Dyskeratosis congenita: clinical features and genetic aspects

Report of a family and review of the literature

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Summary. A large family with dyskeratosis congenita is reported. There were nine affected males, the findings in five of whom are reported. We review 46 cases selected from the literature. The cardinal findings of this inherited multi-system disorder are delineated from these 51 cases. The complications of the disease, including opportunistic infection, are described. The parallel is made between dyskeratosis congenita and Fanconi's anaemia.

The X-linked transmission of dyskeratosis congenita is confirmed by the family pedigree in this report. From the analysis of the families reported in the literature, there appears to be genetic heterogeneity in this disease. The study in our family indicates absence of close linkage between the Xg^a locus and the X-linked recessive form of dyskeratosis congenita.

Dyskeratosis congenita is a rare genodermatosis. The first description of the skin and nail changes characteristic of this disease was by Zinsser in 1910 when he reported two brothers, one of whom also had leukoplakia involving the tongue. Subsequently other similar cases were described primarily in the dermatology literature. We have found 46 reported cases of dyskeratosis congenita in the world's literature involving 40 males, five females, and one of unstated sex (Table I).

The manifestations of the disease are multi-systemic. The disease involves mainly the ectoderm with reticulated hyperpigmentation of the skin, nail dystrophy, and leukoplakia of the mucous membranes. Pancytopenia and malignancy are the serious and fatal complications of this disease.

One half of the reported cases had a positive family history. Unfortunately, the family histories were incomplete in most cases. Thus there are insufficient data to document the mode of inheritance clearly. The disease has occurred almost

exclusively in males and is generally thought to be transmitted as an X-linked recessive trait.

We had an opportunity to study a family in which dyskeratosis congenita segregated in three generations. There were nine affected males and this is the largest family reported to date. Four of the affected family members have been followed in the Genetic and Hematology Clinics of the University of Oregon Medical School. The proband had been under our care for the treatment of aplastic anaemia for 18 months until his death at age 31. He and his three nephews, aged 17, 14, and 11, represent the different stages of dyskeratosis congenita; the findings in this family illustrate the course of the disease.

In this paper we describe the family and review the previously reported cases. From the findings in these cases, the characteristic clinical picture of dyskeratosis congenita which has multisystem involvement is delineated. We report for the first time opportunistic infection as another fatal complication of this disease. Pedigree data from the published reports are analysed to determine the mode(s) of inheritance. Finally, possible mechanisms which will explain the different facets of dyskeratosis congenita are proposed.

Received 5 November 1974.

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FIG. 1. Pedigree of the family. Xg^a blood type is indicated by + and -.

Family history

The pedigree is given in Fig. 1. The maternal grandmother (I.2) was born in Wales, and the maternal grandfather (I.1) came from The Netherlands. Two of their sons (II.10, II.11) were reported to have 'bad skin and bad nails'. They died in their late teens or early twenties from causes unknown to the family. It was not certain whether II.3 was also affected.

The parents of the proband (II.1, II.2) were not related; the mother was a registered nurse. In addition to the proband they had two other similarly affected sons (III.5 and III.19). Although hospital records were not available for review, the death certificates were interesting. III.5 died at 15 years of bronchopneumonia. He had anaemia for one year and 'malnutrition' for two years before his death. Acute pharyngitis was the cause of death in III.19 at age 13. He also had aplastic anaemia and 'severe malnutrition'. Both were mentally retarded.

III.11, sister of the proband, has four affected sons (IV.11, IV.14, IV.17, IV.20). The oldest son by her first marriage (IV.11) was noted to have nail changes when he was between 2 and 5 years old. At 9–10 years he developed dark, 'dirty-looking' skin. She was told by her mother, who until then had kept the family condition a secret, that IV.11 suffered from the same condition as his uncles and great uncles. He was also mentally retarded, sickly, and thin. He had no problems with his eyes or any lesions in his mouth. At 12 he developed infectious hepatitis along with several members of the family. However, his was more severe requiring hospitalization and blood transfusions. He died at another hospital at 17 years of age after an acute respiratory illness of 6 days duration. On admission he was in severe respiratory distress. Fever, cyanosis, tachycardia, and decreased breath sounds in both lung fields were noted. The liver and spleen were not enlarged by

palpation and the external genitalia were normal. His hair was thin and nails rudimentary. The skin of the anterior cervical, axillary, and both lateral hip regions contained mottled areas of hyper- and hypopigmentation. Chest radiology demonstrated hazy, generalized infiltrate bilaterally. He died on the day of admission. Review of the necropsy slides established *Pneumocystis carinii* pneumonia as the immediate cause of death.

