

КАЗАНСКИЙ
ГОСУДАРСТВЕННЫЙ
МЕДИЦИНСКИЙ
УНИВЕРСИТЕТ



2025г.

Тема 2. Исторические вехи биологии в медицине

лекция

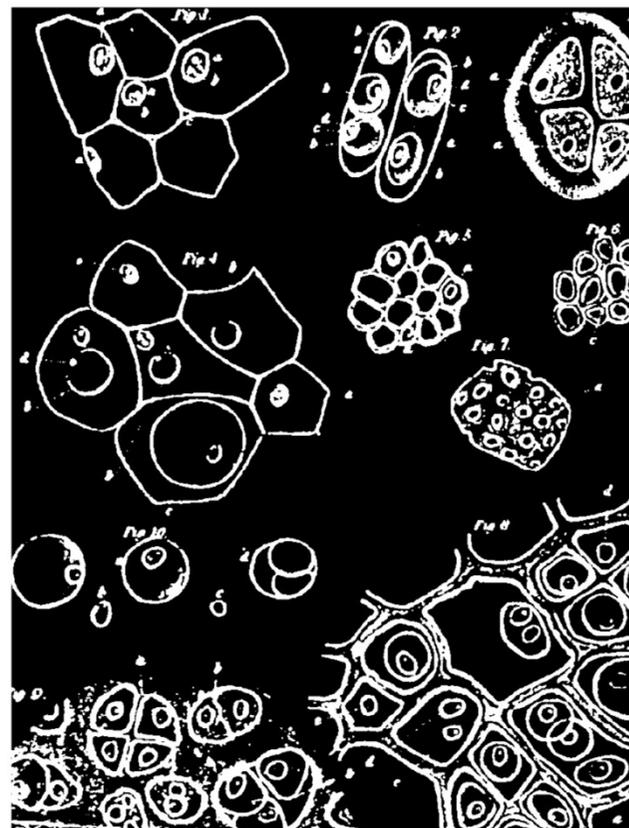
Нуруллин Лениз Фаритович
к.б.н., доцент кафедры
медицинской биологии и генетики
КГМУ



Теодор Шванн
(1810 — 1882)

немецкий цитолог, гистолог,
физиолог

Предшествующие исследования легли в основу сформулированной Т. Шванном (1838) клеточной теории строения организмов.



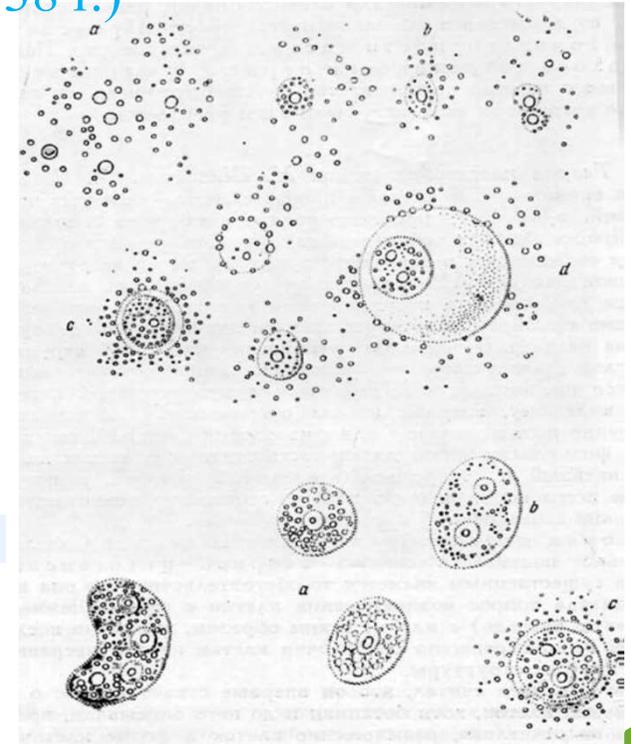
Возникновение клеток по Шлейдену

Теория цитогенезиса (1838 г.)



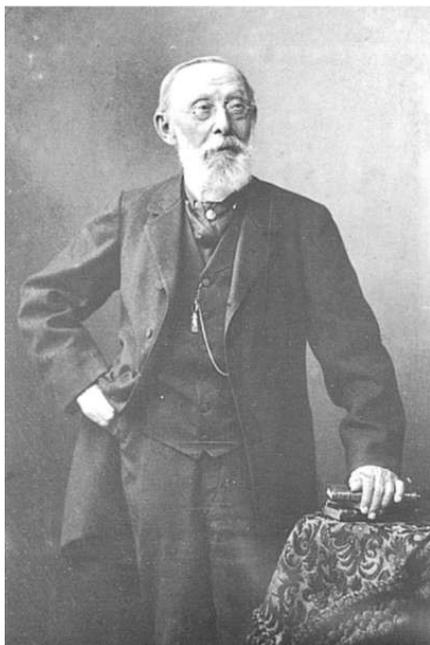
«всякая клетка зарождается из протоплазмы другой клетки, но одни клетки... рождаются путём кариокинетического деления, а другие образуются из протоплазмы без деления самой клетки, внутри её».

— Шлейден М. (1838). Данные о фитогенезисе: В приложении к «Микроскопическим исследованиям» Т. Шванна. М.; Л., 1939. С. 72—74.



