Yonago Acta medica 1999;42:193–200

Epidemiological Surveys of Methicillin-Resistant *Staphylococcus aureus* in Tottori Prefecture, Japan

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To study the isolation frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) and susceptibility of MRSA to antibiotics, a questionnaire survey was performed every half year from 1993 until 1997. The questionnaire was sent to medical doctors, and it asked retroactively about the isolation of *S. aureus* from clinical specimens. The isolation rate of MRSA from patients over 65 years of age was higher, and that from patients under 16 years of age was lower, than the rates in other age groups ($P < 0.01$). Ratios of isolation of MRSA among *S. aureus* strains were from 12 to 38% in the clinics, from 39 to 71% in the small-scale hospitals and from 47 to 62% in large-sized hospitals. These isolation rates increased gradually from 1993 to 1997 ($P < 0.001$). The isolation rate of MRSA from the sputum was higher, and those from pus, pharyngeal secretion and urine were lower, than those from feces and other specimens and from total specimens. The isolation rate of antibiotic-resistant strains of MRSA was highest for penicillins and cepharosporins. MRSA was highly susceptible to arbekacin (isolation rate of resistant strains: 3.0%) and vancomycin (3.0%), and was slightly susceptible to minocycline (21%), doxycycline (24%), amikacin (39%) and dibekacin (37%). These results indicate that more careful surveillance of MRSA and more stringent precautions against nosocomial infection with antibiotic-resistant MRSA are needed in hospitals even in relatively isolated parts of Japan.

Key words: epidemiology; methicillin-resistance; nosocomial infection; *Staphylococcus aureus*

There are many bacteria which evoke nosocomial infections, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella*, *Staphylococcus aureus*, etc. Antibiotic susceptibility of these bacteria varies with genus, species and strain. The serious problem of nosocomial infections with multiply antibiotic-resistant bacteria has increased since the early 1980's (Locksley et al., 1982; Thomson et al., 1982). An outbreak of nosocomial infection with multidrug-resistant *S. aureus* was first reported by Locksley et al. (1982). During a 15-month period, multiply antibiotic-resistant *S. aureus* was transferred from a burn patient to 34 patients in the hospital. Seventeen of the 34 patients died. Typing and plasmid analysis showed the spread of multiply resistant *S. aureus* from the burn unit to the surgical intensive care unit.

In the late 1980's, several patients died from nosocomial infection with methicillin-resistant *S. aureus* (MRSA) in Japan, resulting in some legal proceedings against unwarranted nosocomial infections. We investigated contamination by MRSA in Tottori Prefecture, a relatively isolated prefecture of Japan. The questionnaires were sent to members of medical institutions in Tottori Prefecture, and the trends of infections with MRSA in the clinics and hospitals were analyzed.

Subjects and Methods

Questionnaire surveys

At first, questionnaires were sent to clinical doctors asking whether or not specimens were sent to a clinical laboratory for bacterial exami-

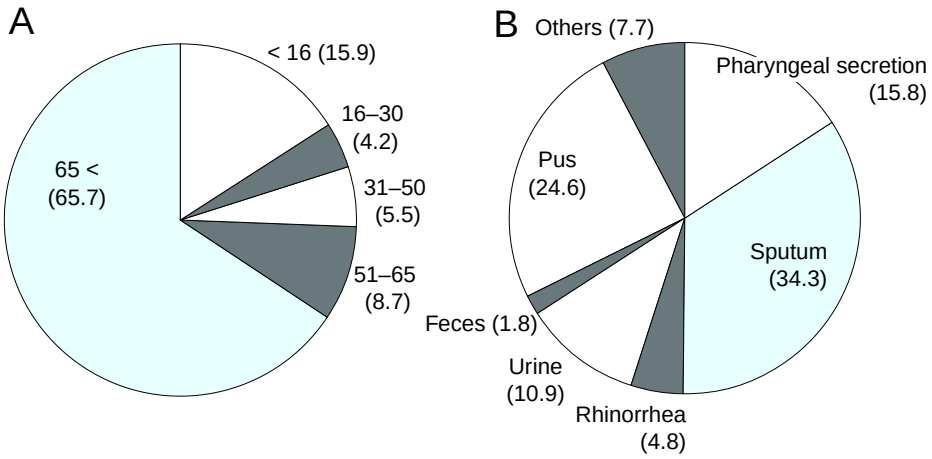

Fig. 1. The frequency of *S. aureus* isolation in various age groups and from different types of specimens. Distribution of *S. aureus* strains isolated in the age groups (**A**) and from various specimens (**B**). Total number of strains isolated was 2,527 during a 5-year period. The isolation frequency (percentage) from each type of specimen is shown in parentheses.

