Disturbances in the oral cavity in pediatric long-term survivors after different forms of antineoplastic therapy

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Abstract

Oral health and disturbances in dental development were studied in long-term survivors after antineoplastic therapy. Fifty-seven children treated with combination chemotherapy and 19 children treated with total body irradiation (TBI) prior to bone marrow transplantation (BMT) were examined. The variables studied were dental caries, salivary flow, salivary microbial counts, enamel disturbances, and disturbances in dental development. The results showed no increased caries experience in children treated with BMT or chemotherapy compared with controls. Children treated with BMT had a significantly lower salivary secretion rate of 0.7 ±0.4 ml/min, compared with 1.1 ±0.5 in the chemotherapy group, and 1.3 ±0.6 in the control group (P < 0.05). The clinical examination showed equal numbers of teeth affected by disturbances in enamel mineralization in the BMT and chemotherapy groups. A mean 15.9 ±8.2 teeth were affected by disturbances in root development in the BMT group compared with 1.2 ±1.6 in the chemotherapy group (P < 0.001). The results show that children who are long-term survivors of pediatric malignant diseases exhibit a wide range of disturbances in the oral cavity. In this study the most severe disturbances are found in children treated with total body irradiation prior to BMT. (Pediatr Dent 16:217–23, 1994)

Introduction

Advances in treatment of malignancy in childhood have resulted in an increasing number of long-term survivors. The treatments include multiagent chemotherapy alone or in combination with radiotherapy or surgery. Bone marrow transplantation (BMT) is now an established therapy for patients with malignant and nonmalignant disorders.

The immediate effects of chemotherapy and irradiation on soft tissues are well documented, but less is known about the long-term effects on oral health and developing dental tissues.[1] In a study by Welbury, et al.,[2] children treated for leukemia or solid tumors had satisfactory dental health with no abnormalities in dental caries or periodontal disease. On the other hand, it has been shown that children receiving antineoplastic therapy had significantly higher mean decayed, missing and filled surface (dmfs) scores compared to controls.[3]

Regarding salivary function, Jones, et al.[4] found that salivary flow rates and levels of mutans streptococci decreased after pretransplant cytoreductive therapy and post-transplant prophylactic antibiotic therapy in adult patients treated with BMT. Normal levels returned with time after the patients left the protected environment. Lactobacilli counts were not affected. Brown, et al.[5] found increased numbers of mutans streptococci and lactobacilli in irradiated patients treated for head and neck cancers several years after therapy.

Concerning the effect on dental development, *Rosenberg, et al.*[6] *reported that in a group of long-term* survivors of pediatric acute lymphoblastic leukemia treated with chemotherapy, 5 of 17 patients exhibited altered dental root development with a marked shortening of premolar roots. Children less than 5 years of age treated with combination chemotherapy and 24 Gy cranial irradiation exhibited disturbances in dental and craniofacial development.[7] Dahllöf, et al.[8] found that all patients conditioned with total body irradiation (TBI) before BMT exhibited severe disturbances in dental development.

The aim of this investigation was to study oral health and disturbances in dental development in children who are long-term survivors after treatment with chemotherapy or BMT.

Methods and materials

Patients

BMT group. Nineteen children (8 boys and 11 girls) younger than 12 years old treated with BMT[9, 10] at Huddinge Hospital who survived more than 3 years were selected for this study. Mean age at the bone marrow transplantation was 6.5±3.5 years. Fifteen children were treated for acute leukemia, one for a B-cell lymphoma, three for Gaucher's disease, and one for a severe combined immunodeficiency. The preoperative conditioning before BMT in patients with malignant diseases, immunodeficiency, and Gaucher's disease included both cyclophosphamide and TBI given as a single dose of 8–10 Gy. In patients with metabolic disorders, cyclophosphamide was combined with TBI (7 Gy) in two patients and busulfan (16 mg/kg) in two patients.[11] To prevent or modify graft-versus-host disease (GVHD), methotrexate (MTX) alone or in combination with cyclosporine (CSA) were given for 1 year

