

## X-ray Crystallography



有的化合物不溶于一般的溶剂—河豚毒素—一般NMR找不到合适的溶剂—本身有能得到结晶，X-衍射是比较好的办法  
NMR is about 25 years younger than X-ray crystallography-青霉素的结晶

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## Introduction to X-ray Crystallography

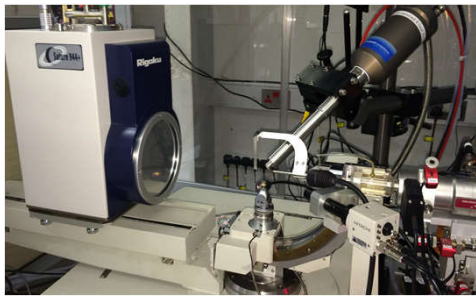
**X-ray crystallography** - highest resolution and reliability structures

**NMR** - enables widely varying solution conditions; characterisation of motions and dynamic, weakly interacting systems, molecules with no ordered structure

### Complementarity of Methods

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## X-ray Crystallography



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## “X-射线” 的发现（1895年）



Wilhelm Roentgen (1845-1923, 1901年诺贝尔物理学奖)革命性地推动了物理学和医学的发展并创立了新的学科，为人类利用X射线诊断与治疗疾病开拓了新途径。X-rays (Roentgen rays)

## The Father of Diagnostic Radiography

诊断放射学之父



William Conrad Röntgen

X-射线把视觉的灵敏度提高了1万倍  
1901年首届诺贝尔物理奖授予了发现X-射线的伦琴



1895年10月德国实验物理学家 Röntgen用一种未知的射线拍摄了他夫人的手的照片，显示出手的骨骼结构引起巨大反响。因为当时无法确定这一新射线的本质，Röntgen把这一新射线称为X-射线。并被应用到医学领域，为人类利用X-射线诊断与治疗疾病开拓了新途径。"X-rays have radically changed the way we see and understand our world - our bodies in particular."

## 伦琴 (Wilhelm Konrad Rontgen)

《100 most influential people in the world》  
伦琴列第71位（旧版72）



伦琴(1845-1923)德国

In 2004 the International Union of Pure and Applied Chemistry named element 111, Rg, a radioactive element with multiple unstable isotopes, after him. X-射线直接影响了20世纪许多重大科学发现。

## “X-射线”与诺贝尔奖



X-射线的发现是19世纪末20世纪初物理学的三大发现(X-射线1896年、放射线1896年、电子1897年)之一,这一发现标志着现代物理学的产生,为诸多科学领域提供了一种行之有效的研究手段。X-射线的发现和研究,对20世纪以来的物理学以至整个科学技术的发展产生了巨大而深远的影响。

一个多世纪以来,因研究X-射线技术、以及使用X-射线进行研究、与X-射线有关的研究而获得诺贝尔奖的已有几十人:

13人因在X-射线研究中有突破性进展而获得了诺贝尔物理学奖;

12人借助X-射线分析手段获得了诺贝尔化学奖;

4人借助X-射线分析获得了诺贝尔生理学及医学奖。

- 1901年, 伦琴就由于发现X-射线而获得了首届诺贝尔物理学奖。
- 1914年, 劳厄由于利用X-射线通过晶体时的衍射, 证明了晶体的原子点阵结构而获得诺贝尔物理学奖。
- 1915年, 布拉格父子因在用X-射线研究晶体结构分享了诺贝尔物理学奖。
- 1917年, 巴克拉由于发现标识X-射线获得诺贝尔物理学奖。
- 1924年, 西格班因在X-射线光谱学方面的贡献获得了诺贝尔物理学奖。
- 1927年, 康普顿与威尔逊因发现X-射线的粒子特性同获诺贝尔物理学奖。
- 1936年, 德拜因利用偶极矩、X-射线衍射法测定分子结构获诺贝尔化学奖
- 1946年, 缪勒因发现X-射线能人为地诱发遗传突变而获诺贝尔生理学医学奖
- 1954年, 鲍林由于在化学键的研究以及用化学键的理论阐明复杂的物质结构而获得诺贝尔化学奖(X-射线衍射研究密不可分)。
- 1962年, 沃森、克里克、威尔金斯因发现DNA的结构分享了诺贝尔生理学、医学奖(以X-射线衍射实验为基础)
- 1962年, 佩鲁茨和肯德鲁用X-射线衍射分析法首次精确地测定了血红蛋白和肌红蛋白的晶体结构而分享了诺贝尔化学奖。
- 1964年, 霍奇金因在运用X-射线衍射技术测定青霉素和维生素B12的结构获得诺贝尔化学奖。

13. 1969年, 哈塞尔与巴顿因用X-射线衍射分析提出“构象分析”的原理同获诺贝尔化学奖。
14. 1973年, 威尔金森与费歇尔因对有机金属化学的研究卓有成效而共获诺贝尔化学奖。
15. 1976年, 利普斯科姆因用低温X-射线衍射和核磁共振等方法研究硼化合物的结构及成键规律的重大贡献获得诺贝尔化学奖。
16. 1979年, 诺贝尔生理学、医学奖破例地授给了对X-射线断层成像仪(CT)作出特殊贡献的豪斯菲尔德和科马克这两位没有专门医学经历科学家。
17. 1980年, 桑格借助于X-射线分析法与吉尔伯特、伯格因确定了胰岛素分子结构和DNA核苷酸顺序以及基因结构而共获诺贝尔化学奖。
18. 1981年, 凯西格班由于在电子能谱学方面的开创性工作获得了诺贝尔物理学奖。
19. 1982年, 克卢格因在测定生物物质的结构方面的突出贡献而获诺贝尔化学奖。
20. 1985年, 蒙蒂特曼与卡尔勒因发明晶体结构直接计算法, 分享了诺贝尔化学奖。
21. 1988年, 戴森霍弗、胡伯尔、米歇尔因用X-射线晶体分析法确定了光合成中能量转换反应的反应中心复合物的立体结构, 共享了诺贝尔化学奖。
22. 1997年, 斯科与博耶和沃克因借助同步辐射装置的X-射线, 在人体细胞内离子传输酶方面的研究成就而共获诺贝尔化学奖。
23. 2002年, 贾科尼因发现宇宙X-射线源, 与戴维森、小柴昌俊共同分享了诺贝尔物理学奖。
24. 2003年, 阿格雷和麦金农因发现细胞膜水通道, 以及对细胞膜离子通道结构和机理研究作出的开创性贡献被授予诺贝尔化学奖(他们的成果采用X-射线晶体成像技术获得)。
25. 2006年, 科恩伯格被授予诺贝尔化学奖, 以奖励他在“真核转录的分子基础”研究领域作出的贡献(他将X-射线衍射技术结合放射自显影技术开展研究)。

