微生物学

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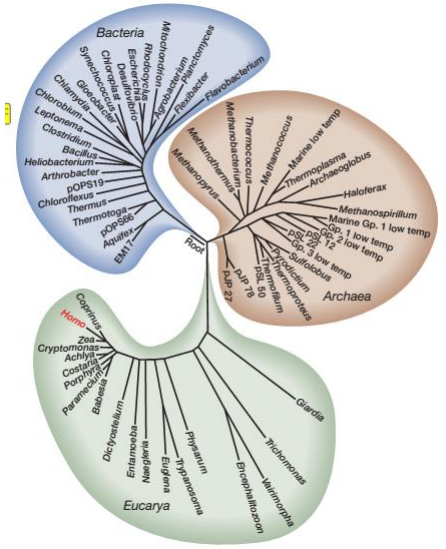
Chapter 1

general introduction

In the field of observation, chance favors only prepared minds.

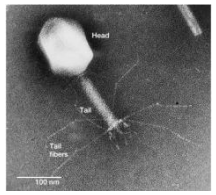
—Louis Pasteur

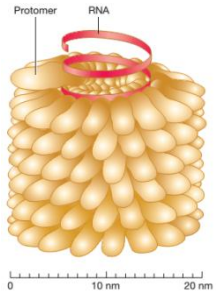


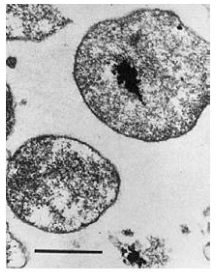
主要内容

1.微生物：概念、特点、类群；
2.微生物学：概念及主要内容及学科分化；
3.微生物学的发展之路：微生物学从奠基到发展及历史其重大事件
4.微生物学在生命科学中的地位：微生物学与其他学科的关系；
5.中国微生物学发展
6.微生物学的未来

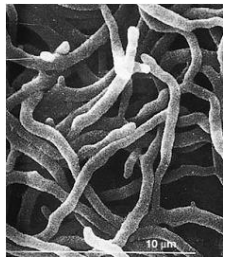

(a) *Morchella esculenta*






Thermoplasma. Transmission e


(a) *S. aureus*



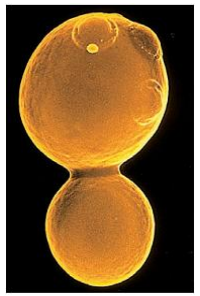
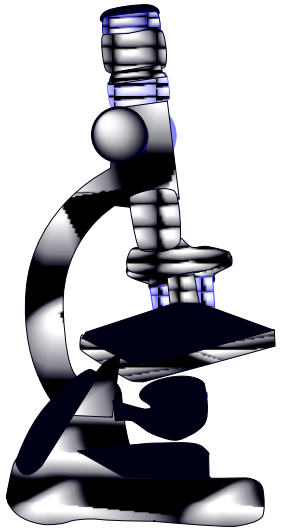

(a) *Saccharomyces cerevisiae:* budding division

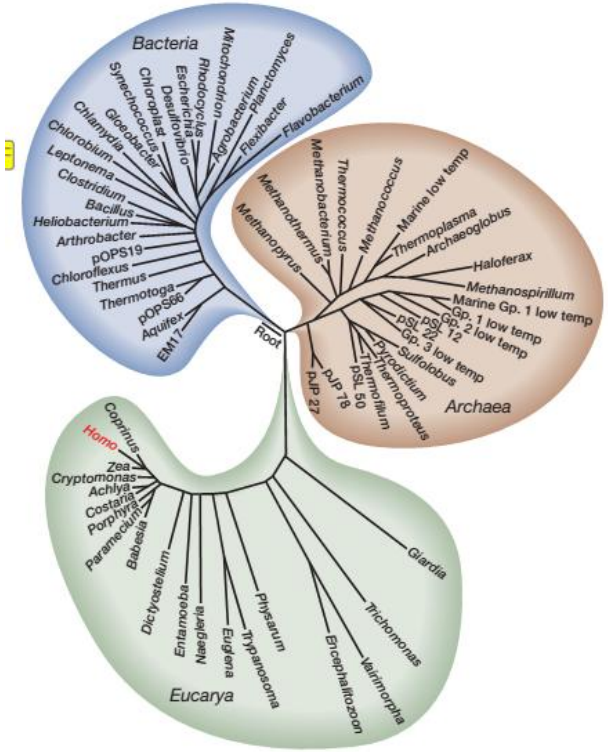

Figure 26.13 Asexual Reproduction in *Ascomyota*. Characteristic conidiospores of *Aspergillus* as viewed with the electron microscope (×1,200).

1.微生物：概念和类群

微生物（**microorganism，microbe**）是一切肉眼看不见或看不清楚的、必须借助显微仪器来观察的、个体微小（**＜0.1mm**）、构造简单的低等生物的总称。



- 微生物
  - 细胞形态的微生物
    - 原核微生物
      - 细菌
        - 细菌
        - 放线菌
        - 蓝细菌
        - 支原体、立克次氏体、衣原体
      - 古菌：极端环境的微生物
    - 真核微生物
      - 真菌
      - 原生动物
      - 显微藻类
  - 非细胞形态的微生物
    - 病毒
    - 类病毒
    - 朊病毒

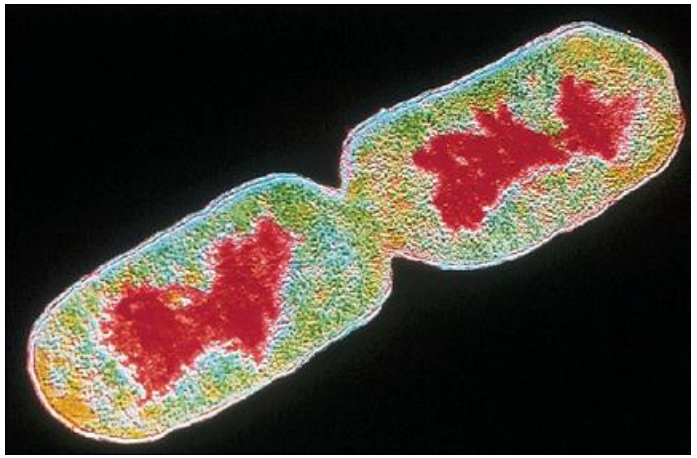


1.微生物的特点

- 个体小、面积大、数量大
- 吸收多、转化快、食谱宽
- 生长旺、代时短、繁殖快
- 基因少，易变异、育种好
- 适应强、分布广、种类多
- 起源早、利用早、发现迟
- 危害大、用处多、产业大
- 资源富、关系杂、研究广

1）个体小、面积大、数量大

- 杆菌的平均长度：2 微米；
- 1500个杆菌首尾相连= 一粒芝麻的长度；
- 10-100亿个细菌加起来重量 = 1毫克
- 面积/体积比：人 = 1，大肠杆菌 = 30万；



Specimen	Approximate diameter or width × length in nm
Oscillatoria	
Red blood cell	7,000
E. coli	1,300 × 4,000
Streptococcus	800–1,000
Poxvirus	230 × 320
Influenza virus	85
T2 *E.coli* bacteriophage	65 × 95
Tobacco mosaic virus	15 × 300
Poliomyelitis virus	27

1）个体小、面积大、数量大

$$A = \frac{S}{V}$$

这样大的比表面积特别有利于它们和周围环境进行物质、能量、信息的交换。微生物的其它很多属性都和这一特点密切相关。

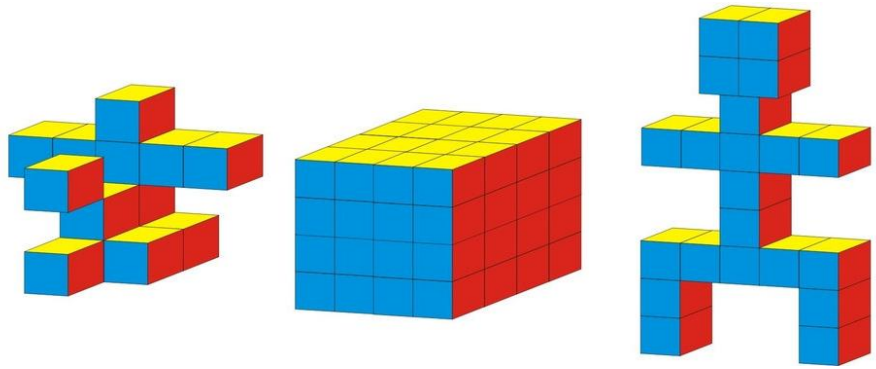


表 1-1 对 $1cm^3$ 固体作 10 倍系列三维分割后的比面值变化

边长	立方体数	总表面积	比面值	近似对象
1.0cm	1	$6cm^2$	6	豌豆
1.0mm	10^3	$60cm^2$	60	细小药丸
0.1mm	10^6	$600cm^2$	600	滑石粉粒
0.01mm	10^9	$6000cm^2$	6000	变形虫
1.0 μ m	10^{12}	$6m^2$	60000	球菌
0.1 μ m	10^{15}	$60m^2$	600000	大胶粒
0.01 μ m	10^{18}	$600m^2$	6000000	大分子
1.0nm	10^{21}	$6000m^2$	60000000	分子

1）个体小、面积大、数量大

微生物无

中。

- 细菌数
- 每张纸
- 每个喷
- 重感冒

- 人体体
- 皮肤表
- 口腔：
- 肠道：
- 粪便干重的1/3是细菌，每克粪便的细菌总数为：1000亿个；

人体体表和体内正常微生物的分布及种类

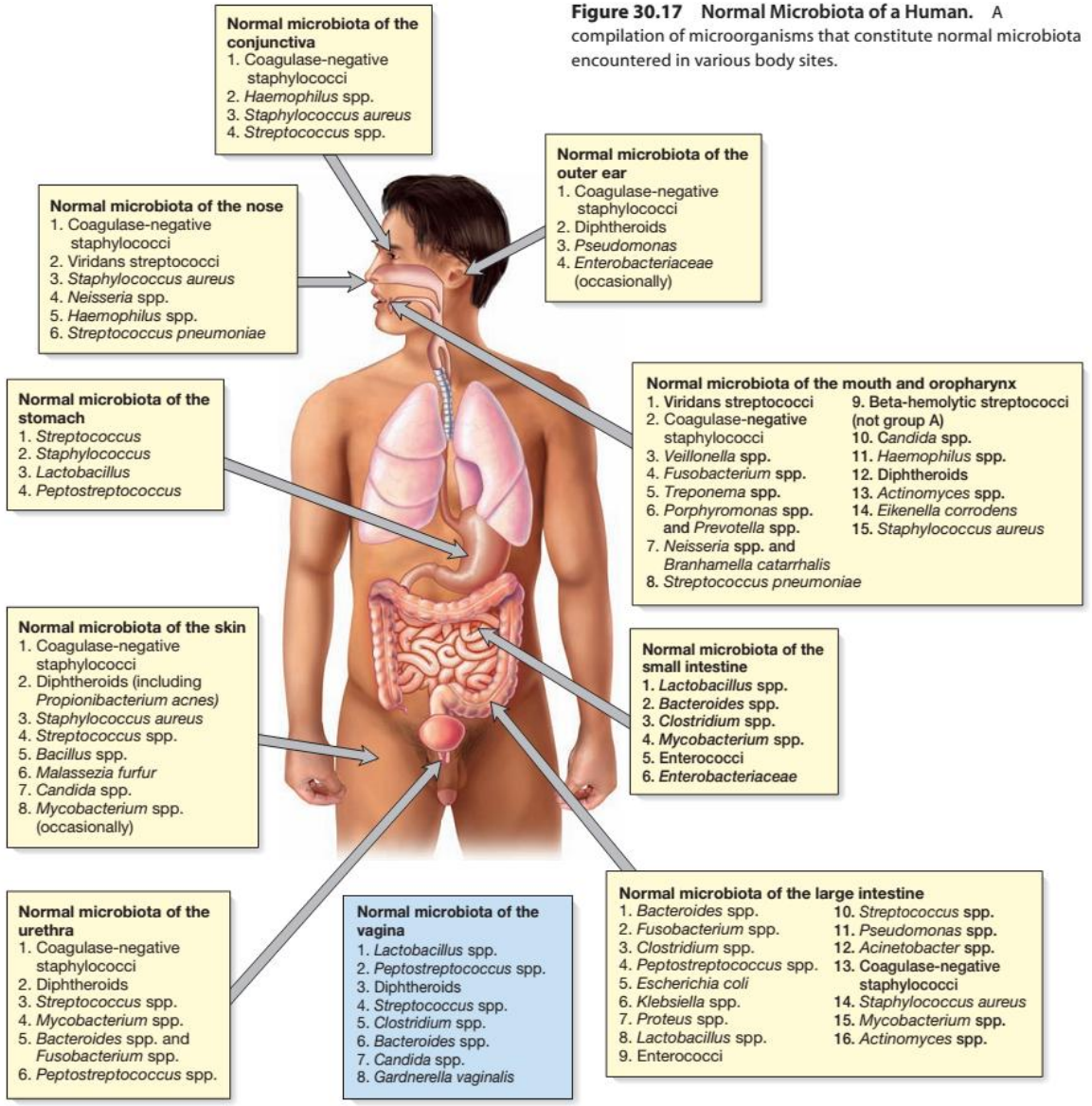


Figure 30.17 Normal Microbiota of a Human. A compilation of microorganisms that constitute normal microbiota encountered in various body sites.

