PIPERACILLIN (T-1220), A NEW SEMISYNTHETIC PENICILLIN: *IN VITRO* ANTIMICROBIAL ACTIVITY COMPARISON WITH CARBENICILLIN, TICARCILLIN, AMPICILLIN, CEPHALOTHIN, CEFAMANDOLE AND CEFOXITIN

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Piperacillin (T-1220) is a new semisynthetic penicillin with an unusually broad spectrum of antimicrobial activity. *In vitro* comparisons of this drug with 6 other beta-lactam antimicrobics (ticarcillin, carbenicillin, ampicillin, cephalothin, cefamandole and cefoxitin) were conducted. These included minimal inhibitory concentrations (MIC) against 394 bacterial isolates, the minimal lethal concentrations (MLC) against 79 of those, as well as the effect of inoculum size on the MIC and MLC of the drugs. Piperacillin had significantly greater activity than did the other penicillins against *Pseudomonas* species and *Klebsiella pneumoniae*. Against *P. aeruginosa* piperacillin was 8- and 16-fold more active than ticarcillin and carbenicillin, respectively. The MLC of piperacillin rarely differed from the MIC by more than one $\log_2$ dilutions except against *P. aeruginosa* in which the MLC was 4-fold greater or more than the MIC of 45% of isolates tested. Ticarcillin, carbenicillin and cefoxitin showed minimal inoculum size effects. Cefamandole results showed the greatest inoculum size variation with 55% and 37% of isolates showing an 8-fold increase in MIC and MLC respectively by increasing inoculum from 10^5 to 10^7 CFU/ml. Piperacillin was intermediately effected having 25% of strains >8-fold increase in MIC.

Piperacillin, sodium 6-[D(−)-α(4-ethyl-2,3-dioxo-1-piperazinylcarbonylamino)-α- phenylacetamido] penicillinate, is a new semisynthetic penicillin derived from aminobenzyl-penicillin (Fig. 1). This compound formerly known as T-1220, has potent antibacterial activity against bacterial species previously refractory to such related compounds as carbenicillin and ticarcillin. In addition, favorable pharmacokinetics and infection studies have been reported in humans and in experimental animals (abstracts 349 and 350, Sixteenth Interscience

Conference on Antimicrobial Agents and Chemotherapy, Chicago, 1976). This *in vitro* investigation directly compares the antimicrobial activity of piperacillin with that of related semisynthetic penicillins carbenicillin, ticarcillin, and ampicillin, plus three reference cephalosporins—cephamycins, cephalothin, cefamandole and cefoxitin.

Materials and Methods

Antibiotics:

The beta-lactam antimicrobic laboratory standard powders were supplied by the following pharmaceutical companies: Piperacillin from Lederle Laboratories, Pearl River, New York; cefamandole and cephalothin from Eli Lilly & Company, Indianapolis, Indiana; cefoxitin from Merck Sharp & Dohme, Rahway, New Jersey; carbenicillin and ticarcillin from Beecham Laboratories, Bristol, Tennessee; and ampicillin from Bristol Laboratories, Syracuse, New York.

Organisms:

A total of 394 bacterial isolates were contributed by the collaborating laboratories for this study. These include 149 strains of the *Enterobacteriaceae*, 160 strains of non-enterobacteriaceae gram-negative bacilli, and 85 strains of gram-positive cocci. They were further subdivided into the following genus and species categories: 29 *Escherichia coli*, 25 *Klebsiella pneumoniae*, 24 *Enterobacter* species, 27 indole-positive *Proteus* species, 24 *Proteus mirabilis*, 20 *Serratia* species, 108 *Pseudomonas aeruginosa*, 10 *Pseudomonas cepacia*, 6 *Pseudomonas fluorescens-putida*, 10 *Pseudomonas maltophilia*, 4 *Pseudomonas stutzeri*, 11 *Acinetobacter anitratus*, 11 *Aeromonas hydrophila*, 30 *Staphylococcus aureus* (10 methicillin-resistant), 15 *Streptococcus faecalis*, 20 *Streptococcus pneumoniae* and 20 *Streptococcus pyogenes*.

