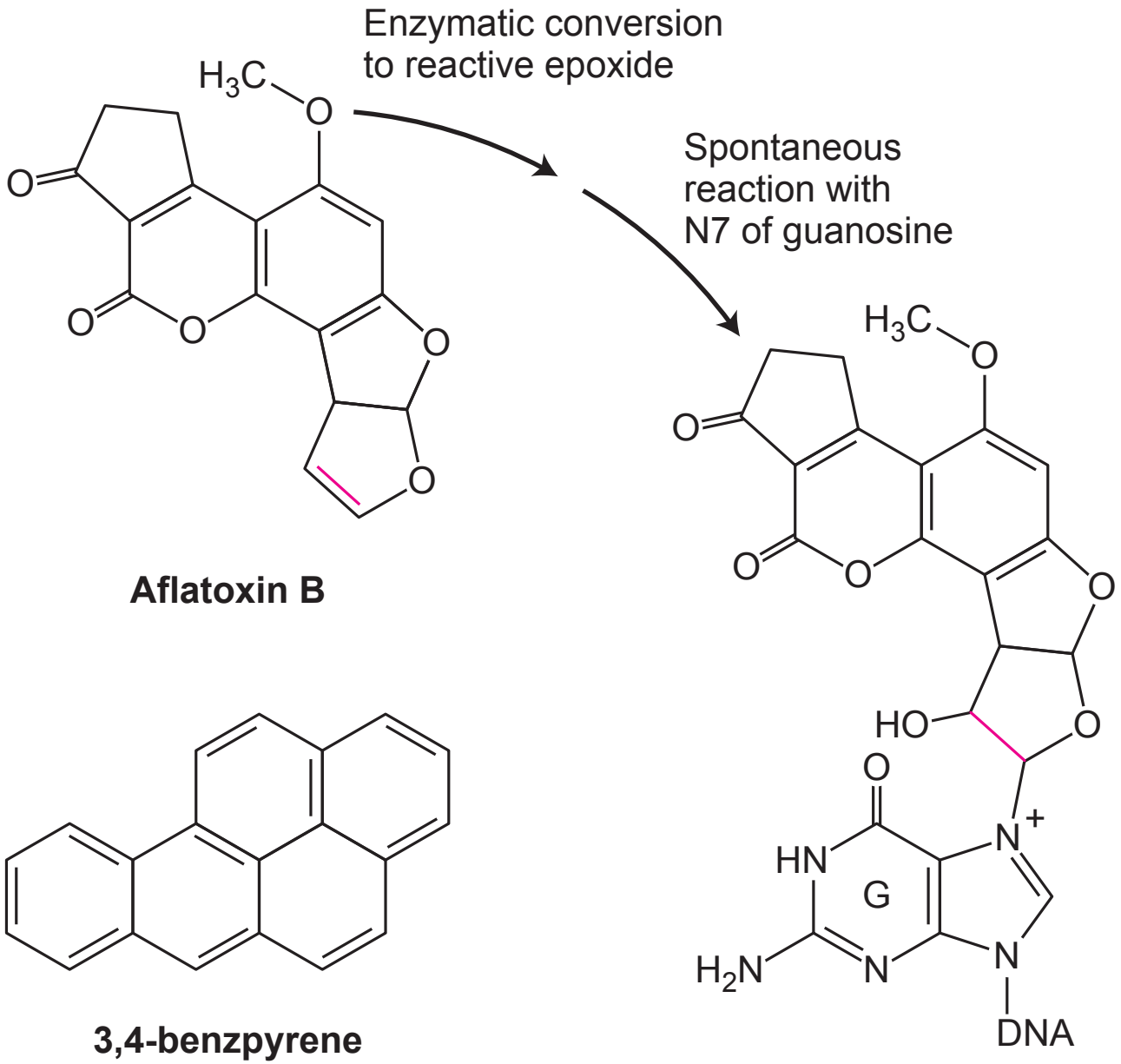
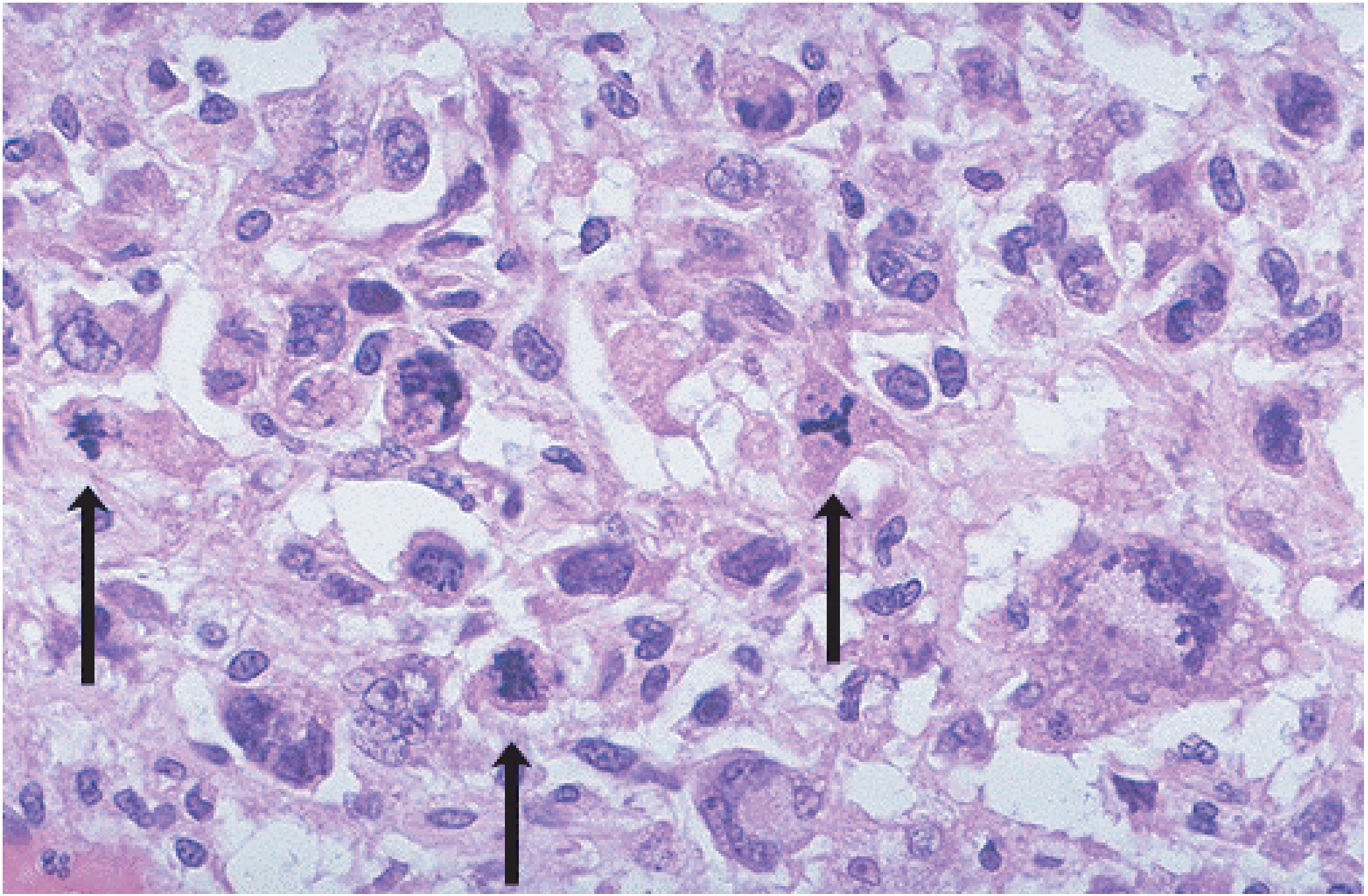
Most environmental causes of cancer are mutagens: mutagenic compounds, X-rays, uv



