Am. J. Hum. Genet. 41:454–464, 1987

Mortality in Achondroplasia

JACQUELINE T. HECHT,* CLAIR A. FRANCOMANO,‡ WILLIAM A. HORTON,* AND J. FRED ANNEGERS†

*Department of Pediatrics and †School of Public Health, University of Texas Health Science Center, Houston; and ‡Departments of Medicine and Pediatrics, The Johns Hopkins Hospital, Baltimore

SUMMARY

Standardized mortality ratios (SMRs) were determined for a historical cohort of achondroplastic individuals identified through the Medical Genetics Clinics of the University of Texas Health Science Center at Houston and Johns Hopkins Hospital, Baltimore. Mortality was increased at all ages, with an overall SMR of 2.27 (95% confidence interval 1.7–3.0). Sudden death accounted for the excess deaths in those <4 years of age, and brain-stem compression was identified as the cause in half of these deaths. Central nervous system and respiratory causes were not significantly increased but accounted for half of the deaths in those 5–24 years of age. SMRs were not significantly increased for those >34 years of age. However, deaths attributed to cardiovascular causes were increased in the 25–54-year-old age group, accounting for 10 of 17 deaths. The overall cardiovascular SMR was 5.2 (95% confidence interval 2.5–9.6). Within this group, severe disability resulting from marked spinal canal stenosis was present in a majority of individuals and may have been a contributing factor in these deaths. This study suggests that the bony abnormalities associated with achondroplasia—i.e., foramen magnum and spinal canal stenosis—may have a significant effect on mortality at all ages but particularly in children. Efforts to minimize these complications are recommended.

INTRODUCTION

Achondroplasia is an autosomal dominant dwarfing condition characterized by macrocephaly and rhizomelic shortening of the extremities (Scott 1977). This

Received September 29, 1986; revision received March 3, 1987.

Address for correspondence and reprints: Jacqueline T. Hecht, Department of Pediatrics, P.O. Box 20708, University of Texas Medical School, Houston, TX 77225.

© 1987 by the American Society of Human Genetics. All rights reserved. 0002-9297/87/4103-0010$2.00

Zydus EX1029
U.S. Patent No. 12,233,106

disorder has been well recognized throughout history (Nelson 1970), and during the past 25 years the natural history has been well studied (Scott 1977). Although certain aspects of morbidity in achondroplasia are well understood, there has until recently been little information about causes of mortality. Individual case reports have suggested (Marin-Padilla and Marin-Padilla 1977; Yang et al. 1977; Bland and Emery 1982)—and the results of a recent case series (Pauli et al. 1984) have demonstrated—that sudden death in early childhood has increased. These early deaths have been attributed to acute brainstem compression resulting from foramen magnum and upper cervical spine stenosis (Pauli et al. 1984). These findings have raised the question of whether mortality in achondroplasia might be altered at other ages. This study was undertaken (1) to determine whether patterns of mortality in achondroplasia differed from those in the general population and, if so, (2) to identify and quantify the observed differences by age and cause of death.

SUBJECTS AND METHODS

A cohort of 733 achondroplastic individuals was identified through the Medical Genetics Clinics of the University of Texas Health Science Center in Houston and The Johns Hopkins Hospital in Baltimore. All diagnoses were confirmed by review of medical records, roentgenograms and/or radiographic reports, and, where available, photographs.

Total person-years were calculated for each individual from the date of his or her first clinic visit to the date of either death, last clinic visit, or most recent contact by telephone or letter. Those who were seen only once and for whom no additional follow-up could be obtained were not included in the study. Age-specific person-years of observation were tabulated. Deaths and specific causes were obtained from death certificates.

The expected number of deaths was determined by multiplying the 1975 general population age-specific mortality (U.S. Department of Health, Education and Welfare 1977) by the person-years in each age group. A standardized mortality ratio (SMR) was calculated for each age group by dividing the observed number of deaths by the expected number of deaths. The 95% confidence interval (CI) for each SMR was calculated by assuming Poisson distribution (Haenszel et al. 1962). Age-specific mortality was calculated by dividing the number of observed deaths by the person-years in each age group and then was compared with that of the general population. Life-table analysis was used to calculate the cumulative mortality and percent survival in each age group (Cutler and Ederer 1958).

