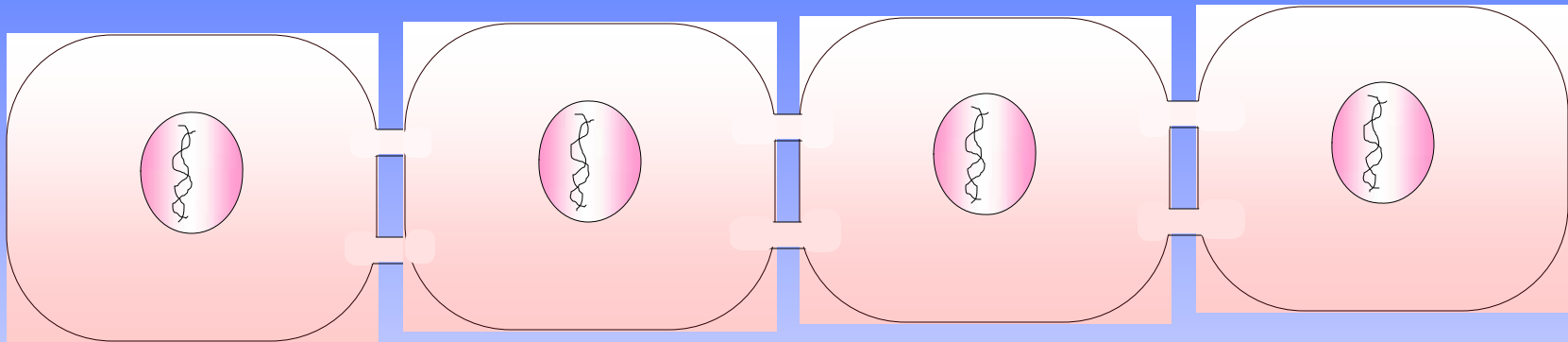
+24	Insulin-like growth factor binding protein-3 (IGFBP-3)
+11	DAP-1 <i>alpha</i>
+10	TNF- <i>alpha</i> converting enzyme
+7	gadd45
+6	Ceramide glucosyltransferase
+6	Prostate apoptosis response protein (par-4)
-5	CD27BP (Siva)
+74	17- <i>beta</i> - hydroxysteroid dehydrogenase (17-HSD)
+20	Cytochrome P450 III A

DNA cell cycle

+ 24	G ₀ S ₂
- 4	Cyclin F

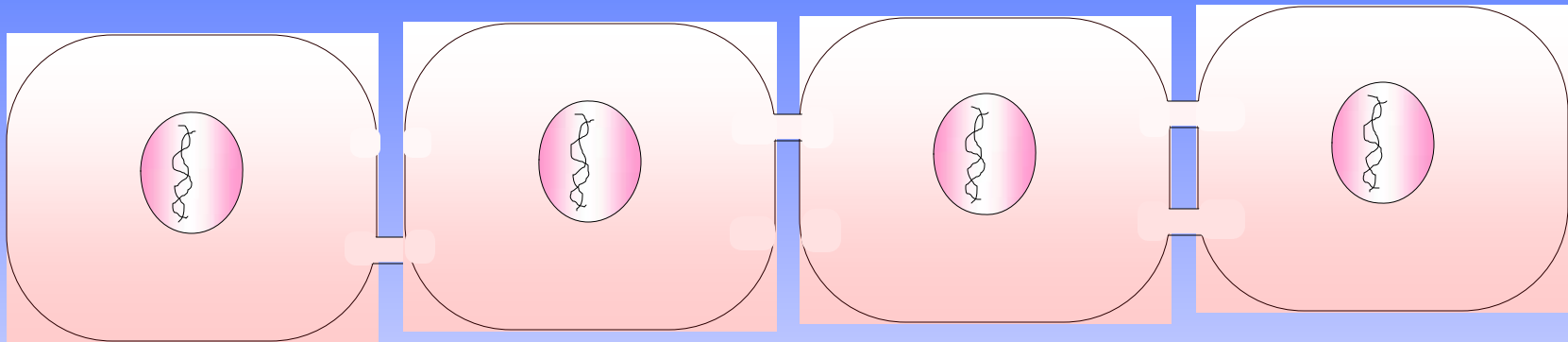
Source: Data from Palmer HG, et al. *Cancer Research* 2003;63:7799-7806.

