EFFECT OF ANTIBIOTICS ON PHAGOCYTOSIS AND BACTERICIDAL ACTIVITY OF HUMAN LEUCOCYTES

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To examine the effect of antibiotics on phagocytosis and bactericidal activity of human neutrophils *in vitro*, 17 antibiotics and 2 antibacterial agents were tested using peripheral neutrophils from normal subjects or patients with complicated pyelonephritis. The effect on phagocytosis was measured by counting engulfed cocci by microscopy, or those which had been labeled with ^{3}H-Lysine with a liquid scintillation counter. Bactericidal activity was measured by QUIE's method[1]. The effect of antibiotics on phagocytosis and bactericidal activity varied with the kind and concentration of antibiotic used. While many antibiotics suppressed phagocytosis and bactericidal activity below the normally clinically accepted maximum concentration levels in blood, CPIZ enhanced these activities markedly, in which the effect of antibiotics differed normal subjects and patients with pyelonephritis.

Although antibiotics have played a valuable role in the treatment of infectious disease and have been widely used, there is a need to better understand the natural defense mechanisms of the host against infection and the effects of antibiotics on them, as literature dealing with these subjects is limited. Among natural human defense mechanisms, we chose to study neutrophils[2~4], which play a leading defensive role in the early stage of infection, especially in that of the urinary tract infections.

I. MATERIALS AND METHODS

Blood donors. The blood donors were young healthy adults (Normal) and patients with complicated pyelonephritis (Pyelonephritis).

Chemotherapeutic agents. The drugs studied were carbenicillin (CBPC), cephaloridine (CER), ampicillin (ABPC), tetracycline (TC), gentamicin (GM), kanamycin (KM), paromomycin (PRM), chloramphenicol (CP), nalidixic acid (NA), sulfamethizole (SMZ), ceftezole (CTZ), cefotiam (CTM), cefmetazole (CMZ), ceftizoxime (CZX), cefoperazone (CPZ), latamoxef (LMOX), cefotaxime (CTX), cefmenoxime (CMX) and cefpimizole (CPIZ). Concentrations tested were ranged from 200 μg to 0.02 μg of drug per ml.

Neutrophils. Neutrophils from heparinized human venous blood were separated with dextran, washed in Hank's balance salt solution (HBSS) and suspended in HBSS.

Bacteria. *Staphylococcus aureus* 209 P, *Staphylococcus aureus* isolated clinically and *Pseudomonas aeruginosa* NCTC 10490 were used. Among MIC measured (Table 1), *S. aureus* 209 P was sensitive

Table 1 Chemotherapeutic agents and MIC for used bacteria (10^{8} cells/ml)

Drug	*S. aureus* 209 P	*P. aeruginosa* NCTC 10490	Drug	*S. aureus* isolated clinically
CBPC	6.25	50	LMOX	200
CER	0.10	>100	CTX	400
ABPC	25	>100	CZX	>400
TC	0.39	25	CMX	100
GM	0.78	3.12	CPZ	>400
KM	0.78	>100	CMZ	25
PRM	3.13	>100	CTZ	100
CP	12.5	>100	CTT	2.0
NA	25	>100	CPIZ	400
SMZ	12.5	>100		

to most of the tested antibiotics, while *S. aureus* isolated clinically and *P. aeruginosa* were resistant to most of them. *S. aureus* 209 P and *P. aeruginosa* were grown in broth for 18 hours at 37°C. *S. aureus* isolated clinically was labeled with ^{3}H-Lysine. An inoculum of *S. aureus* and ^{3}H-Lysine (1 mCi) was added to 250 ml of brain heart medium and incubated at 37°C for 24 hours. The bacterial suspension was centrifuged and washed with sterile isotonic saline three times and then suspended in 30 ml of sterile isotonic saline. The bacterial suspension was stored at 4°C.