RESULTS

Initially, 733 individuals with achondroplasia were identified. Of these, 32 were seen only once, contributed no person-time to the study, and therefore were not included in the study. The final study group was composed of 701 persons, contributing 5,828 person-years of follow-up. The ages at identification and age-specific distribution of the person-years of follow-up are presented in table 1.

TABLE 1

ACHONDROPLASTIC INDIVIDUALS ENTERING EACH INTERVAL AND PERSON-YEAR DISTRIBUTIONS BY AGE FOR THOSE ENTERING AND CARRIED FORWARD FROM THE PRECEDING INTERVAL

Age (Years)	*N*	Person-Years of Follow-up
<1	150	77.3
1–4	120	633.2
5–14	144	1,405.3
15–24	100	1,156.4
25–34	79	903.1
35–44	46	629.0
45–54	46	544.0
55–64	8	315.4
65–74	7	95.5
≥75	1	68.8
	701	5,828.0

Fifty-three deaths, 51 of which were documented by death certificates, were identified in this cohort. Two deaths occurred outside the United States, and death certificates could not be obtained; one of these two deaths was documented by means of parental correspondence in the medical records, the other by a close family friend. Postmortem examinations were done on 29 individuals, but only 11 were available for review.

Figure 1 shows that the age-specific SMRs were increased at all ages and were significantly elevated up to 34 years (fig. 1). The overall SMR of 2.27 (95% CI 1.7–3.0) was significantly increased. The age-specific mortalities showed an increased mortality through age 54 (fig. 2).

Since the mortality experience of the study group could have been biased by persons seeking medical attention for illness related to early death, the mortality experience was recalculated in two ways. Initially, the first year of follow-up was deleted for all individuals. This resulted in a loss of 11 deaths: six in the <1-year-old age group, three in the 1–4-year-old age group, one in the 15–24-year-old age group, and one in the 45–54-year-old age group. The resulting overall SMR was still significantly increased at 2.06 (95% CI 1.3–3.2). The SMR (fig. 3) and age-specific mortality curves were the same as those found when total person-year data were used, with the exception of the <1-year-old age group, which was therefore removed from the analysis.

Second, the data were stratified by duration of follow-up in intervals of 0–2, 2–5, 5–10, and >10 years. SMRs for each duration are shown in table 2. Again, excess mortality and significant SMR were found for the first 2 years, during which mortality is due primarily to sudden death. The SMRs for the 2–5 and 5–10-year intervals were not significant, whereas that for >10 years duration was significant at 3.8 (95% CI 2.3–5.9). These findings suggest that those seeking

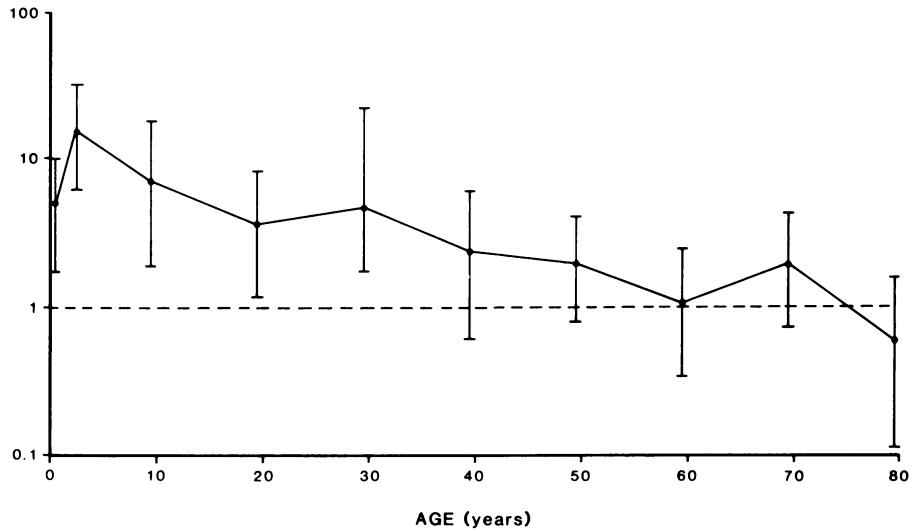

FIG. 1.—Standardized mortality ratio (SMR) curve by age. The SMR is compared to 1 (represented by the horizontal line), which indicates no association. The 95% CI for each point is shown by the bars. The CI includes 1 for ages >35 years.

clinical evaluation were not doing so for medical problems related to early death.