Cancer tends to arise in actively dividing cells

- Epithelial cells (lining of intestine, lungs etc.) = **carcinoma**
- Blood and lymphatic cells = **lukemia, meyloma, lymphoma**
- Connective tissue (bones, tendons muscle) = **sarcoma**

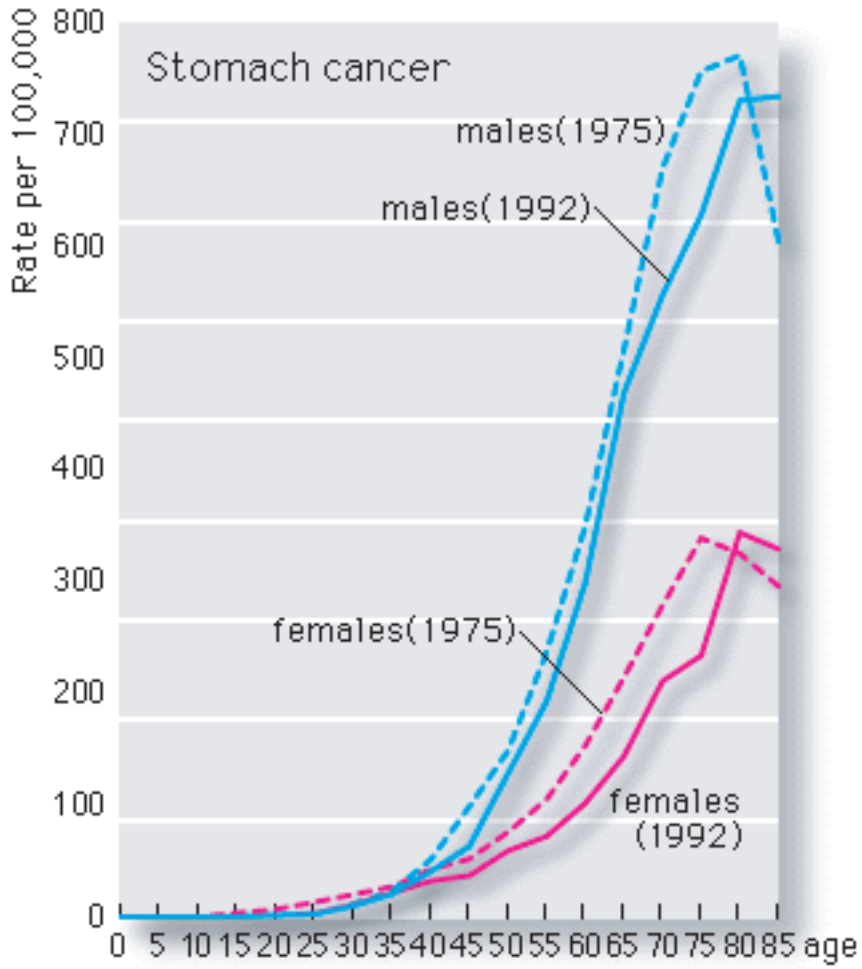


Cancer is a genetic disease of somatic cells

The underlying cause is mutations
that release cells from the normal constraints
that exist in well organized tissues
allowing uncontrolled growth

Which are the key genes that are mutated ?