拓展阅读：口腔微生物群

一篇发表在国际杂志Microbiome上的研究论文中，来自荷兰应用科学研究院等处的研究人员通过研究发现，在接吻的10秒时间内接吻双方在两者口腔中可以转移将近8000万个细菌，而伴侣间一天接吻至少9次，因此伴侣间或许会共享相同的口腔微生物群体

Kort *et al. Microbiome* 2014, **2**:41
http://www.microbiomejournal.com/content/2/1/41

Microbiome

RESEARCH Open Access

Shaping the oral microbiota through intimate kissing

Remco Kort[1,2,3*], Martien Caspers[1], Astrid van de Graaf[2], Wim van Egmond[2], Bart Keijser[1] and Guus Roeselers[1]

2）吸收多、转化快、食谱宽

微生物获取营养的方式多种多样，其食谱之广是动植物完全无法相比的！

消耗自身重量2000倍食物的时间

纤维素、木质素、几丁质、角蛋白、石油、甲醇、甲烷、天然气、塑料、酚类、氰化物、各种有机物均可被微生物作为“粮食”。

如何利用微生物的这一特点？

大肠杆菌：1小时

人　　类：500年（按400斤/年计算）

有资料表明，发酵乳糖的细菌在1小时内可分解其自重1000～10000倍的乳糖

3) 生长旺、代时短、繁殖快

大肠杆菌一个细胞重约10^{-12}克，平均20分钟繁殖一代

24小时后： 4722366500万亿个后代，重量达到：4722吨

48小时后：2.2×10^{43}个后代，重量达到2.2×10^{25}吨

相当于4000个地球的重量！

4) 基因少、易变异、育种好

个体小、结构简、且多与外界环境直接接触

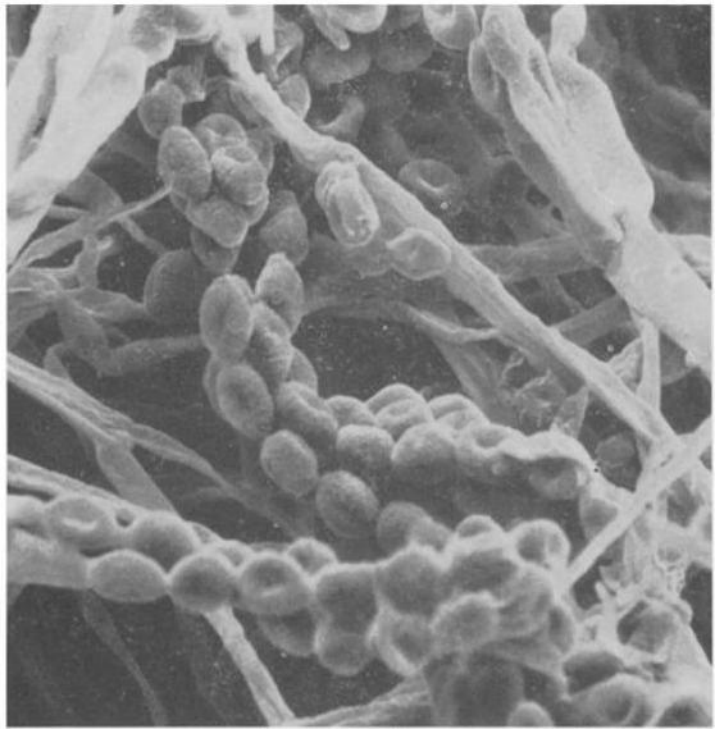
繁殖快、 数量多

突变率：10^{-6} - 10^{-10}

短时间内产生大量的变异后代

青霉素育种：

青霉素G钠盐0.6μ g为1个IU



Penicillium chrysogenum（产黄青霉）

旧名：***Penicillium notatum***（点青霉）

现在：≥90,000单位/ ml

青霉素的生产：

40单位/ ml（1943）

现在：数百万-千万单位/次

青霉素的用量：

最高：10万单位/天（40年代）

易变异：抗生素抗性细菌为例

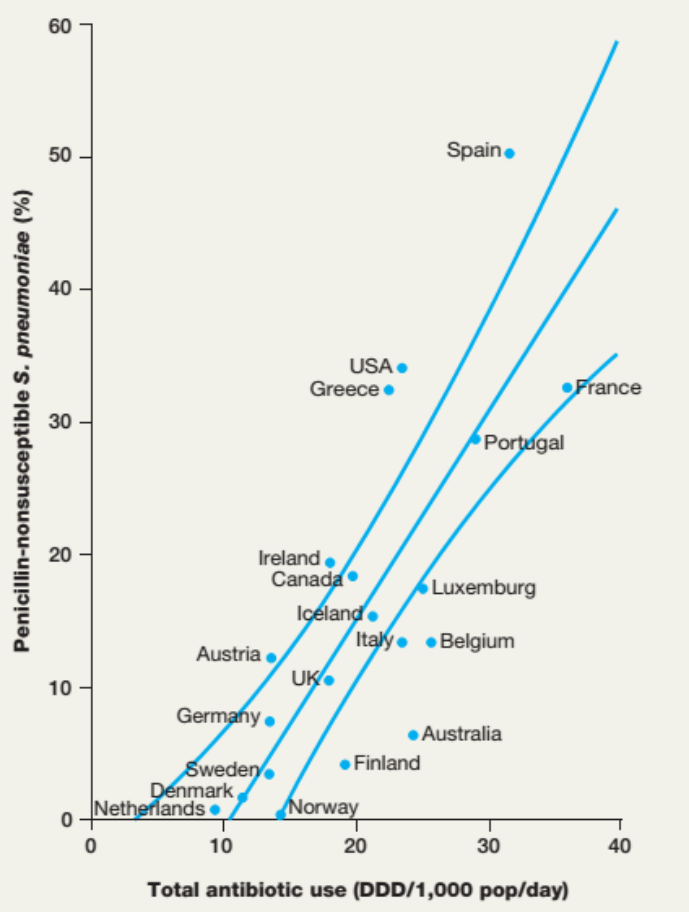
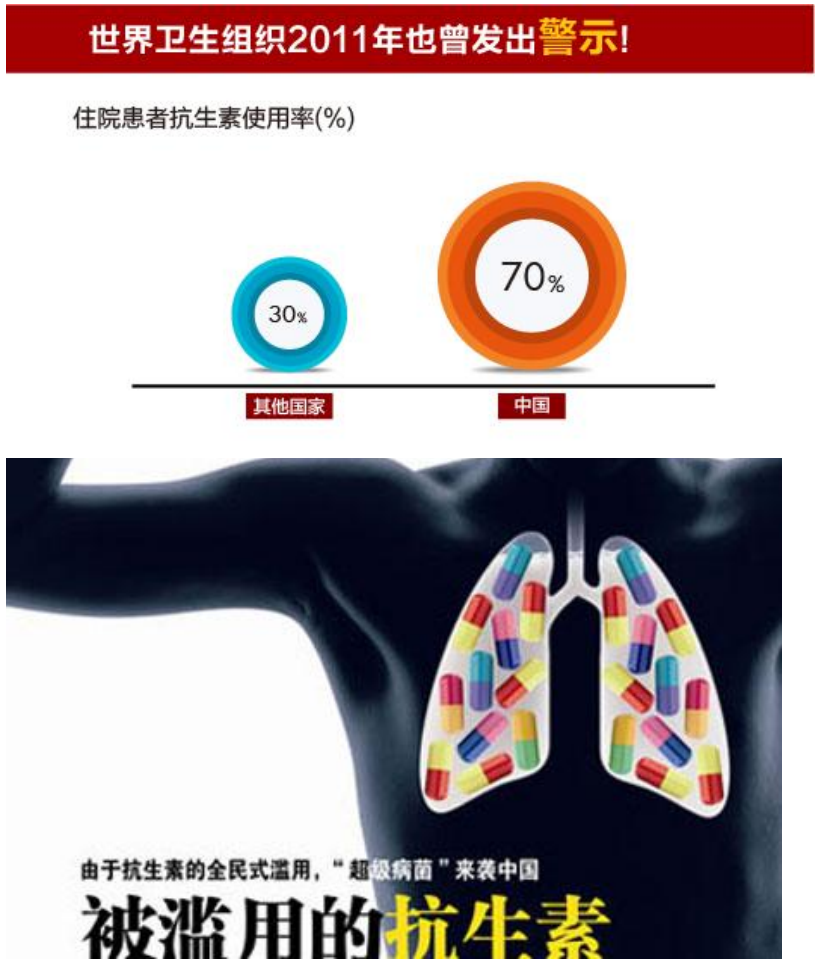


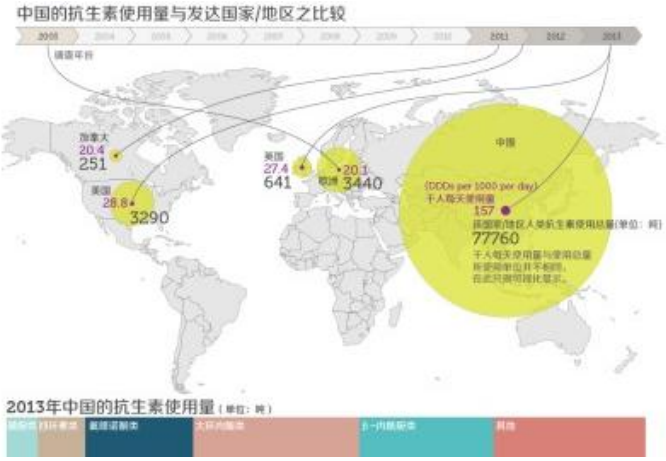
Table 1 Evolution of resistance to clinical antibiotics

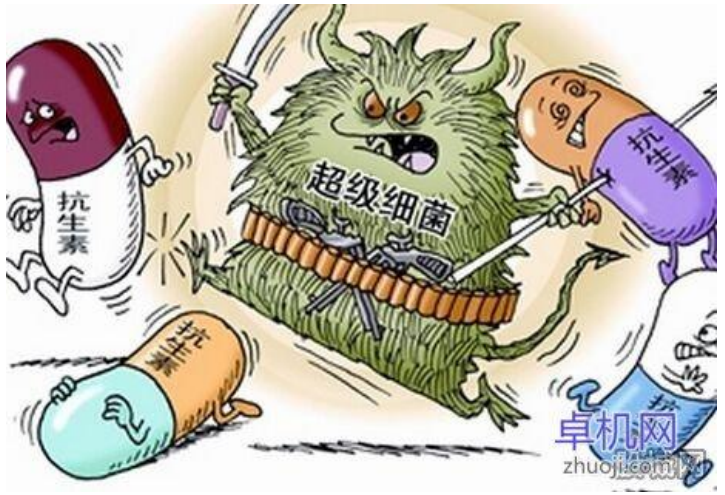
Antibiotic	*Year deployed*	*Clinical resistance observed*[a]	*Ref.*
Sulfonamides	1930s	1940s	38
Penicillin	1943	1946	38
Streptomycin	1943	1959	38
Chloramphenicol	1947	1959	38
Tetracycline	1948	1953	38
Erythromycin	1952	1988	38
Vancomycin	1956	1988	38
Methicillin	1960	1961	38
Ampicillin	1961	1973	38
Cephalosporins	1960s	Late 1960s	38
Nalidixic acid	1962	1962	39
Fluoroquinolones	1980s	1980s	40
Linezolid[b]	1999	1999	41
Daptomycin[b]	2003	2003	42
Retapamulin[b,c,d]	2007	2007	43
Fidaxomicin	2011	2011	44
Bedaquiline[b,e]	2013	?	45

易变异：抗生素抗性细菌为例

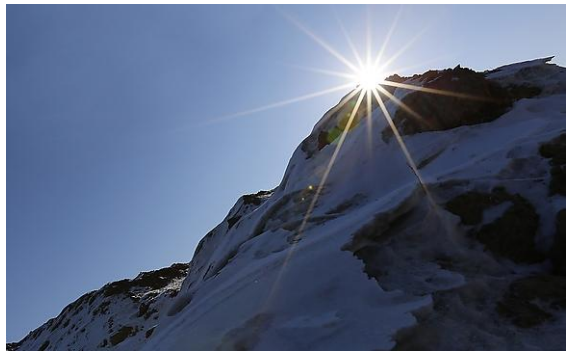
抗生素的滥用引起的灾难性的后果







5）适应强、分布广，种类多




Here are wide areas of the bacteriological landscape in which we have so far detected only some of the highest peaks, while the rest of the beautiful mountain range is still hidden in the clouds and the morning fogs of ignorance. The goal is still lying on the ground, but we have to bend down to grasp it.

—Preface to The Prokaryotes

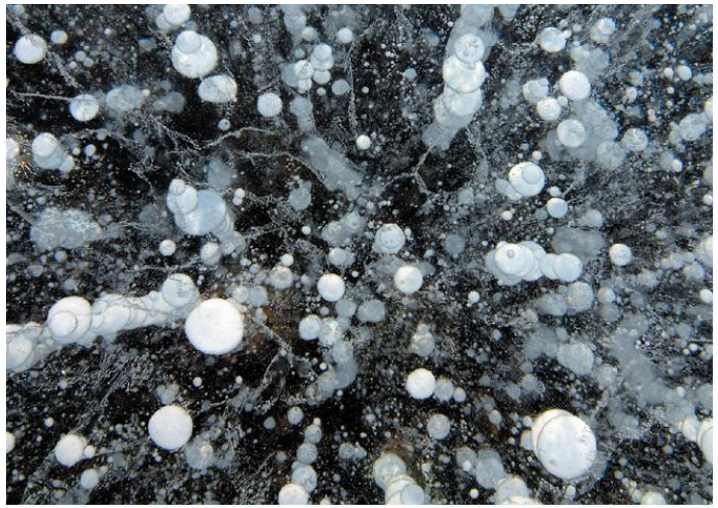
5）适应强、分布广，种类多

Figure 27.15 Massive Growth of the Extreme Acidophile *Ferroplasma* in a California Mine. Slime streamers of *Ferroplasma acidarmanus*, an archaeon, which have developed within pyritic sediments at and near pH 0. This unique procaryote has a plasma membrane and no cell wall.

Figure 27.14 Microorganisms Growing in Extreme Environments. Many microorganisms are especially suited to survive in extreme environments. (L)Salterns turned red by halophilic algae and halobacteria. (R) A hot spring colored green and blue by Cyanobacterial growth.

5）适应强、分布广，种类多

微生物则因其体积小、重量轻，因此可以到处传播以致达到“无孔不入”的地步，只要生活条件合适，它们就可大大繁殖起来。微生物只怕明火，地球上除了火山的中心区域外，从土壤圈、水圈、大气圈直至岩石圈，到处都有微生物家族的踪迹。可以认为，微生物将永远是生物圈上下限的开拓者和各种记录的保持者。



Even extreme environments such as Antarctic ice lakes host microbes.

