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.

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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

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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.

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Case Report

The *proposita* (II.10) was ascertained during a study of an extended family in Newfoundland within whom ocular albinism was segregating (Fig. 1). The report containing the full pedigree and other noteworthy features is published elsewhere (Johnson, Gillan, and Pearce, 1971). At the time of the ascertainment the patient was 52 years of age. She gave a history of nystagmus dating from very early childhood and probably from birth. Her first pair of glasses were obtained at about 12 years of age when she was found to be myopic. Since that time her myopia had increased and 1 year before examination she was wearing -10.00 spheres in each eye, while her recorded visual acuity was approximately 20/200 right and counting fingers left. The right lens was clear but a moderately dense cataract was present in the left. Her younger affected brother (II.12) was also a moderately high myope (-9.50 sphere right and left).

FIG. 1. Pedigree showing the first-degree relatives of the *proposita* (II.10).

Examination at presentation revealed bilateral, pendular, horizontal nystagmus with a slight rotary component in each eye. This was associated with some photophobia. There was no history of night blindness and no colour blindness was detected on testing with the Ishihara charts. Visual acuity in her right eye was unchanged while that of the left had been reduced to hand movements and the cataract was noted to be mature.

She was admitted to hospital for investigation and left cataract extraction. Slit lamp examination revealed areas of atrophy in the iris pigment epithelium. Electronystagmography showed the nystagmus to be ocular in origin. At the time of left cataract extraction photographs were taken of the right fundus. These showed a myopic disc with a generally depigmented posterior fundus, although some granular pigmentation was noted in the macular area (Fig. 2). This feature of widespread depigmentation with smaller normally pigmented areas was also present in the periphery. In the midperiphery of the inferior temporal quadrant some disturbance and

FIG. 2. Right posterior fundus showing myopic disc, depigmented retina, and the vascular, granular macula.

FIG. 3. Right inferior temporal mid-periphery showing irregular clumping of retinal pigment.

probable migration of retinal pigment was also noted (Fig. 3). Cataract extraction was complicated by a small vitreous haemorrhage but at the time of discharge from hospital the left visual acuity was 20/200 and she was preferring to use the left eye for distant and near vision.

Karyotype studies on cultured lymphocytes revealed a normal female chromosome pattern, 46,XX.

Discussion

A search of the literature did reveal a case with features similar to those described above (Waardenburg and van den Bosch, 1956). In the family originally described by Engelhard (1915), the condition was called hereditary nystagmus. Reinvestigation by Waardenburg and van den Bosch revealed the correct diagnosis to be ocular albinism. One of the 47 heterozygous females in their pedigree (III 2.3) had been noted to have an oscillating horizontal nystagmus with photophobia. When she was examined at age 64 in 1913, early cataracts and equal visual acuity were noted. In a later publication she was described as myopic -4.50 D right eye, -2.25 D left eye (Waardenburg, 1970). Engelhard's description of the fundus as recorded by the authors states that 'it contained little pigment'. While this statement is perhaps consistent with either heterozygosity or homozygosity, the patient as the daughter of an affected male was an obligate heterozygote. The chances of her being homozygous were small as her mother was unaffected and not related to the patient's father.

The present case also appears to be heterozygous having inherited the abnormal gene from her mother who was the daughter of a carrier female (Johnson *et al*, 1971). Support for heterozygosity is provided by the presence of pigment in the patient's retina, the absence of the disorder in her father, the lack of the carrier state in two of her sisters, and by her children—an affected son and a non-carrier daughter. Blood grouping of the family revealed no illegitimacy (R. Sanger, personal communication).

The evidence is reasonably strong that the probanda and the patient of Waardenburg were heterozygous for ocular albinism. Ocular albinism is not alone amongst X-linked disorders affecting the retina which show ophthalmoscopic abnormalities in carrier females. In choroideremia, heterozygous females consistently show an irregularity of pigmentation often described as 'pepper and salt' appearance (McCulloch and McCulloch, 1948; Krill, 1967). In retinitis pigmentosa, carrier females may possess the golden, glistening tapetal reflex (Falls and Cotterman, 1948; Weiner and Falls,

1955; Klein *et al*, 1967). Minor abnormalities have also been noted infrequently in females heterozygous for retinoschisis (Sabates, 1966; Eriksson *et al*, 1969).