Матиас Шлейден
немецкий ботаник
(1804–1881)

Клетки могут зарождаться из бесструктурного вещества, а зародыш растения — развиваться из пыльцевой трубки.
БСЭ

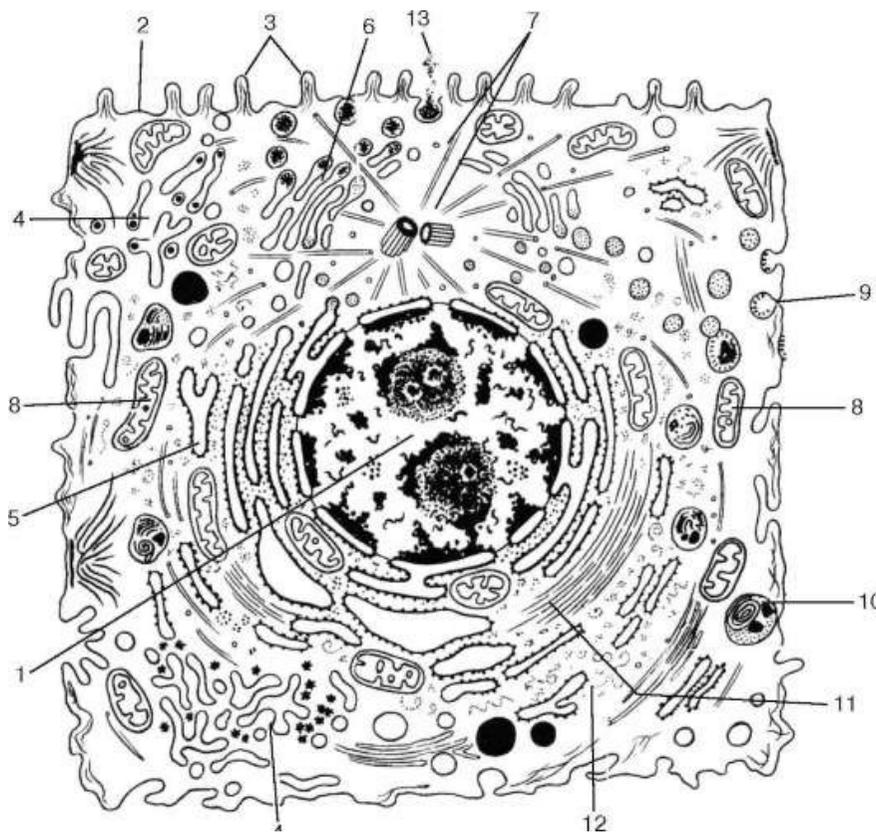


Р. Вирхов (1821-1902)

Р. Вирхов, в противоположность Т. Шванну и М. Шлейдену, отстаивал взгляд на образование новых клеток не из «цитобластемы» - бесструктурной живой субстанции, а путем деления предсуществующих клеток (*omnis cellula e cellula*).

Вирхов создал концепцию клеточной патологии (1858 г.), которая определила главные пути развития медицины на долгое время. Объясняя течение патологических состояний структурно-химическими изменениями на клеточном уровне, эта концепция способствовала появлению патологической анатомии.

Ультрамикроскопическое строение клетки животных организмов



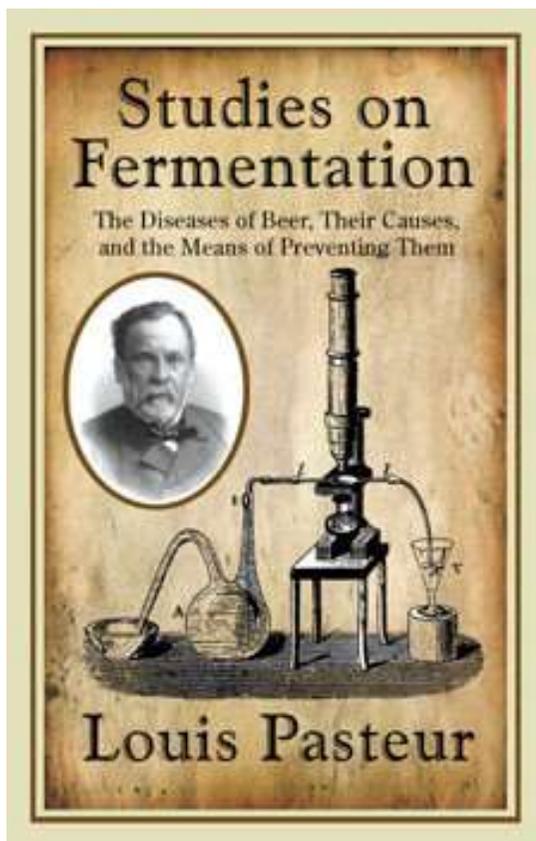
1. ядро;
2. плазмолемма;
3. микроворсинки;
4. агранулярная ЭПС;
5. гранулярная ЭПС;
6. комплекс Гольджи;
7. центриоль и микротрубочки
клеточного центра;
8. митохондрии;
9. цито-плазматические пузырьки;
10. лизосомы;
11. микрофиламенты;
12. рибосомы;
13. выделение гранул секрета



В современном состоянии клеточная теория включает
три основных положения

1. Жизнь в ее структурном, функциональном и генетическом плане обеспечивается только клеткой.
2. Единственным способом возникновения новых клеток является деление существующих клеток.
3. Многоклеточное существо – это совокупность высоко интегрированных в систему организма клеточных ансамблей.

2. Исследования Л. Пастера, доказали невозможность самопроизвольного зарождения жизни, а процессы гниения и брожения вызываются микроорганизмами.



Эти факты произвели переворот в медицине и обеспечили развитие хирургии. В практику были введены антисептика (предупреждение заражения раны посредством химических веществ) и асептика (предупреждение загрязнения путем стерилизации предметов, соприкасающихся с раной). Это открытие послужило стимулом к поискам возбудителей инфекционных болезней и разработке мер по профилактике и лечению инфекционных болезней.