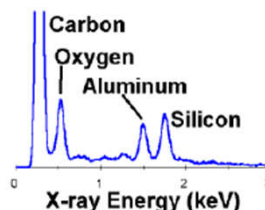
## X-射线的散射

X-ray scattering, X-ray spectroscopy



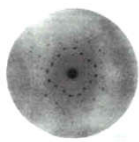
Charles Glover Barkla  
(1877-1944)

1906年因发现X-射线散射现象而获得1917年诺贝尔物理学奖



元素的特征谱线(标识谱线)  
对建立原子结构理论极为重要

## X-射线在晶体中的衍射



Max Theodor Felix Von Laue (1879-1960)

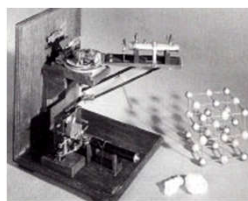
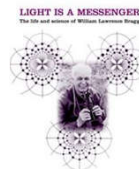
劳厄: 1912年发现X-光衍射, 证明了X-光具有波的性质



索末菲(1868-1951)  
Arnold Sommerfeld

X-光衍射由M. von Laue于1912年发现, 1914年诺贝尔物理学奖。为从实验上观测晶体结构奠定了基础。《自然》杂志把这一发现称为“我们时代最伟大、意义最深远的发现”。表明了X-射线是一种波, 对X射线的认识迈出了关键的一步。

## Light Is A Messenger



1913年1月第一台X-射线光谱仪




A X-ray spectroscopy


Bragg, W. H. The X-ray spectra given by crystals of sulphur and quartz. *Proc. R. Soc. Lond. A* 1914, 89, 575-580. 反映了衍射方向与晶体结构之间的关系。

## X-射线和晶体结构 Bragg's law: $2d\sin\theta = n\lambda$


### A Father, A Son, A Law and A Nobel Prize



Sir William Lawrence Bragg  
(1890 – 1971) 1915 NP



1913年第一台  
X-射线光谱仪

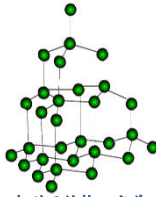


Sir William Henry Bragg  
(1862 – 1942)


利用X-光衍射确定晶体结构的是W. H. Bragg爵士以及他的儿子L. W. Bragg爵士，显示了X射线衍射用于分析晶体结构的有效性(1912-13年)，解释了劳厄的实验事实。证明了能够用X-射线来获取关于晶体结构的信息。


## Lawrence Bragg's work in crystallography changed the way we see the world

### Nobel Prize in Physics in 1915



金刚石结构：完美地说明了碳原子的四个键按正四面体形状排列的结论

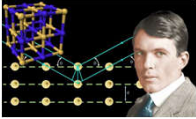





"For their services in the analysis of **crystal structure** by means of X-ray", an important step in the development of X-ray crystallography.

**Bragg was the director of the Cavendish Laboratory, Cambridge,** when the discovery of the structure of DNA was reported by **Watson and Crick** in February 1953. 从1874年至1989年一共产生了29位诺贝尔奖得主。

## William Lawrence Bragg: The Pioneer of X - ray Crystallography



**W. Lawrence Bragg**  
1890–1971  
The begin of X - ray  
Crystallography 1912



1927 Solvay Conference "Electrons and Photons"  
"Probably the most intelligent picture ever taken...."

17 out of the 29 individuals were or would be Nobel laureates incl Compton, Pauli, Niels Bohr, Max Planck, Marie Curie, Lorentz, Einstein and Lawrence Bragg

"Standing on the shoulders of giants" 29

## X-ray crystallography and Structure

### X-Ray Crystallography: crystals scatter X-rays and spots reflect arrangement of atoms

X-ray crystallography is an imaging technique first described in 1913 by the father-and-son duo of William Henry Bragg (1862–1942) and William Lawrence Bragg (1890–1971), in which x-rays are projected onto a crystalline solid to determine atomic positioning and molecular structure.

X-Ray Diffraction Photograph

## 1924年的诺贝尔物理学奖



**Karl Manne Georg Siegbahn**  
1886-1978, 1924 NP




© L. Thémexner


**西格班**获得了1924年的诺贝尔物理学奖，成为继巴克拉之后，又一次因**X-射线学**的贡献而获诺贝尔物理学奖的物理学家。

## X-ray crystallography and Structure


### 物理化学的奇才、饱受争议的人物：德拜，间谍？



**Peter Joseph William Debye** 1884-1966  
荷兰第2位获得诺贝尔化学奖的科学家  
1936 NP, 为衍射仪的制造奠定了基础



**Linus Carl Pauling**  
1901–1994  
得意门生1954 NP



**Lars Onsager**  
1903–1976  
得意门生1968 NP

"通过对偶极矩以及气体中的X-射线和电子的衍射的研究来**了解分子结构**"于**1936年获诺贝尔化学奖**。为了纪念他，把偶极矩的单位称为“德拜”。

**P. J. W. Dedy** 是第一个**因运用X-光衍射**而获得诺贝尔化学奖的科学家。

## “世界物理学全明星梦之队”



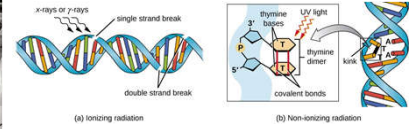
第五次索尔维会议照片（1927），二十世纪物理学和物理学史上最珍贵的一张历史照片，史上最强大脑：**二排左1为德拜(1936 NP)**，Niels Bohr中排右一。