Incidence of stomach cancer as a function of age

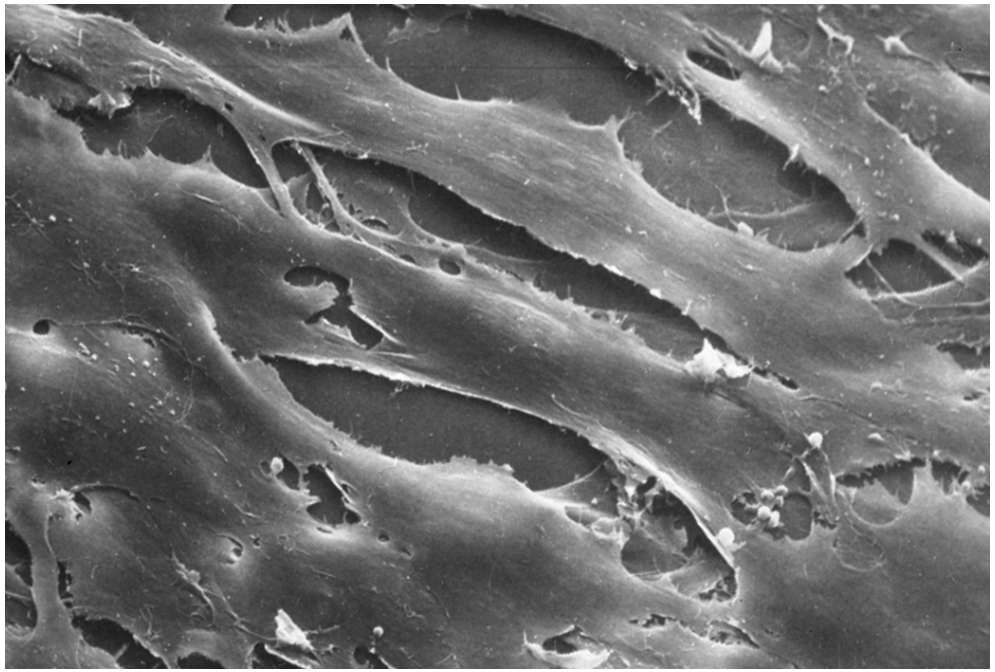


Major complications in understanding the genetic basis of cancer

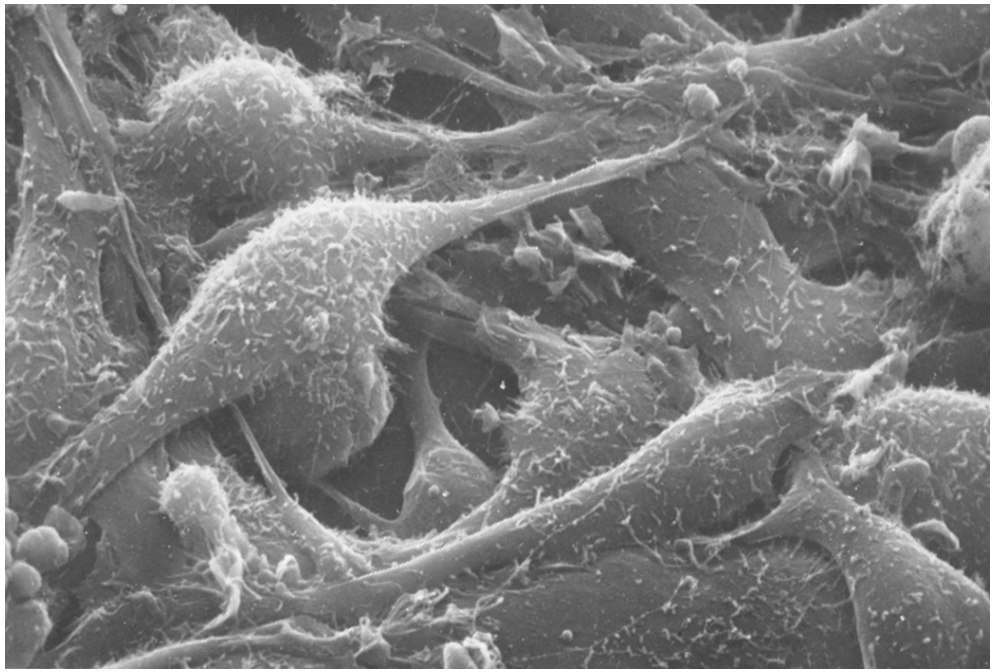
- Multiple mutations are necessary to produce a tumor cell
- Different types of tumor have different genes mutated
- Early initiating events occur rarely in complex tissues and are therefore extremely difficult to detect
- The key initiating event often leads to an increase in mutation rate thus tumor cells often bear many fortuitous mutations

Important aspects of the disease we won't discuss relate to the spread of cancer cells and the formation of large tumors (metastasis and **angiogenesis**)

