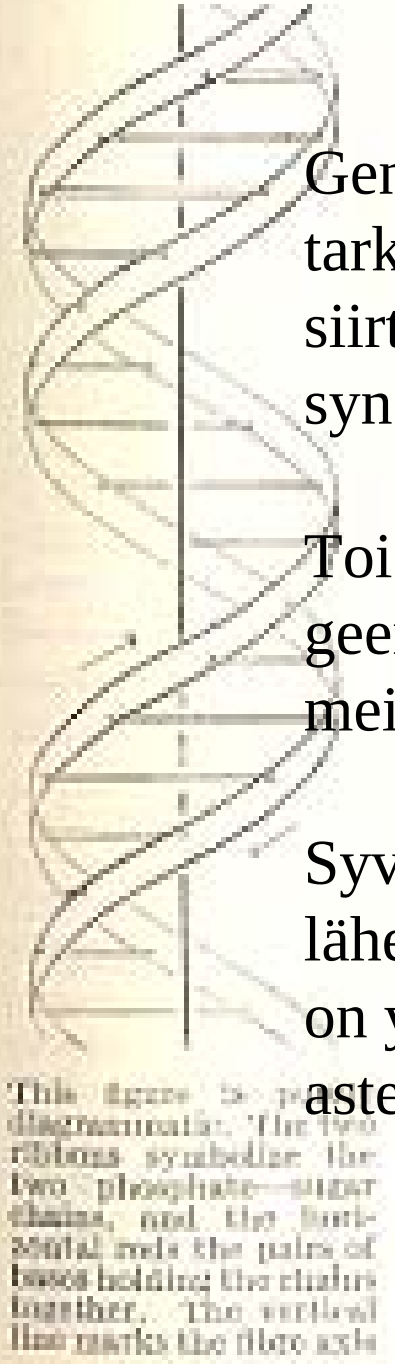
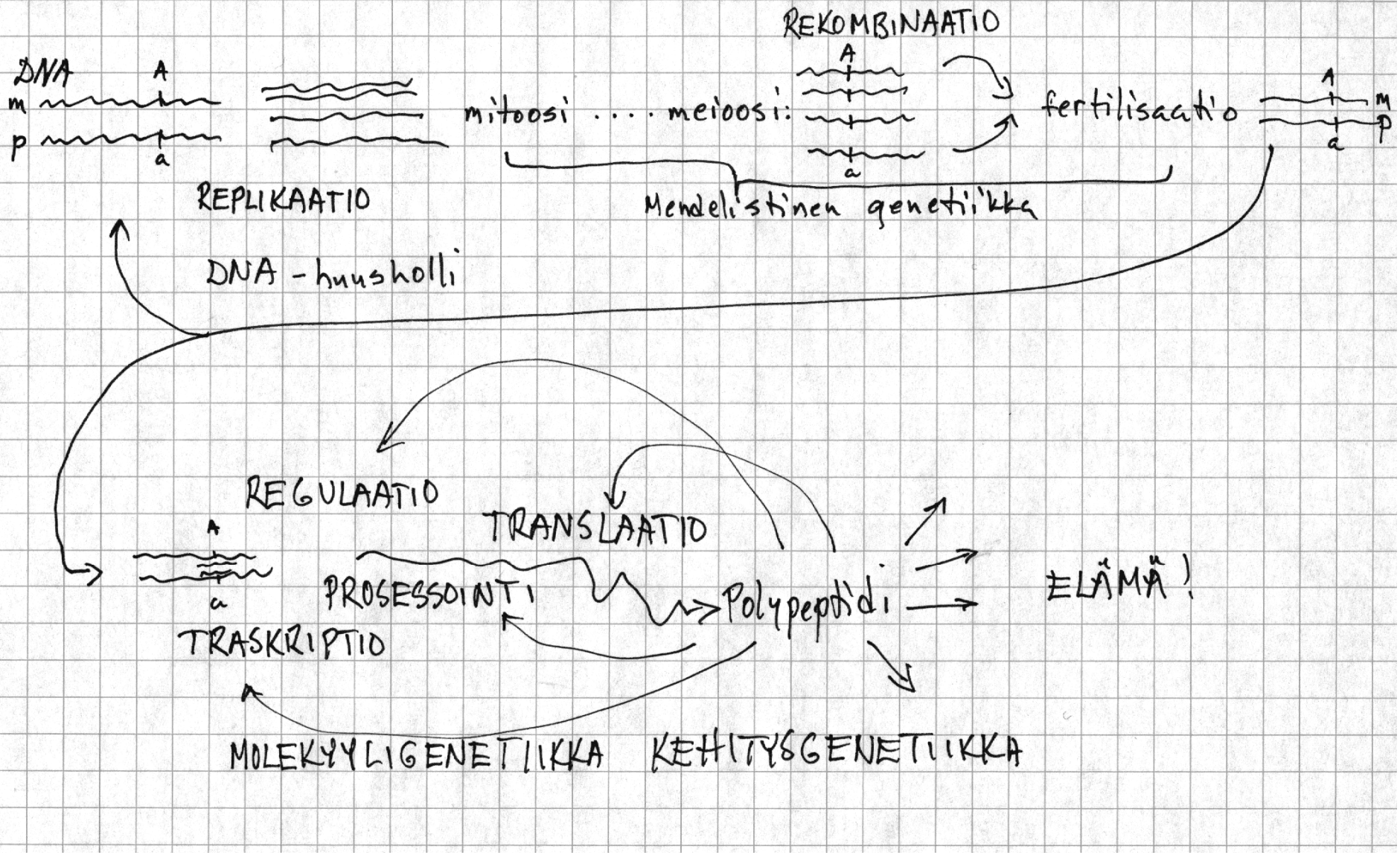


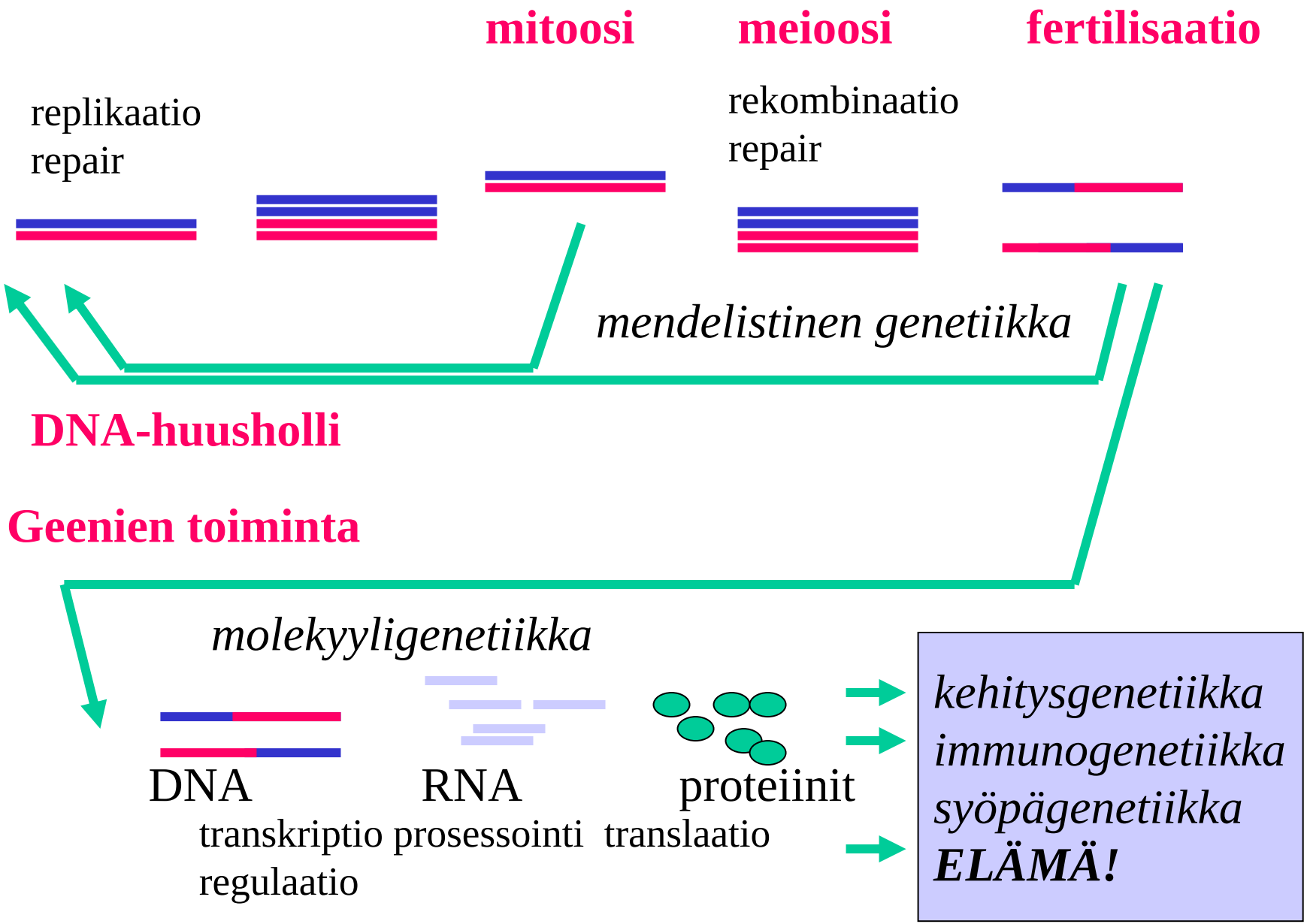
Genetiikan perusteiden luentojen ensimmäisessä osassa tarkasteltiin *transmissiogenetiikkaa* eli sitä, kuinka geenit siirtyvät sukupolvesta toiseen. Mendelistinen g. on sen synonyymi