Twenty-one family members were personally examined. No similarly affected cases other than the proband and three of his nephews (IV.14, IV.17, IV.20) were identified. The unaffected members were of normal intelligence. A coincidental finding was Poland's syndrome (Clarkson, 1962) in IV.10 who was 13 years old. He was born with cutaneous syndactyly of the 2nd to the 5th fingers of the left hand. The metacarpals and middle phalanges were shortened, causing the left hand to be about two-thirds normal size. In addition, the pectoral musculature was absent on the left side.

Case reports

IV.14, IV.17, and IV.20. IV.14 was born on 20 January 1957, IV.17 on 24 June 1960, and IV.20 on 10 June 1963. Their histories and physical findings are very similar and will be discussed together.

These three brothers are the children of III.11 by her second marriage. The family appears to be socio-culturally deficient. The mother (III.11) is 42 and the father (III.12) is 47 years of age. The parents were not related and have enjoyed life-long good health. The gestations and deliveries were normal in the three children; birth weights were about 1800 g, being approximately the same as those of the normal sibs. The skin and nails appeared to be normal at birth. The mother noted nothing unusual about their early developmental landmarks. After one or two years of schooling, each

FIG. 2. Atrophic skin at dorsum of hands and different degrees of nail dystrophy in IV.20 (A), IV.17 (B), and the proband (C).

was considered to be a slow learner and was therefore transferred to a special education class. Physical development has been normal for age. IV.14 developed facial hair and his voice deepened at 15 years of age. Their general health had been excellent. In childhood all of them had measles and chickenpox without complications; IV.14 also had mumps parotitis. Surgical procedures which include circumcisions at birth and an orchiopexy in IV.17 at age 12 were tolerated well. They have normal visual acuity, colour vision, and hearing. There was no history of recurrent infection, fracture, or dysphagia.

The nail changes (Fig. 2) were initially observed at about 2 to 5 years of age. The sequence of changes were identical. At first there were splitting and peeling of nails (IV.20 represents this early stage); then they became longitudinally ridged, friable with irregular free edges and grew very slowly (demonstrable in IV.17). Eventually the nails became smaller than normal and on some digits the rudiments only were left, sometimes without sharp demarcation between the nails and the skin (observed in IV.14). These changes occurred in the fingernails first, followed by similar changes of the toenails. There was no history or evidence of periungual infection.

The characteristic brownish discolouration of the skin appeared in IV.14 when he was 7 or 8 years old, and in his two brothers at about age 9 or 10. It was first noted along the lateral neck and progressed to involve the upper chest, arms, legs, and then the entire body. On close examination there were areas of hyperpigmentation forming a network pattern, and enmeshed between these were areas of hypopigmented skin (Fig. 3). The skin appeared atrophic. Fine telangiectases could also be

FIG. 3. Reticulated hyperpigmented skin seen on the neck of IV.17.

seen in some areas, being more prominent over the butterfly area, pinna, and neck.

The degree of skin involvement seems to be related to age. In IV.20 (age 11) it was limited to the face, neck, upper chest, and certain areas of the extremities, but it was noted over the entire body in IV.14 (age 17). The skin was generally dry and scaly but not sun-sensitive. Atrophic and wrinkled skin was noted over the dorsum of hands (Fig. 2), feet, elbows, and knees and in IV.20 also over the penis. There was a marked hyperkeratosis of the palms and soles with loss of palmar ridge patterns in IV.14 but the degree of keratosis was less in IV.17 and it was minimal in IV.20 whose ridge patterns were clearly identified.

Bullae of the hands and feet were recurrent in areas of trauma and were slow to heal. The three boys as well as their mother complained of excessive sweating all over the body, more marked on the forehead and in the palms and soles, even in cool weather.

At the age of 15 years IV.14 developed epiphora. This problem was ascribed to stenotic lacrimal ducts. Subsequent dilatation relieved the symptom. IV.17 at the age of 14 developed a similar problem. IV.20 had no epiphora although he also was found to have stenotic punctate lacrimalis.