D-evolution step 1



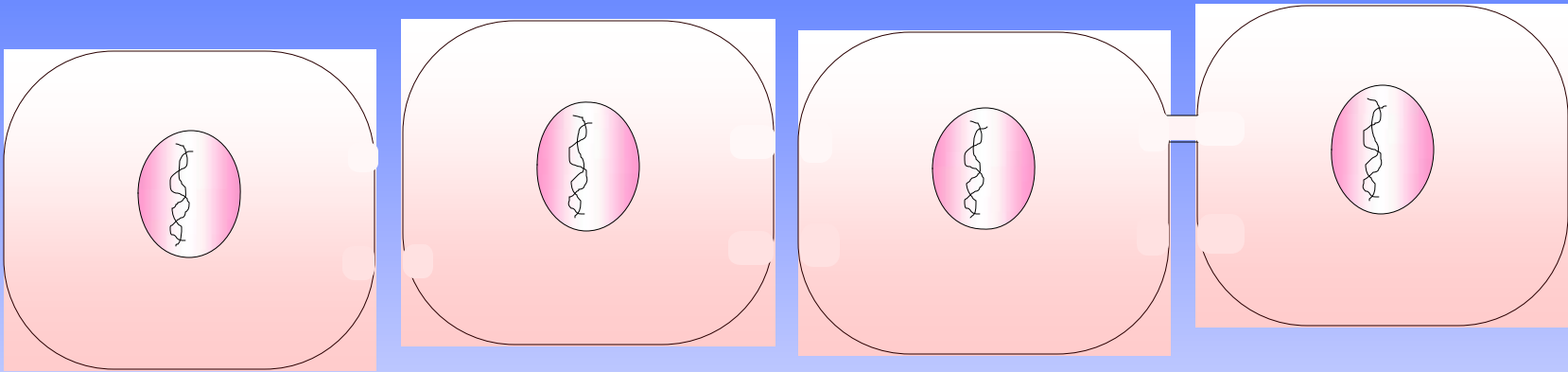
De-coupling

D-evolution step 1



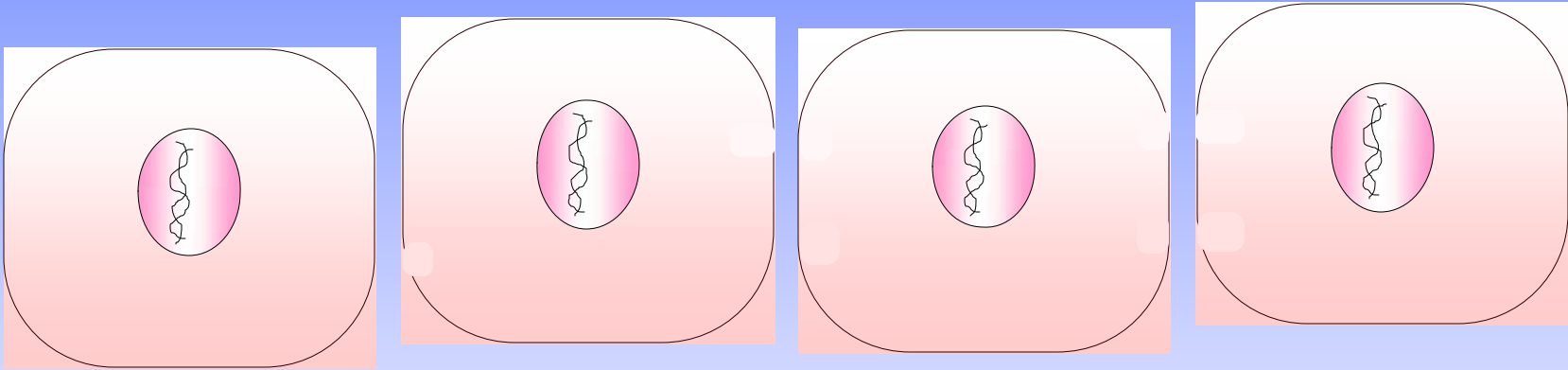
De-coupling

D-evolution step 1



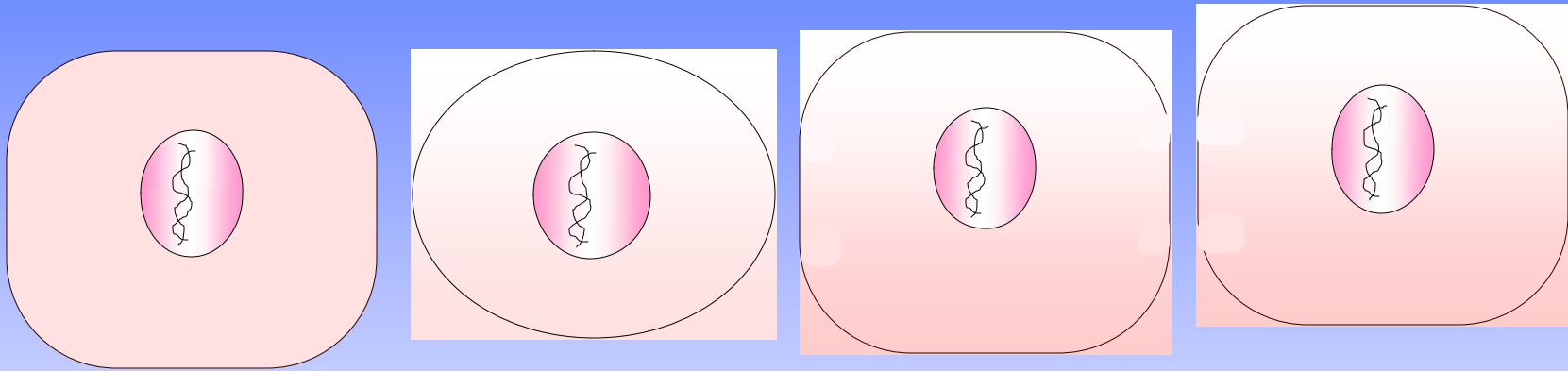
De-coupling

D-evolution step 1



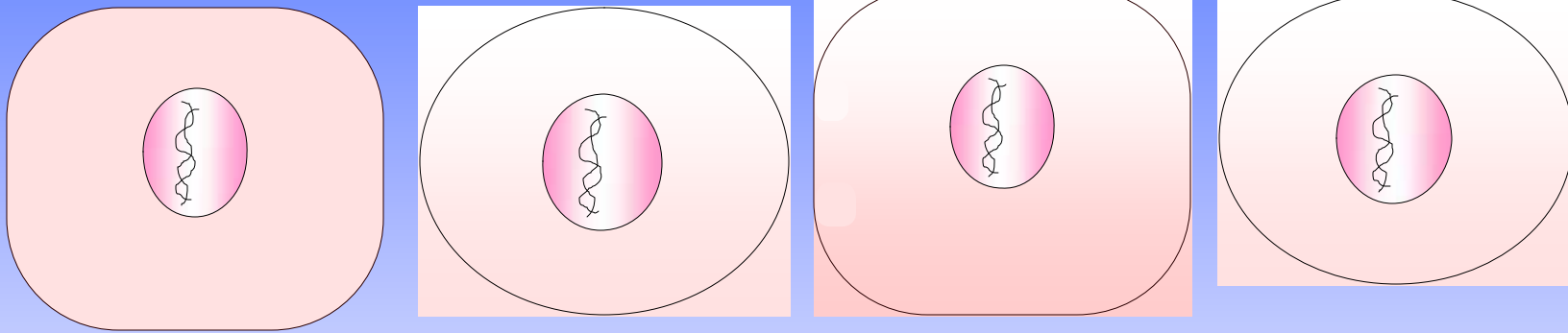
De-coupling

D-evolution step 1



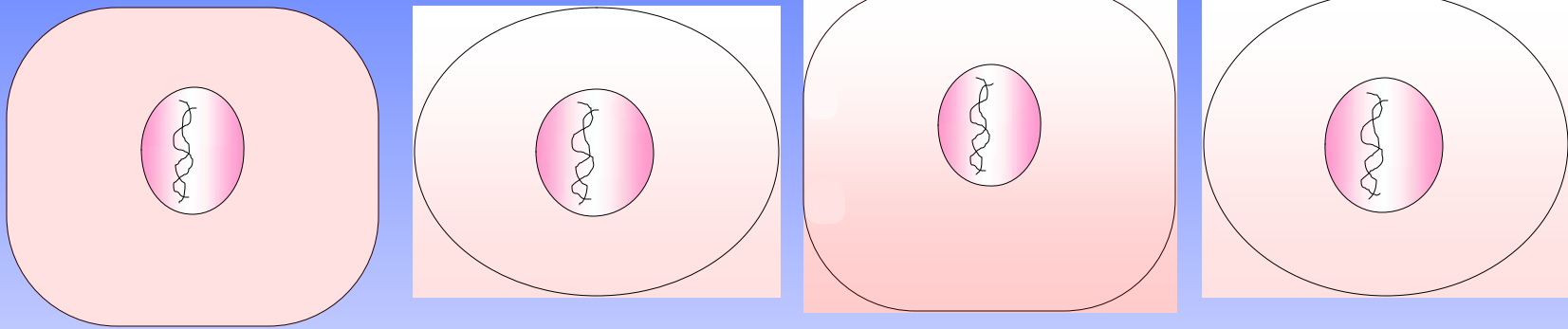
De-coupling

D-evolution step 1



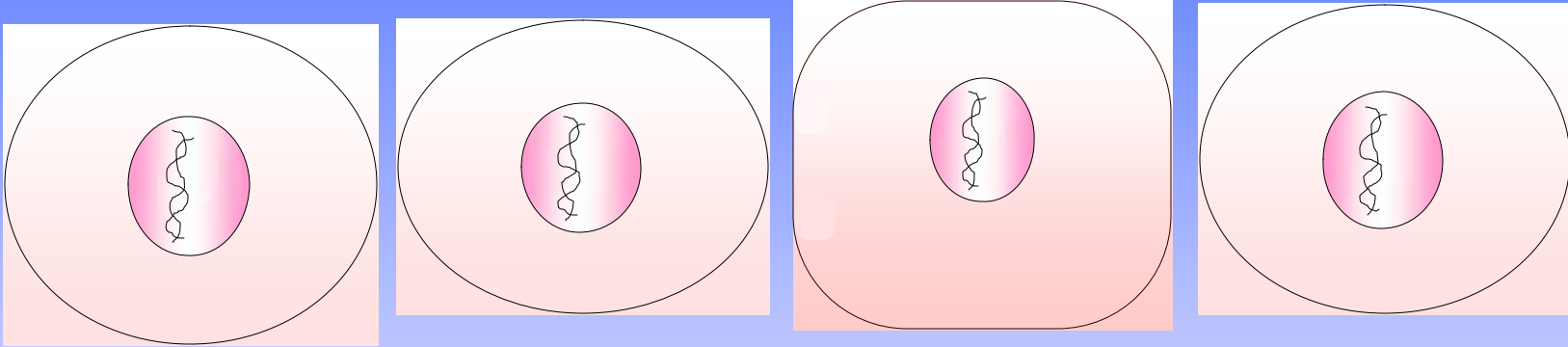
De-coupling

D-evolution step 1



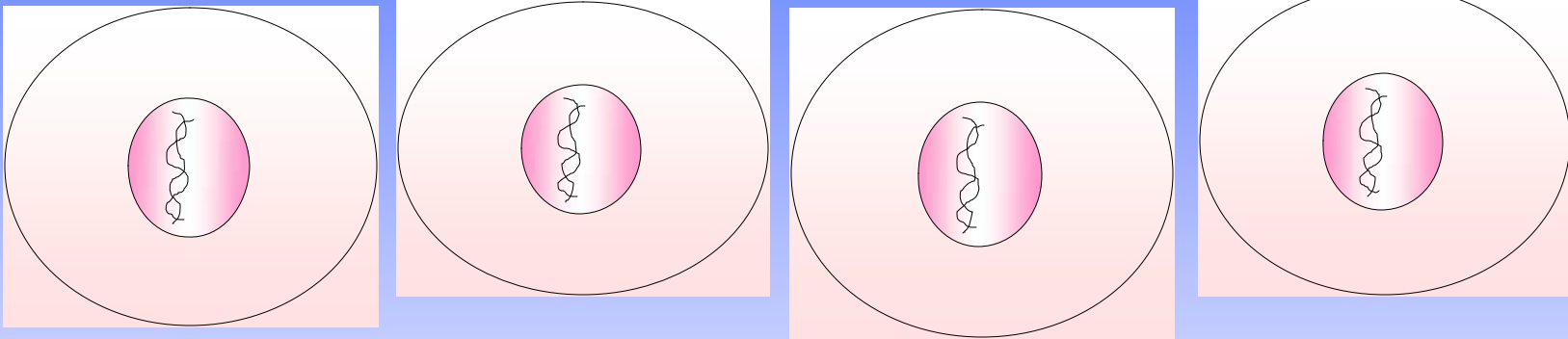
De-coupling

D-evolution step 1



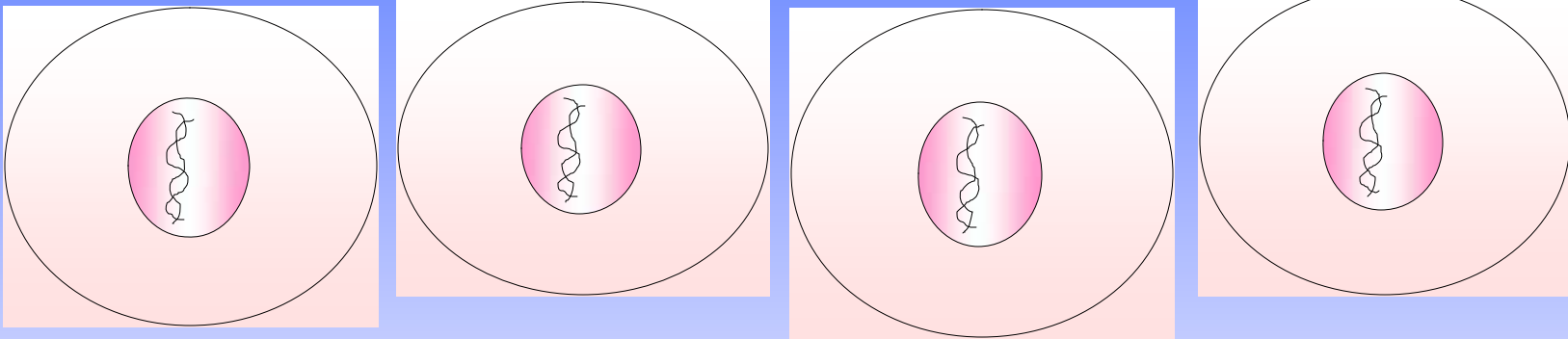
De-coupling

D-evolution step 1



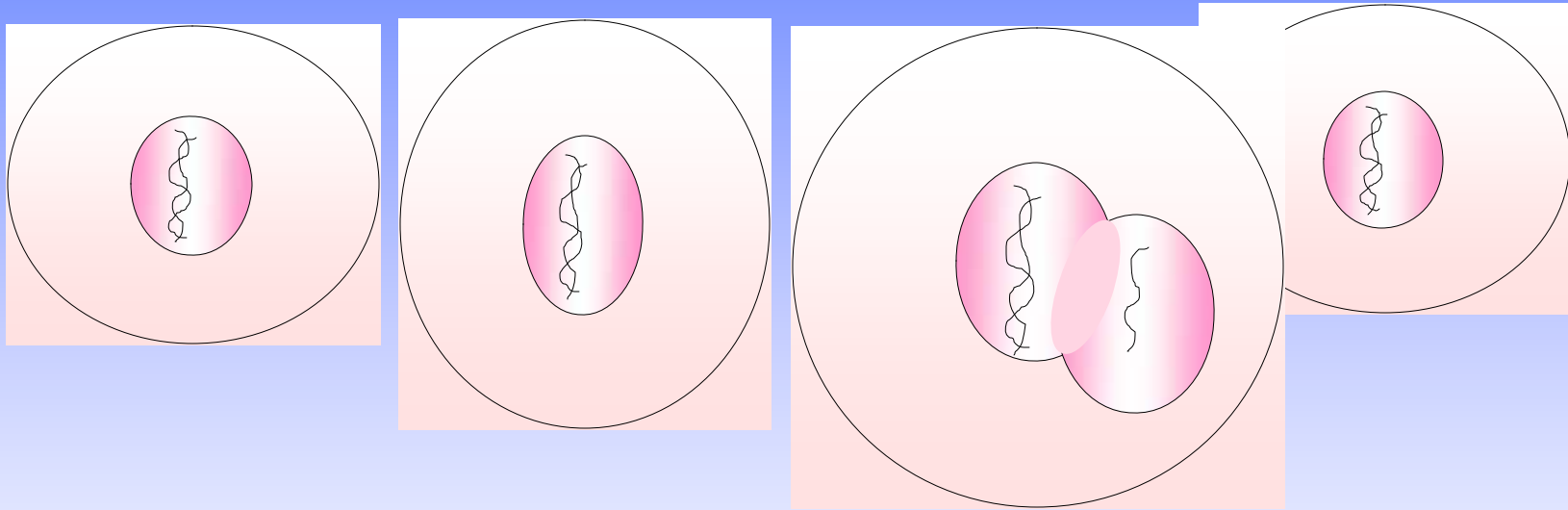
De-coupling

D-evolution step 1



