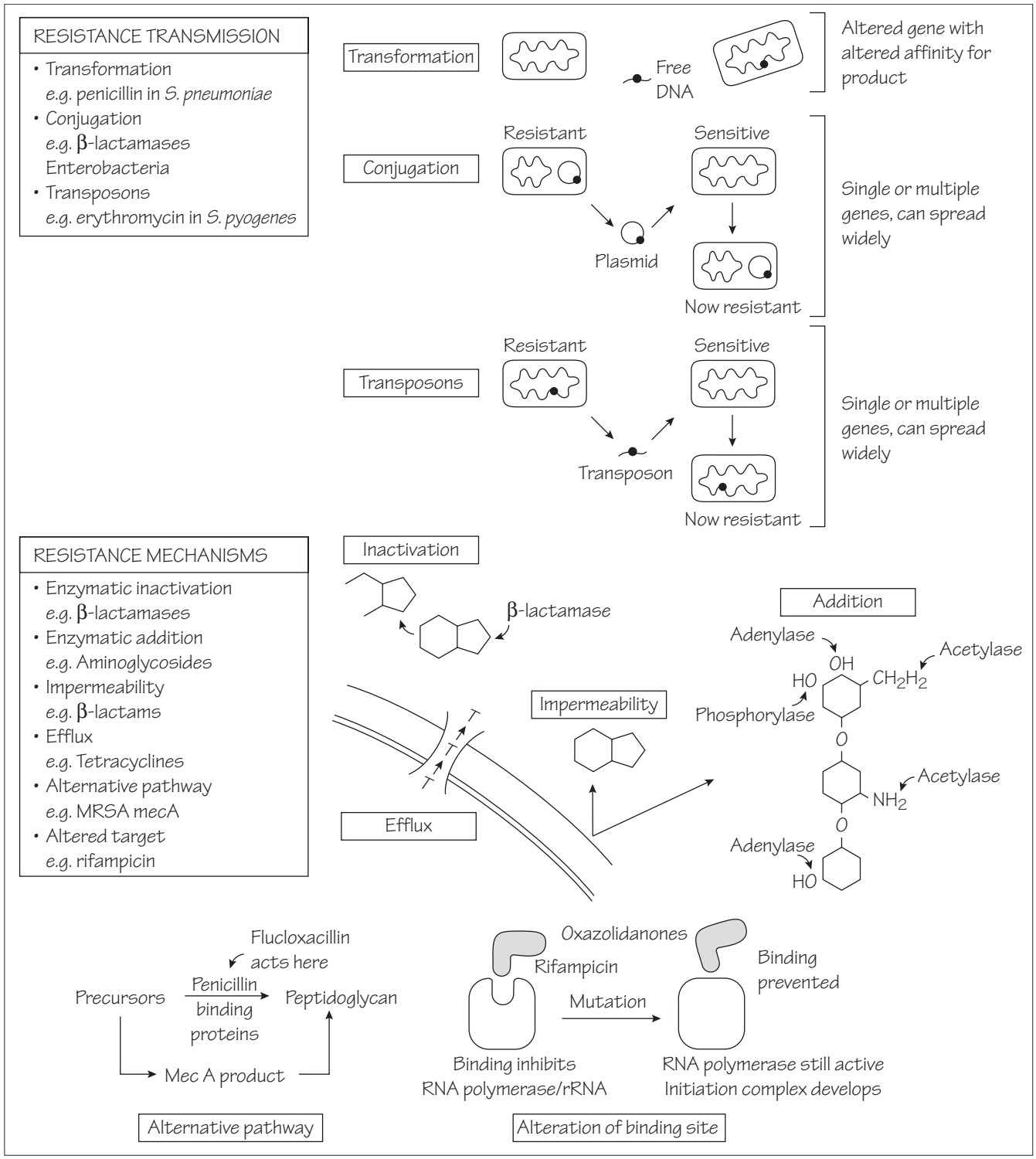
7 **Resistance to antibacterial agents**



Resistance occurs when a previously susceptible organism is no longer inhibited by an antibiotic. This happens because the bacterial gene pool changes, facilitated by its rapid cell division and haploid genome. Organisms may transfer genetic material within and between species. Bacteria do not have a deliberate policy to develop 'resistance genes' or 'virulence factors' to advance their species: they play the genetic lottery. Antibiotic use allows the survival and replication of organisms that have accidentally developed mechanisms to avoid destruction.