Contact methods of antibiotics with neutrophils. The first method used was the direct method. Neutrophils (0.1 ml, 6×10^6/ml), bacteria (0.1 ml, 1×10^8/ml), HBSS (0.4 ml) containing 25% opsonin and HBSS containing various concentrations of antibiotic (0.4 ml) were simultaneously added to a test tube. It should be noted that in this method, there is a possibility of the bacteria being affected by the antibiotic. The second method employed was the indirect method. Neutrophils and HBSS containing various concentrations of antibiotic were added to a test tube and incubated at 37°C for 30 minutes. After neutrophils were washed well with HBSS to remove the antibiotic, neutrophils, bacilli and HBSS containing 25% opsonin were added to the test tube. In this method, bacilli are not affected by the antibiotics.

Phagocytosis assay. *S. aureus* 209 P was used in the first experiment, while *S. aureus* isolated clinically and labeled with ^{3}H-Lysine was employed in the second experiment. Each test tube was tumbled end over end and 37°C for 30 minutes. In the first experiment using *S. aureus* 209 P, the suspension was centrifuged at 150×g for 30 minutes, and the sample smeared onto a coverslip, stained and examined microscopically. The number of cocci inside 50 neutrophils were counted and the average number of cocci per single neutrophil was calculated. In our second experiment using *S. aureus* labeled with ^{3}H-Lysine, the suspension was centrifuged at 150×g for 5 minute, and washed with HBSS twice. The final neutrophils were resuspended in 0.5 ml of HBSS. To 15 ml of Aquasole, a 0.1 ml aliquot of resuspended neutrophils was added for liquid scintillation counting[5].

Bactericidal activity assay. In the first experiment, *P. aeruginosa* was carried out by QUIE's method. In the second, *S. aureus* isolated clinically without labeling was used. The test samples were incubated for 3 hours at 37°C diluted with sterile water and plated on broth plates. The plates were incubated for 48 hours and colonies counted to determine the log of the surviving number of bacteria and activity by MINE's method[6], the formula is

$$K=\log a\cdot p/b\cdot c$$

(a : drug+bacteria, p : neutrophils+bacteria, b : drug+bacteria+neutrophils, c : bacteria).

Positive K signified enhancement while negative K signified suppression.

Table 2 Phagocytosis and bactericidal activity in normal subjects and patients with pyelonephritis

Phagocytosis

	n	Number of engulfed cocci
Normal	10	10.33±1.20*
Pyelonephritis	10	12.38±0.69

Bactericidal activity

	n	*S. aureus* 209 P	*E. coli* NIHJ TC	*P. aeruginosa* NCTC 10490
Normal	10	0.230±0.160	0.457±0.338*	0.540±0.274*
Pyelonephritis	10	0.457±0.338	1.172±0.757	1.052±0.302

* $P<0.05$, (Mean±S.D.)

Bactericidal activity=$\log\frac{C}{P}$, C : Bacteria, P : Neutrophils+Bacteria

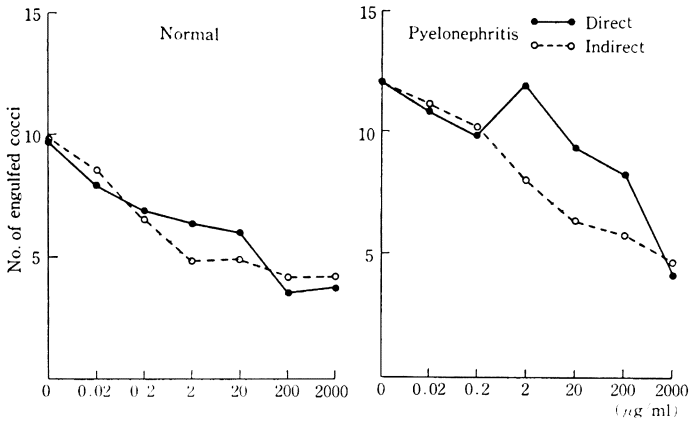
II. RESULTS

Phagocytosis was significantly greater in patients with pyelonephritis than in normal subjects ($P<0.05$) with the number of engulfed cocci being 12.58 in patients with pyelonephritis and 10.33 in normal subjects. As for bactericidal activity, neutrophils separated from patients with pyelonephritis were significantly greater in number than those from normal subjects ($P<0.05$) when *P. aeruginosa* and *E. coli* were used (Table 2), suggesting that neutrophils play a vital role in preventing pyelonephritis.