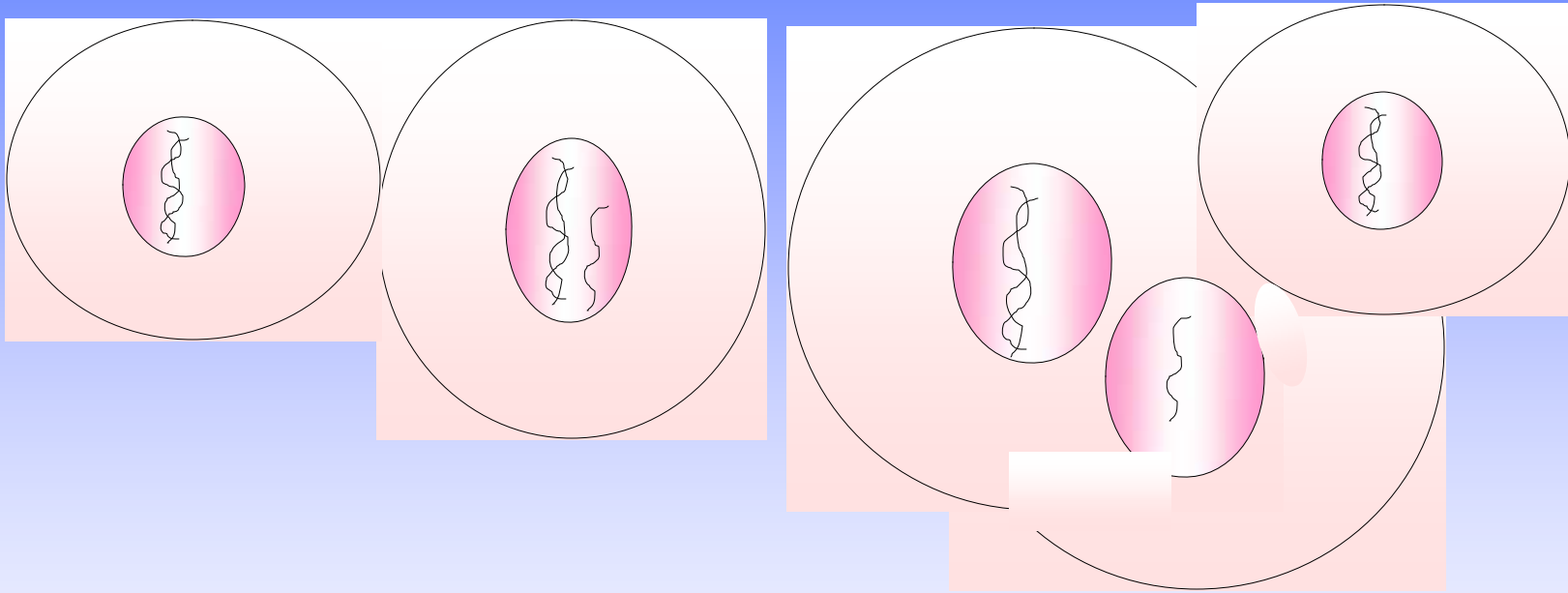
De-coupling

D-volution step 2



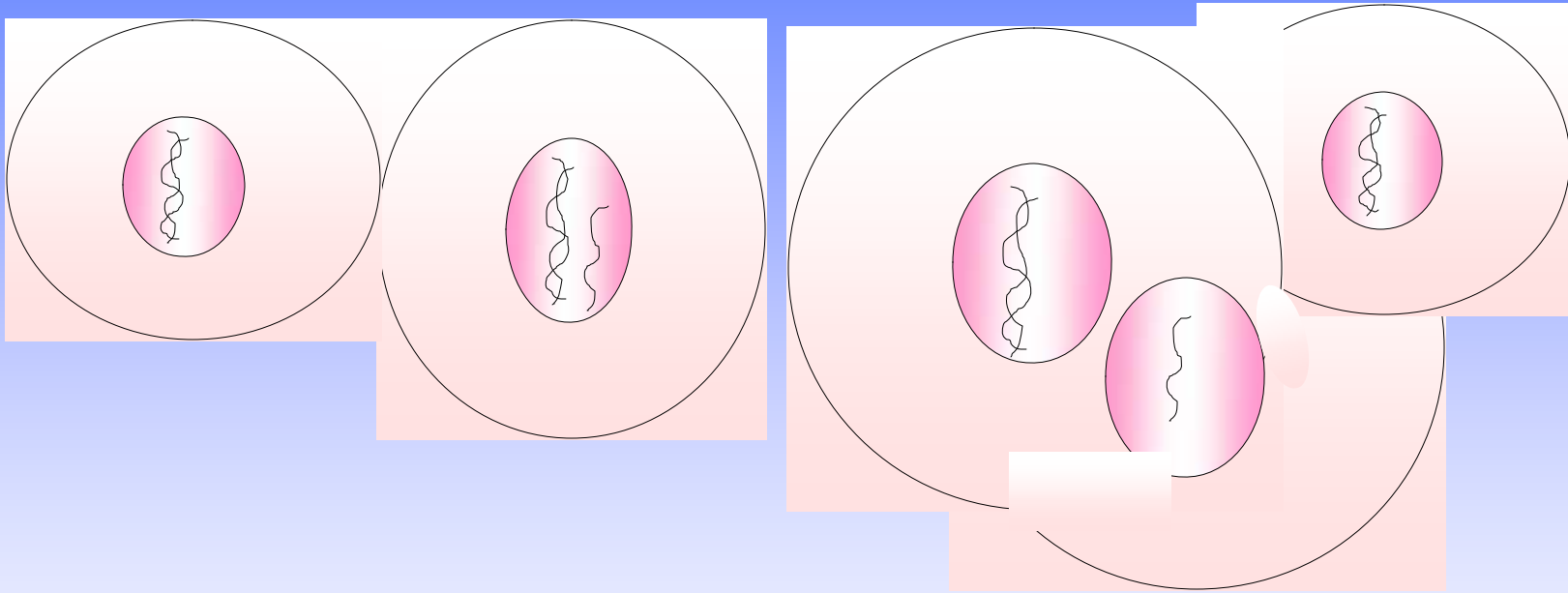
Aberrant Behavior

D-volution step 2



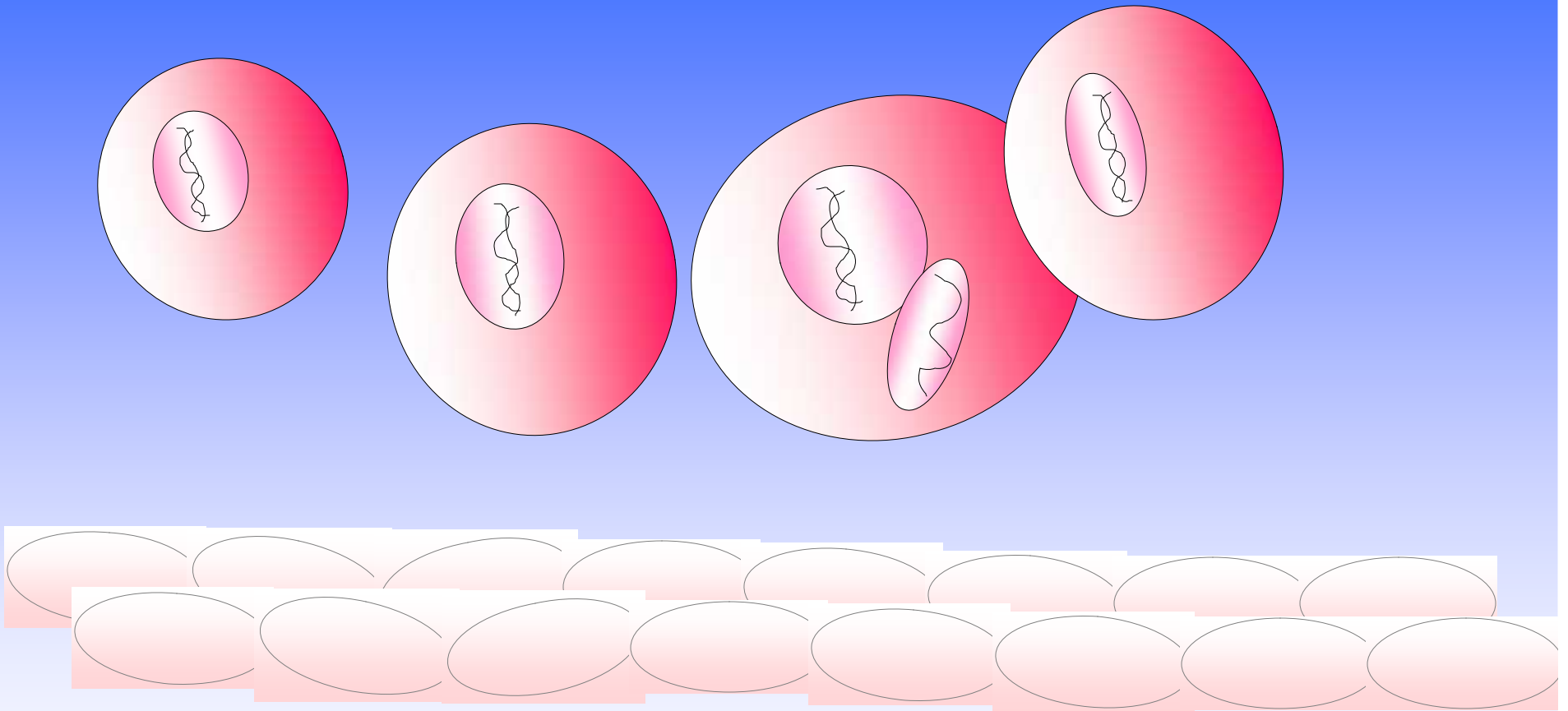
Aberrant Behavior

D-volution step 2



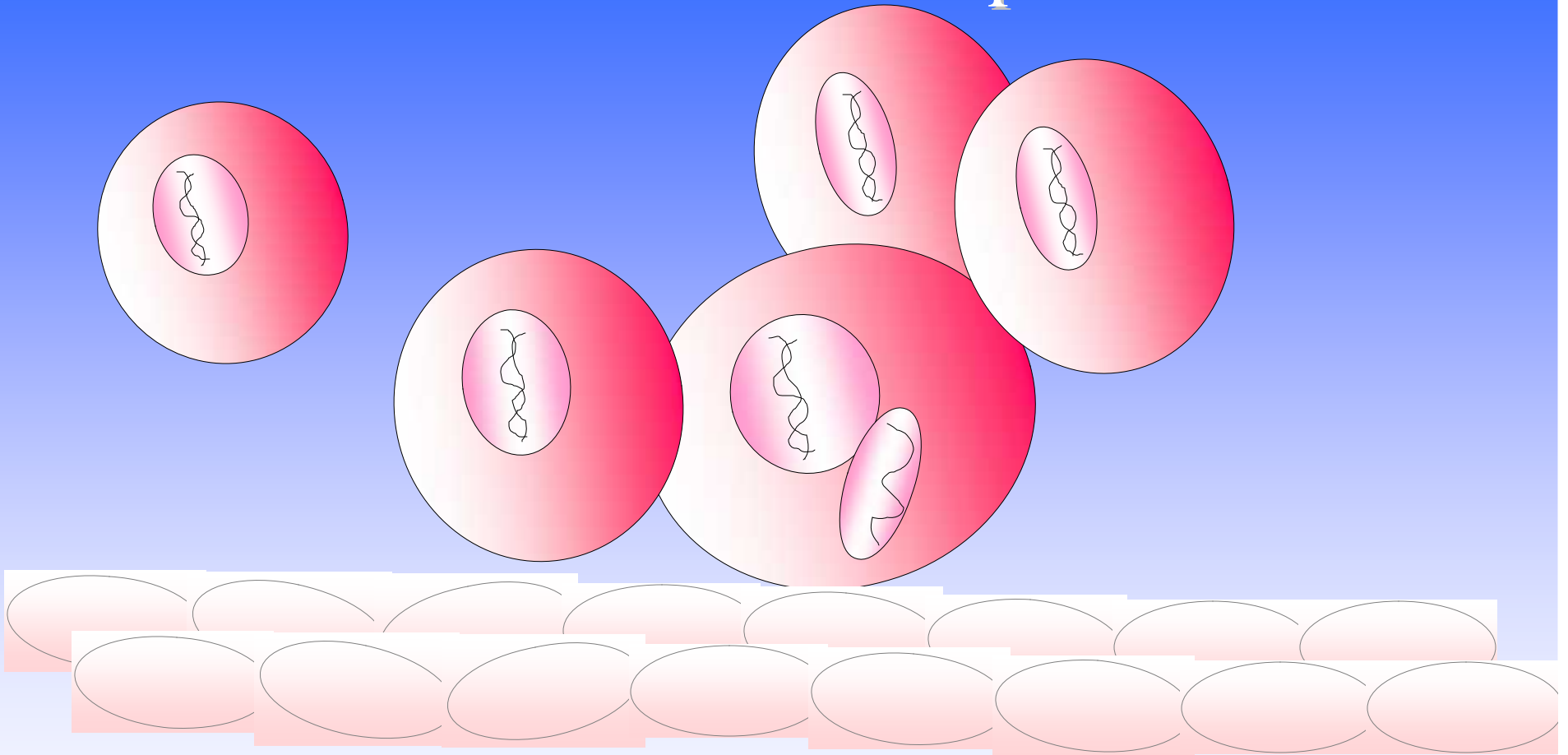
Aberrant Behavior

D-evolution step 3



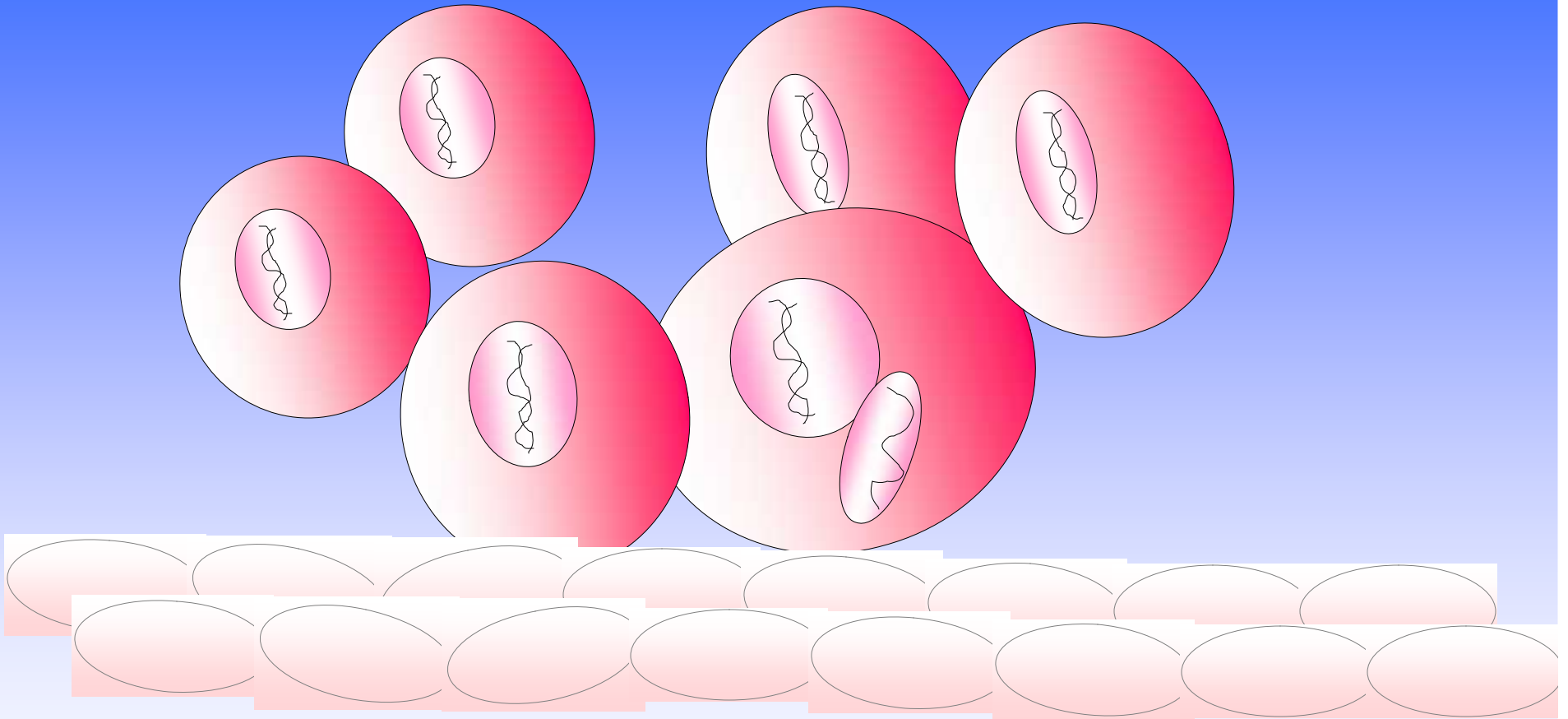
Penetration of the basement membrane

D-volution step 3



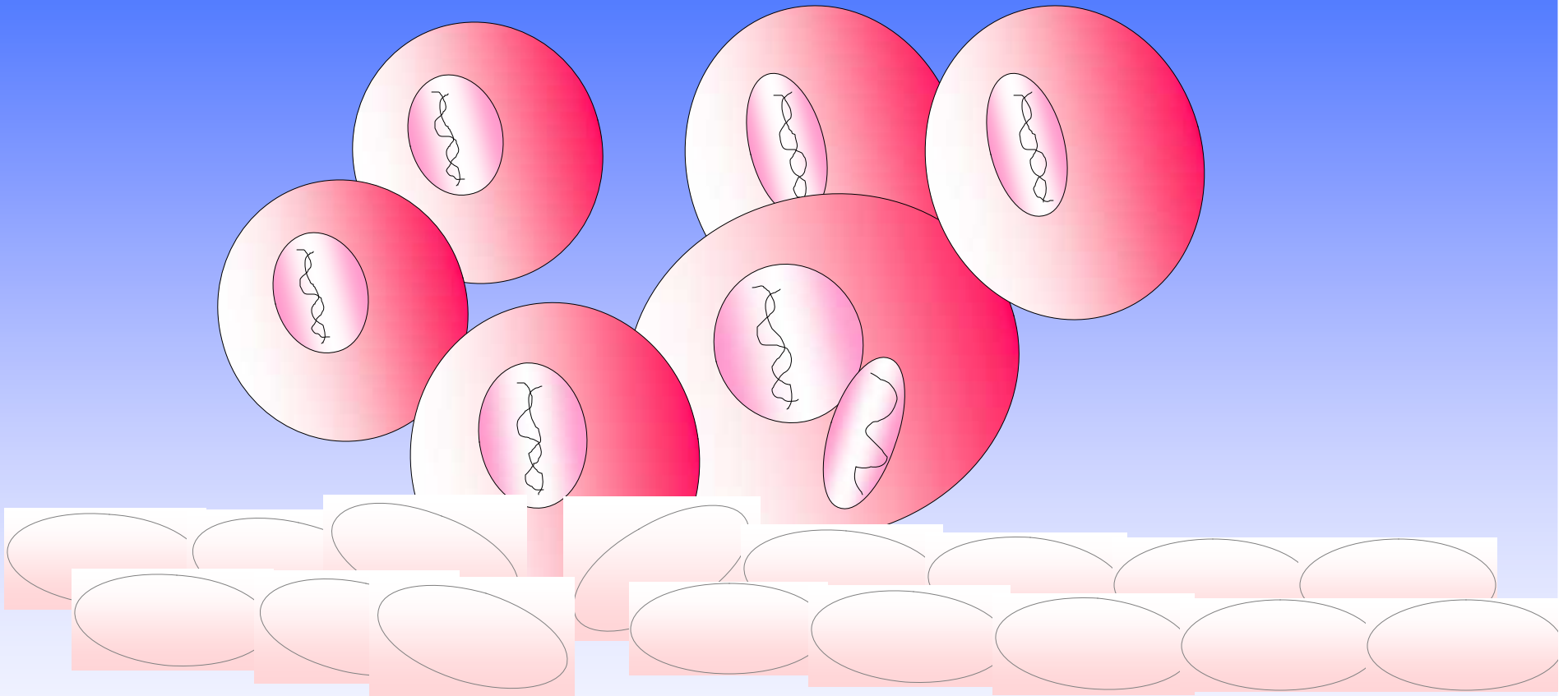
Penetration of the basement membrane

D-evolution step 3



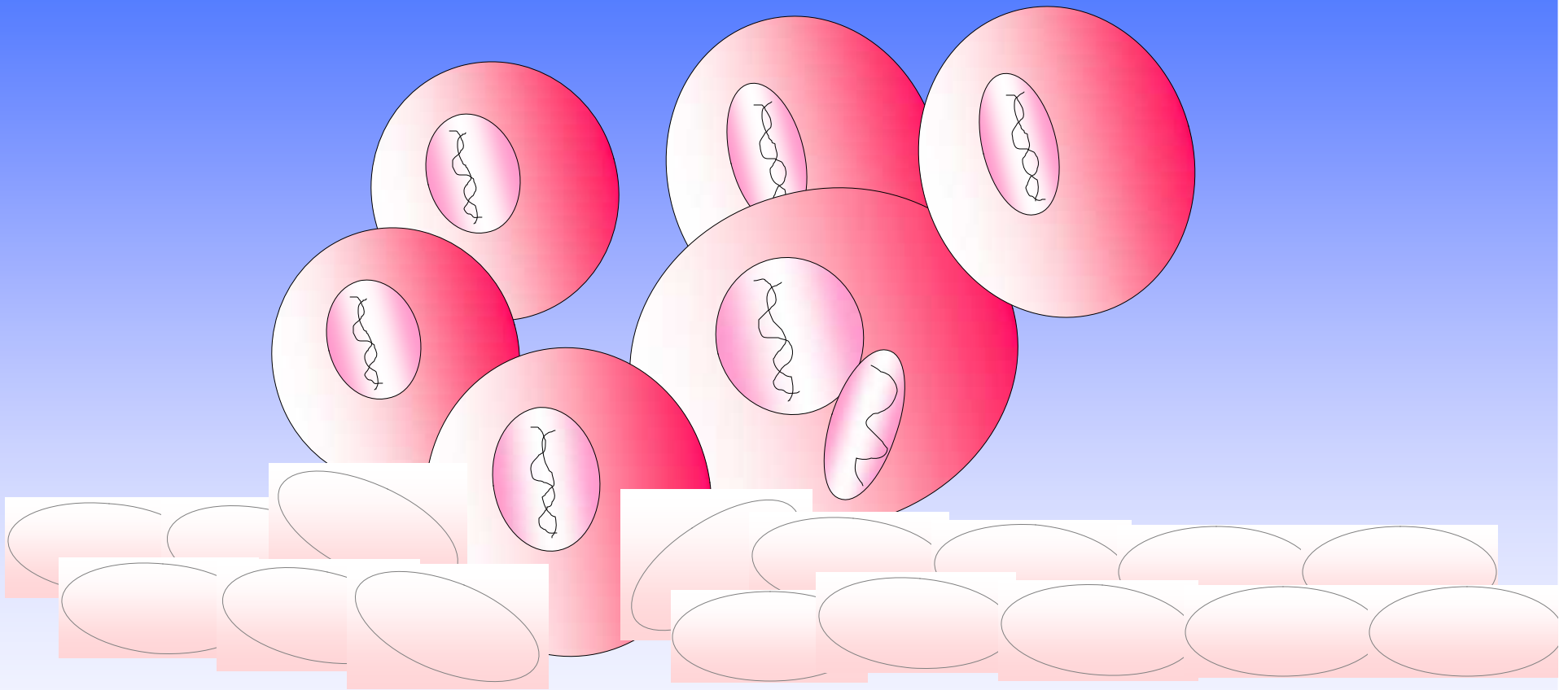
Penetration of the basement membrane

D-evolution step 3



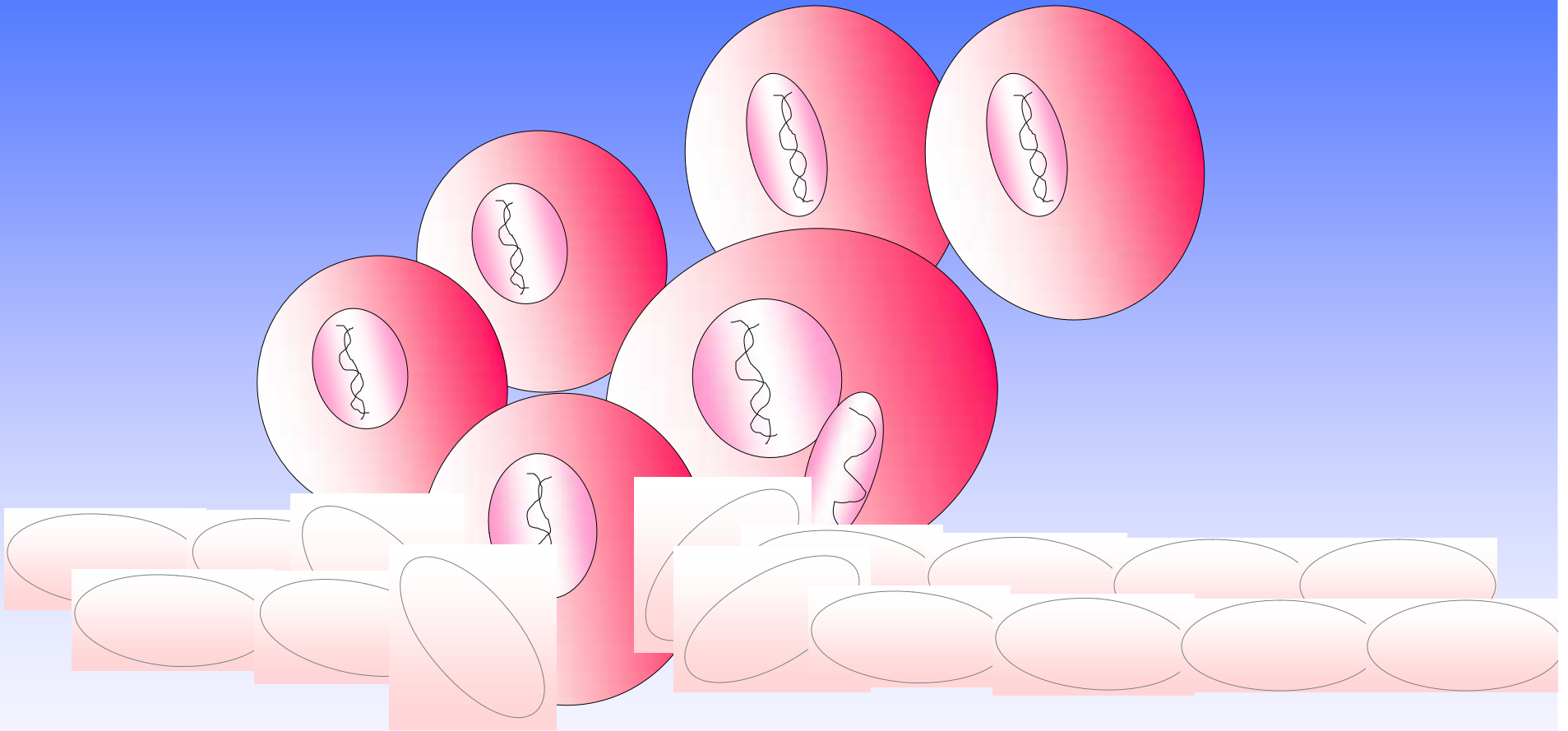
Penetration of the basement membrane

D-evolution step 3