## X-射线诱发遗传突变

1946年诺贝尔生理学-医学奖

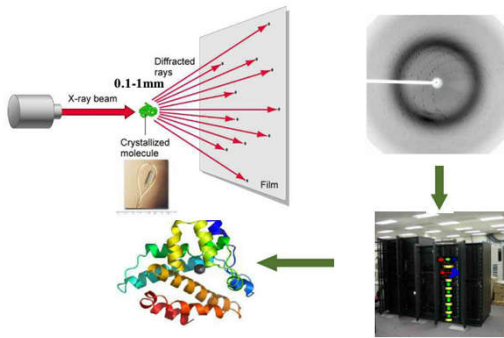


缪勒 (1890-1967)  
Hermann Joseph Muller



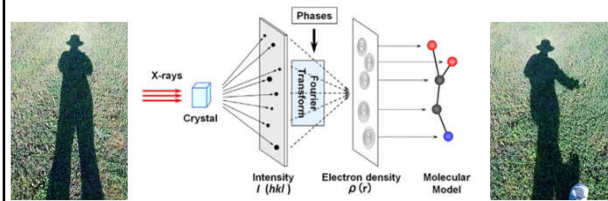
缪勒因发现X-射线能人为地诱发遗传突变而被授予1946年诺贝尔生理学、医学奖。缪勒最早指出放射线对人类的遗传有危害作用。

## X-ray crystallography- Knowing what you do not know



This works a little like trying to figure out how tall a person is by looking at his shadow.

## X-ray Crystallography



By measuring the angles and intensities of diffracted beams, produced as the X-ray beams contact a single crystal, a 3-D picture of the density of electrons within the crystal is produced and from this the positions of the atoms within the crystals, their chemical bonds, can be determined.

## 伊藤博文与“拼死吃河豚”

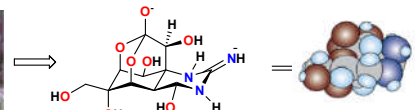


伊藤博文 (1841-1909)  
日本第一个内阁总理大臣  
明治宪法之父



1975年自己百毒不侵日本传奇歌舞伎演员三代目坂东三津五郎吃了四份河豚的肝脏，因而中毒身亡。

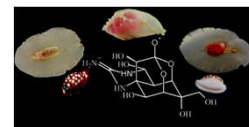
## 河豚毒素 (Tetrodotoxin, TTX)



It is about 1200 times more toxic to humans than cyanide and it has no known antidote.



Yoshimasa Hirata



局部麻醉作用是普鲁卡因的4000倍  
眼镜蛇毒100倍 KCN毒性的1250倍



R. Woodword

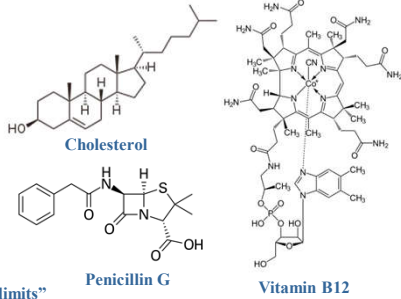
## Dorothy Crowfoot Hodgkin

Using X-ray crystallography to “see” atoms



晶体王国之花  
霍奇金(1910-1994)

Went beyond “feasible limits”  
Figured out something organic chemists could not!

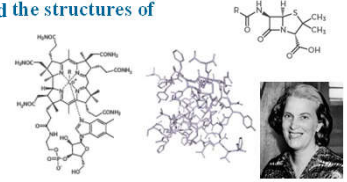


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## Dorothy Crowfoot Hodgkin

Dorothy Hodgkin, one of the outstanding scientists of the 20th century, solved the structures of

- Penicillin, 1945
- Vitamin B12, 1954
- Nobel Prize, 1964
- Insulin, 1969



These achievements had an immense impact on chemistry, biochemistry and medical science, establishing the power of X-ray crystallography, and changing the practice of synthetic chemistry.

## Even More Important She...

Dorothy’s remarkable personality

- Reinvented crystallography
  - From black art ——— scientific tool
- Established use of molecular structure to explain biological function
- **Worked to improve relations between East and West**
- **Interested in World Peace:**
- Is the “Cleverest woman in England”
- Has been called “Gentle Genius”



## Early Interests of a “Gentle Genius”...

Dorothy Hodgkin: Structure as Art

- Chemistry, especially crystals
- Crystals – atoms arranged in regular and repeated pattern
- “A diamond is a girl’s best friend!”
- 16<sup>th</sup> Birthday Party:
  - Received X-ray crystallography book
- Accepted to Oxford University in 1928
- On vacation, studied patterns of mosaic floors
- “You’re finding what’s there and then trying to make sense of what you find.”



Synagogue mosaic floor in Jerusalem.

## She liked to “think with her hands”...

类风湿导致了手指严重扭曲

- Oxford graduation, 1932
- X-ray studies at Cambridge
- PhD with J.D. Bernal 1934
- Own Lab at Oxford in 1934
- Good News:* Complex proteins could be analyzed
- Bad News:* Diagnosed with rheumatoid arthritis

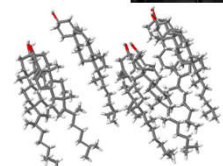


Rheumatoid arthritis never slowed her determined pursuit of science

## Going beyond the limits...

搞科研得诺奖，搞教学教出首相

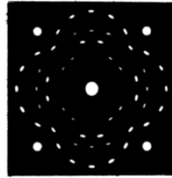
- Took teaching job at Oxford.
- Primitive lab in basement
- Investigated sterols
- Went beyond “feasible limits”
- Figured out something organic chemists could not!
- Victory Dance!



Structure of Cholesterol

### Questions of a "Gentle Genius"...

- Wondered if chemists were right
- Wanted to "see" molecules for herself
- Decided to specialize in new field of X-ray crystallography
- *X-Ray Crystallography*: crystals scatter X-rays and spots reflect arrangement of atoms



X-Ray Diffraction Photograph



### Even Geniuses Fall In Love...

- 1937 married **Thomas L. Hodgkin**

Thomas L. Hodgkin (1910-1982), historian

Hodgkin disease



"Dorothy in love"

- "They really adored each other" – Max Perutz
- He decided she was more creative
- Three children
- (1938, 1941, 1946)



### "Combining two careers and three children proved "reasonably easy"..."

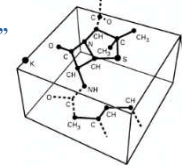
A devoted couple with 3 children  
9 grandchildren,  
3 great-grandchildren

- Thomas also taught at Oxford
- Her arthritis improved w/each pregnancy
- She made time for her kids
- She could switch easily from deep calculations to kid talk!