after BMT.[12] Acute GVHD was treated with prednisolone in combination with azathioprine or CSA. During the aplastic period the children rinsed the oral cavity twice daily with a 0.1 % chlorhexidine solution, nystatin 4x100,000 IU/ml, and 2x0.025% sodium fluoride solution. Follow-up examinations were performed at the department of pediatric dentistry, 3, 6, and 12 months after BMT, and thereafter on a yearly basis. The mean follow-up time after BMT, was 5.4 years (range 3.0–8.6). The children and their parents received instructions in preventive dental care and individualized fluoride prophylaxis based on assessment of caries risk factors. The program consisted of brushing with fluoride toothpaste twice daily, taking fluoride tablets, and applying fluoride varnish every third month. Children with low salivary secretion rates were given treatment with sodium fluoride gel 0.1% in customized trays.

Chemotherapy group. Fifty-seven children (33 boys and 24 girls) younger than 12 years old treated for malignant diseases at the department of pediatric oncology, Karolinska Hospital who survived more than 3 years after therapy were examined. Twenty-one were treated for acute leukemia, nine for lymphoma, six for Wilm's tumor, six for rhabdomyosarcoma, three for histiocytosis-X, three for neuroblastoma, three for optic glioma, three for other CNS-tumors, and three for other tumors. The mean age at diagnosis of their malignant disease was 5.1 ± 3.3 years. The mean follow-up time between the diagnosis and the dental examination was 6.6 years (range 3.0–17.5). The children were treated according to protocols including combinations of chemotherapy and, in some cases, radiotherapy or surgery. None of the children received radiotherapy with the teeth or jaws in the radiation field. Nine of 21 children with acute leukemia received cranial irradiation. During hospitalization, the oral cavity was rinsed daily with a 0.25% hydrogen peroxide solution. These children were not examined by a dentist during hospitalization and received no individual fluoride prophylaxis during followup.

Control groups. For each child treated with BMT, an age- and sex-matched control (N = 19), was selected from patients receiving their dental treatment at the department of pediatric dentistry. They lived in a low-fluoride area and received no additional fluoride prophylaxis apart from brushing twice daily with fluoride toothpaste.

For the radiographic examination, panoramic radiographs were obtained from the patient files at the department of orthodontics (N = 76), selecting only children with a moderate degree of malocclusion. The controls were matched with respect to age and sex.

Dental caries. All children were examined clinically and bite-wing radiographs were exposed. Decayed and filled surfaces were recorded clinically according to Koch.[13] Proximal caries was recorded on bite-wing radiographs when a radiolucency reached into the dentine. A radiolucency limited to the enamel was defined as initial caries.

Salivary factors. Paraffin-stimulated whole saliva was collected during 5 min between 09.00–11.00 hr and the salivary secretion rate was determined. The buffer capacity was estimated using the Dentobuff® (Orion Diagnostica, Espoo, Finland) method.[14] The number of mutans streptococci per ml saliva was estimated according to Gold, et al.[15] and the number of lactobacilli per ml saliva was determined according to the Dentocult® (Orion Diagnostica, Espoo, Finland) method.[16]

Enamel disturbances. All teeth were dried and enamel defects on the buccal and palatal surfaces, the incisal edges, and the cuspal and occlusal surfaces were recorded. Only permanent teeth were examined. Classification of the enamel defects was based on the index of developmental defects in dental enamel.[17]

Disturbances in dental development. A panoramic radiograph was available from all children subjected to antineoplastic therapy. Disturbances in dental development were analyzed using the Dahllöf, et al. method.[18] The disturbances were classified into five major groups: 1) arrested root development and premature apical closure, 2) arrested root development with short "v"-shaped roots, 3) enamel hypoplasia, 4) microdontia, and 5) aplasia. The panoramic radiographs were blinded by group for the examiner.

