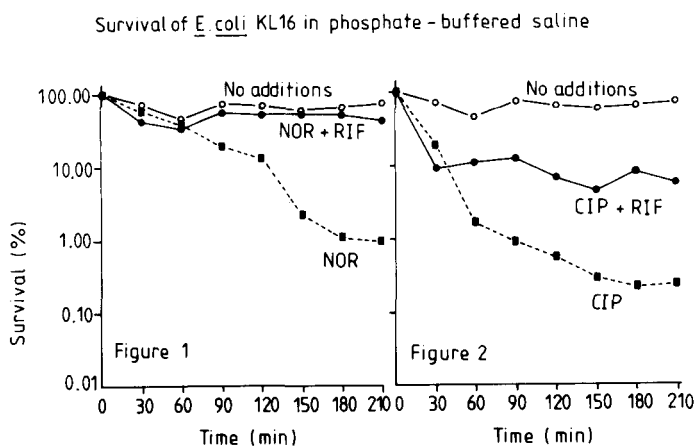


## DETECTION OF A THIRD BACTERIAL MECHANISM IN CIPROFLOXACIN AND OFLOXACIN

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The RNA synthesis inhibitor rifampicin (RIF) abolishes the bactericidal activity of nalidixic acid. It was proposed that nalidixic acid possesses only a single mechanism of action, termed A, which is found in all 4-quinolones and requires dividing bacteria capable of RNA and protein synthesis for its activity (Smith 1984). A different mechanism of action, termed B, which was first identified in ciprofloxacin (CIP) and ofloxacin, is resistant to RIF and does not require dividing bacteria (Ratcliffe and Smith 1984). Norfloxacin (NOR) was found to possess yet another mechanism, termed C, which despite being sensitive to RIF does not require dividing bacteria for its action (Ratcliffe and Smith 1985). Hence mechanism C can be differentiated from mechanism B using RIF with non-dividing bacteria, which have been prevented from multiplying by being suspended in phosphate-buffered saline.

It was decided to investigate if 4-quinolones exhibiting mechanism B also possess mechanism C. When a bacteriostatic concentration of RIF (160 µg/ml) was added to NOR (1.5 µg/ml) in phosphate-buffered saline, Figure 1 shows that the bactericidal activity of NOR against *E. coli* KL16 was abolished. This occurs because NOR's mechanism C requires RNA synthesis.



If CIP possesses only mechanism B, then it would be expected that the addition of RIF would have no effect on CIP's ability to kill non-dividing bacteria. Figure 2 shows that the addition of RIF (160 µg/ml) to CIP (0.15 µg/ml) in phosphate-buffered saline did reduce but did not abolish the ability of CIP to kill *E. coli* KL16. Therefore CIP possesses mechanism C which is inhibited by RIF, as well as mechanism B which is not inhibited by RIF.

When ofloxacin was investigated similar results to those obtained with CIP were observed in that RIF partially reduced but did not abolish ofloxacin's ability to kill non-dividing bacteria.

These results show that CIP and ofloxacin exhibit three distinct bactericidal mechanisms of action against *E. coli* KL16, whilst NOR possesses two mechanisms and nalidixic acid only one mechanism of action. This may help explain the difference in potency found among 4-quinolones.

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