The cause of death was analyzed in the three groups showing the highest SMRs—i.e., the <1-year-old, the 1–4-year-old, and the 5–14 year-old age groups (table 3). Sudden death was reported as the immediate cause of death in nine of 13 patients dying before the age of 5 years. Brain-stem compression was detected in three of the four cases in whom complete autopsies were performed; one of these three cases was in the <1-year-old age group, and two were in the 1–4-year-old age group. In addition, two children died postoperatively—one, 2 years of age, in whom brain-stem compression was found and another, 13 years of age, in whom a subependymoma involving the upper cervical cord was found (Hecht et al. 1984).

Respiratory and central nervous system causes of death accounted for six of the 15 deaths in those 5–24 years of age (table 3). Other common causes of death—e.g., cancer, diabetes, and suicide—were not, as a whole, increased in this group (table 3).

Cardiovascular causes of death accounted for 10 of the 17 deaths in the three age groups that, together, included those 25–54 years of age (fig. 4). The overall cardiovascular SMR for this larger group was significantly increased at 5.2 (95% CI 2.5–9.6), but only SMRs for the 25–34-year-old and 45–54-year-old age groups were significantly increased (fig. 4). Postmortem examinations confirmed the cause of death in only three of these 10 deaths. Six individuals were noted to have marked spinal canal stenosis and disability. In addition, hypercholesterolemia, pulmonary compromise, and morbid obesity were present in one individual each.

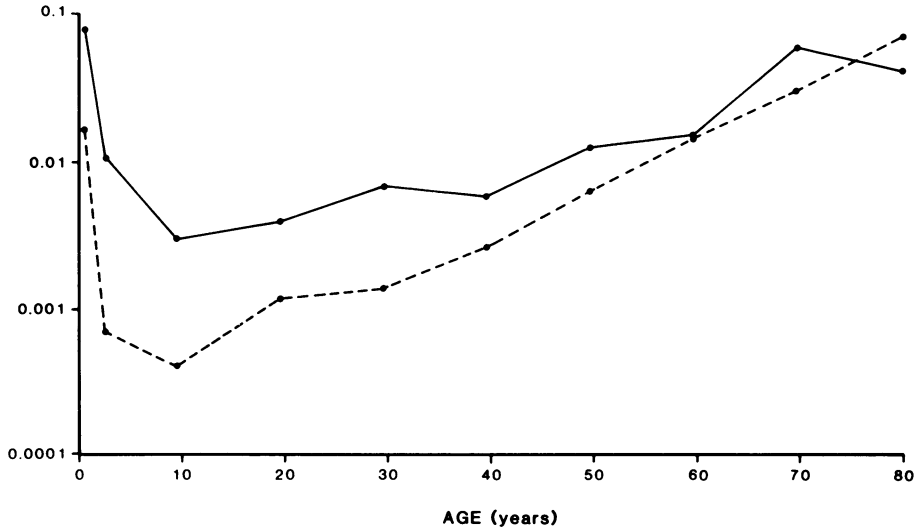

FIG. 2.—Normal (dashed line) and achondroplastic (solid line) significantly age-specific mortality. The overall pattern of mortality is similar—although in achondroplasia it is increased up to 34 years of age.

The survival curve for the entire cohort is shown in figure 5. There was a 7.5% risk of dying during the first year, a 12% risk up to 4 years, and a 14% risk up to 14 years, compared with respective risks of 1.6%, 1.9%, and 2.3% in the general population (fig. 5). For this cohort, the mean survival in those with achondroplasia was 61 years, compared with 71 years for the general population (fig. 5). However, as figure 6 shows, the survival experience for individuals entering the cohort at various adult ages is different; these latter survival curves exclude the high mortality experience of childhood and show a better survival than do the survival curves of the cohort as a whole.

