414 Eur. J. Clin. Microbiol., October 1983, p. 414–425 Vol. 2, No. 5
0722-2211/83/05 0414-12$3.00/0

Review

Antibiotics and Phagocytosis

D. Milatovic

The influence of β-lactam antibiotics, tetracyclines, aminoglycosides, erythromycin and clindamycin on the phagocytosis process is reviewed. The results of the studies published are summarized in tabular form.

In the last 15 years antibiotic modulation of the phagocytosis process has become the subject of increased investigational activity. The published results are, however, to a large extent controversial thus rendering the evaluation of an antibiotic's effect on phagocytosis rather difficult. The studies are often hard to compare because of the variations in methods used for assessing leukocyte functions and the differences in experimental design, including the antibiotic concentrations tested and type of leukocytes and microorganisms used. The purpose of this review is to summarize, mainly in tabular form, the published data on the influence of some selected antibiotics on phagocytosis, enabling the reader to quickly survey the results in this area of research.

Table 1 gives information about which antibiotic concentration, which kind of leukocytes and which microorganism or particle the authors used in their test system. The interactions between antibiotics and the phagocytosis process investigated are arranged in four major groups:

- influence of antibiotics on chemotaxis,
- direct action of antibiotics on the phagocytic cell functions such as engulfment, killing and metabolic response,
- uptake and killing of bacteria altered by previous contact with antibiotics,
- intracellular penetration of the antibiotics and intracellular activity against phagocytized bacteria.

Institute for Medical Microbiology, Technical University Munich, Ismaninger Str. 22, 8000 Munich 80, FRG.

Chemotaxis, defined as the directed migration of leukocytes toward an attractant, is measured in vitro by two methods: the agarose technique and the Boyden chamber. The former is performed in semi-solid medium; the latter consists of two liquid filled compartments separated by a membrane. The open skin window is a variation of the latter method which enables measurement of chemotaxis in vivo. Besides the different methods used, there are other variables that may influence the chemotaxis results obtained by the investigators, as for example the choice of attractant (opsonized particles, bacterial products, activated complement, etc.) and the experimental design (assay performed in the presence of the antibiotic tested, preincubation of the leukocytes with the antibiotic, etc.). Nevertheless, some general tendencies in the published data regarding antibiotic modulation of chemotaxis emerge in the table. Tetracyclines and aminoglycosides seem to depress the chemotactic response of the leukocytes as described by the majority of the investigators. This negative effect was observed in vitro as well as in vivo. Beta-lactam antibiotics tend not to affect chemotaxis. Therapeutic concentrations of erythromycin and clindamycin also do not seem to influence chemotaxis.

The *phagocytic process* can be evaluated by various methods. The uptake rate of microorganisms or particles by leukocytes is most commonly calculated by counting the engulfed intracellular particles on a microscopic slide or by determining the intracellular radioactivity after phagocytosis of radiolabeled bacteria. Leukocyte killing of ingested bacteria is measured microbiologically by plating the surviving bacteria after various time intervals. As the

Table 1: Summary of results published on the influence of β-lactam antibiotics, tetracyclines, aminoglycosides, erythromycin and clindamycin on the phagocytosis process.

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested								
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular	
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Belsheim & Gnarpe (1)	penicillin	64,128	human PMN		0								
	ampicillin	64,128			0								
	mecillinam	64,128			0								
	cefuroxim	64,128			0								
	cefoxitin	64,128			0								
	cefotaxim	64,128			0								
	ceftazidim	64,128			0								
	ceftriaxone	64,128			0								
Forsgren & Schmeling (2)	penicillin	0.5–100	human PMN		0								
	ampicillin	0.5–100			0								
	cephalothin	0.5–100			0								
	cefazolin	0.5–100			0								
Cifarelli et al. (3)	penicillin	30	human MAC	zymosan	↑								
	ampicillin	4.5			↓								
	methicillin	8.1			↓								
	cephalothin	5.6			↓								
	cefazolin	13.1			↓								
Majeski et al. (4)	nafcillin	1, 10	human PMN		↑								
	nafcillin	100, 1000			↓								
	methicillin	1, 10			0								
	methicillin	100			↑								
	methicillin	1000			↓								
	oxacillin	1–1000			0								
	cephalothin	1, 10			0								
	cephalothin	100, 1000			↓								
Root et al. (5)	penicillin	10 × MIC	human PMN	*S. aureus*		0		0					
	penicillin	(0.75 U/ml)		candida			0						
	penicillin	1/4 MIC		*S. aureus*					0	↑	0		
Melby & Midtvedt (6)	cephalothin	30, 300	human PMN	*E. coli*		0							
Downey & Pisano (7)	penicillin	800	guinea-pig PMN	*S. aureus*		0							
Burgaleta et al. (8)	moxalactam	25–400	human PMN		0	0	0						

