*al*., 1981; Kerbs *et al*., 1983; Workowski *et al*., 2015), but quinolone resistance is now often as common as penicillin resistance (MMWR, 2007). Resistance to the third-generation cephalosporins can be due to altered Pen A genes, leading to a mosaic-structure recombinant PBP2.

The production of beta-lactamase in gonococci is plasmid mediated (Elwell *et al*., 1977; Roberts and Falkow, 1977; Handsfield *et al*., 1989). This plasmid is usually similar to the TEM-1 produced by many Gram-negative bacilli (Bergström *et al*., 1978). Moreover, it can be transferred between gonococci and *E. coli* (Kirven and Thornsberry, 1977; Sparling *et al*., 1977). Plasmid-containing gonococcal strains can lose their plasmids and revert to Pen G susceptibility. Initially, there were two distinct types of beta-lactamase-producing *N. gonorrhoeae*. Most strains isolated in, or epidemiologically linked to, the Far East were relatively tetracycline resistant *in vitro*, and they carried a plasmid with a molecular weight of 4.5 megadaltons. Beta-lactamase-producing gonococci linked with West Africa and Europe were tetracycline sensitive, and they contained a smaller 3.2-megadalton plasmid. Over 50% of Far Eastern strains, but initially none of those from West Africa, also contained a 24.5-megadalton conjugative plasmid, which could transfer plasmids to other gonococci and to some other Gram-negative bacilli (Van Embden *et al*., 1980; Handsfield *et al*., 1982). This conjugative plasmid may have conferred a selective advantage on Far Eastern strains, and initially they probably spread more readily than those from West Africa (Perine *et al*., 1977). In 1980, there was a sharp increase in prevalence of infections caused by beta-lactamase-producing gonococci in the Netherlands; these were West Africa–type gonococci, which contained the 24.5-megadalton conjugative plasmid in addition to the 3.2-megadalton plasmid (Van Klingeren *et al*., 1983). Later, another type of penicillinase-producing gonococcus was identified. This was called the Toronto type and carried a 3.05-megadalton plasmid. This was first detected in several Canadian cities and provinces. Later it was also found in Taiwan and other Asian countries, and it might have originated there (Yeung *et al*., 1986; Chu *et al*., 1992). Furthermore, at least three more plasmids have been detected that are involved with beta-lactamase production in gonococci. These are the 2.9-megadalton Rio type, the 4.0-megadalton Nimes type, and the 6.0-megadalton New Zealand type (Van Embden *et al*., 1985; Brett, 1989; Chu *et al*., 1992). By the 1990s, most Pen G–resistant gonococci belonged to one of the following categories: beta-lactamase-producing *N. gonorrhoeae* possessing 2.9-, 3.05-, 3.2-, or 4.4-megadalton beta-lactamase plasmids; strains with plasmid-mediated high-level resistance to Pen G and tetracycline; and strains with chromosomally mediated resistance to Pen G and tetracycline (the 24.5-megadalton conjugative plasmid Tet-M) (Rice and Knapp, 1994a; Rice and Knapp, 1994b).

Over the past 25 years penicillin-resistant gonorrhoea has spread to virtually all countries with notable reports from Rwanda, Tanzania, South Africa, India, Bangladesh, Spain, China, Japan, Russia, Cuba, the UK, France, Denmark, Australia, New Zealand, Latin America, and the USA (Ison *et al*., 1986; Lind, 1990; Bogaerts *et al*., 1998; Divekar *et al*., 1999; Mbwana *et al*., 1999; Bhuiyan *et al*., 1999; Berrón *et al*., 2000; Wenling *et al*., 2000; Dillon *et al*., 2001; Bhatambare and Karyakarte, 2001; Elawad *et al*., 2002; Sosa *et al*., 2003; Bala *et al*., 2003; Herida *et al*., 2004; Heffernan *et al*., 2004; Annual report of Australian Gonococcal Surveillance Pro gramme, 2003; Tanaka *et al*., 2004; Kobenko *et al*., 2005; Dillon *et al*., 2006; De Jongh *et al*., 2007; Wang *et al*., 2007; Palmer *et al*., 2008; Tapsall *et al*., 2008). Most of the high-level resistance is due to beta-lactamase production.

Very recent studies have confirmed these findings (Unemo *et al*., 2016; Chen *et al*., 2016; Lahra *et al*., 2015; Zheng *et al*., 2015; Shimuta *et al*., 2015: Lee *et al*., 2015), and the history of gonococcal resistance emergence has been reviewed (Shigemura and Fujisawa, 2015).

### *NEISSERIA MENINGITIDIS*

The incidence of meningococcal strains that have developed some resistance to Pen G has increased (see Table 3.5), but such resistance has generally low levels such that Pen G remains the drug of choice for these serious infections, including meningococcal meningitis. Nevertheless, although meningitis caused by these strains still responds to Pen G, defervescence may be slower. If the MIC of the meningococcus is higher than 0.5 μg/ml, the disease may not respond to Pen G, and alternative therapy, such as ceftriaxone, cefotaxime, or even chloramphenicol may be needed (Buck, 1994; Woods *et al*., 1994). Relatively Pen G–insensitive meningococci have also been reported from many regions (Sutcliffe *et al*., 1988; Lopardo *et al*., 1993; Block *et al*., 1993; Buck, 1994; Jackson *et al*., 1994; Woods *et al*., 1994; Winterscheid *et al*., 1994; see Table 3.5).

## 3. MECHANISM OF DRUG ACTION

Pen G, similar to other beta-lactam agents, acts primarily on the bacterial cell wall, which is complex and unique to bacteria. Being relatively inelastic, it confers shape on the organism and protects it against damage due to osmotic pressure differences between the cell cytoplasm and the external environment (Koch, 1988). The cytoplasmic membrane lies immediately beneath the cell wall and is pressed up against it by osmotic forces within the cell. The cell wall and the cytoplasmic membrane together form the cell envelope. These component structures are interdependent, and alterations in one may render the other ineffective. The composition of the cell envelope, the complexity of which varies with different bacterial species, has an important role in modifying the action of antibiotics (Costerton and Cheng, 1975). Antibiotics act on protein synthesis within the cell or at a site within the envelope, so that they must pass through part or all of the envelope to reach their target.

In Gram-positive bacteria the major portion of the cell wall consists of a mucopeptide layer (also known as murein or peptidoglycan), which supports the cytoplasmic membrane. This mucopeptide layer consists of a giant molecule, constructed in the form of a net of polysaccharide strands,