retardation. After reviewing photographs of the other cases and examining our patient, we propose that *lid ptosis* rather than *narrow palpebral fissures* is the common eye finding.

All cases described had short stature (average height 145.7 cm, range 136 to 156 cm). Testes were tiny in the 3 cases coming to necropsy, and clinically absent in the 2 living persons. Necropsy showed a small pituitary with normal cytology in 1 case, a normal pituitary in the second, and the pituitary was not mentioned in the third. The association of short stature and hypogonadism with a small pituitary gland in 1 patient, and gonadotropin levels in the lower limits of normal, by bioassay, in 2 patients, led to the interpretation that hypopituitarism was responsible for the endocrine abnormalities (Brun *et al.*, 1974). Endocrine studies in our patient, however, showed normal pituitary responses as indicated by normal thyroid function, normal adrenal-pituitary axis, and normal growth hormone and gonadotropin secretion. Low testosterone levels in our case are in keeping with *primary hypogonadism*. We find no evidence to support hypopituitarism as a necessary part of any of the described cases.

F. THOMAS WEBER, JAIME L. FRIAS,
RICHARD L. JULIUS, AND ALVIN H. FELMAN

*Department of Pediatrics, University of Florida
College of Medicine, Gainesville, Florida 32610*

References

- Baar, H. S., and Galindo, J. (1965). The Borjeson-Forssman-Lehmann syndrome. *Journal of Mental Deficiency Research*, 9, 125-130.
- Borjeson, M., Forssman, H., and Lehmann, O. (1962). An X-linked, recessively inherited syndrome characterized by grave mental deficiency, epilepsy, and endocrine disorder. *Acta Medica Scandinavica*, 171, 13-21.
- Borjeson, M., Forssman, H., and Lehmann, O. (1963). Combination of idiocy, epilepsy, hypogonadism, dwarfism, hypometabolism and morphologic peculiarities inherited as an X-linked recessive syndrome. In *Proceedings on the 2nd International Congress of Mental Retardation, Vienna, 1961*, Part 1, pp. 188-192. Ed. Otto Stur. Karger, Basel.
- Brun, A., Borjeson, M., and Forssman, H. (1974). An inherited syndrome with mental deficiency and endocrine disorder. A patho-anatomical study. *Journal of Mental Deficiency Research*, 18(1), 317-325.
- Cryer, P. E. (1976). *Diagnostic Endocrinology*, pp. 68-69. Oxford University Press, New York.
- Poznanski, A. K., Garn, S. M., Nagy, J. M., and Gall, J. C. (1972). Metacarpophalangeal pattern profiles in the evaluation of skeletal malformations. *Radiology*, 104, 1-13.
- Reiter, E. Root, A. W., and Duckett, G. E. (1976). The response of pituitary gonadotropes to constant infusion of luteinizing hormone-releasing hormone in normal prepubertal and pubertal children and in children with abnormalities of sexual development. *Journal of Clinical Endocrinology and Metabolism*, 43, 400-411.
- Ruanqwit, U., Cavallo, A., Fisher, J. N., and Crigler, U. F., Jr. (1972). Propranolol enhancement of immunoreactive growth hormone response to glucagon in children. *Pediatric Research*, 6, 350.
- Smith, D. W. (1976). *Recognizable Patterns of Human Malformations*, 2nd ed., 467, W. B. Saunders, Philadelphia.

Requests for reprints to Dr. F. Thomas Weber, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida 33610, U.S.A.

Waardenburg-like features with cataracts, small head size, joint abnormalities, hypogonadism, and osteosarcoma

SUMMARY A 32-year-old black man was observed with osteosarcoma and multiple anomalies including deafness, hypopigmentation, cataracts, small head size, hypogonadism, and restricted joint mobility. The birth defects may comprise a new syndrome or combination of syndromes, of which the malignancy may be a part.

Case report

The patient was ascertained in June 1976, during an aetiological assessment of sarcoma patients on a surgical service.