Most of the isolates were tested in duplicate by two of the collaborating laboratories (Center for Disease Control and the Sacramento Medical Center) in a manner previously reported.[1,2] A third laboratory, Kaiser Foundation, also tested a more limited number (MLCs and inoculum size studies). No significant variation in MIC results were encountered between these participating laboratories.

Antimicrobic Susceptibility Testing:

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method. MUELLER-HINTON broth was commercially dispensed in a single lot of plastic trays (Micro Media Systems, San Jose, California) and distributed to the testing laboratories. The trays were stored at $-60°C$ until inoculated. Prior to use the trays were thawed at room temperature (approximately 20~30 minutes) and inoculated with disposable inoculators delivering 5 μl to each well.

At all three laboratories, a logarithmic phase broth culture was diluted to match the turbidity of a 0.5 MACFARLAND standard. The suspension was then diluted 1: 50 in sterile water containing 0.02% Tween 80 and dispensed as described earlier. Final inoculum achieved was 1×10^5 colony forming units (CFU) per ml. For the testing of the fastidious streptococci including *S. pyogenes* and *S. pneumoniae*, the inoculum was standardized in MUELLER-HINTON broth containing 5% lysed rabbit blood and 0.1 ml of this adjusted cell suspension was added to each microdilution well, giving a final concentration of 1×10^5 CFU/ml.

The MIC was recorded as the lowest concentration totally inhibiting bacterial growth (clear well), after approximately 18 hours of incubation at 35°C in a forced air incubator. Occasionally, visible growth occurred in concentrations 1~2 wells above the MIC (the skipped-tube phenomenon).

Minimum lethal concentrations were determined for 79 organisms from seven genera by subculturing 5 μl from each microdilution well. The 5 μl subcultures were transferred to trypticase soy agar with 5% sheep blood. The subcultures were made with multiple inoculum replicator onto a 150×100 mm plate. After 48 hours of incubation, the endpoints were read as the lowest concentration yielding no more than 0.1% survivors (99.9% kill).

The effect of varying the inoculum concentrations on MIC-MLC endpoints was studied on 79 rapid growing facultative anaerobes. Trays were inoculated to achieve final concentrations of 10^3, 10^5, and 10^7 CFU/ml. MICs and MLCs were interpreted as described above.

Results

MIC Comparisons

Table 1 summarizes the cumulative percentage susceptibility results for five bacterial species to increasing concentrations of piperacillin and six other beta-lactam antibiotics. These species were grouped for tabulation because of the bimodal distribution of susceptible bacterial populations. Piperacillin is the most active semisynthetic penicillin against the four *Enterobacteriaceae* species tested. At clinically achievable serum levels piperacillin would inhibit 74~92% of the species tested compared to 36~79% for carbenicillin or ticarcillin and 0~72% for ampicillin. Most noteworthy is the piperacillin activity versus *Klebsiella pneumoniae* where piperacillin inhibits 92% at 64 μg/ml in contrast to 36% at 128 μg/ml for carbenicillin/ticarcillin and 0% at 8 μg/ml of ampicillin. This activity is comparable to that of reference cephalosporin cephalothin (88% at 8 μg/ml) and second generation cephalosporins, cefamandole (92% at 8 μg/ml) and cefoxitin (96% at 4 μg/ml). The latter two compounds possess favorable *in vitro* characteristics as compared to currently available cephalosporin C derivatives[1,2,3]. However, piperacillin also incorporates these features with broader coverage within both *Enterobacter* species and indole-positive *Proteus* species.