目前人类能够在实验室或在工业上培养并利用的微生物不足1%，甚至远低于这个数，绝大多数微生物不可培养！

5）适应强、分布广，种类多

- 数十公里的高空（最高为离地85公里，须用火箭采样）；
- 几千米的地下；
- 强酸、强碱、高热的极端环境；
- 常年封冻的冰川；

科学家从南极3500米冰下取到生命物质

2000年7月24日　北京青年报

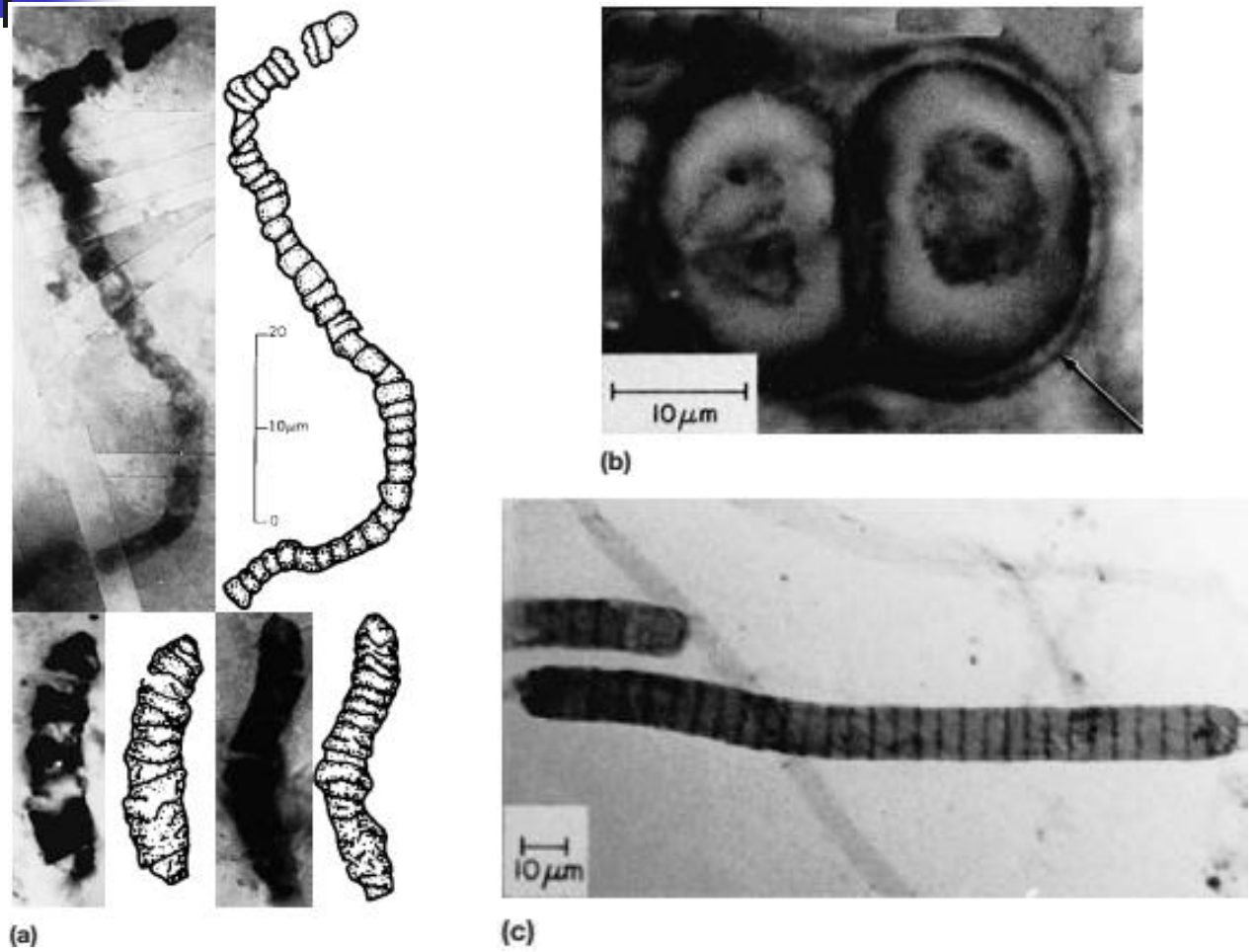
新华社莫斯科7月22日电（记者秦德岐）俄罗斯南极考察站的科学家最近从南极冰下3500多米处钻取到了一些生命物质，这为进一步揭开南极冰层深处的奥秘提供了重要帮助。

据俄《知识就是力量》科普月刊报道，俄科学家利用一种专用微生物钻探装置取得了南极超深度冰层样品。冰层样品在严格消毒和密封的容器中融化，研究人员在融化的冰水中发现了具有生命形式的细菌、硅藻、酵母、菌类。

令科学家惊奇的是，这些富有生命力的有机体竟能在3500多米深的冰层里生存。科学家相信，对于这些生命物质的研究将有助于人们了解南极冰层深处的生态环境，从而进一步发现南极冰层深处鲜为人知的一面。

世界是人类的，更是微生物的，他们才是真正的殖民者！

6） 起源早、利用早、发现迟



Fossilized Bacteria. Several microfossils resembling bacteria are shown, some with.
(a) Thin sections of Archean Apex chert from Western Australia; the fossilized remains of procaryotes are about 3.5 billion years old.
(b) *Gloeodiniopsis,* about 1.5 billion years old, from carbonaceous chert in the Satka Formation of the southern Ural Mountains.The arrow points to the enclosing sheath.
(c) *Palaeolyngbya,* about 950 million years old, from carbonaceous shale of the Lakhanda Formation of the Khabarovsk region in eastern Siberia.

有意思的是，研究最古老的生命学科却最为年轻！

6） 起源早、利用早、发现迟

- 公元前40-20世纪　酿酒、醋、原始啤酒、面包发酵、奶酪。我国殷商时代前就开始出现了曲蘖酿酒
- 公元前11世纪　酱油
- 公元前7世纪　中国人用霉治疡
- 公元6世纪　贾思勰的巨著“齐民要术”记载了制曲和酿酒的技术，还记载了栽种豆科植物可以肥沃土壤
- 公元11世纪　宋朝人开始人痘接种
- 公元17世纪　明朝人吴又可提出“戾气”说
- 公元1798年　Edward Jener 接种牛痘
- ・・・　・・・

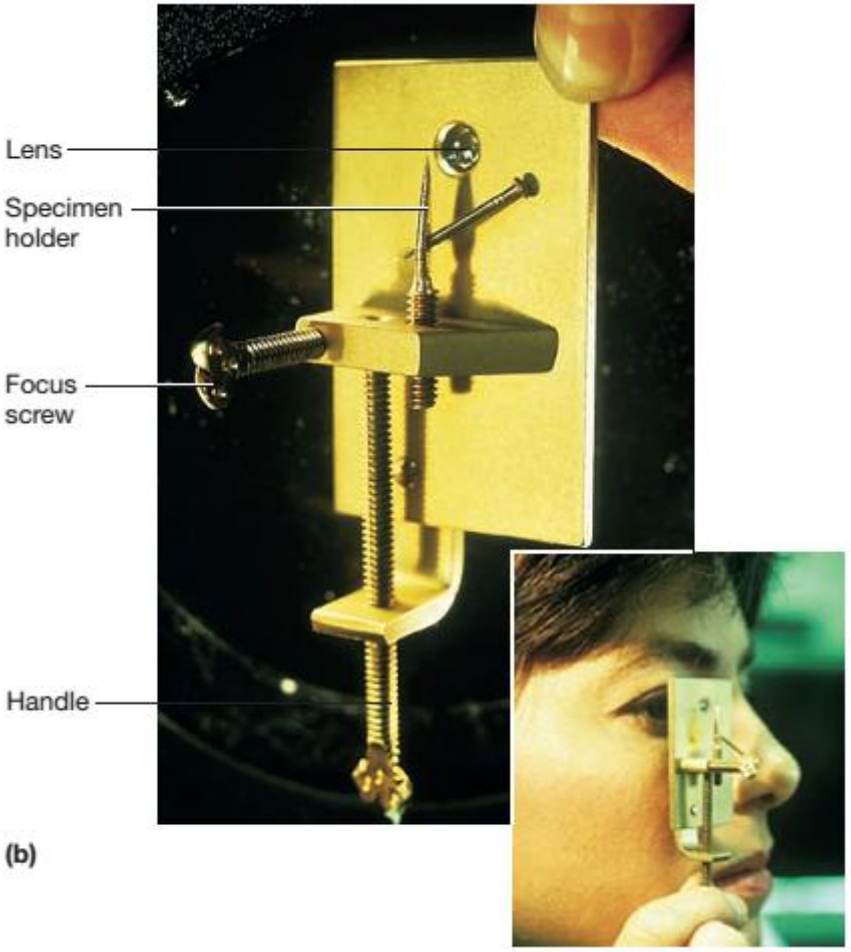
直到17世纪下半叶，Antony van Leeuwenhoek用显微装置观察到活的微生物，宣告了微生物的发现，为微生物的世界打开了一扇通往科学的大门！

6） 起源早、利用早、发现迟

17世纪微生物发现者荷兰科学家
Antony van Leeuwenhoek及使用的显微装置

(a)

(c)

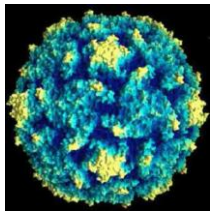


(b)

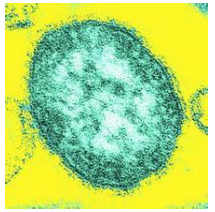
Figure 1.3 Antony van Leeuwenhoek. **(a)** An oil painting of Leeuwenhoek (1632–1723). **(b)** A brass replica of the Leeu microscope. Inset photo shows how it is held. **(c)** Leeuwenhoek's drawings of bacteria from the human mouth.

7）危害大、用处多、产业大

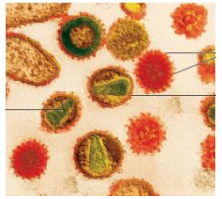
- 公元前12世纪埃及法老Siptah的壁画及木乃伊显示他患过小儿麻痹症；
- 公元6世纪中叶，两次严重的鼠疫重挫了君士坦丁堡，加速了东罗马帝国衰败；
- 天花在中国宋代以前是最致命的疾病，死亡率近1/2；
- 14世纪谈之色变的“黑死病”。公元1348年由热拉亚商人带到欧洲。三年内席卷欧洲，导致2500万约1/3的人口死亡，在接下来的80年里不断肆虐，夺走总计3/4的欧洲人口；
- 16世纪真正征服新大陆印第安帝国的，不是火器、马匹和高效组织，而是欧洲人带来的病菌：麻疹、肺结核、百日咳、流感和恐怖的天花！
- 17世纪明末的的瘟疫或许改变了中国历史前行的路径；
- 1918-20年爆发的世界性的流感导致全球5亿约1/3的人感染，夺去了5000万人的生命，破坏性无与伦比；
- 21世纪初亚洲爆发的SARS，造成巨大的经济损伤和社会恐慌；
- 2014年埃博拉疫情开始在西非流行・・・