nation. If we got the answer "yes", then we sent the following questionnaires every half year from 1993 to 1997. The contents of the questionnaires asked the age and sex of the patient, origins of the specimens, species of *Staphylococcus*, antibiotic susceptibility testing and existence of any abnormal physical background.

Identification of *Staphylococcus* spp. and drug susceptibility testing were usually performed by standard methods. *Staphylococcus* spp. was identified using commercially available identification kits after selection by mannite-positiveness and coagulase activity. Antibiotic susceptibility testing was performed by disk methods (Barry and Thornberry, 1991) and methicillin-resistant or oxacillin-resistant strains of *S. aureus* were defined as methicillin-resistant *S. aureus* (MRSA). However, these methods of testing might have varied in different clinical laboratories.

Statistical analysis

Statistical analysis was performed as follows. Significant differences between the two groups were determined by Student's or Welch's *t*-test. Comparisons of several groups controlled by two factors were made by the two factor analysis of variance or Friedman's test.

Results

Total cases and hospitals

The number of clinics and hospitals was about 460 in May, 1993. A preliminary investigation was performed by sending the doctors in these institutions a questionnaire about whether microbial examinations were done or not. The answer was returned from 370 institutions (80.4%).

Out of 300 medical doctors who answered that microbial examinations were done if necessary, or that the patients were sent to a big hospital, an average of 57 answered the subsequent questionnaires which we sent them twice a year. Accordingly, the average rate of replies was about 20%. Most of the medical doctors in the clinics did not have patients with bacterial infection who needed microbial examination, because the patients were getting better by haphazard treatment with some antibiotics.

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-sensitive *Staphylococcus aureus*

Isolation of S. aureus in the age groups and from various types of specimens

The specimens of 1,391 men and 1,136 women were examined from 1993 until 1997 (Fig. 1A). The ratio of men to women was approximately 5 to 4; the difference between the number of men and women was not significantly different. Comparison of the number of specimens in the various age groups showed that greater numbers of specimens were isolated from the group under 16 years of age (16%) and the group over 65 years of age (66%) than from other age groups. Isolation rates of *S. aureus* in the age groups from 16 to 30 years of age, from 31 to 50 years of age and from 51 to 65 years of age were 4.2%, 5.5% and 8.7%, respectively. These age groups showed similar ratios of men to women. A larger proportion of specimens from women were isolated from the group over 65 years of age (70%) as compared with the proportion from the men isolated from the group over 65 years of age (62%).

In testing the kinds of specimens from which *S. aureus* was isolated (Fig. 1B), sputum (34%) and pus (25%) were the most frequent, and pharyngeal secretion (16%) and urine (11%) were the next most frequent. There was a low rate of isolation from sputum, and relatively higher rates from pus and urine in 1993 (data not shown). The rate of isolation from sputum increased after 1994 and that from pus varied from year to year. Rates of isolation from nasal mucus (rhinorrhea) and urine did not vary from year to year. There were few isolations from blood specimens, and they were included in the group of "Others".

Isolation rate of MRSA

The rates of isolation of *S. aureus* strains from clinical specimens in the period from 1993 until 1997, are shown in Fig. 2. In the clinics, 25 to 75 cases of *S. aureus* were identified during every half-year term and the isolation rate of MRSA varied from 12 to 38%. These isolation rates were significantly lower than those in small- and large-sized hospitals ($P < 0.001$). The isolation rate of MRSA in relatively small-sized hospitals and large-sized hospitals gradually increased from 39% and 47% in the first half of 1993 to over 71% and 62% in the second half of 1997, respectively. Isolation rates of MRSA in clinics and in small- and large-sized hospitals increased significantly as the time elapsed during the period from 1993 until 1997 ($P < 0.001$).

