Genetic Basis of Variation in Bacteria

I. Organization of genetic material in bacteria
- a. chromosomes
- b. plasmids

II. Genetic variation: Source
- a. point mutations
- b. DNA rearrangements

III. Genetic variation: Transmission
- a. transformation
- b. transduction
- c. conjugation

IV. Genetic variation: Implications for pathogenesis

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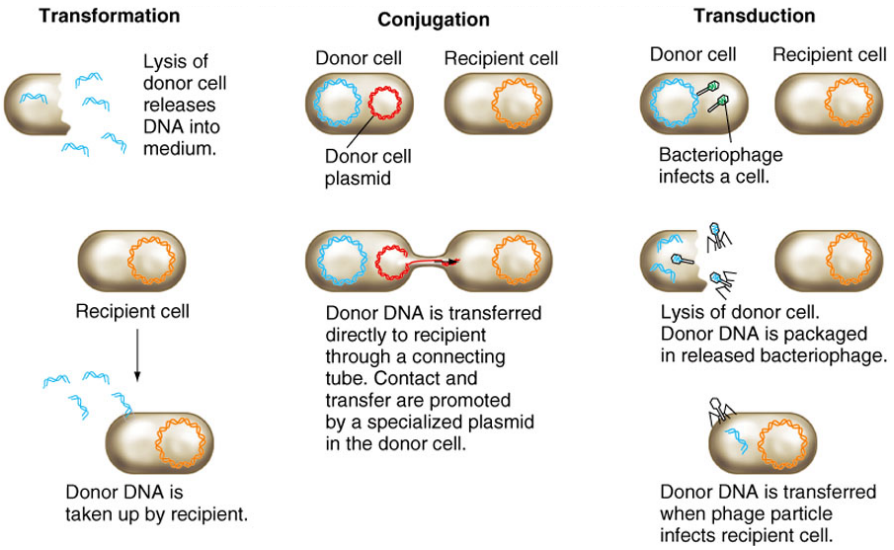
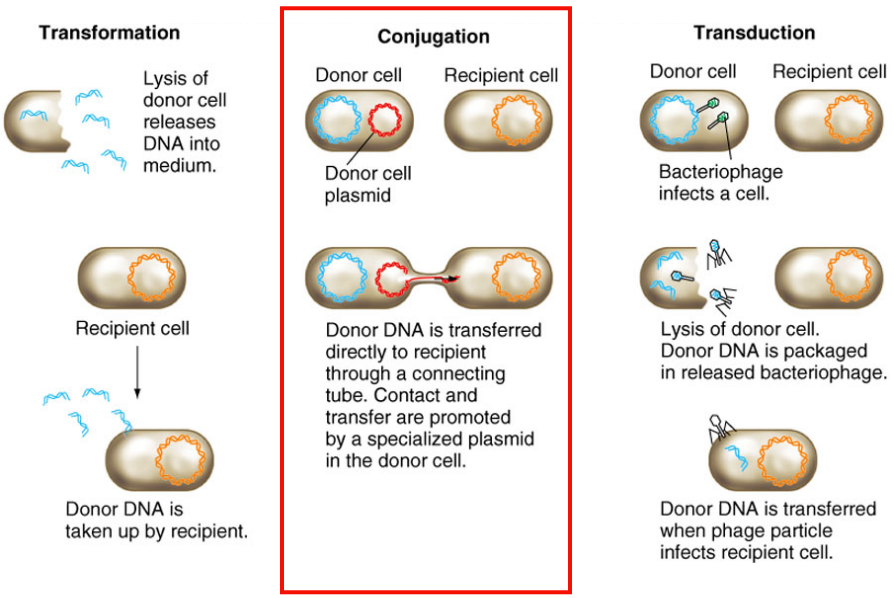
Transmission of genetic variation

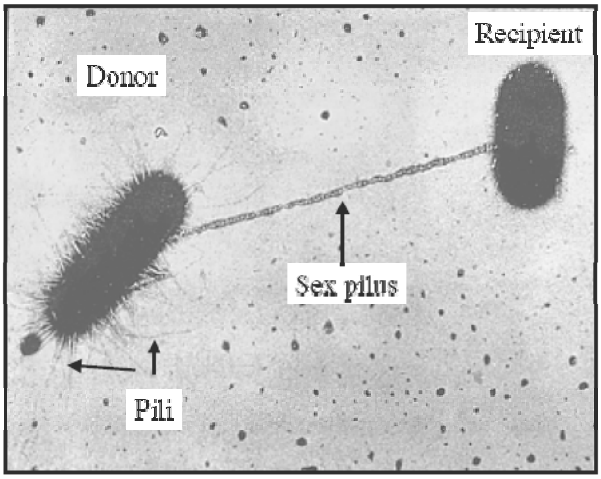


Transmission of genetic variation: conjugation

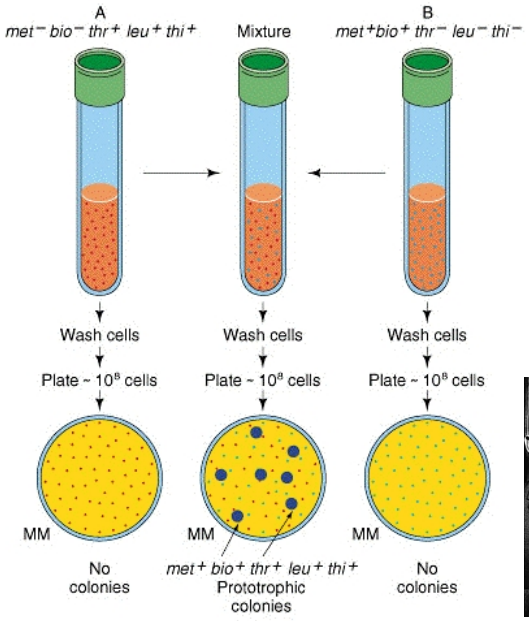


Transmission of genetic variation: conjugation

Bacterial Conjugation is genetic recombination in which there is a transfer of DNA from a living donor bacterium to a recipient bacterium. Often involves a sex pilus.