The hair, eyebrows, and eyelashes were normal. Tooth eruption occurred at an appropriate age. There was wide spacing of the teeth in all of them although they had very mild thrust habit. Multiple mild hypocalcification of the terminal cusp tips was noted in IV.14. Both IV.14 and IV.17 had a small leukoplakic patch at the lateral border of tongue, but leukoplakia was not found in the youngest brother.

The rest of the physical examination on each was negative. IQs were in the 55–65 range.

Complete peripheral blood counts were normal in these three patients. Bone marrow examinations showed varying degrees of hypocellularity.

III.20, the propositus, was born on 23 August 1943 and died on 4 June 1974. He was seen at the University of Oregon Medical School for the first time in June 1972 at the age of 29 with a complaint of occasional brief episodes of epistaxis and questionable haematemesis during the preceding month. The erythroid values were within the normal range. The symptoms recurred in December 1972 at which time he was admitted for complete evaluation. His fingernails and toenails had been rudimentary from birth and the skin had always been dry and mottled. He also sunburned very easily. His teeth were extracted at age 27 due to extensive caries. About the same time there was a marked thinning of the scalp hair.

Sweating was considered normal. He had no history of bullous eruption of the skin or dysphagia. His vision was poor with occasional blurring; epiphora was absent.

The significant past medical history was mumps in childhood and an operation for a fracture of the distal left femur at age 20 years.

He had been married to a 21-year-old mentally re-

tarded woman for 7 months. He completed the eighth grade of a special education course at 21 years.

Physical examination showed a mentally retarded male, appearing aged with sharp facial features (Fig. 4). Height was 130 cm and weight 50.9 kg. The scalp hair was thin, short, fine, and silky; facial hair, eyebrows, and eyelashes were sparse. His eyelids were thin and the palpebral fissures narrow. The punctae lacrimalis were stenotic. The visual acuity was severely impaired to 20/200 in both eyes. Colour vision was defective but not consistent with any diagnostic pattern. The fundoscopic examination showed atrophic optic discs and extensive areas of infarction and haemorrhage obliterating the macula.

The skin of the face, neck, and arms had areas of hypopigmentation surrounded by hyperpigmented areas, forming a reticular pattern. Many fine telangiectases were scattered on the trunk and extremities. The skin of the dorsum of the hands was atrophic; the palms and soles were hyperkeratotic with absence of dermal ridges. The skin was generally warm and moist except over the sun-exposed areas where it was dry and scaly. Local injection of methacholine bromide 1:10 000 produced sweating equally in hypo- and hyperpigmented areas. There were only rudimentary nails present on fingers and toes (Fig. 2). The tongue mucosa was atrophic, smooth, and shiny. No leukoplakia was present on the initial examination. However, one year later hard palate, buccal mucosa, and tongue displayed leukoplakia (Fig. 5). The biopsy showed epithelial hyperplasia and hyperkeratosis with questionable premalignant dysplasia. The heart and lungs were unremarkable; the liver and spleen were not palpable. The penis, testes, and prostate were small.

FIG. 4. The propositus. Note sharp facial features; sparse scalp hair, eyebrows, and eyelashes; and abnormal skin pigmentation.

FIG. 5. Leukoplakia and atrophic mucosa of tongue in the propositus.