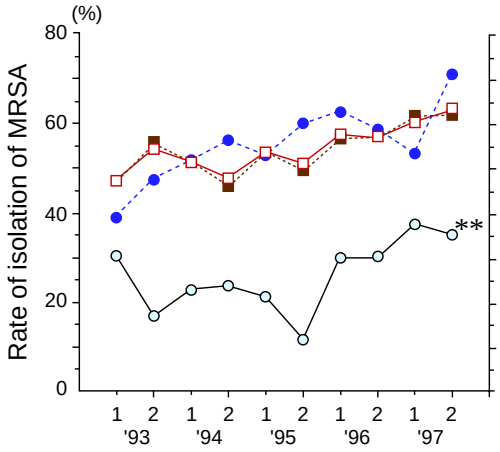

Fig. 2. Isolation rates of MRSA in different kinds of institutions. The isolation rates of MRSA in clinics (○), small- (●) and large- (■) sized hospitals and total isolation rate (□) were investigated every half year. The "1" in the Figure shows the first half of the year and the "2" shows the latter half of the year. The isolation rate of MRSA in clinics was significantly lower (**$P < 0.001$) than that in the other three groups, which were not significantly different from each other. During the period from 1993 until 1997, all four MRSA isolation rates significantly increased ($P < 0.001$).

The total numbers of *S. aureus* and MRSA isolated between 1993 and 1997 were about 3,000 and 2,000, respectively. The isolation rate of MRSA increased gradually and significantly from 47% in the first half of 1993 to 63% in the second half of 1997 ($P < 0.001$).

Isolation of MSSA and MRSA from specimens in various age groups and isolation from various types of specimens

Out of all *S. aureus*-positive specimens, 66% were from patients more than 65 years of age, and 16% were from patients under 16 years of

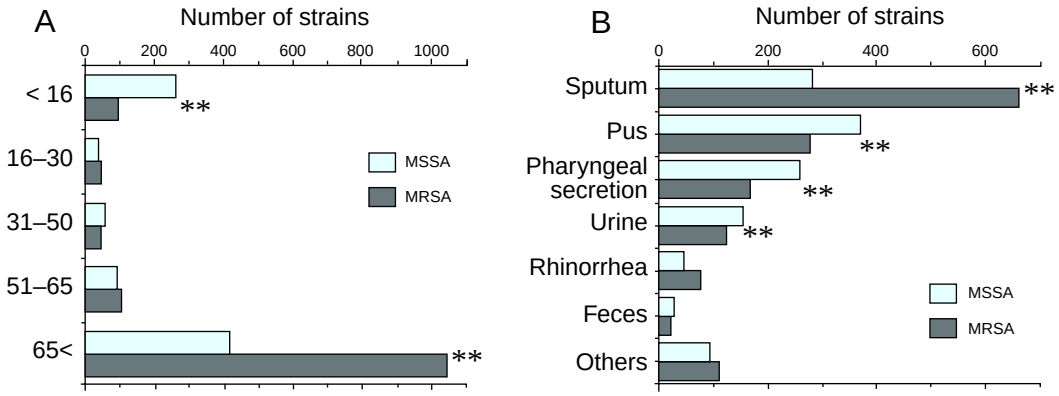

Fig. 3. Isolation of MSSA and MRSA in various age groups and their isolation from various types of specimens. MSSA (□) and MRSA (■) were isolated from various specimens. (**A**) isolation of MSSA and MRSA in age groups. (**B**) isolation of MSSA and MRSA from various specimens. The asterisks indicate a significant difference between the ratios of MSSA to MRSA in the groups with asterisks and the groups without asterisks (**$P < 0.001$).

age (Fig. 1A). The variance of the number of specimens from which methicillin-sensitive *S. aureus* (MSSA) was isolated was not the same as that of MRSA (Fig. 3A). The isolation rate of MRSA in the age group under 16 years of age was significantly lower ($P < 0.001$) and that in the age group over 65 years of age was significantly higher than those in the groups from 16 to 30 years of age, from 31 to 50 years of age and from 51 to 65 years of age, and higher than the isolation rate of MRSA in the total specimens. The isolation rates of MRSA from the patients in the age groups from 16 to 30 years of age, from 31 to 50 years of age and from 51 to 65 years of age and the isolation rate of MRSA from the total specimens, were 54%, 44%, 52% and 61%, respectively, and were not significantly different.