Toisessa osassa ryhdymme tarkastelemaan sitä, mitä geenit ovat, miten ne toimivat ja miten ne tuottavat meille tuttuja elämänilmiöitä

Syvällä tasolla (reduktio) tiedetään paljon, mutta mitä lähemmäksi tosi tärkeitä asioita tullaan, sitä vajavaisempi on ymmärrys. Jos geenejä on 30 000, on ensimmäisen asteen vuorovaikutuksia 30 000 (res/dom) + $30\,000^2$



Genetiikan perusteiden miellekartta



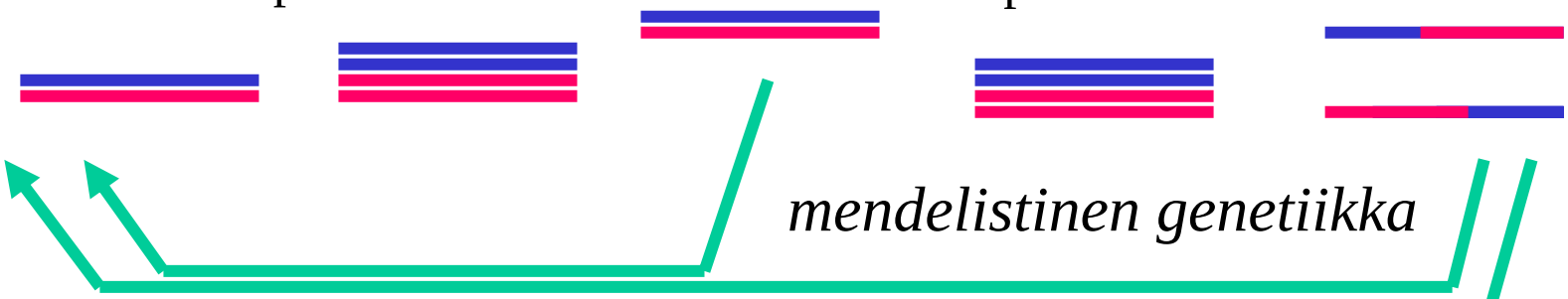
Genetiikan perusteiden miellekartta

CELL 194-

mitoosi **meioosi** **fertilisaatio**

replikaatio

rekombinaatio
repair



mendelistinen genetiikka

DNA-huusholli

Geenien toiminta

molekyyligenetiikka

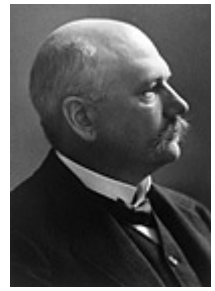
DNA RNA proteiinit

transkriptio prosessointi translaatio
regulaatio

kehitysgenetiikka
immunogenetiikka
syöpägenetiikka
ELÄMÄ!

Genetiikan perusteiden miellekartta: tänään DNA, historia

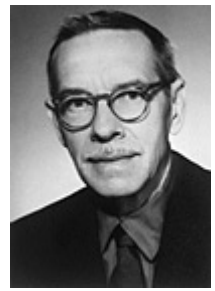
DNA on materiaali joka akkumuloi, säilyttää ja siirtää geneettisen informaation



Miten se keksittiin?

Kemiallinen luonnehtinta: Kossel (*1910*), Todd (*1957*)

Transformaatio: Griffith 1928, Avery, McLeod, McCarty 1944



Transduktio: Hershey & Chase (*1969*)

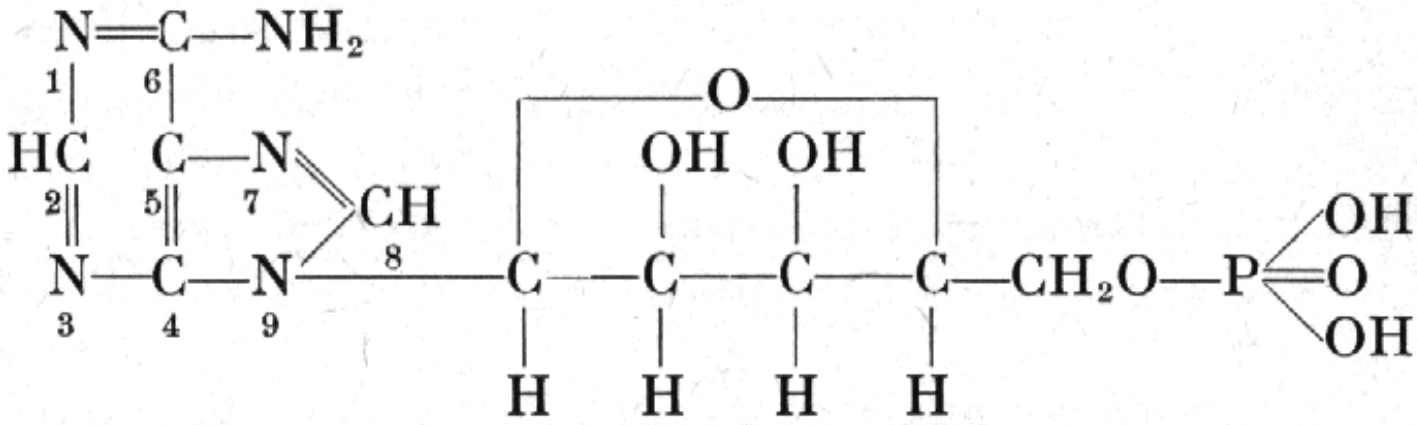
Rakenne: Watson, Crick, Franklin, Wilkins 1953 (*1962*)

Genetiikan oppikirja vuodelta 1950 tietää DNA:sta:

Die Kerne sind vor allem reich an phosphorsäurehaltigen Verbindungen, Nukleinsäuren, die mit Eiweiss zu Nukleoproteiden verbunden sind

DNA:n runsastuminen ennen mitoosia oli havaittu, mutta silti sille haluttiin antaa vain rakenneosan rooli:
liian yksikertainen kemia geeniksi

Nukleinsyrorna äro högmolekylära föreningar (*polynukleotider*), som vid försiktig hydrolys uppdelas i *mononukleotider*. En sådan är sammansatt av tre komponenter, en *kvävebas*, som kan vara ett purin- eller pyrimidinderivat (s. 279), en *sockerart*, som kan vara D-ribos eller 2-deoxi-D-ribos (s. 214), samt *fosforsyra*. Ett exempel på en mononukleotid är *muskeladenylsyra*, innehållande adenin, ribos och fosforsyra:



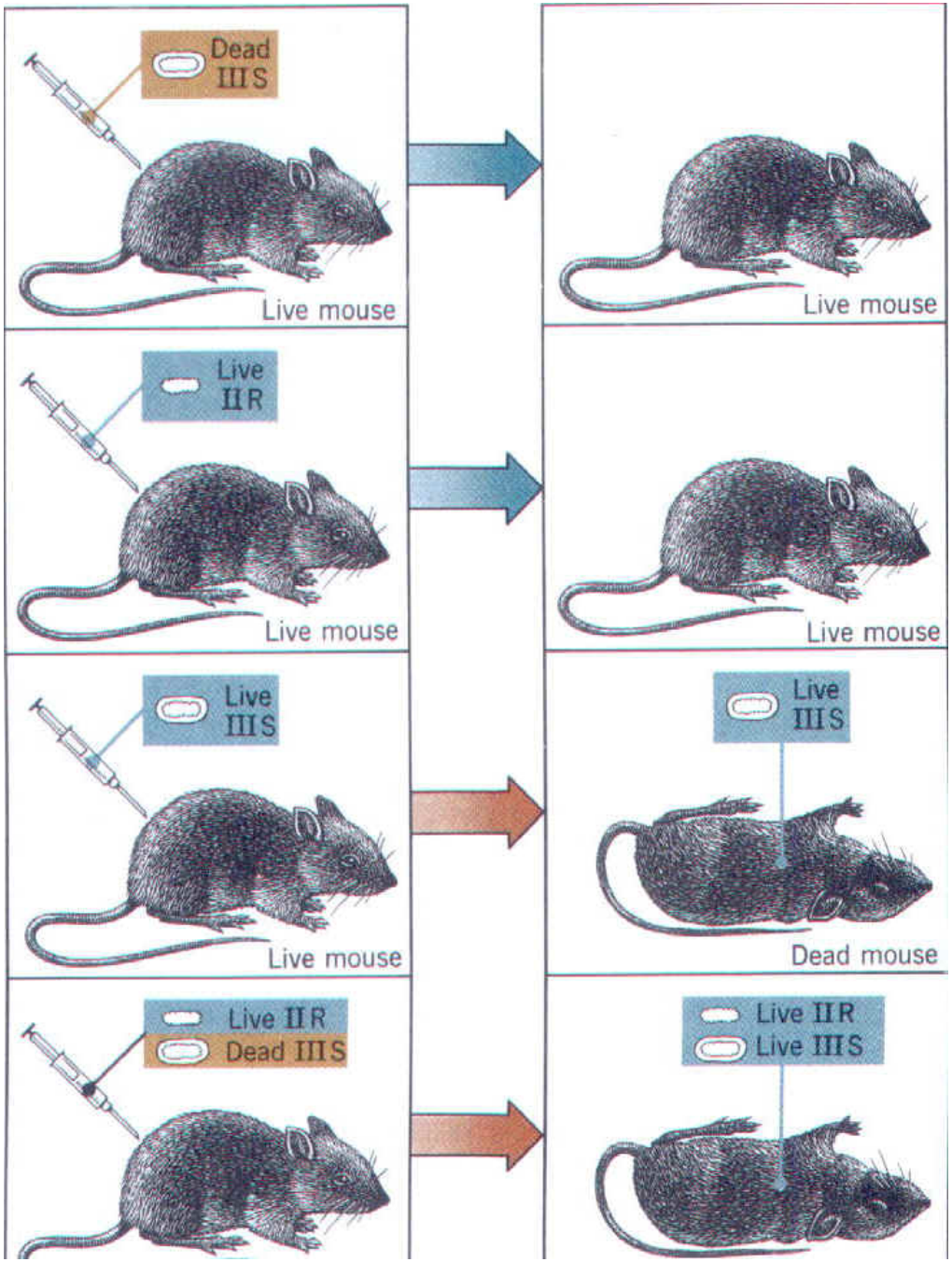
[1] För undersökningar rörande bl.a. nukleinsubstansernas kemi erhöll ALBRECHT KOSSEL (1853—1927), Heidelberg, nobelpriset i medicin 1910. 1957 års nobelpris i kemi tilldelades ALEXANDER TODD, Cambridge, likaledes för arbeten inom detta område.

Geeniksi liian yksinkertainen. **Linus Pauling** oli saanut Nobelin proteiinien perusrakenteen keksimisestä, ja piti paljon yksinkertaisemman deoksiribonukleiinihapon rakennetta ihan omana pikku kakunpalanaan eikä oikein viitsinyt edes ponnistella. Niinpä (hänen mielestään simppelit) Watson ja Crick ehtivät ensin!
(Pauling sai kumminkin toisen Nobelinsa 1962, nimittäin Norjasta)

Mutta kemiat ja rakenteet eivät edes vihjaa, että DNA olisi perinnöllinen aines. Miten siihen päädyttiin?

Kaksi klassista koesarjaa: transformaatio ja transduktio

Bakteerien transformaatio



Transformaatio
Griffith 1928

Kaksi bakteerikantaa (*Streptococcus pneumoniae*):

III Smooth virulentti
II Rough benigni

Keitetty **S** voi muuttaa elävän **R**:n virulentiksi

CELL 196

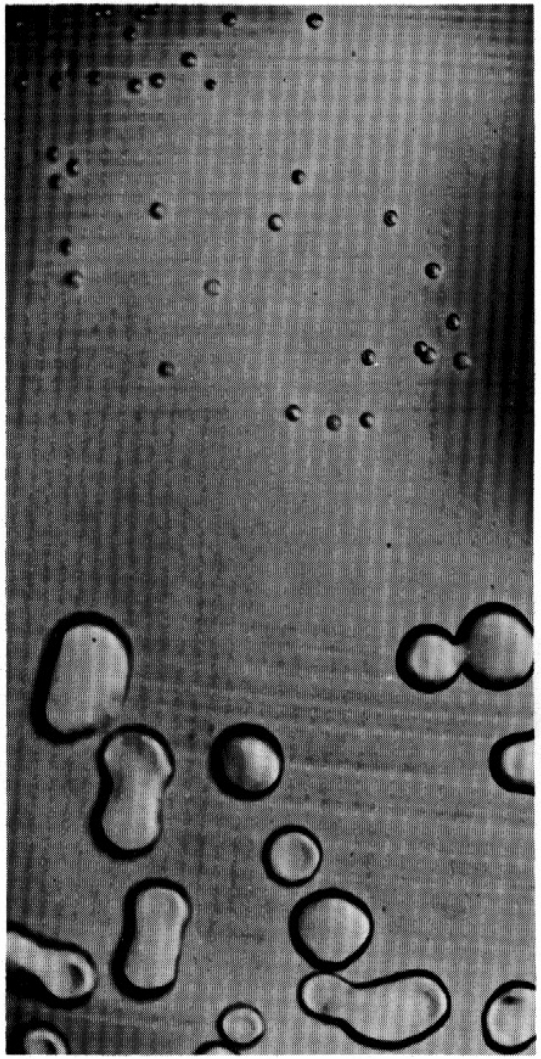


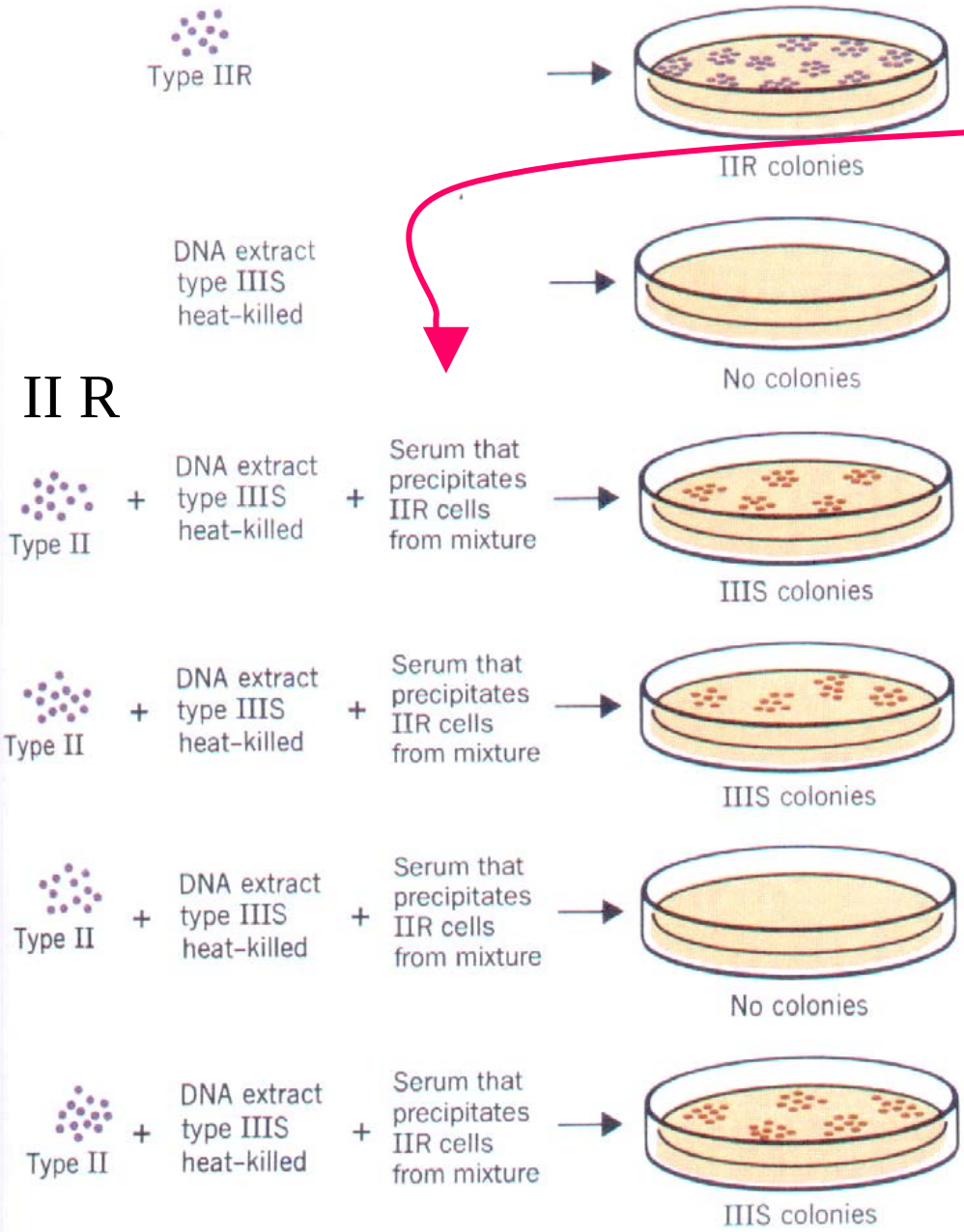
Figure 4-3
Transformation of nonpathogenic R pneumococci (small colonies) to pathogenic S pneumococci (large glistening colonies) by DNA from heat-killed S pneumococci.
[From O. T. Avery, C. M. MacLeod, and M. McCarty. *J. Exp. Med.* 79 (1944):158.]