Gestation, labour, and delivery were normal. The parents were a 16-year-old gravida 1, para 0, black woman, and an unrelated 16-year-old black man. Birthweight was 2.4 kg, and an umbilical hernia and clubfeet were present. Motor and speech development were delayed and at 2 years hearing was found to be impaired. Educational efforts were not made until age 12 when the patient was sent to a school for handicapped children. Greying of hair began at 12 years; beard growth began at about 18 years. He currently lives at home, cares for his personal needs, and has held two manual jobs.

The father's medical and family history were unavailable; the mother had no physical or hearing abnormalities. The only birth defect or pigmentary anomaly among 3 maternal half sibs and other maternal relatives was profound childhood deafness in an otherwise normal cousin. The maternal grandmother had an ovarian granulosa cell tumour, and a maternal aunt had uterine leiomyomata.

In November 1975, the patient was admitted to the National Cancer Institute with histologically typical osteosarcoma of the distal right tibia. Treatment included amputation, adjuvant chemotherapy, and BCG immunotherapy. The patient suffered cardiovascular collapse after receiving the first few millilitres of the seventh course of high dose intravenous methotrexate. This rare, presumably idiosyncratic response recurred on two additional drug challenges (Goldberg *et al.*, 1977). Chemotherapy was completed with adriamycin, and he remains free of malignancy, 19 months after diagnosis.

On physical examination the patient weighed 62.6 kg and was 169 cm tall with eunuchoid body proportions (upper segment 80.5 cm, lower segment 88.5 cm, span 173 cm). The circumference of his normally shaped head was 53.5 cm (3rd centile for 18 years). He had a beaked nose (Fig. 1b). Scalp hair, eyelashes, beard, and chest hair were prematurely

grey. Eyebrows, also grey, were bushy with medial flaring. Sparse hair was present on the arms and leg, and axillary and pubic hair were normal. Irides were blue with marginal brown pigmentation and no heterochromia (Fig. 1a). Funduscopy revealed posterior subcapsular cataracts and albinoid coloration with poor macular differentiation. Visual acuity was 20/60 bilaterally. Distances between the inner canthi, pupils, and outer canthi were 38 mm, 64 mm, and 92 mm. The inferior lacrimal puncta were situated normally, and tearing, taste, and smell were intact. The normally positioned ears lay flat against the head; the pinnae lacked lobules and had thickened lower helices. Tympanic membranes were normal. Air-conduction audiometry showed a profound hearing defect with minimal residual sound perception at low frequencies. Bone-conduction audiometry revealed a bilateral hearing loss of 60–70 db at midfrequencies (500–2000 Hz) with a less severe hearing loss (40–50 db) at other

Fig. The patient: (a) front view: note pale irides and peg-shaped maxillary incisor. Hair growth after adriamycin-induced alopecia is darkly pigmented in contrast with its pretherapy predominantly grey colour; (b) lateral view: apparent mandibular prognathism is attributed to maxillary hypoplasia; (c) palms of hands.

Table Serial measurements of plasma testosterone and gonadotropins

Hormone	Normal adult males	Patient		
		During chemotherapy	After chemotherapy 5 weeks	12 weeks
Testosterone (ng/dl)	250-1250	204	199	213
Luteinising hormone (LH) (mIU/ml)	5-26	24.6, 23.8, 21.6	31.3	30.3
Follicle-stimulating hormone (FSH) (mIU/ml)	5-25	24.3, 20.3	21.4	19.6

frequencies. The right lateral maxillary incisor was peg-shaped, and the left lateral incisor was congenitally absent. The mandibular left canine and premolar projected beyond the arch of the upper teeth. Lateral cephalometric x-ray showed maxillary hypoplasia.

The abdomen was obese with a midline scar from umbilical herniorrhaphy. The penis was 8 cm long; soft testes measured 3.0 cm × 2.0 cm on the right and 2.5 cm × 1.5 cm on the left. There was limited supination bilaterally and incomplete flexion at the interphalangeal joints of the proximally placed thumbs and at the proximal interphalangeal joints of all fingers. The dorsum of the hands appeared wasted. The left foot had valgus deformities of the first to fourth toes. The talus was displaced distally with loss of arch and limited range of motion of the ankle.

