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CC/NUMBER 23
JUNE 9, 1986

Richmond M H & Sykes R B. The β-lactamases of Gram-negative bacteria and their possible physiological role. *Advan. Microb. Physiol.* 9:31-88, 1973.
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The review first attempts a classification of beta-lactamases in gram-negative bacteria and then goes on to describe how the location of the enzyme in the microorganism may influence its ability to protect the bacterium from the killing action of some penicillins and cephalosporins. [The *SCI*® indicates that this paper has been cited in over 465 publications.]

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April 30, 1986

The springboard for the work discussed in this review was the purification of staphylococcal penicillinase, a task carried out in the early 1960s. Thereafter, for a while, things were deceptively straightforward. Staphylococcal penicillinase protected staphylococci that possessed it against the action of penicillin V and penicillin G because the enzyme was liberated into the environment surrounding the bacteria, with the consequence that the antibiotics were destroyed before they even reached their targets.

However, the mid-1960s saw ampicillin introduced into clinical use. This was the first beta-lactam with significant activity against gram-negative bacteria, notably *Escherichia coli*. That *E. coli* could produce beta-lactamase was clear from the earliest literature. Abraham and Chain, for example, reported the fact in 1940. But a quick look convinced me and others that the situation was much more complex than was the case with the staphylococci. For one thing, the enzyme was not liberated from gram-negative bacteria. Secondly, the enzyme had very different properties from those of the staphylococcal enzyme.

A further matter of interest was the observation that although *E. coli* beta-lactamase would destroy cephaloridine in the test tube, this cephalosporin was active against *E. coli* even when the bacteria possessed a beta-lactamase. So why didn't the enzyme protect?

The fact that the enzyme of *E. coli* was different from that of staphylococci led to a survey of the various different types of enzyme to be found in bacteria, and the first part of the review summarised what was known. The situation was further complicated by the fact that the Japanese and others were working in the same field, and it was extremely hard to reconcile their data with ours. The fact that it proved impossible to get their strains certainly didn't help either.

In fact, the classification we used in the review—although useful at the time—has now been superseded by others, notably one devised by my coauthor of the review, Richard Sykes. Nevertheless, it did serve a useful purpose at the time. First, it emphasised that there were many distinct types of beta-lactamase to be found in gram-negative bacteria; secondly, it showed that they fell into reasonably well-defined groups.

By far the more important part of the review presented for the first time in a substantial way the idea that the ability of a beta-lactamase to protect a bacterial cell against the killing effects of penicillins and cephalosporins was greatly influenced by its location in the bacterial cell. Basically, beta-lactams that penetrated the cell poorly were readily destroyed by the enzyme, while those that entered freely exerted their killing effect even though a potentially inactivating enzyme was present.

This observation and its suggested explanation have subsequently led to much work on the penetration of bacterial cells and the location of enzymes within the bacterial cell architecture, something crucial for the effective development of novel beta-lactam antibiotics.[1]

1. **Georgopapadakou N H & Sykes R B.** Bacterial enzymes interacting with beta-lactam antibiotics. (Demain A L & Solomon N A, eds.) *Handbook of experimental pharmacology.* Berlin: Springer-Verlag, 1983. Vol. 67. p. 1-77.

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