Species variation in susceptibility was encountered among the indole-positive *Proteus* species. Piperacillin, carbenicillin and ticarcillin had comparable inhibitory effects against this genus subgroup. Ampicillin and cephalothin are ineffective and cefoxitin is the most active against *Pr. rettgeri* and *Pr. vulgaris*. Cefamandole activity would rank *Pr. rettgeri* > *Pr. morganii* > *Pr. vulgaris* as previously reported.[1,2,3]

Like the second generation cephalosporins, piperacillin had decreased activity against staphylococcal species[1~5]. All methicillin-sensitive *S. aureus* isolates were inhibited by 128 μg/ml of carbenicillin and ticarcillin compared to 85% at 64 μg/ml of piperacillin. Of note is the overlap of MICs of piperacillin and ampicillin against penicillinase-producing and deficient strains in contrast to carbenicillin and ticarcillin which show a clear bimodal distribution of the two groups. Cephalothin was most active among the cephalosporins confirming prior reports[4,5].

The median MIC values for piperacillin and six other beta-lactams against five other isolates are presented in Table 2. These five bacterial species have unimodal narrow susceptibility ranges to beta-lactam antibiotics. All seven antibiotics were effective against *Proteus mirabilis*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Piperacillin was the most active against *Serratia* species with a median MIC of 1 μg/ml. Ampicillin and the three cephalosporins had median MICs ≥ 16 μg/ml. Piperacillin was 8-fold more active than carbenicillin and ticarcillin against *S. faecalis*. Only ampicillin was more active (median MIC = 1 μg/ml) with the cephalosporins medians well above clinically achievable concentrations.

The susceptibility expressed as median MICs of non-enterobacteriaceae gram-negative bacilli are shown in Table 3. Only piperacillin was active against all *Pseudomonas* species tested. Piperacillin was 8~16 times more active than ticarcillin and carbenicillin against *Ps. aeruginosa*, 128~256 times against *Ps. cepacia*, 32 times against *Ps. fluorescence-putida*, 4~8 times against *Ps. stutzeri* and equally inhibitory versus *Ps. maltophilia*. Ticarcillin was one $\log_2$ dilution more active than carbenicillin against *Ps. aeruginosa* confirming prior reports[6,7].

Acinetobacter anitratus isolates were only inhibited by clinically achievable concentrations of piperacillin, carbenicillin and ticarcillin. There was a marked susceptibility variation for *Aeromonas*

Table 1. Cumulative percentage susceptibility of five bacterial species (135 organisms) to increasing concentrations of piperacillin and six other beta-lactam antibiotics.

Organism (#)	Anti-biotic	Cumulative % inhibited @ MIC (μg/ml) of									
		≤0.5	1	2	4	8	16	32	64	128	256
E. coli (29)	PIPER	34	72		79	86	90		93	97	
	CARB		7	28	52	69	79				
	TICAR		17	48	69	76		79			
	AMPI	3	17	55	69	72			86	90	
	CEPHA			10	41	72		86	93		
	CEFAM	72	76		93	97	100				
	CEFOX		14	59	79	90	97		100		
Enterobacter species[a] (24)	PIPER	4	21	63	75	83	88		92	96	
	CARB			4	46	54	58	63	71	75	79
	TICAR			33	54	58		63	67	71	83
	AMPI				4	8	13	17	33	58	71
	CEPHA		4	8		21		25	29	38	46
	CEFAM	17	46	67	71	83		88		92	
	CEFOX			8	17	25				33	54
Klebsiella pneumoniae (25)	PIPER			12	56	80	84	88	92	96	
	CARB								4	36	64
	TICAR								20	36	64
	AMPI						24	40	80	84	
	CEPHA		4	48	80	88	92	96	100		
	CEFAM	40	72	80	88	92	96	100			
	CEFOX		8	72	96				100		
Proteus species[b] (27) Indole-positive	PIPER	52	63	67				70	74		85
	CARB	15	44	48	56	67	70		78		
	TICAR	19	37	41	52	56	67	74	78		81
	AMPI		4	7		11			22	48	63
	CEPHA		4					11	15	19	30
	CEFAM	19	22	37	44	48	58	74	78		85
	CEFOX	4	15	37	52	85	93	96		100	
Staphylococcus aureus (20) Methicillin-sensitive	PIPER	20	25	35	45	50	60		85	95	100
	CARB	20	25		50	75	95	100			
	TICAR	25			50	80	95	100			
	AMPI	25	35	45	55	60		70	90	100	
	CEPHA	95		100							
	CEFAM	55	90	100							
	CEFOX			20	95		100				
Staphylococcus aureus (10) methicillin-resistant	PIPER								10		50
	CARB								20	90	100
	TICAR								20	90	100
	AMPI						10		30	100	
	CEPHA			30	90	100					
	CEFAM				80	100					
	CEFOX						70	100			