The numbers of MSSA and MRSA strains isolated from specimens between 1993 and 1997 are shown in Fig. 3B. There were large variances in the numbers of MSSA and MRSA. The isolation rate of MRSA from sputum was higher, and those from pus, pharyngeal secretion and urine were lower than that of MSSA from each specimen ($P < 0.001$). The isolation rates of MRSA from rhinorrhea, feces, others and total specimens were similar to those of MSSA. Many specimens of sputum were tested from patients over 65 years of age (87% of total specimens of sputum), whereas pharyngeal secretion specimens were largely from patients under 15 years of age (51% of total specimens of pharyngeal secretion).

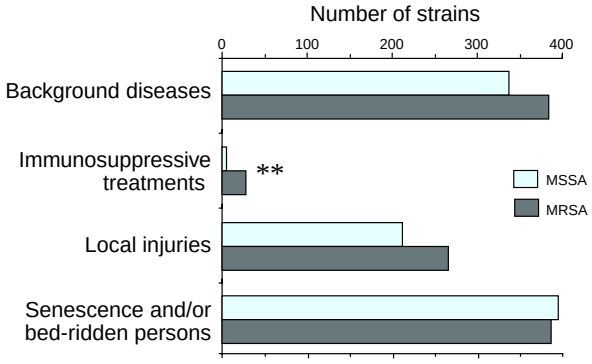

Fig. 4. Isolation of MSSA and MRSA from patients with compromised conditions. MSSA (□) and MRSA (■) were isolated from patients with background diseases, immunosuppresive treatments or local injuries, or from aged and/or bedridden persons. The isolation ratio of MRSA to MSSA from the patients with immunosuppresive treatments is significantly higher than the ratios from the patients of other groups (**$P < 0.001$).

Background of S. aureus infection

We investigated whether or not patients with *S. aureus* infection were compromised hosts. As shown in Fig. 4, the isolation rate of MRSA from patients with immunosuppressive treatments was clearly higher than that of MSSA ($P < 0.001$). However, there were no significant differences in the isolation rates of MRSA among the groups with background diseases, local injuries and senescence and/or bedridden persons.

Patients with background diseases and senescent or bedridden persons were not always predisposed to MRSA. Although only a few specimens were analyzed, it appears that only the immunosuppressive treatments might predispose patients to MRSA, and other factors might include longer terms of treatment or hospitalization.

Antibiotic resistance

The isolation rates of antibiotic-resistant strains of staphylococci were investigated (Table 1). Most (over 95%) MRSA were resistant to ampicillin (ABPC), amoxicillin (AMPC) and piperacillin (PIPC), and the isolation rates of strains resistant to these PCs increased between 1993 and 1997 among total strains of staphylococci. The isolation rates of resistant strains of MSSA varied from 25% (PIPC and SBTPC) to 60% (AMPC).

Cephalosporin antibiotics, such as cefaclor (CCL), cefazolin (CEZ), cefatrizine (CFT), cefmetazole (CMZ), cefotiam (CTM) and ceftazidime (CAZ), were effective against MSSA, but more than 90% of MRSA strains were resistant to these cephalosporins, except for CMZ. Strains resistant to various cephalosporins increased gradually among all staphylococci (data not shown).

MSSA was susceptible to flomoxef (FMOX), imipenem/cilastatin (IPM/CS), latamoxef (LMOX), but MRSA was less susceptible to these antibiotics.

Arbekacin (ABK), minocycline (MINO) and doxycycline (DOXY) were effective against MRSA. However, macrolides were not effective against MRSA, and, for example the isolation rate of MRSA resistant to erythromycin (EM) is shown in Table 1. New quinolone antibiotics had various effects on MRSA, and the average rates of antibiotic resistance to these agents were 40 to 80% throughout this 5 year period.

Table 1. Isolation rate of antibiotic-resistant strains of MSSA, MRSA and total strains of *Staphylococcus* spp.