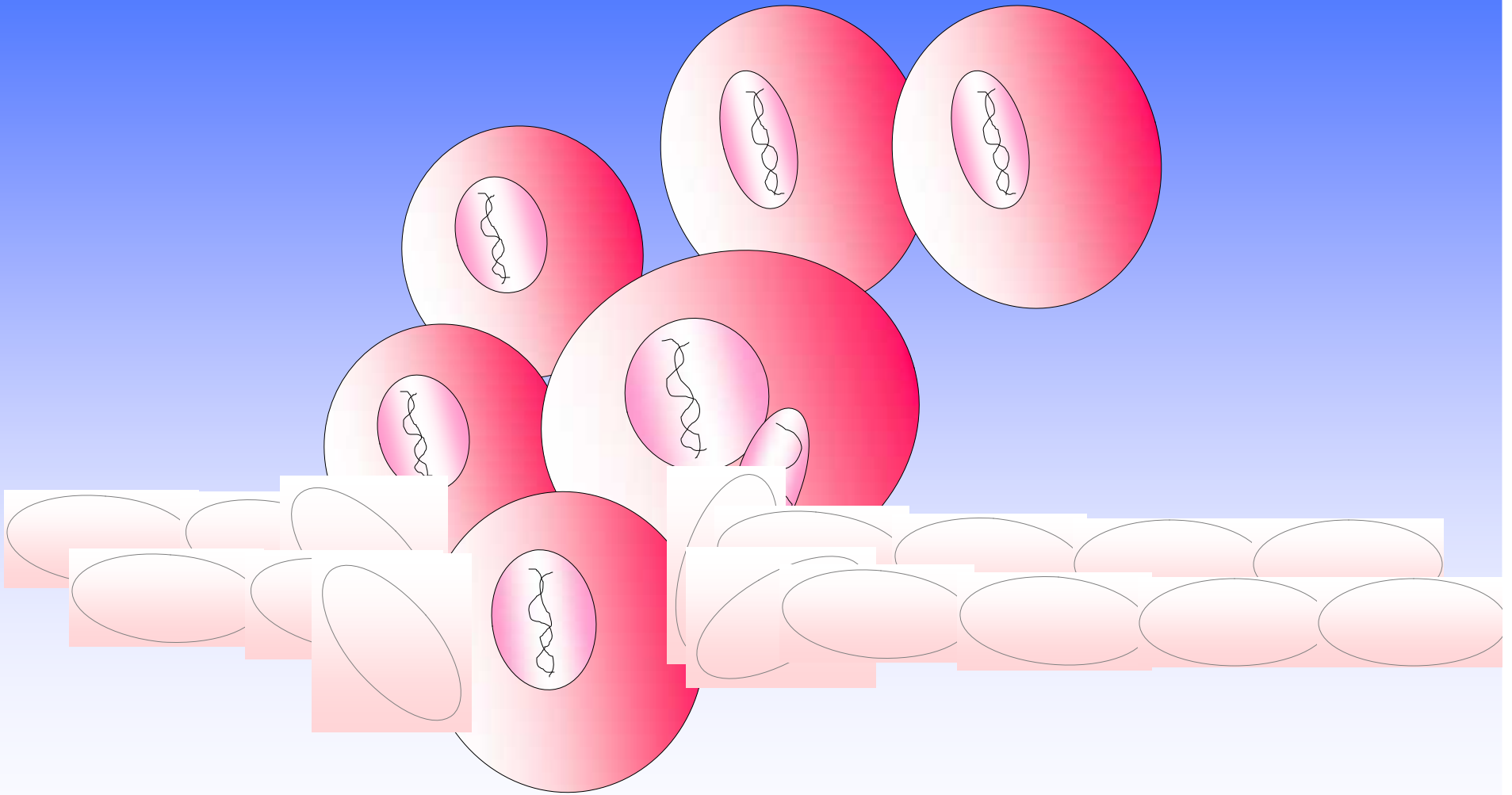
Penetration of the basement membrane

D-evolution step 3



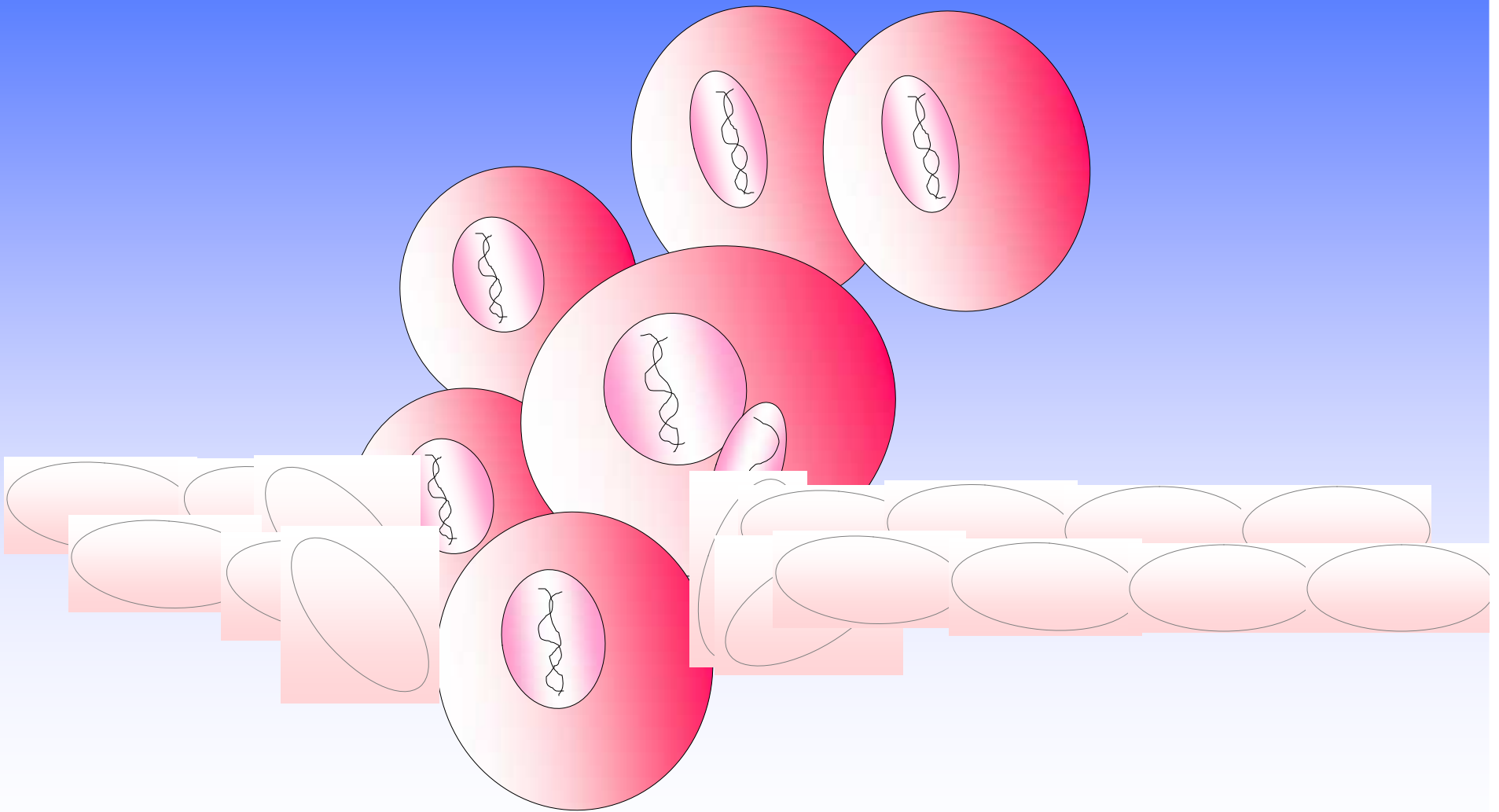
Penetration of the basement membrane

D-evolution step 3



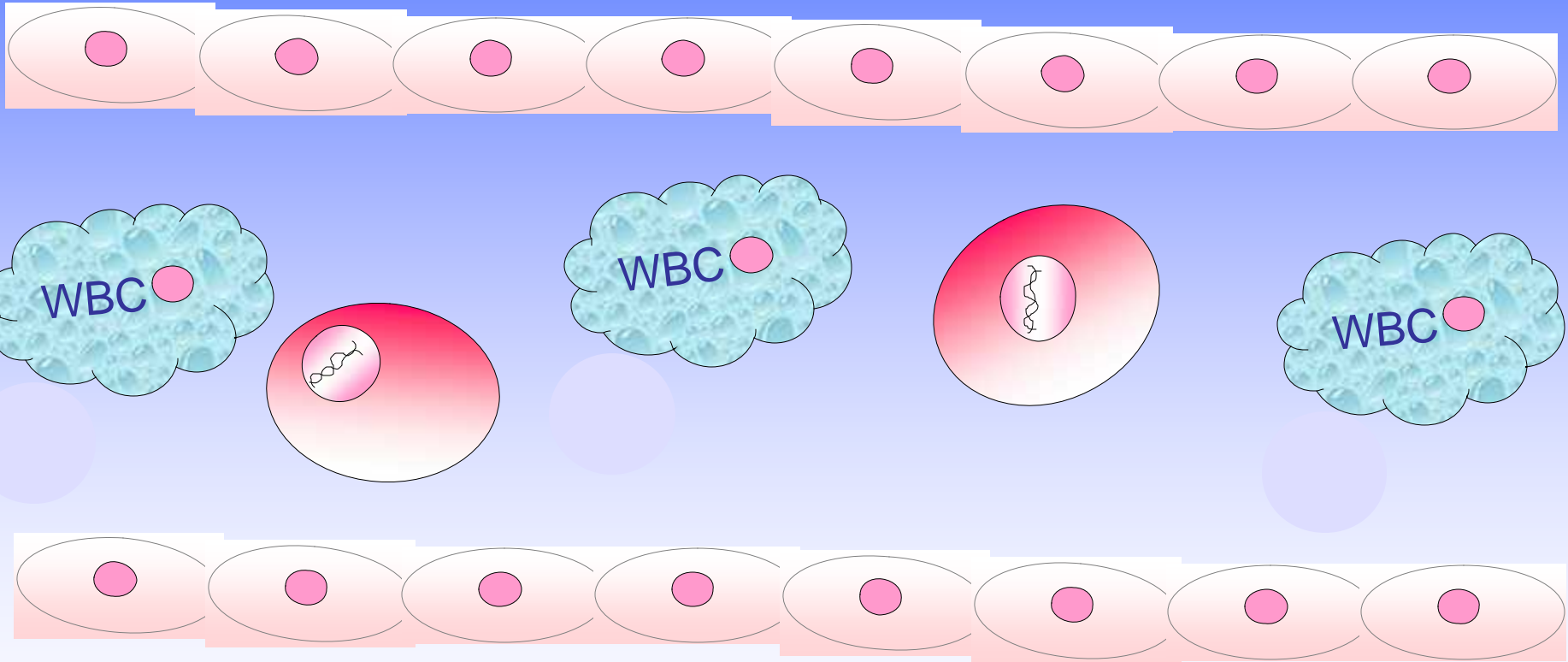
Penetration of the basement membrane

D-evolution step 3



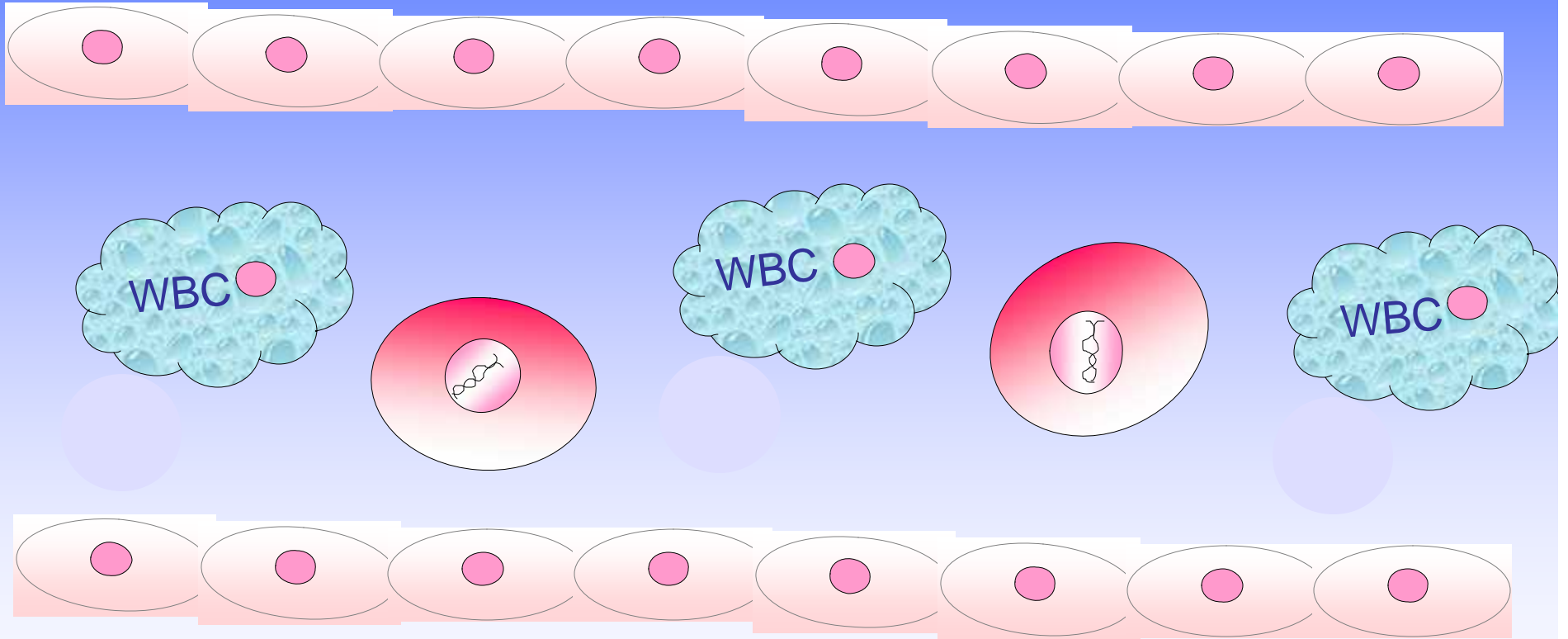
Penetration of the basement membrane

D-evolution step 4



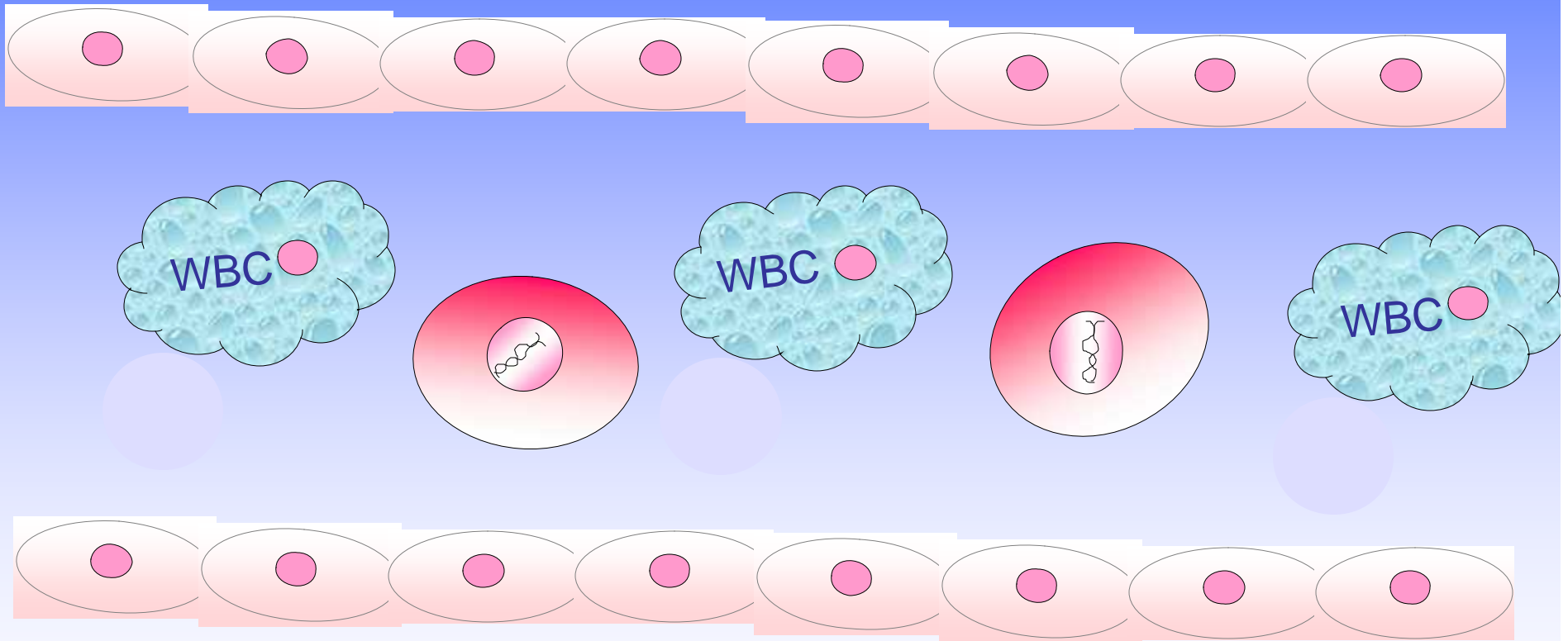
Lymphatic Transport

D-evolution step 4



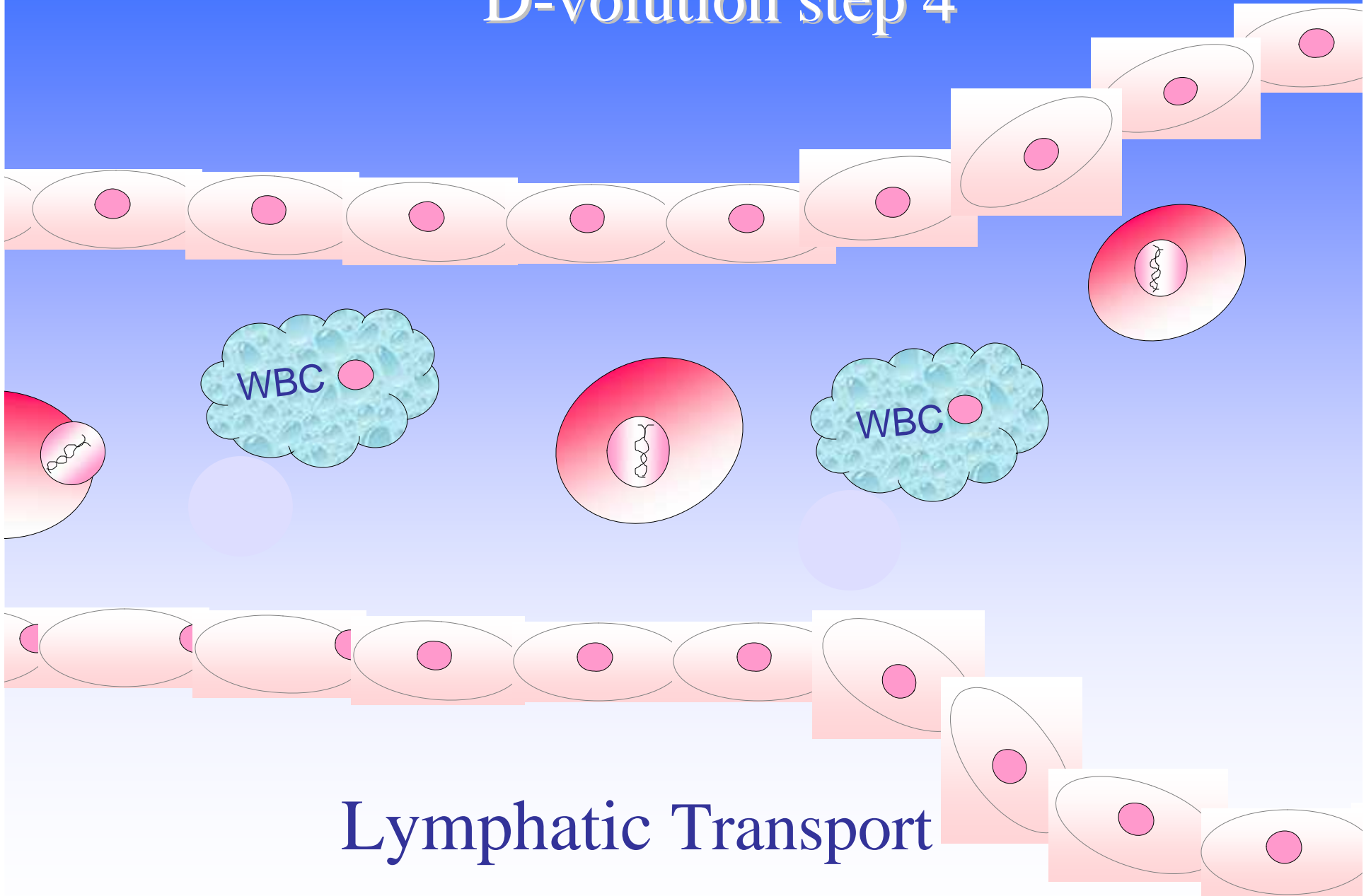
Lymphatic Transport

D-evolution step 4



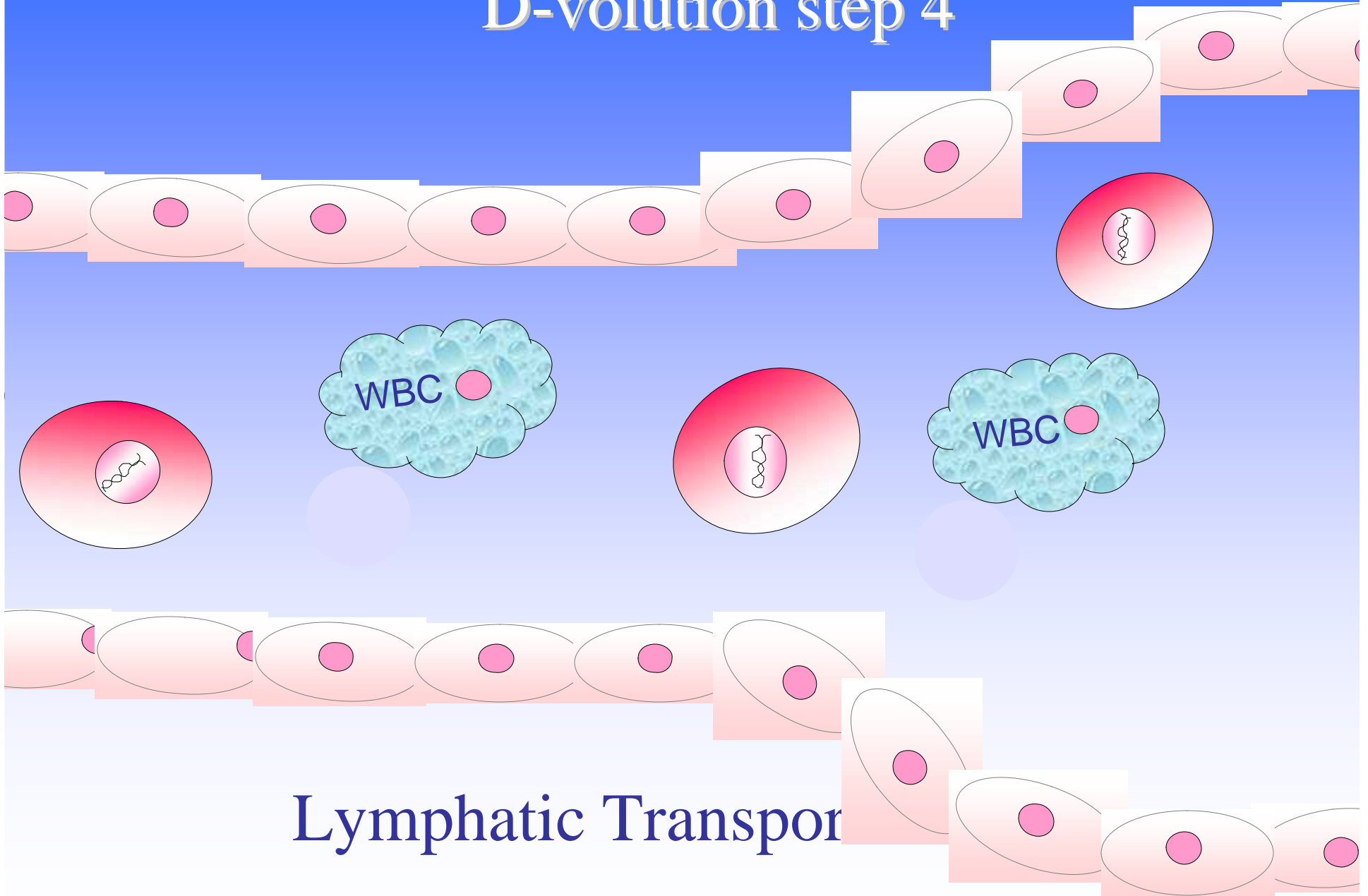
Lymphatic Transport

D-volution step 4



Lymphatic Transport

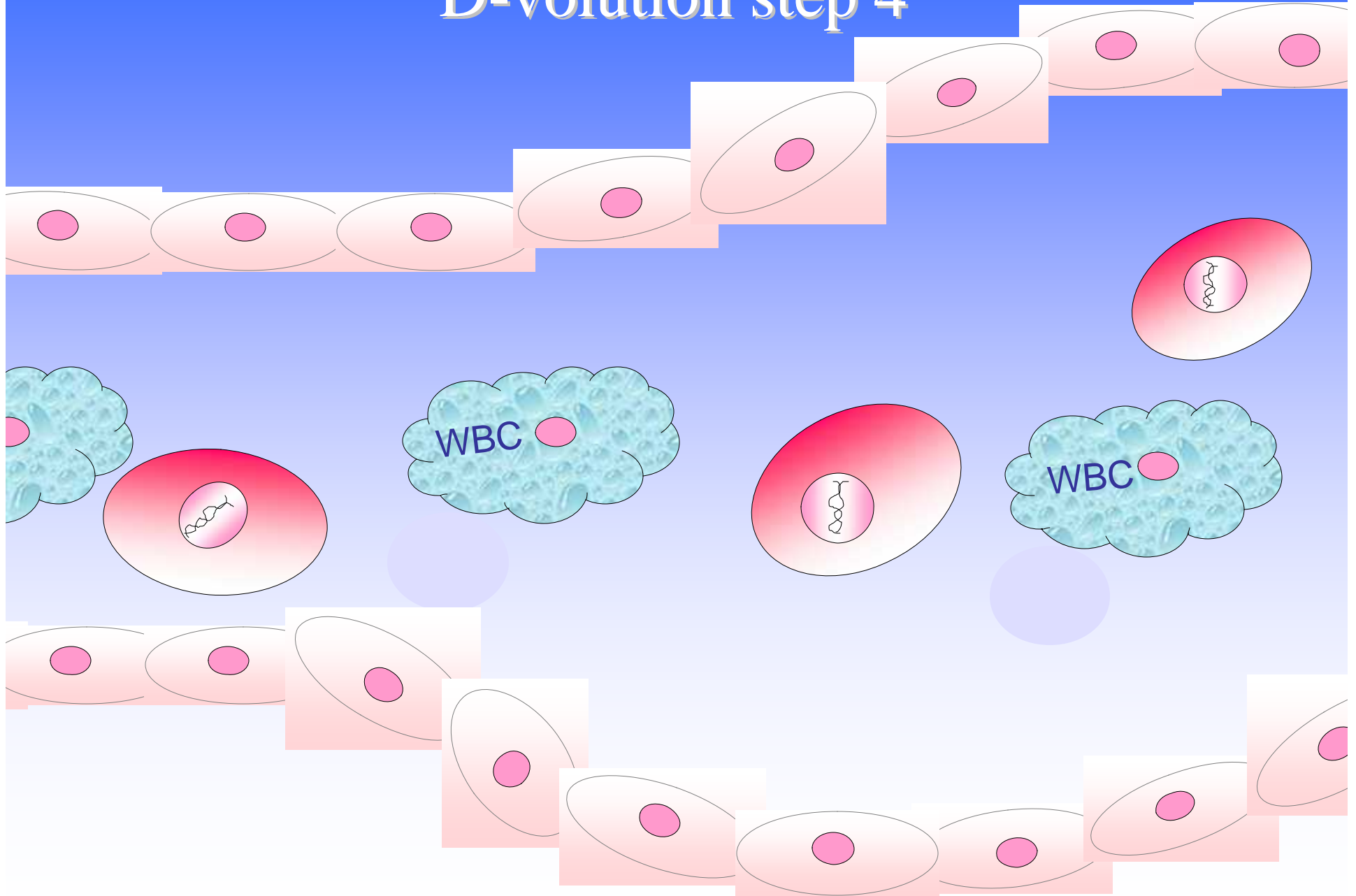
D-evolution step 4