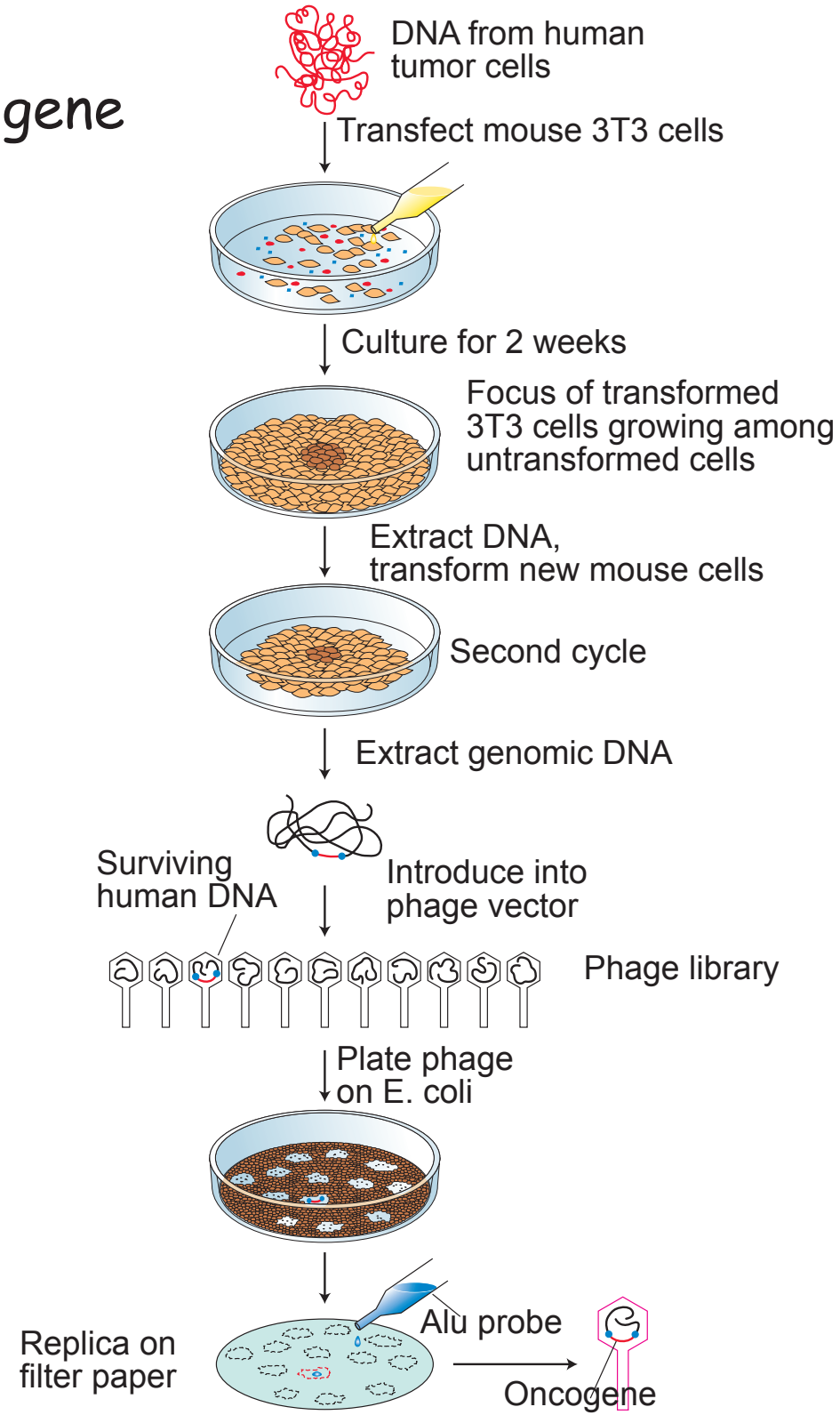
3T3 cells in culture

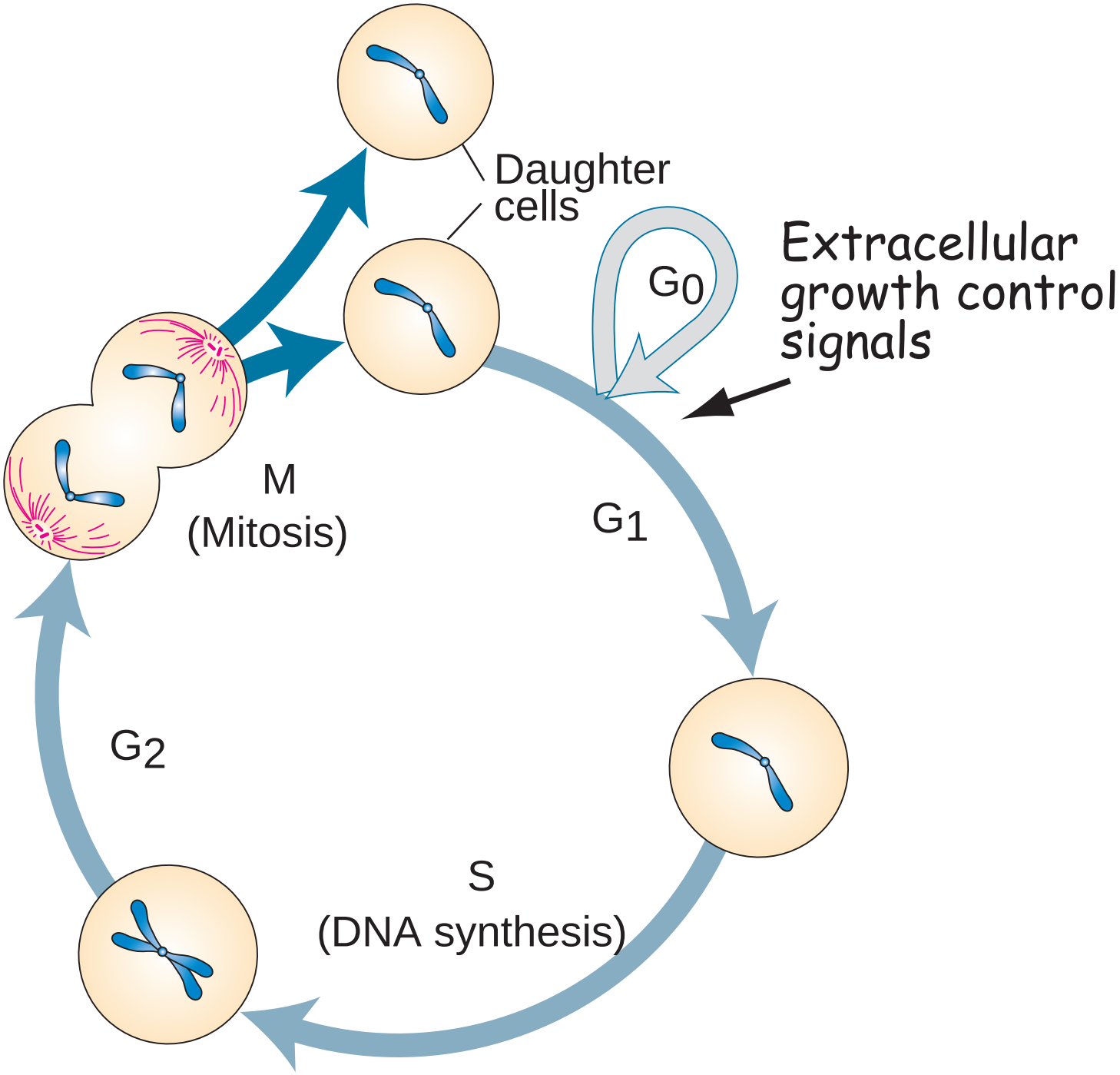


Transformed 3T3 cells

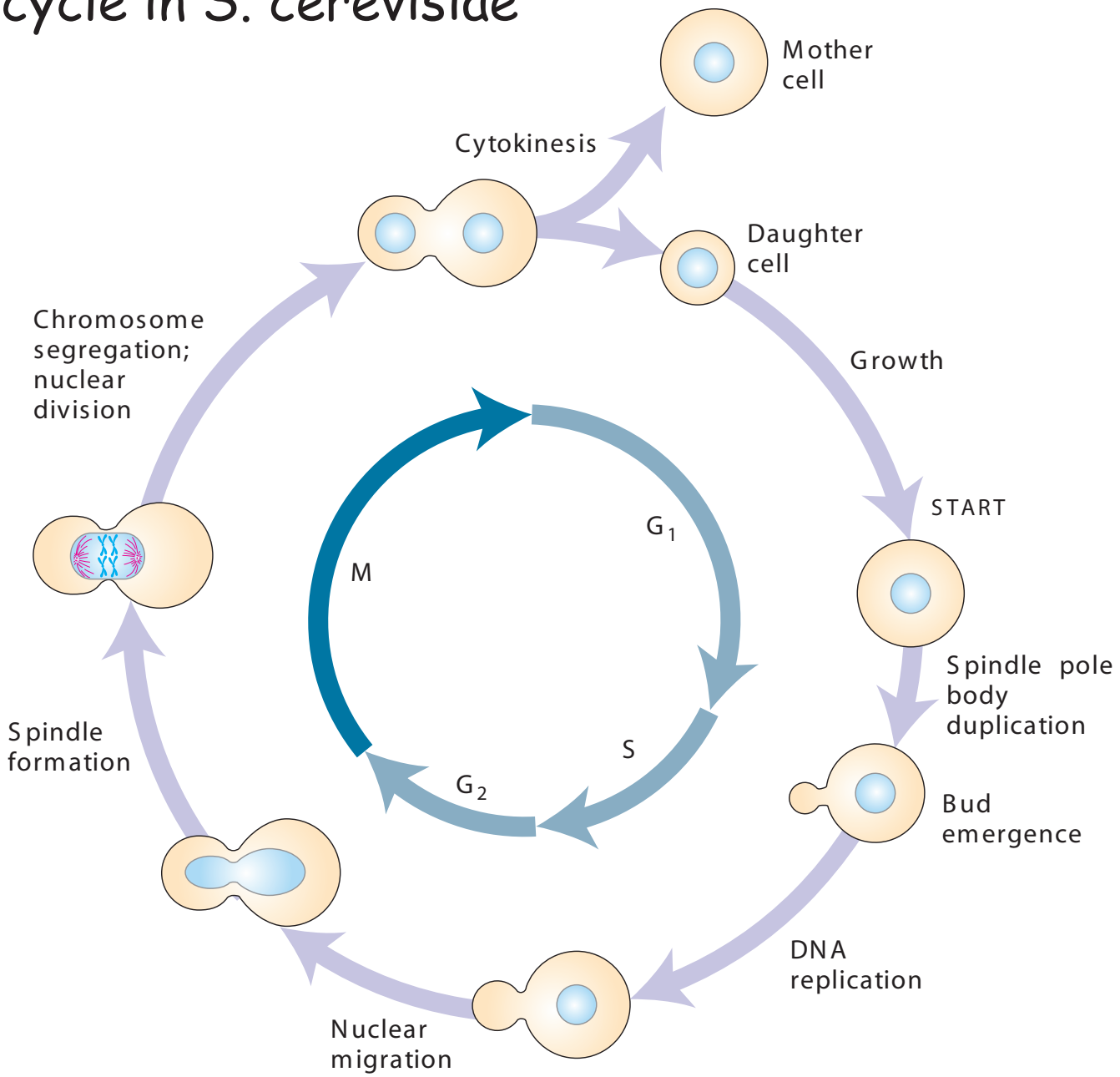