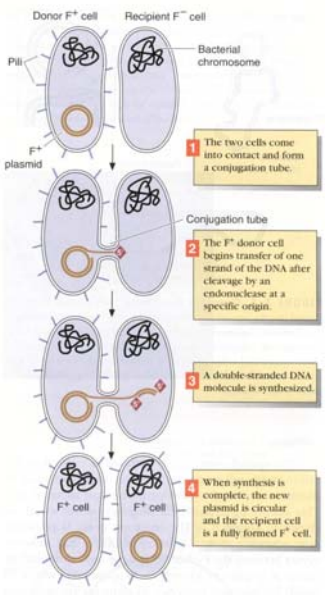


Transmission of genetic variation: conjugation



Transmission of genetic variation: conjugation

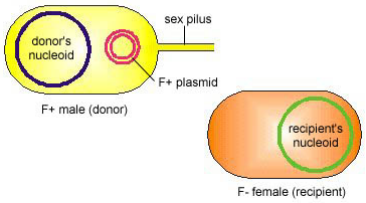
- Direct transfer of DNA from one strain to another.
- Best studied in *E. coli*, and approximately a third of freshly isolated *E. coli* have plasmids.
- Conjugative plasmids have been found in approximately 30 genera of bacteria, mostly gram-negative. Antibiotic-resistance plasmids RP4 & R68.45 can propagate and promote conjugation in virtually any gram-negative bacterium.
- Some gram-positive conjugate such as *Streptococci, Staphylococcus, Streptomyces, Clostridium,* and *Bacillus*.



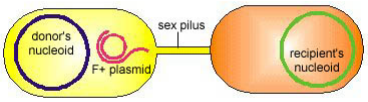
Transmission of genetic variation: F+ conjugation

F+ Conjugation- Genetic recombination in which there is a transfer of a large (95kb) plasmid F+ plasmid (coding only for a sex pilus) but not chromosomal DNA from a male donor bacterium to a female recipient bacterium. Involves a sex (conjugation) pilus. Other plasmids present in the cytoplasm of the bacterium, such as those coding for antibiotic resistance, may also be transferred during this process. F can be transferred from *E. coli* to *Salmonella, Shigella*, and *Proteus*.

Transmission of genetic variation: F+ conjugation

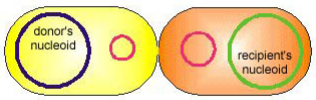


1. The F+ male has an F+ plasmid coding for a sex pilus and can serve as a genetic donor

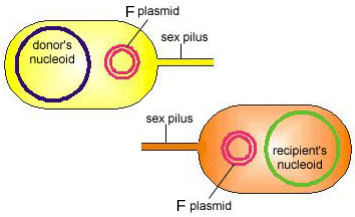


2. The sex pilus adheres to an F- female (recipient). One strand of the F+ plasmid breaks

Transmission of genetic variation: F+ conjugation



3. The sex pilus retracts and a bridge is created between the two bacteria. One strand of the F+ plasmid enters the recipient bacterium



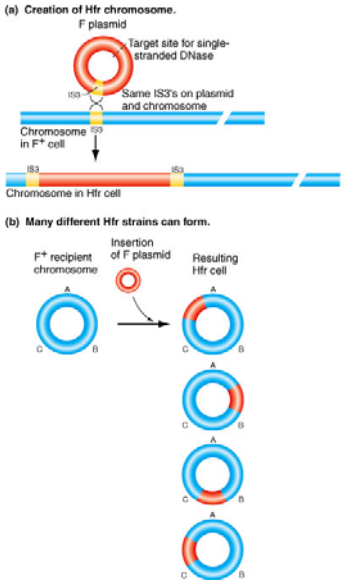
4. Both bacteria make a complementary strand of the F+ plasmid and both are now F+ males capable of producing a sex pilus. There was no transfer of donor chromosomal DNA although other plasmids the donor bacterium carries may also be transferred during F+ conjugation.

http://www.cat.cc.md.us/courses/bio141/lecguide/unit4/genetics/recombination/conjugation/f.htm

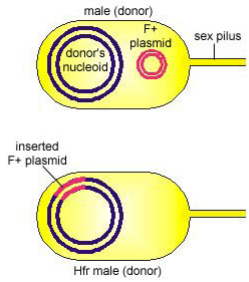
Transmission of genetic variation: Hfr conjugation

Hfr conjugation: Genetic recombination in which fragments of chromosomal DNA from a male donor bacterium are transferred to a female recipient bacterium following insertion of an F+ plasmid into the nucleoid of the donor bacterium. Involves a sex (conjugation)pilus.

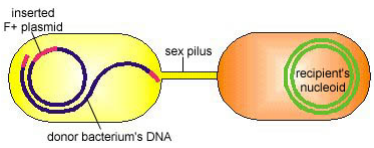
- F+ plasmids can exist extrachromosomally or integrated into the host chromosome.
- Integration occurs at a frequency of 10^{-5} per generation.
- Integration occurs via homologous recombination between IS-elements on the plasmid and IS-elements in the chromosome.