The skin was dry, shiny, and smooth with extensive areas of hyperkeratoses on the ulnar regions and the lower leg, hyperpigmented papules on the chest, back, and malar regions of the face, and excess melanin pigmentation on the palms and the sole of the foot. A single *café-au-lait* spot on the back was 1.5 cm in diameter; four elsewhere were smaller. There was decreased pigmentation of the middle of the lower lip. Repigmentation of BCG scars was normal. Nails of fingers and toes were dysplastic and longitudinally ridged. Sweat pores and sweat were present. Each palm had a simian crease, lateral displacement of the base of the longitudinal crease, and hypothenar dermal ridge dysplasia (Fig. 1c). Phalangeal creases and ridge counts were normal.

Routine haematology and chemistry tests were normal. Radiographic skeletal survey and intravenous pyelogram were normal except for thoracolumbar scoliosis and a square pelvis with narrow iliac wings and a wide outlet consistent with delayed weight bearing. Computerised axial tomography of the brain showed no defects other than small head size. Bilateral buccal smears were Barr-body negative and the Giemsa-banded karyotypes of peripheral leucocytes were normal 46,XY. Low levels of plasma testosterone and high levels of plasma LH were obtained on serial measurements (Table). No HLA A or B antigens were detected on 3 separate occasions by Terasaki's

method (Terasaki and McClelland, 1964); HLA was 2. The A, B, and C haplotypes of the mother were, respectively, 30, 33; 35; and 2, 4. Psychometric evaluation with the nonverbal portion of the Wechsler Adult Intelligence Scale and with nonverbal tests designed for children suggested mental retardation in excess of auditory and language impairment.

Discussion

The described pattern of abnormalities shares features with several syndromes but does not permit a unifying diagnosis. Deafness, hypopigmentation, and hypogonadism were major findings. The low plasma testosterone and high plasma LH are consistent with testicular rather than with pituitary hypogonadism. Though some cancer chemotherapeutic agents can cause azoospermia, destruction of germinal elements, and testicular atrophy, these effects have not been attributed to either methotrexate alone or adriamycin (Sieber and Adamson, 1975). Moreover, the eunuchoid features of this patient antedated chemotherapy.

Premature greying, cataracts, and hypogonadism congenital deafness, blue irides, and albinoid fundi are compatible with Waardenburg syndrome, an autosomal dominant disorder (Fraser, 1976). Dystopia canthorum, the major manifestation used to distinguish the syndrome from other auditory-pigmentary disorders, was difficult to evaluate in this patient. Though often identified by clinical impression, this sign is more accurately evaluated by interocular measurements. The distance between the patient's medial canthi seemed large and exceeded that of his mother, while his interpupillary and outer canthal distances were less than hers. The inferior lacrimal puncta were not, however, laterally displaced as is usual in dystopia, and the palpebral fissure length was normal. Standards for adult American blacks are not available, but the patient's interocular measurements were normal compared with standards for African blacks (Soussi, 1974). His measurements also gave normal values in formulae developed to evaluate dystopia (Arias, 1971). The patient's small head size, however, may invalidate comparisons with standard

measurements. This uncertainty regarding the presence of dystopia and the negative family history argue against Waardenburg syndrome. Furthermore, hypogonadism, small head size, cataracts, and limb and ectodermal defects have not been described with the syndrome.

Premature greying, cataracts, and hypogonadism are features of Werner syndrome (Epstein *et al.*, 1966). This autosomal recessive disorder predisposes to sarcoma, but the patient did not have the senile appearance and other cardinal manifestations of this disease. Furthermore, this syndrome cannot account for congenital deafness, small head size, and ocular hypopigmentation. Likewise, the patient's history and pattern of anomalies were inconsistent with a variety of other disorders, including ectodermal dysplasias, congenital viral infections, and the deafness-hypogonadism syndromes of Richards-Rundle, Weinstein (Rimoin and Schimke, 1971), and Edwards (Edwards *et al.*, 1976).

The patient's age at tumour development and the tumour's location were somewhat unusual. Osteosarcoma occurs primarily during the adolescent growth spurt in the sites of major bone growth, the distal femur and proximal tibia. The tumour is infrequent in the third and fourth decades but its incidence increases over age 40, at which time the major sites of involvement are long and flat bones affected by Paget's disease. Osteosarcoma also occurs in association with hereditary retinoblastoma, solitary skeletal defects, and damage from bone-seeking radioisotopes and previous radiotherapy (Fraumeni, 1975). The patient did not have any known predisposing disease or unusual exposure to ionising radiation.