II Rough (ei patogeeninen)

III Smooth (tappaisi hiiren)

Koe tehdään petrimaljoilla. Ei aina tarvitse hiiriä tappaa: bakteerin ominaisuus näkyy muutenkin

Transformaatiokoe



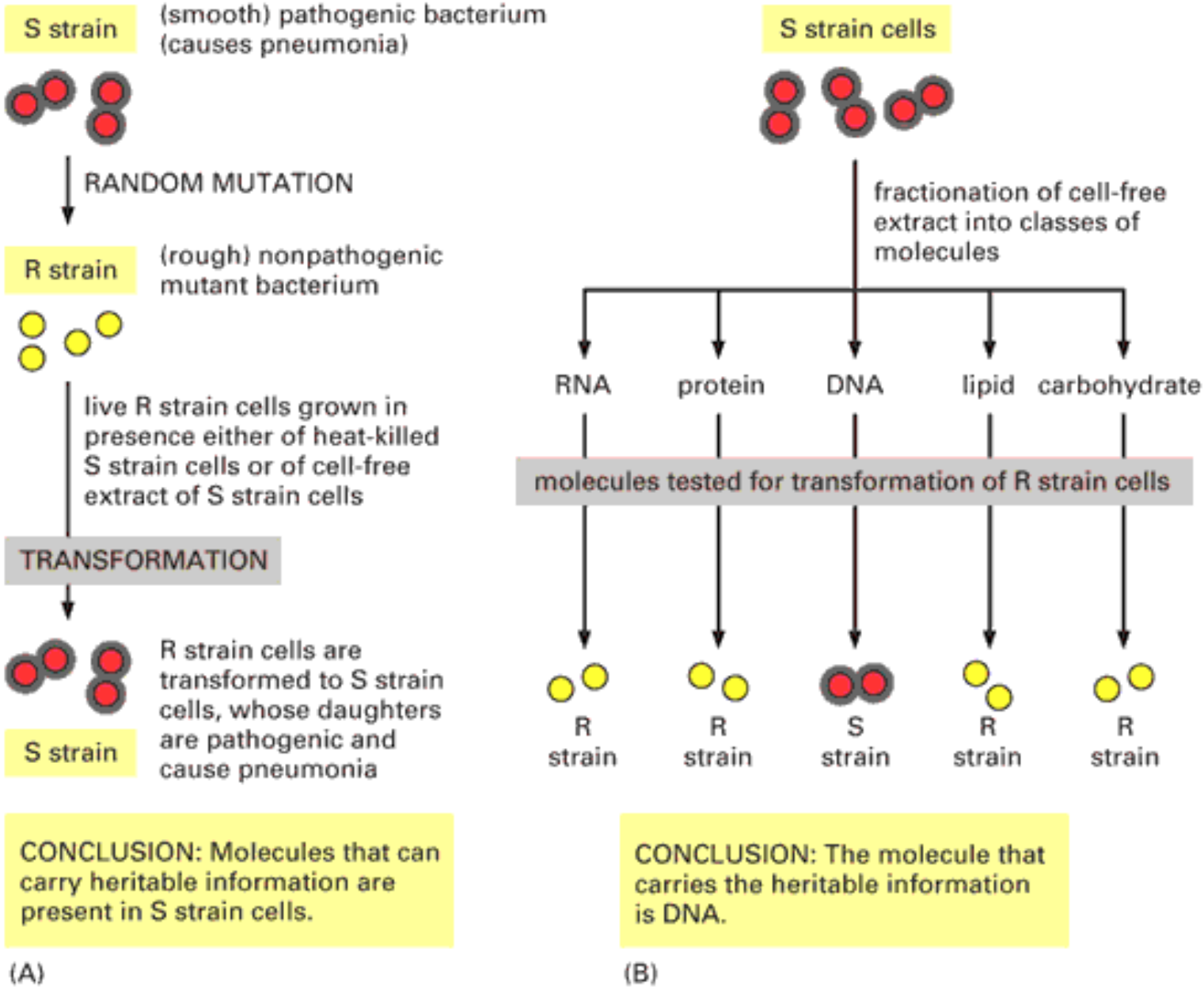
II R -solut poistetaan liuoskasvatuksesta vasta-ainesaostuksella ja sitten näyte "maljataan"

kontrolli

proteiinit tuhottu (*proteinaasi*)

DNA tuhottu (*DNAasi*)

RNA tuhottu (*RNAasi*)



CELL 196

Avery, McLeod, McCarty 1944

Bakteerien transformaatio

DNA:n "kloonauksen" perusmenetelmä

Bakteerisolu ottaa DNA:ta sisäänsä ja integroi sen omaansa

DNA monistuu bakteerin kanssa, vaikka kuinka paljon

Muitakin soluja voidaan transformoida, esimerkiksi ihmisen soluja: ilman transformaatioita ne eivät edes elä kauan viljelmässä

"Geeninsiirto" = transformaatio

[Vain yksi pieni ongelma: miten saadaan tapahtumaan *integraatio*, eli se, että joku DNA menee soluun eikä tule syödyksi/tuhotuksi? Meidän soluilla on semmonen taipumus.]

Bakteerien transduktio:

aiheuttajana virukset eli faagit (syöjät)