Transmission of genetic variation: Hfr conjugation

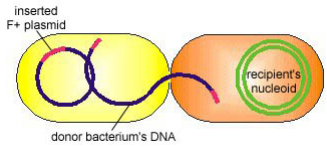


1. An F+ plasmid inserts into the donor bacterium's nucleoid to form an Hfr male.

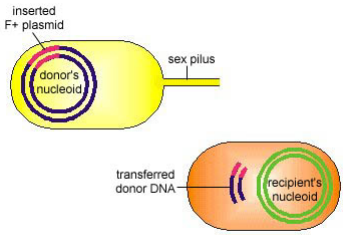


2. The sex pilus adheres to an F- female (recipient). One donor DNA strand breaks in the middle of the inserted F+ plasmid.

Transmission of genetic variation: Hfr conjugation

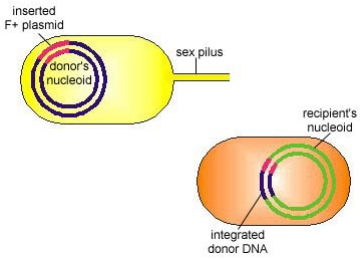


3. The sex pilus retracts and a bridge forms between the two bacteria. One donor DNA strand begins to enter the recipient bacterium. The two cells break apart easily so the only a portion of the donor's DNA strand is usually transferred to the recipient bacterium.



4. The donor bacterium makes a complementary copy of the remaining DNA strand and remains an Hfr male. The recipient bacterium makes a complementary strand of the transferred donor DNA.

Transmission of genetic variation: Hfr conjugation

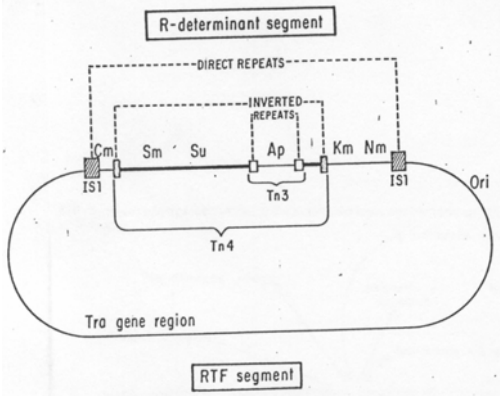


5. The donor DNA fragment undergoes genetic exchange with the recipient bacterium's DNA. Since there was transfer of some donor chromosomal DNA but usually not a complete F+ plasmid, the recipient bacterium usually remains F-

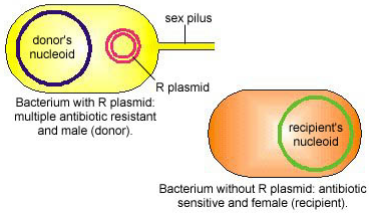
http://www.cat.cc.md.us/courses/bio141/lecguide/unit4/genetics/recombination/conjugation/hfr.htm I

Transmission of genetic variation: R-plasmid conjugation

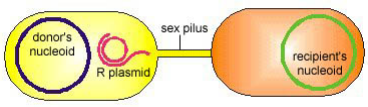
- R factors - Drug-resistance plasmids first isolated in late 1950's in *Shigella* during an outbreak of dysentery. The first plasmid isolated carried resistant determinants to four different antibiotics: chloramphenicol, tetracycline, streptomycin, and sulfonamides. Latter the same plasmid was found in *E. coli*.
- In patients given oral tetracycline, the predominant fecal *E. coli* isolates carry tetracycline-resistance R plasmids within one week.



Transmission of genetic variation: R-plasmid conjugation

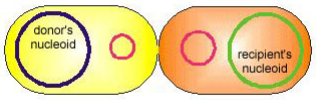


1. The bacterium with an R-plasmid is multiple antibiotic resistant and can produce a sex pilus (serve as a genetic donor).

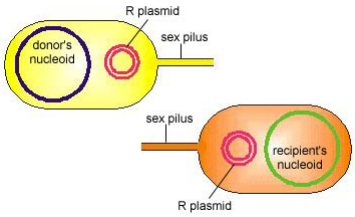


2. The sex pilus adheres to an F- female (recipient). One strand of the R-plasmid breaks.

Transmission of genetic variation: R-plasmid conjugation



3. The sex pilus retracts and a bridge is created between the two bacteria. One strand of the R-plasmid enters the recipient bacterium.



4. Both bacteria make a complementary strand of the R-plasmid and both are now multiple antibiotic resistant and capable of producing a sex pilus.

http://www.cat.cc.md.us/courses/bio141/lecguide/unit4/genetics/recombination/conjugation/r.html

Transmission of genetic variation: R-plasmid conjugation

Properties of some R plasmids

Plasmid	Origin	Resistances	Size (kb)
RP1	England	CbKmTc	36
R527	Spain	CbCmGmKmSmSuTcHg	49
pMG5	Japan	AkKmSuTmBorHgPmrTer	280
pMG90	France	CbCmGmKmSmSuTcTmBorHg	150
Rms149	Germany	CbGmSmSuTra$^-$	36
pMG38	USA	CbGmKmSuTcTmHg	53
FP110	Australia	Cma*Pae*Fp110	60
pMG25	South Africa	CbCmGmKmSmSuTmBor	66
pMG69	Ireland	CbGmKmSmSuTcTmTra$^-$	47

