neoplastic disease. Leukaemia has been reported in 2 patients with D group chromosomal aberrations (Schade *et al*, 1962; Zuelzer *et al*, 1968).

The present cases of D-trisomy each had, at necropsy, a tumour of an adrenal gland. In case 1, the tumour was regarded as a probable carcinoma because of its size, cellularity, and irregular histological arrangement, because the cells were basophilic and arranged in cords and acini, it was considered to have originated from the definitive cortex. Marin-Padilla, Hoefnagel, and Benirschke (1964) described 2 cases of D-trisomy in which the adrenal glands were enlarged and morphologically abnormal. However, the association of D-trisomy with an adrenal cortical carcinoma is most unusual. A 5-year-old boy with an anaplastic adrenal carcinoma had, on chromosome analysis of the peripheral lymphocytes, an extra large sub-metacentric chromosome similar to group B (Pascasio *et al*, 1967). Ellwood and Pearson (1968) found normal karyotypes in 2 girls with adrenal cortical carcinomas.

In case 2, a microscopic neuroblastoma was present in the adrenal medulla. This tumour is frequently seen as an incidental finding in infants who die before the age of 3 months (Beckwith and Perrin, 1963). The child with neuroblastoma described by Mittelbach and Szekely (1934/1935) had a cleft lip and palate, microcephaly, cerebral atrophy, absence of the corpus callosum, widely patent ductus arteriosus, and patent foramen ovale—features suggestive of D-trisomy. Cytogenetic findings in children with neuroblastoma have been variable; Nichols (1968) did not observe any abnormality but recently Wakonig-Vaartaja *et al* (1971) who studied 21 children with neuroblastoma noted an increased number of abnormal metaphases in pretreatment samples of peripheral blood and bone marrow.

Summary

Two unrelated infants with D-trisomy and adrenal tumours are reported. The first patient who died aged 15 days had a large adrenal cortical carcinoma; the second who died aged 5 days had a microscopic neuroblastoma. The relationship of chromosome changes and the development of malignant tumours is discussed.

N. C. NEVIN, J. A. DODGE, and INGRID V. ALLEN

Human Genetics Unit, Department of Medical Statistics, and Departments of Child Health and Pathology, The Queen's University of Belfast

REFERENCES

- Beckwith, J. B. and Perrin, E. V. (1963). In situ neuroblastomas. A contribution to the natural history of neural crest tumors. *American Journal of Pathology*, **43**, 1089–1100.
- Ellwood, L. C. and Pearson, H. A. (1968). Normal lymphocyte karyotypes in adrenocortical carcinoma. *Lancet*, **1**, 302.
- Geiser, C. F. and Schindler, A. M. (1969). Long survival in a male with 18-trisomy syndrome and Wilm's tumour. *Pediatrics*, **44**, 111–116.
- Harnden, D. G. (1970). *Genetic Concepts and Neoplasia*, p. 31. Williams and Wilkins, Baltimore.
- Marin-Padilla, M., Hoefnagel, D., and Benirschke, K. (1964). Anatomic and histopathologic study of two cases of D₁ (13–15) trisomy. *Cytogenetics*, **3**, 258–284.
- Miller, R. W. (1966). Relation between cancer and congenital defects in man. *New England Journal of Medicine*, **275**, 87–93.
- Mittelbach, M. and Szekely, P. (1934/1935). Ein Fall von Neuroblastom des Nebennierenmarkes mit mehreren Missbildungen. *Frankfurt Zeitschrift für Pathologie*, **47**, 517–521.
- Nichols, W. W. (1968). Cytogenetic aspects of neuroblastoma. *Journal of Pediatric Surgery*, **3**, 143–146.
- Pascasio, F. M., Jesalva, P. S., Cruz, E. P., and Alikpala, S. (1967). Extra large chromosome in adrenocortical carcinoma. *Lancet*, **1**, 1107.
- Schade, H., Schoeller, L., and Schultze, K. W. (1962). D-Trisomie (Patau-Syndrom) mit kongenitaler myeloischer Leukämie. *Medizinische Welt*, **2**, 2690–2692.
- Sternberg, W. H., Barclay, D. L., and Kloepfer, H. W. (1968). Familial XY gonadal dysgenesis. *New England Journal of Medicine*, **278**, 695–700.
- Wald, N., Borges, W. H., Li, C. C., Turner, J. H., and Harnois, M. C. (1961). Leukaemia associated with mongolism. *Lancet*, **1**, 1228.
- Wakonig-Vaartaja, T., Helson, L., Baren, A., Koss, L. G., and Murphy, M. L. (1971). Cytogenetic observations in children with neuroblastoma. *Pediatrics*, **47**, 839–843.
- Zuelzer, W. W., Thompson, R. I., and Mastrangelo, R. (1968). Evidence for a genetic factor related to leukaemogenesis and congenital anomalies: chromosomal aberrations in pedigree of an infant with partial D trisomy and leukaemia. *Journal of Pediatrics*, **72**, 367–376.