Table 1 (continued)

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested							
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration / Activity
Welch et al. (9)	penicillin	200	human PMN	zymosan				0				
				yeast		0	0					
	carbenicillin	200		zymosan				0				
	cefazolin	200		zymosan				0				
	cephaloridin	200		zymosan				0				
	ceforanide	200		zymosan				0				
	cefamandol	200		zymosan				0				
	ampicillin	2, 20		zymosan				0				
	ampicillin	200		zymosan				↓				
	ampicillin	200		yeast		↓	0					
	cephalothin	2		zymosan				0				
	cephalothin	20, 200		zymosan				↓				
	cephalothin	20, 200		yeast		0	↓					
	cephalexin	2, 20		zymosan				0				
	cephalexin	200		zymosan				↓				
	cephalexin	200		yeast		↓	0					
McDonald et al. (10)	penicillin	0.5 (10 × MIC)	human PMN	*S. aureus*						↑		
	amoxicillin	1.0 (10 × MIC)		*S. aureus*						↑		
	amoxicillin	30 (4 × MIC)		*E. coli*						↑		
	ampicillin	40 (4 × MIC)		*E. coli*						↑		
	cefoxitin	20 (4 × MIC)		*E. coli*						↑		
Horne & Tomasz (11)	penicillin	1/2 MIC	human PMN	B streptococci						↑		
	piperacillin	1/2 MIC								↑		
	methicillin	1/2 MIC								↑		
	cephaloridin	1/2 MIC								↑		
	cefadroxil	1/2 MIC								↑		
	cefoxitin	1/2 MIC								↑		
Lorian & Atkinson (12)	oxacillin	1/2, 1/4 MIC	human PMN	*S. aureus*					0	↓		
	nafcillin	1/2, 1/4 MIC							0	↓		
Gemmell & Abdul-Amir (13)	penicillin	1/2, 1/4 MIC	human PMN	A. streptococci	0				0		0	
				S. pneumoniae	0				0		0	
Friedman & Warren (14)	nafcillin	0.1 (subinh.)	mouse MAC	*S. aureus*					↑	↑		
	penicillin	subinh.							0	0		
	oxacillin	subinh.							0	0		
	methicillin	subinh.							0	0		

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Chemotaxis	Parameters tested							
						Phagocytic cell function			Antibiotic altered bacteria			Intracellular	
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Adam et al. (15)	ampicillin	0.05 (subinh.)	human MN	*L. monocytogenes*					↑				
Milatovic (16)	penicillin	1/3 MIC	human PMN	*S. aureus*					0				
	piperacillin	1/3 MIC							0				
	cefotiam	1/3 MIC							0				
Nishida et al. (17)	carbenicillin	1/4–1/16 MIC	rabbit PMN	*P. aeruginosa*						↑			
	sulbenicillin	1/4–1/16 MIC								0			
Alexander & Good (18)	penicillin	0.01–1000 U	human PMN	*S. aureus*						↑			0
Easmon (19)	penicillin	100, 200	human PMN	*S. aureus*								0	0
	cefazolin	50, 100										0	0
Jacobs et al. (20)	penicillin	4 ×, 10 ×, 40 × MBC	human PMN	*H. influenzae*								0	0
	ampicillin	4 ×, 10 ×, 40 × MBC										0	0
Mandell (21)	penicillin	0.01	human PMN	*S. aureus*								0	
Lobo & Mandell (22)	ampicillin	100	mouse MAC	*E. coli*									0
	ampicillin	100	human MAC										0
Mandell & Vest (23)	penicillin	100	human PMN	*S. aureus*									0
	methicillin	100											0
	cephalothin	100											0
Holmes et al. (24)	penicillin	100 U/ml	human PMN	*S. aureus*									0
Solberg (25)	penicillin	25–1000 U/ml	human PMN	*S. aureus*									0
Johnson et al. (26)	penicillin	10	rabbit MAC									0	
	cephalexin	10										0	
	cefamandol	10										0	
	cefazolin	10										0	
Cole & Brostoff (27)	penicillin	1.2	mouse MAC	*L. monocytogenes*									+
Veale et al. (28)	penicillin	2	human PMN	*N. gonorrhoeae*								+	+
	penicillin	2	human MN	*N. gonorrhoeae*								+	+