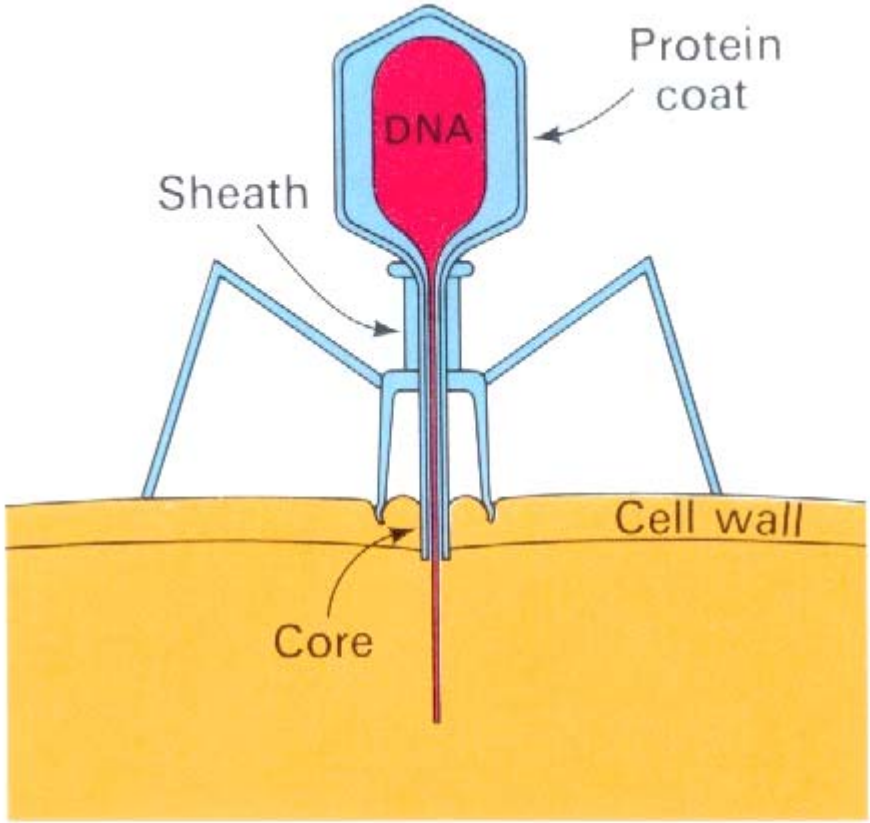
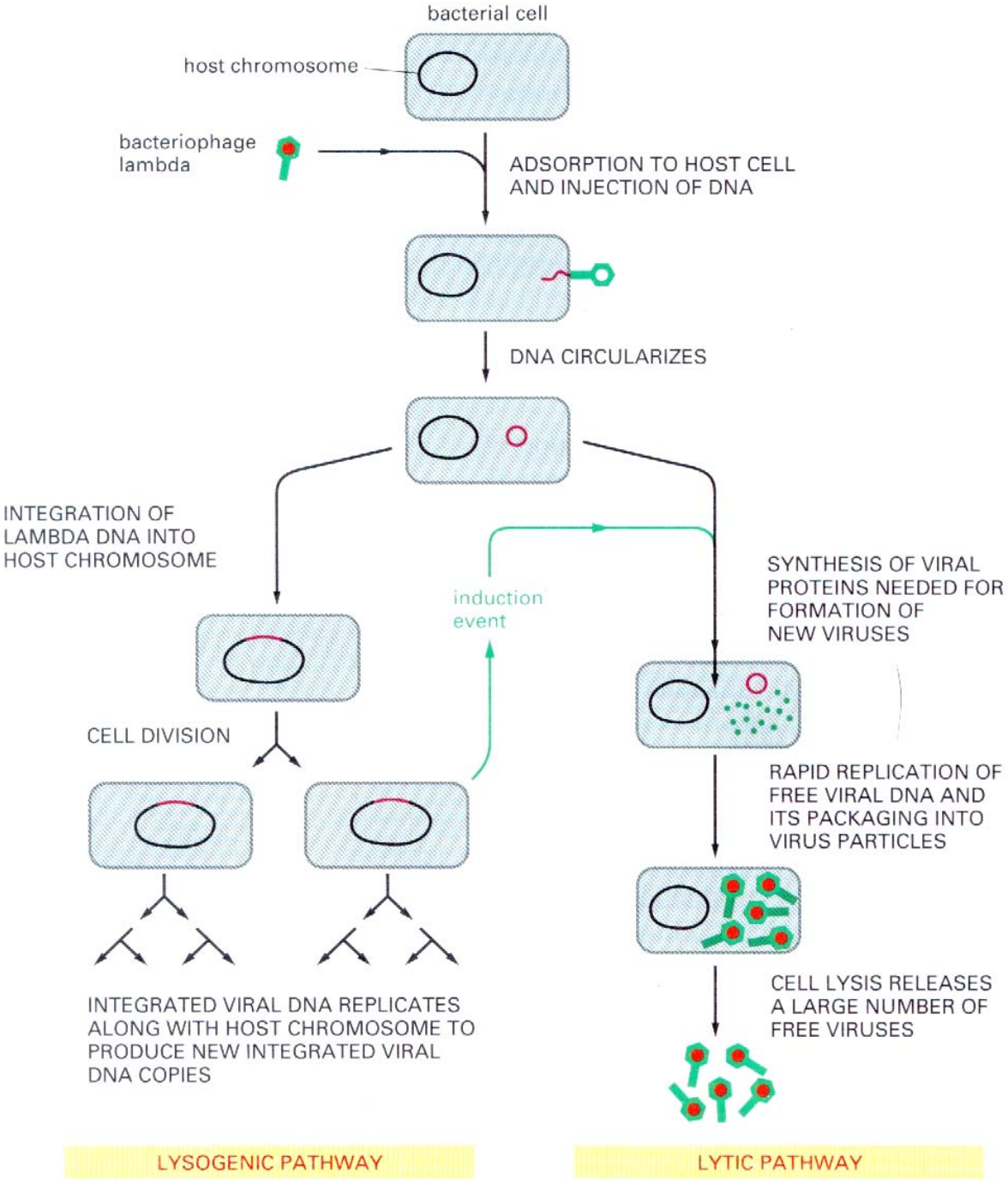


Figure 4-5
Diagram of a T2 bacteriophage injecting its DNA into a bacterial cell. [After W. B. Wood and R. S. Edgar. Building a bacterial virus. Copyright © 1967 by Scientific American, Inc. All rights reserved.]

Bakteriofaagi (virus) T2

CELL 325



Bakteriofaagit ovat viruksia, mutta varsin monimutkaisia

Niiden perimä on DNA

Faagi lambda osaa elää kahdella tavalla, lyyttisesti ja lysogeenisesti

CELL 325

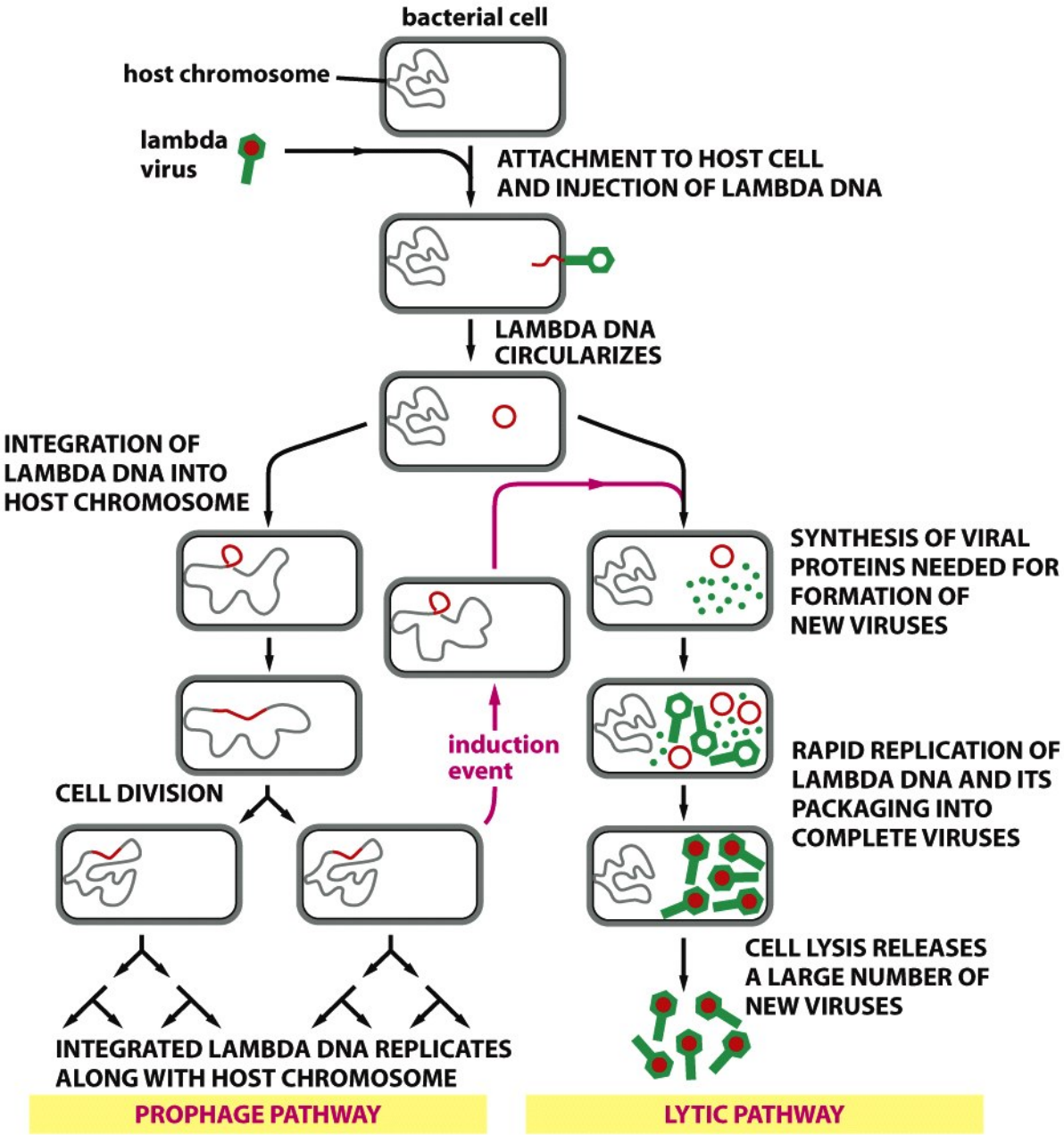


Figure 5-78 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Bakteriofaagit ovat viruksia, mutta varsin monimutkaisia