Table 1. Caries experience in patients

Variables	*Chemotherapy Group (N = 57)*		*BMT Group (N = 19)*		*Control* Group (N = 19)*	
	x	*SD*	*x*	*SD*	*x*	*SD*
Age at examination	11.7	4.7	11.9	3.9	11.9	3.9
Age at diagnosis	5.1	3.3	6.5	3.5	—	—
Permanent dentition						
DFS†	5.1	9.7	3.5	2.8	2.7	3.5
DS	1.3	4.2	0.6	0.3	0.3	0.6
CI††	2.3	3.8	3.4	5.2	4.3	5.7
Deciduous dentition						
dfs	5.4	6.4	4.1	4.0	4.3	5.0
ds	2.7	5.6	0.6	0.7	0.6	1.2
ci	1.6	2.7	0.6	1.5	1.2	2.3

* No statistically significant differences were found using Student's *t*-test; † D-decayed, F-filled, S-surfaces; ‡ CI-caries initial.

Table 2. Salivary microbial counts and buffer capacity

Variables	*A Chemotherapy Group (N = 57)* N	*B BMT Group (N = 19)* N	*C Control Group (N = 19)* N	*Significance**		
				A-B	*B-C*	*A-C*
Mutans streptococci (no. children > 10^6/ml saliva)	22/52	5/19	1/23	n.s.	n.s.	**
Lactobacilli (no. children > 10^6/ml saliva)	16/53	6/19	1/23	n.s.	n.s.	*
Buffer capacity (no. children pH < 4.5)	18/50	8/19	1/23	n.s.	**	*

* Chi-square test, levels of significance: * $P < 0.05$, ** $P < 0.01$.

All clinical examinations and ratings of enamel and dental disturbances were performed by one examiner (MN).

Results

Clinical variables

Dental caries. As shown in Table 1 there were no statistically significant differences in caries experience between the three groups, for the primary or the permanent dentition. The mean number of decayed and filled surfaces (DFS) in the permanent dentition in the chemotherapy group was 5.1 (range 0–51) and DS was 1.3 (range 0–4). The children treated with BMT had a mean DFS 3.5 (range 0–14) and mean DS 0.6 (range 0–6). The control group had a mean DFS 2.7 (range 0–13) and a mean DS 0.3 (range 0–2). Twenty-one percent of the children in the chemotherapy group were caries free, 4% in the BMT group, and 13% in the control group. In the chemotherapy group the mean DFS in children with hematological malignancies was 6.5 ± 12.2 compared with 3.6 ± 6.0 in those treated for solid tumors. The difference in caries experience was not statistically significant.

Salivary factors. Children treated with BMT had a significantly lower salivary secretion rate 0.7 ± 0.4 ml/min, compared with children treated with chemotherapy, 1.1 ± 0.5 ml/min ($P < 0.05$), and the healthy controls 1.3 ± 0.6.($P < 0.05$). Mutans streptococci and lactobacilli could be detected from all patients in the three groups examined. As shown in Table 2, a significantly higher proportion of the children treated with BMT ($P < 0.01$) or chemotherapy ($P < 0.05$) harbored high counts of mutans streptococci compared with controls, and a higher proportion of the children in the chemotherapy and BMT groups exhibited a low buffer capacity of the saliva ($P < 0.01$).

Disturbances in enamel mineralization. A mean number of 4.1 ± 5.0 teeth were affected by disturbances in enamel mineralization in the chemotherapy group compared with 4.6 ± 4.6 in the BMT group, which is significantly higher than healthy controls, 0.7 ± 1.4 ($P < 0.05$). As can be seen in Table 3, white/cream colored opacities were most commonly diagnosed in all three groups, followed by yellow/brown opacities. Six children in the BMT group, treated with TBI between 1.0 and 11.6 years, did not exhibit any clinical signs of enamel disturbances.