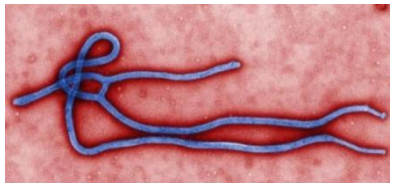
脊髓灰质炎病毒



麻疹病毒

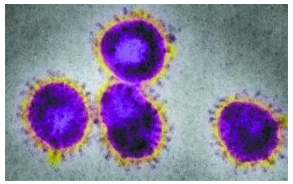


艾滋病毒

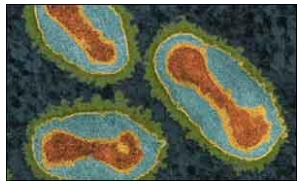


埃博拉病毒

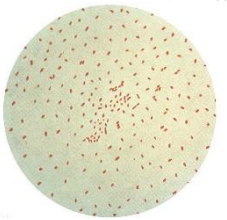
鼠疫杆菌



SARS 病毒

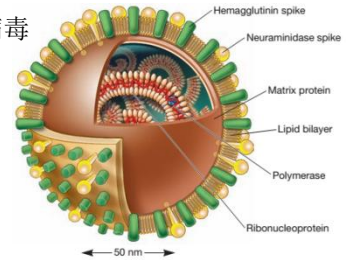


天花病毒

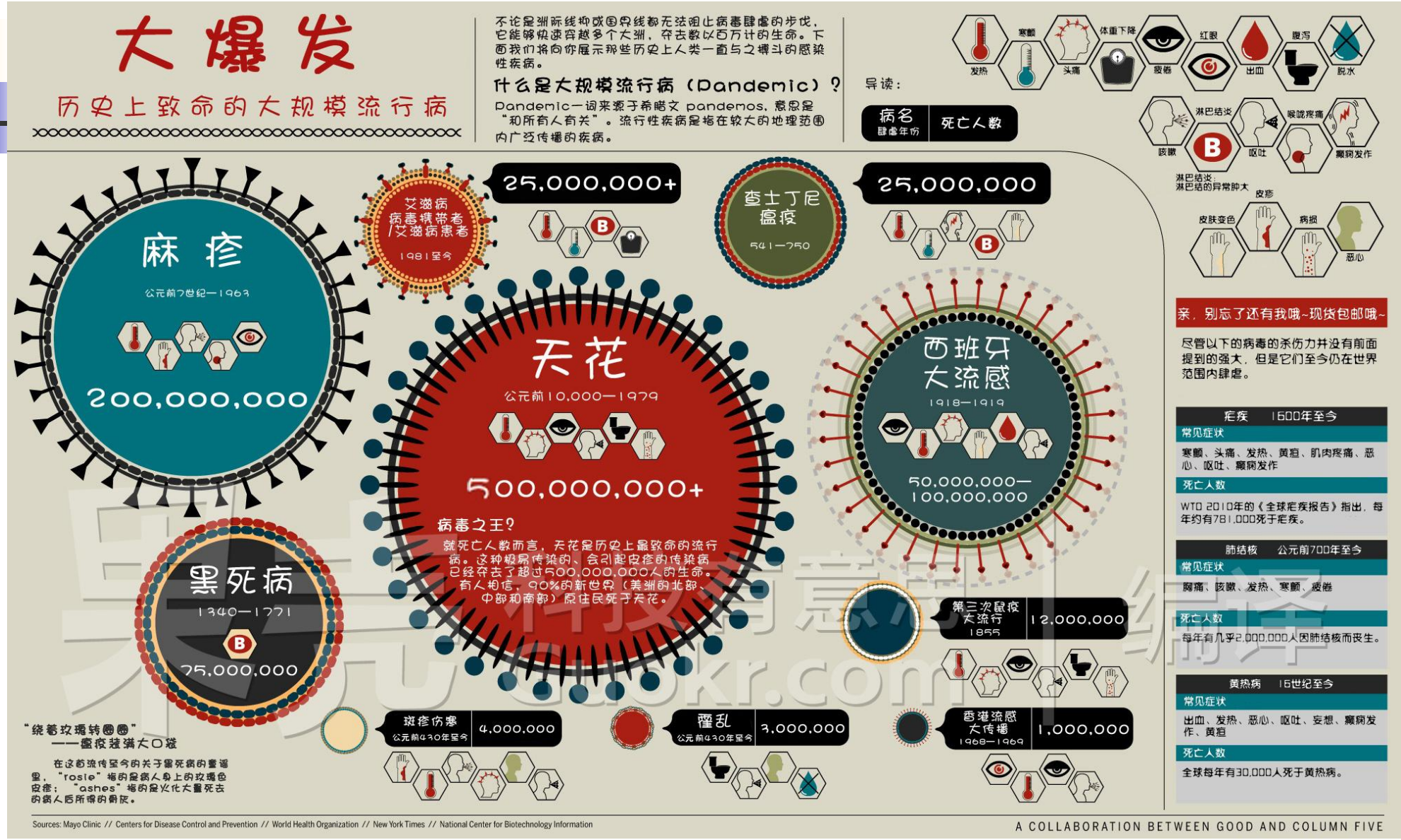


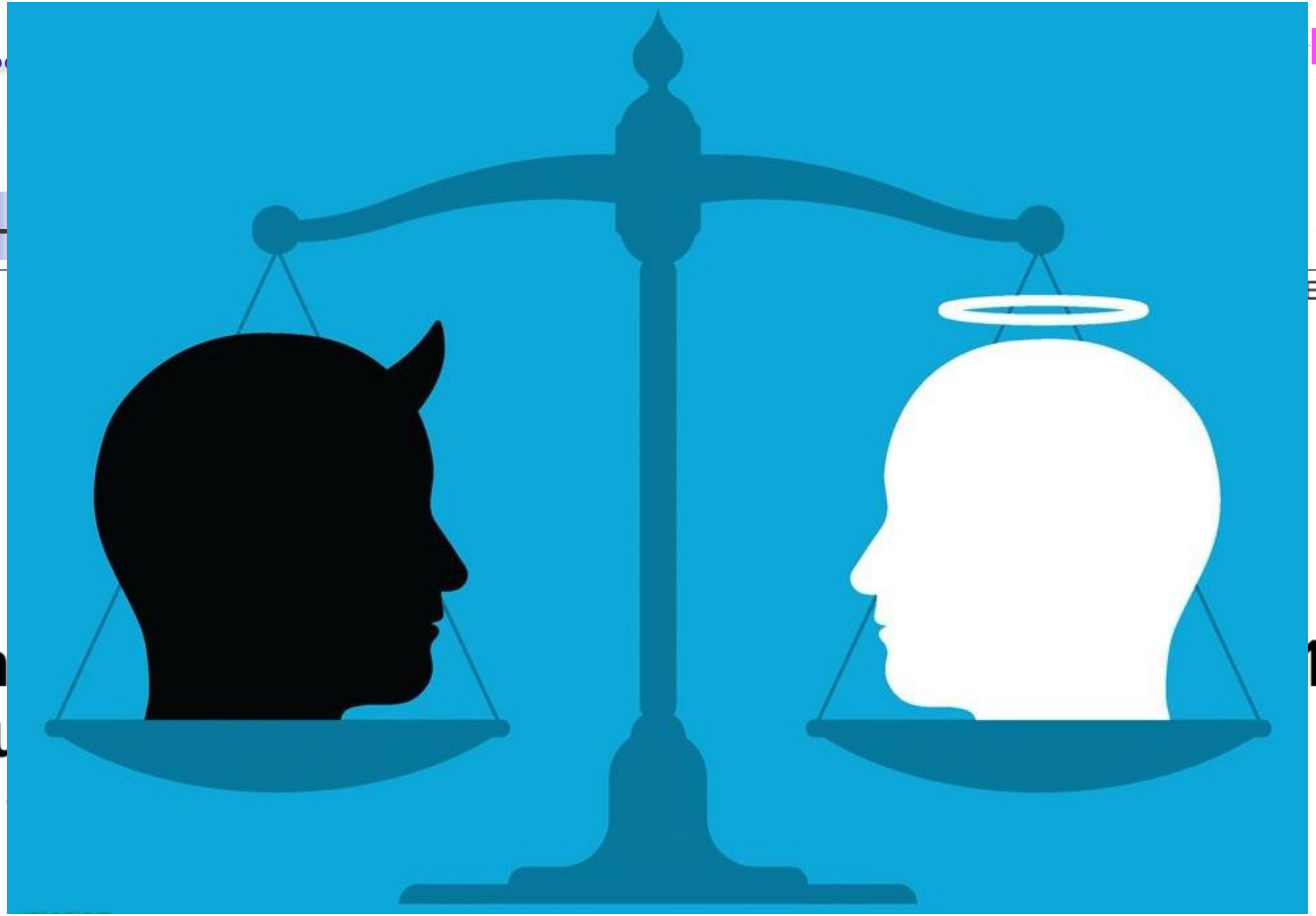
百日咳杆菌

流感病毒



杀手榜排名


大爆发
历史上致命的大规模流行病
不论是洲际线抑或国界线都无法阻止病毒肆虐的步伐，它能够快速穿越多个大洲，夺去数以百万计的生命。下面我们将向你展示那些历史上人类一直与之搏斗的感染性疾病。
什么是大规模流行病（Pandemic）？
Pandemic一词来源于希腊文 pandemos，意思是“和所有人有关”。流行性疾病是指在较大的地理范围内广泛传播的疾病。
导读：
发热 寒颤 头痛 体重下降 疲倦 红眼 出血 腹泻 脱水
淋巴结炎 咳嗽 吸吐 喉咙疼痛 癫痫发作
淋巴结炎：淋巴结的异常肿大
皮疹 皮肤变色 病损 恶心
病名 肆虐年份 死亡人数
麻疹 公元前7世纪—1963 200,000,000
艾滋病 病毒携带者/艾滋病患者 1981至今 25,000,000+
查士丁尼瘟疫 541—750 25,000,000
天花 公元前10,000—1979 500,000,000+
病毒之王？
就死亡人数而言，天花是历史上最致命的流行病。这种极易传染的、会引起皮疹的传染病已经夺去了超过500,000,000人的生命。有人相信，90%的新世界（美洲的北部、中部和南部）原住民死于天花。
西班牙大流感 1918—1919 50,000,000—100,000,000
黑死病 1340—1771 B 75,000,000
“绕着玫瑰转圈圈”——瘟疫莎满大口袋
在这首流传至今的关于黑死病的童谣里，“rosie”指的是病人身上的玫瑰色皮疹；“ashes”指的是火化大量死去的病人后所得的骨灰。
斑疹伤寒 公元前430年至今 4,000,000
霍乱 公元前430年至今 3,000,000
第三次鼠疫大流行 1855 12,000,000
香港流感大传播 1968—1969 1,000,000
亲，别忘了还有我哦~现货包邮哦~
尽管以下的病毒的杀伤力并没有前面提到的强大，但是它们至今仍在世界范围内肆虐。
疟疾 1600年至今
常见症状
寒颤、头痛、发热、黄疸、肌肉疼痛、恶心、呕吐、癫痫发作
死亡人数
WTO 2010年的《全球疟疾报告》指出，每年约有781,000死于疟疾。
肺结核 公元前700年至今
常见症状
胸痛、咳嗽、发热、寒颤、疲倦
死亡人数
每年有几乎2,000,000人因肺结核而丧生。
黄热病 16世纪至今
常见症状
出血、发热、恶心、呕吐、妄想、癫痫发作、黄疸
死亡人数
全球每年有30,000人死于黄热病。
Sources: Mayo Clinic // Centers for Disease Control and Prevention // World Health Organization // New York Times // National Center for Biotechnology Information
A COLLABORATION BETWEEN GOOD AND COLUMN FIVE



Gen
influ
1N1

Michael

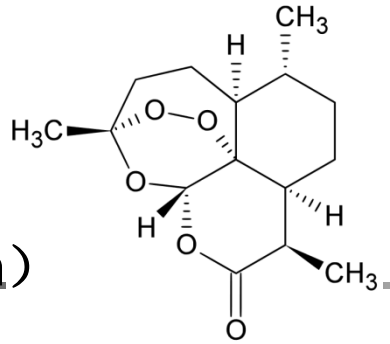
7）危害大、用处多、产业大

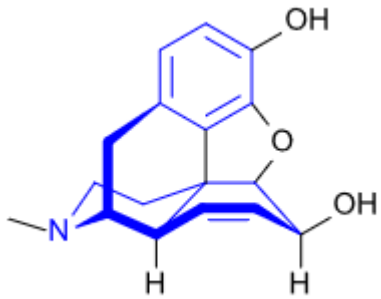
产业巨大

- 制药：抗生素、疫苗
- 酒类：白酒、红酒、啤酒
- 食品：面包、奶酪、醋、酱、泡菜
- 工业原料：酒精、氨基酸
- 其他：维生素、酶、生物试剂

2006年微生物相关的产业总值已达2000亿美元.目前的市场分析预测：2016年抗生素产值将达到440亿美元！

青蒿素
（artemisinin）





吗啡
（morphine）

NEWS IN FOCUS

GLOBAL HEALTH

Malaria drug made in yeast causes market ferment

Synthetic biology delivers combination therapies into an uncertain market.

BY MARK PEPLOW

"It's been a dream project — but it's been a long dream," says Jay Keasling, a biochemical engineer at the University of California, Berkeley. Seven years ago, he and his team genetically engineered yeast to produce artemisinic acid (D.-K. Ro *et al. Nature* **440,** 940–943; 2006), a precursor to the best malaria treatments available: artemisinin-based combination therapies (ACTs). Synthetic biology, Keasling hoped, could produce the drug more cheaply and reliably than natural sources, benefiting the roughly 200 million people infected with malaria each year.

Keasling's pipe dream has turned into a drug pipeline. In 2008, Paris-based pharmaceutical company Sanofi licensed the yeast that he helped to develop, and at an artemisinin conference in Nairobi last month, Keasling learned that the company had produced almost 39 tonnes of artemisinic acid — the first industrial-scale deployment of synthetic biology for drug production. The stock could be converted to at least 40 million treatments, says Keasling.

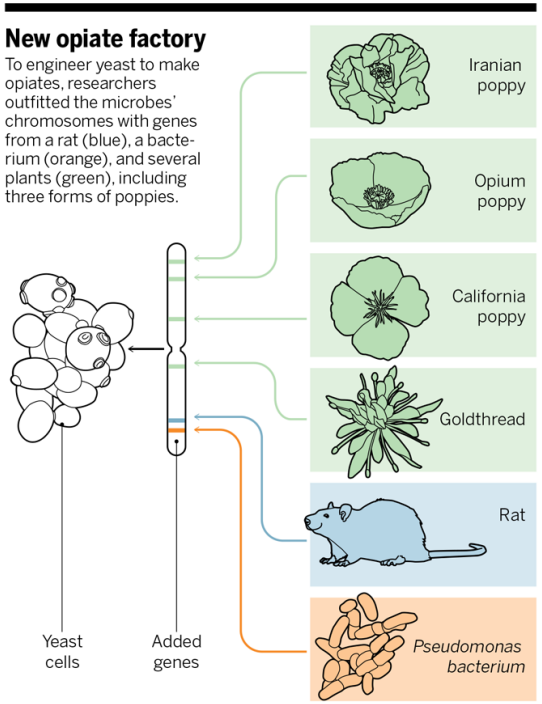
But the elegant science faces some messy realities. This year will see the end of one of the main funding routes for ACTs — the Affordable Medicines Facility — Malaria (AMFm) programme, run by the Global Fund to Fight AIDS, Tuberculosis and Malaria in Geneva, Switzerland. Its demise may not leave enough alternative funding to pay for the extra treatments made possible by the semi-synthetic process. Furthermore, if Sanofi's product is rushed into pharmacies at similar prices to existing products, it could disrupt an already volatile market (see *Nature* **466,** 672–673;

LAURA NEWMAN/PATH

People in malaria-prone countries could soon be treated with drugs made by engineered yeast.

Science, 4 september 2015

Complete biosynthesis of opioids in yeast



8）资源富、关系杂、研究广

微生物资源包括：
- 食品生产资源
- 天然产物资源
- 生态建设资源
- 矿物冶炼资源
- 生物降解资源
- 能源开发资源
- 医药保健资源
- 疫苗开发资源
- 基因资源

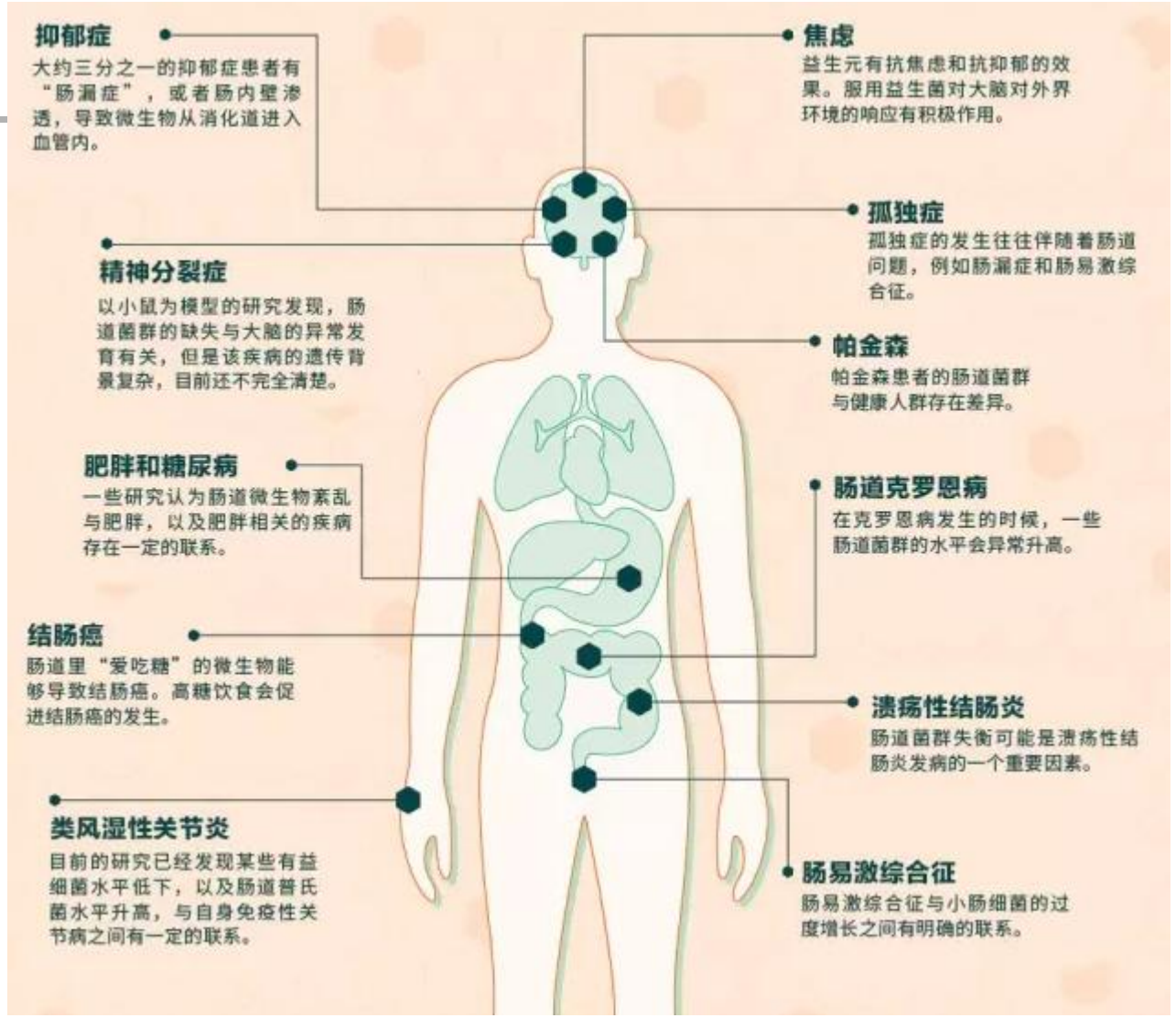
微生物在自然界的生存是群体混杂的，无论在自然界还是在生物体内外，都是多种微生物混杂生长，并在漫长的的演化历史中，形成了非常复杂的生物关系和种群多样性。