Niiden perimä on DNA

Faagi lambda osaa elää kahdella tavalla, lyyttisesti ja lysogeenisesti

CELL 325

Bakteerien transduktio

Bakteriofaagi (virus) välittää geenejä

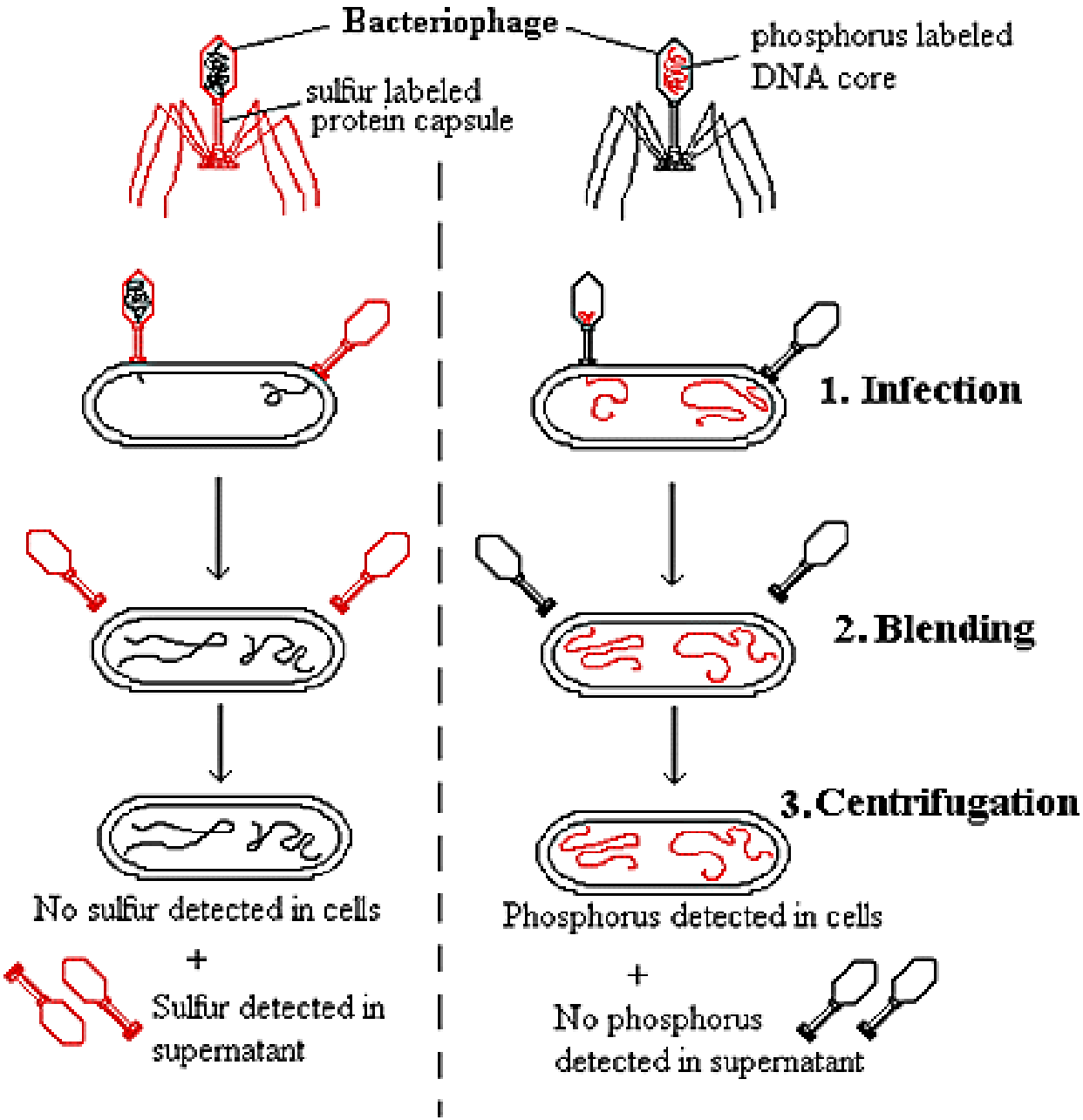
Sen tarkoituksena on istuttaa oma DNA:nsa bakteerin DNA:n sekaan ja käyttää bakteerin koneistoja itsensä monistamiseen

Ohessa voi siirtyä bakteerien geenejä: transduktio

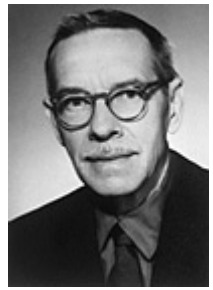
Seuraavakin koe kuuluu ***klassisiin*** kokeisiin

Se ei testaa transduktiota, vaan faagin perintöaineksen laatua

Kokeessa ei seurata ”geeniä” vaan kemiallisia yhdisteitä isotooppitekniikalla



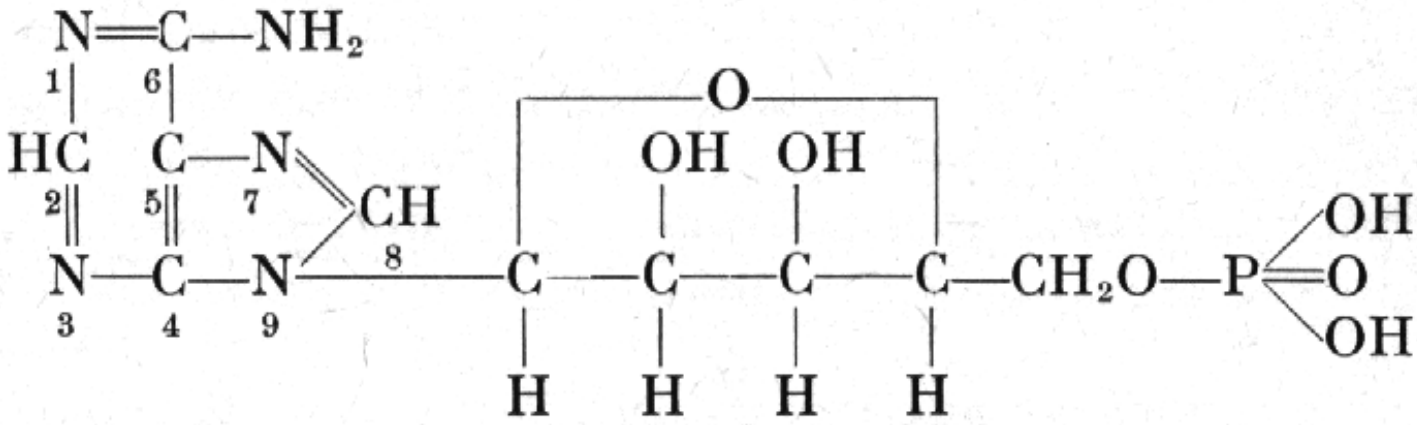
The Hershey-Chase Experiment



Hershey

(Nobel *1969*)

Nukleinsyrorna äro högmolekylära föreningar (*polynukleotider*), som vid försiktig hydrolys uppdelas i *mononukleotider*. En sådan är sammansatt av tre komponenter, en *kvävebas*, som kan vara ett purin- eller pyrimidinderivat (s. 279), en *sockerart*, som kan vara D-ribos eller 2-deoxi-D-ribos (s. 214), samt *fosforsyra*. Ett exempel på en mononukleotid är *muskeladenylsyra*, innehållande adenin, ribos och fosforsyra:



[1] För undersökningar rörande bl.a. nukleinsubstansernas kemi erhöll ALBRECHT KOSSEL (1853—1927), Heidelberg, nobelpriset i medicin 1910. 1957 års nobelpris i kemi tilldelades ALEXANDER TODD, Cambridge, likaledes för arbeten inom detta område.