Transmission of resistance determinants between bacteria

Transformation

Many bacterial species can take-up naked DNA and incorporate it into their genome: this is called transformation. It is unlikely that whole 'resistance genes' are taken up in this way. *Streptococcus pneumoniae* takes-up part of penicillin-binding protein genes from closely related species. The altered gene produces a penicillin-binding protein which binds penicillin less avidly and so is not inhibited by penicillin to the same extent. The organism is still able to synthesize peptidoglycan and maintain its cell wall in the presence of penicillin. Resistance to penicillin by *Neisseria gonorrhoeae* also develops in the same way.

Conjugation

Plasmids are circular portions of DNA which are found in the cytoplasm. Multiple copies may be present and, following cell division, are found in the cytoplasm of each daughter cell. Many genes are carried on plasmids, including metabolic enzymes, virulence determinants and antibiotic resistance. The process of conjugation occurs when plasmids are passed from one bacterium to another. In this way 'resistance genes' can spread rapidly in populations of bacterial species that share the same environment, e.g. within the intestine. Combined with antibiotic selective pressure, e.g. in hospitals, multiresistant populations may develop.

Transposons and integrons

Transposons and integrons are moveable genetic elements able to encode transposition. They can move between the chromosome and plasmids, and between bacteria. Many functions, including antibiotic resistance, can be encoded on a transposon. Resistance to methicillin among *Staphylococcus aureus* and that of *Neisseria gonorrhoeae* to tetracycline probably entered the species by this route. Integrons are important in transmission of multiple drug resistance in Gram-negative pathogens. Resistance genes can also be mobilized by bacteriophages.

Mechanisms of resistance

Antibiotic modification

Enzyme inactivation

One of the most common resistance mechanisms occurs when the organism spontaneously produces an enzyme which degrades the antibiotic. Many strains of *Staphylococcus aureus* produce an extracellular enzyme, β-lactamase, which breaks open the β-lactam ring of penicillin, inactivating it. Many other organisms are capable of expressing enzymes which degrade penicillins and cephalosporins. These include *Escherichia coli*, *Haemophilus influenzae* and *Pseudomonas* spp. Often the genes that code for these enzymes can be found on mobile genetic elements (transposons) and can be transmitted between organisms of different species.

Enzyme addition

Bacteria may express enzymes that add a chemical group to the antibiotic, inhibiting its activity. Bacteria become resistant to aminoglycosides by expressing enzymes that inactivate the antibiotic by adding an acetyl, amino or adenosine group to the antibiotic molecule. The different members of the aminoglycoside family differ in their susceptibility to this modification, amikacin being the least susceptible. Aminoglycoside-resistance enzymes are possessed by Gram-positive organisms, such as *Staphylococcus aureus*, and Gram-negative organisms, such as *Pseudomonas* spp.

Impermeability

Some bacteria are naturally resistant to antibiotics because their cell envelope is impermeable to particular antibiotics. Gram-negative organisms, especially *Pseudomonas* spp., are impermeable to some β-lactam antibiotics. Aminoglycosides enter bacteria by an oxygen-dependent transport mechanism and so have little effect against anaerobic organisms.

Efflux mechanisms

Bacteria, for example *E. coli*, may become resistant to tetracyclines by the acquisition of an inner membrane protein which actively pumps the antibiotic out of the cell. Streptococci may become resistant to macrolides using an efflux pump.

Alternative pathway

Another common bacterial mechanism is the development of an alternative pathway to circumvent the metabolic block imposed by the antibiotic. *Staphylococcus aureus* becomes resistant to methicillin or flucloxacillin when it acquires the gene *mecA*. This codes an alternative penicillin-binding protein (PBP2′) which is not inhibited by methicillin. Although the composition of the cell wall is altered, the organism is still able to multiply. Similar alterations to the penicillin-binding proteins of *Streptococcus pneumoniae* are responsible for resistance in this organism.

Alteration of the target site

Rifampicin acts by inhibiting the β-subunit of RNA polymerase. Resistance develops when the RNA polymerase gene is altered by point mutations, insertions or deletions. The new RNA polymerase is not inhibited by rifampicin and resistance occurs