Transmission of genetic variation: R-plasmid conjugation

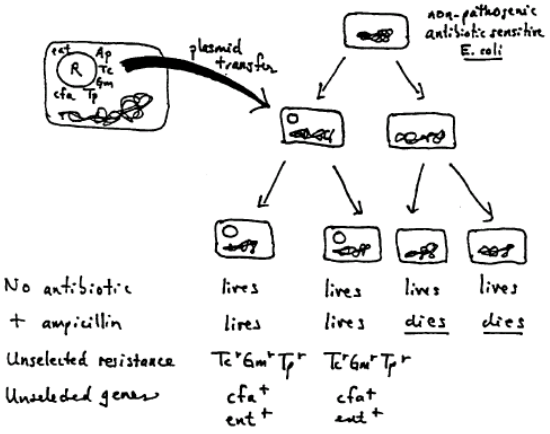
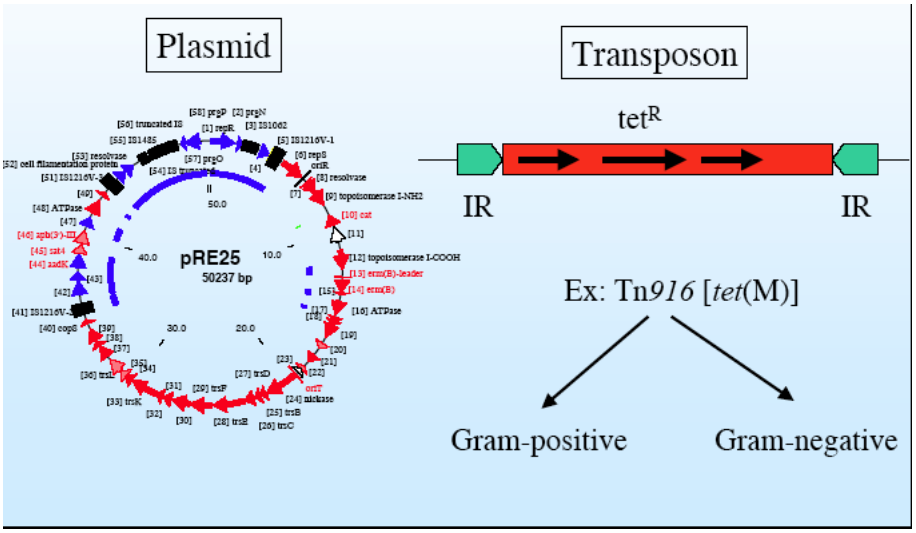
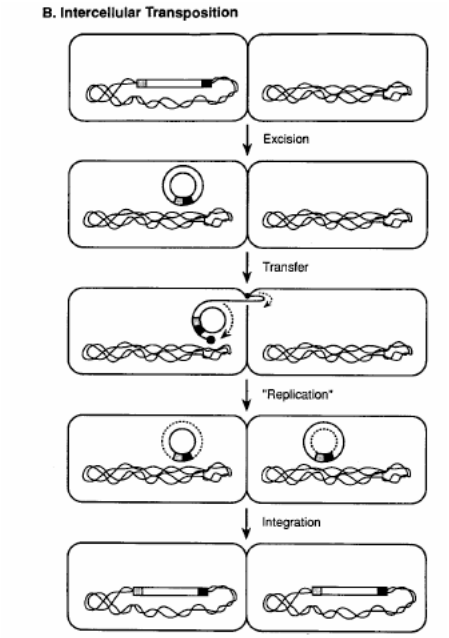


Fig. 6. Indirect selection for multiple resistance.

Transmission of genetic variation: conjugation



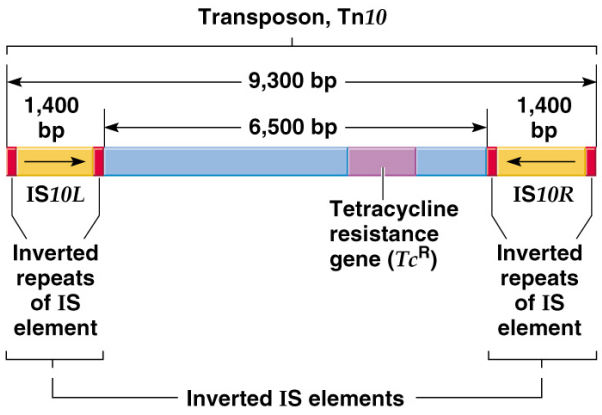
Transmission of genetic variation: conjugative transposition



Transmission of genetic variation: conjugative transposition

Composite transposons (Tn):

- **Carry genes (e.g., a gene for antibiotic resistance) flanked on both sides by IS elements.**
- **Tn10 is 9.3 kb and includes 6.5 kb of central DNA (includes a gene for tetracycline resistance) and 1.4 kb inverted IS elements.**
- **IS elements supply transposase and ITR recognition signals.**