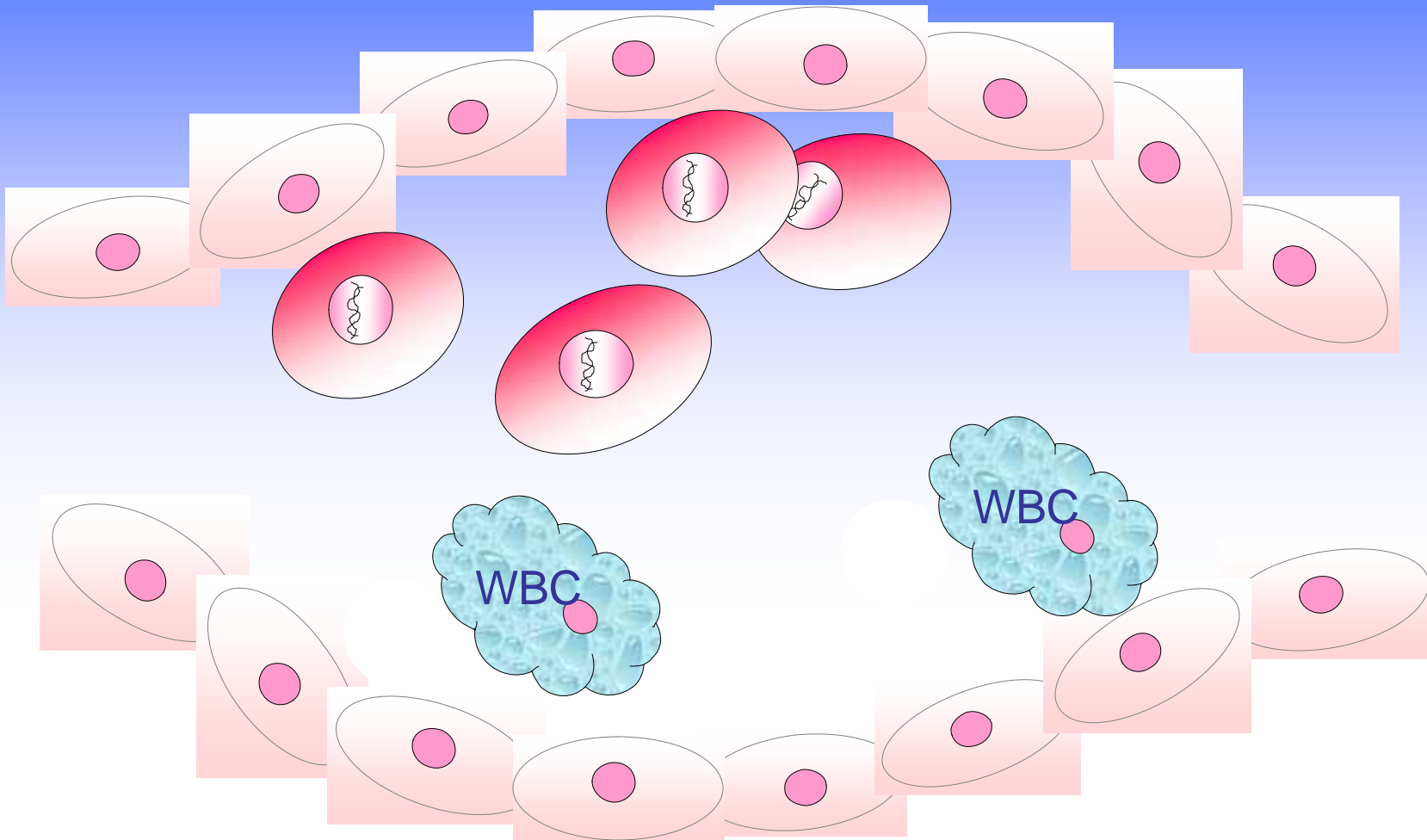
Lymphatic Transport

D-volution step 4

BC

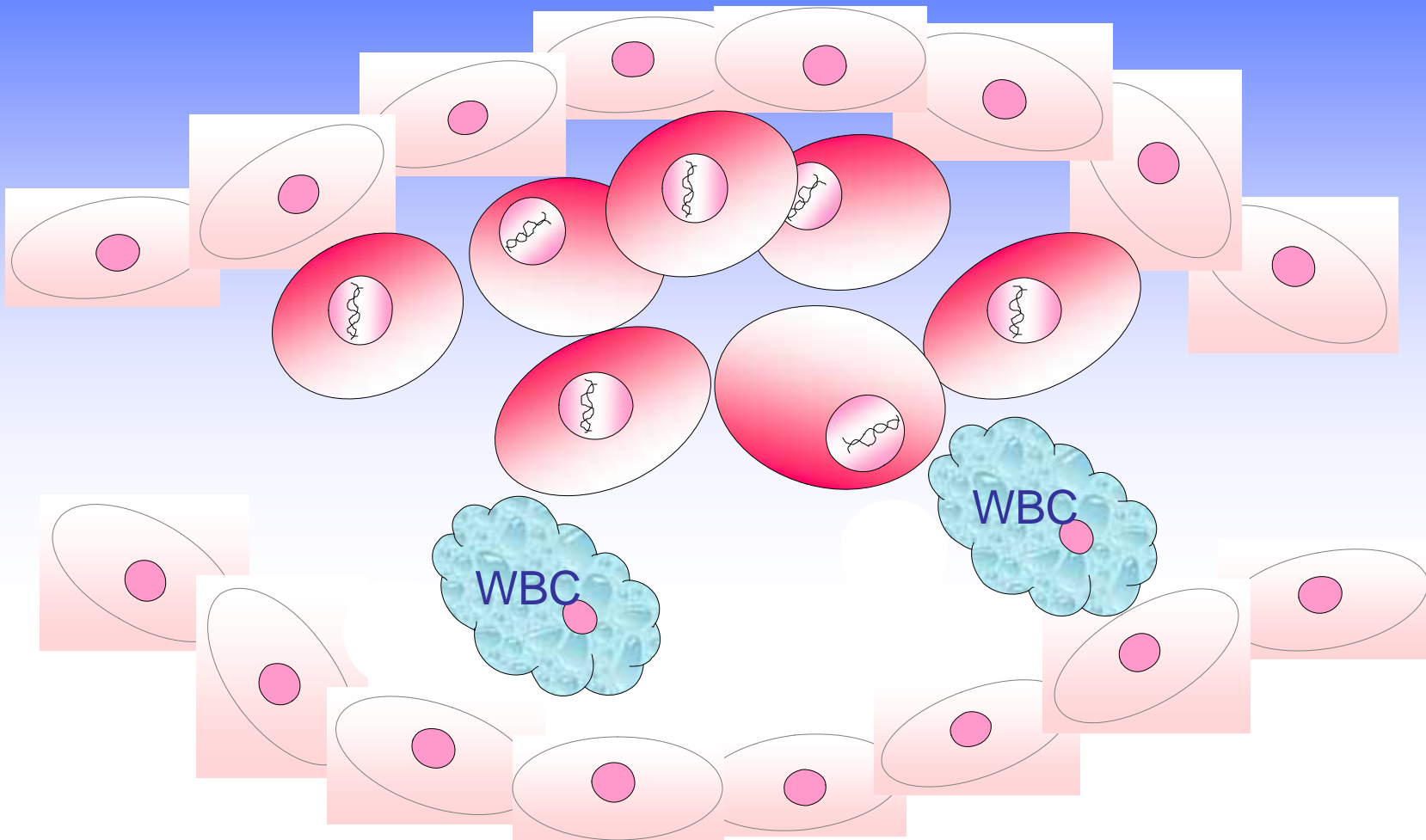


D-evolution step 5



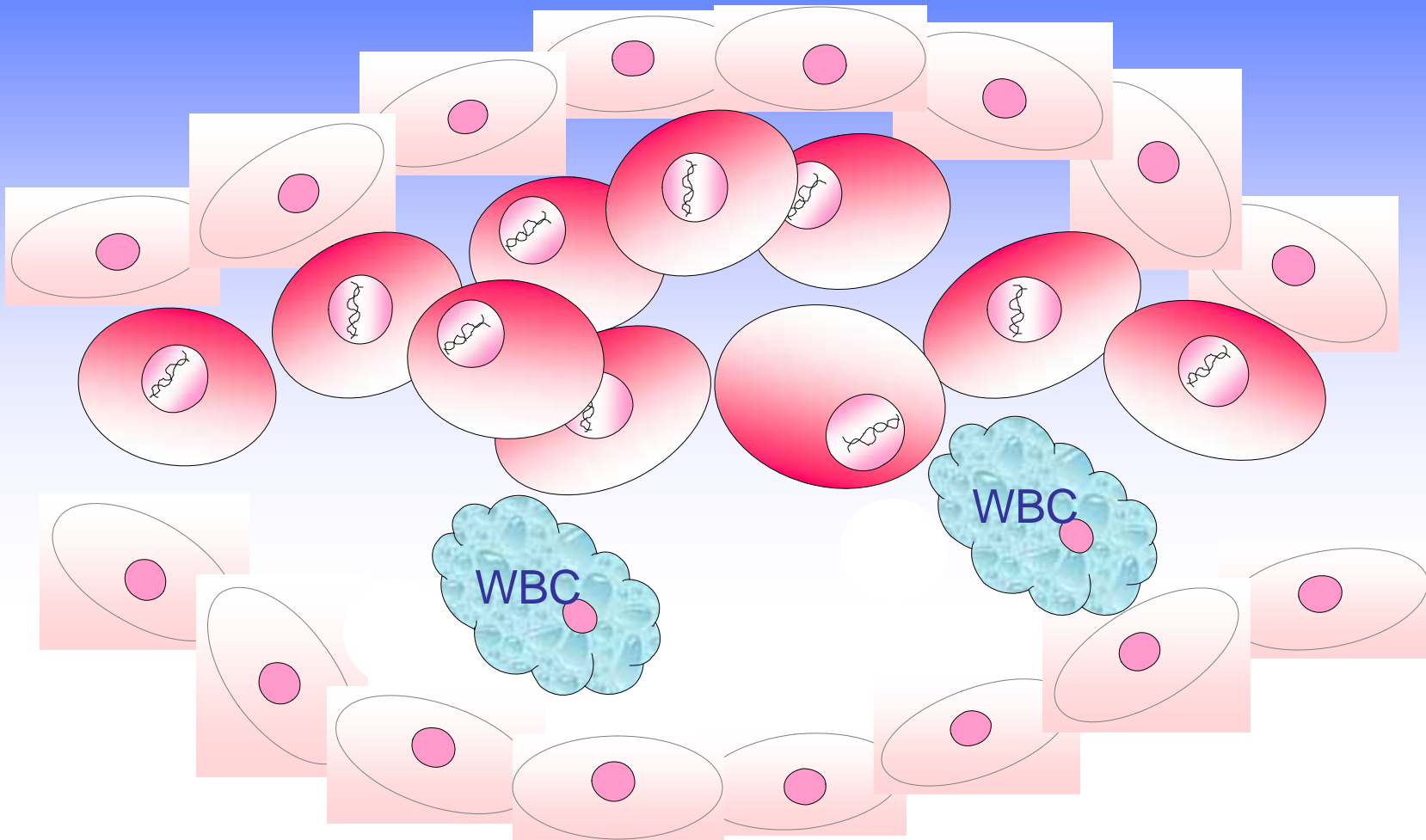
Population expansion in lymph node

D-evolution step 5



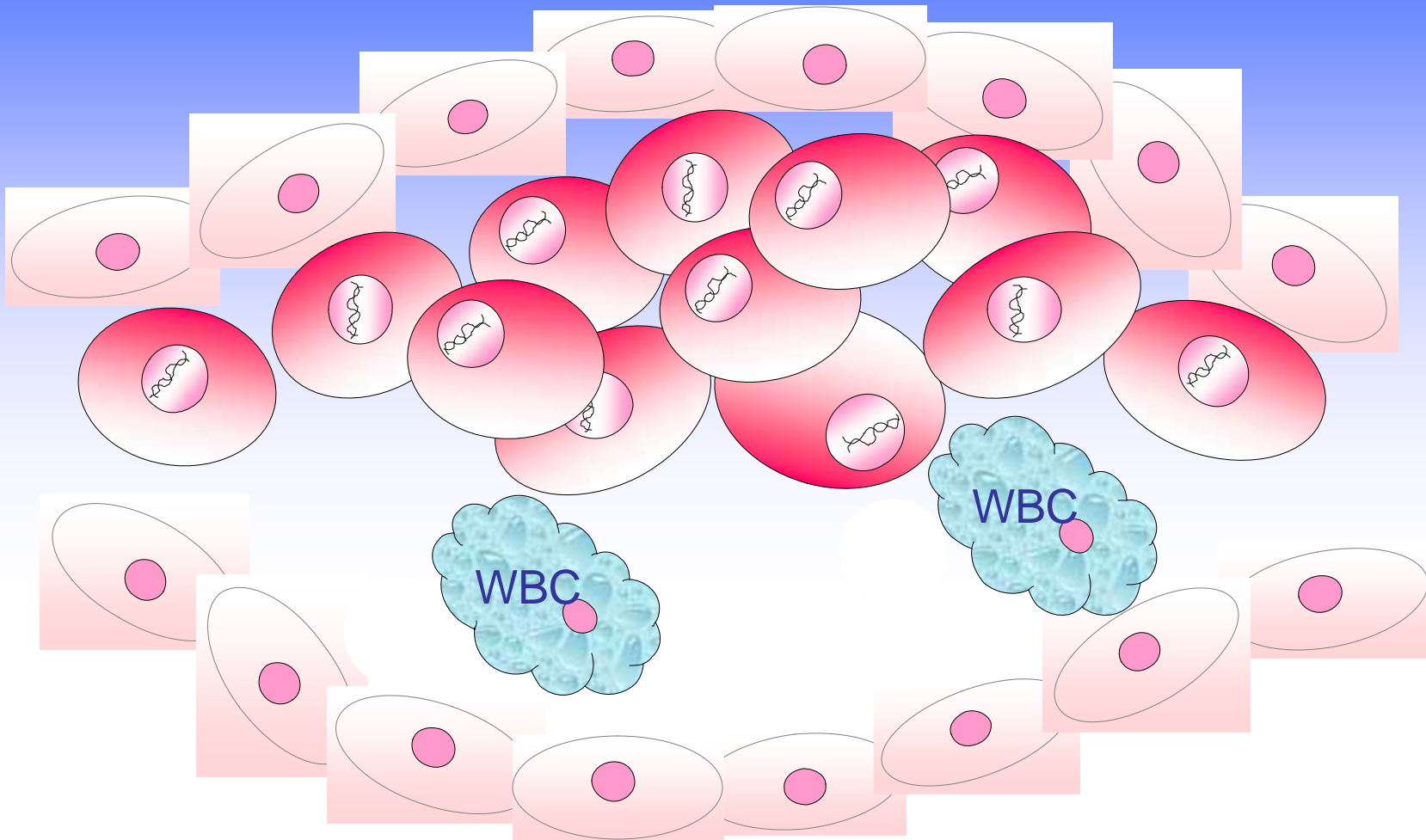
Population expansion in lymph node

D-evolution step 5



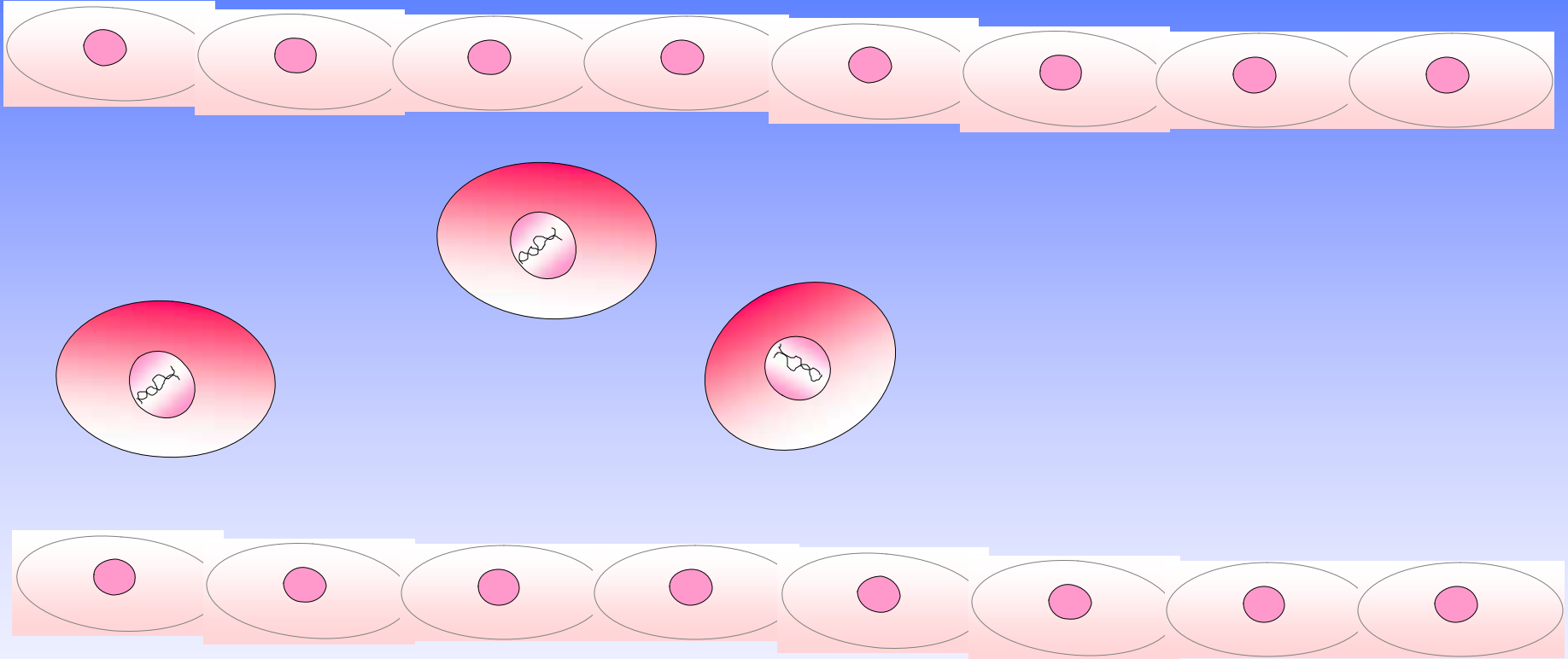
Population expansion in lymph node

D-evolution step 5



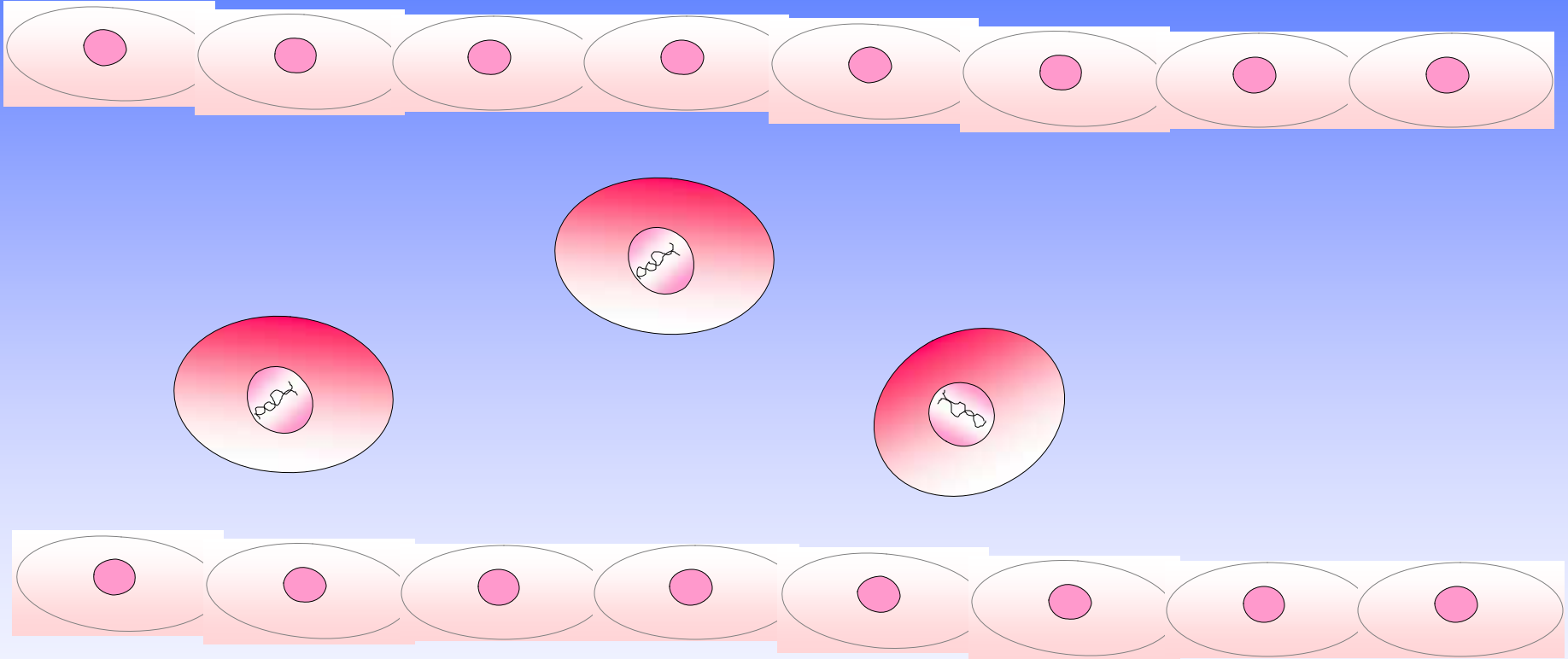
Population expansion in lymph node

D-evolution step 6



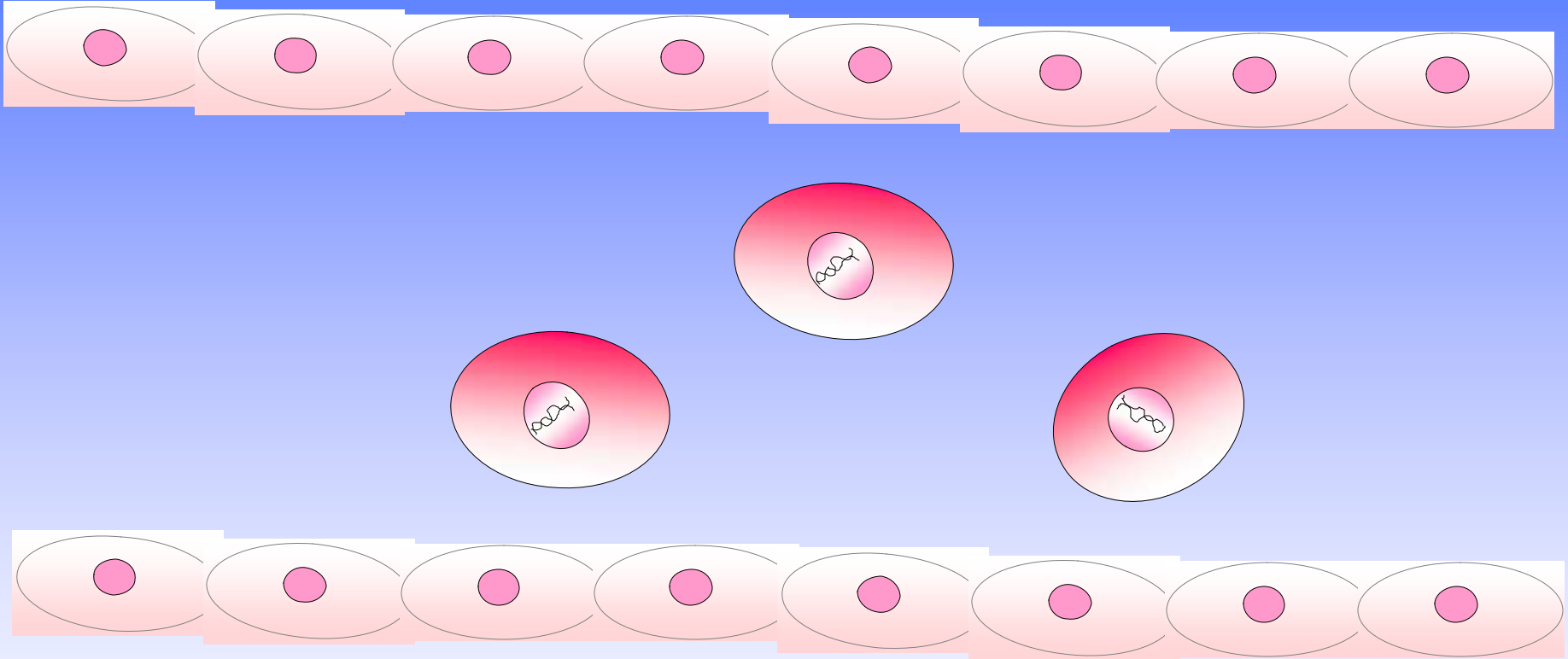
Flow to host tissue

D-evolution step 6



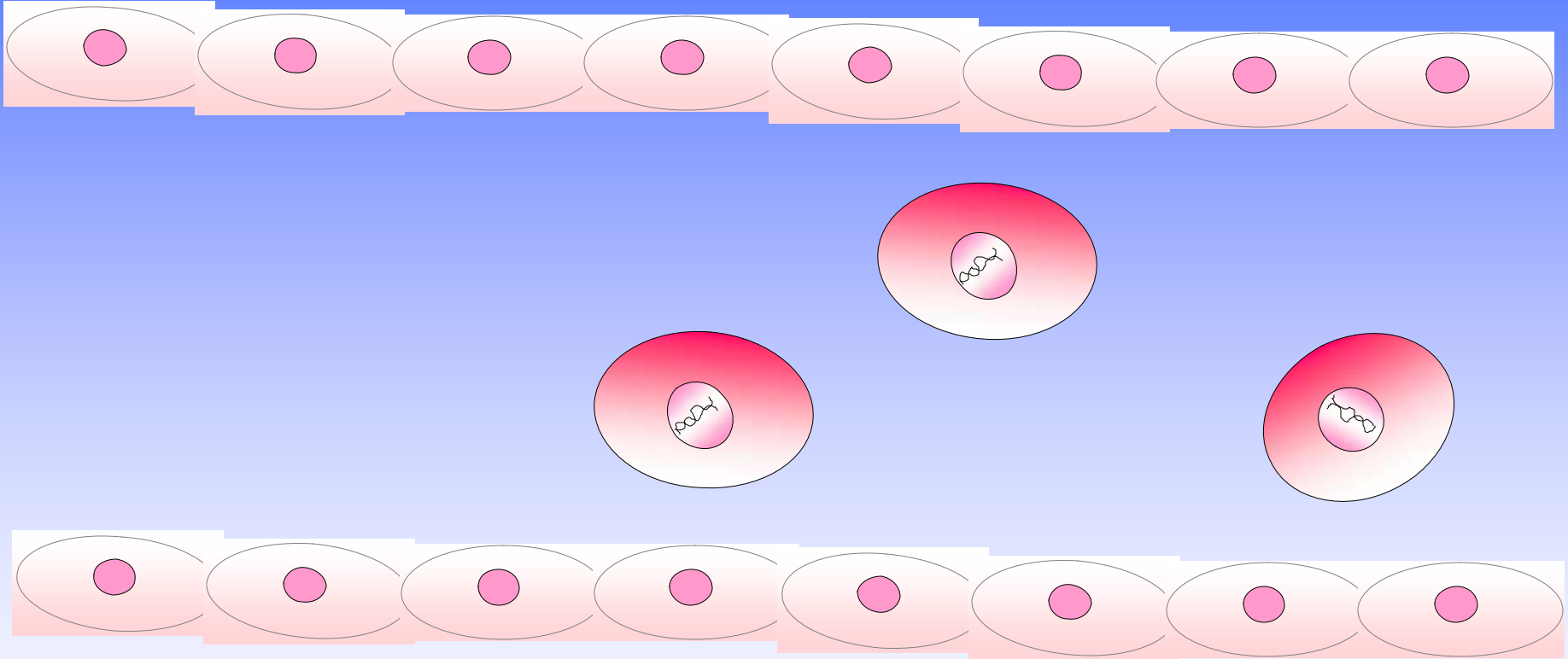
Flow to host tissue

D-evolution step 6