Isolation of the Ras oncogene from human tumor cells

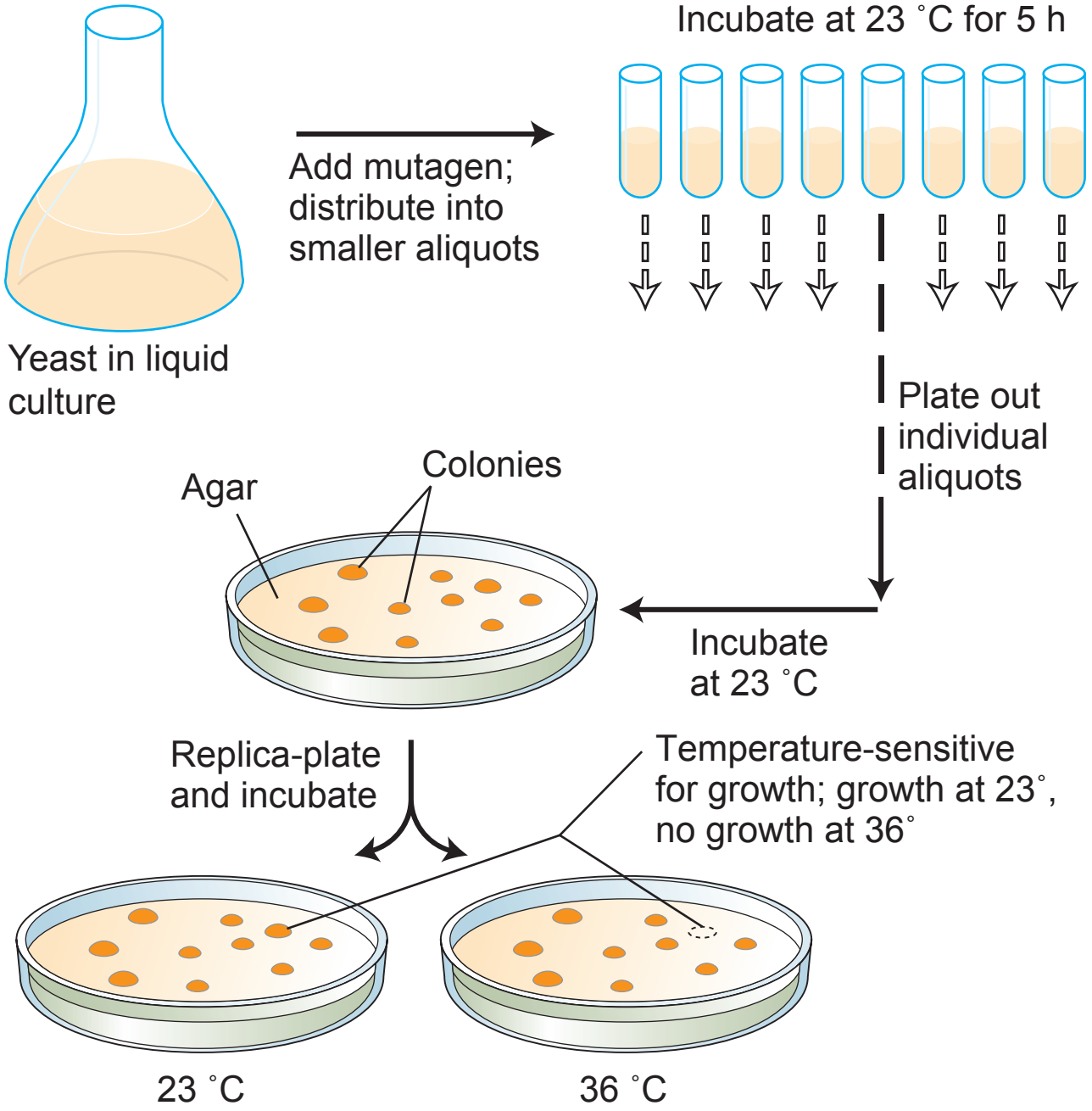



Daughter cells
Extracellular growth control signals
G0
M
(Mitosis)
G1
S
(DNA synthesis)
G2