TABLE I
CLINICAL MANIFESTATIONS OF DYSKERATOSIS CONGENITA IN 51 CASES

Report	Case	Sex	Age when reported (yr)	Age at onset (yr)	Hyperpigmentation	Skin atrophy	Hyperhidrosis of palms and soles	Hyperkeratosis of palms and soles	Bullous formation	Acrocyanosis	Nail dystrophy	Leukoplakia	Extensive caries or early dental loss	Alopecia	Epiphora
Zinsser (1910)	1 } 2 }	M M	18 29	4	+		+			+	*	+		-	
Engman (1926; 1935)	3 } 4 }	M M	22-32 18-26	8-9 7	+	+					+	*	+	+	
Cole <i>et al</i> (1930; 1955; 1957)	5	M	20-50	Childhood	*	+	+	+	+	+	*	+	+	+	+
Wise (1943); Garb and Rubin (1944); Garb (1947; 1958)	6 } 7 }	M M	25-36 21-33	5 12	+	+	+	-	+	+	+	+	+	-	+
Jansen (1951)	8	M	21	12	+	+	+		+		+	+		-	*
Kitamura and Hirako (1955; case 2)	9	M	14	10	*	+		-	-		+		-	-	-
Costello and Buncke (1956); Costello (1957)	10	M	18-20	Birth	*	+	+	+	*		+	+	+	-	-
Koszewski and Hubbard (1956)	11 } 12 }	M M	26 20	Childhood	*		+				*	+	+	+	
Basex and Dupré (1957); Calmettes <i>et al</i> (1957)	13†	M	11-12	7	+		+	-	-		*	+	-	-	+
Pastinszky <i>et al</i> (1957)	14	M	21	5	+	+	+	+			+	+	+	+	*
McDonald and Goldschmidt (1960; case 2)	15	M	8	4							+			-	+
Grekin and Schwartz (1962); Inoue <i>et al</i> (1973)	16	M	11-16	5	+			-			*	+			+
Sato and Hannibal (1962)	17	M	20	13	*		+	+			+	+			+
Sorrow and Hitch (1963)	18	F	31-33	Childhood	*	-	+				*	*	+		+
Bodalski <i>et al</i> (1963)	19 20	M M	10 6	1 3	* *	 +	+	-	 +	 +	+	+	+		+
Milgrom <i>et al</i> (1964)	21	M	44		+	+	-	-	-		+	+	-	+	-
Georgouras (1965)	22	F	8	Birth	*			+	+	+	+	+	-	-	
Bryan and Nixon (1965)	23 24 25 26 27	M M M M M	31 39 16 14 9	 24 10 Birth 8	+	 +	 +	 +	 +	 +	+	+	+	-	-

+ = present; - = absent; * = earliest manifestation(s); † = positive family history; I = infection; B = bleeding; M = malignancy. Related cases are bracketed.

Low intelligence	Dysphagia	Hyposthenic build	Small testes and penis	Anaemia	Leukopenia and/or thrombocytopenia	Hepatomegaly	Splenomegaly	Cause of death
-		+				-	-	
-		+		+	+	-	+	I, M
+	+	+	+	+	-			M
+				+	+	+	+	I
+		-		+	+	-	+	
+		+	+	+	+			
+	+	+	+	-	-			
	+	+	+	+	+	-	-	I
-	-	-	-	+	+	-	-	
-		-	-	-	-	-	-	
-				+	*			B
		-	-	+	+	-	+	I, B
				-	-			
-	+	+		*	+	-	-	M
+			+	+	+		+	
-		-		+	+		+	
-	+	+	-	+	+	-	-	
	+	-		+	+	+	-	
				-	+	+	+	I
-		-	-	-	-	-	-	
-		+		+	-	-	+	
-		-	-	+	+	-	+	
-			-	+	-	-	-	

The evaluation in December 1972 demonstrated no specific bleeding site. X-rays of the gastrointestinal tract and skeleton and intravenous urogram were normal. The complete blood count was as follows: haemoglobin 8.5 g/dl, haematocrit 24%, reticulocytes 0.7%, platelets $22 \times 10^9/l$, white blood cells $1.7 \times 10^9/l$ with a normal differential. Bone marrow biopsy was markedly hypocellular.

The clinical course over the subsequent one and one-half years was without incident. He was treated with nandrolone decanoate and occasional blood transfusions with the haemoglobin levels ranging from 4 to 10 g/dl, white blood counts 0.8 to $3.2 \times 10^9/l$, platelets 1 to $110 \times 10^9/l$, and reticulocytes 0.1 to 5.4%. Proctosigmoidoscopy at 30 years revealed no leukoplakia or mass lesion. The endocrine studies to be reported were consistent with hypogonadotropic hypogonadism.

Approximately one month before death the patient developed a low grade fever without any specific complaints. He gradually deteriorated and expired at the age of 31 years. Necropsy revealed disseminated cytomegaloviral infection.

Other laboratory data. The urine was negative for amino acids and the radiology of sella turcica appeared normal in all four patients. They had normal immunoglobulin levels but absence of delayed hypersensitivity response to several skin tests. Further immunological investigations are in progress.

Studies of the proband's lymphocytes repeatedly showed a poor response to phytohaemagglutinin (PHA) stimulation with a mitotic index of 5/1000. No structural abnormality or increased chromosomal breakage was observed. Bone marrow preparations were studied on two occasions; only four out of 1000 cells had mitotic activity; the cells' metaphases were not of adequate quality to provide a definitive result. Skin fibroblast cultures were attempted twice (one of the specimens was obtained immediately after death), but the tissue did not respond to the culture procedure.