Antibiotic name	Number of strains tested	Rate of resistant strains of: MSSA (%)	MRSA (%)	Total (%)
ABPC	903	57.3	94.0	72.2
AMPC	348	67.4	96.7	74.7
PIPC	1,062	24.6	96.8	79.6
SBTPC	408	24.5	64.2	43.8
CCL	804	16.2	96.3	52.1
CEZ	1,136	4.9	96.0	51.4
CMZ	1,195	3.0	71.4	39.8
CTM	1,194	3.2	93.9	54.6
CAZ	694	12.3	94.9	62.2
SBT/CPZ	515	18.0	90.7	53.8
FMOX	1,195	5.8	64.8	30.5
IPM/CS	1,340	9.2	77.7	47.5
LMOX	344	5.4	94.8	82.6
ABK	381	2.3	3.0	2.7
AMK	1,063	10.5	38.7	26.2
DKB	381	36.1	36.9	34.9
EM	75	36.3	92.2	60.9
CLDM	428	30.5	86.2	55.4
MINO	2,022	3.2	21.1	11.6
DOXY	386	0.9	24.2	15.3
NFLX	593	26.2	80.6	55.6
OFLX	591	19.3	56.5	33.0
LVFX	805	9.3	41.4	27.2
FOM	1,054	12.3	72.1	45.3
VCM	841	1.2	3.0	2.3

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

ABPC, ampicillin; AMPC, amoxicillin; PIPC, piperacillin; SBTPC, sultamicillin; CCL, cefaclor; CEZ, cefazolin; CMZ, cefmetazole; CTM, cefotiam; CAZ, ceftazidime; SBT/CPZ, sulbactam/cefoperazone; FMOX, flomoxef; IPM/CS, imipenem/cilastatin; LMOX, latamoxef; ABK, arbekacin; AMK, amikacin; DKB, dibekacin; EM, erythromycin; MINO, minocycline; DOXY, doxycycline; CLDM, clindamycin; NFLX, norfloxacin; OFLX, ofloxacin; LVFX, levofloxacin; FOM, fosfomycin; VCM, vancomycin.

Although MRSA was resistant to fosfomycin (FOM) at a rate of 60% during this 5-year period, very few strains of vancomycin (VCM)-resistant MRSA were observed.

Discussion

Tottori Prefecture is located on Japan's western coast along the Sea of Japan, 200 km northwest of Osaka. It is one of the smallest prefectures in Japan, having a population of about 630,000 in an area of about 3,500 km^2. The chief industries are farming and fishery. Tottori Prefecture is thus a relatively isolated and rural district of Japan. However, this area is widely contaminated with MRSA, or multiply antibiotic-resistant *S. aureus*.

Nosocomial infections with MRSA have been observed in all parts of the world, especially in the advanced countries. Careful surveillance of MRSA has been performed in large cities and districts (Aparicio, 1992; Marples and Reith, 1992; Mylotte et al., 1992; Heffernan et al., 1993; Ida et al., 1994; Voss et al., 1994; Zaman and Dibb, 1994; Riley and Rouse, 1995; Maguire et al., 1996; Johnson et al., 1997; Schmitz et al., 1997). Schmitz et al. (1997) observed the incidence of MRSA isolates over a period of 3 years and reported that from a total of 7,814 *S. aureus* isolates, 6.3% were methicillin resistant. Furthermore, the highest incidence, 7.8%, was found in a 1,500-bed hospital, and the lowest incidence, 0.5%, was in a smaller 200-bed hospital. In a general hospital in Jaddah in Saudi Arabia, the isolation frequency of MRSA was 7.5% (Zaman and Dibb, 1994). In US hospitals, 66,132 *S. aureus* isolates were tested and it was found that the percentage of MRSA rose from 2.4% in 1975 to 29% in 1991, and that hospitals with many beds (500 or more beds) were higher in percent MRSA than hospitals with few beds (< 200 beds) (Panlilio et al., 1992).

The isolation frequency of MRSA in Japan increased up to 60% by 1993 (Hashimoto, 1993), which is a much higher incidence of MRSA than those in the above-mentioned reports. In our surveys in Tottori Prefecture, the total isolation rate of MRSA increased from 47% in 1993 to 63% in 1997, and was higher in general hospitals than in clinics (Fig. 2). The reasons why the isolation rates of MRSA in hospitals were higher than those in clinics were not clear. Generally speaking, when a high dose of antibiotics was used in hospitals, antibiotic-resistant strains of microorganisms easily appeared in the same circumstances. The doctors in many clinics used the antibiotics for several days only on the patients, who were suspected of infection before isolation of microorganisms. The patients attending the clinics may only come in contact with antibiotics for relatively short time.