Roentgenological variables

Disturbances in dental development were diagnosed on panoramic radiographs (Table 4). In the control group no disturbances were found. Eighteen of 19 patients receiving TBI prior to BMT exhibited arrested root development and premature apical closure compared with eight of 30 patients receiving chemotherapy ($P < 0.001$). All types of disturbances were more frequent in children treated with BMT compared with those treated with chemotherapy, except for enamel hypoplasias (Figs 1 a, b). Children treated with BMT exhibited a mean number of 15.9 ± 8.2 teeth with disturbances in root development compared with 1.2 ± 1.6 teeth

Table 3. Prevalence of disturbances in enamel mineralization in the permanent dentition

Enamel defect	**A** *Chemotherapy Group (N = 50)*		**B** *BMT Group (N = 17)*		**C** *Control* Group (N = 17)*	
	N	*%*	*N*	*%*	*N*	*%*
White/cream opacity	34	68*	10	59	5	29
Yellow/brown opacity	13	26	7†	41	1	6
Fine white lines	8	16	5	29	1	6
Hypoplasia	4	8	2	12	0	0

* Chi-square test, level of significance: white/cream opacity A vs C $P < 0.05$.

† Yellow/brown opacity B vs C $P < 0.05$.

Table 4. Number of patients exhibiting disturbances in dental development diagnosed on panoramic radiographs

Treatment	*Age at diagnosis (years)* $\bar{x} \pm SD$	*Type of disturbances*•				
		I†	*II*	*III*	*IV*	*V*
Hematological malignancies	6.2 ± 1.4	8/30	2/30	6/30	3/30	3/30
Solid tumors	5.4 ± 2.3	2/27 ***	2/27 ***	n.s. 1/27 ***	*** 4/27 ***	*** 8/27 n.s.
Bone marrow transplantation	6.5 ± 3.5	18/19	11/19	8/19	13/19	11/19

• Classification of disturbances: I) arrested root development with short "v"-shaped roots, II) arrested root development with premature apical closure, III) enamel hypoplasia, IV) microdontia, and V) aplasia.

† Chi-square test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; n.s. = nonsignificant.

in the chemotherapy group ($P < 0.001$) and 0.4 ± 0.7 teeth in the control group ($P < 0.001$). Table 5 shows the distribution of dental disturbances in individual BMT patients treated with TBI. Children younger than 5.4 years of age at TBI show the most extensive and severe disturbances.

Discussion

The results of this study indicate that children who are long-term survivors after pediatric malignant diseases exhibit a wide range of disturbances in the oral cavity. Children who were treated with TBI prior to BMT exhibited more severe and extensive disturbances in dental development than children treated with chemotherapy only.

The preventive regime combining the use of fluoride and chlorhexidine was successful in controlling caries in the BMT-treated children. The mean number of new DF surfaces was higher in the chemotherapy group than the BMT group, but the difference did not reach statistical significance. The children treated with chemotherapy did not receive any additional fluoride prevention during induction therapy and follow up. Conflicting results have been reported previously concerning the caries experience in children treated for malignant diseases. The results of this study agree with Nunn, et al.[19] and Maguire, et al.,[20] who compared treated children to their siblings and found no differences in dental caries, gingivitis, or oral hygiene. On the other hand, Pajari, et al.[3] and Purdell-Lewis, et al.[21] reported an increased dmfs and DMFS values, although no bite-wing radiographs were assessed in their studies. In contrast to Pajari, et al.[3] no increased caries activity could be found in children with hematological malignancies compared with those who had solid tumors.