The effect of antibiotics on phagocytosis as measured microscopically :

The effect of CBPC on phagocytosis in normal subjects and pyelonephritis patients in shown in Fig. 1. In both the direct and indirect method, CBPC markedly suppressed phagocytosis in normal subjects as well as in pyelonephritis patients in proportion to its concentration. It was potent enough to suppress phagocytosis below the normally clinically accepted maximum concentration levels in

Fig. 1 Effect of CBPC on phagocytosis in normal subjects and pyelonephritis patients



blood.

Data for each concentration were expressed as % when one in a zero concentration was considered to be 100%. The criteria for schematic representation are shown below.

Table 3 Effect of antibiotics on phagocytosis in normal subjects with the direct method

	Dilution (μg/ml)					
	0.02	0.2	2	20	200	2000
CBPC	↓	↓	↓↓	↓↓	↓↓↓	↓↓↓
CER	→	→	→	↓	↓↓	↓↓
ABPC		↓	↓↓	↓↓	→	↓
TC	→	→	→	→	↓↓	↓↓
GM			↑	↑↑	↓	↓↓
KM		↓	↓	↑↑	↑	→
PRM	↑↑↑	↑↑	→	→	→	↓↓
CP	→	↓	↓	↓↓	↓↓	↓↓
NA	↑	↓	→	→	↓	↓
SMZ		→	↓	↓↓	↑	↑↑

Table 4 Effect of antibiotics on phagocytosis in normal subjects with the indirect method

	Dilution (μg/ml)					
	0.02	0.2	2	20	200	2000
CBPC	→	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
CER	→	↓	↓↓	↓↓↓	↓↓↓	↓↓↓
ABPC		→	→	→	↑	↑
TC	↓	→	↓	↓	↓	↓↓
GM		→	↓	↓	↓	↓
KM		→	→	→	→	→
PRM	↑	↓	↑	↓	↓↓	↓↓↓
CP	↓	↓	↓	↓	↓	↓↓
NA	→	↓	↓	→	↓↓	↓↓
SMZ		↑	→	→	→	→

→ : 0%～±9%
↑, ↓ : ±10%～±29%
↑↑, ↓↓ : ±30%～±49%
↑↑↑, ↓↓↓ : ±50%～

Upward pointing arrows indicate enhancement, and those pointing downward indicate suppression, the degrees of which are indicated by the number of arrows.

In normal subjects, using the direct method, CBPC, CER, ABPC and CP markedly suppressed phagocytosis, NA mildly suppressed it and PRM in the low concentrations enhanced it mildly (Table 3). In normal subjects, using the indirect method, CBPC and CER markedly suppressed phagocytosis in proportion to their concentrations. TC, GM, PRM at high concentrations, CP and NA suppressed it moderately. ABPC at high concentrations enhanced it mildly. KM and SMZ had no effect. In the direct and indirect method, CBPC, CER, TC, CP

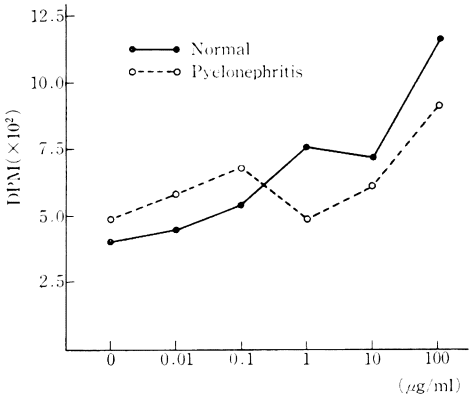
Table 5 Effect of antibiotics on phagocytosis in pyelonephritis patients with the direct method