Genetic variation: Implications for pathogenesis and antibiotic resistance

I. Transduction
    a. *Vibrio cholera*
    b. Corynebacterium diphtheriae
    c. Neisseria meningitidis

II. Transformation
    a. *Neisseria gonorrhoeae* pilin variation

III. Conjugation
    a. *Bacillus spp.*
    b. Enterococcus faecium

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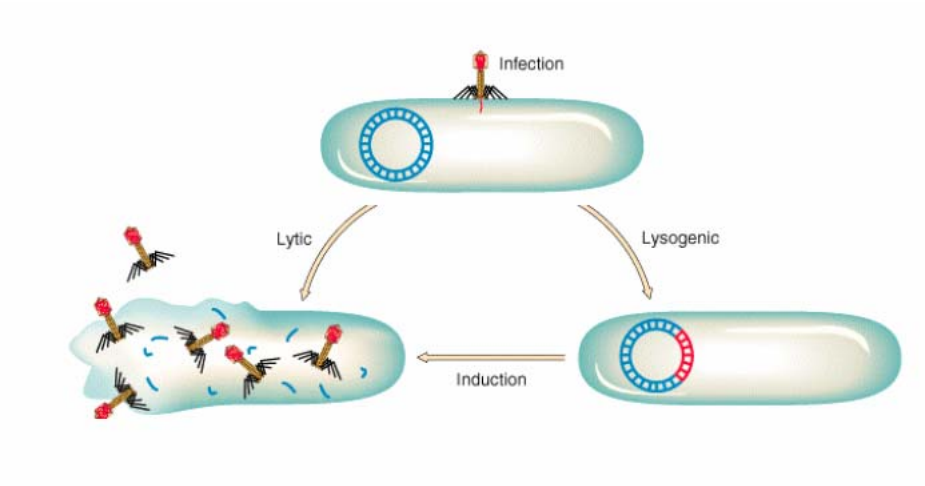
Transmission of genetic variation: transduction



Transduction: Examples of Virulence Factors Carried by Phage

Bacterium	Phage	Gene Product	Phenotype
Vibrio cholerae	CTX phage	cholerae toxin	cholera
Escherichia coli	lambda phage	shigalike toxin	hemorrhagic diarrhea
Clostridium botulinum	clostridial phages	botulinum toxin	botulism (food poisoning)
Corynebacterium diphtheriae	corynephage beta	diphtheria toxin	diphtheria
Streptococcus pyogenes	T12	erythrogenic toxins	scarlet fever

Transduction: *Corynebacterium diphtheriae*

STUDIES ON THE VIRULENCE OF BACTERIOPHAGE-INFECTED STRAINS OF CORYNEBACTERIUM DIPHTHERIAE[1]

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Department of Public Health and Preventive Medicine, University of Washington, School of Medicine, Seattle, Washington

Received for publication February 26, 1951

The relationship of naturally occurring avirulent strains to virulent strains of *Corynebacterium diphtheriae* is an unanswered question in the epidemiology of diphtheria and in the evolution of the diphtheria bacillus. The detailed investigations reported here have revealed that avirulent strains of *C. diphtheriae* infected with bacteriophage have yielded virulent *C. diphtheriae strains.*

Transduction: *Corynebacterium diphtheriae*

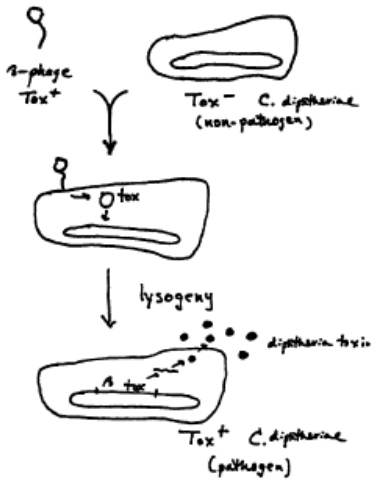


Figure 8. Lysogenic conversion in *C. diphtheriae*

Transduction: *Corynebacterium diphtheriae*

TABLE 3

Subcutaneous tests of bacteriophage lysates in guinea pigs*

STRAIN NO.	CULTURE PLUS SALINE	CULTURE PLUS PHAGE A	CULTURE PLUS PHAGE B	CULTURE PLUS PHAGE B AND ANTITOXIN
444	0/3†	0/1	4/4	0/2
1174	0/1	0/1	2/2	0/1
1180	0/1	0/1	2/2	0/1
770	0/1	0/1	2/2	0/1
411	0/1	0/1	0/1	0/1
Total	0/7	0/5	10/11	0/6

* All cultures and culture lysates were washed off agar media with 0.85 per cent saline and inoculated in 1.0-ml doses.

† The numerator represents the number of guinea pigs that died; the denominator, the total number tested.

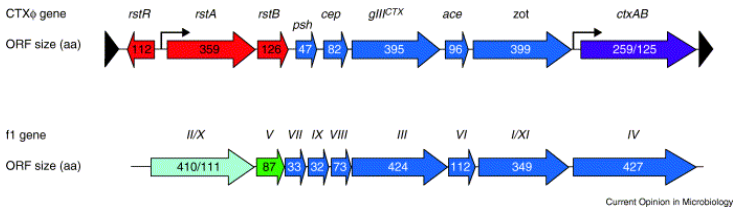
Transduction: *Vibrio cholera*

Lysogenic Conversion by a Filamentous Phage Encoding Cholera Toxin

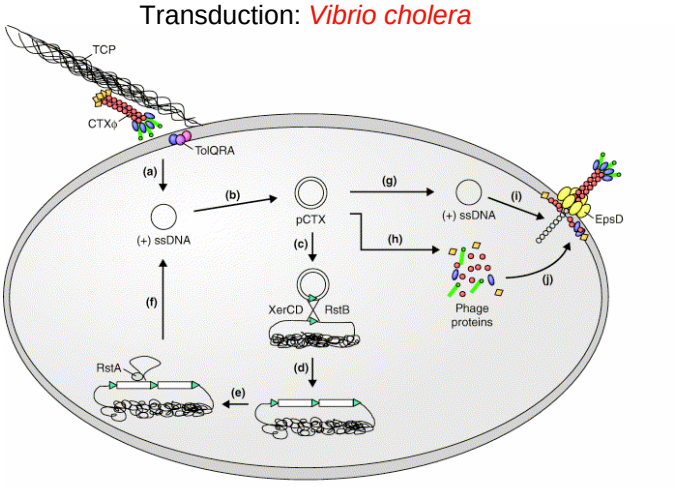
Matthew K. Waldor* and John J. Mekalanos

Vibrio cholerae, the causative agent of cholera, requires two coordinately regulated factors for full virulence: cholera toxin (CT), a potent enterotoxin, and toxin-coregulated pili (TCP), surface organelles required for intestinal colonization. The structural genes for CT are shown here to be encoded by a filamentous bacteriophage (designated CTXΦ), which is related to coliphage M13. The CTXΦ genome chromosomally integrated or replicated as a plasmid. CTXΦ used TCP as its receptor and infected *V. cholerae* cells within the gastrointestinal tracts of mice more efficiently than under laboratory conditions. Thus, the emergence of toxigenic *V. cholerae* involves horizontal gene transfer that may depend on in vivo gene expression.