### Her Project During WW II...

- 1940 Britain at war
- Penicillin – "high security secret"
- Structure looked hopeless
- Started from scratch 1942
- 1946 Mission Accomplished
- Proved she was "master crystallographer"



Structure of Penicillin G

### Dorothy Hodgkin Determined the Chemical Structure of Penicillin



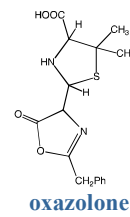
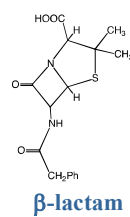
Molecular model of penicillin by Dorothy Hodgkin, c. 1945

牛津大学科学博物馆中摆放着霍奇金发现青霉素分子结构的示意模型，黑色线圈表示电子云，从线圈的密度能推断出是什么原子

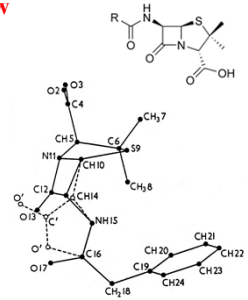


### Penicillin Chemical Formula

"A magnificent start to a new era of crystallography"



1946



● β-lactam atomic positions  
○ Oxazolone atomic positions

**GOOGLE**

**Google commemorated Hodgkin's 104th birthday, May 12, 2014**

Sir Robert Robinson did not like the  $\beta$ -lactam structure because this would be unstable, unlike penicillin. All they were taken aback when a young woman solved...

John W. Cornforth said "If penicillin turns out to have the  $\beta$ -lactam structure I shall give up chemistry and grow mushrooms." He did not keep his threat but later received a Nobel prize for his enzyme work 30 years later, in 1975.

### Life after WW II got complicated...

A teacher, mother, friend, and guide all rolled into one-"warm, simple, affectionate, and caring"

- Commuter spouses
- Dorothy's sister and family moved in
- Always had guests:
  - Third World leaders
  - Scientists
  - Children's friends
- Christmas parties

Dorothy with husband and daughter

### On to Bigger and Better Things...

8 years, 2500 X-ray photographs

#### Nobel Prize Given for Vitamin B<sub>12</sub> Studies

Dorothy Crowfoot Hodgkin honored for determining structure by x-ray techniques; U.S. and U.S.S.R. share physics prize

Hodgkin et al., *Nature* 1955, 176, 325

### Going Beyond the Limits...

- Developed unbeatable repertoire of skills
- 10,000 calculations by hand took months/years
- Beavers and Lipson Strips – the early computer system
- Vitamin B12, published in *Nature* in 1954

Fellow of the Royal Society in 1947  
harder to achieve than the Nobel

Beavers and Lipson Strips

### Vitamin B<sub>12</sub> Structure (1948-1957)

#### Vitamin B<sub>12</sub> Synthesis (1960-1976)

- In 1956, Dorothy Hodgkin was able to obtain and solve the X-ray crystal structure of vitamin B<sub>12</sub>
- Wilhelm Friedrich and Konrad Bernhauer from Stuttgart successfully converted cobalamic acid to vitamin B<sub>12</sub>

Total synthesized by Woodward & A. Eschenmoser

Dorothy Hodgkin  
Won the Nobel Prize in 1964 for her advancement of X-ray crystallographic techniques in the structural determination of biological molecules

### Winning the Nobel Prize...

'Grandmother wins Nobel Prize' "牛津主妇获得了诺贝尔奖"

**Nobel prize for a wife from Oxford**

- 1964 Nobel Prize in Chemistry
- Did not share prize
- 5<sup>th</sup> Woman
- 1<sup>st</sup> British Woman
- Did not stop research
- Next project: Insulin (777 atoms)

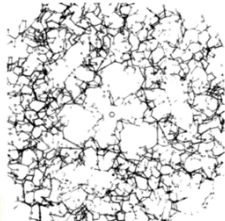
"一项完全不属于家庭主妇的技能"

Dorothy Hodgkin

## “Late Night News from Dorothy...”

The three-dimensional structure of insulin 1934-1969

- Computers now available
- Structure is “so complicated and irregular”
- 1969 “...Insulin Is Solved
- 70,000 X-ray spots
- “Crisis in Organic Chemistry”



Atomic Structure of  
6 insulin molecules  
Dorothy's greatest scientific achievement



## Insulin-A Storytelling Molecule



Frederick Banting and Charles Best with one of the first diabetic dogs to receive insulin, 1923 NP



Frederick Sanger  
1918-2013, 1958 NP



Dorothy C. Hodgkin  
1910-1994, 1964 NP

The human insulin protein is composed of 51 amino acids

## A Woman as Clear as A Crystal

玩转科学家、母亲、妻子三个角色



分别与其曾孙子、丈夫、三个孩子、实验室成员



C. Darwin, J. H. Raper, G. C. Clutton-Brock, J. Drenth, F. W. C. Whitby, D. M. Hodgkin, A. M. Percival, R. C. M. Macdonald, S. S. Holt, G. T. R. Jones, J. Drenth, P. M. Green

## Dorothy C. Hodgkin——

霍奇金 “中国人民的老朋友”



唐有祺院士



廖鸿英 (1905-1998)

## 八次来访我国的“中国人民的老朋友”



1977年观看牛胰岛素晶体结构



霍奇金在中国



梁栋材等陪霍奇金登长城



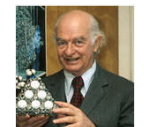
## 化学家唐有祺院士



1978年，唐有祺在英国科学家霍奇金家中作客



1947年，唐有祺在加州理工学院



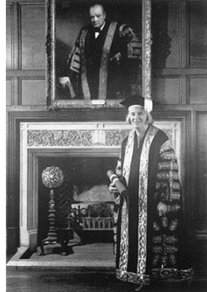
Linus Pauling



## “Cleverest Woman in England”...

Royal Society at the youthful age of 37

- 1965 Queen Elizabeth gave her the Order of Merit, second
- 1960s and 70s worked for Peace organizations for 13 years
- Elected chancellor of Bristol University in 1970-88 **布里斯托大学**
- Effect on Margaret Thatcher and Mikhail Gorbachev
- The first woman to win the Copley Medal (RS) in 1976