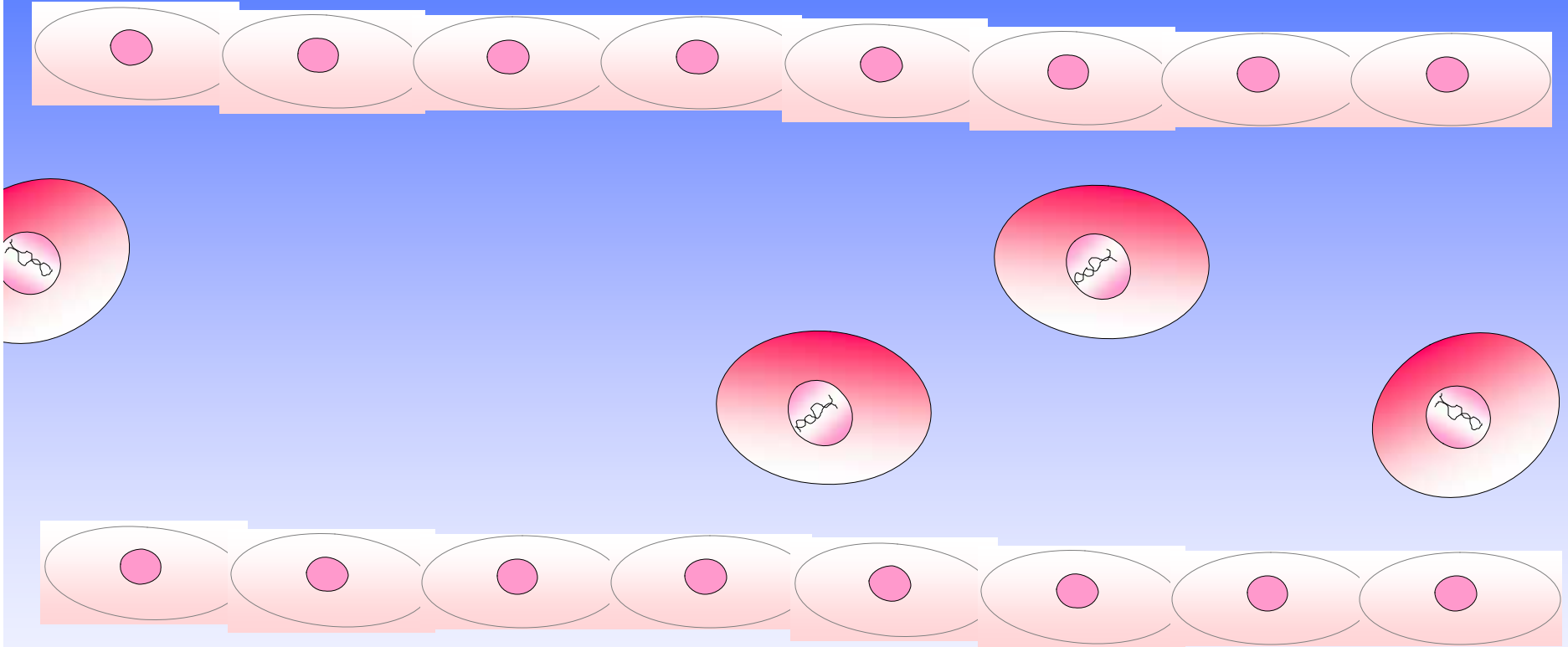
Flow to host tissue

D-evolution step 6



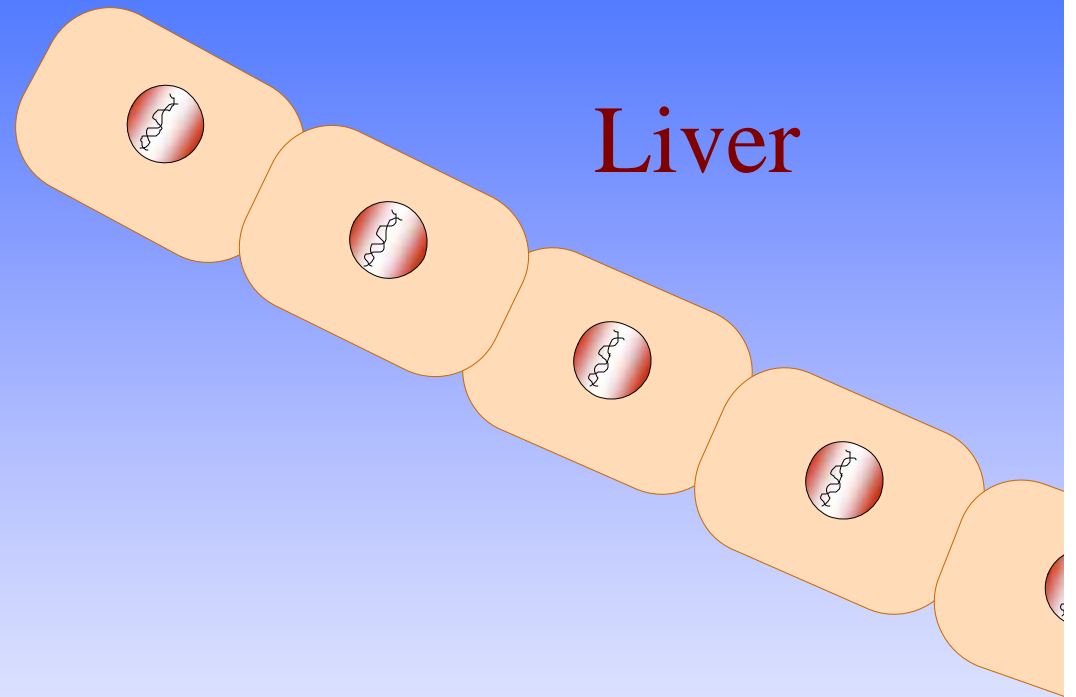
Flow to host tissue

D-evolution step 6



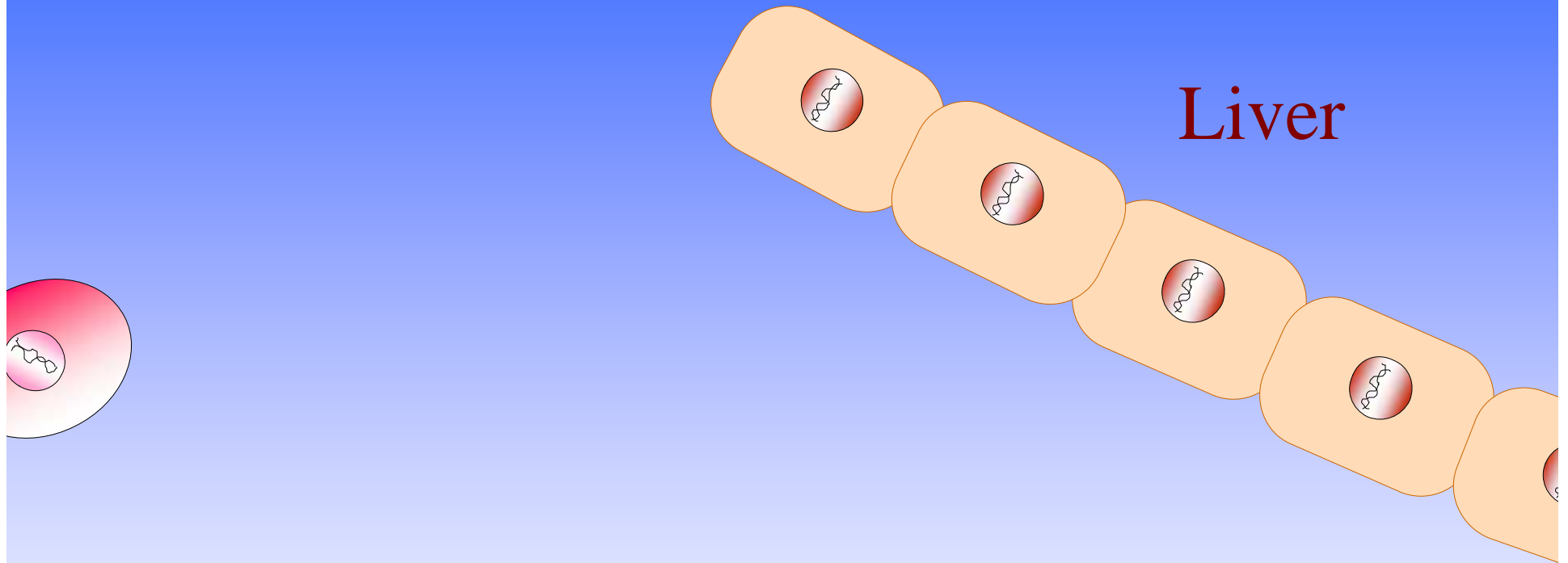
Flow to host tissue

D-volution step 7



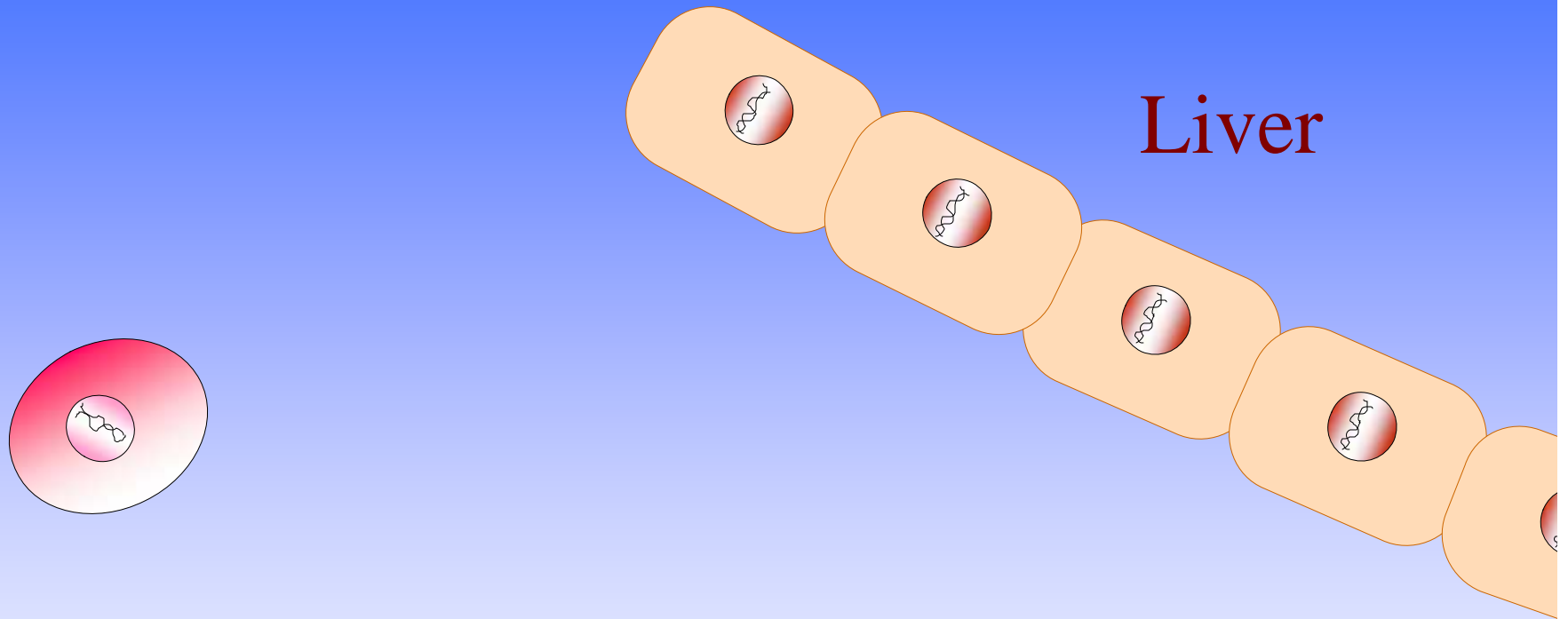
Attachment to epithelium of
host tissue

D-evolution step 7



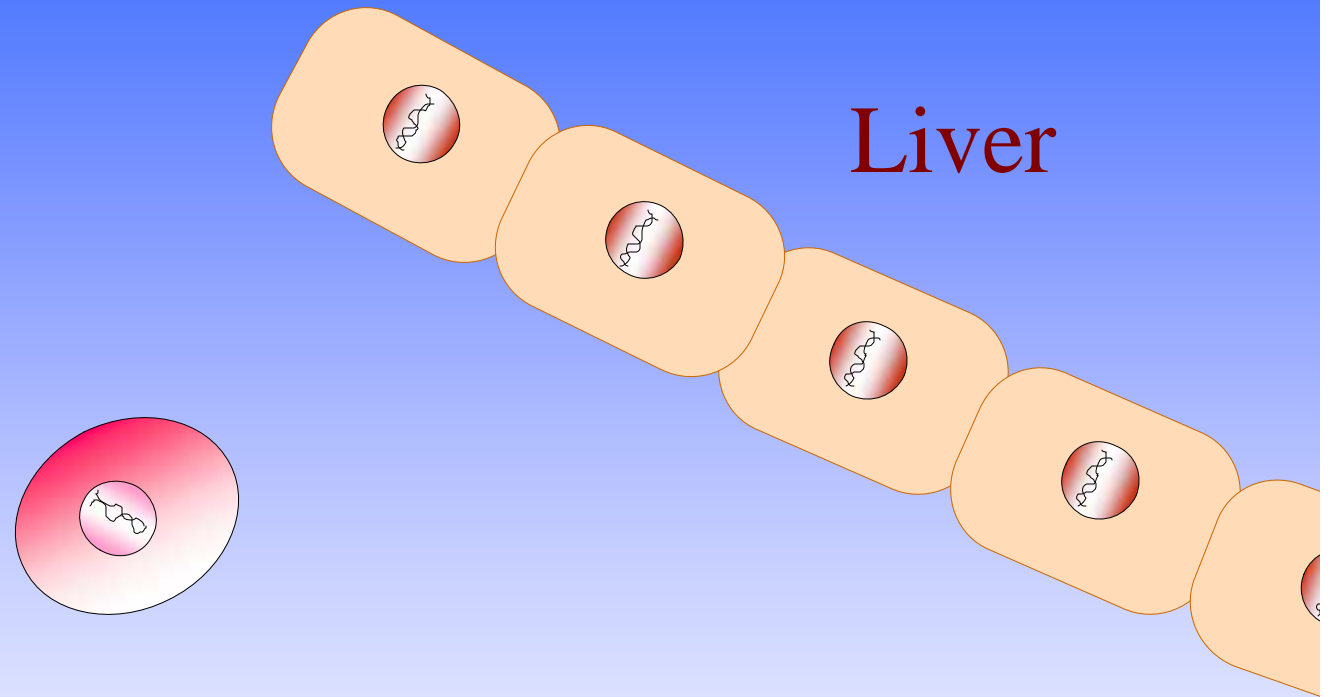
Attachment to epithelium of
host tissue

D-evolution step 7



Attachment to epithelium of
host tissue

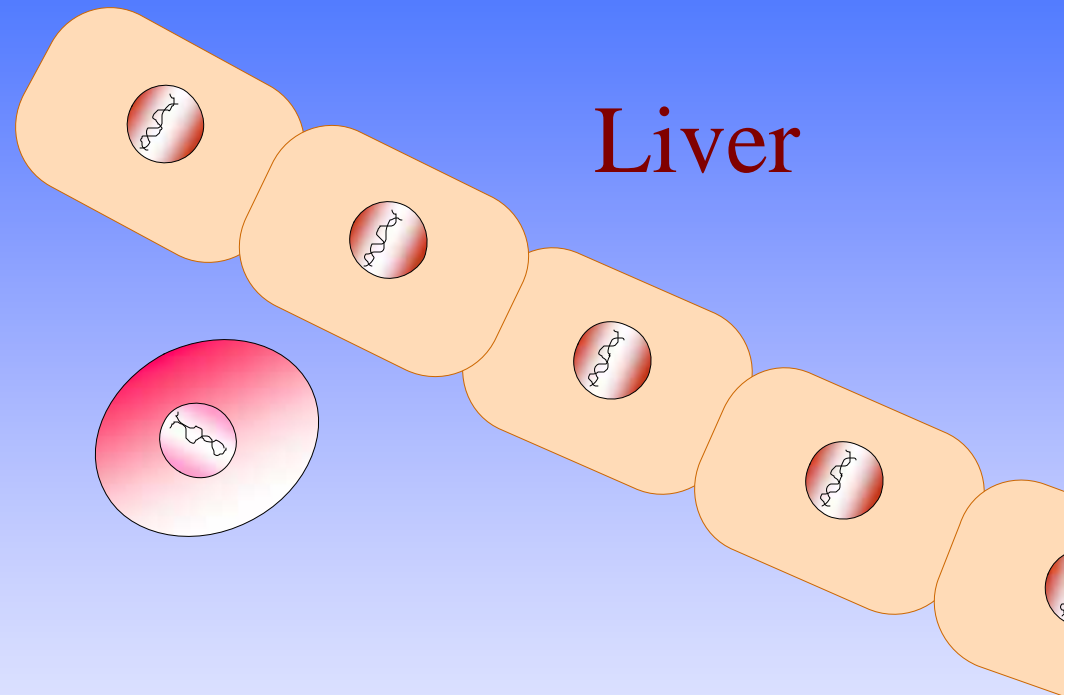
D-evolution step 7



Liver

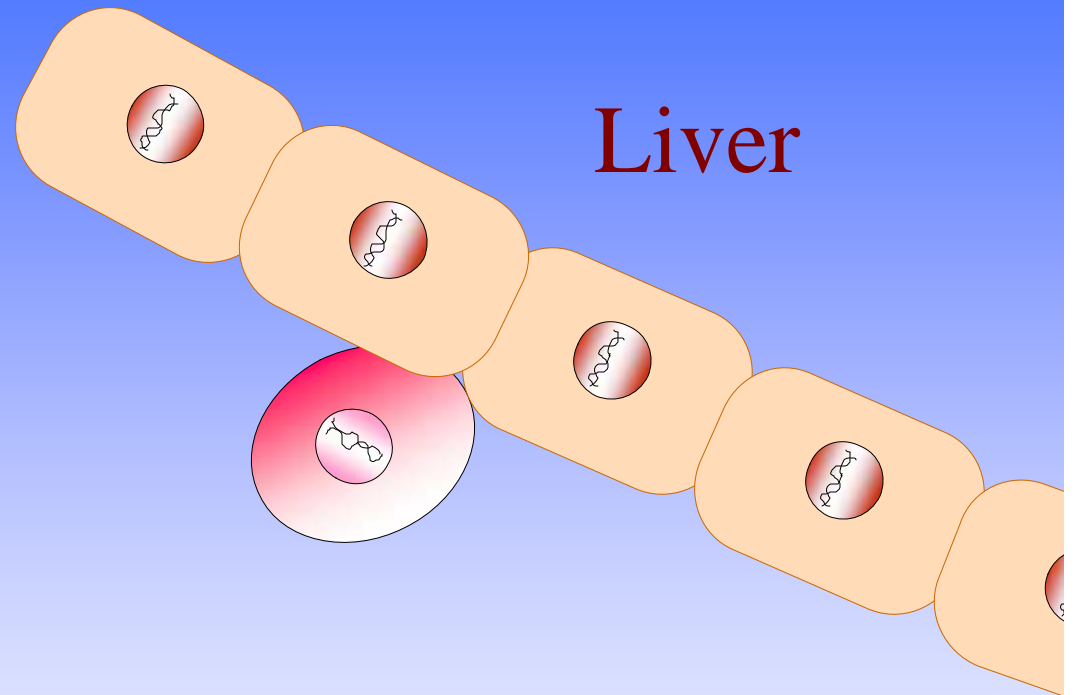
Attachment to epithelium of
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D-volution step 7