Transduction: *Vibrio cholera*



Transduction: *Vibrio cholera*



Current Opinion in Microbiology

Model of the key steps (infection, integration, replication, assembly and secretion) in the life cycle of CTX. (a) CTX infection of *V. cholerae* requires TCP and TolQ, TolR and TolA. The single stranded DNA of CTX ((+) ssDNA) loses its protein coat and is transported into the bacterial cytoplasm. (b) DNA complementary to the phage genome is synthesized to generate pCTX, the replicative (plasmid) form of CTX. (c) The chromosome-encoded recombinases XerC and XerD, along with the phage-encoded protein RstB, are required for integration of pCTX into the chromosome at or near the *V. cholerae* dif site. (d) Recombination between nearly identical sequences in pCTX and the *V. cholerae* chromosome (green triangles) generates either a single CTX prophage or (as shown) tandem prophages. (e) Tandem prophages can serve as a template for production of extrachromosomal phage DNA. This process is initiated by the phage-encoded protein RstA; (f) it results in the formation of the single-stranded phage genome ((+)ssDNA). (g) pCTX can serve as a template for further replication of the phage genome; (h) its genes can also be transcribed and translated, resulting in synthesis of phage proteins. (i and j) Phage proteins are thought to be inner membrane proteins prior to insertion into phage particles. Phage DNA (chain of circles) is simultaneously packaged into virions and secreted from the cell. Phage secretion depends upon the outer membrane channel EpsD. Ss, single-stranded.

Transduction: *Neisseria meningitidis*

A chromosomally integrated bacteriophage in invasive meningococci

Emmanuelle Bille,[1] Jean-Ralph Zahar,[1] Agnes Perrin,[1] Sandrine Morelle,[1] Paula Kriz,[2] Keith A. Jolley,[3] Martin C.J. Maiden,[3] Catherine Dervin,[4] Xavier Nassif,[1] and Colin R. Tinsley[1,4]

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[2]National Reference Laboratory for Meningococcal Infections, National Institute of Public Health, 100 42 Prague, Czech Republic
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Cerebrospinal meningitis is a feared disease that can cause the death of a previously healthy individual within hours. Paradoxically, the causative agent, *Neisseria meningitidis*, is a common inhabitant of the human nasopharynx, and as such, may be considered a normal, commensal organism. Only in a small proportion of colonized people do the bacteria invade the bloodstream, from where they can cross the blood–brain barrier to cause meningitis. Furthermore, most meningococcal disease is caused by bacteria belonging to only a few of the phylogenetic groups among the large number that constitute the population structure of this genetically variable organism. However, the genetic basis for the differences in pathogenic potential remains elusive. By performing whole genome comparisons of a large collection of meningococcal isolates of defined pathogenic potential we brought to light a meningococcal prophage present in disease-causing bacteria. The phage, of the filamentous family, excises from the chromosome and is secreted from the bacteria via the type IV pilin secretin. Therefore, this element, by spreading among the population, may promote the development of new epidemic clones of *N. meningitidis* that are capable of breaking the normal commensal relationship with humans and causing invasive disease.

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Transduction: *Neisseria meningitidis*

Table I. Properties of the island's ORFs

Gene	Protein length	Presence in meningococcal strains: In 29 "invasive"	Presence in meningococcal strains: In 20 "noninvasive"	Protein homologies (BlastP)[a]	Conserved domains (BlastP)[b]
ORF1, NMA1792	429	27	0	ORF C7 [*Ralstonia solanacearum* plasmid] (NP_052309.1), 9×10^{-24}; RstA1 protein [*Vibrio cholerae* prophage] (NP_231106.1), 1×10^{-11}	replication initiation factor (pfam02486), 6×10^{-42}; phage replication protein RstA (COG2946), 4×10^{-143}
ORF2, NMA1793	104	29	1	NS[c]	NS
ORF3, NMA1794	67	29	1	NS	NS
ORF4, NMA1795	77	29	1	NS	NS
ORF5, NMA1796	102	29	1	NS	NS
ORF6, NMA1797	547	29	2	NS	Neisserial TspB proteins
ORF7, NMA1798	95	29	2	NS	NS
ORF8, NMA1799	401	29	2	ORF C6 [*Ralstonia solanacearum* plasmid] (NP_052316.1), 2×10^{-31}; phage-related protein [*Xylella fastidiosa*] (NP_779131.1), 3×10^{-18}	zonular occludens toxin (Zot) (pfam05707), 7×10^{-47}; NS
ORF9, NMA1800	323	26	0	transposase [*Escherichia coli* IS621] (BAC76887.1), 3×10^{-37}	transposase (COG3547), 1×10^{-17}