a. Includes *Enterobacter cloacae* (10), *Enterobacter aerogenes* (8) and *Enterobacter agglomerans* (6).
b. Includes *Proteus morganii* (12), *Proteus rettgeri* (9), *Proteus vulgaris* (6).

hydrophila to the seven antimicrobics with cefamandole and piperacillin being most active.

Among the 108 *Ps. aeruginosa* isolates tested, several strains were resistant (≥8 μg/ml) to gentamicin and/or tobramycin. These 14 isolates and the sensitive strains of *Ps. aeruginosa* are shown in Table 4. Increased resistance to the aminoglycosides was accompanied by increased resistance to the semisynthetic penicillins *e.g.* piperacillin, carbenicillin and ticarcillin. Only the piperacillin MICs remained at or below clinically achievable concentrations for these gentamicin resistant and gentamicin-tobramycin resistant strains.

MIC-MLC Comparisons

The MLC/MIC ratios for piperacillin, ticarcillin and carbenicillin are shown in Table 5. Only 2

Table 2. Median MIC concentrations (μg/ml) of selected bacterial species having unimodal population distributions to piperacillin and six other beta-lactam antibiotics.

Antibiotic	*Proteus mirabilis* (24)[a]	*Serratia* species (20)	*Streptococcus*		
			faecalis (15)	*pneumoniae* (20)	*pyogenes* (20)
Piperacillin	≤0.5	1.0	4.0	≤0.25	≤0.25
Carbenicillin	≤0.5	4.0	32	≤0.25	≤0.25
Ticarcillin	≤0.5	4.0	32	≤0.25	≤0.25
Ampicillin	1.0	32	1.0	≤0.25	≤0.25
Cephalothin	2.0	>256	32	≤0.25	≤0.25
Cefamandole	≤0.5	32	32	≤0.25	≤0.25
Cefoxitin	2.0	16	>256	1.0	0.5

a. Number of isolates tested.

Table 3. Median MIC concentrations (μg/ml) for non-Enterobacteriaceae gram-negative bacilli including 138 isolates of *Pseudomonas* species to piperacillin and six other beta-lactam antibiotics.

Antibiotic	*Pseudomonas*					*Acinetobacter anitratus*	*Aeromonas hydrophila*
	aeruginosa (108)[a]	*cepacia* (10)	*fluorescens-putida* (6)	*maltophilia* (10)	*stutzeri* (4)	(11)	(11)
Piperacillin	2.0	1.0	8.0	8.0	≤0.5	8.0	2.0
Carbenicillin	32	256	>256	8.0	4.0	8.0	256
Ticarcillin	16	128	256	8.0	2.0	4.0	128
Ampicillin	>256	>256	128	>256	≤0.5	16	>256
Cephalothin	>256	>256	>256	>256	256	256	256
Cefamandole	>256	>256	>256	64	32	16	1.0
Cefoxitin	>256	64	>256	64	8.0	32	8.0

a. Number of isolates tested

Table 4. Relationship of piperacillin, carbenicillin and ticarcillin MIC values in *Pseudomonas aeruginosa* isolates having aminoglycoside resistance.