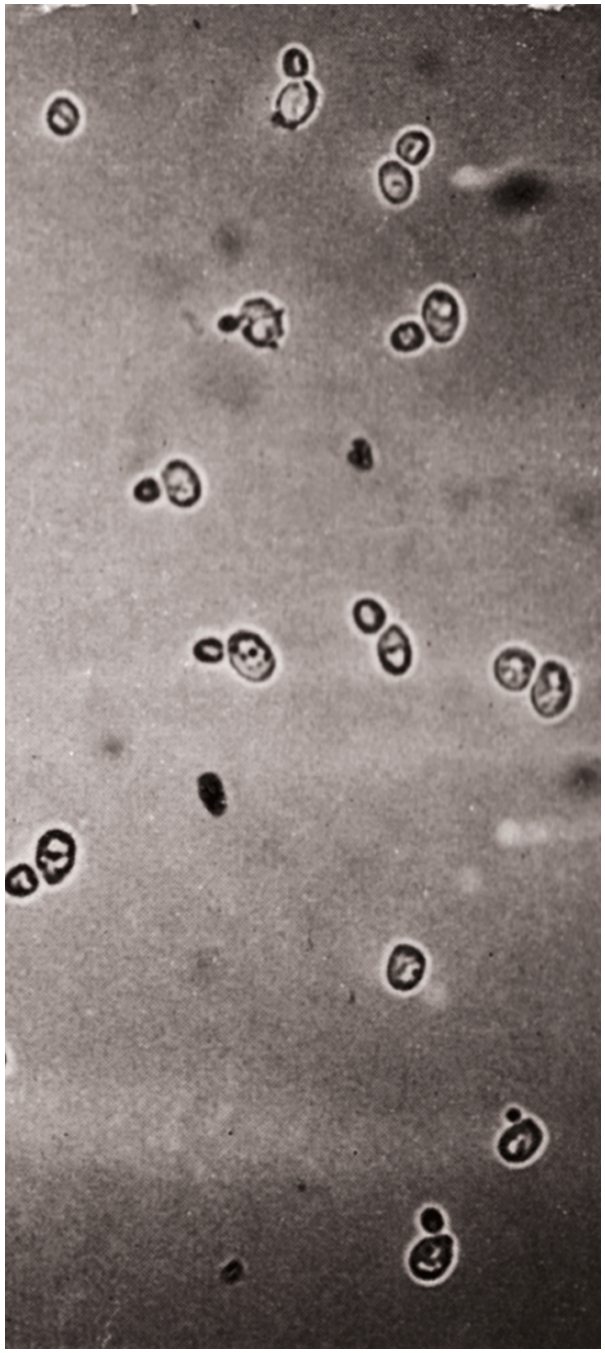
Cell cycle in S. cerevisiae



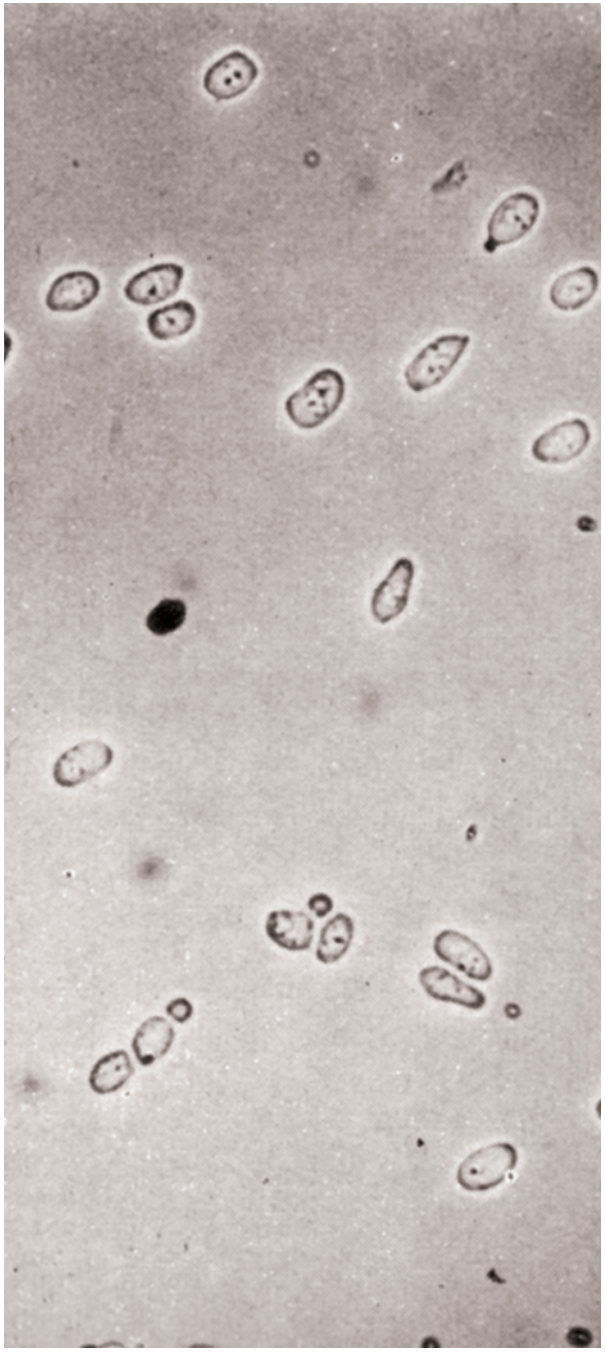
A genetic screen for cell cycle mutants



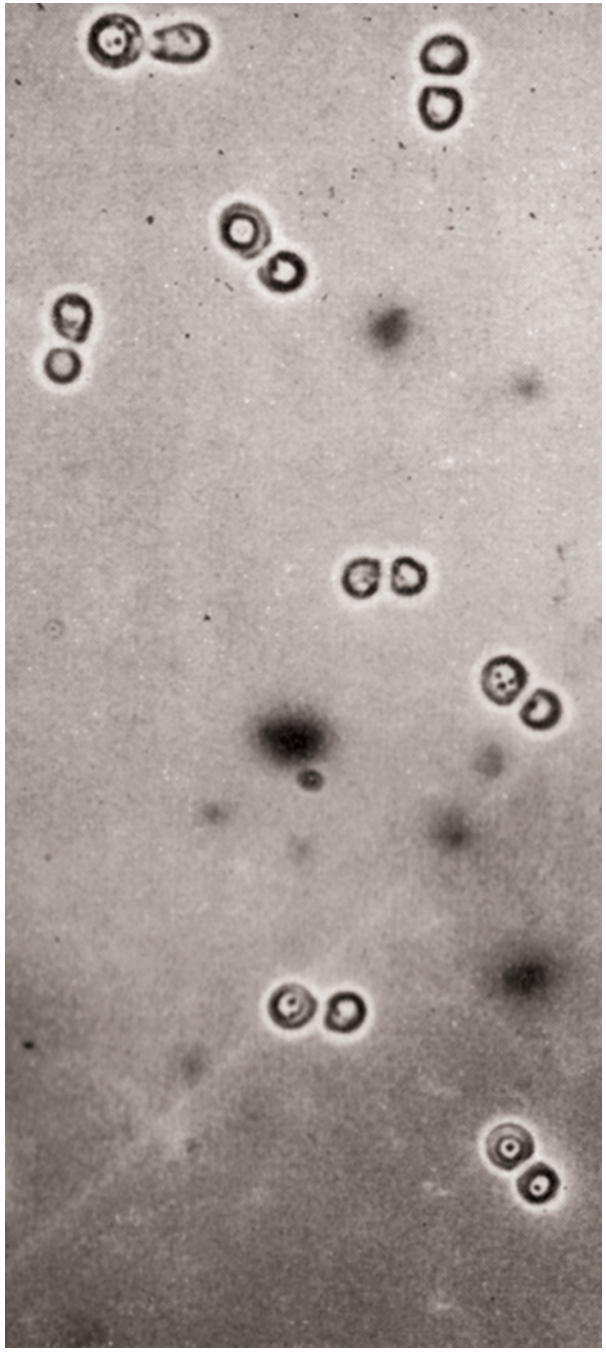
Wild type



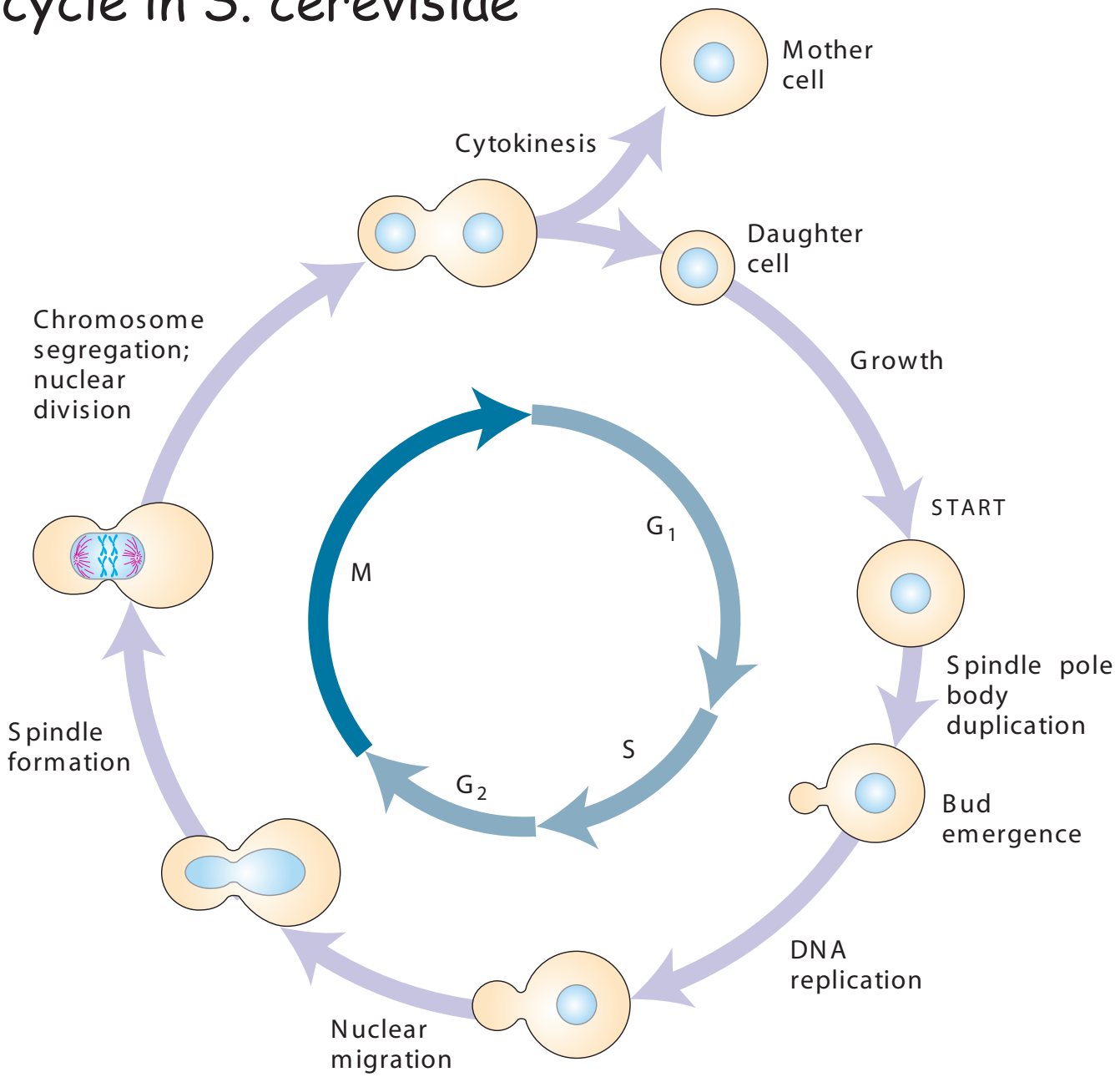
cdc28 mutant



cdc7 mutant

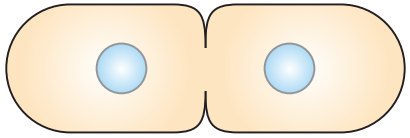


Cell cycle in S. cerevisiae