Transduction: *Neisseria meningitidis*

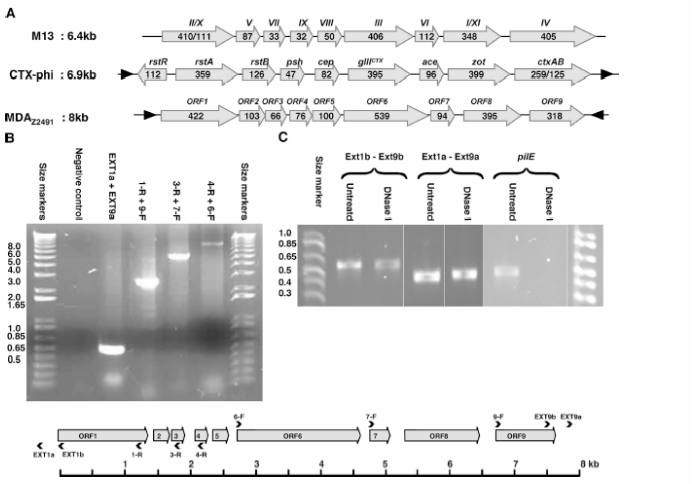

Figure 2. Preliminary characterization of the genetic island. (A) Comparison of the organization of the genetic island with that of coliphage M13 and *V. cholerae* bacteriophage CTX-phi (after reference 20). (B) The island exists in an extrachromosomal, closed-circular form. PCR amplifications of total DNA of strain Z2491 with oligonucleotide pairs directed toward opposite ends of the element yielded fragments of sizes expected from a circular form of the island (EXT1a + EXT9a, 0.43 kb; EXT1b + EXT9b, 0.66 kb; 1-R + 9-F, 2.4 kb; 3-R + 7-F, 5.0 kb; 4-R + 6-F, 7.4 kb). Positions of the oligonucleotides are shown on the map below the gel figures. (C) The element is secreted in a nuclease-resistant form. Treatment with DNase I had no significant effect on the material amplifiable by the circular form–specific primer pairs EXT1a-EXT9a or EXT1b-EXT9b (note that the difference in intensities of the products EXT1b-EXT9b is due to the typical experimental variation). In contrast, the signal due to contaminating chromosomal DNA (the pilin gene pilE, amplified with pilin-specific primers) was abolished by nuclease treatment.

Transformation: *Neisseria gonorrhoeae* pilin variation

DNA transformation leads to pilin antigenic variation in *Neisseria gonorrhoeae*

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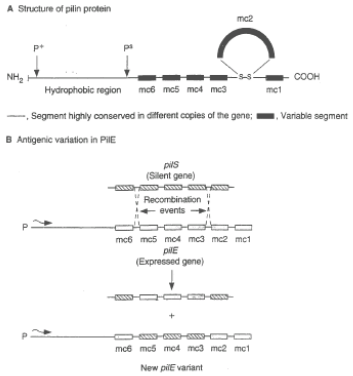
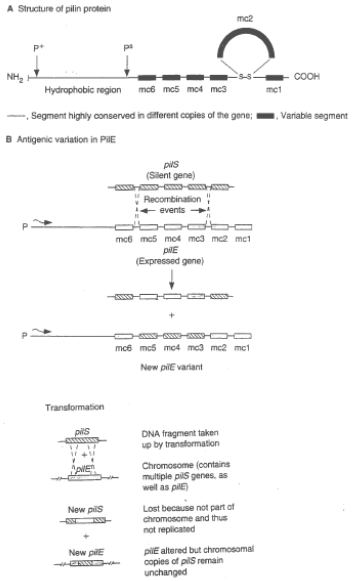
Transformation: *Neisseria gonorrhoeae* pilin variation

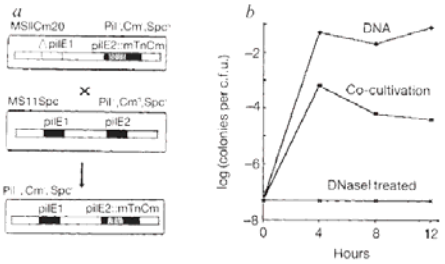


Transformation: *Neisseria gonorrhoeae* pilin variation



Transformation: *Neisseria gonorrhoeae* pilin variation

Fig. 1 Transfer of a pilin marker between strains. *a*, Diagram showing parental bacterial cells and selected progeny. MS11Cm20, was non-piliated (Pil$^-$) due to a deletion of *pilE1* and a mini-transposon insertion in *pilE2*, chloramphenicol-resistant (Cm^r) due to the mini-transposon, and spectinomycin-sensitive (Spc^s). MS11Spc, was Pil$^-$, Cm^s, and Spc^s. The strain that was selected after mixing of the two strains was Pil$^+$, Cm^r and Spc^r, having retained the intact *pilE1* locus, acquired the Cm^r gene carried by the mini-transposon in *pilE2* by transformation, and retained the Spc^r allele. *b*, Frequency of Cm^r, Spc^r colonies after various times of mixing. 'DNA' shows the results using purified MS11Cm20 DNA, 'co-cultivation' indicates mixing of the strains, and 'DNaseI', the level of detection of this experiment. No colonies appeared at zero time or after DNaseI treatment.
Methods. A 980-base pair (bp) *Hin*dIII/*Cla*I DNA fragment encoding pilin was subcloned from pNG1100BH1 (ref. 3) into the



Conjugation: *Bacillus spp.*

Bacillus anthracis, *Bacillus cereus*, and *Bacillus thuringiensis*—
One Species on the Basis of Genetic Evidence