Aminoglycoside susceptibility	No. Tested	Median(range) MIC in μg/ml;		
Gentamicin / Tobramycin		Piperacillin	Ticarcillin	Carbenicillin
Sensitive / Sensitive	94	2.0(≤0.5~128)	16(≤0.5~>256)	32(≤0.5~>256)
Resistant / Sensitive	6	32(8~64)	256(64~>256)	256(128~>256)
Resistant / Resistant	8	64(16~256)	>256(128~>256)	>256(256~>256)

a. Sensitive is = or less than 4 μg/ml to both aminoglycosides tested in cation supplement MUELLER-HINTON broth.

of 79 organisms (3%) had MLC values more than 8-fold higher than the piperacillin MIC. These included single strains of *Proteus morganii* and *Pseudomonas aeruginosa*. Ticarcillin had the most with 3/79 and carbenicillin the least with 1/79. MLC/MIC ratios were also determined for ampicillin, cephalothin, cefamandole and cefoxitin. Cefamandole demonstrated the widest variation between inhibitory and cidal endpoints confirming previous reports[1,2]. Seventeen percent of MLCs were >8-fold greater than cefamandole MICs. Nearly all of these were *Enterobacter* species, indole-positive *Proteus* species and *Serratia*. Cefoxitin had ratios similar to piperacillin and superior to other cephalosporins[1,2].

Inoculum Size MIC-MLC Comparisons

The effects of inoculum size on MIC and MLC results were studied on 79 organisms at 10^3, 10^5,

Table 5. MIC-MLC comparison of piperacillin, carbenicillin and ticarcillin for 79 organisms @ 10^5 CFU/ml inoculum size.

Organism (#)	Antibiotic	MLC/MIC ratios			
		1	2	4	8 or more
E. coli (10)	Piperacillin	8	1	1	0
	Ticarcillin	8	1	1	0
	Carbenicillin	8	2	0	0
Klebsiella pneumoniae (10)	Piperacillin	8	2	0	0
	Ticarcillin	8	2	0	0
	Carbenicillin	5	5	0	0
Enterobacter species[a] (10)	Piperacillin	8	1	1	0
	Ticarcillin	10	0	0	0
	Carbenicillin	4	5	1	0
Proteus mirabilis (10)	Piperacillin	10	0	0	0
	Ticarcillin	10	0	0	0
	Carbenicillin	10	0	0	0
Indole-positive *Proteus* species[b] (10)	Piperacillin	7	1	1	1
	Ticarcillin	6	2	1	1
	Carbenicillin	5	4	0	1
Serratia marcescens (10)	Piperacillin	6	3	1	0
	Ticarcillin	5	1	3	1
	Carbenicillin	4	3	3	0
Pseudomonas aeruginosa (9)	Piperacillin	2	3	3	1
	Ticarcillin	4	3	1	1
	Carbenicillin	1	4	4	0
Staphylococcus aureus (10)	Piperacillin	6	3	1	0
	Ticarcillin	9	0	1	0
	Carbenicillin	10	0	0	0

a. Includes five strains each of *Ent. aerogenes* and *Ent. cloacae*.
b. Includes *Proteus morganii* (5), *Proteus rettgeri* (3) and *Proteus vulgaris* (2).

and 10^7 colony forming units/ml (Table 6). Only those organisms (listed in Table 5) not having off-scale MIC values were tabulated. Lower numbers of cefamandole MIC and MLC were noted due to a large incidence of ≤ 0.5 μg/ml MIC-MLC values among the *Enterobacteriaceae* in addition to >256 μg/ml MIC-MLC against *Ps. aeruginosa, Serratia* and some *Proteus* species.

Ticarcillin, carbenicillin and cefoxitin showed minimal variation (increase) in MIC or MLC when the inoculum was raised from 10^3 to 10^5 CFU/ml and 10^5 to 10^7 CFU/ml. Ninety-two to 100% of the endpoints were ≤ 3 $\log_2$ dilutions. Piperacillin was similar to the above agents at $10^3 \sim 10^5$ CFU/ml, but had 24~25% of MIC-MLC results markedly altered (>8-fold increase) by inoculum increases to 10^7 CFU/ml. Nearly all isolates having piperacillin susceptibility inoculum effect were *Klebsiella pneumoniae* (mean MIC-MLC increase = 64-fold). Cefamandole MICs and MLCs were markedly increased by raising inoculum

Table 6. Percent of isolates having MIC or MLC results within 3 $\log_2$ dilutions (≤ 8 fold increase) after increasing the inoculum concentration 10^2 CFU/ml for piperacillin, ticarcillin, carbenicillin, cefamandole and cefoxitin.

