Progress in Pediatric Hematology/Oncology, Volume II

# BONE TUMORS IN CHILDREN

Norman Jaffe, M.B. Bch., Dip. Paed.

Progress in Pediatric Hematology/Oncology, Volume II

# BONE TUMORS IN CHILDREN

**Norman Jaffe, M.B. Bch., Dip. Paed.**
Professor of Pediatrics, University of Texas Cancer Center
Division Chief, Division of Solid Tumors
M.D. Anderson Hospital and Tumor Institute
Houston, Texas

**Carl Pochedly, M.D.**
**Denis R. Miller, M.D.**
Series Editors

PSG Publishing Company, Inc.
Littleton, Massachusetts

Library of Congress Cataloging in Publication Data
Main entry under title:

Bone tumors in children.

(Progress in pediatric hematology/oncology ; v. 2)
Includes index.
1. Bones—Tumors. 2. Tumors in Children.
I. Jaffe, Norman. II. Series. [DNLM: 1. Bone neoplasma—In infancy and childhood. W1PR677E v. 2 / WE258 B7121]
RC280.B6B68 618.9'29'9471. 77-94881
ISBN 0-88416-142-0



Printed in the United States of America.

International Standard Book Number: 0-88416-142-0

International Standard Book Series Number: 0-88416-136-6

Library of Congress Catalog Card Number: 77-94881

# EDITORS AND CONTRIBUTORS

Progress in Pediatric Hematology/Oncology
Volume II
BONE TUMORS IN CHILDREN

**Series Editors**

Carl Pochedly, M.D.
Denis R. Miller, M.D.

**Contributors to this Volume**


Norman Jaffe, M.B. Bch., Dip. Paed.
Professor of Pediatrics
University of Texas Cancer Center
Division Chief, Division of Solid Tumors
M.D. Anderson Hospital & Tumor Institute
Houston, Texas

John G. Camblin, M.D.
Staff Physician, Orthopedics Section
Veterans Administration Hospital
Instructor, Department of Orthopedics
College of Medicine
University of Florida
Gainesville, Florida

J. Robert Cassady, M.D.
Associate Professor of Radiation Therapy
Harvard Medical School
Radiotherapist, Joint Center for Radiation Therapy
Children's Hospital Medical Center
Boston, Massachusetts

David C. Dahlin, M.D.
Chairman, Department of Surgical Pathology
Mayo Clinic and Mayo Foundation
Professor of Pathology
Mayo Medical School
Rochester, Minnesota

Frederick R. Eilber, M.D.
Associate Professor of Surgery
Division of Oncology
School of Medicine
University of California
Los Angeles, California

William F. Enneking, M.D.
Professor and Chairman
Department of Othopedics
College of Medicine
University of Florida
Gainsville, Florida

Robert M. Filler, M.D.
Surgeon-in-Chief
Hospital for Sick Children
Professor of Surgery
University of Toronto
Toronto, Ontario, Canada
Formerly Chief of Clinical Surgery
Children's Hospital Medical Center and
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Todd T. Grant, M.D.
Assistant Professor of Othopedic Surgery
Division of Orthopedics
Department of Surgery
School of Medicine
University of California
Los Angeles, California

Sydney Heyman, M.D.
Nuclear Radiologist
Children's Hospital Medical Center
Instructor of Radiology
Harvard Medical School
Boston, Massachusetts

Ronald B. Irwin, M.D.
Resident in Orthopedics (Oncology)
Mayo Graduate School of Medicine University of Minnesota
Rochester, Minnesota

John A. Kirkpatrick, M.D.
Radiologist-in-Chief
Children's Hospital Medical Center
Professor of Radiology
Harvard Medical School
Boston, Massachusetts

Ralph C. Marcove, M.D.
Chief, Bone Tumor Service
Hospital for Joint Diseases
Associate Attending at Memorial Sloan-Kettering Cancer Center and the Hospital for Special Surgery
Clinical Associate Professor of Surgery
Cornell University Medical College
New York, New York

Donald L. Morton, M.D.
Associate Professor of Surgery
Division of Oncology
School of Medicine
University of California
Los Angeles, California

Antoinette L. Pieroni, ACSW
Chief Social Worker
Sidney Farber Cancer Institute
Boston, Massachusetts

Gerald Rosen, M.D.
Attending Pediatrician, Department of Pediatrics
Memorial Sloan-Kettering Cancer Center
New York, New York