霍奇金 (1910-1994)

## President of Pugwash

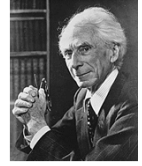
A devoted protagonist of world peace



1975-1988



Thinkers' Lodge, Pugwash, Nova Scotia, Canada, site of the first Pugwash conference in 1957



Bertrand Russell (1872-1970)

**帕格沃什科学和世界事务会**  
(Pugwash Conferences on Science and World Affairs)  
**Nobel Peace Prize in 1995**

## Faith In the Socialist

Social and political activism



Lomonosov Gold Medal Russian Academy's highest accolade in 1982



Linus Pauling in 1970



Lenin Peace Prize in 1986 Russian Academy's highest accolade



1950

## 撒切尔夫人和霍奇金



和刚卸任的首相撒切尔夫人交谈1991年



Her list of students, colleagues and co-workers includes the names of over 110 men and women from over 20 countries.

## The End of A Beautiful Life...

- 1977 retired to house near Oxford
- Thomas died 1982



- Traveled to scientific and peace conferences
- Wheelchair bound from arthritis and broken pelvis
- Died at home July 29, 1994 at the age of 84



Dorothy Crowfoot Hodgkin, 1910-1994

## The Life of A “Gentle Genius”...



**“晶体化学皇后”  
“晶体魔术师”**




**“I was captured for life by chemistry and by crystals.”**  
Dorothy Hodgkin




Among the 71 British Nobel Prize winners for science,  
**Meet the only woman.**

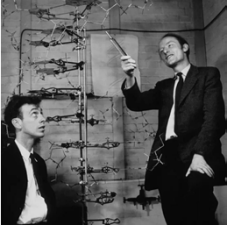
We all need science. Science needs women. You can help.  
www.dorothyhodgkinproject.com



**What are major works and discoveries by Dorothy?**  
**How did you become familiar with the work of Dorothy Hodgkin?**  
**Why do you think that Dorothy is considered a heroine of science?**  
**What inspires you about Dorothy?**  
**What do you find the most fascinating about the work of Dorothy Hodgkin?**  
**Why is Dorothy Hodgkin our heroine of science?**



**The Role of the X-ray in the Elucidation of the Structure of DNA**



DNA分子双螺旋结构的发现，让人类解开了自己的“遗传密码”，同时催生了许多新药物开发、新疗法发现，“亲子鉴定”的实现，给人类带来巨大的福祉。 417

**1962年的诺贝尔生理学奖或医学奖**

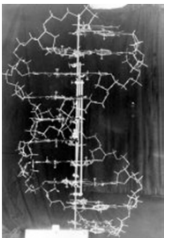


**Two unknown scientists**  
沃森James Watson和克里克F.H. C. Crick




**A Structure for Deoxyribonucleic Acid**  
J. D. Watson and F. H. C. Crick (1)  
April 25, 1953 (2), Nature (3), 171, 737-738  
We wish to suggest a structure for the salt of deoxyribonucleic 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 (4) and Corey (5). They kindly made their manuscript available to us in advance of publication. Their model consists of three interlocked chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion,  
**最有价值的论文-不足千字 Nature, 1953 April 25**

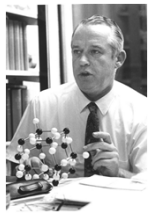
**Donohue and Chargaff's Input Turned out to be Critical**



**The original DNA model**



**Erwin Chargaff (1905–2002)**  
*Chargaff's rules* 1950  
A=T, G=C




**Jerry Donohue (1920–1985)**  
Pauling Assistant

**"We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances" Donohue knew structural chemistry inside and out.**

**Man Who Opened the Door to DNA**

**诺贝尔奖级的发现**



**Erwin Chargaff (1905–2002)**

**腺嘌呤**  
Adenine


**胸腺嘧啶**  
Thymine

**腺嘌呤**  
Adenine

**胞嘧啶**  
Cytosine

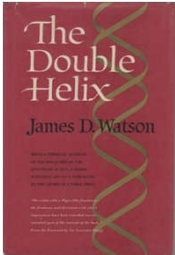
**鸟嘌呤**  
Guanine

**Chargaff's Rules**

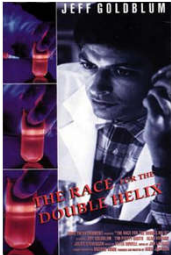


Adenine Thymine **Now this was a really big discovery.** Cytosine Guanine

### The Double Helix: A Personal Account of the Discovery of the Structure of DNA



*Life Story* (known as *The Race for the Double Helix* in the United States) is a 1987 TV film



In 1998, the Modern Library placed *The Double Helix* at number 7 on its list of the **100 best nonfiction books of the 20th century**. In 2012, *The Double Helix* was named as one of the 88 "Books That Shaped America" by the Library of Congress. **But both Crick and Wilkins protested publication.**

### 《时代》：美国历史上最具影响力的20大人物

2012

20世纪最重要三大科学发现：**相对论、量子力学和DNA双螺旋**



詹姆斯·沃森 (James Watson) DNA之父, 第14位



Albert Einstein 第11位



Steve Jobs 第17位

### Lies, Thieves and DNA

"There's a myth which is, you know, that Francis and I basically stole the structure from the people at King's. I was shown Rosalind Franklin's x-ray photograph and, whooo! that was a helix, and a month later we had the structure, and Wilkins should never have shown me the thing. I didn't go into the drawer and steal it, it was shown to me, and I was told the dimensions, a repeat of 34 angstroms, so, you know, I knew roughly what it meant and, uh, but it was that the Franklin photograph was the key event. It was, psychologically, it mobilized us..."

James Watson, James Watson, Center for Genomic Research Inauguration, Harvard, September 30, 1999.

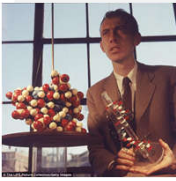

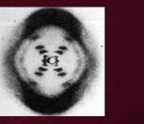






Photo 51

Watson wrote of the photo, "The instant that I saw the picture my mouth fell open and my pulse began to race."