DISCUSSION

The results of the present study demonstrate that mortality in those with achondroplasia is increased at all ages. Mortality from all causes was significantly increased from birth to 34 years of age, and mortality attributed to cardiovascular causes was increased between the ages of 25 and 54 years. The survival curves for the entire cohort revealed that the mean life expectancy for the patient with achondroplasia is ~10 years less than that for the general population. However, life expectancy was relatively better in those who survived early childhood.

This study was based on a cohort of individuals identified through two medical genetics clinics. The use of such patients was of concern because of the possibility that they had sought medical care for illnesses that led to their death shortly afterward. However, recalculation of the SMRs after removing the first

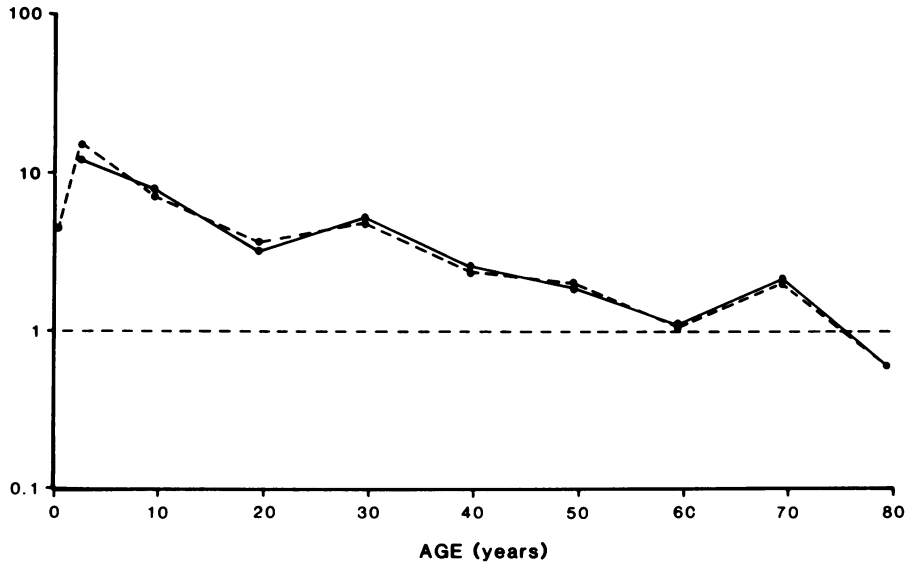

FIG. 3.—Standard-mortality-ratio curve for total person-years (represented by the dashed line) and person-year minus 1-year curve (represented by the overlapping solid line) are shown. For the latter curve, there is no value for the <1-year-old age group because all deaths occurred prior to the first year of follow-up and thus drop out of the calculation. The curves show the same pattern of mortality and overlap, suggesting that persons entering the cohort were not dying shortly after their first clinic visit and thus biasing the results.

person-year follow-up and by duration of time in study indicated that no such bias had been introduced in the initial calculations—i.e., that survival experience was not biased by sick individuals.

The most common immediate cause of death during the first 4 years of life was sudden death, which accounted for nine of 13 deaths. Indeed, the risk of dying suddenly during the first year was 7.5%, and between the ages of 1 and 4 years it was 2.5%. The specific cause of death was not determined in six cases, but brain-stem compression was detected in three of the four cases in whom complete autopsies were performed. In addition, one child 2 years of age and

TABLE 2

SMR BY DURATION OF TIME IN STUDY

Years after Entry into Study	SMR (CI)
0–2	2.4 (1.3–3.9)
2–5	0.9 (0.3–1.8)
5–10	1.6 (0.9–2.8)
>10	3.8 (2.3–5.9)