These morphological abnormalities, found to a greater or lesser extent in females heterozygous for X-linked disorders have been explained by the Lyon hypothesis (Lyon, 1961), although this is not universally accepted (Grüneberg, 1967). If inactivation occurs as suggested (Lyon, 1962) at an early stage when only a few embryonic cells are destined to become the pigment epithelium of the iris and retina, the random process may occasionally be expected to inactivate a greater number of X chromosomes bearing the normal allele than of those bearing the albino allele resulting in little retinal pigment.

Although we cannot definitely exclude depigmentation resulting from the high myopia as a contributing factor to the development of the nystagmus, we consider the most likely explanation of the clinical phenotype in this patient to be heterozygosity for ocular albinism. Considerable variation in the amount of visible retinal pigment possessed by these carriers has been previously noted (Falls, 1951). Therefore, in the occasional case the amount of pigment present in the retinal pigment epithelial cells may well be reduced to such a level that normal macular fixation is no longer possible and nystagmus results.

Summary

A female heterozygous for ocular albinism is described who showed the nystagmus, photophobia and visual impairment of the hemizygous male. The clinical and genetic features of the phenotype have been interpreted as consistent with the Lyon hypothesis although the patient's myopia cannot be excluded as a contributory factor to the development of the nystagmus.

W. G. PEARCE

Sunnybrook Hospital and the Hospital for Sick Children

G. J. JOHNSON*

St. Michael's Hospital

J. G. GILLAN

Toronto, Canada

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A Duarte Variant with Clinical Signs

Patients with the Duarte variant of galactosaemia are usually healthy, despite functional and structural abnormalities in their galactose-1-phosphate uridyl transferase (Beutler *et al*, 1965; Mathai and Beutler, 1966; Gitzelman, Poley, and Prader, 1967; Ng *et al*, 1969). We describe an infant with abnormal signs associated with the enzyme phenotype of a homozygous Duarte variant.

Case Report

A 2-month-old boy was admitted to the hospital because of jaundice since the 3rd day of life.

The pregnancy and delivery were normal. He weighed 3.2 kg at birth, was 52 cm long, and had a head circumference of 34 cm. Apgar scores were 9 at 1 minute and 10 at 5 minutes. Physical examination after birth was normal. He was blood group O, type Rh positive, as was his mother. His diet from birth was Enfamil, which he tolerated well. He was slightly jaundiced when discharged from the nursery on the 3rd day; the liver edge was 1 cm below the right costal margin.

He continued to gain, in spite of mild jaundice apparent at office visits at 11 days and 6 weeks of age. The total serum bilirubin concentration at 6 weeks was 3.9 mg/100 ml, of which 3.6 mg/100 ml was in the conjugated (direct reading) form. The jaundice deepened, and the weight gain lessened during the 2 weeks before admission.

He was the 2nd child of healthy, unrelated, 23-year-old parents. His 3-year-old sister had been well as an infant, and there was no history of milk intolerance, jaundice, or liver disease in the family.

He was icteric on admission. The liver was felt 4 cm below the right costal margin; the spleen was not felt. Two veins were prominent in the right upper quadrant. He had signs of a cold. Weight (4.5 kg) and length (55 cm) were in the 25th centile; head circumference (37.5 cm) was in the 10th centile. Motor development was normal.

Total serum bilirubin concentrations on consecutive days were 5.7 and 7.4 mg/100 ml, 3.6 and 3.4 mg/100 ml of which, respectively, were in the conjugated (direct reading) form. The white cell count was 19,650 cells/mm³, with a lymphocytosis of 85%. Red cells values were normal and included a haemoglobin concentration of 12.6 g%, hematocrit of 38.5%, and reticulocyte count of 1.6%. The urinalysis was normal; reducing sugars were not detected. Faecal and urinary urobilinogen, throat and urine cultures, serum protein electrophoresis, and serum enzymes were normal, except for 282 mU/ml of serum glutamic-oxaloacetic transaminase.

A diagnosis of biliary atresia was considered. Other abnormalities found a few days later during evaluation for surgery in another hospital were: a palpable spleen, 1½ cm below the left costal margin; dark, bile-stained urine with excessive urobilinogen; an acholic stool; an elevated, rising aldolase concentration; hematocrit values ranging from 28 to 36% and reticulocytosis of up to 6.2%. The serum bilirubin concentration remained 5.0 mg/100 ml, of which 3.6 mg/100 ml was in the conjugated form. A radioactive rose bengal test suggested but did not confirm an obstruction.

Surgery exposed a green, non-fibrotic liver and an unusually small, bile-containing gallbladder, which was incised, drained, and irrigated. An operative cholangiogram revealed patent ducts and normal flow. The consulting pathologist described 'marked fatty infiltration, bile retention, periportal fibrosis (and cirrhosis) and