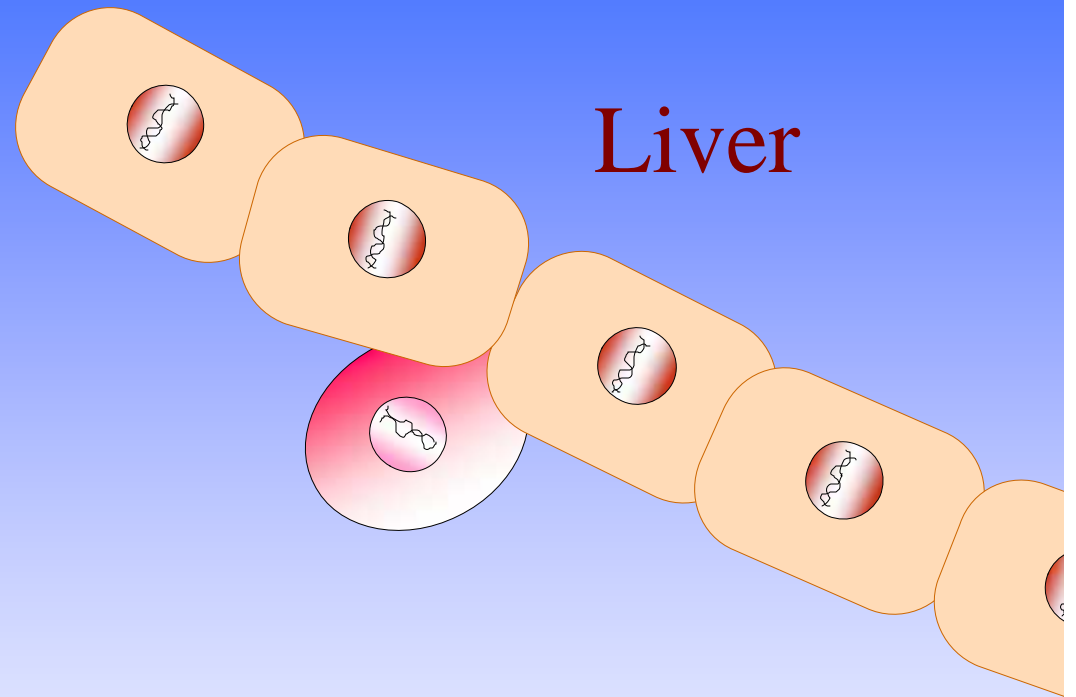
Attachment to epithelium of
host tissue

D-evolution step 7



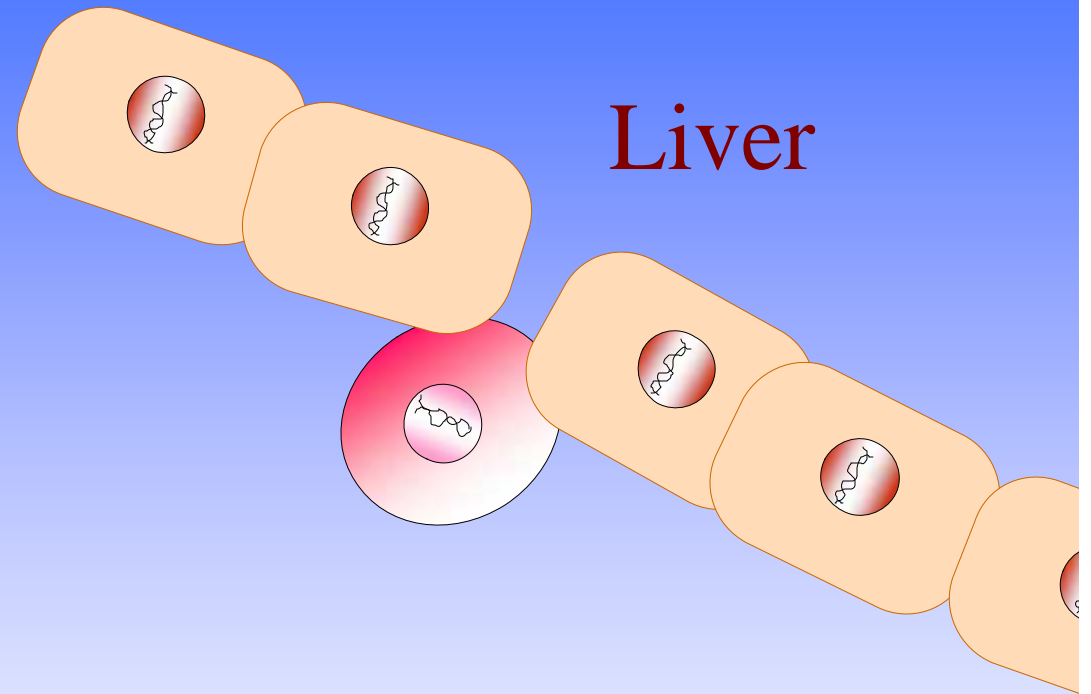
Attachment to epithelium of
host tissue

D-evolution step 7



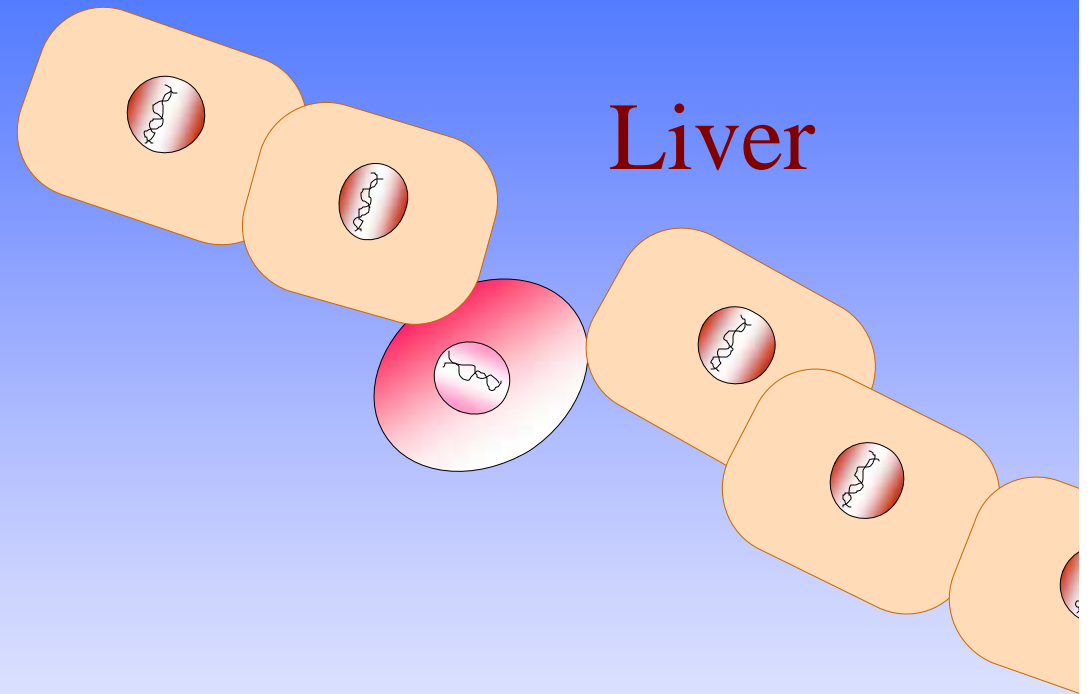
Attachment to epithelium of
host tissue

D-volution step 8



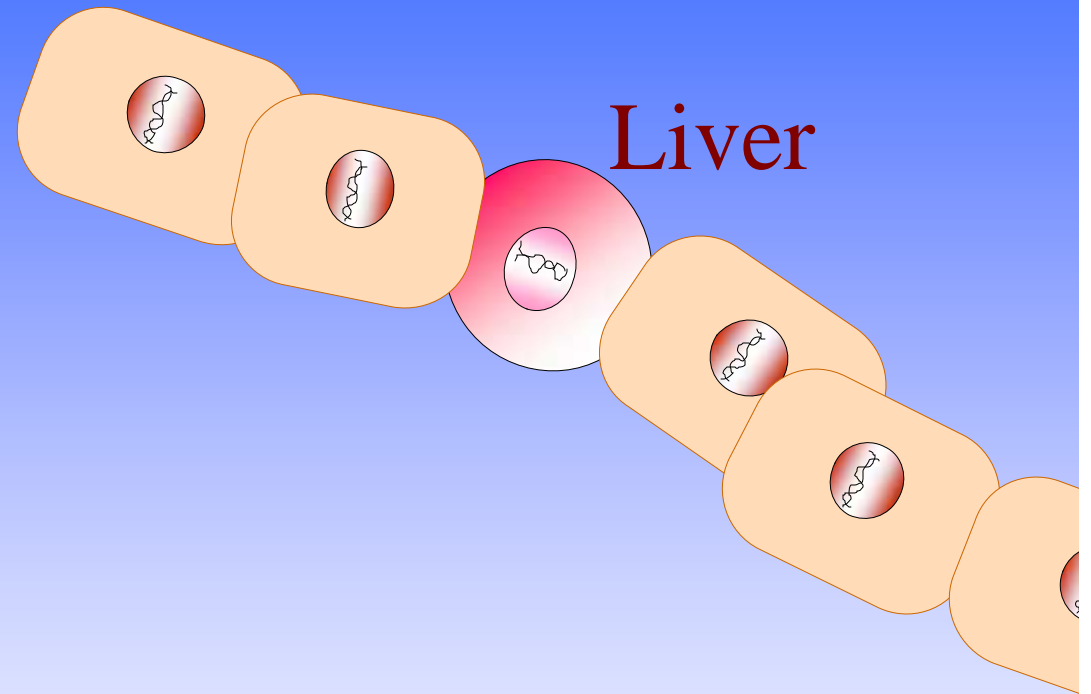
Penetration of epithelium

D-volution step 8



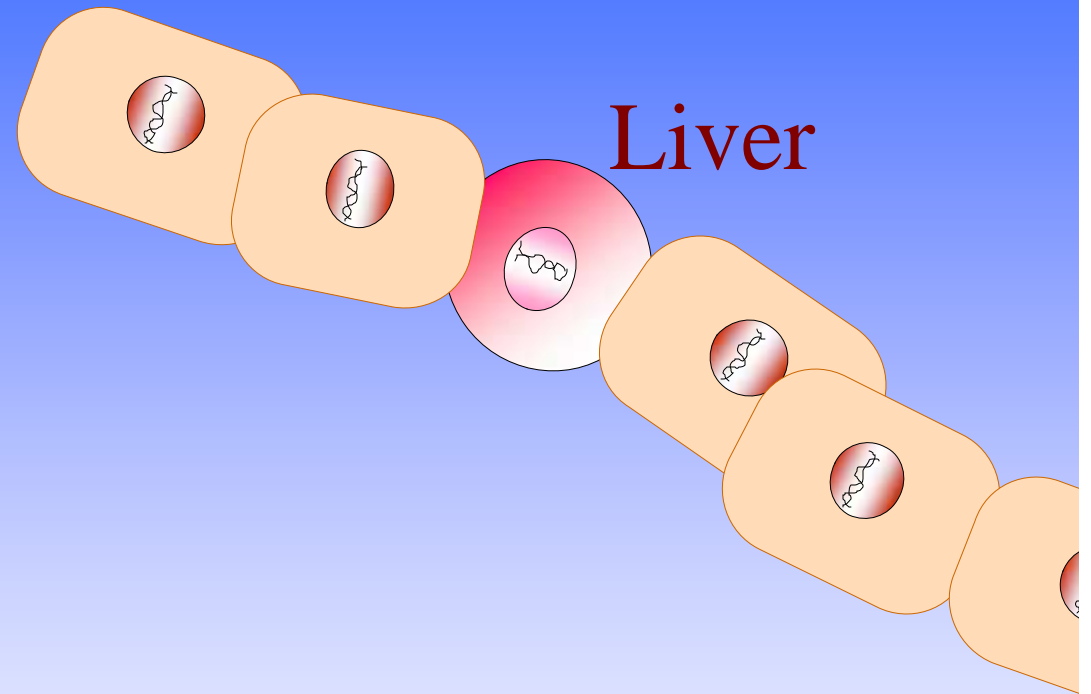
Penetration of epithelium

D-volution step 8



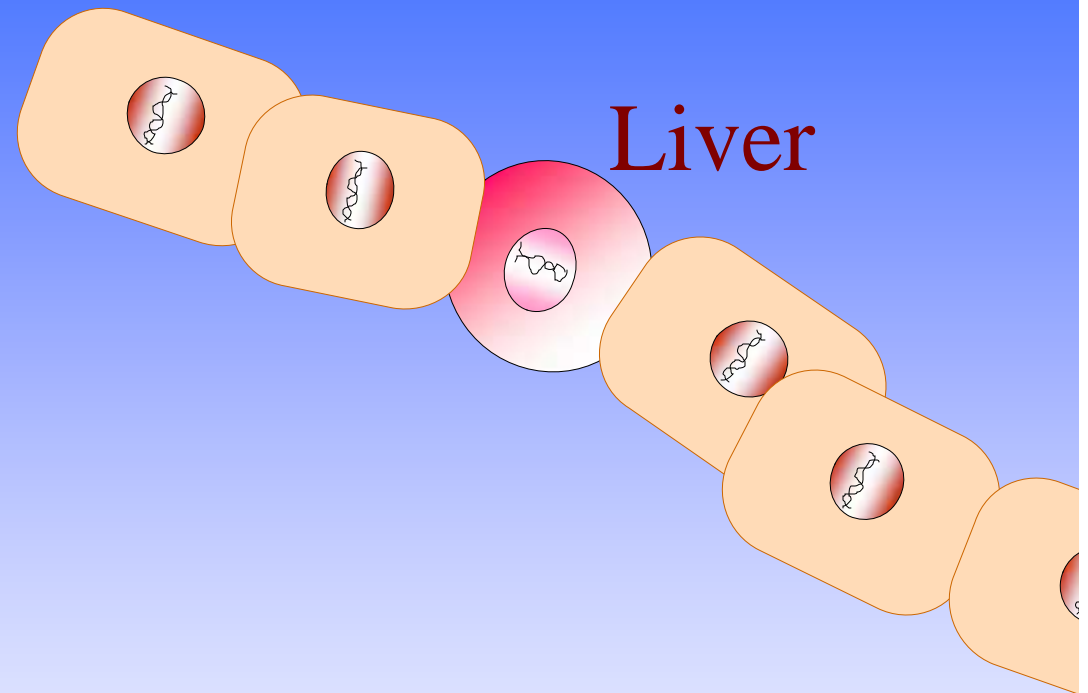
Penetration of epithelium

D-volution step 8



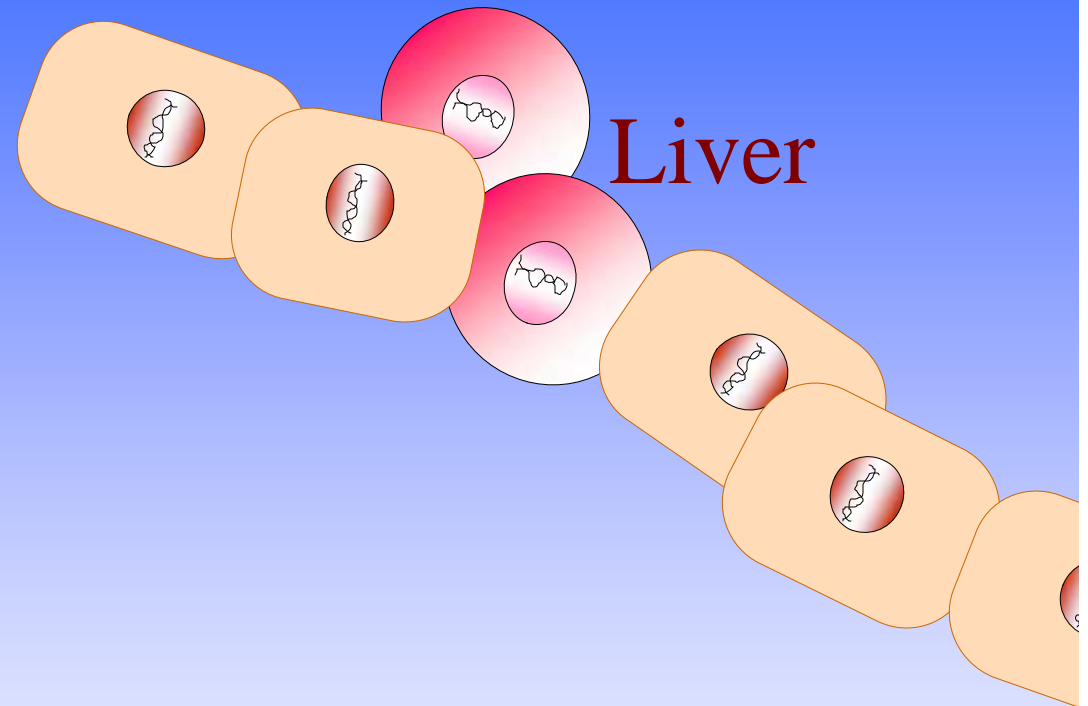
Penetration of epithelium

D-evolution step 9



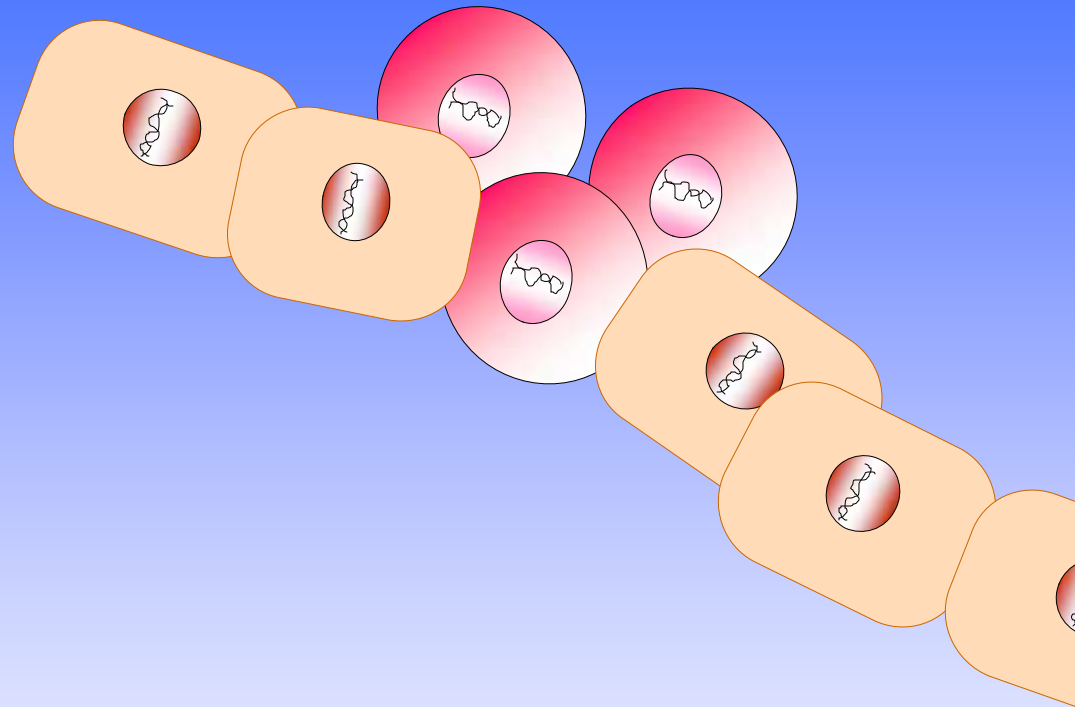
Expansion of malignant clone
in new range can be rapidly fatal

D-evolution step 9



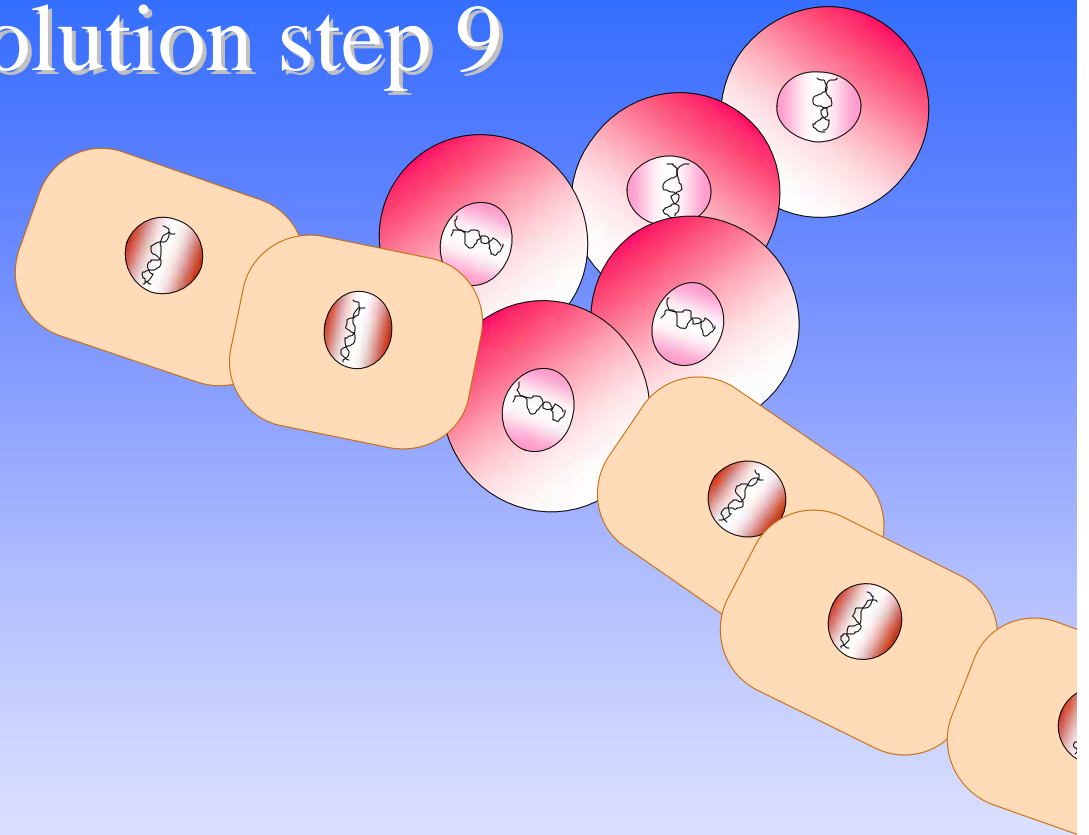
Expansion of malignant clone
in new range can be rapidly fatal

D-evolution step 9



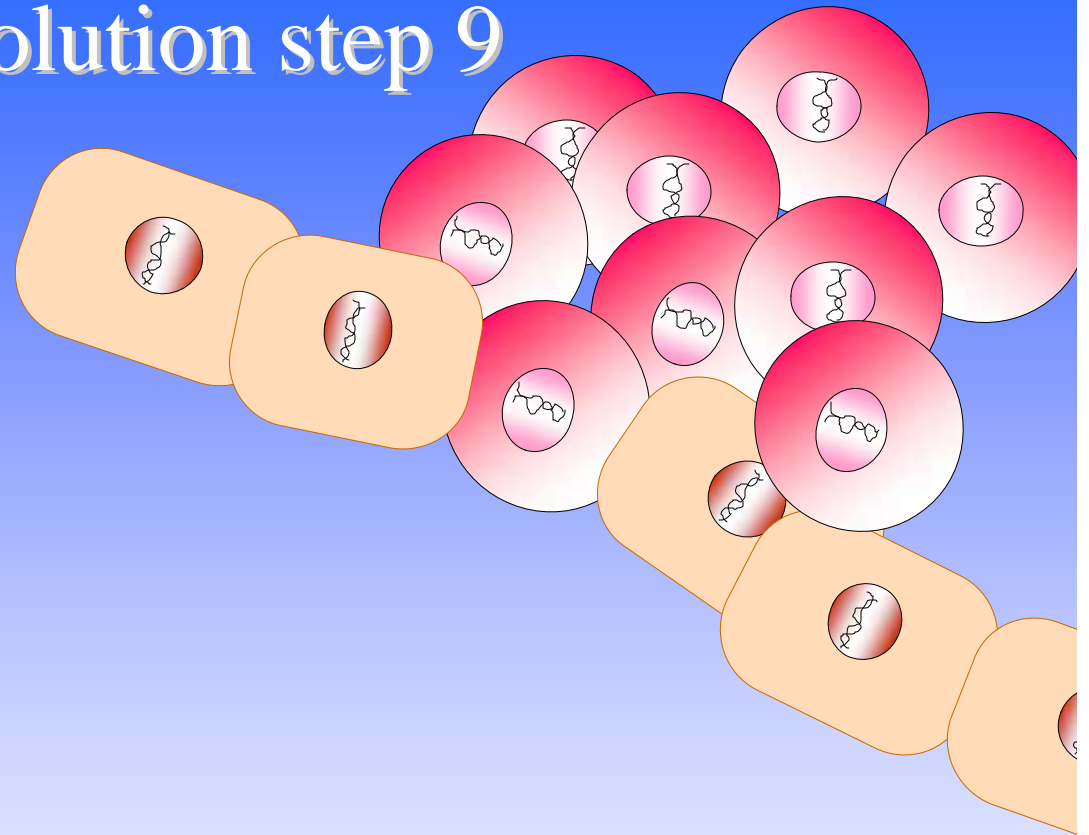
Expansion of malignant clone
in new range can be rapidly fatal

D-evolution step 9



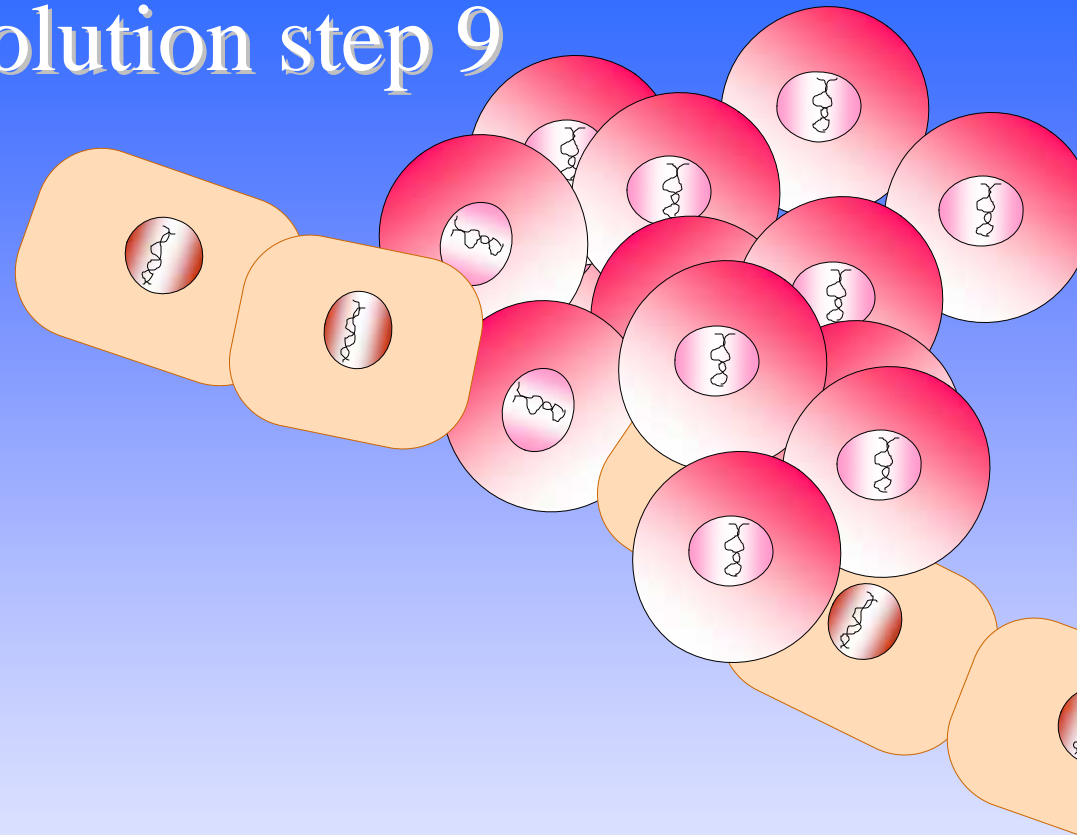
Expansion of malignant clone
in new range can be rapidly fatal

D-evolution step 9



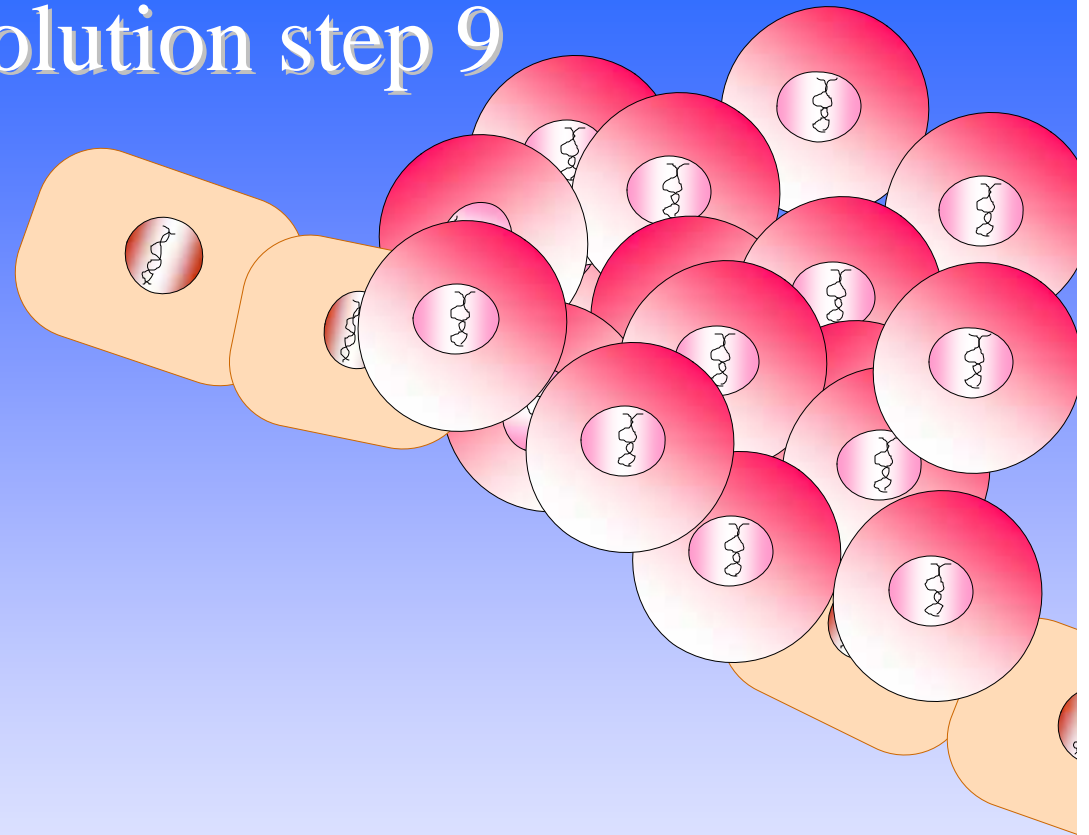
Expansion of malignant clone
in new range can be rapidly fatal

D-evolution step 9

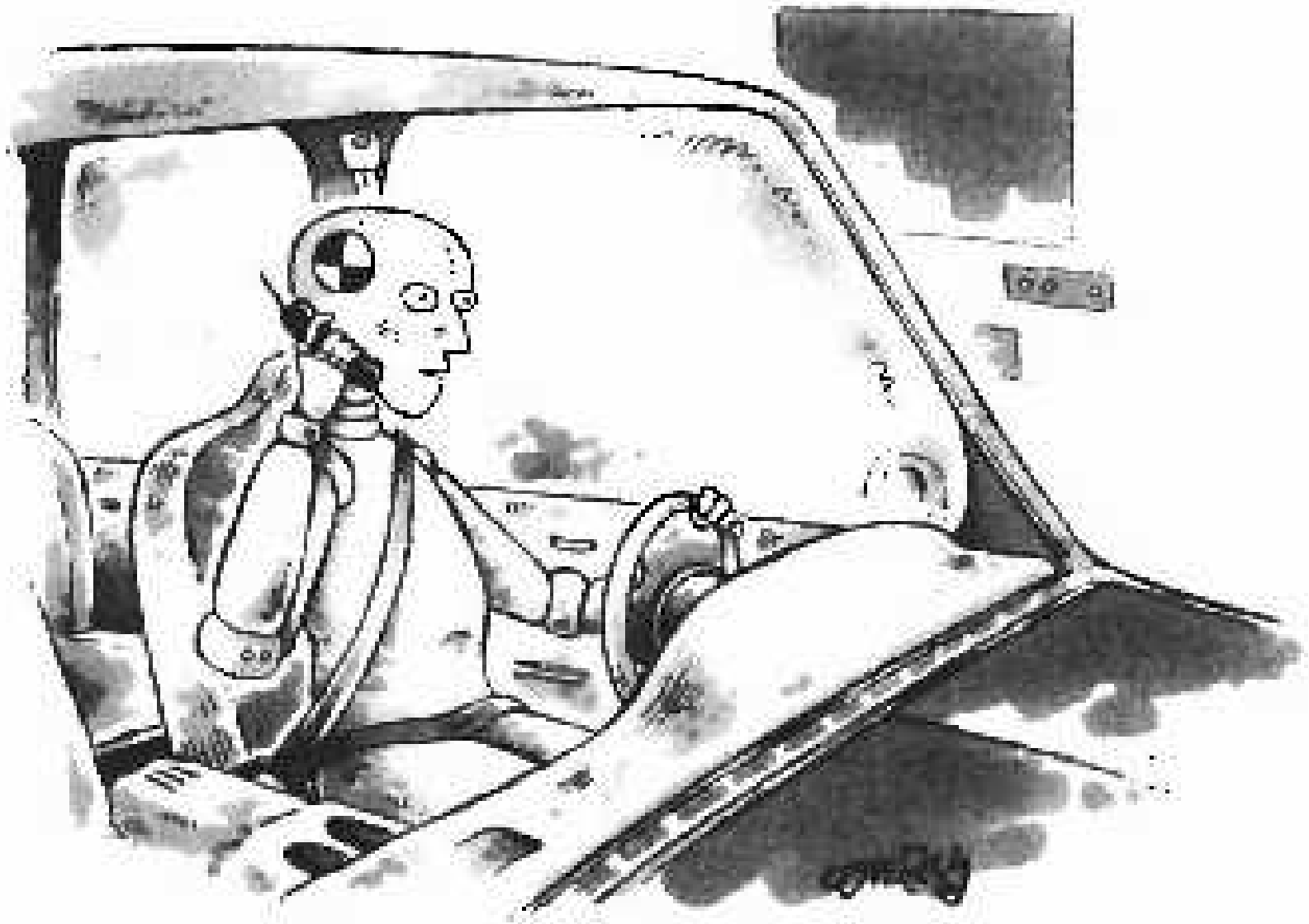


Expansion of malignant clone
in new range can be rapidly fatal

D-evolution step 9



Expansion of malignant clone
in new range can be rapidly fatal



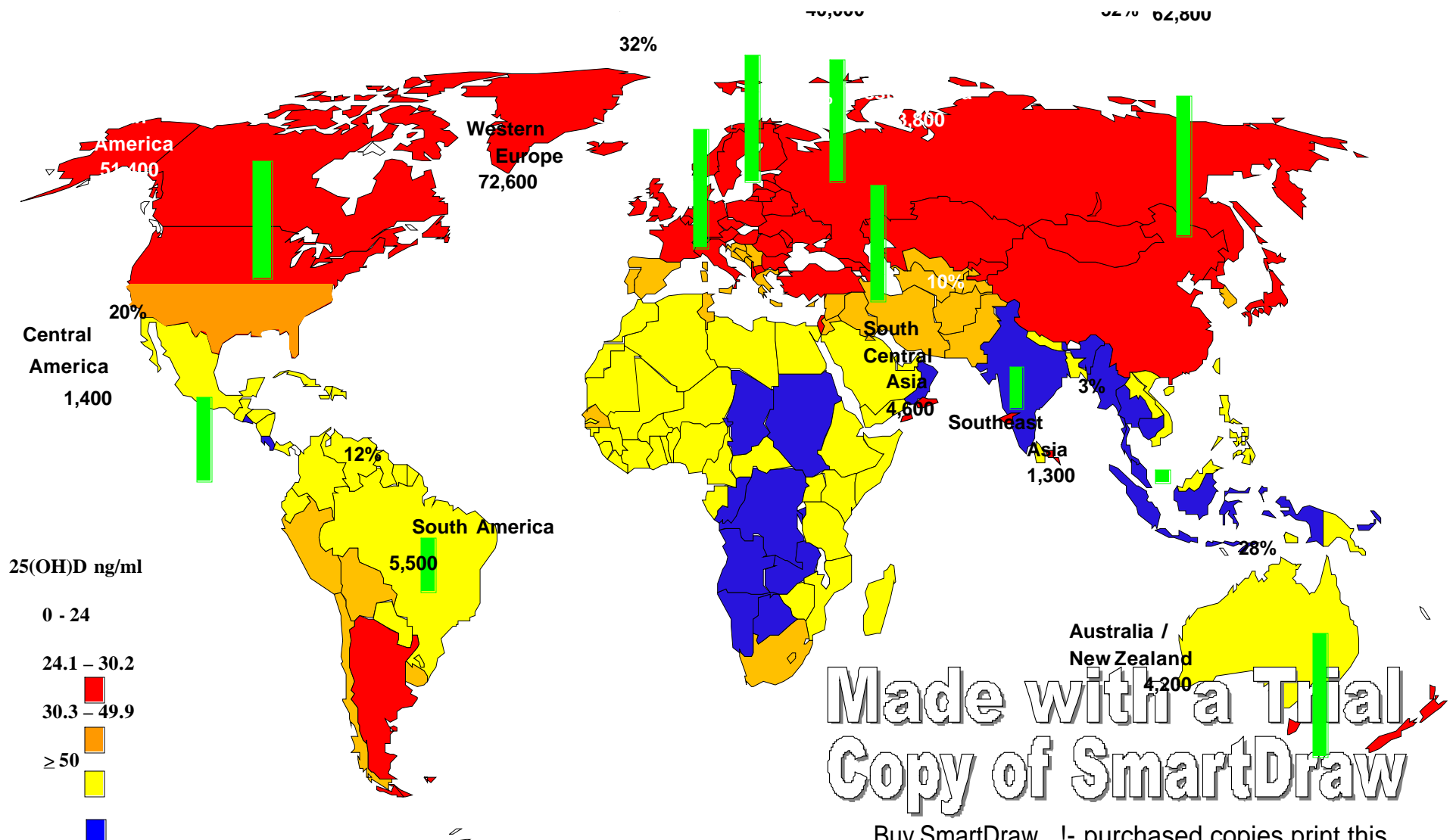
Well, I'd better go now. I'm almost at the wall