地球环境丰富的类型孕育出丰富多彩的微生物世界，各种生物内部和生物之间的关系都为研究生命科学提供了丰富的材料，为破解生命的奥秘提出了大量的课题，为人类理解生命和人与自然和谐相处提供了智慧和机遇。微生物学已经演变成了一大门类丰富、学科多样、交叉联系的研究领域，不断在深度和广度上拓展，推动生命科学向前发展。

当前微生物学研究的热点

肠道微生物是如何影响我们的身体和大脑的？

与其说我们是人类，还不如说我们的身体是微生物的“殖民地”。大量的研究表明，我们体内寄居着数万亿计的微生物，数量比构成人体的细胞数还多。生活在我们消化道里的细菌对我们的健康有重要作用。肠道菌群失衡会导致身体和精神上的一些列疾病。

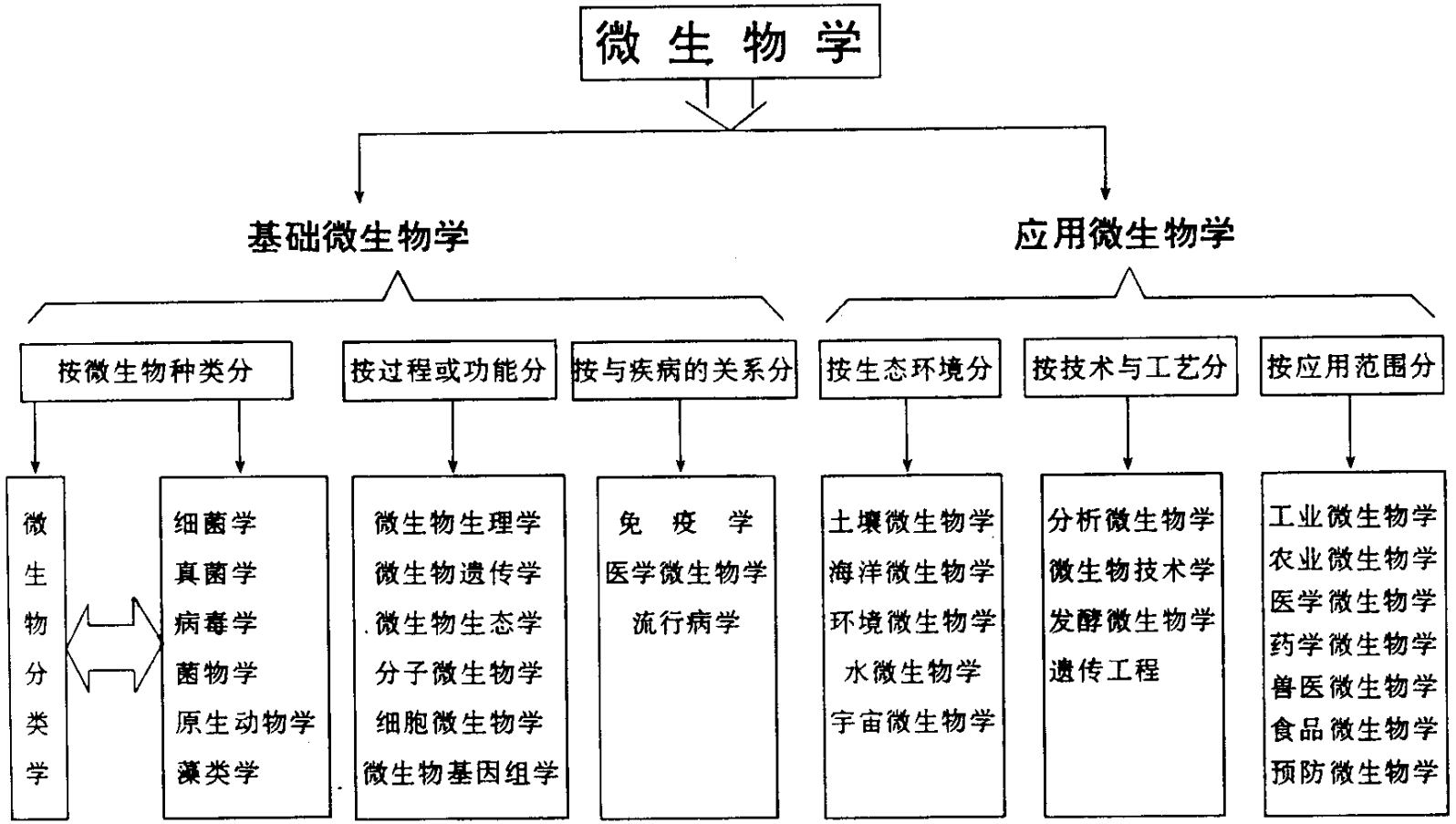


2、微生物学的研究内容及分科

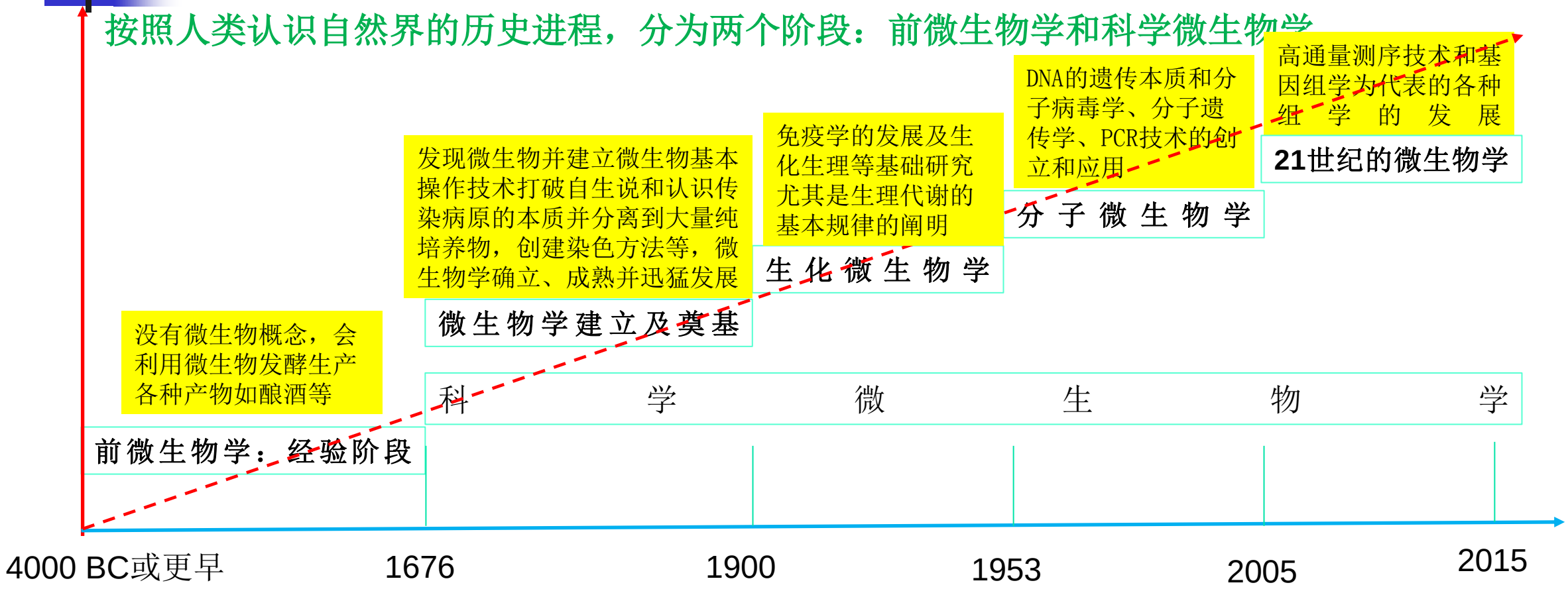
◆微生物学（microbiology）:指以微生物为研究对象并包括一整套微生物研究方法的综合学科。

- 研究内容：研究微生物的形态结构、生理生化、生长繁殖、遗传变异以及微生物的进化、分类、生态等生命活动规律及其应用等。
- 基本理论：普通微生物学、分类学、生理学、生态学、遗传学。
- 按研究对象划分：病毒学、细菌学、真菌学。
- 按生活环境划分：土壤微生物学、海洋微生物学。
- 按应用划分：工业微生物学、农业微生物学、医学微生物学。

2.微生物学学科分化


微 生 物 学
基础微生物学
应用微生物学
按微生物种类分
按过程或功能分
按与疾病的关系分
按生态环境分
按技术与工艺分
按应用范围分
微生物分类学
细菌学
真菌学
病毒学
菌物学
原生动物学
藻类学
微生物生理学
微生物遗传学
微生物生态学
分子微生物学
细胞微生物学
微生物基因组学
免 疫 学
医学微生物学
流行病学
土壤微生物学
海洋微生物学
环境微生物学
水微生物学
宇宙微生物学
分析微生物学
微生物技术学
发酵微生物学
遗传工程
工业微生物学
农业微生物学
医学微生物学
药学微生物学
兽医微生物学
食品微生物学
预防微生物学

3.微生物学的发展之路


按照人类认识自然界的历史进程，分为两个阶段：前微生物学和科学微生物学
没有微生物概念，会利用微生物发酵生产各种产物如酿酒等
前微生物学：经验阶段
发现微生物并建立微生物基本操作技术打破自生说和认识传染病原的本质并分离到大量纯培养物，创建染色方法等，微生物学确立、成熟并迅猛发展
微生物学建立及奠基
免疫学的发展及生化生理等基础研究尤其是生理代谢的基本规律的阐明
生化微生物学
DNA的遗传本质和分子病毒学、分子遗传学、PCR技术的创立和应用
分子微生物学
高通量测序技术和基因组学为代表的各种组学的发展
21世纪的微生物学
科学微生物学
4000 BC或更早
1676
1900
1953
2005
2015

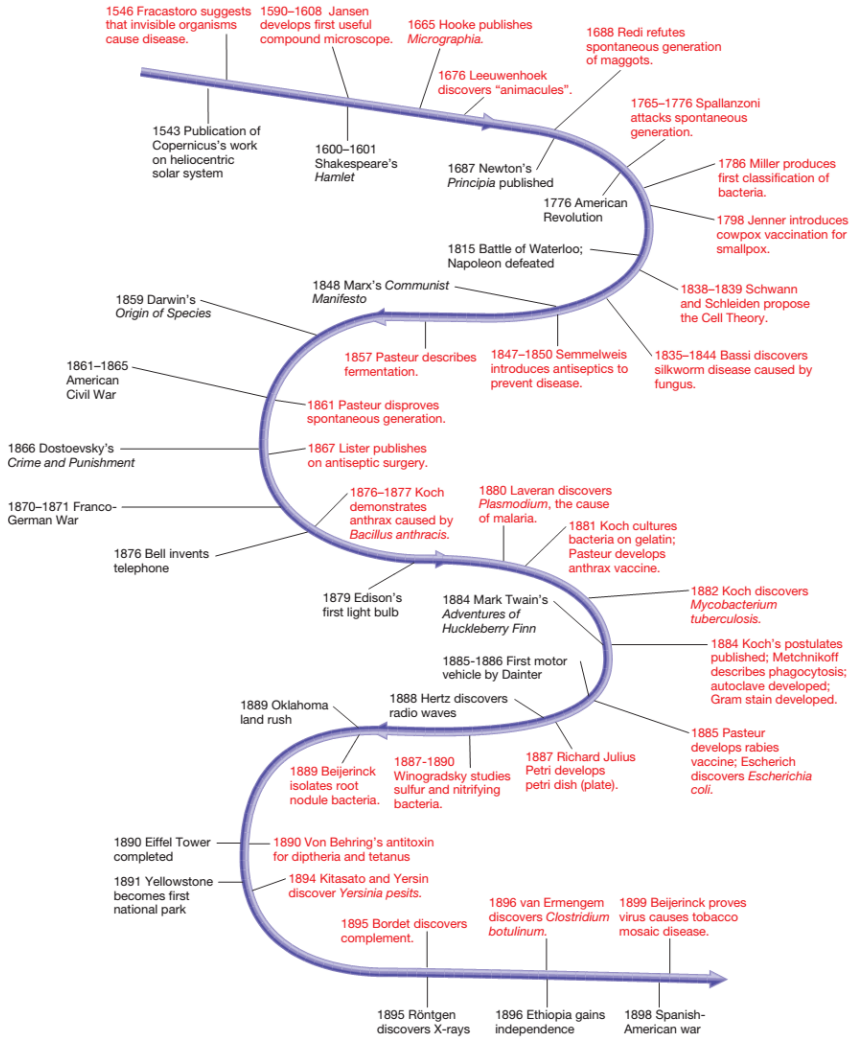


Figure 1.2(a) Some Important Events in the Development of Microbiology (1546–1899). Milestones in microbiology are marked in red; other historical events are in black.