Millainen sitten on DNA:n rakenne

1) rihmamainen, havaittiin jo varhain

2) C/G ja A/T parisääntö huomattiin: määrät vaihtelee synkronisesti

3) ei sitten muuta kuin röntgendiffraktiota tekemään: miten kaukana on atomit toisistaan kiteessä (linkki)

Linus Paulingin ja muidenkin näkökulma!

Oregon State University (OSU) on laittanut hienot, ammattimaiset verkkosivut DNA:n rakenteen keksimisestä.

LINUS PAULING AND

The Race for DNA

A Documentary History

Utilizing over 800 scanned documents, photographs, audio clips and video excerpts, this website narrates the breathless details of the pursuit of the discovery of the double helix structure of DNA. Scattered throughout the project are images of a number of very important and extremely rare items, all of which are held within The Valley Library's Ava Helen and Linus Pauling Papers, and many of which have not been previously displayed. Also featured are two original documents hitherto unknown to scholars interested in this period. It is expected that this website will serve as a primary reference point for individuals interested in the history of DNA -- both researchers and lay people alike.

Start by reading our Introduction, or choose one of the three sections:

Narrative

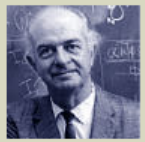
An illustrated, thirty-four page account of the drama behind the race for the double helix, written from the largely overlooked perspective of Linus Pauling. Read Narrative.

All Documents and Media

A wealth of primary sources - over three hundred letters, manuscripts, photographs, published papers, audio-visual snippets and more - provide an important scholarly perspective on the DNA story. View All Documents and Media.
Alternate View: Image Catalogue

Linus Pauling Day-By-Day

A detailed, illustrated look at all of Linus Pauling's personal and professional communications and activities for each day of the years 1952 and 1953. Presented in user-friendly calendar form. Browse Linus Pauling Day-By-Day.





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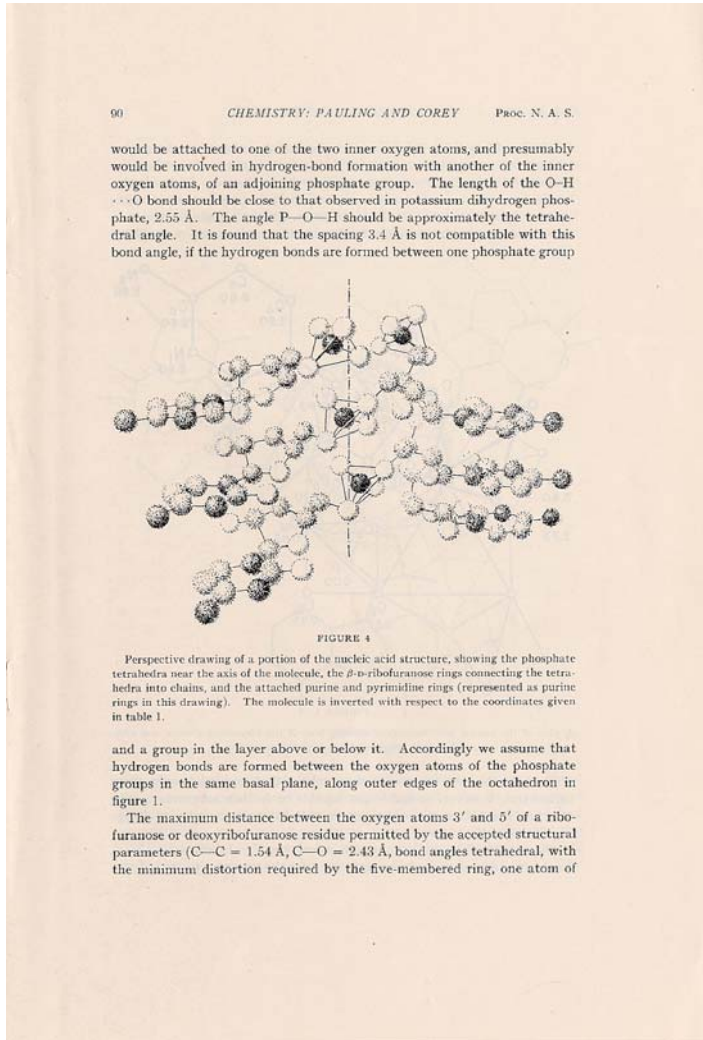
Paulingin ja muidenkin näkökulma!

Oregon State University (OSU) on laittanut hienot, ammattimaiset verkkosivut DNA:n rakenteen keksimisestä.

A Proposed Structure for the Nucleic Acids, February 1953
Notes: *Proceedings of the National Academy of Sciences*
Vol. 39, No. 2, pp. 84-97. February, 1953.
Author(s): Linus Pauling Robert B. Corey

Paulingin DNA-malli oli hieno, mutta ei oikea



90 CHEMISTRY: PAULING AND COREY Proc. N. A. S.

would be attached to one of the two inner oxygen atoms, and presumably would be involved in hydrogen-bond formation with another of the inner oxygen atoms, of an adjoining phosphate group. The length of the O–H ···O bond should be close to that observed in potassium dihydrogen phosphate, 2.55 Å. The angle P—O—H should be approximately the tetrahedral angle. It is found that the spacing 3.4 Å is not compatible with this bond angle, if the hydrogen bonds are formed between one phosphate group

FIGURE 4

Perspective drawing of a portion of the nucleic acid structure, showing the phosphate tetrahedra near the axis of the molecule, the β-D-ribofuranose rings connecting the tetrahedra into chains, and the attached purine and pyrimidine rings (represented as purine rings in this drawing). The molecule is inverted with respect to the coordinates given in table 1.

and a group in the layer above or below it. Accordingly we assume that hydrogen bonds are formed between the oxygen atoms of the phosphate groups in the same basal plane, along outer edges of the octahedron in figure 1.

The maximum distance between the oxygen atoms 3′ and 5′ of a ribofuranose or deoxyribofuranose residue permitted by the accepted structural parameters (C—C = 1.54 Å, C—O = 2.43 Å, bond angles tetrahedral, with the minimum distortion required by the five-membered ring, one atom of

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).
[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

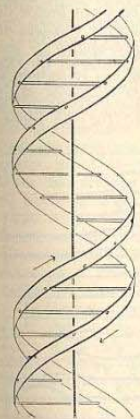
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge.
April 2.

[1] Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).
[3] Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).
[4] Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).
[5] Astbury, W. T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Camb. Univ. Press, 1947).
[6] Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).

Molecular Structure of Deoxypentose Nucleic Acids

WHILE the biological properties of deoxypentose nucleic acid suggest a molecular structure containing great complexity, X-ray diffraction studies described here (cf. Astbury[1]) show the basic molecular configuration has great simplicity. The purpose of this communication is to describe, in a preliminary way, some of the experimental evidence for the polynucleotide chain configuration being helical, and existing in this form when in the natural state. A fuller account of the work will be published shortly.

The structure of deoxypentose nucleic acid is the same in all species (although the nitrogen base ratios alter considerably) in nucleoprotein, extracted or in cells, and in purified nucleate. The same linear group of polynucleotide chains may pack together parallel in different ways to give crystalline[1–3], semi-crystalline or paracrystalline material. In all cases the X-ray diffraction photograph consists of two regions, one determined largely by the regular spacing of nucleotides along the chain, and the other by the longer spacings of the chain configuration. The sequence of different nitrogen bases along the chain is not made visible.

Oriented paracrystalline deoxypentose nucleic acid ('structure *B*' in the following communication by Franklin and Gosling) gives a fibre diagram as shown in Fig. 1 (cf. ref. 4). Astbury suggested that the strong 3·4-A. reflexion corresponded to the internucleotide repeat along the fibre axis. The ~ 34 A. layer lines, however, are not due to a repeat of a polynucleotide composition, but to the chain configuration repeat, which causes strong diffraction as the nucleotide chains have higher density than the interstitial water. The absence of reflexions on or near the meridian immediately suggests a helical structure with axis parallel to fibre length.