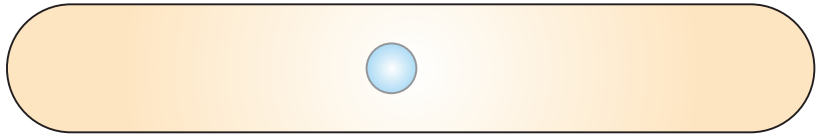


Opposite effects of cdc2 alleles in S. pombe

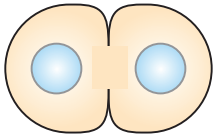
$cdc2^{+}$ (wild type)

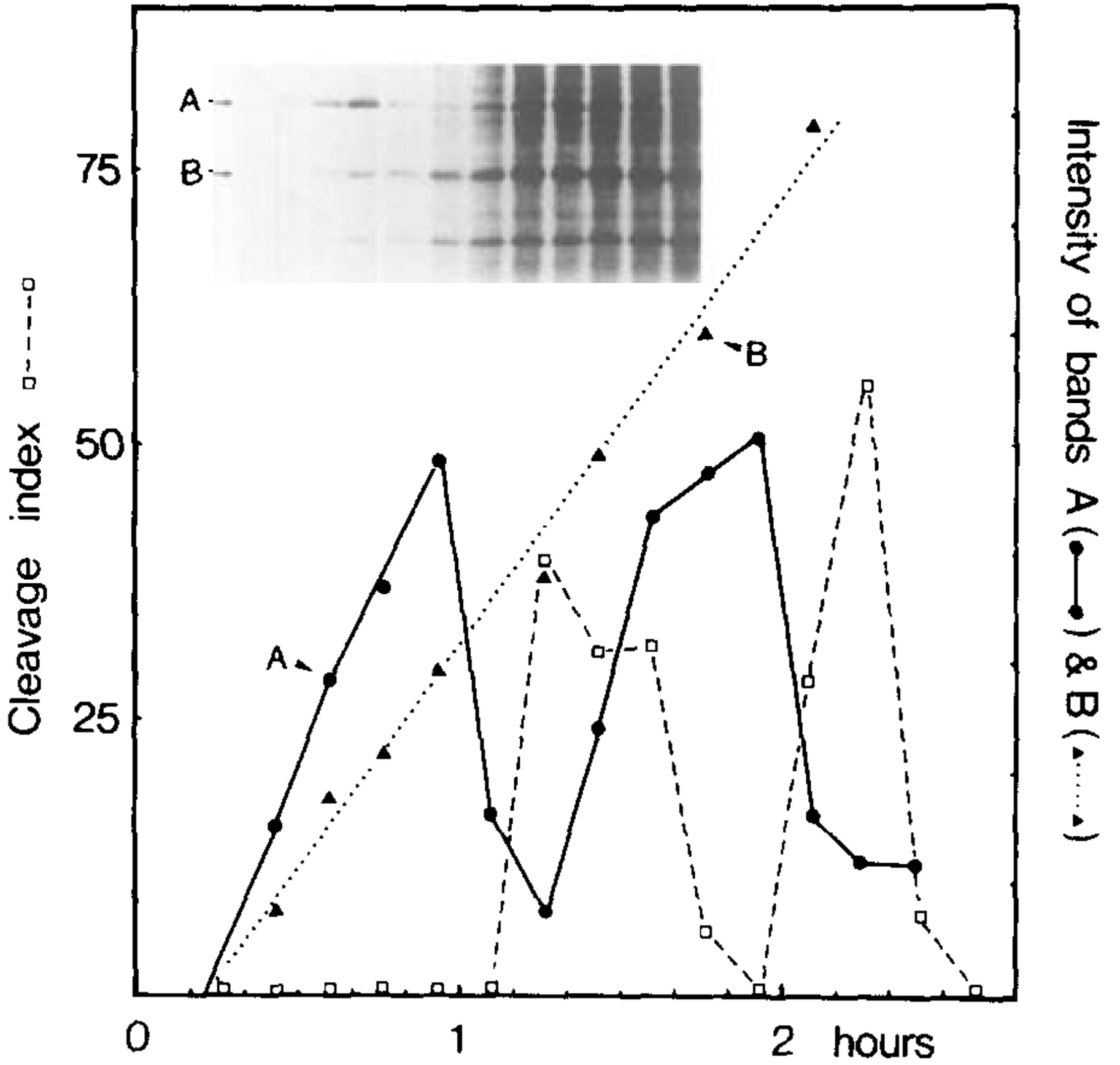


$cdc2^{-}$ (recessive)



$cdc2^{D}$ (dominant)




A
B
75
50
25
Cleavage index
A
B
0
1
2 hours
Intensity of bands A (●—●) & B (▲·····▲)

What is the basic organization of the cell cycle ?