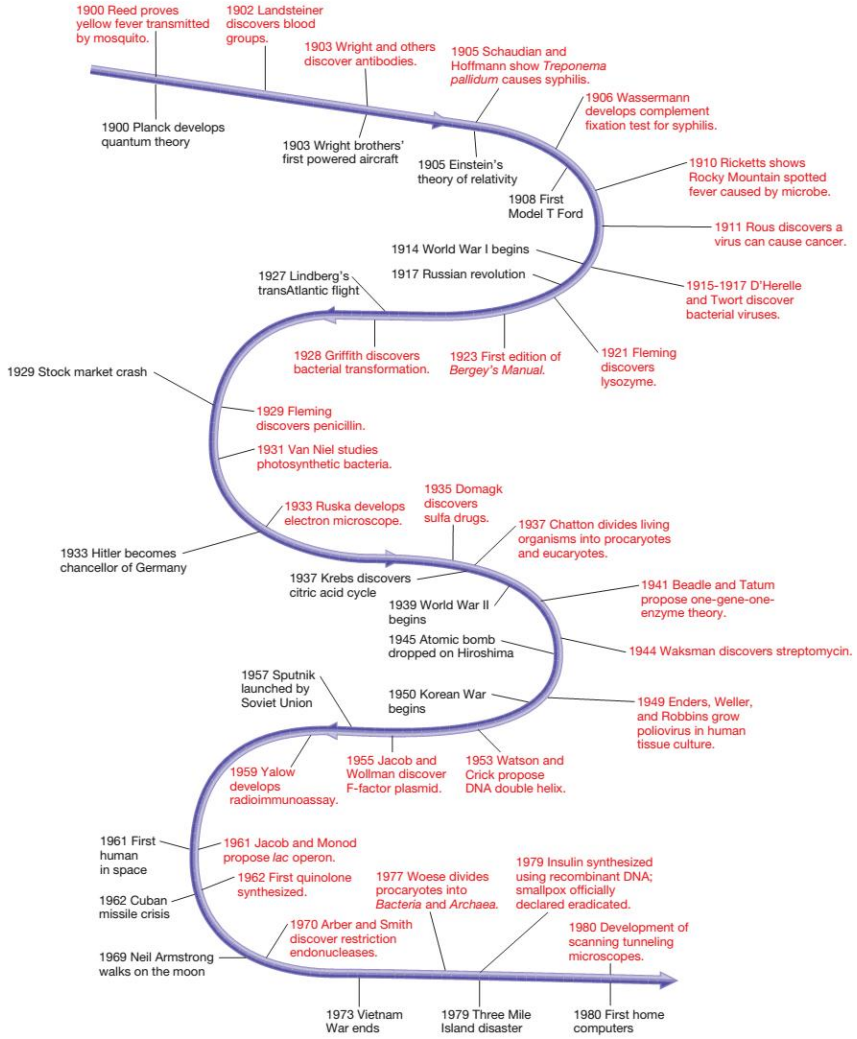
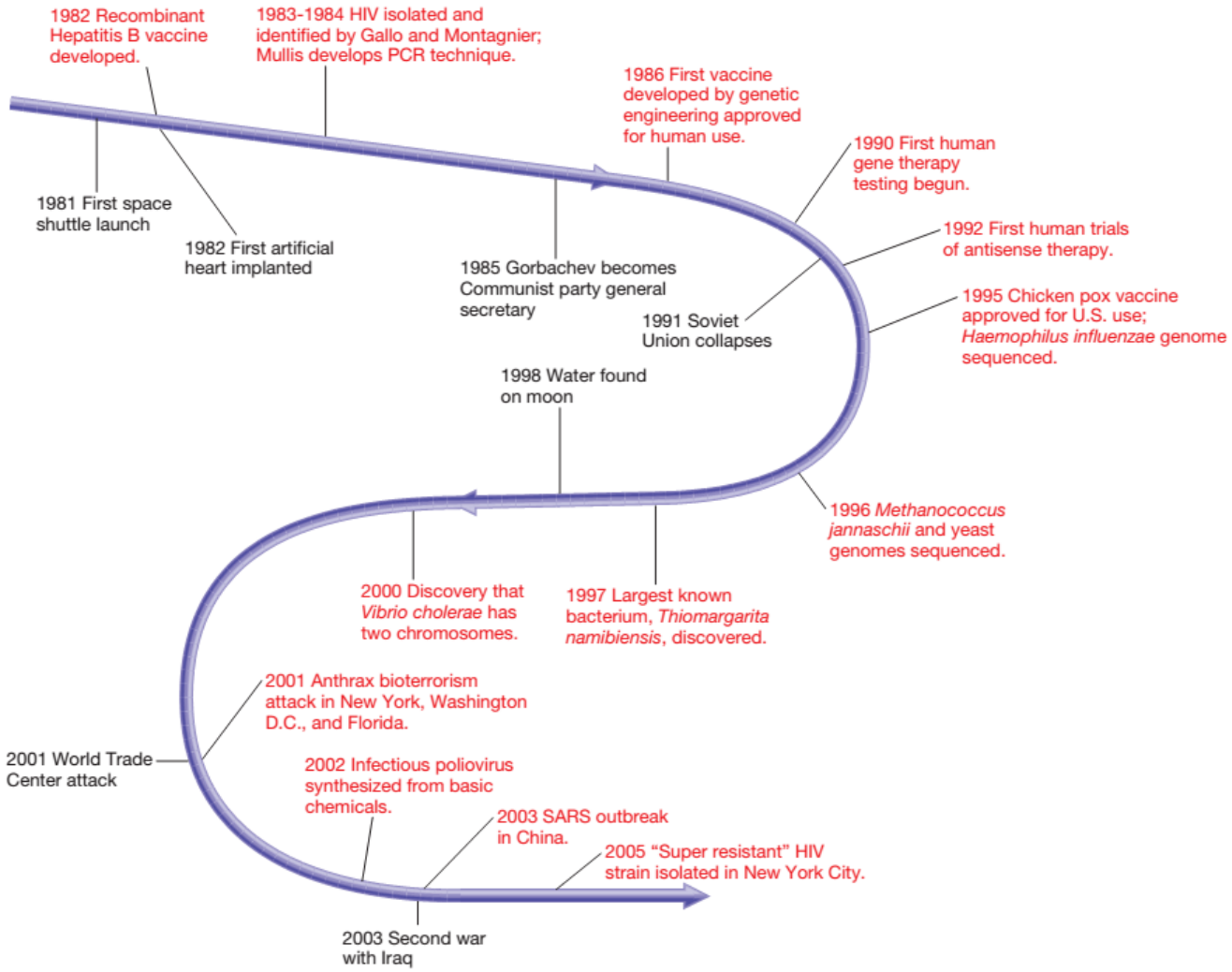


Figure 1.2(b) Some Important Events in the Development of Microbiology (1900–1980). Milestones in microbiology are marked in red; other historical events are in black.

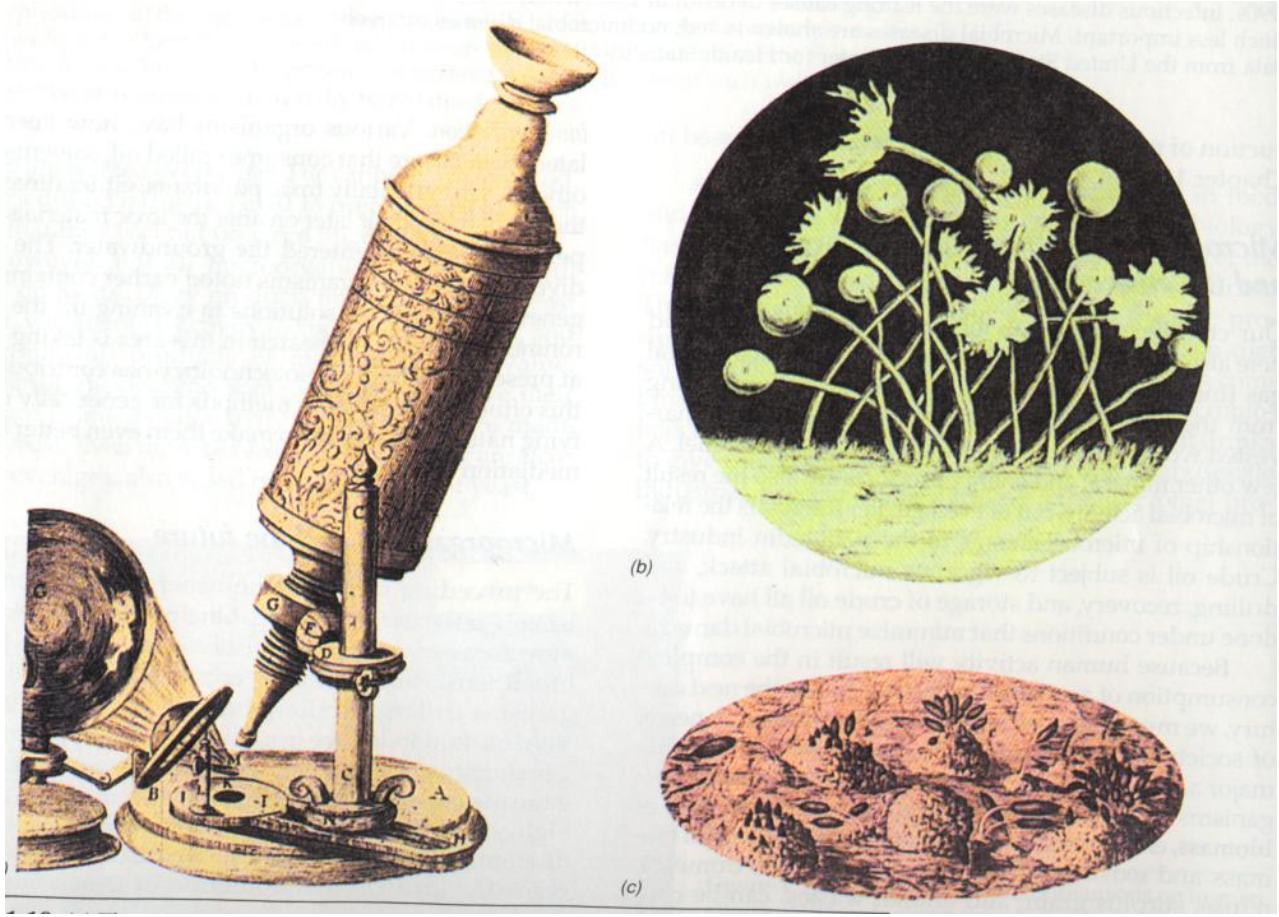
微生物学发展史是一部诞生于文艺复兴之后，伴随着启蒙运动和第一次工业革命逐步建立并发展起来的科学，伴随着人类与疾病的斗争逐渐深入研究的历史，是现代遗传学、分子生物学、基因工程舞台上精彩的主角，在当代的产业领域占有极为重要的地位和份额，在未来的人类社会将发挥越来越重要的作用。



3.1.微生物的发现

- 古罗马哲学家Lucretius (about 98－55 B.C）和医学家 Girolamo Fracastoro (1478－1553) 建议疾病是由看不见的生物所致。但仅仅是经验判断和推测。

- 1664年，英国人胡克（Robert Hooke）曾用原始的显微镜对生长在皮革表面及蔷薇枯叶上的霉菌进行观察。并出版了一幅微生物的图片。

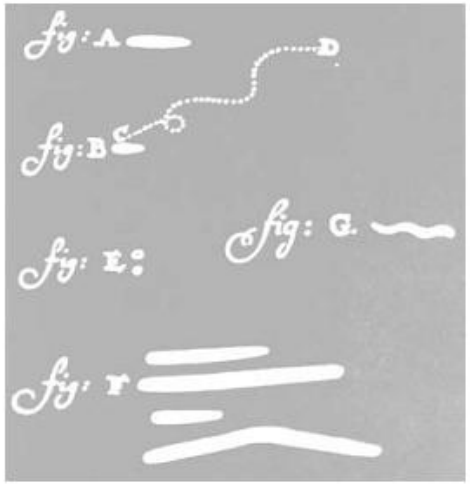


3.1. 微生物的发现

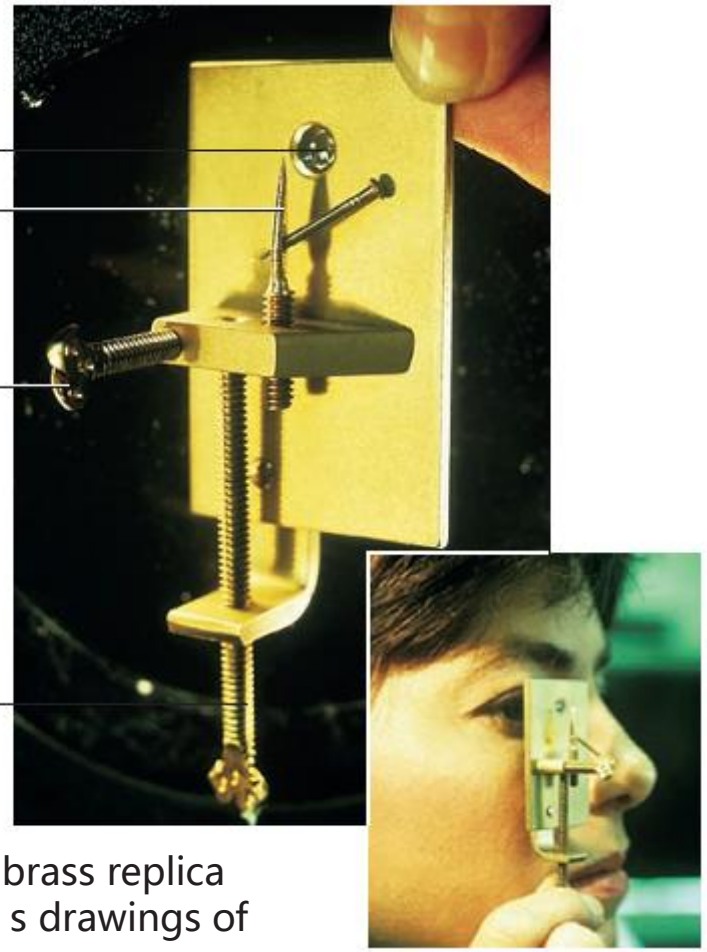
（50-300倍）

◆微生物学的发现者属于荷兰人列文虎克（Antony van leeuwenhoek），1673年，是他首次观察到了口腔中的细菌并发表了他的文章，准确的描绘了微生物的形态和尺度。他没有上过大学，是一个只会荷兰语的小商人，在1680年被选为英国皇家学会的会员。

(a)



(c)



(b)

Antony van Leeuwenhoek. (a) An oil painting of Leeuwenhoek (1632–1723). (b) A brass replica of the Leeuwenhoek microscope. Inset photo shows how it is held. (c) Leeuwenhoek’ s drawings of bacteria from
the human mouth.

3.2.微生物学的奠基

1）.微生物学之父： Louis Pasteur

自然发生说（spontaneous generation）：that living organisms could develop from nonliving matter. Even Aristotle (384–322 B.C.) thought some of the simpler invertebrates could arise by spontaneous generation.