### Great Scientists aren't always Great People

#### 'Father of DNA' James Watson Stripped of Honors Over More Ugly Racism Comments

"最让人讨厌的诺奖得主"

Nobel medal for DNA discovery nets \$4.7M at auction in 2014

Watson expressed the belief that some races are inherently less intelligent than others-有些种族天生不如其他种族聪明 (智力差异)

### "DNA之父"詹姆斯·沃森在苏州成立细胞代谢研究中心

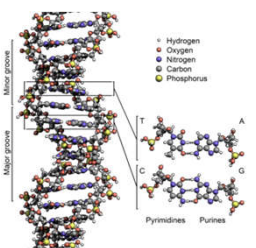


Women should have the right to have abortions if tests could determine their children would be homosexual.

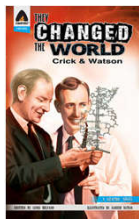

He has previously argued that stupidity is a disease that should be cured "it would be great" if women were genetically engineered to be pretty.

### "Why You Are You. Nearer Secret of Life"

#### Crick and Watson's DNA molecular model, 1953

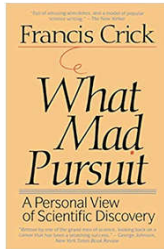


- Hydrogen
- Oxygen
- Nitrogen
- Carbon
- Phosphorus

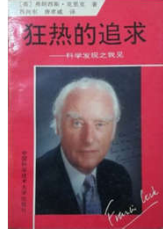



Unlike Franklin and Wilkins who favored data collection, measurable results and interpretation, Watson and Crick **utilized the model building approach.**

## What Mad Pursuit-A Personal View of Scientific Discovery



Francis Crick  
1916-2004



In this book, Crick gives important insights into his work on the DNA structure, along with the Central Dogma of molecular biology and the genetic code, and his later work on neuroscience.

"It may be the most famous [scientific] drawing of the 20<sup>th</sup> century, in that it defines modern biology"

生命的旋梯



Crick's Nobel prize sold at auction for a cool \$2 M 2013



Odile Crick (1920-2007) British artist  
Francis Harry C. Crick (1916-2004)

"The Secret of Life"  
A twisted ladder

## Francis Crick's \$5.3 Million Letter to Son

"We have discovered the secret of life"



In 1953, Francis Crick wrote a letter to his 12-year-old son Michael, describing his discovery. Michael Crick put that letter up for auction on April 2013-the 60th anniversary of the historic discovery of the structure of DNA .

## Watson and Crick's Acknowledgments

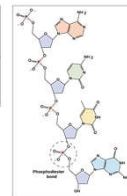
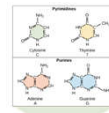
Within their paper, Watson and Crick stated that they were indebted to certain individuals for assisting in their research:

Dr. Jerry Donohue for his advice and criticism on the model

Specifically with respects to interatomic distances  
Wilkins and Franklin for their published works



Jerry Donohue  
(1920-1985)



Maurice Wilkins  
1916-2004



Rosalind Franklin  
1920-1958

## History of DNA

1869 DNA isolated by **Friedrich Miescher**



Miescher



Levene

1919 Defining the composition of DNA  
**Phoebus A. Theodore Levene**

1938 DNA polymer **Rudolf Signer**  
Student of W. Lawrence Bragg



Signer



Avery



Chargaff

1944 DNA carries the genetic code  
**Oswald Avery**

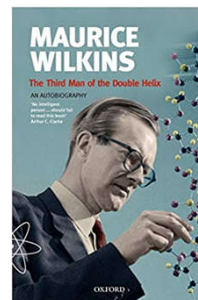
1950 DNA pattern **Erwin Chargaff**

1953 Structure for DNA  
**J. Watson and F. Crick**



## The "Third Man"—Maurice Wilkins

The Nobel Prize in Physiology or Medicine 1962  
**Maurice Wilkins did not enjoy the limelight**



Rosalind Franklin  
1920-1958



Maurice Wilkin  
(1916-2004)  
威尔金斯

What if Wilkins and Franklin had been able to work together?  
Was Wilkins qualified?

### The Great Race and Lessons

John T. Randall  
University of London

Wilkins

W. Lawrence Bragg  
Cavendish Lab 29 NP

Franklin

Watson

Calltech

Pauling

Crick

The structure of DNA:  
Cooperation and competition

### From Triple Helix to Double Helix

Raymond G. Gosling  
(1926-2015)

Photo 51

Maurice Wilkins  
(1916-2004)

James D. Watson  
1928—  
“A questioning attitude is a greater scientific asset”

Max F. Perutz  
(1914-2002)

Linus C. Pauling  
1901-1994

## Rosalind Franklin

Do You Know her ?  
Her Research on the **Structure of DNA** resulted in the Real Evidence of a **Helix** and **helped** Watson and crick conclude about the Double Helical **Structure of DNA**.

**What Secret Behind “The Secret of Life”**  
获奖名单将不是沃森、克里克和威尔金斯，而是沃森、富兰克林和克里克？

### Using X-rays to See Through DNA

A rough sketch of photo 51 in May 1952,  
A photo that changed the world

Rosalind Elsie Franklin  
(1920 –1958)

“The most beautiful X-ray photographs of any substance ever taken.”  
John Desmond Bernal

The most important advance in biology during the 20<sup>th</sup> century

### Why Wilkins and Franklin Did not Able to Work Together?

“World’s Worst Boss”

Rudolf Signe  
1903-1990

DNA from R. Signer

Sir John T. Randall  
(1905 – 1984)

Sir John Turton Randall was an English physicist and biophysicist, credited with radical improvement of the cavity magnetron, an essential component of centimetric wavelength radar, which was one of the keys to the Allied victory in the Second World War. It is also the key component of microwave ovens.