Antibiotic (#)	$10^3 \sim 10^5$ CFU/ml[a]		$10^5 \sim 10^7$ CFU/ml[b]	
	MIC	MLC	MIC	MLC
Piperacillin (48)	94	97	76	75
Ticarcillin (51)	98	94	92	92
Carbenicillin (54)	100	98	96	98
Cefamandole (24)	100	62	45	63
Cefoxitin (68)	98	95	96	96

a. Comparison of MIC and MLC results at 10^5 CFU/ml inoculum concentration compared to those at 10^3 CFU/ml.
b. Comparison of MIC and MLC results at 10^7 CFU/ml inoculum concentration compared to those at 10^5 CFU/ml.

concentrations. From 38 to 55% of the strains tested had cefamandole MIC-MLCs showing increases of >8-fold with several isolates MLC 32- to 128-fold higher at 10^7 CFU/ml.

Discussion

Piperacillin (T-1220) belongs to the semisynthetic group of penicillins and is structurally similar to ampicillin. More extensive α-substitutions have provided this compound with a broad antimicrobial spectrum that includes gram-positive and gram-negative bacteria, especially *Pseudomonas, Klebsiella, Serratia, Proteus* and *Enterococci.* The compound is poorly absorbed orally, but high serum concentrations are achieved by parenteral routes.

Other new semisynthetic penicillins that most resemble piperacillin are BL-P1654 (Bristol), PC-904 (Sumitomo) and pirbenicillin (CP-33,994-2, Pfizer). All of these antimicrobics have antipseudomonas activity 8- to 16-fold that of carbenicillin[8~10]. However, each has one or more disadvantages when compared to piperacillin. BL-P1654 is adversely affected by both serum and increased inoculum concentrations, has a limited spectrum versus all *Proteus* species and lastly is toxic to some animal species[11]. PC-904 also is less active than piperacillin against *Proteus mirabilis*, the indole-positive *Proteus* species and *Serratia* species[9]. Like PC-904, pirbenicillin has little activity on *Proteus* species and is significantly more protein bound than piperacillin[10]. Piperacillin compared to carbenicillin and ticarcillin had a wider antimicrobial spectrum and increased activity, particularly against *Pseudomonas* species, *Serratia* and *Klebsiella pneumoniae*. Like the new cephalosporins, piperacillin showed excellent inhibitory activity against *Enterobacter* species and indole-positive *Proteus* species, while adding the *Enterococci, Serratia* species, and *K. pneumoniae* to its spectrum. Only ampicillin was superior to piperacillin against *S. faecalis*.

The only apparent drawbacks to piperacillin were the slight inoculum size effects on MIC and MLCs at 10^7 CFU/ml levels, particularly among *K. pneumoniae* isolates. Also piperacillin is susceptible to beta-lactamase activity similar to carbenicillin, ticarcillin and ampicillin. These features may limit its efficacy against beta-lactamase-producing *S. aureus, H. influenzae, N. gonorrhoeae* and some populations of *Enterobacteriaceae* including *E. coli*.

The combination of excellent *in vitro* inhibiting effects on a wide spectrum of bacteria and *in vivo* pharmacology makes piperacillin (T-1220) a very promising parenteral antimicrobic. If dosages were used permitting piperacillin serum levels of 64 μg/ml, this would inhibit 96% of the gram-positive and negative organisms in a clinical isolate study of 10,858 strains[12]. Ninety-one percent would be covered by concentrations of 16 μg/ml. These *in vitro* data coupled with a 22% serum protein binding, active urinary excretion (66%), high biliary concentrations, favorable human pharmacokinetics, and effective treatment of experimental animal infection favors further human *in vivo* investigations. Additional *in vitro* studies on anaerobic bacteria are also needed.