The unusual HLA phenotype merits comment. The type and relative frequency of alleles at each HLA locus vary by race (Bach and van Rood, 1976). Typing done with Caucasian antisera may not detect antigens that are rare in Caucasian populations. Consequently, lack of recognition of one of the A or B antigens is frequent in blacks. However, the failure to detect any A and B antigens has not occurred before in leucocyte assays on about 166 000 individuals (P. I. Terasaki, 1977, personal communication). The patient's A phenotype cannot be explained on the basis of segregation of alleles present in his mother, since she has 2 identifiable alleles at this locus.

In sum, the patient has a distinctive pattern of birth defects and an unusual HLA phenotype in combination with osteosarcoma. This unique array of abnormalities may represent the fortuitous coexistence of unrelated growth disturbances or, perhaps, a new syndrome.

Note added in proof: In July 1977, 6 months after the completion of all treatment, HLA A33 and B15 were detected in the patient (A. H. Johnson and F. E.

Ward, Division of Immunology, Duke University Medical Center). The previous results remain puzzling: on each earlier occasion cells were viable, adequate in number, and the patient had received no adriamycin for as long as 5 weeks. Short-lived differential suppression of antibodies of HLA A and B but not C by chemotherapy is a possible explanation.

We are grateful to Dr S. A. Rosenberg and his colleagues, Surgery Branch, NCI for permission to report their patient. We thank Dr K. J. Rothman for critical evaluation of the manuscript.

DILYS M. PARRY, ANDREW W. SAFYER, AND
JOHN J. MULVIHILL

*Clinical Epidemiology Branch,
National Cancer Institute,
Bethesda, Maryland, USA*

References

- Arias, S. (1971). Genetic heterogeneity in the Waardenburg syndrome. *Birth Defects: Original Article Series VII*, No. 4, 87-101.
- Bach, F. H., and van Rood, J. J. (1976). The major histocompatibility complex—genetics and biology. *New England Journal of Medicine*, **295**, 806-813.
- Edwards, J. A., Sethi, P. K., Scoma, A. J., Bannerman, R. M., and Frohman, L. A. (1976). A new familial syndrome characterized by pigmentary retinopathy, hypogonadism, mental retardation, nerve deafness and glucose intolerance. *American Journal of Medicine*, **60**, 23-32.
- Epstein, C. J., Martin, G. M., Schultz, A. L., and Motulsky, A. G. (1966). Werner's syndrome. *Medicine*, **45**, 177-221.
- Fraser, G. R. (1976). *The Causes of Profound Deafness in Childhood*, pp. 90-132. The Johns Hopkins University Press, Baltimore and London.
- Fraumeni, J. F., Jr. (1975). Bone cancer: epidemiologic and etiologic considerations. In *Primary Bone Cancer: The Multidiscipline Disease*, pp. 17-27. Ed. by J. M. Vaeth. Karger, Basel and New York.
- Goldberg, N. H., Romolo, J. L., Austin, E. H., Drake, J., and Rosenberg, S. A. (1978). Anaphylactoid type reactions in two patients receiving high dose intravenous methotrexate. *Cancer* (in press).
- Rimoin, D. L., and Schimke, R. N. (1971). *Genetic Disorders of the Endocrine Glands*, pp. 305-356. C. V. Mosby, Saint Louis.
- Sieber, S. M., and Adamson, R. H. (1975). Toxicity of antineoplastic agents in man: chromosomal aberrations, antifertility effects, congenital malformations, and carcinogenic potential. *Advances in Cancer Research*, **22**, 57-155.
- Soussi, J. T. (1974). *Light-eyed Negroes and the Klein-Waardenburg syndrome*, pp. 14-25. MacMillan Press, New York.
- Terasaki, P. I., and McClelland, J. D. (1964). Microdroplet assay of human serum cytotoxins. *Nature*, **204**, 998-1000.

Requests for reprints to Dr Dilys M. Parry, Clinical Epidemiology Branch, National Cancer Institute, Landow Building, Room A521, Bethesda, Maryland 20014, U.S.A.