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HENNING A. JOHANSEN,[1] AGNES FOUET,[4] MICHÈLE MOCK,[4] IDA HEGNA,[1,2]
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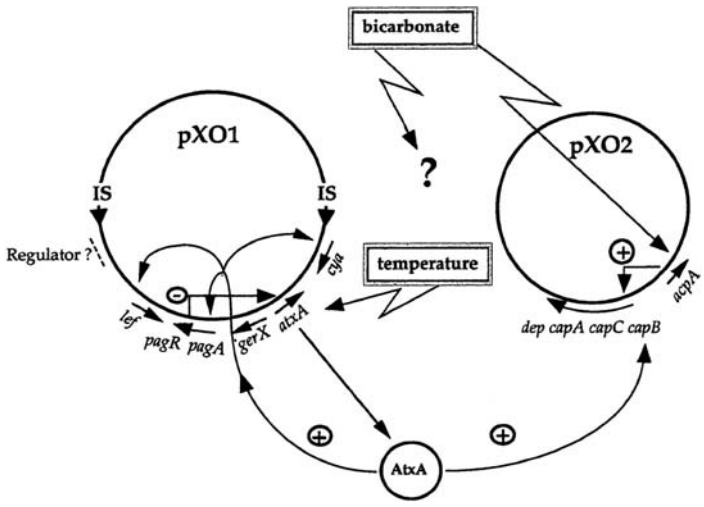
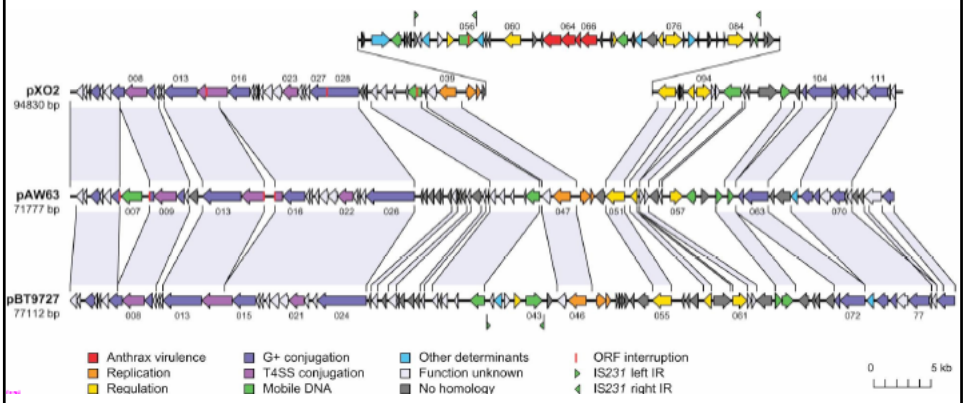
Bacillus anthracis, ***Bacillus cereus***, and ***Bacillus thuringiensis*** are members of the ***Bacillus cereus*** group of bacteria, demonstrating widely different phenotypes and pathological effects. ***B. anthracis*** causes the acute fatal disease anthrax and is a potential biological weapon due to its high toxicity. ***B. thuringiensis*** produces intracellular protein crystals toxic to a wide number of insect larvae and is the most commonly used biological pesticide worldwide. ***B. cereus*** is a probably ubiquitous soil bacterium and an opportunistic pathogen that is a common cause of food poisoning. In contrast to the differences in phenotypes, we show by multilocus enzyme electrophoresis and by sequence analysis of nine chromosomal genes that ***B. anthracis*** should be considered a lineage of ***B. cereus***. This determination is not only a formal matter of taxonomy but may also have consequences with respect to virulence and the potential of horizontal gene transfer within the ***B. cereus*** group.

Conjugation: *Bacillus spp.*



Conjugation: *Bacillus spp.*



Conjugation: *Bacillus spp.*

Identification of anthrax toxin genes in a *Bacillus cereus* associated with an illness resembling inhalation anthrax

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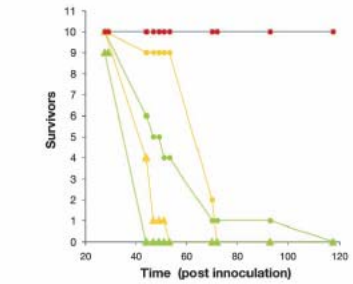

Fig. 4. Survival of A/J mice i.p. challenged with *B. cereus* G9241 (green), *B. anthracis* Sterne (yellow), and *B. cereus* ATCC10987 (red). High-spore dose (1×10^4) and low-spore dose (1×10^3) are represented by triangles and circles, respectively. The experiment was monitored for 14 days, after which the mice inoculated with *B. cereus* ATCC10987 were still alive.

Conjugation: *Enterococcus faecium*

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0021-9193/93/010117-11$02.00/0

Vol. 175, No. 1

Characterization of Tn*1546*, a Tn*3*-Related Transposon Conferring Glycopeptide Resistance by Synthesis of Depsipeptide Peptidoglycan Precursors in *Enterococcus faecium* BM4147

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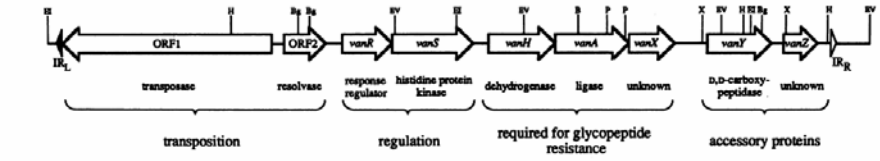

Genetic Basis of Variation in Bacteria

I. Organization of genetic material in bacteria
   a. chromosomes
   b. plasmids

II. Genetic variation: Source
   a. point mutation
   b. DNA rearrangements

III. Genetic variation: Transmission
   a. transformation
   b. transduction
   c. conjugation

IV. Genetic variation: Implications for pathogenesis

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