Are the steps of the cycle mechanistically linked ?
"substrate-product" model

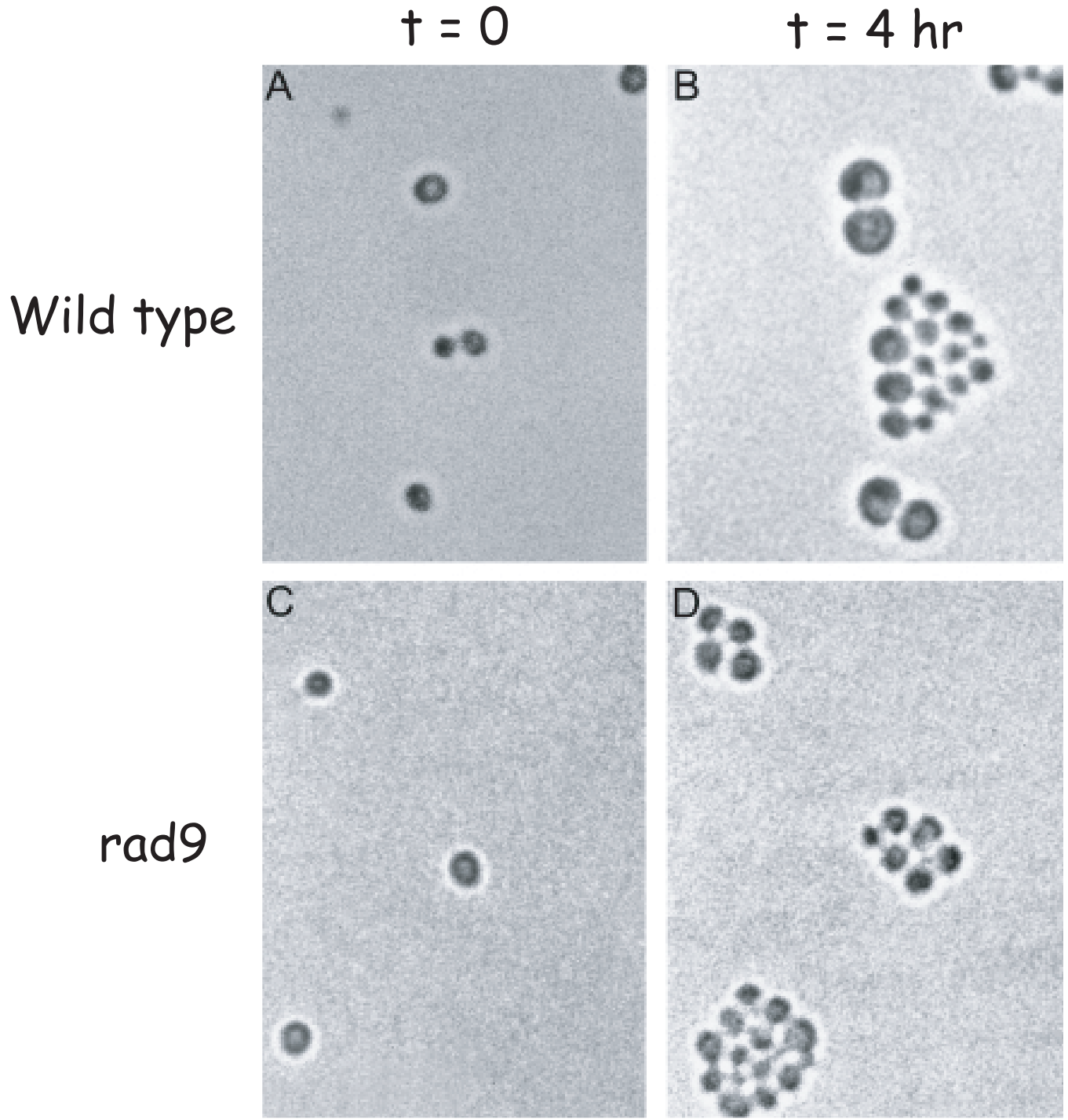
Is there an autonomous "cell cycle clock" ?

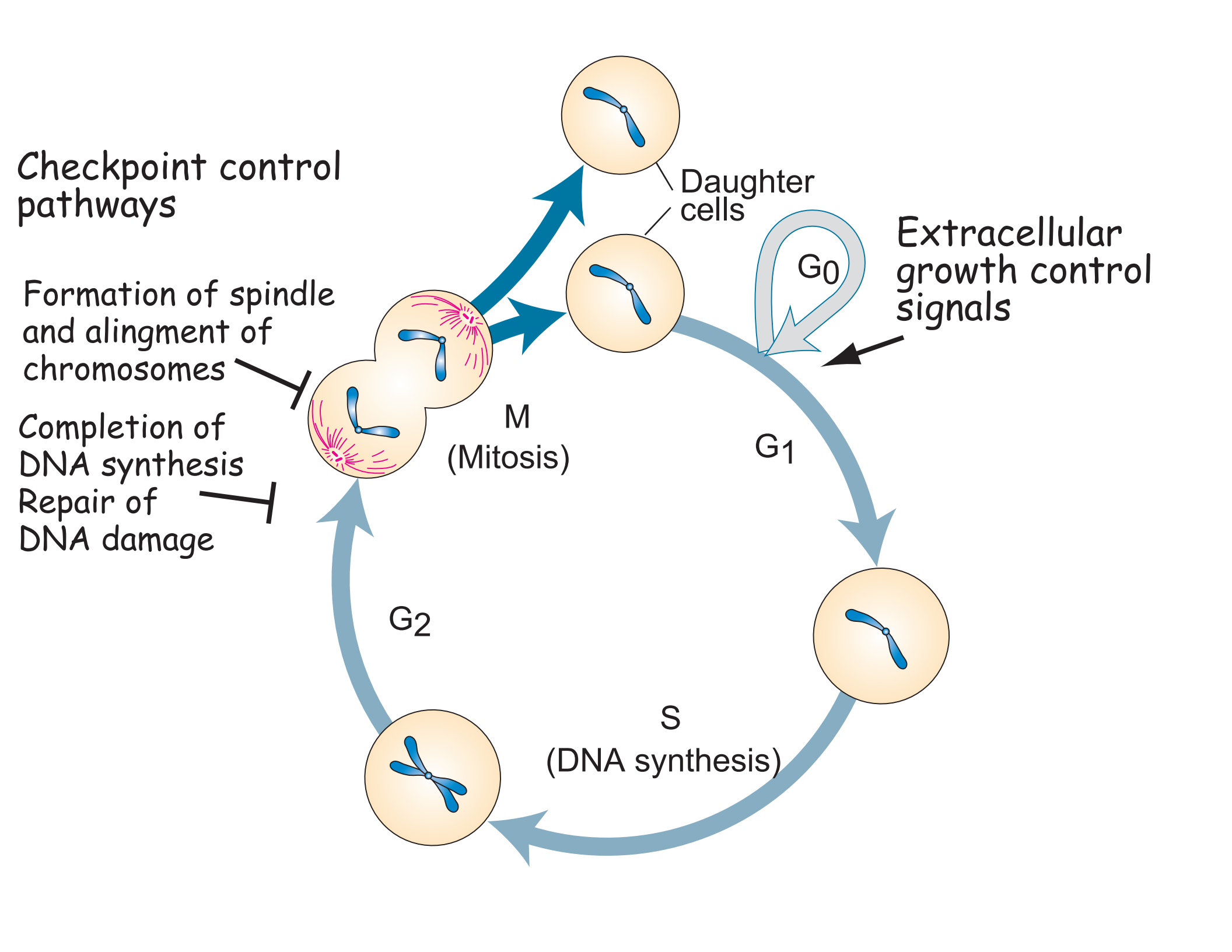
There is there an autonomous "cell cycle clock"
which is composed of cyclin + CDK

The amount of cyclins oscillates
throughout the cell cycle

However, the steps of the cycle are linked
by negative feedback loops
known as "checkpoint control" pathways

After X-rays




Checkpoint control pathways
Formation of spindle and alingment of chromosomes
Completion of DNA synthesis
Repair of DNA damage
Daughter cells
Extracellular growth control signals
G0
M
(Mitosis)
G1
S
(DNA synthesis)
G2

General types of mutations leading to cell transformation

Activation of growth control pathways
signaling quiescent cells to divide inappropriately

Inactivation of checkpoints
allowing cells with damaged DNA or misaligned chromosomes
to divide allowing high mutation rates and chromosome imbalances

Inactivation of DNA repair genes
allowing high mutation rates causing other oncogenic mutations

Oncogene —

dominant gain-of-function mutations
promote cell transformation

Tumor suppressor gene —

recessive, loss-of-function mutations
promote cell transformation