渊深而鱼生之，山深而兽往之，人富而仁义附焉。
—司马迁(BC145-90)《货殖列传序》

天下万物生于有，有生于无。
—老子

昔年河畔，曾叨君子之风；今日囊中，复照圣人之典
–《腐草为萤赋》

自然发生说激起法国人Louis Pasteur(1822–1895) 的兴趣，他设计实验并一劳永逸地解决了问题！

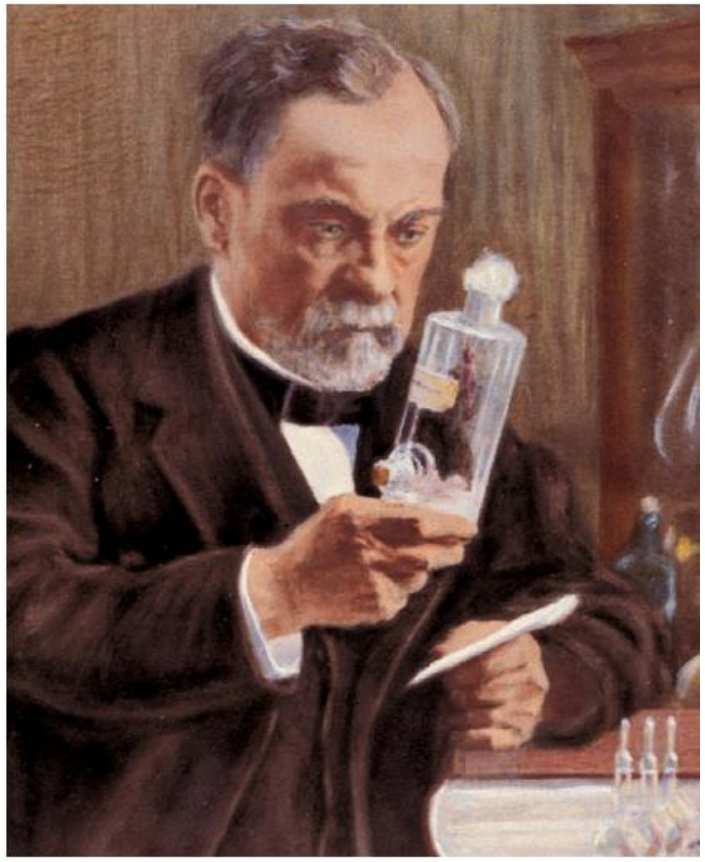
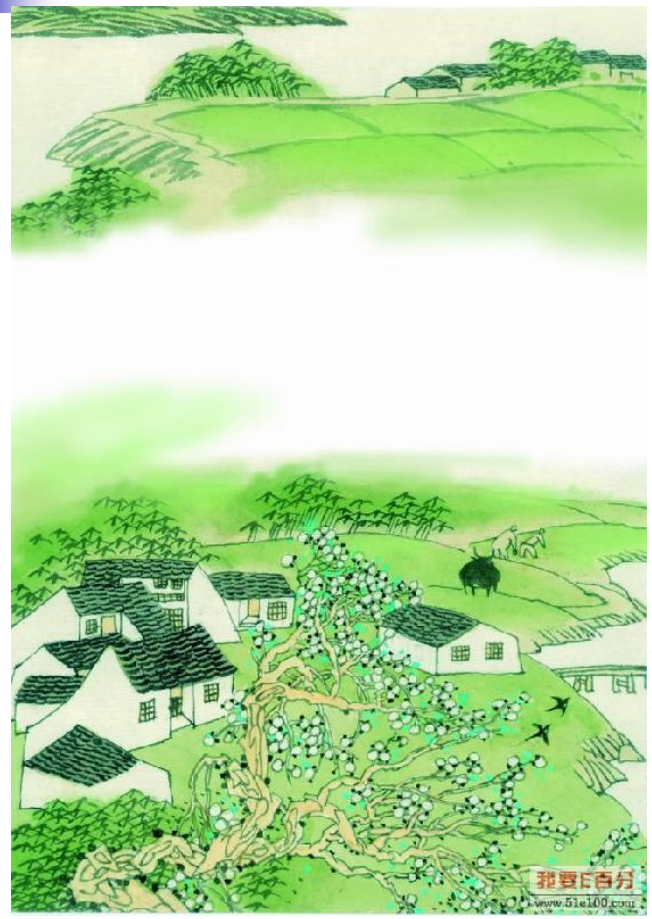


Figure 1.4 Louis Pasteur. Pasteur (1822–1895) working in his laboratory.

自然发生说（spontaneous generation）之文艺版

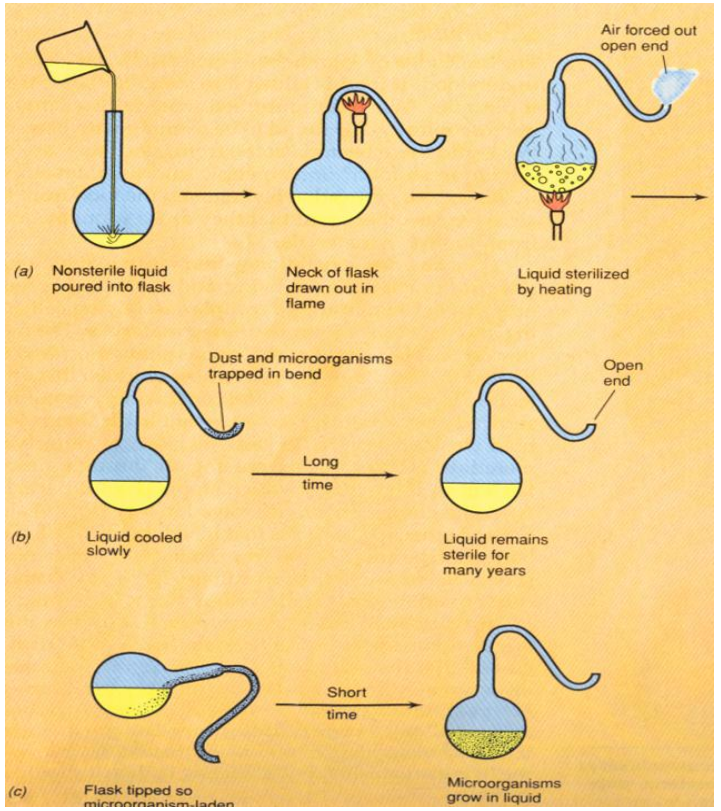


青青河畔草，绵绵思远道。一束青草，生在河畔，熏沐了君子的德风。到了秋天，霜露凋残，在荒寒中变成萎黄，蛰伏过大雪纷飞的冬天，化作一粒萤火，飞在夏夜的原野上。浪漫的文青把它捉来，盛在囊中，照亮了诗经里的关关雎鸠…

3.2.微生物学的奠基

1.法国人Louis Pasteur 1859年否定自然发生说

著名的曲颈瓶实验



3.2.微生物学的奠基

- 英国医生John Tyndall（1820－1893）给予了自然发生学说最后一击。1877年他证明肉汤暴露于空气中是因为灰尘携带孢子，如果空气中没有孢子，即使暴露空气肉汤不会变坏。他和德国人Ferdinand Cohn(1828－1898)各自独立发现存在能抗热的芽孢存在。

19世纪50年代以后，自然发生说彻底破产，使微生物科学真正摆脱了神秘主义思想的桎梏，奠定了微生物学唯物主义的坚实基础，并得以迅猛发展，终于迎来了微生物学发展的黄金时代！

如果你重复Louis Pasteur的曲颈瓶实验，如果实验失败，原因何在?

3.2.微生物学的奠基

◆ 巴斯德的其他贡献

(1) 发现并证实发酵是由微生物引起的；

化学家出生的巴斯德涉足微生物学是为了治疗“酒病”和“蚕病”

(2) 免疫学——预防接种：

首次制成狂犬疫苗，禽霍乱疫苗

(3)其他方面：

巴斯德消毒法：60～65℃作短时间加热处理，杀死病原微生物

Louis Pasteur

中学时，他在学校表现普通，但很爱问问题，凡事追根究底，甚至因此成为某些老师的眼中钉。就这样不断地发问、学习，对化学、物理和艺术都有深厚兴趣的巴斯德渐渐变成优秀的学生。

1870年普法战争开打，法国战败投降。面对普鲁士军队的暴行，巴斯德愤慨地将德国波昂大学颁发给他的医学博士学位证书退还，以示抗议。这时意大利愿意给他一栋住宅，一个实验室和丰富的薪酬，请他到意大利研究，但却被巴斯德拒绝，他觉得国家在受难中，不能因为个人生活的舒适便离开苦难的故乡！

3.2.微生物学的奠基

2.柯赫(Robert Heinrich Herman Koch)

（1）开发了研究微生物的方法、技术

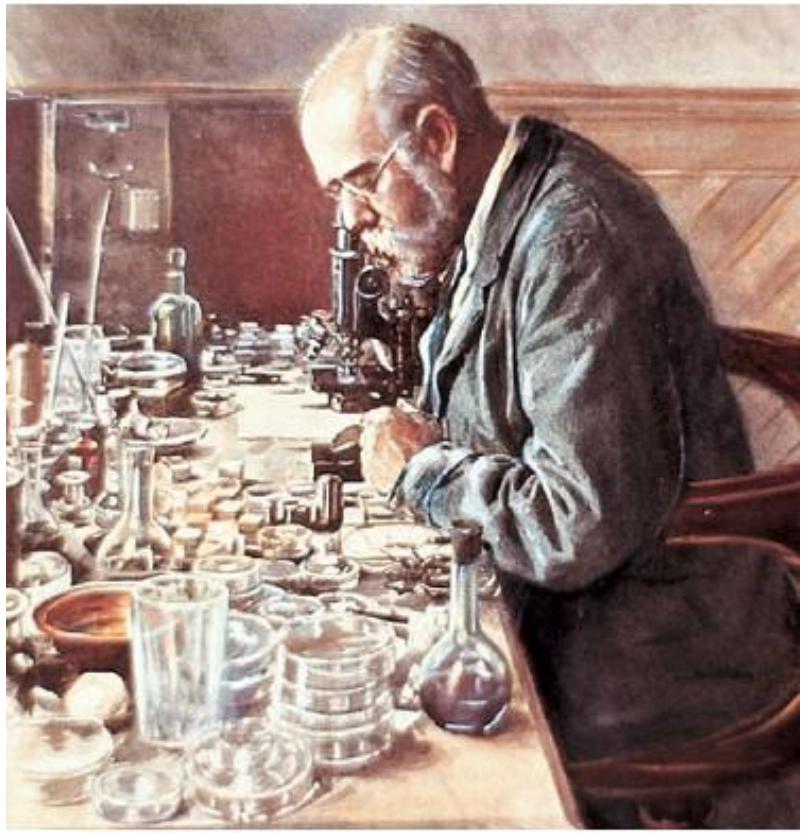
a）细菌纯培养方法的建立

土豆切面→营养明胶→营养琼脂（平皿）

b）设计了各种培养基，实现了在实验室内对各种微生物的培养

c）流动蒸汽灭菌

d）染色观察和显微摄影



R. Koch. **(1843-1910),德国微生物学家**

3.2.微生物学的奠基

（2）对病原细菌的研究作出了突出的贡献：

- 具体证实了炭疽杆菌是炭疽病的病原菌；
- 发现了肺结核病的病原菌；（1905年获诺贝尔奖）
- 证明某种微生物是否为某种疾病病原体的基本原则

——著名的柯赫原则（Koch` Postulates）

3.2.微生物学的奠基

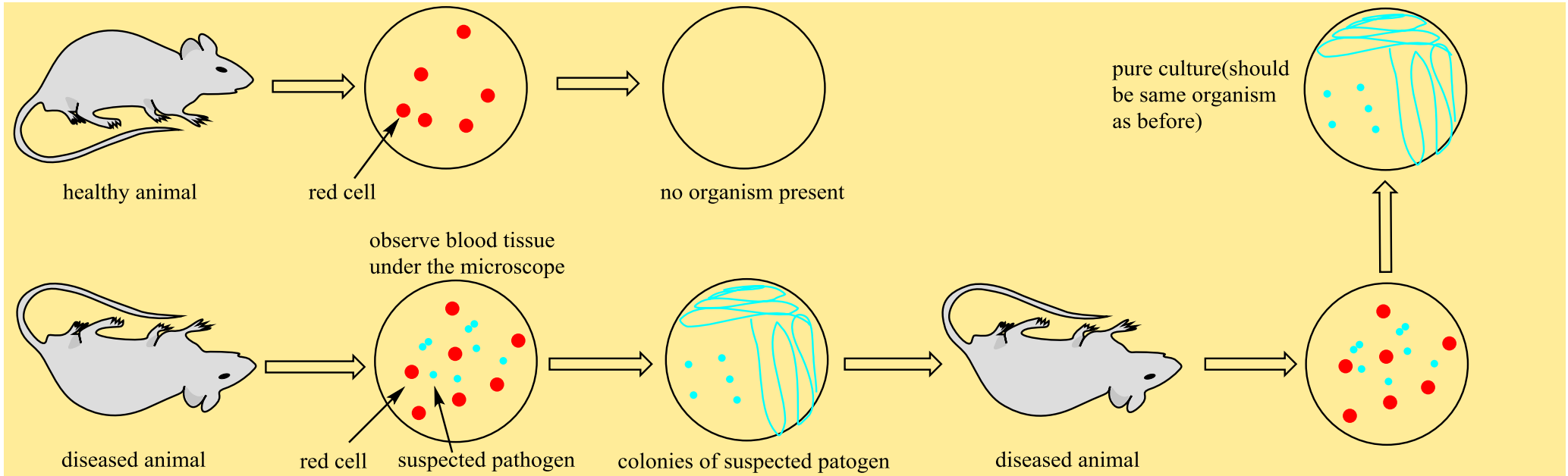
柯赫法则（Koch`Postulates）

1、 在每一相同病例中都出现这种微生物；
2 、要从寄主分离出这样的微生物并在培养基中培养出来；
3、用这种微生物的纯培养接种健康而敏感的寄主，同样的疾病会 重复发生；
4 、从试验发病的寄主中能再度分离培养出这种微生物来。

Table 1.1 Koch's Application of His Postulates to Demonstrate that *Mycobacterium tuberculosis* is the Causative Agent of Tuberculosis.

Postulate	Experimentation
1. The microorganism must be present in every case of the disease but absent from healthy organisms.	Koch developed a staining technique to examine human tissue. *M. tuberculosis* cells could be identified in diseased tissue.
2. The suspected microorganisms must be isolated and grown in a pure culture.	Koch grew *M. tuberculosis* in pure culture on coagulated blood serum.
3. The same disease must result when the isolated microorganism is inoculated into a healthy host.	Koch injected cells from the pure culture of *M.tuberculosis* into guinea pigs. The guinea pigs subsequently died of tuberculosis.
4. The same microorganism must be isolated again from the diseased host.	Koch isolated *M. tuberculosis* from the dead guinea pigs and was able to again culture the microbe in pure culture on coagulated blood serum.

科赫法则（Koch postulates）



1.the suspected pathogenic organism should be present in all cases of the disease and absent in healthy animals

2.the suspected organism should be grown in pure culture

3.cells of suspected organism in the pure culture should cause disease in a healthy animal

4.the suspected organism should reisolated and shown to be same as the original

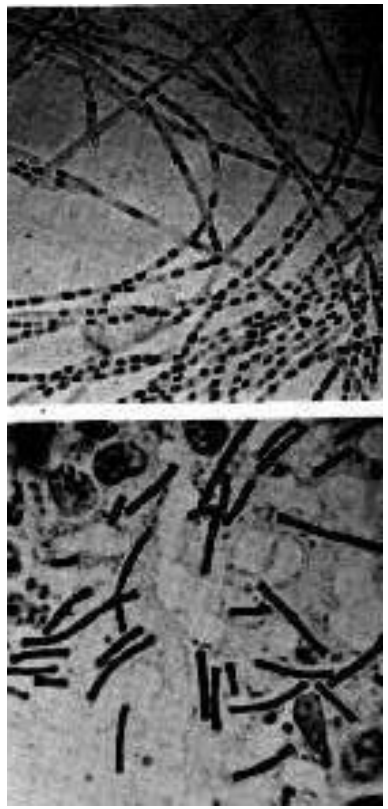
Disease

1.2 Koch's Molecular Postulates

Although the criteria that Koch developed for proving a causal relationship between a microorganism and a specific disease have been of great importance in medical microbiology, it is not always possible to apply them in studying human diseases. For example, some pathogens cannot be grown in pure culture outside the host; because other pathogens grow only in humans, their study would require experimentation on people. The identification, isolation, and cloning of genes responsible for pathogen virulence have made possible a new molecular form of Koch's postulates that resolves some of these difficulties. The emphasis is on the virulence genes present in the infectious agent rather than on the agent itself. The molecular postulates can be briefly summarized as follows:

1. The virulence trait under study should be associated much more with pathogenic strains of the species than with nonpathogenic strains.
2. Inactivation of the gene or genes associated with the suspected virulence trait should substantially decrease pathogenicity.
3. Replacement of the mutated gene with the normal wild-type gene should fully restore pathogenicity.
4. The gene should be expressed at some point during the infection and disease process.
5. Antibodies or immune system cells directed against the gene products should protect the host.