Table 1 (continued)

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested							
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Forsgren & Schmeling (2)	doxycycline	0.5–100	human PMN		↓								
	lymecycline	0.5–100			↓								
	tetracycline	0.5–100			↓								
Gnarpe et al. (29)	doxycycline	1	human PMN		0								
	doxycycline	10–100			↓								
	doxycycline	200 mg i.v.			↓								
	doxycycline	200/100/100 mg p.o./p. day			↓								
	lymecycline	1			0								
	lymecycline	10–100			↓								
	lymecycline	2 × 300 mg p.o./p. day			↓								
Martin et al. (30)	tetracycline	0.01–10	human PMN		↓								
	tetracycline	30–300			↑								
	tetracycline	1 g p.o.			↓								
	tetracycline	1, 300						0					
Majeski & Alexander (31)	tetracycline	10–1000	human PMN		↓								
	chlortetracycline	10–1000			↓								
	oxytetracycline	10–1000			↓								
	doxycycline	10–1000			↓								
	methacycline	10–1000			↓								
	demeclocycline	10–1000			↓								
	minocycline	10–1000			↓								
Gange (32)	tetracycline	2, 20, 200	human PMN		0								
Forsgren et al. (33)	doxycycline	0.5, 2.5, 10, 25	human PMN		↓								
	doxycycline	200/100/100 mg p.o./p. day			↓								
	lymecycline	0.5			0								
	lymecycline	2.5, 10, 25			↓								
	tetracycline	0.5, 2.5			0								
	tetracycline	10, 25			↓								
Gnarpe & Belsheim (34)	doxycycline	64, 128	human PMN	yeast	↓	↓							
	lymecycline	64, 128			↓	↓							

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested							
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Melby & Midtvedt (6)	oxytetracycline	10	human PMN	*E. coli*		0							
	oxytetracycline	100				↓							
Melby & Midtvedt (35)	oxytetracycline	10	rat PMN	*E. coli*		0							
	oxytetracycline	100				↓							
	doxycycline	10, 100				↓							
Melby & Midtvedt (36)	doxycycline	200/100/100 mg p. os/p. day	human PMN	*E. coli*		0							
	doxycycline	100 mg/kg/day	rat PMN			0							
Forsgren et al. (37)	doxycycline	1.6	human PMN	yeast		0							
	doxycycline	3.1–12.5				↓							
	tetracycline	1.6				0							
	tetracycline	3.1–12.5				↓							
	tetracycline	lg p. os				↓							
Munoz & Geister (38)	chlortetracycline	0.01–1000	human PMN	*S. albus*		↓							
Altura et al. (39)	tetracycline	12 mg/rat/day	rat PMN	colloidal carbon		↓							
Hoeprich & Martin (40)	tetracycline	0.01–1 μM/ml	human PMN	*S. aureus*		0	0						
Welch et al. (9)	doxycycline	2	human PMN	zymosan				0					
	doxycycline	20		zymosan				↓					
	doxycycline	20		yeast		0	↓						
	tetracycline	2, 20		zymosan				↓					
	tetracycline	5, 20, 200		yeast		0	↓						
Cifarelli et al. (3)	doxycycline	0.2	human MAC	zymosan		↑							
	tetracycline	0.4				↑							
Adam et al. (15)	tetracycline	0.05 (subinh.)	human MN	*L. monocytogenes*					↑				
Milatovic (16)	doxycycline	1/3 MIC	human PMN	*S. aureus*					↑				
Park & Dow (41)	tetracycline	10–500	human PMN									+	
	oxytetracycline	4 × 250 mg/die										+	
Johnson et al. (26)	tetracycline	10	rabbit MAC									+	