### A Master of X-Ray Techniques

**Wilkins Thought**

Randall  
↓  
Wilkins  
↓  
Franklin  
↓  
Gosling

**Franklin Thought**

Randall  
↘  
Wilkins  
↙  
Franklin  
↓  
Gosling

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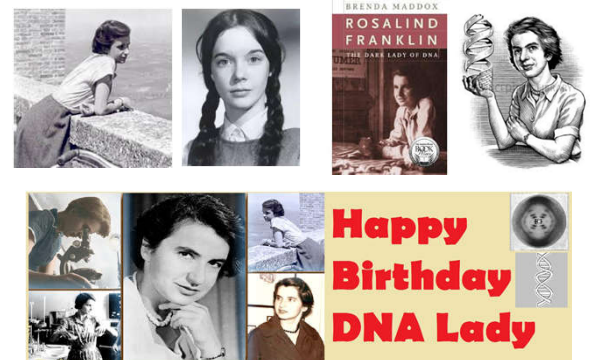
## “黑暗女神” (Dark Lady) ——罗莎琳·富兰克林



Rosalind Elsie Franklin (1920-1958) 流传千古的DNA分子X-衍射图1953


富兰克林已经想到了DNA的双螺旋结构，只是还未来得及发表论文而已。然而这张图竟在她完全不知情的情况下，被同实验室的威尔金斯（同获1962年诺贝尔奖）拿给了沃森和克里克观看。沃森和克里克才在1953年4月25日，得以在《Nature》上发表一篇不足千字的重磅论文。

## Rosalind Franklin: The Dark Lady of DNA




Happy  
Birthday  
DNA Lady

## Rosalind Franklin - Great Minds in Science Article



"Mother of DNA"-Behind the Scenes of DNA

“如果富兰克林当年没有逝世，她应该代替一位领奖者在领奖台上”。




## THE Crystallographer

Rosalind Franklin

From left to right: Anne Cullis, Francis Crick, Donald Caspar, Aaron Klug, Rosalind Franklin, Odile Crick, and John Kendrew.

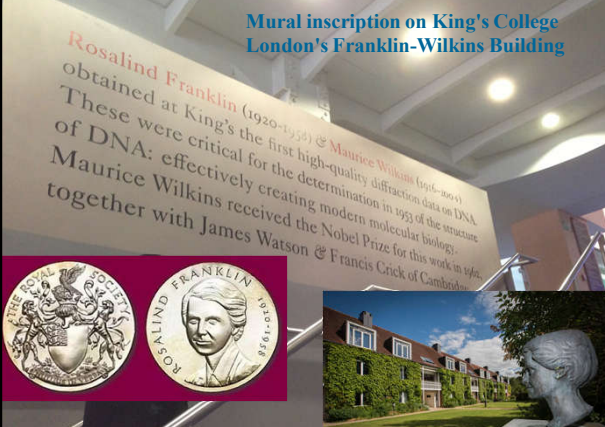
## Ray Gosling, Herbert Wilson and Maurice Wilkins and Alexander Stokes at a reunion at King's in 1993



3 papers were published in *Nature*, April 1953, to announce a structure for DNA

## Mural inscription on King's College London's Franklin-Wilkins Building

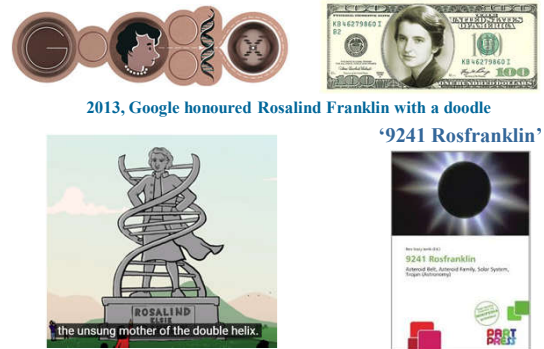
Rosalind Franklin (1920-1958) & Maurice Wilkins (1916-2005) obtained at King's the first high-quality diffraction data on DNA. These were critical for the determination in 1953 of the structure of DNA: effectively creating modern molecular biology. Maurice Wilkins received the Nobel Prize for this work in 1962 together with James Watson & Francis Crick of Cambridge.



### Rosalind Franklin - Wronged Heroine



### Rosalind Franklin: DNA's Unsung Hero



### 'The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins'



2005, the DNA sculpture (donated by James Watson) in Cambridge

### Rosalind Franklin University



### Franklin-Wilkins Building in King's College London



### She's Worth Another Look

Without Rosalind Franklin's groundbreaking work, it may have taken another decade before the double helix structure of DNA had been fully realized



Ronald G. W. Norrish (189-1978) NP 1967



Jacques Merin (1904-1973)

Received her PhD from Cambridge in 1945 with five scientific papers

### Linus Pauling-the acknowledged world master at solving complex molecular structures



The Triple Helix of DNA



Linus Pauling (1901-1994)



alpha helix

Linus Pauling did not have access to Franklin's high-quality x-ray diffraction images, which were key factors in Watson and Crick's development of the correct model. In 1954, Pauling won the Nobel Prize in chemistry "...for his research into the nature of the chemical bond and its application to the elucidation of the **structure of complex substances**"

### Pauling announced structure of DNA

#### The Race for DNA



The *PNAS* description 14 pages appears in February 1953 and a *Nature* note appeared in the journal's February 21 issue.

Lessons-Humility should not be underrated. A questioning attitude is ultimately a greater scientific asset.

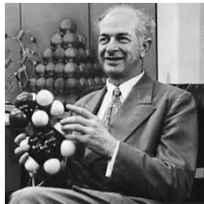
### From Proteins to DNA



Oswald Theodore Avery (1877-1955)



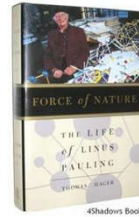
William Lawrence Bragg Physic-molecular biology



Linus Pauling Chemistry-molecular biology

In 1951, both Bragg and Linus Pauling wanted to find the structure of the master molecule of life, the gene. But both were focused on proteins, although Oswald Theodore Avery published genetic traits of DNA in 1944.

### Why Did Pauling Lose the "Race" to James Watson and Francis Crick?



Why did Pauling fail to discover the double helix?

Linus Pauling, one of the most important scientists of all time

1901 LINUS PAULING was born in Portland, Oregon. His parents were Lucy and Herman Pauling.

Human died in 1910 and Lucy joined the family household.

All the age of 10 Linus discovered his "talent" in Chemistry. He was interested in a Chemistry Set.

Linus decided he wanted to be a chemist when he was 12.

He graduated in 1922 with a Bachelor's Degree in Chemical Engineering.

He later went on to earn a Ph.D. in MATHEMATICAL CHEMISTRY from Caltech.

He received the NOBEL PRIZE in CHEMISTRY for the discovery of the ALPHA HELIX model of DNA.