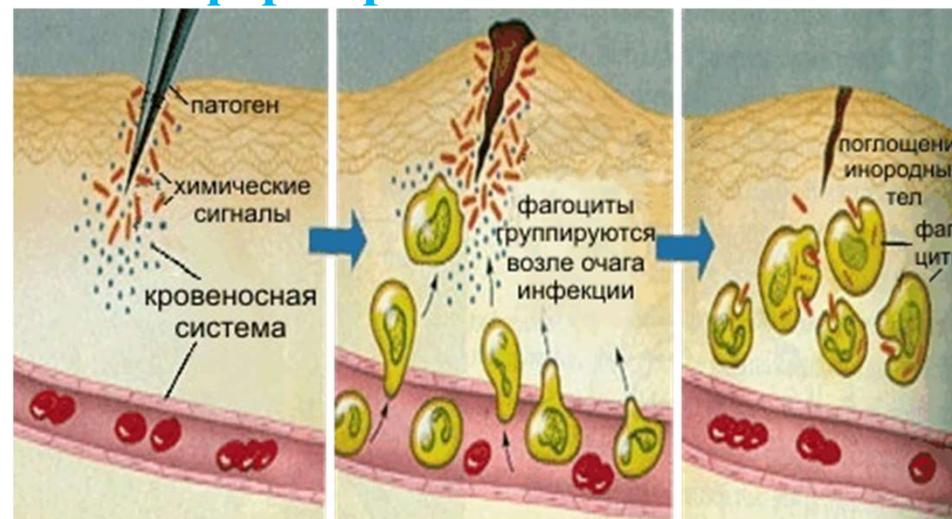


Луи Пастер
(1822-1895)

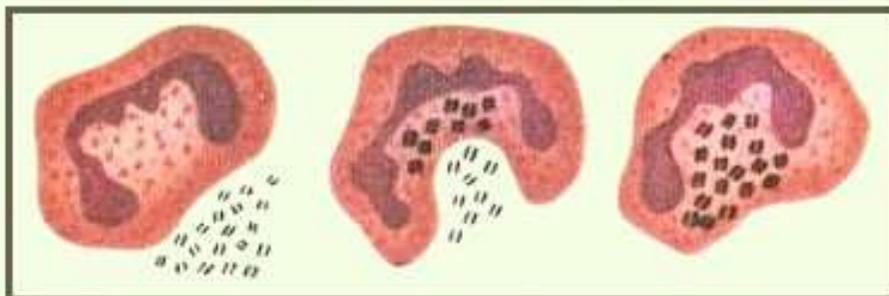
французский микробиолог, химик,
один из основоположников
микробиологии и иммунологии.

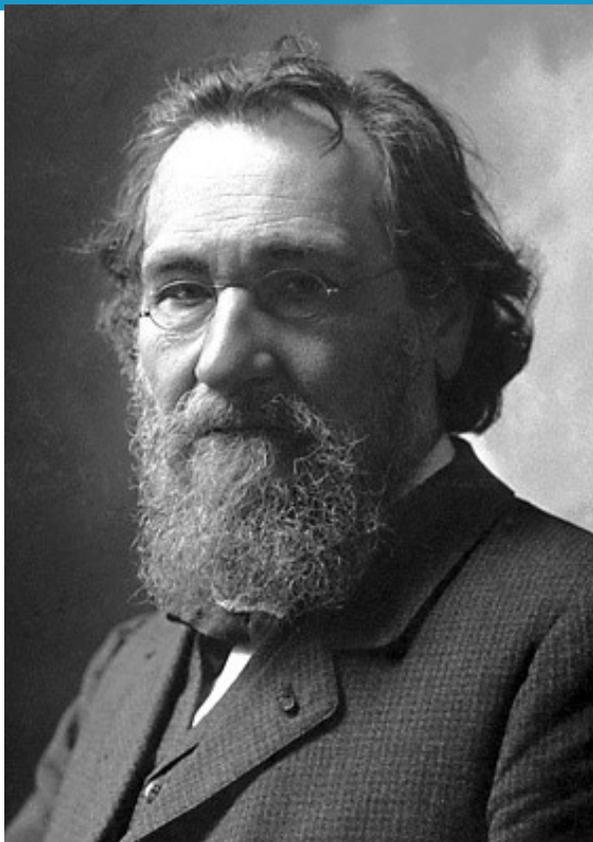
Показал микробиологическую сущность брожения, многих болезней человека. Его работы в области строения кристаллов и явления поляризации легли в основу стереохимии. Доказал невозможность самозарождения опытным путем. Создал технологию, названную позже в его честь пастеризация.

3. Изучение И.И. Мечниковым процессов пищеварения у низших многоклеточных организмов способствовало формированию знаний о механизмах клеточного иммунитета.



Фагоцитоз - лейкоциты, захватывающие вредных микробов





Илья Ильич Мечников
(1845-1916)

русский и французский биолог микробиолог,
цитолог, эмбриолог, иммунолог, физиолог и
патолог.

Один из основоположников эволюционной эмбриологии, первооткрыватель фагоцитоза и внутриклеточного пищеварения, создатель сравнительной патологии воспаления, фагоцитарной теории иммунитета, теории фагоцителлы, основатель научной геронтологии.