Fritz Schajowicz, M.D.
Professor of Pathology
Faculty of Medicine
University of Buenos Aires
Italian Hospital
Buenos Aires, Argentina

Franklin H. Sim, M.D.
Consultant, Department of Orthopedics
Mayo Clinic and Mayo Foundation
Assistant Professor of Orthopedic Surgery
Mayo Medical School
Rochester, Minnesota

Wataru W. Sutow, M.D.
Pediatrician, M.D. Anderson Hospital & Tumor Institute
Professor of Pediatrics
University of Texas System Cancer Center
Houston, Texas

Salvador Treves, M.D.
Chief, Pediatric Nuclear Medicine
Children's Hospital Medical Center
Instructor of Radiology
Harvard Medical School
Boston, Massachusetts

Hugh Watts, M.D.
Assistant Professor in Orthopedics
Harvard Medical School
Associate in Orthopedic Surgery
Children's Hospital Medical Center
Boston, Massachusetts

Ralph R. Weichselbaum, M.D.
Assistant Professor of Radiation Therapy
Harvard Medical School
Radiotherapist, Joint Center for Radiation Therapy
Radiotherapist
Peter Bent Brigham Hospital
Boston, Massachusetts

Robert H. Wilkinson, M.D.
Radiologist
Children's Hospital Medical Center
Associate Professor of Radiology
Harvard Medical School
Boston, Massachusetts

# PREFACE

Bone cancer serves as a prototype for the coordinated multidisciplinary treatment of malignancy. Such treatment is essential if optimum results are to be achieved. Therapy also must be carefully integrated since occasionally concepts appear as opposing forces. This is not unexpected since the "correct" treatment for most cancers is by no means firmly established. A fundamental principle, however, is that the plan of management must be sufficiently flexible to accommodate changing circumstances.

No attempt has been made to disguise controversies or differences of opinion. These emerged on a number of occasions between contributors and myself and, indeed, are known to exist among other contributors. This is illustrated particularly in the growing interest in limb preservation for osteosarcoma where diverse approaches center on operative technique, types of endoprostheses and use of preoperative chemotherapy and radiation therapy. This manual is replete with such diversities—an inevitable consequence of new discoveries and innovative changes.

Whenever concepts could not be resolved, authors were permitted wide discretion to express their own views. This resulted in some degree of overlap and duplication. However, it is precisely in the differences and diverse opinions that the strength of this work must lie. Inevitably, contemporary forms of treatment will be provided but the controversy surrounding such treatment must provoke vigorous stimuli to improve the results and prevent complications.

The responsibility of weighing the decision, examining the controversy and implementing treatment is assumed by the primary physician. He must serve as a patient's anchor to windward and often support his charge through a perilous journey. To alleviate his burden, this book has summoned assistance from the accumulated experience of investigators from diverse disciplines. It is in this spirit that I express a sense of deep gratitude to my distinguished colleagues and contributors without whose help and expertise this work would not have materialized.

Norman Jaffe

# CONTENTS

# 1 Malignant Bone Tumors in Children: Incidence and Etiologic Considerations

Norman Jaffe, M.B.Bch., Dip.Paed.

1. Host factors
   a. Growth
   b. Sex
   c. Metabolism
   d. Familial and genetic factors
   e. Ethnic factors
   f. Immune defects
   g. Target cell
2. Environmental factors
   a. Viruses
   b. Trauma
   c. Ionizing radiation
   d. Chemicals

Cancer ranks second behind accidents as the most common cause of death in children under 14 years of age.[1,2] Among cancers, the malignant bone tumors are relatively rare, occurring sixth in general incidence and in the following order: leukemia, tumors of the central nervous system, tumors of lymphoid tissue, neuroblastoma, Wilms' tumor, bone cancer, rhabdomyosarcoma, and retinoblastoma. Table 1 adapted from the Third National Cancer Survey, depicts the incidence of malignant tumors in 1,925 white children diagnosed between 1969 and 1971.[3] A similar incidence was observed in 225 black children.

The etiology of the skeletal sarcomas is unknown. Speculation draws primarily on factors derived from exogenous sources, particularly radiation therapy or viruses acting on host factors, but genetic influences must also be considered.

Investigations reported in this chapter were supported in part by research grant CA-06516 from the National Cancer Institute and by grant RR-05526 from the Division of Research Facilities and Resources, National Institutes of Health.