The salivary secretion rate was significantly reduced in children conditioned with TBI before BMT compared with the chemotherapy group and controls. This is in contrast to a study in adults[4] subjected to 10.2 Gy fractioned TBI before BMT. In a cross-sectional followup

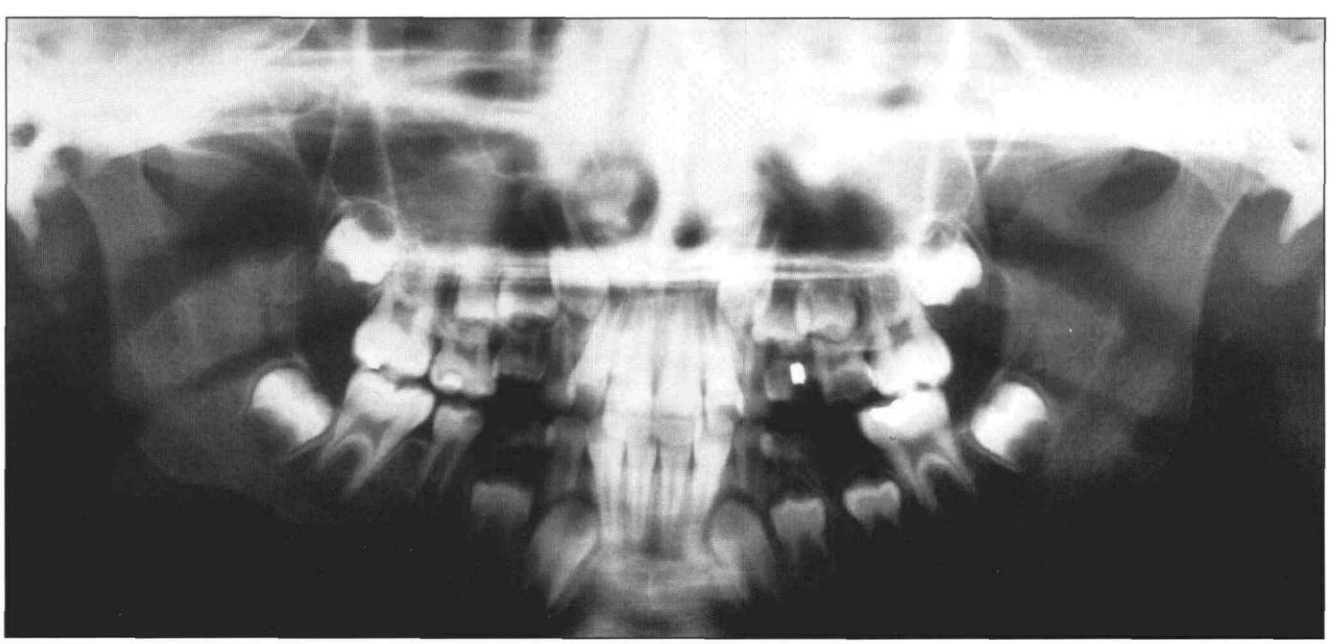

Fig 1A. Panoramic radiograph of an 8-year-old boy diagnosed with a B-cell lymphoma at 4.2 years of age showing short "v"-shaped roots of the first permanent molars.