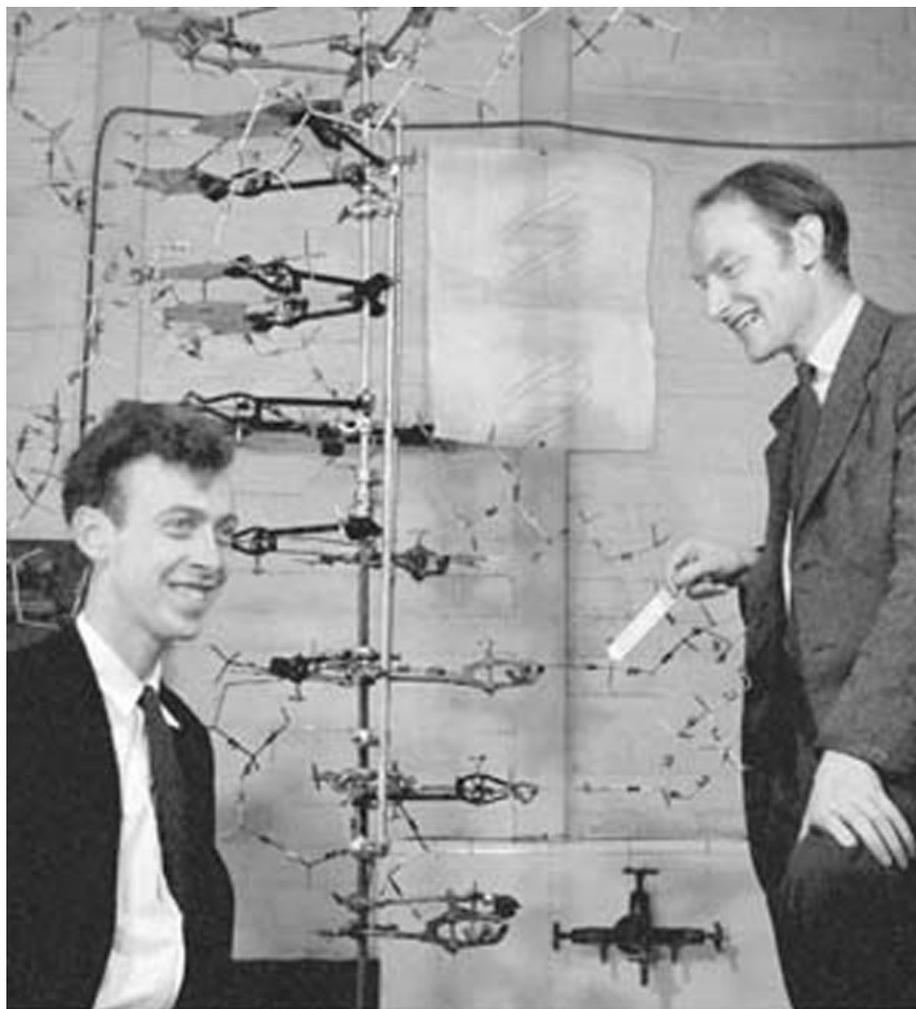
Методами эмбриологии доказал единство происхождения позвоночных и беспозвоночных животных.

Лауреат Нобелевской премии в области физиологии и медицины (1908).



4. Открытие модели строения молекулы ДНК Дж. Уотсоном и Ф. Криком (1953 г.) явилось ключевым этапом развития молекулярной биологии и определило приоритетные направления современной медицины в поисках путей профилактики, диагностики и лечения болезней человека.

Развитие получили методы генетической инженерии, а на ее основе биотехнологии и генной коррекции наследственных болезней. Создание рекомбинантных молекул ДНК, определило возможность получения в промышленных масштабах гормонов (инсулина, соматотропина), антибиотиков и биологически активных веществ. Появились новые методы ДНК-диагностики наследственных болезней, а также вирусных и протозойных инфекций.



Пионер молекулярной биологии

С 1951 по 1953 г. Розалин проведя рентгеноструктурные исследования молекул ДНК, выявила А- и В-формы ДНК, рассчитала функцию Паттерсона и, используя специальный метод суперпозиции, показала, что фосфатные группы должны располагаться снаружи молекулы ДНК. Получила фотографию №51 в мае 1952 года после сточасовой экспозиции волокон В-формы ДНК на рентгеновском дифрактометре. Крестообразное расположение дифракционных пятен служило прямым указанием на структуру в виде спирали. Анализ данных позволил сделать вывод, что спираль ДНК состоит из двух нитей, в которой фосфатные группы располагаются снаружи, а основания внутри спирали. Определила шаг спирали (3,4 нм) и её периодичность (10 пар на виток). Нашла объяснение факту отсутствия дифракционных пятен на четвёртой линии и ослабления интенсивности пятен на шестой линии в том, что нити спирали не зеркально симметричны относительно оси спирали: одна нить сдвинута относительно другой нити по вертикали примерно на три восьмых витка спирали.



Розалинд Франклин

Rosalind Franklin

25 июля 1920 — 16 апреля 1958

английский биофизик и

рентгенограф

is no obvious formula for its construction; and what is obvious, of course, varies between observers. Perhaps it should therefore be a matter of some surprise that present probability theory applied to science in fact works as well as it does; and if we could discover how it is that it does work so well, we might be able to see how it is that it does not appear to work quite well enough.

I wish to express my gratitude to the Perrott Electors of Trinity College, Cambridge, under whom the new description of this psychical research problem was originally made, and to Prof. A. C. Hardy, of Oxford, who generously provided a grant for the research to continue in his Department. I should also like to thank Sir Ronald Fisher, by whose writings and conversation I have been greatly helped.

- ¹Coover, John E., "Experiments in Psychical Research" (Stanford University Press, 1927).
²Hardon, R. H., *Proc. Soc. Psych. Res.*, **41**, 24 (1935).
³Blair, J. B., "Extra-Sensory Perception" (London, 1935).
⁴Forrad, H. J., *Psychol.*, **38**, 20 (1903).
⁵Edmond, Alfred, *J. Soc. Psych. Res.*, **36**, 377 (1932).
⁶Palmer, Ronald A., "The Basis of ESP-Perception" (London, 1937).
⁷Kerwin, John Stewart, "A Treatise on Probability" (London, 1927).
⁸Venn, John, "The Logic of Chance" (London, 1905).

EVIDENCE FOR 2-CHAIN HELIX IN CRYSTALLINE STRUCTURE OF SODIUM DEOXYRIBONUCLEATE

By ROSALIND E. FRANKLIN* and R. G. GOSLING
 Wheatstone Physics Laboratory, King's College, London, W.C.2

WATSON AND CRICK¹ have proposed a structure for sodium deoxyribonucleate consisting of two co-axial helical chains related by a diad axis. We have shown² that the main features of their structure are consistent with certain important features of our X-ray diagrams of structure *B* (the high-humidity less-ordered form of the salt). A subsequent closer investigation of density and water content in relation to the prominent equatorial spacing, and also of equatorial intensities calculated from a projection of the proposed structure (kindly provided by Watson and Crick), makes it clear that in detail the structure is not consistent with the observed equatorial reflexions. Both density and intensity considerations lead us to favour a more compact helical structure in which the phosphorus atoms lie on a helix of radius about 8.5 Å, rather than 10 Å. This value also lies within the range of spread of the more diffuse layer-line peaks.

We are more concerned here, however, with evidence which confirms in principle the type of structure suggested by Watson and Crick, than with criticism on points of detail.