TABLE 3

IMMEDIATE CAUSE OF DEATH FOR 53 INDIVIDUALS WITH ACHONDROPLASIA

Age (in years) and Immediate Cause of Death	N
1:	
Sudden death	6
1–4:	
Sudden death	3
Brain-stem compression	1
Aortic stenosis	1
Accidental causes	1
Pneumonia	1
Total	7
5–14:	
Hydrocephalus	2
Cervical subependymoma	1
Pneumonia	1
Total	4
15–24:	
Pneumonia	1
Apnea	1
Seizure	2
Accidental causes	1
Total	5
25–34:	
Cardiovascular causes	2
Brain-stem compression	1
Meningitis	1
Alcohol	1
Accidental causes	1
Total	6
35–44:	
Cardiovascular causes	2
Seizure	1
Suicide	1
Total	4
45–54:	
Cardiovascular causes	6
Diabetic nephropathy	1
Total	7
55–64:	
Cardiovascular causes	2
Cancer	2
Accidental causes	1
Total	5
65–74:	
Cardiovascular causes	5
Cancer	1
Total	6
≥75:	
Cardiovascular causes	2
Emphysema	1
Total	3

NOTE.—Numbers are actual number dying of that specific cause; in some cases, autopsy findings differed from immediate cause of death as listed on death certificate.

one child 13 years of age died following surgery to correct brain-stem and upper cervical spinal cord compression, respectively. These data support previous findings that foramen magnum and cervical spine stenosis and associated compression of the lower brain stem and spinal cord (1) is a clinically significant problem in achondroplasia (Hecht et al. 1985) and (2) may lead to sudden death during early childhood (Pauli et al. 1984).

No particular cause accounted for the increased mortality between the ages of 5 and 24 years. However, problems related to the central nervous system (three cases) and respiratory systems (four cases) accounted for two-thirds of these deaths (table 3).

Cardiovascular causes of death were significantly increased between the ages of 25 and 54 years and accounted for 10 of 17 deaths in this age group. The

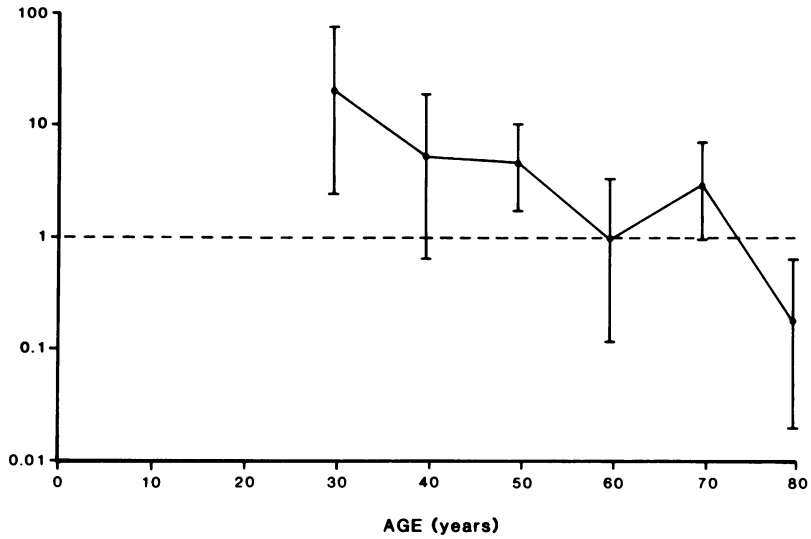

FIG. 4.—Cardiovascular SMR curve by age. The SMR value was compared to 1, (represented by the dashed horizontal line), which is the null value of no association. The 95% CI for each value is shown by the vertical bars. Cardiovascular mortality is significantly increased in the 25–34-year-old and 44–54-year-old age groups.