Table 1 (continued)

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested								
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular	
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Khan et al. (42)	gentamicin	1.25, 2.5 mg/kg i.m.	human PMN		↓								
	gentamicin	1			0								
	gentamicin	4–40			↓								
	amikacin	500 mg i.m.			↓								
Belsheim & Gnarpe (1)	gentamicin	64, 128	human PMN		↓								
	amikacin	64, 128			↓								
Forsgren & Schmeling (2)	gentamicin	0.5–100	human PMN		0								
	kanamycin	0.5–100			0								
Goodhart (43)	gentamicin	10	human PMN		↓								
	amikacin	20			↓								
Majeski et al. (4)	gentamicin	1–1000	human PMN		0								
Seklecki et al. (44)	gentamicin	0.5–8	human PMN		↓			0					
	tobramycin	0.5–8			↓			0					
	netilmicin	0.5–8			↓			0					
	amikacin	2–32			↓			0					
	kanamycin	2–32			↓			0					
Burgaleta et al. (8)	gentamicin	5–40	human PMN	candida	↓								
	gentamicin	10				0	0						
Melby & Midtvedt (6)	gentamicin	5, 100	human PMN	*E. coli*		↓							
Cifarelli et al. (3)	gentamicin	5.4	human MAC	zymosan		↑							
	tobramycin	2.7				↑							
	streptomycin	16.9				0							
Ferrari et al. (45)	gentamicin	5–40	human PMN	candida		↓							
	sisomycin	5–40				↓							
	tobramycin	5–40				↓							
	ribostamycin	5–40				↓							
	amikacin	5–40				↓							

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested								
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular	
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Welch et al. (9)	gentamicin	20	human PMN	candida		0	↓						
	gentamicin	20		zymosan				↓					
	kanamycin	20		zymosan				0					
	amikacin	20		zymosan				0					
	sisomicin	20		zymosan				0					
Horne & Tomasz (11)	gentamicin	1/2, 1 × MIC	human PMN	B streptococci						0			
Root et al. (5)	gentamicin	1/4 MIC	human PMN	*S. aureus*						0			
McDonald et al. (10)	gentamicin	4 × MIC	human PMN	*E. coli*						↑			
Nishida et al. (17)	gentamicin	1/4–1/64 MIC	rabbit PMN	*P. aeruginosa*						0			
	kanamycin	1/4–1/64 MIC								0			
Lobo & Mandell (22)	gentamicin	100	mouse MAC	*E. coli*									0
	gentamicin	100	human MAC										0
Mandell & Vest (23)	gentamicin	100	human PMN	*S. aureus*									0
	streptomycin	100											0
Easmon (19)	gentamicin	2.5	human PMN	*S. aureus*									0
	gentamicin	5, 10											+
Johnson et al. (26)	gentamicin	18	rabbit MAC									+	
Forsgren & Schmeling (2)	erythromycin	0.5–25	human PMN		0								
	erythromycin	100			↓								
Majeski et al. (4)	erythromycin	1–10	human PMN		0								
	erythromycin	100–1000			↓								
v. Rensburg et al. (46)	erythromycin	1–10 mM	human PMN	candida	↑	0							
		25 mM			0	0							
		50–100 mM			↓	0							
		4 × 250 mg/die p. os			0	0							
Melby & Midtvedt (35)	erythromycin	10, 100	rat PMN	*E. coli*		↓							

Table 1 (continued)

