that one would expect an increasing bactericidal effect with increasing concentration.

In 1948 Eagle and Musselman noticed an in-vitro paradoxical effect of penicillin against streptococci and Staphylococcus aureus, i.e. a decrease instead of increase in bactericidal activity at concentrations well above the MBC. (Eagle & Musselman, 1948). Such paradoxical effects have also been observed with ampicillin and Streplococcus faecalis (Stille & Uffelman, 1973; Yourassowsky, Van der Linden & Schoutens, 1976) carbenicillin and Proteus mirabilis (Yourassowsky, Van der Linden & Schoutens, 1976) meccillinam and Providencia stuartii (Kerry, Hamilton-Miller & Brumfitt, 1976), ceftoxime and Staph. aureus and Pseudomonas aeruginosa (Shah, Troche & Stille, 1979) and aminoglycosides and Gram-negative bacilli (Lorian et al., 1979).

When studying penicillin in-vitro Eagle and his colleagues defined four 'effective' concentrations of the drug: (1) the lowest level, which reduces the rate of multiplication but does not kill a measurable proportion of the organisms; (2) a slightly higher concentration which is bactericidal for the susceptible organisms but does not kill the more resistant variants in the culture and therefore fails to sterilize the suspension; (3) at a somewhat higher concentration the drug kills all the organisms in a given suspension; (4) still higher concentration at which organisms are killed at a maximal rate and the rate is not effected by a further increase (Eagle, Fleischman & Musselman, 1950). To these four properties one should add the fifth property, namely the paradoxical effect. The 'sensitivity' of a bacterial strain—the MIC—would lie between the concentrations 2 and 3 and the level 1 would correspond to minimum active concentration (MAC) as defined by Lorian, Sabath & Simionesco and Shah & Stille in 1973.

Eagle and his co-workers could show, that the paradoxical in-vitro observation did correlate with an adverse effect in vivo (Eagle, Fleischman & Musselman, 1950). The dosage of 200 mg/kg penicillin given to mice infected with Group B β-haemolytic streptococci killed the organism more slowly than 3 mg/kg and considerably slower when compared with other organisms, such as Group A β-haemolytic streptococci, Type I and Type III pneumococci, all of which did not show paradoxical in-vitro effect. Similar observations were reported in studies on the recovery of bacteria from the toxic effects of penicillin (Eagle & Musselman, 1949). Group B β-haemolytic streptococci and Streptococcus faecalis exposed briefly to higher concentrations of penicillin required less time to recover from the toxic effects of penicillin than when they were exposed to lower concentrations for an equal period of time. Seven other strains (of six other species) did not show this effect. Eagle and his colleagues had suggested that 'in the therapeutic use of penicillin consideration must therefore be given to the fact that, with certain zonal strains the concentrations provided by sodium penicillin in ordinary therapeutic dosage may kill the organism at a greatly reduced rate, and that in order to effect cure treatment must then be continued for a longer aggregate period than would otherwise be necessary' (Eagle, Fleischman & Musselman, 1950).

So far, perhaps because of lower drug concentration at the site of infection, there is no evidence of an adverse effect of high dosage of antibiotics in the treatment of patients with infections caused by organisms with paradoxical in-vitro behaviour.

II. Comment and bibliography

During the past few decades there have been numerous reports of anomalous drug activity where the usual direct relationship between concentration of antibacterial compounds and inhibition of growth is reversed. The reports of this phenomenon constitute a miscellaneous collection and are often reported under titles that give no indication that the effect is described in the text. As it is most likely that further examples will be discovered and studied it has been thought worthwhile to collect and present the bibliography while it is yet of reasonably modest length. No attempt has been made to review the field in a formal way and discussion of it is restricted to a few pertinent comments.

The earliest observations were made by Eagle and his colleagues in their work on penicillin and these have been widely acknowledged by later workers; the term 'Eagle effect' has often been used to describe similar
phenomena reported since. Other early work that is however commonly overlooked is that done by Albert and his colleagues in their work on the antibacterial action of oxine (Albert et al., 1953). In describing the phenomenon the authors observed 'this is surely one of the most paradoxical effects yet demonstrated in the whole literature of disinfection'. These observations became incorporated in Albert's book on selective toxicity where the effect is referred to as 'concentration quenching'. Other terms used by subsequent workers have included 'anomalous', 'paradoxical', 'window', 'target', 'self-reversal' and 'skipped tube'. It is probably premature to suggest any universal term to describe these paradoxical effects.

The antimicrobial compounds involved in the effect include simple molecules such as silver nitrate as well as a range of antibiotics while the organisms that exhibit the effect are correspondingly varied. The zones have been shown by broth dilution, agar dilution and agar diffusion methods. It is important to emphasize that the reports cited here do not include those concerned with drug dependence or drug stimulation both of which, where demonstrated by agar diffusion methods, may be sometimes confused with the paradoxical zones.

Although the majority of the observations in this field have been concerned with in-vitro phenomena, some studies and numerous speculations have been made concerning their significance in vivo.

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References
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