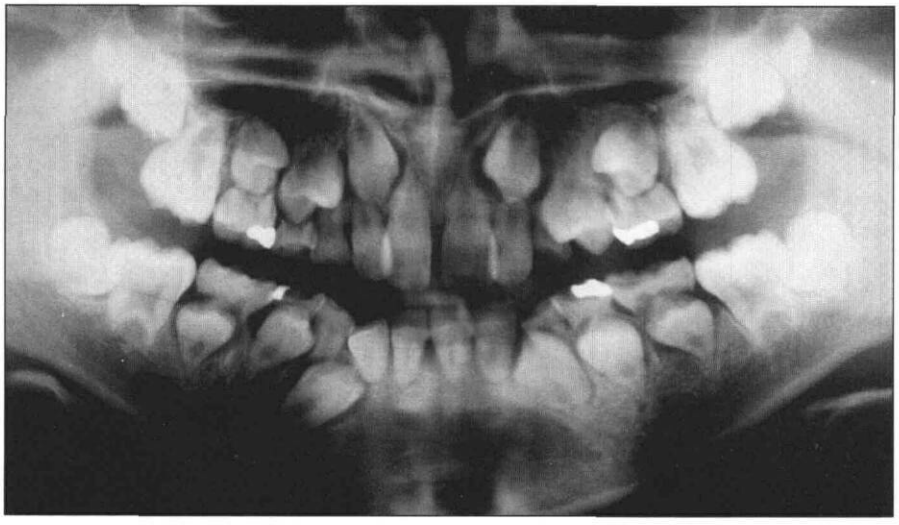

Fig 1B. An 11-year-old boy diagnosed with acute lymphoblastic leukemia at 4.8 years of age, treated with BMT at 5.4 years of age exhibiting severe disturbances in dental development.

2.2 years after TBI, no statistically significant differences in salivary secretion rate were found compared with pre-TBI values. Studies on salivary secretion in children treated for malignant diseases are few. Fromm, et al.[22] studied late effects in 20 children treated for soft tissue sarcomas of the head and neck. Severely reduced parotid secretory activity tended to follow radiation doses ≥ 45 Gy to >50% of the parotid gland volume. Eight of 11 parotid glands receiving these radiation doses failed to secrete. In our study, eight of 19 children had a salivary secretion rate ≤ 0.5 ml/min. Contrary to our previous report,[23] 3.4 years after BMT a significantly reduced salivary secretion rate was found in children receiving a 10 Gy single dose TBI. The results of this study indicates that 10 Gy TBI is the primary causative agent to the reduction in salivary flow.

Thirty-two percent of the children treated with BMT exhibited high counts of mutans streptococci. A shift in the microbial flora has been seen in patients who receive radiation therapy with an increased number of mutans streptococci and lactobacilli in saliva.[5,24–26] Applying 1% chlorhexidine gel reduces the absolute bacterial counts of mutans streptococci and lactobacilli. One week after termination of therapy, the microbial counts already showed a rapid recovery in patients treated with irradiation.[20] In agreement with a previous study,[27] the buffer capacity of stimulated whole saliva was lower in children in both treated groups than in controls.

Disturbances in enamel mineralization were frequent in these groups. No statistically significant difference was found between children receiving only chemotherapy compared with those receiving 10 Gy TBI during the period of tooth formation. The clinical appearance of the disturbances in enamel mineralization are minor. In agreement with Pajari, et al.[28] and Nunn, et al.,[19] white/cream opacities were the most often diagnosed enamel lesions.

Cytotoxic drugs have a short half-life in the human body and the drugs are metabolized or excreted from within 24 hr up to a few days. Thus, the effect on fully

Table 5. Disturbances in dental development diagnosed on panoramic radiographs in 19 children conditioned with total body irradiation before bone marrow transplantation

Patient	*Age at BMT (years)*	*Age at exam. (years)*	*Diagnosis**	*Type of disturbances†*				
				I	*II*	*III*	*IV*	*V*
1	1.0	9.0	AML	6	6	8	7	–
2	1.7	7.8	ALL	6	4	6	–	2
3	2.2	7.3	CML	6	2	8	2	9
4	2.6	5.5	ALL	4	4	2	5	3
5	2.8	5.8	Gaucher	2	–	–	6	–
6	3.2	11.8	AML	4	24	4	1	3
7	4.3	12.3	ALL	13	10	–	5	4
8	5.4	11.6	ALL	10	18	–	2	2
9	5.8	10.7	AML	4	–	–	1	1
10	7.2	10.3	Lymphoma	–	–	1	–	–
11	8.1	14.2	AML	12	2	1	–	4
12	8.1	13.1	AML	5	3	–	4	2
13	9.2	15.0	ALL	4	–	1	2	–
14	9.3	12.3	ALL	9	3	–	3	–
15	9.7	16.7	Gaucher	10	–	–	–	8
16	10.1	14.1	Immunodef.	8	–	–	–	6
17	10.1	16.2	ALL	4	8	–	4	–
18	10.7	16.7	AML	4	–	–	–	–
19	11.6	17.6	ALL	3	–	–	1	–

* AML = acute myelogenous leukemia, ALL = acute lymphoblastic leukemia, CML = chronic myelogenous leukemia.