The ratios of MRSA to MSSA in the age group under 16 years of age and in the group over 65 years of age were significantly different from those in the other age groups (both: $P < 0.01$). The isolation frequency of MRSA in the group under 16 years of age was lower and that in the group over 65 years of age was higher than those in the other groups (Fig. 3A). These differences are due to the fact that most of the patients over 65 years of age were bedridden patients with compromised conditions who were hospitalized due to some diseases, whereas many of the children under 16 years of age were outpatients who visited clinics, and only a few were admitted to the hospital.

Investigating the clinical specimens for isolation of MRSA, 46% out of 1,449 MRSA strains were isolated from sputum, and 19% were from pus, although *S. aureus* strains were observed at the rate of 34% in sputum and at the rate of 25% in pus. Ida et al. (1994) also reported that the isolation frequency of MRSA was high in sputum (42.9%) and pus (33.1%). As shown in Fig. 3B, the isolation frequency of MRSA strains from sputum was significantly higher, and that from pus was lower, than that of total *S. aureus* strains. Sputum is collected for isolation of bacterium from aged persons who are often infected by opportunistic pathogens, and suffer from chronic pulmonary diseases or general diseases. Pus was examined not only from decubitus, but also from various lesions such as wound infections, catheter insertions, post-operation and local infections, and MRSA was often iso-

lated from the decubitus that occurred in the aged and bedridden persons. However, wounds were observed in persons of various ages (data not shown), and this might be one reason why the isolation rate of MRSA from pus was not as high as that from sputum.

S. aureus has been one of the most dangerous organisms causing nosocomial infections during past 20 years. Many guidelines have been considered and adopted to protect against nosocomial infections (Crowcroft et al., 1996; Wenzel et al., 1998). Strategies for the surveillance and control of MRSA include quantitative antibiogram (Marple and Reith, 1992; Panlilio et al., 1992; Voss et al., 1994; Blanc et al., 1995; Schito et al., 1996), phage-typing and DNA-restriction map by pulsed-field gel electrophoresis (Aparicio et al., 1992; Mlynarczyk et al., 1996).

According to the study reported by Ida et al. (1996), more than 80% of MRSA strains were highly resistant to methicillin, and were also resistant to macrolide antibiotics and toburamycin. MRSA was also resistant to gentamicin (60%), minocycline (50%) and ofloxacin (70%). Only a small percentage of strains were resistant to arbekacin, and most of the MRSA tested were susceptible to vancomycin. Schito et al. (1996) reported that doxycycline, chloramphenicol, co-trimoxazole, ofloxacin and ciprofloxacin (ratios of resistant strains: < 1%) were effective against MRSA. Other authors reported that MRSA was susceptible to vancomycin, amikacin, bacitracin, chloramphenicol, framycetin, fusidic acid and novobiocin (Riley and Rouse, 1995). Our study showed that only vancomycin and arbekacin were effective against MRSA, and that minocycline and doxycycline were partially effective against MRSA (Table 1).

In the course of comparing these data with other reports, especially with reports from foreign countries (Aparicio et al., 1992; Marples and Reith, 1992; Mylotte et al., 1992; Heffernan et al., 1993; Voss et al., 1994; Zaman and Dibb, 1994; Riley and Rouse, 1995; Maguire et al., 1996; Johnson et al., 1997; Schmitz et al., 1997), it became clear that the isolation rates of MRSA from patients in hospitals are exceptionally high. Even in a relatively isolated area like Tottori Prefecture, the increased incidence of MRSA has occurred. There will be increasing numbers of victims of MRSA infection, if we leave MRSA as it is. We must grapple with this difficult problem.

Acknowledgment: The authors are also grateful to all the medical doctors in Tottori Prefecture for replying to the questionnaires.

This work was supported by a grant from the Tottori Prefecture Health Promoting Council.

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(Received August 13, Accepted September 6, 1999)