	Dilution (μg/ml)					
	0.02	0.2	2	20	200	2000
CBPC		↓	→	↓	↓↓	↓↓↓
CER		↓	↓	↓	↓↓↓	↓
ABPC		→	→	↓	↑	↑
TC	↓	↓	↓	↓	↓	↓
GM		→	↓↓	↓↓	↓	↓
KM		↓	↓	→		↑
PRM		↓	↑↑	→	↓↓↓	↓↓↓
CP	↓	↓	↓	↓↓	↓↓	↓↓
NA	↑	↑	→	→	↑	→
SMZ	→	→	→	↑↑	↑	↑

Table 6 Effect of antibiotics on phagocytosis in pyelonephritis patients with the indirect method

	Dilution (μg/ml)					
	0.02	0.2	2	20	200	2000
CBPC		↓	↓↓	↓↓	↓↓↓	↓↓↓
CER		↑	→	→	↓↓	→
ABPC		↓	↓↓	↓↓↓	↓↓↓	↓↓↓
TC		→	↓	↓	↓↓	↓↓↓
GM		↑	↑	→	↑	↑↑
KM		→	↓	↑	↓↓	→
PRM		↓	↓	↓	↓↓↓	↓↓↓
CP	↓	↓	↓	↓	↓↓	↓↓
NA	→	↑	↑	↑	↑	↑
SMZ		↓	→	↓	→	↓

Fig. 2 Effect of CPIZ on phagocytosis in normal subjects and pyelonephritis patients



and NA showed almost the same tendency (Table 4).

In pyelonephritis patients, using the direct method, CBPC and CP markedly suppressed phagocytosis in proportion to their concentrations. CER, TC, GM and PRM in high concentrations suppressed it moderately. NA and SMZ enhanced it mildly (Table 5). In pyelonephritis patients, using the indirect method, CBPC, ABPC, TC, PRM and CP mardekly suppressed it in proportion to their concentrations, SMZ suppressed it mildly. GM and NA enhanced it mildly. CBPC, TC, PRM and NA exhibited the same tendency with both methods (Table 6).

The effect of cephem antibiotics on phagocytosis as measured labeled cocci with a liquid scintillation counter :

The effects of CPIZ on phagocytosis in normal subjects and pyelonephritis patients with the direct method is shown in Fig. 2. CPIZ markedly enhanced phagocytosis in proportion to the concentration in normal subjects and pyelonephritis patients, which the maximum effect was observed to be about three times that seen in a control not given CPIZ, as well as that observed in pyelonephritis patients. In normal subjects, with the direct method, CPIZ markedly enhanced phagocytosis, and CTZ, CMZ and LMOX enhanced it moderately. CTM and CTX had no effect at all and CZX suppressed it mildly (Table 7). Engulfed cocci were counted simultaneously by microscopy and using a liquid scintillation counter, with the results correlating well in both procedures[4] The utilization of labeled bacteria proved to be a rapid, simple and accurate qualitative assay of phagocytosis. Henceforth, we believe that this method should be utilized in the investigation of the effect of antibiotics on phagocytosis.

Table 7 Effect of cephem antibiotics on phagocytosis in normal subjects with the direct method

	Dilution (μg/ml)					
	0.05	0.1	0.4	1.56	12.5	100
Ceftezole(CTZ)	↑	↑	→	→	↑	→
Cefotiam(CTM)	→	→	→	→	→	↑
Cefmetazole(CMZ)	→	→	→	↑↑	↑↑	→
Ceftizoxime(CZX)	→	→	↓	↓	↓	↓
Cefotaxime(CTX)	→	→	↓	→	→	→
Latamoxef (LMOX)	↑	↑	↑	→	→	→
Cefpimizole(CPIZ)	↑	↑↑	↑↑	↑↑↑	↑↑↑	↑↑↑

The effect of antibiotics on bactericidal activity using *P. aeruginosa* :

The effect of PRM on bactericidal activity in normal subjects and patients with pyelonephritis using the direct and indirect methods is shown in Fig. 3. As all data were positive for K, PRM enhanced bactericidal activity moderately under all condition. Almost the same tendency was noted with both methods.