Congenital Hypothyroidism in Association with a Ring Chromosome 18

Previous reports of hypothyroidism in association with short arm deficiency of chromosome 18 (Bühler, Bühler, and Stalder, 1964; Uchida *et al*, 1965) have suggested a possible role for this chromosome in the embryogenesis of the thyroid gland. The present finding of a ring chromosome 18 in a girl with congenital hypothyroidism lends further support to this hypothesis.

Case Report

This girl presented at 10 years 9 months with a complaint of visual hallucinations of 3 weeks' duration. She had been the product of a 38-week uneventful pregnancy and normal delivery. Her birth weight was 3.18 kg,

Received 24 March 1971.

length 44.4 cm, and head circumference 31.7 cm. At birth, 'clubbed feet' and a 'mongolian' appearance were noted, but no other anomalies. On the 4th day of life she was mildly jaundiced; no umbilical hernia was observed. Her developmental milestones were all retarded: she rolled over at 8 months, sat at 11 months, spoke at 18 months, and walked at 24 months. She was constipated from birth.

On physical examination at presentation, the patient's height was 116.2 cm, weight 22.8 kg, and head circumference 47.6 cm, all below the 3rd centile. She was a quiet, lethargic child with a rounded face and low hair-line who showed obvious signs of hypothyroidism, including carotenaemia, a depressed nasal bridge, cool dry skin, and pallor (Fig. 1). She had normal eyes and ears,

a high arched palate, and a short, but not webbed neck. There was a small, but palpable thyroid gland, with a palpable pyramidal lobe. Her blood pressure was 100/80 and pulse 88 per minute. Neurological examination was within normal limits except for apparent mental retardation and a marked delay in relaxation of tendon reflexes. She had minimal clinodactyly and normal palmar creases.

Complete blood count, urinalysis, serum electrolytes, blood sugar, and urea nitrogen were normal. Serum carotene was 192 $\mu\text{g}/100\text{ ml}$ and cholesterol 374 mg/100 ml. Total serum proteins were 8.3 g/100 ml, with normal patterns on electrophoresis and immunoelectrophoresis. Urine amino acids were normal by paper chromatography. Her protein-bound iodine was

FIG. 1. The proposita at age 10 (left) and after 2 years' thyroid replacement (right).

5.1 $\mu\text{g}/100\text{ ml}$, and her serum thyroxine 0.3 $\mu\text{g}/100\text{ ml}$. The thyroid 24-hour ^{131}I uptake was 8%; after 2 days of TSH stimulation the uptake was 6%. There were no circulating antibodies to thyroglobulin demonstrated by tanned red blood cell agglutination. Plasma cortisol was 21.1 $\mu\text{g}/100\text{ ml}$ at 8 am and 11.1 $\mu\text{g}/100\text{ ml}$ at 4 pm. Urinary 17-ketosteroids and 17-hydroxysteroids were 1.5 and 1.1 mg/24 hr respectively. Following the administration of intravenous crystalline insulin (0.1 units/kg), there was a fall in blood sugar from 60 to 32 mg/100 ml with a rise in circulating growth hormone from 2.0 to a peak of 22.7 m $\mu\text{g}/\text{ml}$. An electrocardiogram and an electroencephalogram both showed generalized low voltage activity, but no other abnormality. A skull x-ray showed a small symmetrical skull with no intracranial calcification. Chest x-ray was normal. Her bone age at the wrist was 8 years with no epiphyseal dysgenesis. Psychological testing while hypothyroid showed a mental age of 4 years 6 months.

With thyroid replacement therapy, her myxoedema disappeared, her thyroid gland ceased to be palpable, and she grew 18.3 cm in 2 years. At 12 years 2 months, her mental age was 6-7 years. Pubic hair and breast development began at 12½ years.

Family History

Both parents are of French-Canadian extraction. At the time of the patient's birth, the father was 32 years old and the mother 26. Both were in good health and neither had received significant amounts of radiation. The patient was the 5th of 7 children—all the sibs are well. There is no family history of thyroid disease or mental retardation. The parents and sibs all showed normal levels of protein-bound iodine and serum thyroxine, and none had circulating anti-thyroglobulin agglutinins.