† Classification of disturbances: I) arrested root development with short "v"-shaped roots, II) arrested root development with premature apical closure, III) enamel hypoplasia, IV) microdontia, and V) aplasia.

differentiated cells as ameloblasts and odontoblasts will only be transient, and undifferentiated surviving cells will continue to differentiate.[29,30] Radiation therapy as chemotherapy induces qualitative changes in enamel but also — to a greater degree — quantitative changes as seen in the increased prevalence of disturbances in root formation and microdontia in children treated with TBI, indicating that the cells in the Hertwig's root sheath are extremely radiosensitive.[31] The severity and extent of disturbances in tooth formation are related to age at TBI. Children treated between 3.2 and 5.4 years of age exhibited the most severe disturbances. At this age interval, root formation is in initial stage for all permanent teeth except the second and third molar. The results also indicate that there are individual differences between patients — the same treatment results in a variable number of teeth affected and severity of the lesions in different individuals. These results support Sonis, et al.[7] who showed that children younger than 5 years old who had received cranial irradiation in combination with combination chemotherapy exhibited disturbances in dental development — mainly in root development. The teeth affected were the posterior maxillary teeth. It is possible that previous cranial irradiation to nine patients in the chemotherapy group may have affected the results.

Conclusions

In conclusion, the results of this study showed:

1. No increased caries prevalence in children subjected to anti-neoplastic therapy
2. Children treated with TBI during BMT exhibited a decreased salivary secretion rate
3. Enamel disturbances were equally distributed in children treated with chemotherapy only or TBI
4. Children treated with TBI exhibited severe disturbances in root development.

Furthermore our results showed that children who completed antineoplastic therapy should be subjected to follow-up examinations with specific attention to disturbances in growth and development, but also to caries prevention, salivary function, and changes in the oral microflora.

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Curtis L. Mathis, Jr. ~ Waco, Texas
Kraig C. McKee ~ Pittsburgh, Pennsylvania
Timothy E. McNutt, Sr. ~ Nashville, Tennessee
Alton G. McWhorter ~ Dallas, Texas
Barbara J. Merlo ~ Munster, Indiana
Mark L. Meyer ~ Winston-Salem, North Carolina
Anthony F. Morelli ~ LaGrange, Illinois
Mary M. O'Connor ~ San Diego, California
Kenneth B. Rogers ~ Winter Haven, Florida
Michael S. Rosenbaum ~ Dresher, Pennsylvania
Brian J. Sanders ~ Indianapolis, Indiana
David E. Shapter ~ Erie, Pennsylvania
Daniel J. Shoemaker ~ Middletown, Connecticut
Maureen T. Short ~ Diamond Bar, California
John M. Smith ~ Parma Heights, Ohio
Chester K. Smyth ~ Salt Lake City, Utah
Roberto Solares ~ Mexico City, Mexico
Edward A. Souza ~ Ft. Riley, Kansas
Wayne E. Svoboda ~ Clarksville, Tennessee
Fredric S. Tatel ~ Glenwood, Illinois
Luke Y. Teruya ~ Kaneohe, Hawaii
Richard J. Thill ~ Anaheim, California
John B. Thornton ~ Birmingham, Alabama
Wayne Turk ~ Scarsdale, New York
Bradley J. Vance ~ Tacoma, Washington
R. Michael Weaver ~ Fayetteville, North Carolina
Theresa M. White ~ Oklahoma City, Oklahoma
B. Gene Whitehead ~ Clearwater, Florida