Authors	Antibiotic tested (mg/l)		Leukocytes	Microorganism or particle	Parameters tested								
					Chemotaxis	Phagocytic cell function			Antibiotic altered bacteria			Intracellular	
						Uptake	Killing	Metabolic response	Uptake	Killing	Metabolic response	Penetration	Activity
Melby & Midtvedt (6)	erythromycin erythromycin	10 100	human PMN	*E. coli*		0 ↓							
Welch et al. (9)	erythromycin	20, 200	human PMN	yeast		0	0	0					
McDonald et al. (10)	erythromycin	2.5 (10 × MIC)	human PMN	*S. aureus*						↑			
Gemmell & Abdul-Amir (13)	erythromycin	1/2, 1/4 MIC	human PMN	A streptococci B streptococci *S. pneumoniae*	0 0 0				0 ↑ 0		0 ↑ 0		
Johnson et al. (26)	erythromycin	18.4	rabbit MAC									+	
Forsgren & Schmeling (2)	clindamycin clindamycin	0.5–25 100	human PMN		0 ↓								
Gange (32)	clindamycin	1–100	human PMN		0								
Majeski et al. (4)	clindamycin clindamycin	1–100 1000	human PMN		0 ↑								
Welch et al. (9)	clindamycin	20, 200	human PMN	yeast		0	0	0					
McDonald et al. (10)	clindamycin	0.5 (10 × MIC)	human PMN	*S. aureus*						↑			
Gemmell et al. (47)	clindamycin	1/2, 1/4 MIC	human PMN	A streptococci					↑	↑			
Milatovic (16)	clindamycin	1/3 MIC	human PMN	*S. aureus*					↑				
Gemmell & Abdul-Amir (13)	clindamycin	1/2, 1/4 MIC	human PMN	A streptococci B streptococci *S. pneumoniae*	↑ 0 ↑				↑ ↑ ↑		↑ ↑ ↑		
Johnson et al. (26)	clindamycin	10	rabbit MAC									+	
Klempner & Styrt (48)	clindamycin clindamycin	1 10	human PMN	*S. aureus*								+ +	+

PMN = Polymorphonuclear leucocytes, MN = Monocytes, MAC = Macrophages.
↑ = Enhancement.
↓ = Depression.
0 = No effect.

phagocytosis process is accompanied by activation of the leukocyte metabolism, several tests are based on measurement of this metabolic response, for example the chemiluminescence assay, myeloperoxidase-mediated protein iodination, the nitroblue tetrazolium reduction test, etc. The same problems of comparability arise as already mentioned for the chemotaxis results, and are even more pronounced in studies on interaction between antibiotics and the phagocytosis process. Experiments conducted by leaving the antibiotic in the test system during the phagocytosis assay are hard to interpret since any antibiotic effect could be related to interaction between the antibiotic and any of the assay compounds and not necessarily the phagocytic cell.

The best conformity of results has been obtained in experiments with tetracyclines which seem to exert a negative influence on the phagocytic activity of the leukocytes. Beta-lactam antibiotics and erythromycin tend to have no effect. Data available on the influence of aminoglycosides on phagocytic cell function is conflicting and in the case of clindamycin there are not enough studies done to draw any conclusions.

Antibiotic exposed bacteria have been shown to undergo morphologic and biochemical changes (46). The question arises whether leukocytes act differently upon these altered bacteria compared to normal bacteria. Most of the investigators pretreated the bacteria with subinhibitory concentrations of the antibiotic tested; some used high concentrations but only very short incubation times. The results obtained in this kind of phagocytosis study mainly depend on the target microorganism chosen.

It appears that β-lactam antibiotics render certain bacterial species like *Staphylococcus aures, Escherichia coli* and group B streptococci more susceptible to leukocyte killing. The enhanced killing does not seem to be preceded by an increased uptake of these bacteria. Clindamycin treatment of the bacteria results in enhanced engulfment and subsequently killing by the leukocytes. Concerning the aminoglycosides, four studies have been done with gentamicin, but each with a different bacterial species. Thus, the enhanced killing of gentamicin treated *Escherichia coli* needs to be confirmed by other studies. There is also not enough data available on the effect of tetracyclines and erythromycin, but a tendency towards enhanced phagocytosis of bacteria exposed to these antibiotics can be recognized.