Cancer and Vitamin D

Global Impact

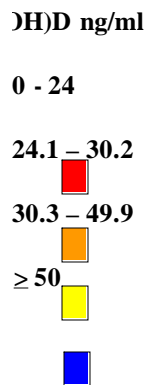
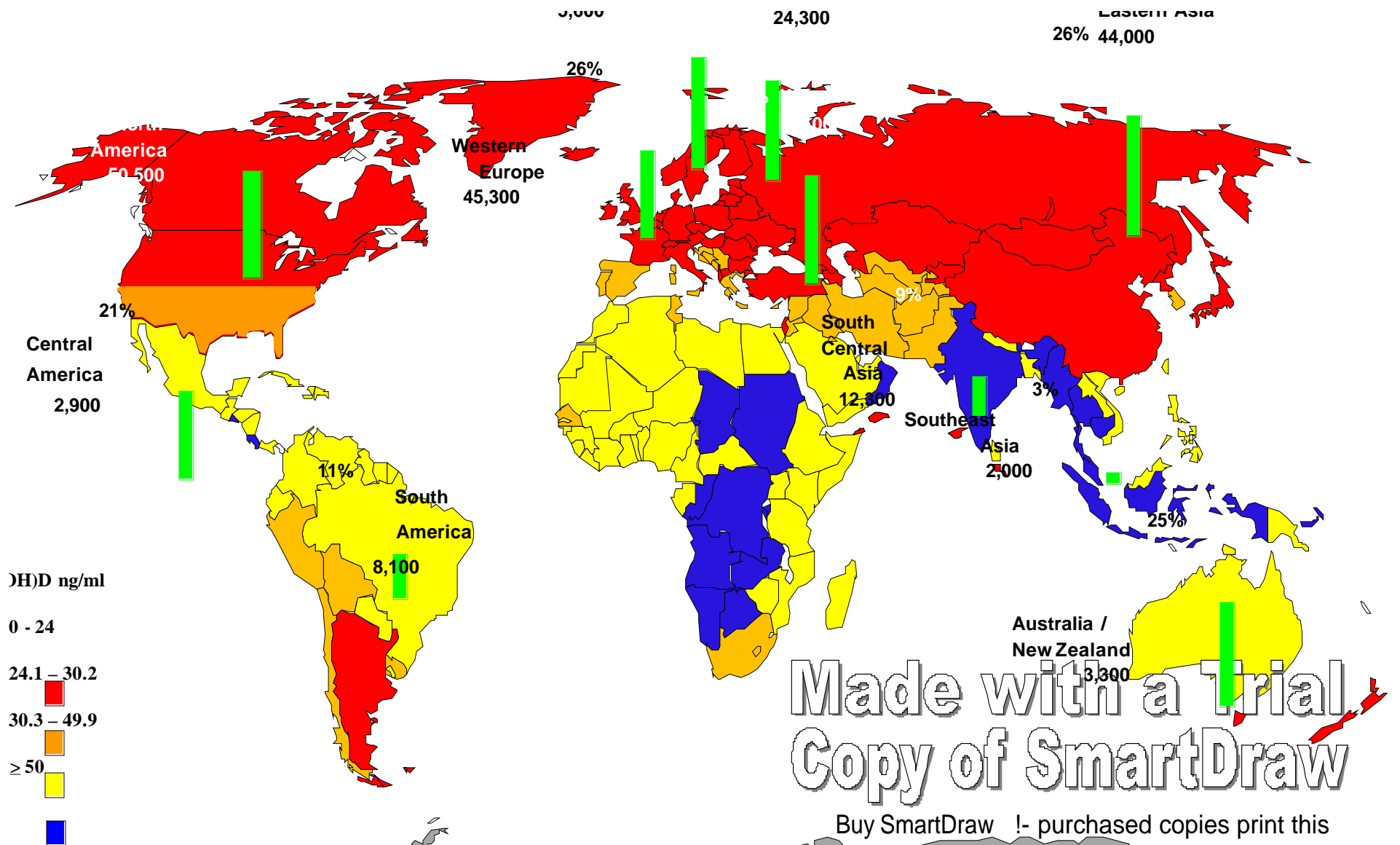
Dose-response relationships from cohort studies were used to estimate the number and percent of cancer cases that could be prevented worldwide by vitamin D₃ supplementation



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Estimated 25(OH)D serum levels (see legend) and projected percentage prevention of colon cancer cases (bars) with 2,000 IU/day of vitamin D₃ and 3-10 minutes daily of noon sunlight seasonally, when weather permits



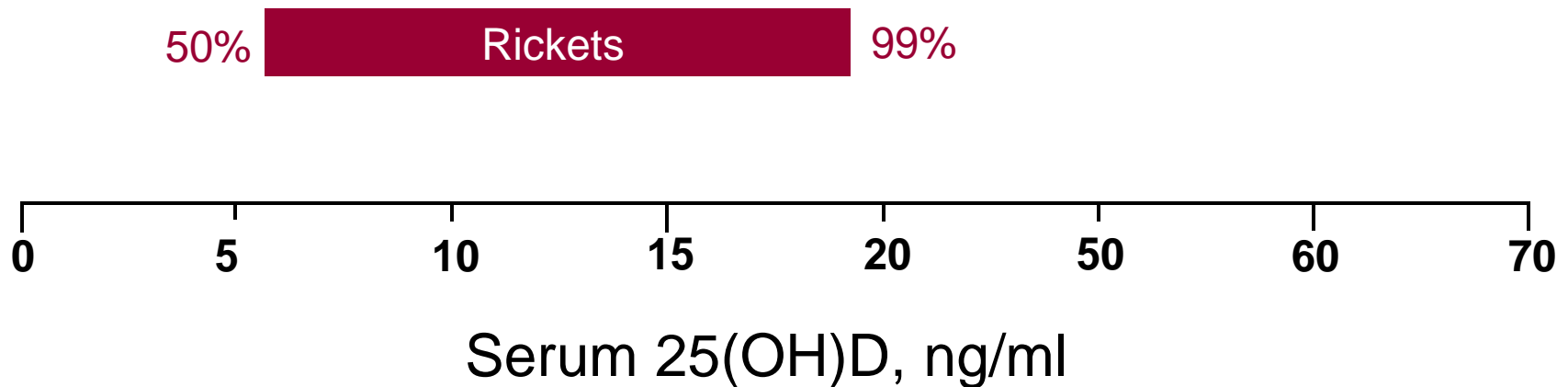
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Estimated 25(OH)D serum levels (see legend) and projected percentage reduction of breast cancer cases (bars) with 2,000 IU/day of vitamin D₃ and 3-10 minutes daily of noon sunlight seasonally, when weather permits

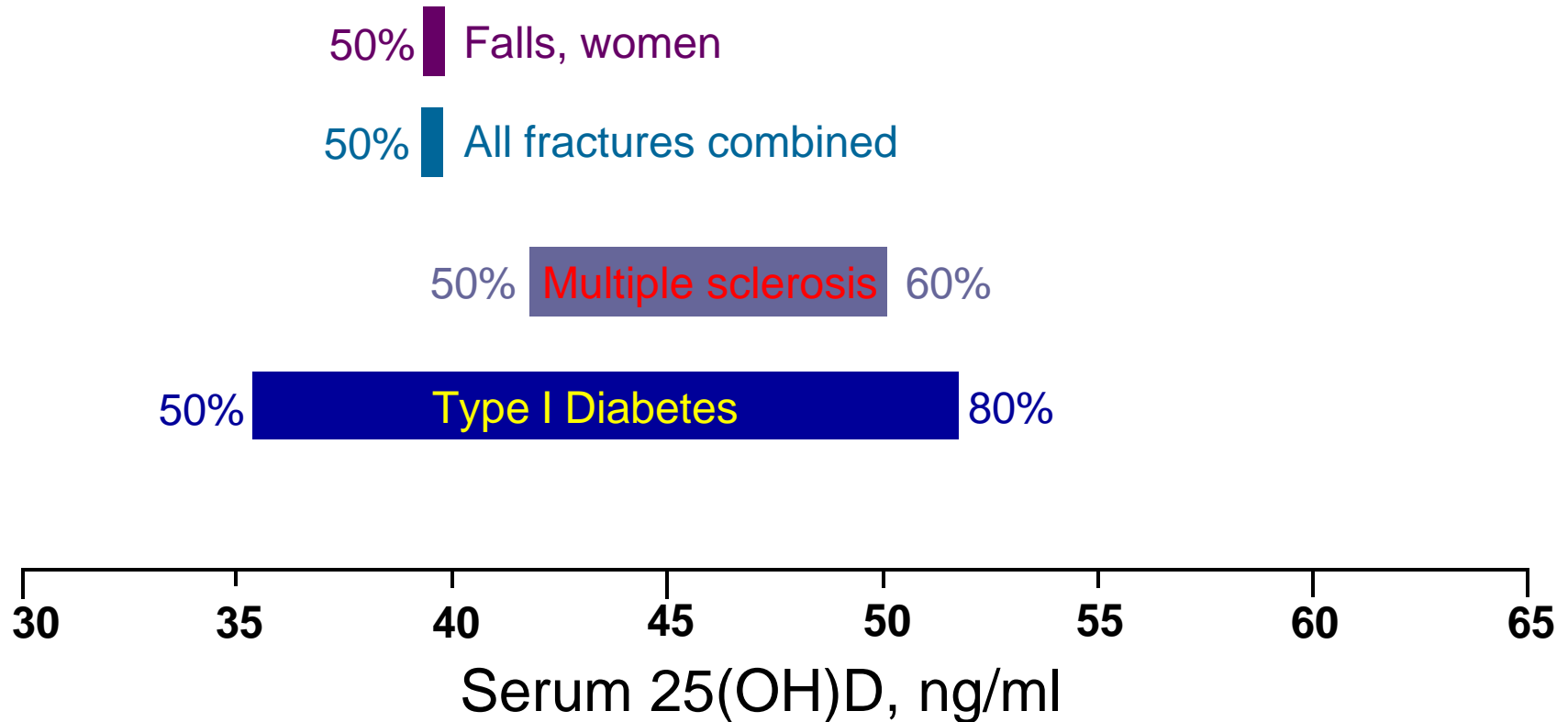
Visit www.smartdraw.com or call 1-800-768-3729

Proportion of Rickets Prevented, by Serum 25(OH) D Level



Source: Arnaud SB et al. Serum 25-hydroxyvitamin D in infantile rickets.
Pediatrics. 1976 Feb;57(2):221-5

Estimated Proportion of other Conditions Preventable by Specified Range of Serum 25(OH) D Level



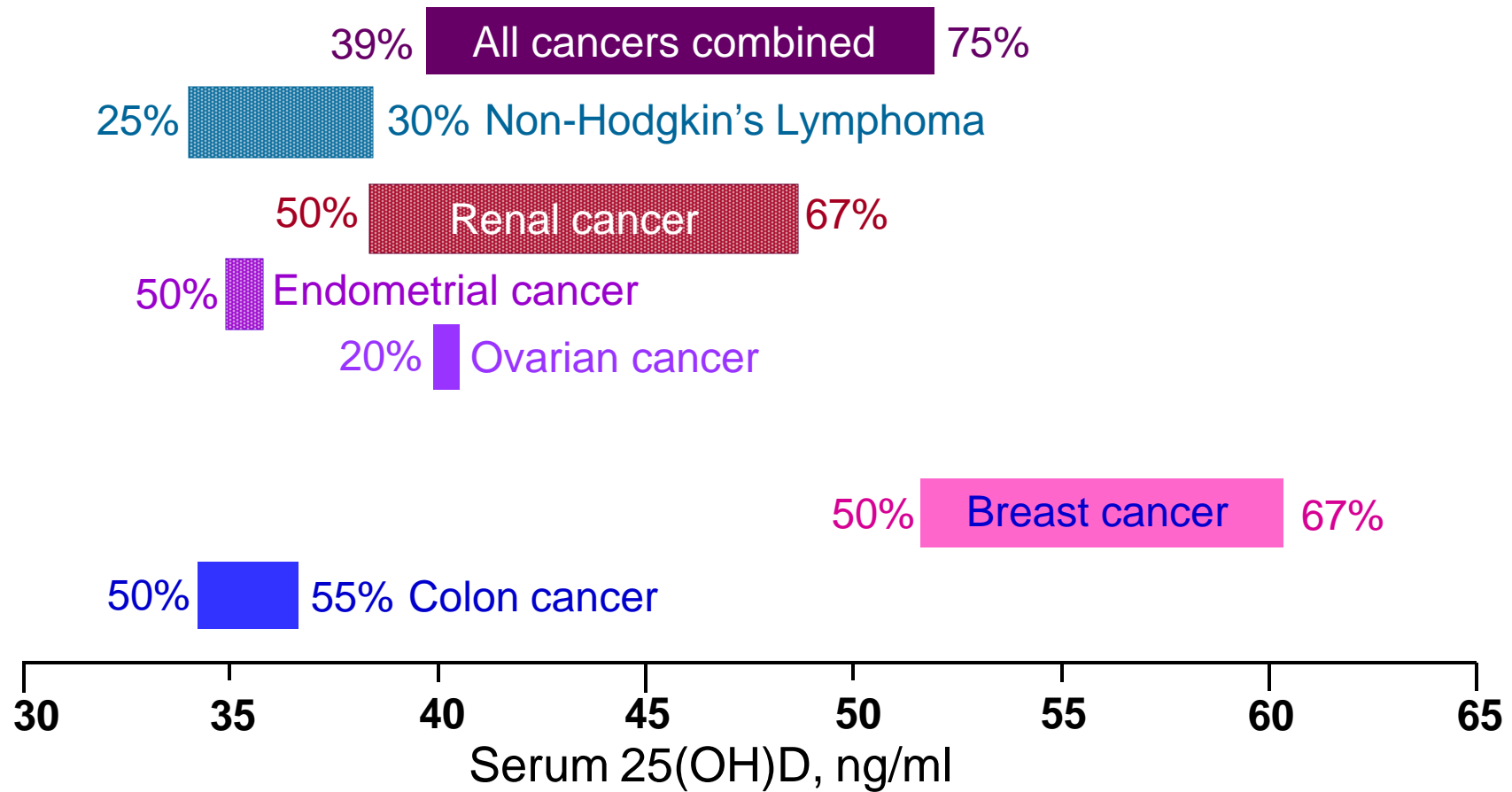
Hyppönen E, et al. Lancet 2001;358:1500-3.

Munger KL, et al. JAMA. 2006;296:2832-8.

Bischoff-Ferrari HA, et al. JAMA. 2005;293:2257-64.

Broe KE, et al. J Am Geriatr Soc. 2007;55:234-9.

Estimated Proportion of Cancers Preventable by Serum 25(OH) D Range



Gorham ED, et al. Am J Prev Med. 2007;32:210-6.

Garland CF, et al. Am Assoc Ca Res Mtg San Diego April 14, 2008

Li H, et al. PLoS Med. 2007;4:103.

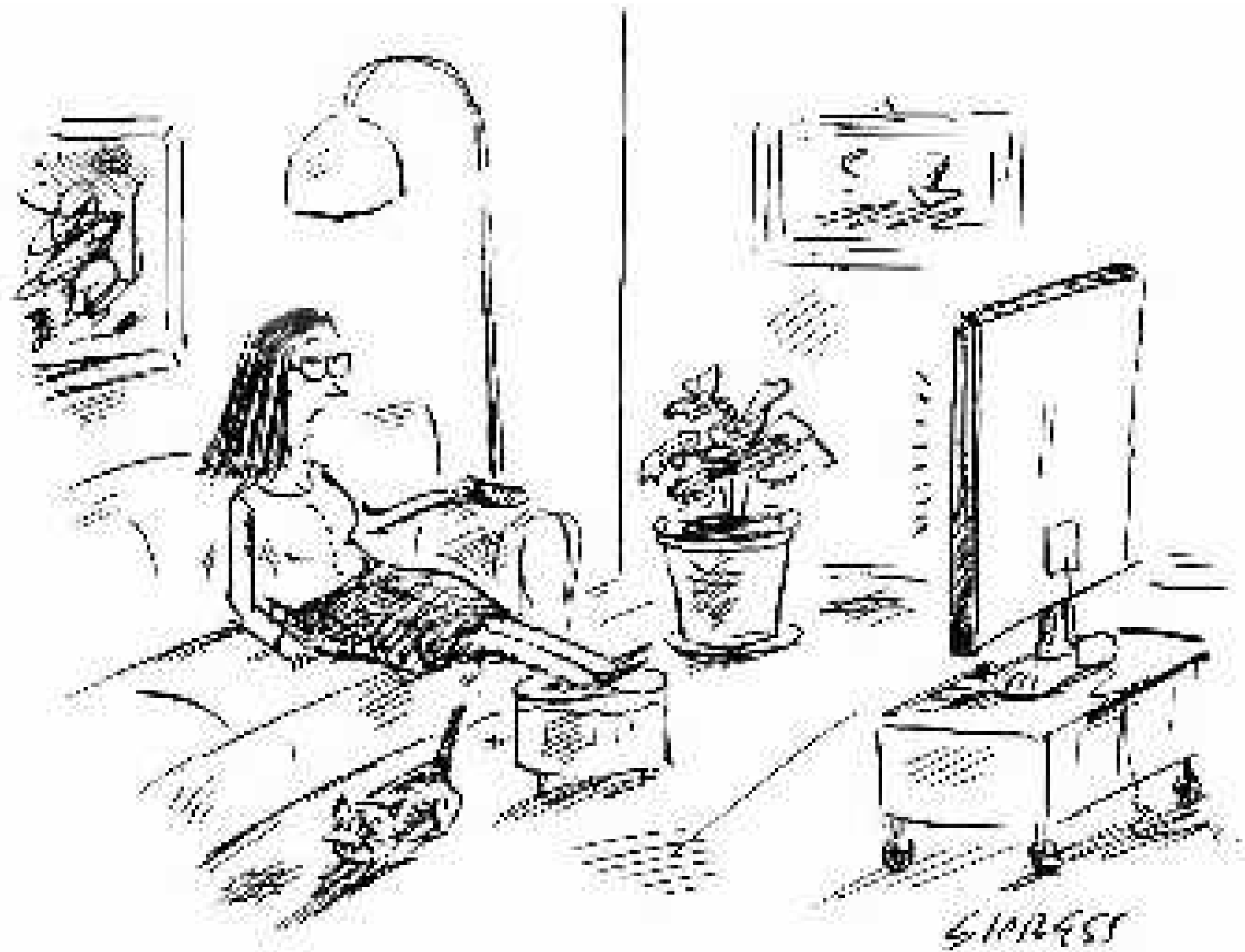
Tworoger SS, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:783-8.

Mohr SB, et al. Prev Med. 2007;45:323-4.

Mohr SB, et al. Int J Cancer. 2006;119:2705-9.

Purdue MP, et al. Cancer Causes Control. 2007;18:989-99.

Lappe JM, et al. Am J Clin Nutr. 2007;85:1586-91.



Ask your doctor if taking a pill to solve all your problems is right for you

Gauging your Vitamin D Status

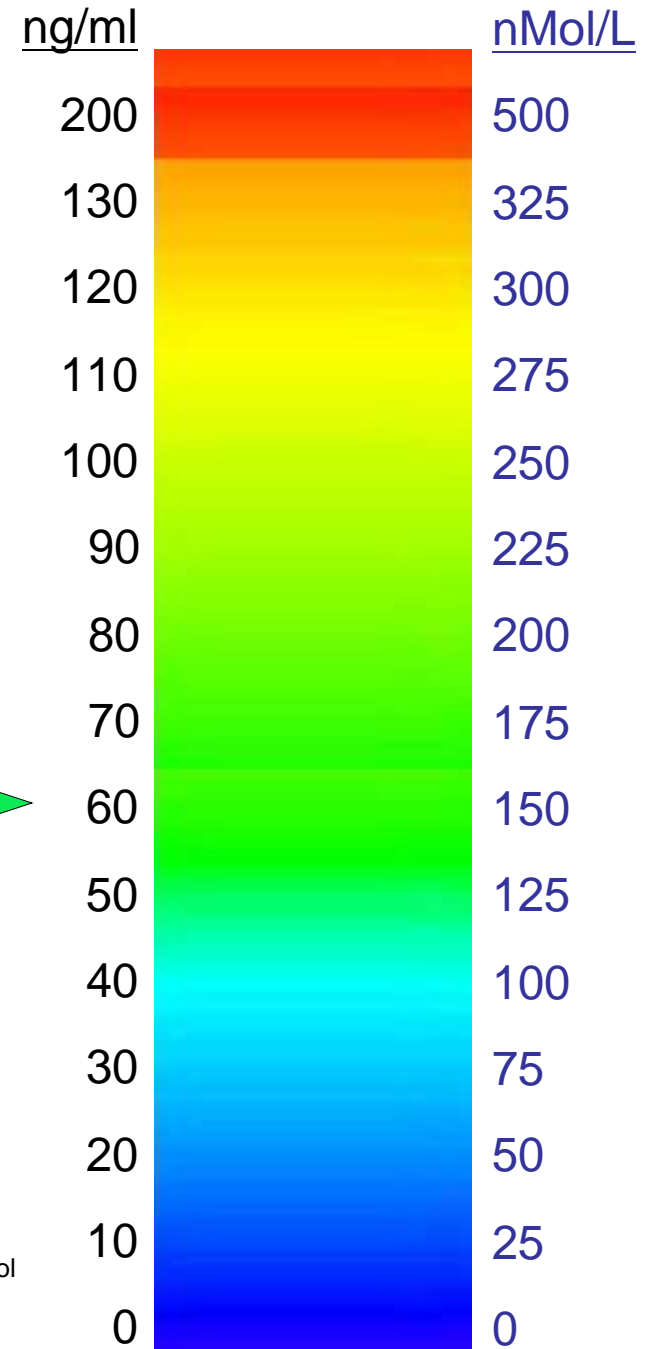
What is the optimal serum 25 (OH) Vitamin D concentration?

People living in sunny places with minimal clothing that doesn't limit vitamin D photosynthesis have serum 25(OH)D levels of 54 to 90 ng/ml (1).

A good target is:

60 nanograms/ml

A useful rule of thumb is that for every 100 IU of vitamin D₃ ingested, there is a gain 1 ng/ml in serum 25 (OH)D. Example: If the patient's current level is 20 ng/ml, 4,000 IU/day would raise it to 60 ng/ml (2).



1. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317-22

2. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77:204-10.



Cancer and Vitamin D

Conclusions

Serum target: 40-60 ng/ml

Minimum oral intake of vitamin D₃ at 30 degrees or higher, in general:

Adults: 2,000-2,400 IU (NAS NoAEL)

Children 1-12 years: 2,000 IU

Infants: 1000 IU