**Table 1**
**Malignant Neoplasms in White Children under Fifteen Years of Age in the United States**

| Diagnosis | No. of Cases | Rate* |
|---|---|---|
| Leukemia | 651 | 42.1 |
| Lymphoma | 204 | 13.2 |
| Central nervous system | 370 | 23.9 |
| Sympathetic nervous system | 148 | 9.6 |
| Neuroblastoma | 123 | |
| Other | 25 | |
| Retinoblastoma | 52 | 3.4 |
| Kidney tumor | 121 | 7.8 |
| Wilms' tumor | 117 | |
| Other | 4 | |
| Liver tumor | 29 | 1.9 |
| Bone tumor | 86 | 5.6 |
| Osteosarcoma | 51 | |
| Ewing's sarcoma | 26 | |
| Other | 9 | |
| Gonadal and germ cell tumors | 34 | 2.2 |
| Ovary | 17 | |
| Testis | 16 | |
| Other | 1 | |
| Teratoma, nongonadal | 5 | 0.3 |
| Soft tissue tumors | 130 | 8.4 |
| Rhabdomyosarcoma | 69 | |
| Other | 61 | |
| Melanoma | 11 | 0.7 |
| Miscellaneous | 84 | 5.4 |
| Total | 1,925 | 124.5 |

Adapted from Young and Miller.[3]
*Rates per million per year based on 1970 survey-area population of 5,151,699. Total U.S. 1970 population of white children under 15 years of age was 49,001,683.

## HOST FACTORS

### Growth

Osteosarcoma appears more commonly at the growing ends of bones and appears to be closely related to bone growth. This has been observed in dogs, where the relative risk of osteosarcoma in giant breeds such as the St. Bernard and Great Dane is approximately 200 times that for small- or medium-sized breeds, and a similar pattern has been detected in humans.[4-8] The incidence of osteosarcoma in humans appears to peak in two age groups. The first peak is in the 10- to 20-year-old age group, coinciding with the pubertal growth spurt. The second occurs at a more advanced age and may possibly be related to incidence of Paget's disease.

## Sex

Osteosarcoma is distinctly more common in males, and this may also be related to bone growth. Average heights, by individual years of age, for boys and girls are similar (although the pubertal growth spurt in females has a somewhat earlier onset, and this may account for the earlier appearance of bone tumors in girls). Also until the age of 13, mortality rates from bone cancer are virtually identical for both sexes. After age 13, however, boys grow taller than girls, and the mortality rate for boys exceeds that for girls.[6]

## Metabolism

Several studies have revealed abnormalities in carbohydrate metabolism and in insulin and somatomedin levels in patients with osteosarcoma.[9,10] Two abnormal patterns of glucose metabolism have been detected. The first is reflected by a glucose tolerance curve which is compatible with "chemical diabetes" coupled with hyperinsulinism. This was noted in patients with active disease. Reversion of the abnormal carbohydrate patterns to normal accompanied arrest of the tumor. High levels of somatomedin were also found. The latter is inhibited by estradiol, and since estrogens have been used to arrest linear growth in females, their therapeutic use in osteosarcoma was also considered.

The second pattern involved development of hypoglycemia and hypoinsulinemia following oral glucose administration. This phenomenon was seen in three patients who survived their disease. Whether the pattern is related to secretion of the hypothalamic hormone somatostatin is unknown.

Abnormal carbohydrate metabolism has also been reported in patients with chondrosarcoma and fibrosarcoma.[11,12] One author has also advanced a hypothesis suggesting that anabolic steroid hormones may promote neoplasia of bone and bone marrow at adolescence.[13]

## Familial and Genetic Factors

Incidences of osteosarcoma in siblings have been reported in several families.[14-21] The disease has also been observed in a father and daughter.[19-21] An increasing number of reports have also described an association between retinoblastoma, particularly a bilateral familial type, and the subsequent development of osteosarcoma of the lower extremities.[7,22,23] Two siblings with bilateral retinoblastoma in infancy later developed osteosarcoma of the

femur (at 9 and 11 years of age, respectively).[18] Bilateral retinoblastoma is genetically transmitted as an autosomal dominant. The foregoing data suggest that a similar genetic influence may possibly go on to produce osteosarcoma.