Intracellular penetration, and especially intact microbicidal activity of the antibiotics once they have penetrated the leukocytes, are important questions in terms of the fact that certain microorganisms, for example *Mycobacterium tuberculosis* and *Legionella pneumophila*, can survive and multiply inside the phagocytic cells.

Generally, radiolabeled antibiotics are used to determine the intracellular concentration. To establish whether the antibiotic is active intracellularly leukocytes containing ingested bacteria are incubated with the antibiotic tested and the number of intracellularly surviving bacteria is determined microbiologically.

Although not included in the table rifampin should be mentioned in this context because it is the only antibiotic for which penetration and bactericidal activity on phagocytized bacteria has been demonstrated uniformly by several authors (19, 21–23, 26). The majority of the numerous studies performed with β-lactam antibiotics were unable to document an intracellular effect of these antibiotics. Concerning the other antibiotics listed in the table, it is not possible to make a statement on whether these antibiotics also display bactericidal activity inside the phagocytic cells although an intracellular accumulation is described by a few investigators. Either there is no or not enough data available (tetracycline, erythromycin and clindamycin) or the findings are contradictory (aminoglycosides).

In conclusion it can be said that a survey of the literature dealing with the effect of antibiotics on the phagocytosis process leaves an impression of confusion. As long as the methods for testing the phagocytosis parameters are not standardized in any way, the problems of comparability and interpreation will remain although with time more studies on this subject will be performed thus making more data available. Nevertheless, at this point we have obtained some more or less obvious indications that certain antibiotics may influence phagocytosis negatively (tetracyclines and aminoglycosides) or positively in an indirect way by interacting with the microorganisms to be phagocytized (β-lactam antibiotics and clindamycin).

Although the clinical relevance of these results can only be presumed from the few in vivo studies performed (29, 30, 33, 36, 37, 39, 42) these possible side effects of antibiotics should not be ignored, especially in the treatment of immunocompromised patients.