If a 2-chain helical molecule exists in structure *B*, then such a molecule, in modified form, must also exist in structure *A* (the crystalline form obtained at 75 per cent relative humidity), since the change *A* → *B* is readily reversible. The purpose of this communication is to point to evidence for a 2-chain helical molecule in structure *A*.

For structure *A* we have measured the positions and intensities of reflexions and have calculated the cylindrically averaged Patterson function³. The work is now at British College Crystallographic Laboratory, 21 Tavistock Square, London, W.C.1.

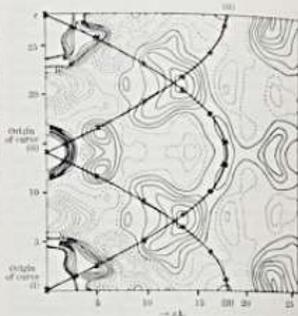


Fig. 1. Cylindrical Patterson function of crystalline sodium deoxyribonucleate. (i), theoretical peak for inter-lattice P-P vector.

is described in detail elsewhere⁴. The Patterson function is reproduced in Fig. 1. The theoretical curve for the Patterson function of a smooth helix of radius 9.0 Å, is also shown (curve (ii)). The very strong peak at height $c = \frac{1}{2}$ on the fibre axis suggests that the phosphate groups of the two chains are separated by approximately $\frac{1}{2}c$. We therefore added to Fig. 1 curve (iii), which completes the theoretical Patterson function for two smooth co-axial helices separated by $\frac{1}{2}c$ (i.e. the pitch of the helix). Curves (i) and (iii) together closely pass through a large proportion of the important Patterson peaks. Moreover, if we take into account the fact that the real structure contains, not smooth helices, but phosphate groups equally spaced along such helices, the agreement is even better.

The only near-meridional reflexion in the X-ray diagram of structure *A* is a rather weak one on the eleventh layer-line. This suggests that there are eleven nucleotides per turn of the helix. (This is sufficiently near to the number ten, found for structure *B*^{5,6,7}, for the reversible transformation *A* ↔ *B* to be plausible.) Further, we may suppose that the well-resolved peak at 5.7 Å, from the pseudo-origin peak at $c = \frac{1}{2}$ represents a P-P vector, and this distance is exactly that between neighbouring phosphorus atoms if eleven are equally spaced along one turn of a helix of radius 9 Å. In Fig. 1 we have marked with a cross the theoretical positions of intra-molecular Patterson peaks to be expected for this arrangement, assuming that the phosphorus atoms on one helix lie vertically above those on the other. The agreement with the observed Patterson peaks is seen to be remarkably good.

In Fig. 2 we have marked on the Patterson function the positions of all inter-molecular P-P vectors obtained when, in the unit cell described below, there is one molecule (that is, two chains) associated with each lattice point. The circles in Fig. 2 have each only $\frac{1}{11}$ of the weight of the crosses in Fig. 1, and 1.22 and 1.44 of the weight of the pseudo-lattice points (relating phosphate residues only) shown by crosses

near the half- c height in Fig. 2. The lattice points relating the whole structure are denoted by larger crosses near to the origin level in *c*. In addition to this weighting, for correlation with the cylindrically averaged Patterson function, the weight of each calculated peak should be considered as inversely proportional to x , since in averaging it must be spread over a circle of radius x . When these factors are taken into account, it will be seen that agreement between calculated and observed Patterson peaks is still good.

Space group, density and the unit cell. Using the cylindrical Patterson function, we have been able to identify the lattice vectors (indicated in Fig. 2) and hence to index all 66 observed reflexions. The unit $b = 29.8$ Å; $c = 28.4$ Å; $a = 96.7$ Å. If the unit cell is truly monoclinic, the space group can only be *C*₂, since the molecule contains asymmetric carbon atoms. Again, since the structure of the phosphate sugar backbone chain is non-centric, the symmetry axis cannot pass through such a chain, but must relate the chains one to another in pairs. There must, therefore, be an even number of chains associated with each lattice point.

In order to calculate the number of nucleotides in the unit cell, it is necessary to know both the density and the water content. Unfortunately, these quantities can only be measured on a polycrystalline mass, and these must remain some uncertainty as to the true density and water content of the crystallites. Our measurements⁸ gave a density of 1.47 gm./c.c. at 75 per cent relative humidity and a water content of about 40 per cent of the dry weight (or about 8H₂O per nucleotide). We have confirmed that the specimens used for these measurements were in the form of structure *A* and not structure *B*. These results correspond to twenty-three nucleotides per lattice point, which is in reasonable agreement with the suggestion that the primitive unit cell contains eleven nucleotides on each of two chains.

The three-dimensional Patterson function. After establishing the unit cell and indexing the reflexions, the complete three-dimensional Patterson function

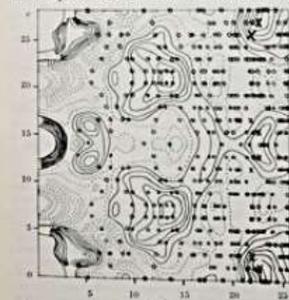


Fig. 2. Cylindrical Patterson function of crystalline sodium deoxyribonucleate. O, theoretical peak for inter-lattice P-P vector.

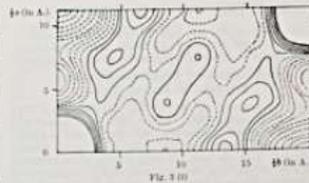


Fig. 3 (i)

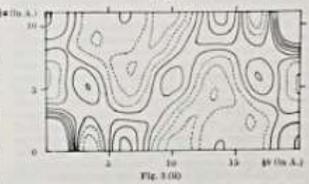


Fig. 3 (ii)

Three-dimensional Patterson function of crystalline sodium deoxyribonucleate. Sections in *a-b* plane at (i) $c = 0$, (ii) $c = \frac{1}{2}$.