Data for each concentration is schematically represented with criteria as shown below.

K

→ : $\sim\pm0.1$

↑, ↓ : $\pm0.1\sim\pm0.5$

↑↑, ↓↓ : $\pm0.6\sim\pm0.9$

↑↑↑, ↓↓↓ : $\pm1.0\sim$

Upward pointing arrows indicate enhancement, and those pointing downward indicate suppression, the degrees of which are indicated by the number of arrows.

Fig. 3 Effect of paromomycin on bactericidal activity in normal subjects and pyelonephritis patients

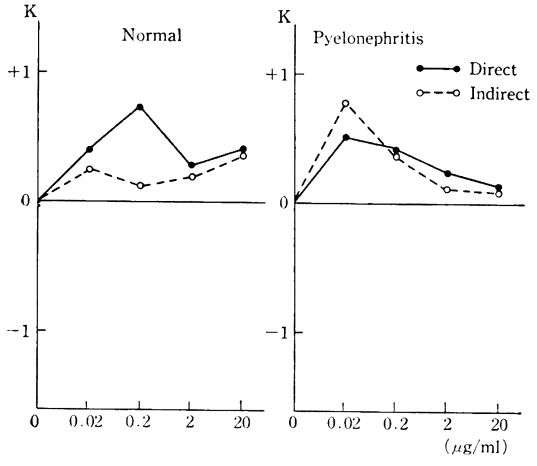


Table 8 Effect of antibiotics on bactericidal activity in normal subjects with the direct method

	Dilution (μg ml)				
	0.02	0.2	2	20	200
CBPC	↓	↑	↓	↑	
CER	↑	↑	↑↑	↑↑	
ABPC	↑	↓	→	↓	→
TC	→	→	→	↑	
GM	→	↓	↓		
KM	→	↑	↑	↑	↑
PRM	↑	↑↑	↑	↑	
CP	↓	↓↓	↓	↓	↓
NA	↓	↓	↓	↓	↓
SMZ	→	→	↓	↑	→

Table 9 Effect of antibiotics on bactericidal activity in normal subjects with the indirect method

	Dilution (μg ml)				
	0.02	0.2	2	20	200
CBPC	↑	↓	↓↓	↓↓↓	
CER	→	→	↑	→	
ABPC	↓↓	→	↓	↓	→
TC	↑	↑	↓	↑	
GM	↓	↓↓	↓↓		
KM	↓	↓	↑	↓↓	↓↓↓
PRM	↑	→	↑	↑	
CP	→	→	↓↓	↓	↓
NA	↑	↑	↑	→	↓
SMZ	↓	↑	→	↑	↓

In normal subjects, with the direct method, GM, CP and NA suppressed bactericidal activity mildly, while CER, KM and PRM enhanced it mildly. TC had no effect (Table 8). In normal subjects, with the indirect method, CBPC, GM and KM markedly suppressed it and CP mildly suppressed it, while PRM, NA and SMZ enhanced it mildly. ABPC, GM, PRM and CP exhibited the same tendency with both methods (Table 9).