References

1. **Belsheim, J. A., Gnarpe, G. H.:** Antibioticis and granulocytes. Direct and indirect effects on granulocyte chemotaxis. Acta Pathologica et Microbiologica Scandinavica (C) 1981, 89: 217–221.
2. **Forsgren, A., Schmeling, D.:** Effect of antibiotics on chemotaxis of human leukocytes. Antimicrobial Agents and Chemotherapy 1977, 11: 580–584.
3. **Cifarelli, A., Forte, N., Lombardi, L., Pepe, G., Paradisi, F.:** The effect of some antibiotics on phagocytic activity in vitro. Journal of Infection 1982, 5: 183–188.
4. **Majeski, J. A., McClellan, M. A., Alexander, J. W.:** Effect of antibiotics on the in vitro neutrophil chemotactic response. American Surgeon 1976, 42: 785–788.
5. **Root, R. K., Isturiz, R., Molavi, J. A., Metcalf, J. A., Malech, H. L.:** Interactions between antibiotics and human neutrophils in the killing of staphylococci (studies with normal and cytochalasin B-treated cells). Journal of Clinical Investigation 1981, 67: 247–259.
6. **Melby, K., Midtvedt, T.:** Effects of some antibacterial agents on the phagocytosis of ^{32}P-labelled *Escherichia coli* by human polymorphonuclear cells. Acta Pathologica et Microbiologica Scandinavica (B) 1980, 88: 103–106.
7. **Downey, R. J., Pisano, J. C.:** Some effects of antimicrobial compounds on phagocytosis in vitro. Journal of the Reticuloendothelial Society 1965, 2: 75–88.
8. **Burgaleta, C., Martinez-Beltran, J., Bouza, E.:** Comparative effects of moxalactam and gentamicin on human polymorphonuclear function. Antimicrobial Agents and Chemotherapy 1982, 21: 718–720.
9. **Welch, W. D., Davis, D., Thrupp, L. D.:** Effect of antimicrobial agents on human polymorphonuclear leukocyte microbicidal function. Antimicrobial Agents and Chemotherapy 1981, 20: 15–20.
10. **McDonald, P. J., Wetherall, B. L., Pruul, H.:** Postantibiotic leukocyte enhancement. Increased susceptibility of bacteria pretreated with antibiotics to activity of leukocytes. Reviews of Infectious Diseases 1981, 3: 38–44.
11. **Horne, D., Tomasz, A.:** Hypersusceptibility of penicillin-treated group B streptococci to bactericidal activity of human polymorphonuclear leukocytes. Antimicrobial Agents and Chemotherapy 1981, 19: 745–753.
12. **Lorian, V., Atkinson, B.:** Killing of oxacillin-exposed staphylococci in human polymorphonuclear leukocytes. Antimicrobial Agents and Chemotherapy 1980, 18: 807–813.
13. **Gemmell, C. G., Abdul-Amir, M. K.:** Antibiotic-induced changes in streptococci with respect to their interaction with human polymorphonuclear leukocytes. In: Nelson, J. D., Grassi, C. (ed.): Current chemotherapy and infectious disease. Volume II. American Society for Microbiology, Washington, D. C., 1980, p. 810–812.
14. **Friedman, H., Warren, G. H.:** Enhanced susceptibility of penicillin-resistant staphylococci to phagocytosis after in vitro incubation with low doses of nafcillin (38177). Proceedings of the Society for Experimental Biology and Medicine 1974, 146: 707–711.
15. **Adam, D., Schaffert, W., Marget, W.:** Enhanced in vitro phagocytosis by human monocytes in the presence of ampicillin, tetracyclin, and chlorampenicol. Infection and Immunity 1974, 9: 811–814.
16. **Milatovic, D.:** Effect of subinhibitory antibiotic concentrations on the phagocytosis of *Staphylococcus aureus*. European Journal of Clinical Microbiology 1982, 1: 97–101.
17. **Nishida, M., Mine, Y., Nonoyama, S., Yokota, Y.:** Effect of antibiotics on the phagocytosis and killing of *Pseudomonas aeruginosa* by rabbit polymorphonuclear leukocytes. Chemotherapy 1976, 22: 203–210.
18. **Alexander, J. W., Good, R. A.:** Effect of antibiotics on the bactericidal activity of human leukocytes. Journal of Laboratory and Clinical Medicine 1968, 71: 971–983.
19. **Easmon, C. S. F.:** Antibiotics and intracellular staphylococci. In: Jeljaszewicz, J. (ed.): Staphylococci and staphylococcal infections. Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene 1981, Supplement 10: 847–850.
20. **Jacobs, R. F., Wilson, C. B., Laxton, J. G., Hass, J. E., Smith, A. L.:** Cellular uptake and intracellular activity of antibiotics against *Haemophilus influenzae* type b. Journal of Infectious Diseases 1982, 145: 152–159.
21. **Mandell, G. L.:** Interaction of intraleukocytic bacteria and antibiotics. Journal of Clinical Investigation 1973, 52: 1673–1679.
22. **Lobo, M. C., Mandell, G. L.:** The effect of antibiotics on *Escherichia coli* ingested by macrophages. Proceedings of the Society for Experimental Biology and Medicine 1973, 142: 1048–1050.
23. **Mandell, G. L., Vest, T. K.:** Killing of intraleukocytic *Staphylococcus aureus* by rifampicin. In vitro and in vivo studies. Journal of Infectious Diseases 1972, 125: 486–490.