Familial tendencies for the development of other forms of bone cancer have also been suggested by a series of reports of siblings affected with Ewing's sarcoma and chondrosarcoma.[24 25] More recently, a new familial cancer syndrome has been suggested by the detection of benign and malignant tumors including retinoblastoma, carcinoma of the bladder, and a possible case of multifocal osteosarcoma.[26] The occurrence of osteosarcoma in one child and other malignant tumors in a brother or sister has also been reported.[14 27 28] The literature further documents several pedigrees with mammary adenocarcinoma, fibrosarcoma, brain tumors, adrenocortical neoplasms, or osteosarcoma.[14 29 30] More rarely, osteosarcoma may arise in an abnormal bone.[31 32]

### Ethnic Factors

Several investigators have reported ethnic differences in the incidence of bone cancer. For example, Ewing's sarcoma virtually does not occur in blacks or in the Japanese.[33 34] The very rare incidence of this disease in racial groups native to Africa has also been observed.[35 36] This suggests a form of genetic resistance. In contrast, there is no great difference between the incidence of osteosarcoma in blacks and in whites.

### Immune Defects

Persons with primary immune deficiency and cytogenetic syndromes are prone to certain cancers, particularly lymphoma and leukemia.[37] Malignant non-Hodgkin's lymphoma of bone is occasionally encountered in the pediatric age group, and conversion to acute lymphoblastic leukemia in this condition is not unusual. The etiology of the disease, therefore, may be linked to the etiology of leukemia. However, there is no known relationship between the etiology of leukemia and that of other primary bone cancers.

### Target Cell

The study of primary tumors of the musculoskeletal system inevitably leads to the conclusion that they represent a continuum of malignant processes originating in the mesenchymal cell. Such tumors exhibit overlapping features, and represent various degrees

of differentiation of connective tissue, muscle, smooth muscle, cartilage, and bone. Jeffree and Price have aptly stated that today's fibroblast may be tomorrow's osteoclast.[38]

The interrelationship of bone and soft tissue is evidenced by osteocytic and chondrocytic tumors originating in soft tissues, and by chondrocytic elements in metastatic soft tissue sarcomas such as cystosarcoma phyllodes.[39-43] Osteosarcoma has also been detected in solitary enchondroma, fibrous dysplasia, Maffucci's syndrome, and osteocartilaginous exostosis.[44-49]

## ENVIRONMENTAL FACTORS

### Viruses

Both soft tissue and skeletal induced oncornavirus sarcomas have been identified in mice, rats, and wooly monkeys.[50,51] However, most of the sarcomagenic viruses of animals are incomplete and require coinfection with leukemia viruses to form the viral genome fragment necessary for synthesis of the viral envelope in the host cells. That this mechanism is responsible for human sarcomas remains to be determined.

In hamsters, the incidence of "spontaneous" osteosarcoma is low. However, osteosarcomas have developed after inoculation with filtrate from human osteosarcoma.[52] Sera from patients with osteosarcoma have also reacted immunologically with these hamster osteosarcomas. This implies that the hamster tumors were induced by human osteosarcoma virus.[53]

In man, antibody and cell-mediated reactions against soft tissue and skeletal sarcomas have also been demonstrated. In particular, studies by Eilber and Morton reveal that antibodies were present in osteosarcoma patients and in 85% of their normal, healthy family members.[54] In contrast, only 29% of normal blood donors showed antibody.

These data would imply a viral etiology, though as yet, there is no concrete evidence that osteosarcoma is caused by a virus or that malignant neoplasms are contagious in the usual sense. Intense, broadly based biologic research is currently in progress, and the demonstration that a virus can be implemented in the etiology of human cancers would not be unexpected.

### Trauma

Trauma is usually associated with the discovery of bone tumors, particularly osteosarcoma, and this is generally considered

to be coincidental. It is of interest, however, that some bone infarcts have been shown to be present in the development of osteosarcoma in man.[55] Tumors of various types have been observed on the walls of bone cysts and have complicated chronic osteomyelitic sinuses.[56] This has led to the hypothesis that bone disorders with prolonged periods of excessive cellular activity are prone to producing neoplastic change.