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References

1) BARRY, A. L.; C. THORNSBERRY, R. N. JONES, P. C. FUCHS, T. L. GAVAN & E. H. GERLACH: Cefuroxime, *in vitro* comparison to six other parenteral cephalosporins. (in press), 1977
2) JONES, R. N.; C. THORNSBERRY, A. L. BARRY, P. C. FUCHS, T. L. GAVAN & E. H. GERLACH: BL-S786, a new parenteral cephalosporin. II. *In vitro* antimicrobial activity comparison with six related cephalosporins. J. Antibiotics 30: 583~592, 1977
3) JONES, R. N. & P. C. FUCHS: Comparison of *in vitro* antimicrobial activity of cefamandole and cefazolin with cephalothin against over 8,000 clinical bacterial isolates. Antimicr. Agents & Chemoth. 9: 1066~1069, 1976
4) JONES, R. N.; P. C. FUCHS, T. L. GAVAN, E. H. GERLACH, A. L. BARRY & C. THORNSBERRY: BL-S786,

a new parenteral cephalosporin. I. A collaborative *in vitro* susceptibility comparison to cephalothin against 5,762 clinical bacterial isolates. J. Antibiotics 30: 576~582, 1977

5) JONES, R. N.; P. C. FUCHS, T. L. GAVAN, E. H. GERLACH, A. L. BARRY & C. THORNSBERRY: Cefuroxime, a new parenteral cephalosporin: Collaborative *in vitro* susceptibility comparison with cephalothin against 5,887 clinical bacterial isolates. Antimicr. Agents & Chemoth. 12: 47~50, 1977
6) FUCHS, P. C.; T. L. GAVAN, E. H. GERLACH, R. N. JONES, A. L. BARRY & C. THORNSBERRY: Ticarcillin: a collaborative *in vitro* comparison with carbenicillin against over 9,000 clinical bacterial isolates. Am. J. Med. Sci. (in press). 1977
7) FUCHS, P. C; C. THORNSBERRY, A. L. BARRY, T. L. GAVAN, E. H. GERLACH & R. N. JONES: Ticarcillin, carbenicillin and BL-P1908: *In vitro* comparison of three antipseudomonal semisynthetic penicillins. J. Antibiotics 30: 1106~1114, 1977
8) PRICE, K. E.; F. LEITNER, M. MISIEK, D. R. CHISHOLM & T. A. PURSIANO: BL-P1654, a new broad spectrum penicillin. Antimicr. Agents & Chemoth. -1970: 17~29, 1971
9) NOGUCHI, H.; Y. EDA, H. TOBIKI, T. NAKAGOME & T. KOMATSU: PC-904, a novel broad-spectrum semisynthetic penicillin with marked antipseudomonal activity: Microbiological evaluation. Antimicr. Agents & Chemoth. 9: 262~273, 1976
10) WISE, R.; J.M. ANDREWS & K.A. BEDORD: Pirbenicillin, a semisynthetic penicillin with antipseudomonal activity. J. Antimicr. Chemoth. 3: 175~183, 1977
11) SCOY, R. E. V.; E. WARREN & J. A. WASHINGTON: *In vitro* antimicrobial activity of a new semisynthetic penicillin BL-P1654. Antimicr. Agents & Chemoth. -1970: 12~16, 1971
12) GERLACH, E. H.; P. C. FUCHS, R. N. JONES, T. L. GAVAN, A. L. BARRY & C. THORNSBERRY: Piperacillin, a new parenteral broad spectrum penicillin: Collaborative *in vitro* susceptibility comparison with carbenicillin against 10,858 clinical bacterial isolates. Antimicr. Agents & Chemoth. (in press), 1978