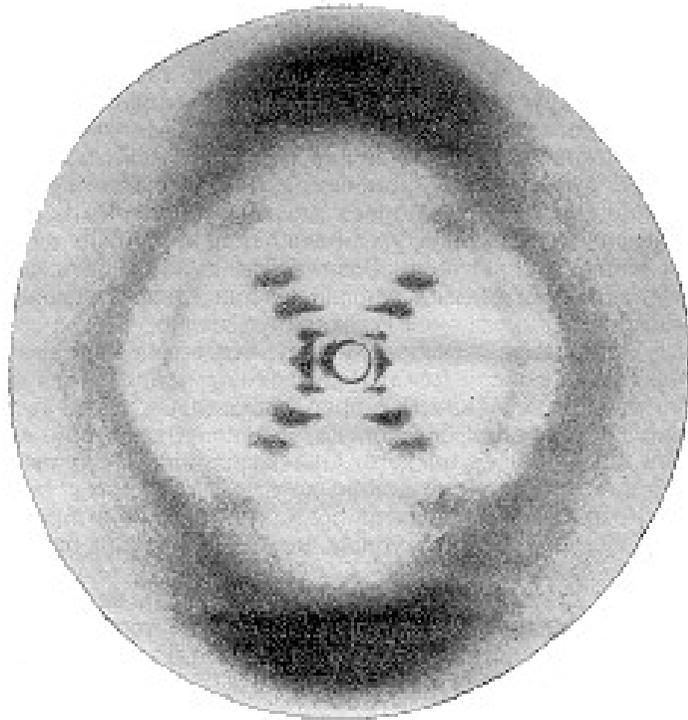
was calculated. This will be published and discussed in detail elsewhere. The *a-b* sections at heights $c = 0$ and $c = \frac{1}{2}$ are shown in Fig. 3. The very strong peak at $a = b = 0$, $c = \frac{1}{2}$ suggests a pseudo-lattice of the unit cell. On the other hand, all features of the zero section other than the origin peak are almost entirely reversed in the section $c = \frac{1}{2}$. This at once suggests that only a part of the structure repeats at $c = \frac{1}{2}$. This is exactly what would occur for two co-axial chains related by a diad axis, as suggested by Watson and Crick. The phosphate groups repeat at $c = \frac{1}{2}$, as indicated in Fig. 1; but, since the two chains run in opposite directions, this will not be true of the rest of the molecule.

Relationship between structure *A* and structure *B*. In conclusion, we suggest that the unit in structure *A* is, as in structure *B*, two co-axial helical chains running in opposite directions. In the change from *B* to *A* the number of residues per turn increases from ten to eleven and the pitch of the helix decreases from 34 Å to 28 Å. In structure *A* the phosphate groups lie on a helix of radius 9 Å, with a separation of approximately $\frac{1}{2}c$ between the phosphate groups of the two co-axial chains.

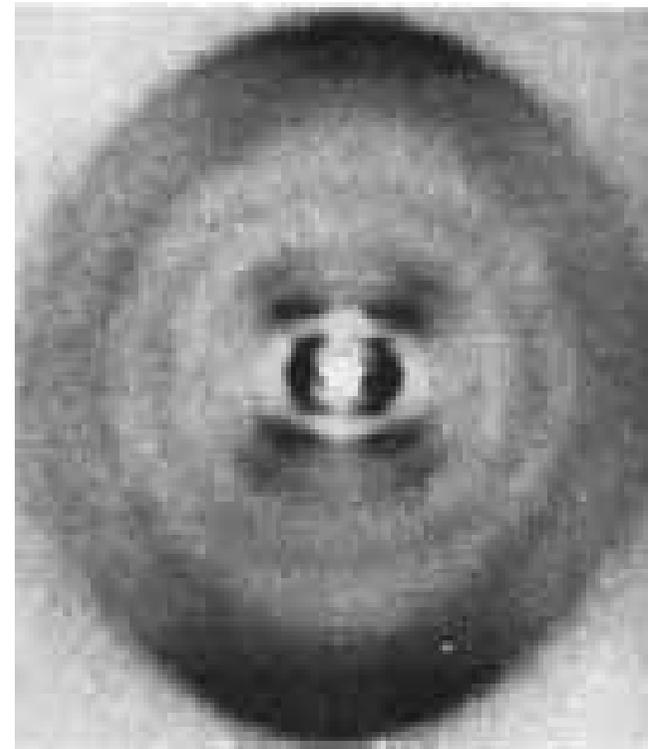
The vertical component of the inter-base distance is thus decreased from 3.4 Å, in structure *B* to 2.55 Å, in structure *A*. This indicates that in structure *A* the planes of the bases cannot be perpendicular to the fibre axis. The positions of the strong reflexions on the sixth, seventh and eighth layer-lines suggest that the angle of tilt is about 25°.

We are grateful to Prof. J. T. Randall for his interest and encouragement. One of us (R. E. F.) acknowledges the award of a Turner and Newall Fellowship. [June 25, 1953.]

- *Watson, J. D., and Crick, F. H. C., *Nature*, **171**, 377 (1952).
²Franklin, R. E., and Gosling, R. G., *Nature*, **171**, 740 (1952).
³MacGillivray, C. H., and Bragg, R. M., *Acta Cryst.*, **1**, 156 (1948).
⁴Franklin, R. E., and Gosling, R. G., *Acta Cryst.* (in the press, Part II).
⁵Franklin, R. E., and Gosling, R. G., *Acta Cryst.* (in the press, Part I).



Рентгенограмма В-формы ДНК, полученная Розалинд Фрэнклин в конце 1952 г. Фотография 51 — рентгенограмма волокон натриевой соли тимусной ДНК в В-форме.