Table 10 Effect of antibiotics on bactericidal activity in pyelonephritis patients with the direct method

	Dilution (μg/ml)				
	0.02	0.2	2	20	200
CBPC	↑	↑	→		
CER	→	↓	↑	→	
ABPC	↑	↑	↑	↑↑	
TC	→	↑	↑	↑	
GM	↑	↑	→		
KM	↑	→	↑	↓	↓
PRM	↑	↑	↑	↑	
CP	↑↑	↑↑	↑	↑↑	↑
NA	↓↓	↓	↓↓	↓	↓
SMZ	→	↑	↑	→	↑

Table 11 Effect of antibiotics on bactericidal activity in pyelonephritis patients with the indirect method

	Dilution (μg/ml)				
	0.02	0.2	2	20	200
CBPC	→	↓	↓↓		
CER	↑	↓	↓↓	↓	
ABPC	↑	↑	↑	↑↑	
TC	→	↑	↑	↑	
GM	↓↓	↑↑			
KM	↑	↑↑↑	↑	↑	↓↓↓
PRM	↑↑	↑	↑	→	
CP	↑	→	↑	↑	→
NA	↑	→	↓	↓	↓↓
SMZ	↓	↑	↑	→	↑

In pyelonephritis patients, with the direct method, CP markedly enhanced bactericidal activity and ABPC, TC, GM, PRM and SMZ enhanced it mildly. NA suppressed it moderately (Table 10). In pyelonephritis patients, with the indirect method, ABPC, TC, KM at low concentrations, PRM, CP and SMZ enhanced bactericidal activity mildly, while CBPC, CER and NA at high concentrations suppressed it mildly. ABPC, TC, KM, PRM, CP, NA and SMZ exhibited the same tendency with both methods (Table 11).

The effect of cephem antibiotics on bactericidal activity using *S. aureus* isolated clinically without labeling :

Table 12 Effect of cephem antibiotics on bactericidal activity in normal subjects with the direct method

	Dilution (μg/ml)					
	0.05	0.1	0.4	1.56	12.5	100
Ceftezole(CTZ)	↓	↓	→	↓	→	↑
Cefotiam(CTM)	↑	↑↑	↑↑	↓	→	→
Cefmetazole(CMZ)	↑↑	↑↑	↓	→	↓	→
Ceftizoxime(CZX)	↓	↓	↓	→	↓	→
Cefoperazone(CPZ)	↓	↓	↓	↓	↓	↓
Latamoxef (LMOX)	→	→	→	→	→	↑
Cefmenoxime(CMX)	→	→	→	→	↑	→
Cefpimizole(CPIZ)	↑	↑	↑	→	↑	↑

In normal subjects, with the direct method, CPIZ and CTM enhanced bactericidal activity mildly, while LMOX and CMZ had no effect, and CZX and CPZ suppressed it mildly (Table 12).

III. DISCUSSION

MUNOZ (1950) examined the effect of aureomycin on phagocytosis of human leucocytes *in vitro*, and reported that aureomycin suppressed phagocytosis in proportion to its concentration[7]. SENECA (1966) examined the effect of 12 antibiotics and 3 antibacterial agents on phagocytosis *in vitro*. Most of the drugs tested suppressed phagocytosis in proportion to their concentrations[8]. OOTAGURO (1972) studied the effect of antibiotics on bactericidal activity of pediatric normal subjects and patients treated with long-term chemotherapy. Bactericidal activity was reported to be significantly lower in patients treated with long-term chemotherapy than in normal subjects. He also demonstrated the effect of antibiotics on leucocyte function *in vivo*[9].