Cytology

The patient's buccal smear was sex-chromatin positive. Metaphase preparations from leucocyte and skin fibroblast cultures showed a majority of cells with 46 chromosomes including a ring; a few cells showed either 45 chromosomes and no ring, or 47 chromosomes and two rings (Table I). Autoradiographic analysis following the incorporation of H^3 -thymidine (specific activity 1.9 C/mM) into leucocyte cultures (1 $\mu\text{C}/\text{ml}$ of medium for 6 hours incubation) showed that the ring and one member of the 17-18 group were most heavily labelled

FIG. 2. Chromosomes of the E group from propoita with autoradiographs following incubation with H^3 -thymidine shown below each chromosome.

TABLE I
SUMMARY OF CHROMOSOME COUNTS AT METAPHASE

Tissues	45,XX,E-	46,XX,Er	47,XX,Er,Er	Tetraploid	Total No. of Cells Analysed
Leucocytes (3 days in culture)	12	87	—	1	100
Fibroblasts	5	84	2	9	100

TABLE II
DERMATOGLYPHIC FINDINGS IN THE PROPOSITA AND FAMILY

	Sex	Age (yr)*	Digital Patterns										Total Ridge Count†	ard Angles‡ (combined values of right and left sides)
			Left					Right						
			V	IV	III	II	I	I	II	III	IV	V		
Proposita	F	11	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	W ^o	L ^u	82	110°
Father		42	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	A	L ^u	L ^u	L ^u	81	83°
Mother		37	L ^u	A	A	L ^u	A	A	A	A	A	L ^u	22	103°
Sib 1	M	16	L ^u	W ^s	L ^u	W ^s	L ^u	L ^u	W ^s	L ^u	W ^s	L ^u	148	101°
Sib 2	M	15	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	W ^s	L ^u	W ^s	W ^s	110	94°
Sib 3	F	14	L ^u	A	A	A	A	A	A	L ^u	L ^u	A	3	112°
Sib 4	M	12	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	85	97°
Sib 5	M	10	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	W ^o	106	100°
Sib 6	F	7	L ^u	L ^u	L ^u	L ^u	A	A	L ^u	L ^u	W ^s	L ^u	82	95°

Analyses were carried out according to the methods suggested by Holt (1968).

* Age when the prints were taken.

† Mean for males: 132.36, SD = 45.28. Mean for females: 121.36, SD = 46.48.

‡ Mean for males: 92.5°, SD = 14.2 (infants); 88.2°, SD = 15.9 (school children); 85.0°, SD = 15.3 (adults). Mean for females: 97.5° SD = 19.6 (infants); 89.8°, SD = 17.5 (school children); 85.9°, SD = 15.7 (adults).

(Fig. 2). This is consistent with identification of this ring as a chromosome 18. The morphology of all the other chromosomes was normal. Buccal smears and karyotypes of the parents and sibs were all normal.

Dermatoglyphs

Palm and finger prints were analysed according to the methods of Holt (1968) and the results (Table II) compared to normal sex- and age-adjusted values published by this author. The proposita, her mother, and 2 female sibs showed combined right and left palmar atd angles outside the normal range. All members of the family, with the exception of one sib, showed total ridge counts below the normal mean value; the mother and one sib (but not the proposita) had ridge counts below the normal range and showed 7 simple digital arches each.

Discussion

The majority of this child's leucocyte and skin fibroblast cells showed a 46,XX,18r karyotype, and no cells with a normal karyotype were observed. The cells with 45,XX,18r- and 47,XX,18r,18r karyotypes may have arisen from non-disjunction of the ring chromosome *in vitro*, since ring chromosomes are known to behave irregularly in cell division. The failure to find any cells with a normal karyotype suggests that the ring chromosome originated before fertilization.

In contrast to the characteristic trisomy 18 syndrome, the clinical features associated with deficiencies of one or both arms of chromosome 18 do not appear to constitute a distinct clinical entity

(Migeon, 1966; Palmer, Fareed, and Merritt, 1967). Our patient is the third in whom hypothyroidism has been reported in association with partial monosomy 18. Bühler *et al* (1964) reported a 3-year-old girl with a deficiency of the short arm of chromosome 18 and mild hypothyroidism thought to be due to a coupling defect in thyroxine synthesis; no goiter was felt and the only malformation was slight epicanthal folds bilaterally. Uchida *et al* (1965) referred to a 4-year-old girl reported by Hickox in whom a deficiency of the short arm of chromosome 18 was associated with mild hypothyroidism, hypertelorism, and pterygium colli. Migeon (1966), in reviewing the reported cases of short arm deficiency of chromosome 18, noted the common features of (1) significant mental retardation; (2) short stature; (3) absence of cardiac, renal, or gastrointestinal malformations; (4) presence of minor congenital malformations such as hypertelorism, micrognathia, and low-set ears. In our patient, the mental retardation, microcephaly, and short stature were probably at least in part a result of untreated hypothyroidism, but the rounded facies, low hair line, high arched palate, and the club feet noted at birth would appear to be more directly related to the chromosomal abnormality. Nitowsky *et al* (1966) have suggested that the minimal clinical abnormality associated with deficiencies of chromosome 18 may indicate that much of the deficient segment of the chromosome is ordinarily heterochromatic with little active genetic material. An alternative explanation which would

account for the phenotypic variability in these cases would be the expression of recessive genes present on the hemizygous segments of the normal chromosome 18.

