news and views

Transferable drug resistance in the gonococcus

from J. R. Saunders

GONORRHOEA is currently the most prevalent human communicable bacterial disease. Despite the emergence of strains of the causative organism *Neisseria gonorrhoeae* (the gonococcus) with increasing resistance to penicillin, single high doses of this antibiotic have generally proved effective. The discovery last year of infections in Britain, the Far East and the USA which were refractory to this regimen has caused understandable alarm amongst clinicians (see for example, *Center for Disease Control Morbidity and Mortality Weekly Report* **25**, 261; 1976; Percival *et al.*, *Lancet* **ii**, 1379; 1976; Phillips *Lancet* **ii**, 656; 1976), and the current policy of treating gonorrhoea 'blind' with penicillin has therefore been questioned. The culprits for these recent outbreaks are highly penicillin-resistant gonococci producing the TEM β-lactamase (penicillinase). This enzyme is specified by the widely dispersed transposon A (TnA) and its acquisition by *N. gonorrhoeae* had been widely predicted. TnA is commonly located on R plasmids in the Enterobacteriaceae, *Pseudomonas aeruginosa* and *Haemophilus influenzae* and it seems probable that gonococci have acquired it by contact with one of these organisms.

Almost all gonococci so far studied contain a plasmid of about 2.5 Mdal which has no known function (see for example Mayer *et al. Infect. Immun.* **10**, 1974; Palchaudhuri *et al. Infect Immun.* **11**, 114; 1975). Some gonococcal strains contain an additional plasmid of about 25 Mdal (Stiffler *et al. J. Bact.* **122**, 1293; 1975). But so far all known antibiotic resistances in *N. gonorrhoeae* have been shown to be determined by chromosomal genes. Two groups working independently, Roberts and Falkow (this issue of *Nature*, page 630) and B. I. Eisenstein *et al.* (*Science* **195**, 998; 1977) now show that at least two species of β-lactamase plasmid exist in gonococci, one, from Far East strains, of about 4.4 Mdal, and one, from British strains, of about 3.2 Mdal, in addition to the resident cryptic plasmids. The origin of these resistance plasmids is not yet clear. They may have been received in entirety from other Gram negative bacteria, in particular from *H. influenzae*, which contains similar β-lactamase plasmids (de Graaf *et al. J. Bact.* **126**, 439; 1976). Alternatively they may have arisen by transposition of TnA to resident gonococcal plasmids. The 'donors' of TnA in this case could have been R plasmids which are capable of entering but not subsequently maintaining themselves in *N. gonorrhoeae*. Whatever mechanism is involved, the different plasmid complements of the British and Far East strains suggest that the TEM β-lactamase gene has been acquired by *N. gonorrhoeae* on at least two separate occasions. The 4.4 Mdal β-lactamase plasmid is widely distributed amongst gonococcal strains known to be different on the basis of their nutritional requirements (auxotypes). This implies that considerable interstrain transfer has occurred. It is well known that chromosomal antibiotic resistance markers can be transferred between gonococci by transformation, which is the only mechanism of genetic exchange so far reported in *N. gonorrhoeae*. However, Roberts and Falkow have found that covalently closed circular DNA of either type of β-lactamase plasmid cannot transform *N. gonorrhoeae*. This indicates that transformation plays no significant part in the dissemination between strains of the β-lactamase plasmids.

Roberts and Falkow, and Eisenstein *et al.* have now shown that the 4.4 Mdal β-lactamase plasmid can be transferred by conjugation to other gonococci, to *Neisseria flava* and to *Escherichia coli*. This plasmid is, however, too small to encode sex factor activity itself and only those strains which also carry the 25 Mdal cryptic plasmid can act as donors. The β-lactamase producing strains isolated in the UK, which all lack this larger plasmid, cannot therefore donate penicillin resistance to other bacteria. The 25 Mdal plasmid is thus apparently acting as a gonococcal sex factor and it is of interest that this plasmid has not yet been found in recipient bacteria which have acquired the β-lactamase plasmid from donor strains. This suggests that covalent linkage between the two plasmids is not necessary for transfer but it is not yet clear whether the gonococcal sex factor is totally incapable of transferring itself to other bacteria. However, similar mobilisation of non-self-transmissible plasmids by transfer factors is well documented in the Enterobacteriaceae. It will be of great interest to determine the molecular and genetic properties of this sex factor and whether it is of gonococcal origin.

The discovery of sex factor activity in the gonococcus has serious clinical and epidemiological implications. First, it increases the probability that more strains of *N. gonorrhoeae* will acquire genes for resistance to penicillins and other drugs. It also makes more likely the transfer of resistance genes to a close relative of the gonococcus, *N. meningitidis*, the causative agent of epidemic meningitis. Meningitis is more likely to be fatal than gonorrhoea and the situation is complicated by the fact that *N. meningitidis* is carried without ill effect in the throats of many healthy individuals. Transfer of β-lactamase genes to this organism could occur either directly from *N. gonorrhoeae*, from enteric bacteria, or from *H. influenzae*, also a common inhabitant of human throats and which can cause disease. Furthermore, *H. influenzae* has in recent years acquired both the TEM β-lactamase and the ability to conjugate. In contrast, however, the gonococcal sex factor could benefit research workers by providing a means of genetic transfer in addition to transformation for analysing the genetic determinants of pathogenicity in *N. gonorrhoeae*.

There is obviously a certain irony in the possession of sexuality by *N. gonorrhoeae*. If the gonococcal sex factor determines the synthesis of sex pili, these should provide adsorption sites on donor cells for male-specific bacteriophages. The possession by gonococci of their own venereal pathogens would indeed be divine justice. □