## Ionizing Radiation

Ionizing radiation is oncogenic in man and has been responsible for the development of leukemia and other human cancers, including osteosarcoma, chondrosarcoma, and fibrosarcoma.[57-59] Radium 224 has been implicated in the development of bone sarcoma in 30 of 270 patients under the age of 20 who were treated empirically for tuberculosis.[60] The sarcoma developed at sites other than those of the primary tuberculous infection. Similar sarcomas have been documented in radium-watch-dial workers and radium chemists.[61 62]

Therapeutically administered external beam irradiation has also been implicated in the development of osteosarcoma. Tumors developed following therapy administered for a variety of benign and malignant conditions. The doses of radiation varied from 800 rad (for bursitis) to 1,300 rad (for retinoblastoma).[63 64] Postirradiation osteosarcomas have also developed in extraosseous tissue following treatment for diseases of the colon, uterine cervix, and base of the brain (suprasellar area, for pituitary tumors).[65-67] Similar factors have been linked to the development of chondrosarcomas.[68 69] No excess of bone cancer has, however, resulted from whole-body irradiation among the atomic bomb survivors in Japan.[70] Furthermore, no correlation has been found between bone cancer mortality in various countries and measurements of radioactivity in drinking water.[71] Thus, ionizing radiation would appear to be associated with development of cancer only through external high-dose irradiation as used in cancer therapy, and through external bone-seeking radioisotopes in occupational or medicinal use.[58 72]

## Chemicals

No chemically induced bone tumors have been identified in man, although the risk of chemical carcinogenesis has been demonstrated in laboratory animals. This has been reported with such diverse agents as methylcholanthrene 20, beryllium oxide, and zinc beryllium silicate.[73-77] However, the risk of bone cancer in

beryllium workers does not appear to be elevated.[78] Of as yet undertermined significance is the report of development of osteosarcoma in a patient with thalidomide embryopathy.[79]

Studies to determine the etiology of cancer are currently investigating host, epidemiologic, and environmental factors. The immunologic surveillance system is also under examination. Medical knowledge and discoveries gained in these areas will undoubtedly be applied to attempts not only to identify but also to avoid the causes of human bone cancer. At present, however, despite an increasing volume of literature and anecdotal cases, and an increasing number of research activity, this etiology remains unknown.

## REFERENCES


1. *Vital Statistics of the United States, 1973.* Vol. 2, Part B. US Department of Health, Education, and Welfare, Public Health Service, 1975.

2. *Incidence of Childhood Cancer in harris County, Texas, 1958–1970,* Leukemia Section, Center for Disease Control. February, 1972.

3. Young J.L., Jr. and Miller, R.W.: Incidence of malignant tumors in United States children. *J Pediatr* 86:254–258, 1975.

4. Tjalma, R.A.: Canine bone sarcoma: estimation of relative risks as a function of body size. *J Natl Cancer Inst* 36:1137–1150, 1966.

5. Fraumeni, J.F., Jr.: Stature and malignant tumors of bone in childhood and adolescence. *Cancer* 20:967–973, 1967.

6. Miller, R.W.: Relation between cancer and congenital defects: an epidemiologic evaluation. *J Natl Cancer Inst* 40:1079–1085, 1968.

7. Glass, A.G. and Fraumeni, J.F., Jr.,: Epidemiology of bone cancer in children. *J Natl Cancer Inst* 44:187–199, 1970.

8. Price, C.H.G.: Primary bone-forming tumours and their relationship to skeletal growth. *J Bone Joint Surg* [Br] 40:574–593, 1958.

9. McMaster, J.H.: Carbohydrate metabolism in osteosarcoma. *Orthop* (SICOT) 1:19–21, 1977.

10. Scranton, P.E., Jr., McMaster, J.H., Kenny, F.M. et al: Investigation of carbohydrate metabolism and somatomedin in osteosarcoma patients. *J Surg Oncol* 7:403–409, 1975.

11. Marcove, R.C. and Francis, K.L.: Chondrosarcoma and altered carbohydrate metabolism. *N Engl J Med* 268:1399–1401, 1963.

12. Turner, M. and Horne, C.: Primary fibrosarcoma of lung and diabetes mellitus. *Br J Surg* 57:713–715, 1970.

13. Acheson, R.M.: A hypothesis regarding the possible role of anabolic steroid hormones as promoters of neoplasia of bone and bone marrow at adolescence. *Yale J Biol Med* 36:43–52, 1963.

14. Miller, C.W. and McLaughlin, R.E.: Osteosarcoma in siblings: report of two cases. *J Bone Joint Surg* 59A:261–262, 1977.

15. Harmon, T.P. and Morton, K.S.: Osteogenic sarcoma in four siblings. *J Bone Joint Surg* 48B:493–498, 1966.

16. Pohle, E.A., Stovall, W.D., and Boyer, H.N.: Concurrence of osteogenic sarcoma in two sisters. *Radiology* 27:545–548, 1936.