In the present study, the effect of 17 antibiotics and 2 antibacterial agents on phagocytosis and bactericidal activity of human leukocytes, respectively, were studied *in vitro* using peripheral neutrophils from normal subjects or patients with complicated pyelonephrities. While in other studies, the kind of antibiotics and their concentrations were limited, and blood donors were healthy adults, we studied many drugs and various concentrations ranging from 2,000 μg/ml to 0.02 μg/ml, utilizing blood from both normal subjects as well as patients with pyelonephritis, as it is considered important to clarify these results in patients with infectious diseases reliant on antibiotics. In our experiments, two techniques were utilized simultaneously and the results were compared. When studying the effect of antibiotics on leucocyte function using bacteria, the effect of the antibiotics on the bacteria cannot be disregarded. Bacteria which were resistant to the tested antibiotics were used in conjunction with the indirect method, although the conditions associated with the direct method are the same as those present in the host. The same results were observed in the direct and indirect methods with 66.7% of the drugs tested. Although a method for studying the effect of antibiotics on neutrophil functions is yet to be established, we believe that the procedures used in our experiments were reasonable. In comparing our results with those of other papers, some data agreed, but discrepancies did exist[8,10~15]. One reason for differences in the data is attributed to the different experimental methods. With regard to CPIZ, maximum phagocytosis was observed at the concentration of 100 μg/ml, where in the number of engulfed cocci was three times greater than at zero concentration. The chemotaxis of neutrophils to infected regions was greater than necessary. If antibiotics suppress neutrophil phagocytotic and bactericidal activity, a reduction in neutrophil function will occur in a large number of neutrophils. The half life of a neutrophil is about 7 hours, and new neutrophils replace damaged ones. Thus, the effect of antibiotics on neutrophil functions should not be disregarded. If antibiotics which enhance neutrophil function, such as CPIZ, are administered, results better than those expected from their MIC will be obtained.

The effect of antibiotics on leucocyte function varied with the antibiotic used and its concentration. In observing neutrophils microscopically, neutrophils which showed morphological changes had been suppressed by antibiotics. However, investigation of the antibiotic mechanism of action with regard to bacteria and the effect of antibiotics on leukocyte function revealed no relationship. Our results and those of other authors have dealt with the effect of antibiotics on neutrophil functions, but the antibiotic mechanism or point of action on neutrophils have not yet been clarified. In the future, our attempts will include the application of electron microscopy and biochemical examination to clarify these important points.

CONCLUSIONS

1) Phagocytosis and bactericidal activity varied according to the kind and concentration of antibio-

tic used.

2) Many antibiotics suppressed phagocytosis and bactericidal activity below normally clinically accepted maximum concentration levels in blood.

3) The same results were observed in both the direct and indirect method in 66.7% of drugs tested.

4) The effect of antibiotics on leucocytic functions differred in normal subjects and patients with pyelonephritis.

5) Phagocytotic and bactericidal activity was significantly greater in patients with pyelonephritis than in normal subjects. These results suggest that neutrophils play a vital role in preventing pyelonephritis.

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抗生物質のヒト白血球貪食能と殺菌能に対する影響

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抗生物質が感染症の治療に果した役割は大きく高く評価されている。一方抗生物質の生体感染防御機構に対する影響を前もって把握しておくことは重要と考えるが，文献上検討された薬剤の種類と濃度は限局されたものである。著者らは感染防御機構より感染初期に主役を演じ，尿路感染症と密接な関係を有する好中球を選び検討した。

抗生物質のヒト白血球貪食能と殺菌能に対する影響を *in vitro* で検討するために，17 種の抗生物質と 2 種の抗菌剤について，濃度は 200 μg/ml から 0.02 μg/ml について検討した。好中球は正常人と複雑性腎盂腎炎患者末梢血より Dextran で分離して使用した。感染症例の好中球で検討することは意義深いと考えた。貪食能は，鏡検で好中球に取り込まれた細菌をカウントする方法と ^{3}H-Lysine で細菌を標識し，取り込まれた細菌数を液体シンチレーションカウンターで求める二方法を使用し，殺菌能は QUIE の方法で行なった。腎盂腎炎患者好中球貪食能と殺菌能は正常人に比べ亢進を示し感染を防御する方向に働いていた。抗生物質の貪食能と殺菌能への影響は使用した薬剤の種類と濃度で異なった。多数の抗生物質は常用量使用時の血中最高濃度以下の濃度で貪食能と殺菌能を低下させた。CPIZ は貪食能と殺菌を著明に亢進せしめた。抗生物質の白血球機能に対する影響は正常人と腎盂腎炎白血球で異なった。抗生物質の白血球機能に対する影響のメカニズムは今後の課題である。