24. **Holmes, B., Quie, P. G., Windhorst, D. B., Pollara, B., Good, B. A.:** Protection of phagocytized bacteria from the killing action of antibiotics. Nature 1966, 210: 1131–1132.
25. **Solberg, C. O.:** Proctection of phagocytized bacteria against antibiotics. Acta Medica Scandinavica 1972, 191: 383–387.
26. **Johnson, J. D., Hand, W. L., Francis, J. B., King-Thompson, N., Corwin, R. W.:** Antibiotic uptake by alveolar macrophages. Journal of Laboratory and Clinical Medicine 1980, 95: 429–439.
27. **Cole, P., Brostoff, J.:** Intracellular killing of *Listeria monocytogenes* by activated macrophages (Mackaness system) is due to antibiotic. Nature 1975, 256: 515–517.
28. **Veale, D. R., Finch, H., Smith, H.:** Penetration of penicillin into human phagocytes containing *Neisseria gonorrhoeae*. Intracellular survival and growth at optimum concentrations of antibiotic. Journal of General Microbiology 1976, 95: 353–363.
29. **Gnarpe, H., Belsheim, J., Persson, S.:** Tetracycline interference with leukocyte chemotaxis in vitro and in vivo. Infection 1978, 6, Supplement 1: 98–101.
30. **Martin, R. R., Warr, G. A., Couch, R. B., Yeager, H., Knight, V.:** Effects of tetracycline on leukotaxis. Journal of Infectious Diseases 1974, 129: 110–116.
31. **Majeski, J. A., Alexander, J. W.:** Evaluation of tetracyclin in the neutrophil chemotactic response. Journal of Laboratory and Clinical Medicine 1977, 90: 259–265.
32. **Gange, R. W.:** Neutrophil chemotaxis in the presence of antibiotics. A reevaluation using an agarose technique. British Journal of Dermatology 1980, 103: 51–59.
33. **Forsgren, A., Banck, G., Beckman, H., Bellahsene, A.:** Antibiotic-host defence interactions in vitro and in vivo. Scandinavian Journal of Infectious Diseases 1980, Supplement 24: 195–203.
34. **Gnarpe, H., Belsheim, J.:** Direct and indirect effects of antibiotics on granulocyte activity. Journal of Antimicrobial Chemotherapy 1981, 8, Supplement C: 71–78.
35. **Melby, K., Midtvedt, T.:** The effect of eight antibacterial agents on the phagocytosis of ^{32}P-labelled *Escherichia coli* by rat polymorphonucelar cells. Scandinavian Journal of Infectious Diseases 1977, 9: 9–12.
36. **Melby, K., Midtvedt, T.:** Studies on the phagocytic activity of human and rat polymorphonuclear cells exposed to doxycycline in vivo. Chemotherapy 1981, 27: 452–458.
37. **Forsgren, A., Schmeling, D., Quie, P. G.:** Effect of tetracycline on the phagocytic function of human leukocytes. Journal of Infectious Diseases 1974, 130: 412–415.
38. **Munoz, J., Geister, R.:** Inhibition of phagocytosis by aureomycin. Proceedings of the Society for Experimental Biology and Medicine 1950, 75: 367–370.
39. **Altura, B. M., Hershey, S. G., Ali, M., Thaw, G.:** Influence of tetracycline on phagocytosis, infection, and resistance to experimental shock. Relationship to microcirculation. Journal Reticuloendothelial Society 1966, 3: 447–457.
40. **Hoeprich, P. D., Martin, C. H.:** Effect of tetracycline, polymyxin B, and rifampin on phagocytosis. Clinical Pharmacology and Therapeutics 1970, 11: 418–422.
41. **Park, J. K., Dow, R. C.:** The uptake and localization of tetracycline in human blood cells. British Journal of Experimental Pathology 1970, 51: 179–182.
42. **Khan, A. J., Evans, H. E., Glass, L., Chang, C. T., Nair, S. R.:** Abnormal neutrophil chemotaxis and random migration induced by aminoglycoside antibiotics. Journal of Laboratory and Clinical Medicine 1979, 93: 295–300.
43. **Goodhart, G. L.:** Effect of aminoglycosides on the chemotactic response of human polymorphonuclear leukocytes. Antimicrobial Agents and Chemotherapy 1977, 12: 540–542.
44. **Seklecki, M. M., Quintilliani, R., Maderazo, G. G.:** Aminoglycoside antibiotics moderately impair granulocyte function. Antimicrobial Agents and Chemotherapy 1978, 13: 552–554.
45. **Ferrari, F. A., Pagani, A., Marconi, M., Stefanoni, R., Siccardi, A. G.:** Inhibition of candidacidal activity of human neutrophil leukocytes by aminoglycoside antibiotics. Antimicrobial Agents and Chemotherapy 1980, 17: 87–88.
46. **Lorian, V.:** Effects of subminimum inhibitory concentrations of antibiotics on bacteria. In: Lorian, V. (ed.): Antibiotics in laboratory medicine. Williams and Wilkins, Baltimore, 1980, p. 342–408.