The molecular approach cannot always be applied because of problems such as the lack of an appropriate animal system. It also is difficult to employ the molecular postulates when the pathogen is not well characterized genetically.



3.3 微生物学的发展

免疫学的发展：

- 巴斯德研制出狂犬病疫苗，禽霍乱疫苗；
- Emil von Behring (1854－1917) and Shibasaburo Kitasato发明抗毒素（抗血清），为体液免疫开了先河；
- Elie Metchnikoff(1845－1916) 发现一些血液白细胞能吞噬一些病菌，打开了细胞免疫的大门・・・

医药微生物学的发展

- 1929年，Alexander Fleming发现霉菌*Penicillium notatum*(点青霉) 现在称为*Penicillium chrysogenum*(产黄青霉)生产青霉素penicillin;
- 1943年，美国人Selman Waksman 在链霉菌中发现链霉素streptomycin和新霉素neomycin、链丝菌素streptothricin等，并发明抗生素“antibiotics”一词。

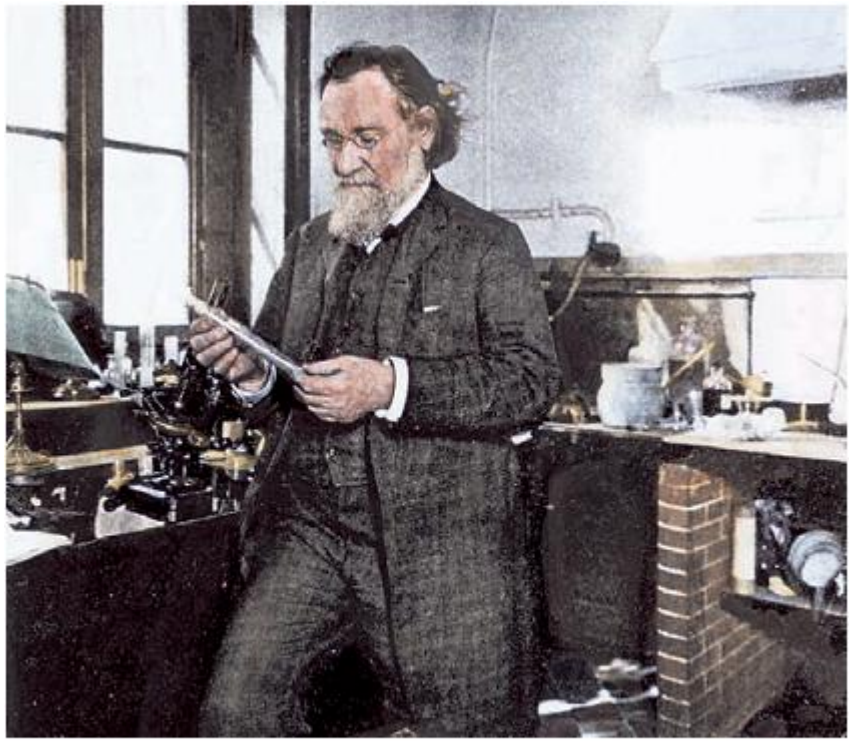
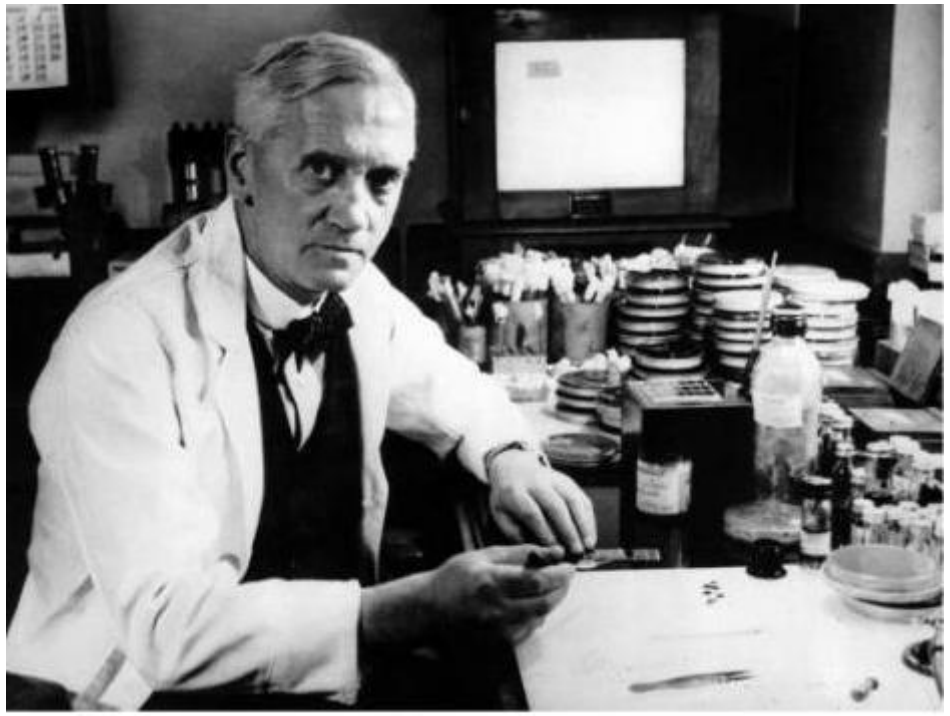


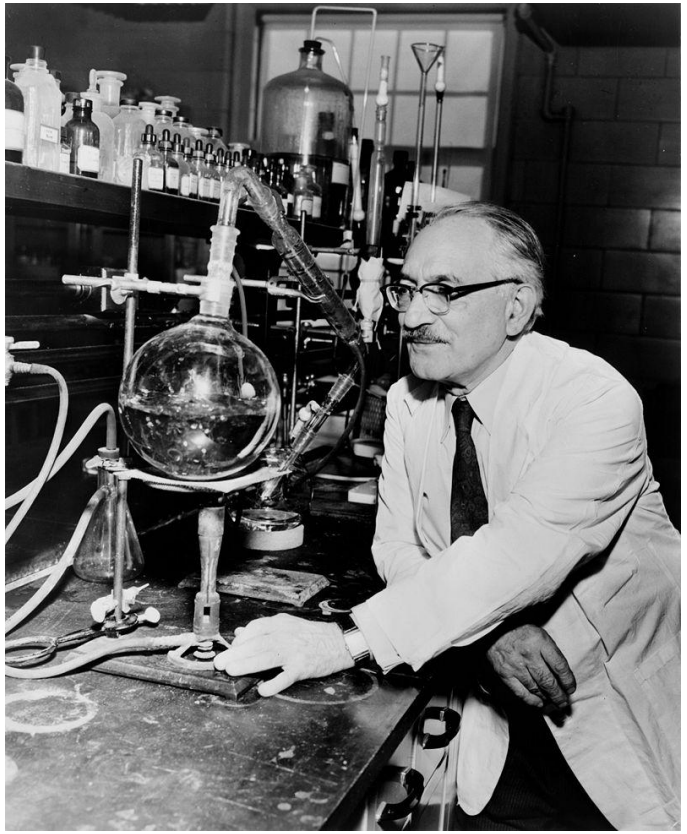
Figure 1.8 Elie Metchnikoff. Metchnikoff (1845–1916) shown here at work in his laboratory.

抗生素研究的两位大师

1945 Nobel Prize



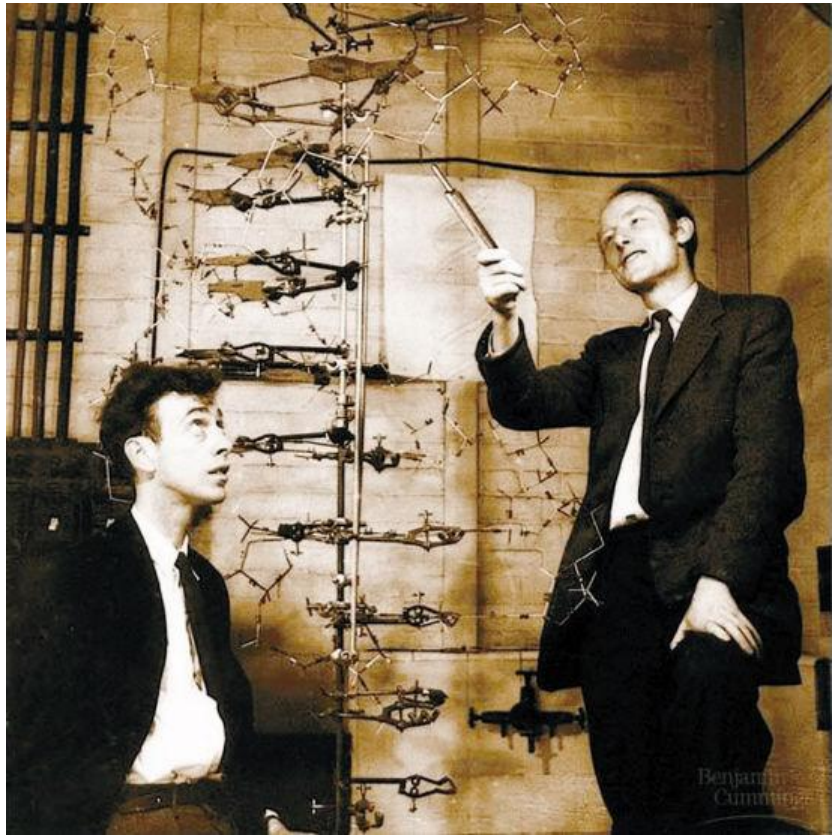
Alexander Fleming (1881-1955)



Selman Waksman (1888-1973)

1952 Nobel Prize

Watson and Crick published the article(below) in NATURE in 1953



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).

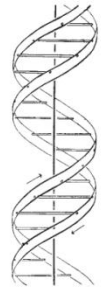
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

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).
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[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

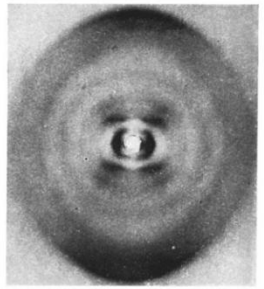

Fig. 1. Fibre diagram of deoxypentose nucleic acid from *B. coli*. Fibre axis vertical

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[5] 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-

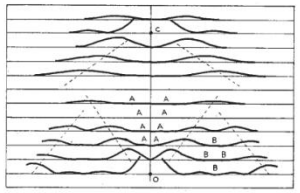

Fig. 2. Diffraction pattern of system of helices corresponding to structure of deoxypentose nucleic acid. The squares of Bessel functions are plotted about 0 on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mass at 20 A. diameter and remainder distributed 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.

3.3 微生物学的发展

微生物学在上个世纪的大发展，逐渐成为门类齐全、学科分化和交叉多样的庞大学科群，其中有1/3诺贝尔奖被授予从事微生物研究的科学家。进入21世纪，以高通量测序技术为代表的生命科学推动微生物学进入组学时代：基因组学(genomics)、微生物组学（microbiomics）、病毒组学(viromics)、抗性组学(resistomics) 、代谢组学(metabolomics)、宏基因组学(megagenomics)等，微生物学将在能源、制药、免疫和医学及生态治理等方面大展身手，为人类文明做出更大贡献。

期待在座的诸君大显身手！

3.4 微生物学发展过程中的重大事件

- 1890　Von Behring制备抗毒素治疗白喉和破伤风；
- 1892　Ivanovsky 提供烟草花叶病毒是由病毒引起的证据；
- 1928　Griffith发现细菌转化；
- 1929　Fleming发现青霉素；
- 1944　Avery等证实转化过程中DNA是遗传信息的载体；
- 1953　Watson和Crick提出DNA双螺旋结构；
- 1970～1972　Arber、Smith和Nathans发现并提纯了 DNA限制性内切酶

3.4 微生物学发展过程中的重大事件

- 1977　Woese提出古生菌是不同于细菌和真核生物的特殊类群
  Sanger首次对镰f×174噬菌体DNA进行了全序列分析；
- 1982～1983　Prusiner发现朊病毒(prion)；
- 1983～1984　Mullis　建立PCR技术；
- 1995　第一个独立生活的细菌(流感嗜血杆菌)全基团组序列测定完成；
- 1996　第一个自养生活的古生菌基因组测定完成；
- 1997　最大的细菌*Thiomargarita namibiensis* 被发现；

3.4 微生物学发展过程中的重大事件

- 2000　发现弧菌*Vibrio cholerae*有两个染色体；
- 2003　纽约分离到超级抗性的HIV毒株。
- 2005　SARS在中国爆发；发现藻类病毒mimivirus；
- 2006　在酵母菌细胞构建代谢途径来生产青蒿酸；
- 2010　第一个人工合成的细胞“辛西娅”诞生；
- 2014　埃博拉病毒疫情在非洲爆发;智利发现最大病毒Pandoravirus；
- 2015　在酵母体内生物合成阿片类药物；

• • •　　• • •

4.微生物学在生命科学中的地位

1. 微生物是生物学基本理论研究中的理想实验对象，
对微生物的研究促进许多重大生物学理论问题的突破

- 基因和酶关系的阐明及“一个基因一个酶”的假说；
- 遗传的物质基础的阐明；
- 基因概念的发展；
- 遗传密码的破译；
- 基因表达调控机制的研究；
- 生物大分子合成的中心法则；

4.微生物学在生命科学中的地位

2．对生命科学研究技术的贡献

细胞的人工培养；

突变体筛选；

DNA重组技术和遗传工程；

3．微生物与“人类基因组计划”

作为模式生物；

基因与基因组的功能研究的重要工具；

5.中国微生物学发展

汤非凡　戴芳澜　高尚荫　陈华癸　邓子新　高 福　陈化兰







鲜有世界级的原创性的学术成果，也缺乏产业方面里程碑性的贡献，无论学术还是产业，长期处于学习、模仿和跟踪研究的水平。缺乏世界一流人才，缺乏世界一流学术，缺乏世界一流产业。

改革开放30多年来，中国迅速崛起。国家的教育面貌发生巨大改变，人才面貌巨大改变，科研和产业面貌巨大改变。虽然还有差距，但是，中国人追赶世纪一流教育、科技、产业的信心越来越强，脚步越来越快，实力越来越强，差距越来越小・・・

微生物，高科技、大产业！——路甬祥

6.微生物学的未来…

Thanks for your attention!