17. Roberts, C.W. and Roberts, C.P.: Concurrent osteogenic sarcoma in brother and sisters. *JAMA* 105:181–185, 1935.

18. Schimke, R.N., Lowman, J.T., and Cowan, G.A.B.: Retinoblastoma and osteogenic sarcoma in siblings. *Cancer* 34:2077–2079, 1974.

19. Swaney, J.J.: Familial osteogenic sarcoma. *Clin Orthop* 97:64–68, 1973.

20. Epstein, L.I., Bixler, D., and Bennett, J.E.: An incident of familial cancer including three cases of osteogenic sarcoma. *Cancer* 25:889–891, 1970.

21. Mulvihill, J.J., Gralnick, H.R., Whang-Peng, J. et al: Multiple childhood osteosarcomas in an American Indian family with erythroid macrocytosis and skeletal abnormalities. *Cancer* 40:3115–3122, 1977.

22. Jensen, R.D. and Miller, R.W.: Retinoblastoma: epidemiologic characteristics. *N Engl J Med* 285:307–311, 1971.

23. Bolande, R.P.: Childhood tumors and their relationship to birth defects. In Mulvihill, J.J., Miller, R.W., and Fraumeni, J.F., Jr. (eds): *Genetics of Human Cancer*. Raven Press, New York, 1977, pp 43–75.

24. Hutter, R.V.P., Francis, K.C., and Foote, F.W., Jr.: Ewing's sarcoma in siblings: report of the second known occurrence. *Am J Surg* 107:598–603, 1964.

25. Schajowicz, F. and Bessone, J.E.: Chondrosarcoma in three brothers: a pathological and genetic study. *J Bone Joint Surg* 49:129–141, 1967.

26. Chan, H. and Pratt, C.B.: A new familial cancer syndrome? A spectrum of malignant and benign tumors including retinoblastoma, carcinoma of the bladder and other genitourinary tumors, thyroid adenoma, and a probable case of multifocal osteosarcoma. *J Natl Cancer Inst* 58:205–207, 1977.

27. Miller, R.W.: Deaths from childhood leukemia and solid tumors among twins and other siblings in the United States, 1960–67. *J Natl Cancer Inst* 46:203–209, 1971.

28. Draper, G.J., Head, M.M., and Kinnier-Wilson, L.M.: Occurrence of childhood cancers among siblings and estimation of familial risks. *J Med Genet* 19:81–90, 1977.

29. Bottomley, R.H., Trainer, A.L., and Condit, P.T.: Chromosome studies in a 'cancer family.' *Cancer* 28:519–528, 1971.

30. Fraumeni, J.F., Jr., Vogel, C.L., and Easton, J.M.: Sarcomas and multiple polyposis in a kindred. *Arch Intern Med* 121:57–61, 1968.

31. Klenerman, L., Ockenden, B.G., and Townsend, A.C.: Osteosarcoma occurring in osteogenesis imperfecta. *J Bone Joint Surg* 49B:314–323, 1967.

32. Knight, J. and David, S.: Sarcomatous change in three brothers with diaphyseal aclasis. *Br Med J* 1:1013–1015, 1960.

33. Miller, R.W.: Ethnic differences in cancer occurrence: genetic and environmental influences, with particular reference to neuroblastoma. In Mulvihill, J.J., Miller, R.W., Fraumeni, J.F., Jr. (eds): *Genetics of Human Cancer*. New York, Raven Press, 1977, pp 1–4.

34. Jensen, R.D., and Drake, R.M.: Rarity of Ewing's tumour in Negroes. *Lancet* 1:777, 1970.

35. Davies, J.N.P.: Childhood tumours. In Templeton, A.C. (ed): *Tumours in a Tropical Country*. Springer-Verlag, Berlin, 1973, pp 306–343.

36. Williams, A.O.: Tumors of childhood in Ibadan, Nigeria. *Cancer* 36:370–378, 1975.

37. Fraumeni, J.F., Jr.: Genetic factors. In Holland, J.F. and Frei, E., III (eds): *Cancer Medicine*. Lea & Febiger, Philadelphia, 1973, pp 7–15.

38. Jeffree, G.M. and Price, C.H.G.: Bone tumors and their enzymes: a study of the phosphatases, nonspecific esterases and betaglucuronidase of osteogenic and cartilaginous tumours, and fibroblastic and giant cell lesions.