He used his talents as a spokesman for Anti-Nuclear weapons during his service during the Cold War.

He was a leading advocate for the benefits of VITAMIN C (a sometimes controversial view).

FEB 28 is LINUS PAULING DAY. A public holiday in Oregon.

Linus passed away in 1994.

### 鲍林1973和1981年两次访问中国



1991年唐有祺和鲍林



1986年卢嘉锡和鲍林

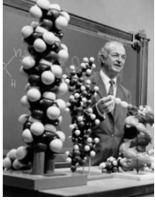


鲍林夫妇在长城1973



## 加州理工学院的Linus Pauling讲席教授

"I have a rather small foot for these shoes"

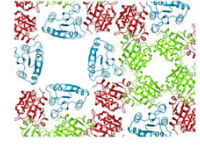


2018年，诺贝尔化学奖迎来了历史上第五位女性得主——加州理工学院的Frances H. Arnold教授，在“酶的定向进化”的贡献

## What Is A Protein Structure?

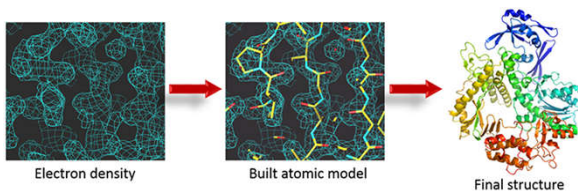
Is it a:

- pretty cartoon...
- space-filling set of spheres...
- picture of the protein in the crystal...
- computational picture of the protein...
- representation of atoms that satisfies experimental constraints...
- model!!!



458

## From the Electron Density to the Structural Model



The calculation of the electron density map (left) allows the building of the atomic model step by step (middle) and leads to the three-dimensional model of the structure (right)

**STRUCTURE SOLVERS** Over 25 crystal structures per day

X-ray crystallography has long been the dominant method for deducing high-resolution protein structures, but cryo-electron microscopy is catching up.

**X-RAY CRYSTALLOGRAPHY** X-rays scatter as they pass through a crystallized protein; the resulting waves interfere with each other, creating a diffraction pattern from which the position of atoms is deduced.

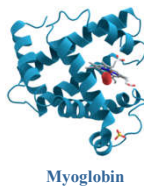
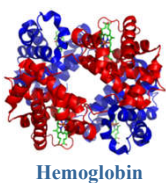
**CRYO-ELECTRON MICROSCOPY** A beam of electrons is fired at a frozen protein sample. The emerging scattered electrons pass through a lens to create a magnified image on the detector, from which their structure can be worked out.

BERKELEY LAB

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## Using X-rays to Crack Nature's Codes

1962 Nobel Prize in Chemistry

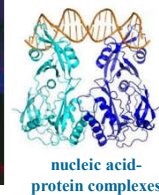


The first protein crystal structures were reported by Max Perutz and Sir John Kendrew in 1960. The Lab. of Molecular Biology (LMB) at Cambridge, 14 of whose scientists have won NPs.

Franklin and Wilkins would have been awarded this Nobel Prize ?

## 1982 Nobel Prize in Chemistry

She would have shared the Nobel Prize

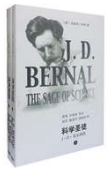


Rosalind Franklin 1920-1958

She Was The Best In Everything

The development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes.

### The Sage of Science—J. D. Bernal



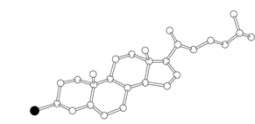
Dorothy Hodgkin  
(1910–1994)



Rosalind Franklin  
(1920–1958)



John Desmond Bernal  
科学学奠基人



John Desmond Bernal  
1901–1971



### Discovery of DNA's structure opened the door of genetic research and application



Collaboration and communication — sharing pieces of the puzzle — has played a critical role in many scientific discoveries

### Computer Assisted Tomography (CT) 计算机辅助X-射线断层成像仪

1979年诺贝尔生理或医学奖



Godfrey N. Hounsfield  
1919–2004  
1970年研制成用于  
头部扫描的CT机

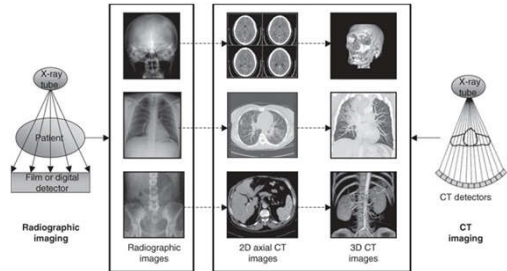


Allan M. Cormack  
1924–1998  
1961年对数学重建方  
法用于放射医学

两位获奖者都不是医学专家,但开创了医学诊断的新时代

### X-ray Computed Tomography (CT)

计算机辅助X-射线断层成像仪



### MRI Vs X-CT

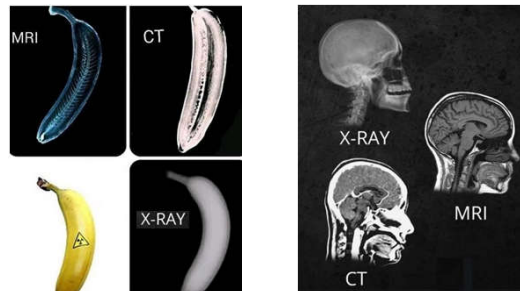
MRI的成像原理与X-CT不同

CT是用X-射线来照射人体, X-射线穿过人体不同的断层组织后会发生不同程度的衰减,通过测定衰减数值的大小并将其转化成像,从而获得断层的扫描图像。

MRI则是通过对静 磁场中的人体施加某种特定频率的射频脉冲,使机体组织中的质子(即氢原子核)受到激发而发生NMR,当中止射频脉冲后,质子在弛豫过程中发射出MRI信号而成像。因此,与X-射线或CT等成像技术相比, MRI不是利用电离辐射成像,因此伤害性小,这是其最显著的优点。

MRI能够对病变进行早期诊断,因为核磁共振现象是通过检测人体内的化学变化而识别人体组织, X-射线及X-CT成像技术是通过人体内的物理(形态)变化而识别人体组织,形态变化说明病变已发展到了一定程度。

### The More You Know—— MRI, CT and X-Ray



## What's Next ? Reading Brain?



# 谢谢大家

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