Our patient clearly had some thyroid tissue, as indicated by physical examination and the presence of some ^{131}I accumulation in the neck. But whether the hypothyroidism is a result of a structural malformation in the gland or a defect in thyroxine synthesis was unfortunately not completely resolved before therapy was initiated. However, the presence of a striking difference between her protein-bound iodine ($5.1 \mu\text{g}/100 \text{ ml}$) and her serum thyroxine ($0.3 \mu\text{g}/100 \text{ ml}$) suggests that she was synthesizing an abnormal iodinated peptide. Such a defect in thyroxine synthesis might result from the action of a recessive gene on the hemizygous portion of her normal chromosome 18. The coincidence in 3 patients, including the present case, of hypothyroidism with loss of genetic material from chromosome 18 suggests that at least one gene responsible for thyroid function may be located on this chromosome. The significance of the abnormal dermatoglyphics in several members of this family is not clear.

Summary

A girl with apparent congenital hypothyroidism and minimal visible anomalies was found to have a ring chromosome, identified by autoradiography as chromosome 18. The hypothyroidism appeared to be related to a defect in thyroxine synthesis with the production of abnormal iodinated protein. It is suggested that at least one gene responsible for thyroid function may be located on chromosome 18.

The authors would like to express their thanks to Dr G. E. C. Ducasse for the dermatoglyphic analysis and Dr J. L. Hamerton for advice and encouragement. This work was supported by grants from the Medical Research Council and the Children's Hospital Research Foundation.

J. S. D. WINTER, K. AHLUWALIA, and M. RAY

The Winnipeg Children's Hospital Research Foundation and the Department of Paediatrics, University of Manitoba, Canada

REFERENCES

- Bühler, E. M., Bühler, U. K., and Stalder, G. R. (1964). Partial monosomy 18 and anomaly of thyroxine synthesis. *Lancet*, **1**, 170-171.
- Holt, S. B. (1968). *The Genetics of Dermal Ridges*. Thomas, Springfield, Illinois.
- Migeon, B. R. (1966). Short arm deletions in group E and chromosomal 'deletion' syndromes. *Journal of Pediatrics*, **69**, 432-438.
- Nitowsky, H. M., Sindhvananda, N., Konigsberg, U. R., and Weinberg, T. (1966). Partial 18 monosomy in the cyclops malformation. *Pediatrics*, **37**, 260-269.
- Palmer, C. G., Fareed, N., and Merritt, A. D. (1967). Ring chromosome 18 in a patient with multiple anomalies. *Journal of Medical Genetics*, **4**, 117-123.
- Uchida, I. A., McRae, K. N., Wang, H. C., and Ray, M. (1965). Familial short arm deficiency of chromosome 18 concomitant with arhinencephaly and alopecia congenita. *American Journal of Human Genetics*, **17**, 410-419.

Nystagmus in a Female Carrier of Ocular Albinism

Ocular albinism is a rare hereditary disorder long considered by pedigree analysis to be due to an abnormal gene on the X chromosome. This was eventually confirmed by the demonstration of close linkage between the loci for ocular albinism and for the Xg^a blood group (Fialkow, Giblett, and Motulsky, 1967; Pearce, Sanger, and Race, 1968). The condition as found in affected males is characterized by a deficiency of pigment in the retinal pigment epithelium and in the pigment epithelial layer of the iris. The most striking clinical feature is the nystagmus with accompanying photophobia and visual impairment which probably result from the deficiency of retinal pigment. So distinctive a feature is this nystagmus that before the initial recognition of ocular albinism as a separate entity by Vogt (1925), it had been included in the group of disorders termed congenital nystagmus. Later heterozygous females were noted to have minor fundus abnormalities characterized by stripe-like areas of depigmentation alternating with normally pigmented patches in the periphery of the retina (Vogt, 1942; Falls, 1951). Similarly irregular diaphanous areas were visible in the iris on retro-illumination (Waardenburg and van den Bosch, 1956). No visual complaints, however, were associated with these changes.

In this communication a female heterozygous for ocular albinism is described who displays the congenital nystagmus, photophobia, and visual impairment one associates with the hemizygous male.

Received 7 June 1971.