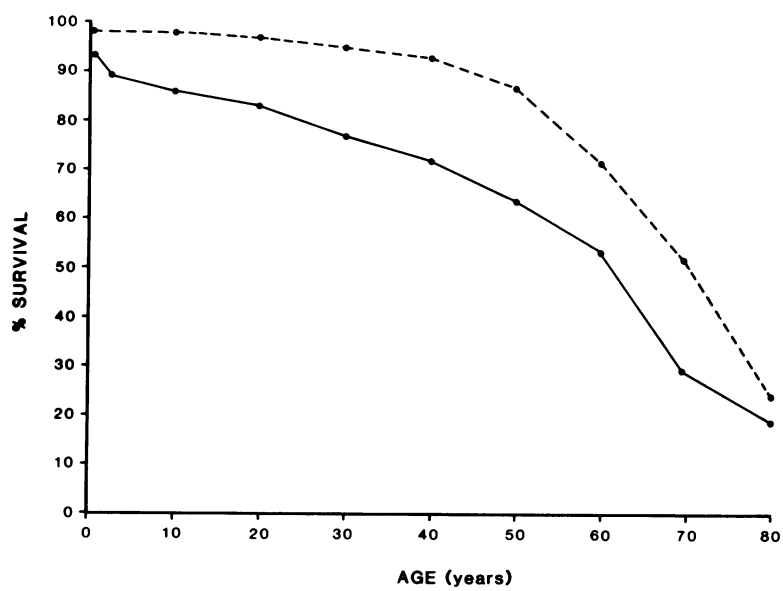

FIG. 5.—Normal (dashed line) and achondroplastic (solid line) survival curves. Survival for each group was calculated as $1 - (1 - e^{-ID(\Delta T)}$, and cumulative survival was calculated as $1 - (1 - e^{-\mathrm{sum}ID(\Delta T)}$, where ID = incidence density and T = time interval.

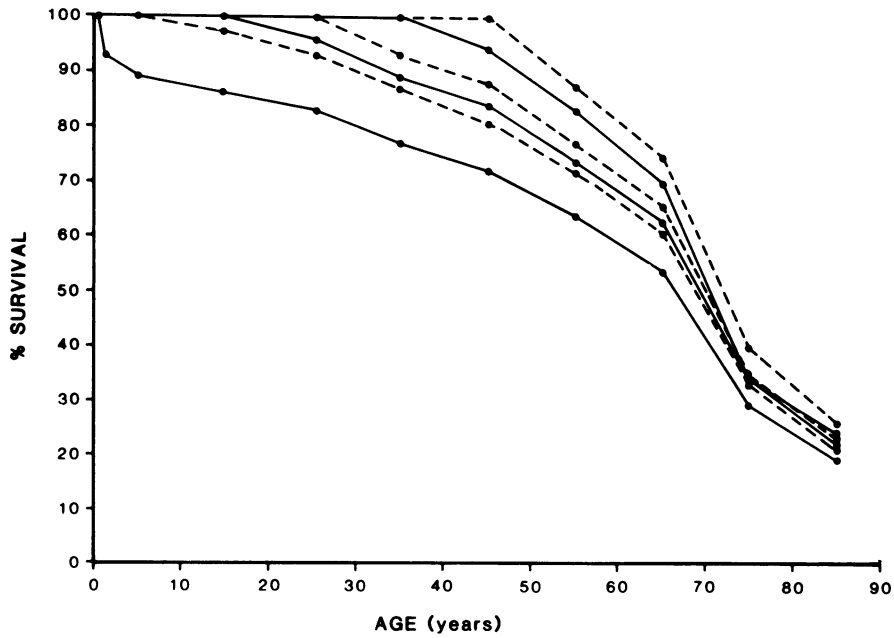

FIG. 6.—Survival curves based on time of entry into the cohort, compared with the survival curve of the entire achondroplasia cohort (bottom solid line) (survival calculated as in fig. 5). The former curves show relatively better survival because they do not include the increased mortality experience of early childhood.

factors responsible for this increase are presently unknown. One possibility is misclassification, since only three of the 10 cardiovascular deaths were documented by postmortem examination. Six of these 10 individuals had a history of moderate to severe disability from spinal canal stenosis, and spinal canal compression may have contributed to their sudden deaths. Alternatively, severe spinal compromise may be a factor predisposing to cardiovascular death. For example, cardiovascular deaths are reportedly increased in the transverse myelitis population (Hackler 1977; Chap and Price 1982). Other known major cardiovascular risk factors, such as hypertension and hyperlipidemia, were incompletely documented in the patient files, and currently there is no data as to whether cardiovascular risk factors occur more commonly in achondroplasia than in the general population.