Рентгенограмма волокон ДНК кишечной палочки, полученная Уилкинсом

"To the solid ground"
Of nature treads the Mind that waits for "Yes" - W. H. Auden

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MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribonucleic acid (D.N.A.). This structure has several 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 two intertwined chains, with the phosphate 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 in 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.² 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.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each twisted round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate-ester groups joining the deoxyribose 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 sequence of the atoms in the two chains runs in opposite directions. Each chain loosely resembles Furberg's model No. 1; that is, the bases are on the outside. The configuration of the sugar and the phosphate is as shown in Figure 1. The sugar being roughly perpendicular to the structure has roughly every 3.4 Å in the z-direction. We have assumed an angle of 36° between adjacent residues in the same

equipment, and to Dr. G. R. H. Johnson and the captain and officers of H.M.S. Discovery II for their part in making the observations.

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(Reprinted from Nature, Vol. 171, p. 364, May 30, 1953)

GENETICAL IMPLICATIONS OF THE STRUCTURE OF DEOXYRIBONUCLEIC ACID

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

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

THE importance of deoxyribonucleic acid (DNA) in living cells is undisputed. It is found in all dividing cells, largely if not entirely in the nucleus, where it is an essential constituent of the chromosome. Many lines of evidence indicate that it is the carrier of a part of if not all the genetic specificity of the chromosome and thus of the gene itself.

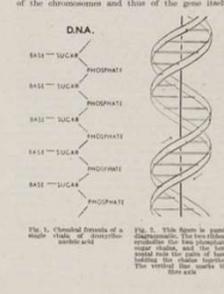


Fig. 1. Chemical formulae of a nucleotide unit of DNA.

King's College, London. One of us (J. D. W.) has been asked by a Fellowship from the National Foundation for Infantine 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, 1953

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Molecular Structure of Deoxyribose Nucleic Acid

When the biological properties of deoxyribose nucleic acid suggest a molecular structure containing great complexity, X-ray diffraction studies are particularly useful. 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 that form when in the natural state. A fuller account of the work will be published shortly. The structure of deoxyribose nucleic acid in the same in all respects (although the nitrogen base may be either adenine, guanine, cytosine, or thymine, and in particular nucleoside). The same linear group of polynucleotide chains may stack together parallel to each other to give crystalline, semi-crystalline or amorphous forms. In all cases the X-ray diffraction patterns consist of two regions, one of moderate intensity, and the other by the larger spacing of the chain configuration. The evidence of different nitrogen bases along the chain is not made visible.

Several general features of deoxyribose nucleic acid structure are shown in the following communication by Fig. 1 (cf. ref. 2). As already mentioned, the nucleotide repeat along the fibre axis. The same unit is repeated along the fibre axis, but in a repeat unit the polynucleotide chains have higher density than the nucleoside chains. The evidence of different nitrogen bases along the chain is not made visible.

Diffraction by Helices

It may be shown (also by Fraser, unpublished) that the intensity distribution in the diffraction pattern of a helix of rotors (rather than of spheres) is given by the square of Bessel functions. A uniform continuous helix gives a series of lines of material corresponding to the helix pitch, the intensity distribution along the axis being given by the square of J_0 , the zero order Bessel function. A screw helix gives a series of lines of material corresponding to the helix pitch, the intensity distribution along the axis being given by the square of J_0 , the zero order Bessel function.

The X-ray diffraction photograph of crystalline deoxyribonucleic acid (see diagram) is shown in Fig. 1. In view of the very complex helical structure (for example, the general transformation of helicity) it is remarkable that the diffraction pattern is so perfect, for each crystallite indicates a large volume of molecular simplicity. We have found no differences in the diffraction patterns of crystalline deoxyribose nucleic acid obtained from calf thymus, mouse sarcoma, human white blood cells, E. coli, pneumococci and *Penicillium* spores, although the ratio of bases in the deoxyribose acid varies considerably with species. These facts, combined with the simplicity of the sequence of nitrogen bases, and the hydrogen bonding between them, produce a centralization of the diffraction pattern which is only rarely met by a simple crystal. A qualitative view of the X-ray diffraction pattern shows several features which point clearly to the type of structure involved. The first feature to be noted is that the data may be interpreted with maximum accuracy by assuming that the molecules are ordered and intensive measured and plotted in reciprocal space. By using a high-resolution photo-camera, about a hundred and twenty separate reflections were recorded from a single specimen. Intensity was measured using a microphotometer. The following features are observed: (1) The intensity of the reflections is very high, and the intensity of the reflections is very high, and the intensity of the reflections is very high.



Fig. 2. X-ray diffraction pattern of deoxyribose nucleic acid from calf thymus.

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Фото из архива Нобелевского фонда.

Фрэнсис Гарри
Комптон Крик

Доля приза: 1/3



Фото из архива Нобелевского фонда.

Джеймс Дьюи Уотсон

Доля приза: 1/3

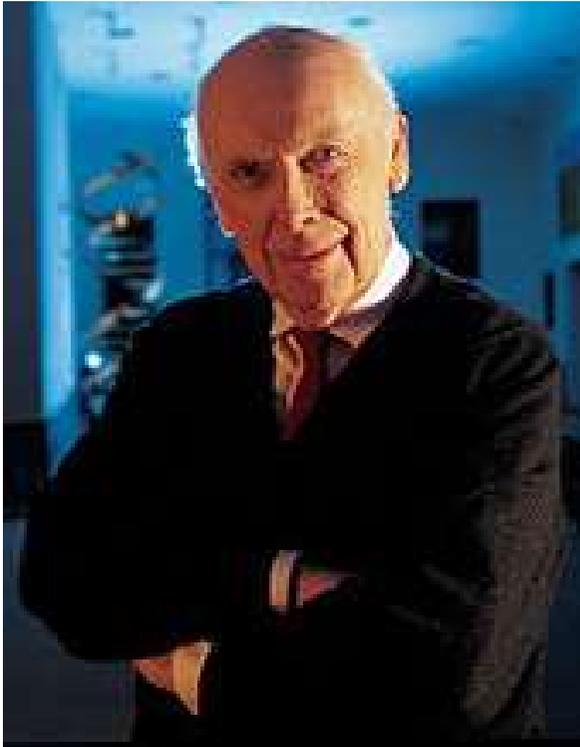


Фото из архива Нобелевского фонда.