Diffraction by Helices

It may be shown[5] (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is given by the squares of Bessel functions. A uniform continuous helix gives a series of layer lines of spacing corresponding to the helix pitch, the intensity distribution along the *n*th layer line being proportional to the square of J_n, the *n*th order Bessel function. A straight line may be drawn approximately through

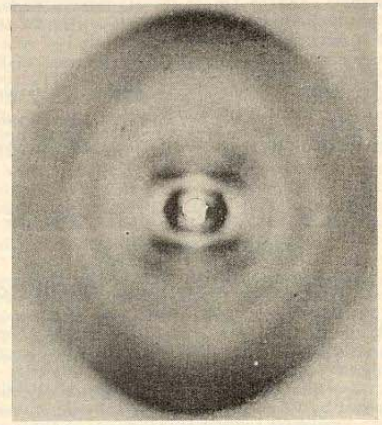


Fig. 1. Fibre diagram of deoxypentose nucleic acid from *B. coli*. Fibre axis vertical

the innermost maxima of each Bessel function and the origin. The angle this line makes with the equator is roughly equal to the angle between an element of the helix and the helix axis. If a unit repeats *n* times along the helix there will be a meridional reflexion (J_n^2) on the *n*th layer line. The helical configuration produces side-bands on this fundamental frequency, the effect[6] being to reproduce the intensity distribution about the origin around the new origin, on the *n*th layer line, corresponding to *C* in Fig. 2.

We will now briefly analyse in physical terms some of the effects of the shape and size of the repeat unit or nucleotide on the diffraction pattern. First, if the nucleotide consists of a unit having circular symmetry about an axis parallel to the helix axis, the whole diffraction pattern is modified by the form factor of the nucleotide. Second, if the nucleotide consists of a series of points on a radius at right-angles to the helix axis, the phases of radiation scattered by the helices of different diameter passing through each point are the same. Summation of the corresponding Bessel functions gives reinforcement for the inner-

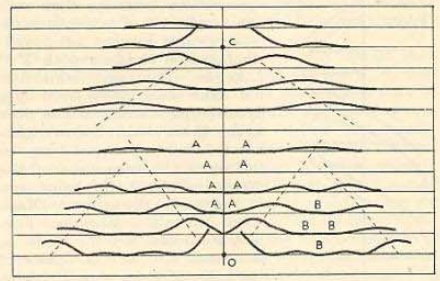


Fig. 2. Diffraction pattern of system of helices corresponding to structure of deoxypentose nucleic acid. The squares of Bessel functions are plotted about 0 on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mass at 20 A. diameter and remainder distributed along a radius, the mass at a given radius being proportional to the radius. About *C* on the tenth layer line similar functions are plotted for an outer diameter of 12 A.

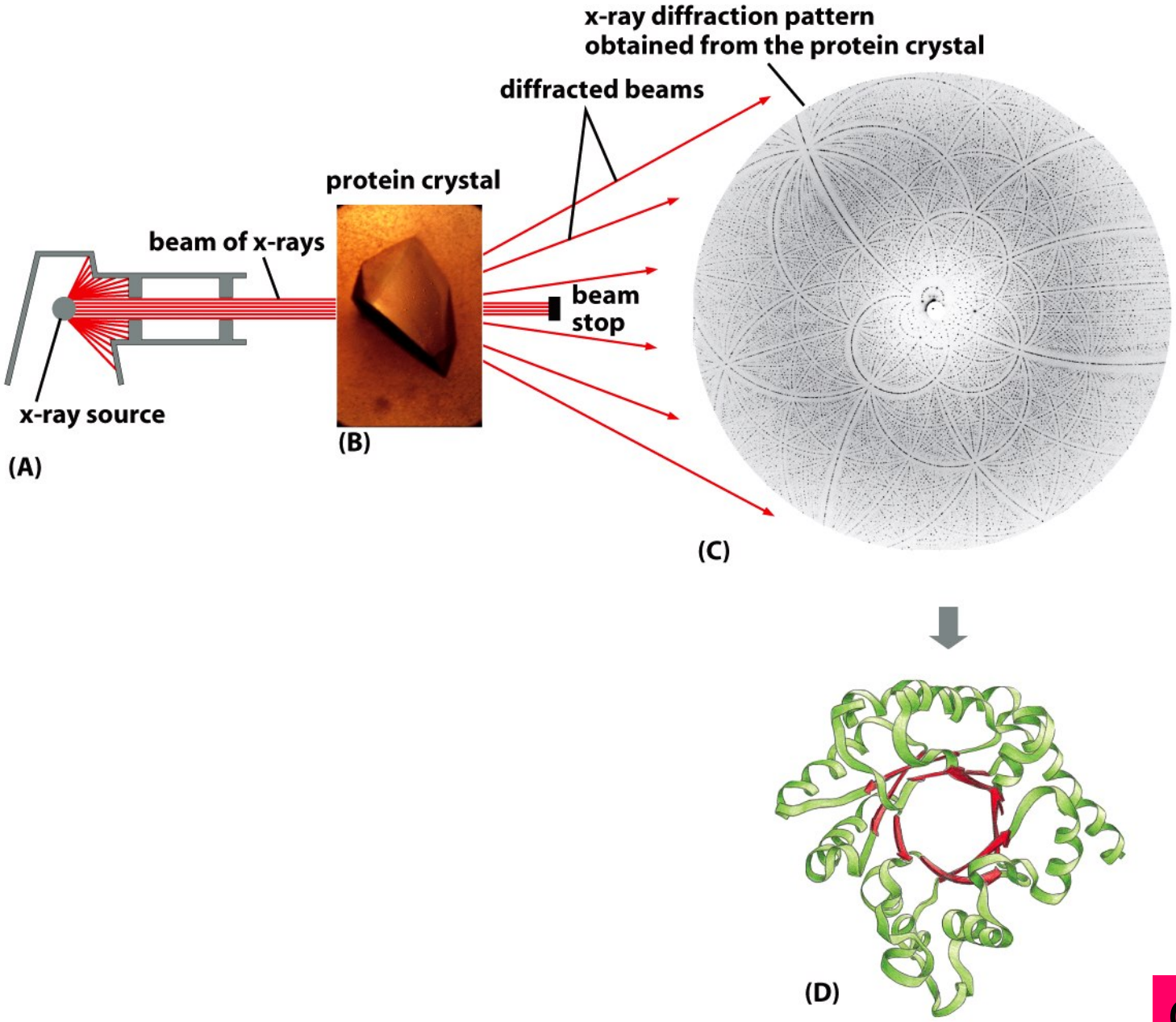


Figure 8-28 Molecular Biology of the Cell 5/e (© Garland Science 2008)

CELL 528

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Timeline

pre 1920s

JOHANN GREGOR MENDEL
The laws of heredity

FRIEDRICH MIESCHER
The discovery of DNA

CARL ERICH CORRENS
HUGO DE VRIES
ERICH VON TSCHERMAK-SEYSENEGG
Rediscovery of Mendel's laws

THOMAS HUNT MORGAN
The genetics of fruit flies

1920-49

HERMANN MULLER
X-ray mutants

BARBARA MCCLINTOCK
Jumping genes

GEORGE WELLS BEADLE
EDWARD LAWRIE TATUM
One gene, one enzyme

JOSHUA LEDERBERG
Conjugating bacteria

OSWALD THEODORE AVERY
The transforming factor

EVELYN WITKIN
DNA repair mechanisms

1950-54

ERWIN CHARGAFF
Chargaff's ratios

ROSALIND ELSIE FRANKLIN
DNA X-ray diffraction

MARTHA CHASE
ALFRED DAY HERSHEY
The blender experiment

LINUS PAULING
The triple helix

JAMES DEWEY WATSON
FRANCIS HARRY COMPTON CRICK
The double helix

SEYMOUR BENZER
The genetics of phage

1955-59

FRANCIS HARRY COMPTON CRICK
The Central Dogma

PAUL CHARLES ZAMECNIK
MAHLON HOAGLAND
Transfer RNAs

MATTHEW STANLEY MESELSON
FRANKLIN WILLIAM STAHL
Semi-conservative replication

ARTHUR KORNBERG
DNA polymerase

1960s

SYDNEY B
Messe

MARSHAL
The ge

FRANÇOIS
JACQUES
The la

ROY JOHN
Repet

http://www.dnai.org/timeline/index.html

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pre 1920s | 1920-49 | early 50s | late 50s | 1960s | 1970s | 1980s | 1990-2000-

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DNA HOME

Timeline

land Opens
Rosa Parks refuses to give up her seat on a bus
Hungarian Revolution
Suez Crisis
TV Remote control i
1956

pre 1920s | 1920-49 | early 50s | late 50s | 1960s | 1970s | 1980s | 1990-2000-

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