The results of the present study have important implications for the management of achondroplasia. First, the greatest threat to life during the first 5 years, especially during the first year, is from sudden death—most likely to be due to compression of the brain stem and/or upper cervical spinal cord. Evaluation of this physiological area through radiographic (i.e., computerized tomography and magnetic resonance imaging) and neurophysiologic (i.e., somatosensory evoked potential studies, polysomnography, and complete neurologic examina-

tion) testing should be considered a part of routine care for children at least up to the age of 5 years. Second, particular attention should be given to respiratory complaints, especially during the first 3 decades of life. Last, adults with achondroplasia should be carefully evaluated for cardiovascular risk factors—including family history, hypertension, hyperlipidemia, obesity, and smoking—and every effort should be made to minimize them.

Although life expectancy in those with achondroplasia was found to be shortened, there may be prognostic indicators that differentiate those at high risk for life-threatening sequelae. For example, severely disabled adult individuals may be at greater risk than those with little or no disability. Aggressive medical intervention at all ages to avoid the complications of spinal canal stenosis may help to shift life expectancy toward that of the general population.

ACKNOWLEDGMENT

We wish to thank Bob Schwartz for excellent computer assistance, Barbara Bernhardt, Kay Smith, and the "little people" and their families, who provided important follow-up information on individuals in this study. This study was partially supported by National Institutes of Health grant HD20691, March of Dimes clinical research grant 6-363, and the Garrett Research Fund of the Johns Hopkins Hospital.

REFERENCES

Bland, J. D., and J. L. Emery. 1982. Unexpected death of children with achondroplasia after the perinatal period. Dev. Med. Child Neurol. **24**:489–492.

Chap, T. L., and M. Price. 1982. Survival from spinal cord injury. J. Chronic Dis. **35**:487–492.

Cutler, A. J., and F. Ederer. 1958. Maximum utilization of the life table method in analyzing survival. J. Chronic Dis. **8**:699–712.

Hackler, R. H. 1977. A 25 year prospective mortality study in the spinal cord injured patient: comparison with long-term living paraplegic. J. Urol. **117**:486–488.

Haenszel, W., D. B. Loveland, and M. G. Sirhen. 1962. Lung cancer mortality as related to residence and smoking histories in white males. J. Natl. Cancer Inst. **28**:1001.

Hecht, J. T., I. J. Butler, and C. I. Scott. 1984. Long-term neurological sequelae in achondroplasia. Eur. J. Pediatr. **143**:58–60.

Hecht, J. T., F. W. Nelson, I. J. Butler, W. A. Horton, C. I. Scott, Jr., E. R. Wassman, C. M. Mehringer, D. L. Rimoin, and R. M. Pauli. 1985. Computerized tomography of the foramen magnum: achondroplastic values compared to normal standards. Am. J. Med. Genet. **20**:355–360.

Marin-Padilla, M., and T. M. Marin-Padilla. 1977. Developmental abnormalities of the occipital bone in human chondrodystrophies (achondroplasia and thanatophoric dwarfism). Birth Defects Original Article Ser. **13**:7–23.

Nelson, M. A. 1970. Orthopaedic aspects of the chondrodystrophies: the dwarf and his orthopaedic problems. Ann. R. Coll. Surg. Engl. **47**:185–210.

Pauli, R. M., C. I. Scott, Jr., E. R. Wassman, Jr., E. F. Gilbert, L. A. Leavitt, J. Ver Hoeve, J. G. Hall, M. W. Partington, K. L. Jones, A. Sommer, W. Feldman, L. O. Langer, D. L. Rimoin, J. T. Hecht, and R. Lebowitz, 1984. Apnea and sudden unexpected death in infants with achondroplasia. J. Pediatr. **104**:342–348.

Scott, Jr., C. I. 1977. Medical and social adaptation in dwarfing conditions. Birth Defects Original Article Ser. **13**:29–43.

U.S. Department of Health, Education and Welfare. 1977. Vital statistics of the United States 1975. Vol. **2**. U.S. Department of Health, Education and Welfare, Hyattsville, MD.

Yang, S. S., D. P. Corbett, A. J. Brough, K. P. Heidelberger, and J. Bernstein. 1977. Upper cervical myelopathy in achondroplasia. Am. J. Clin. Pathol. **68**:68–72.