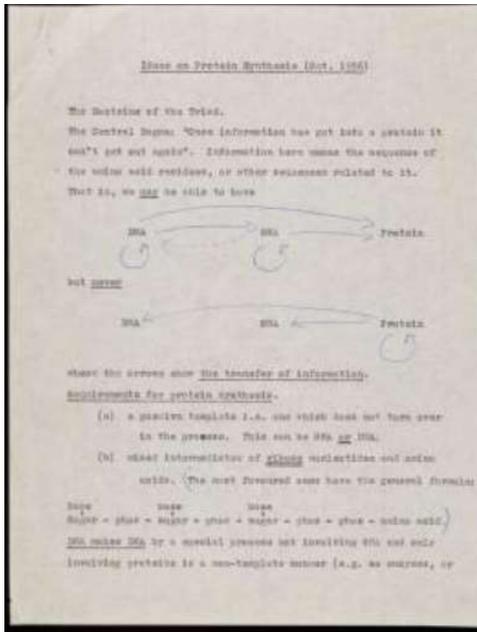
Морис Хью Фредерик
Уилкинс

Доля приза: 1/3

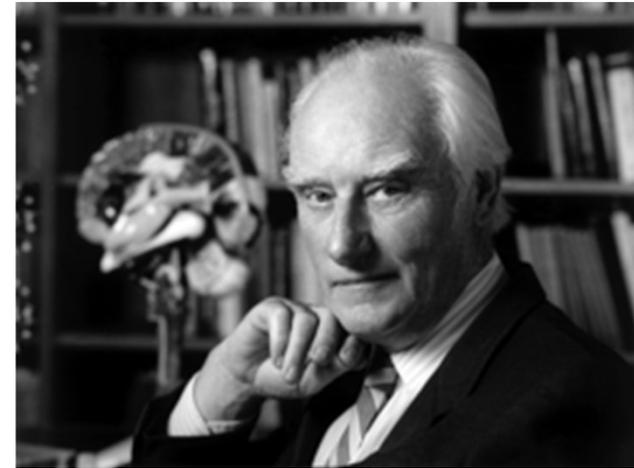
Нобелевская премия по физиологии и медицине 1962 года была присуждена совместно Фрэнсису Гарри Комптону Крику, Джеймсу Дьюи Уотсону и Морису Хью Фредерику Уилкинсу «за открытия, касающиеся молекулярной структуры нуклеиновых кислот и ее значения для передачи информации в живом материале».



Джеймс Дьюи Уотсон
(род. 6 апреля 1928г)
американский биолог



The earliest written description of “The Central Dogma” in a manuscript entitled “Ideas on protein synthesis (October 1956)”. Credit: Wellcome Library, London.



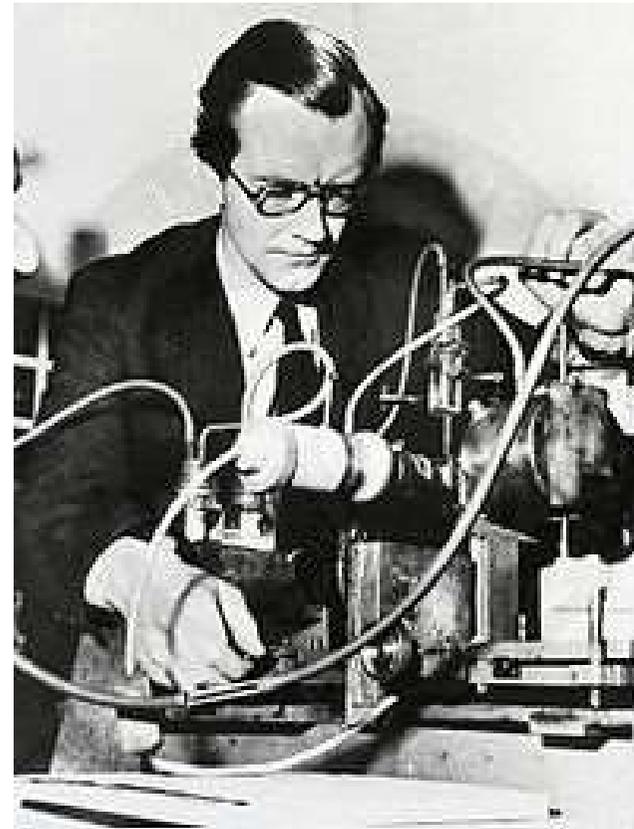
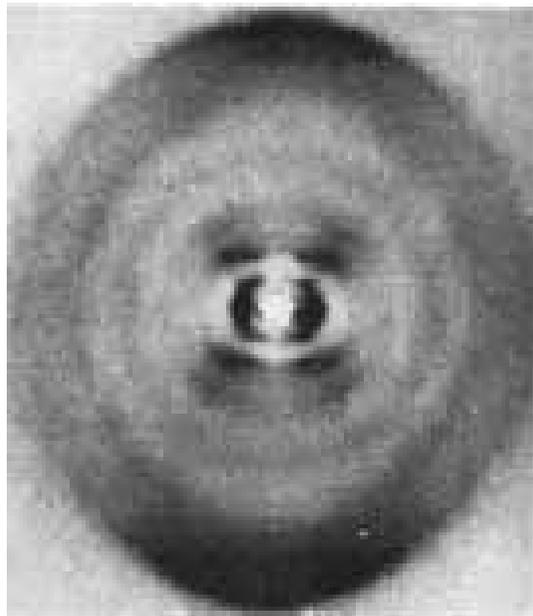
Фрэнсис Крик
(1918-2004)

Крик известен тем, что сформулировал центральную догму молекулярной биологии: генетическая информация передается в клетке в одну сторону, от ДНК к РНК, а затем к белку.

Центральная догма молекулярной биологии

ДНК ↔ РНК → белок

Рентгенограмма волокон ДНК
кишечной палочки,
полученная Уилкинсом



Морис Хьюг Фредерик Уилкинс
(1916-2004)
биофизик



Благодарю
за внимание!