The peripheral lymphocytes and the bone marrow cells of IV.14, IV.17, and IV.20, however, showed good mitotic response to PHA stimulation. There were no rearrangements or increased number of chromosomal breaks. Chromosome studies of the skin fibroblasts showed similar results.

Results

Our four patients had the characteristic manifestations of dyskeratosis congenita. The earliest finding was nail dystrophy which developed in early childhood, and was probably present at birth in the proband. Later the atrophic reticulated telangiectatic hyperpigmentation appeared; it was first evident on the neck, upper chest, and face with later extension over the arms, legs, and trunk. The atrophic skin of the dorsum of hands and feet and hyperkeratosis of palms and soles were present in all of the four patients, but bullous formation of the

TABLE 1—continued

Report	Case	Sex	Age when reported (yr)	Age at onset (yr)	Hyperpigmentation	Skin atrophy	Hyperhidrosis of palms and soles	Hyperkeratosis of palms and soles	Bullous formation	Acrocyanosis	Nail dystrophy	Leukoplakia	Extensive caries or early dental loss	Alopecia	Epiphora
Addison and Rice (1965)	28	M	22	Child-hood	+	+	+				+	—	+	—	+
	29	F	24–25		+							+			
Rollier <i>et al</i> (1966)	30	F	11	11	*	+	+	+	+		+	—	+	+	
Silva (1966)	31	M	18	6	*	+		+		+	+	+	—		+
Orfanos and Gattmann (1966)	32	M	12	7	+	+	+				+	*	—	+	+
Bureau <i>et al</i> (1967)	33	?	3/12	3/12	*			+				+		+	—
Degos <i>et al</i> (1969)	34†	F	28	7	*		+	+			+	+			+
Kubicz (1970)	35†	M	24	9	*		+	+	+		*				
Barrière and Welin (1970)	36	M	7	1	+	—	+	+	+		*	+		+	+
Cannell (1971)	37	M	32	13	*	+	+	—			*	+	+	+	+
Nazzaro <i>et al</i> (1972)	38	M	45	Child-hood	*	+					+	+	+	+	+
	39	M	47	Child-hood	*	+					+	+	+	+	+
Steier <i>et al</i> (1972)	40	M	21	4	*	+	+	+			+	+	+	+	+
	41	M	18		+	+		+			+			+	
Ortega <i>et al</i> (1972)	42	M	11	4	+						*	+		+	+
Reich (1973)	43	M	18	9–11	+	+					*				+
	44	M	12	7	*				+		+	+			+
Morrison (1974)	45	M	15	7	+	+	+		+		*	—			+
	46	M	20	8	+						*	—			+
Present family	IV.11	M	17	2–5	+					—	*			+	
	IV.14	M	15–17	2–5	+	+	+	+	+	—	*	+	—	—	+
	IV.17	M	12–14	2–5	+	+	+	+	+	—	*	+	—	—	+
	IV.20	M	9–11	2–5	+	+	+	+	+	—	*	—	—	—	+
	III.20	M	29–31	Birth	+	+	—	+	—	—	*	+	+	+	+
Occurrence/ Frequency					50/50	28/30	25/28	18/25	14/18	6/11	46/47	39/44	20/32	18/35	29/37
Percentage					100	93	89	72	78	55	98	87	63	51	78

+ = present; — = absent; * = earliest manifestation(s); † = positive family history; I = infection; B = bleeding; M = malignancy. Related cases are bracketed.

skin and hyperhidrosis of palms and soles were present in the nephews only. The different degrees of nail and skin involvement, being mildest in the youngest nephew (IV.20) and most marked and extensive in the propositus, reflect the progressive nature of the disease. The oral leukoplakia was observed in the propositus and his two older nephews

(IV.14 and IV.17) but was absent in IV.20. Wide spacing and hypocalcification of the teeth were the only abnormal dental findings. Excessive tearing was a complaint in IV.14 and IV.17 although all the affected individuals had some degree of stenosis of the punctae lacrimalis. The propositus had extensive retinal atrophy with infarctions and hae-

Review of the literature

Family histories, clinical findings, and laboratory data on 46 of the previously reported cases of dyskeratosis congenita are summarized in Table I together with the findings in our four patients and IV.11 whose medical records and necropsy slides were reviewed by us.

Although approximately 60 patients were reported or mentioned in the literature as having dyskeratosis congenita, several cases are not included in Table I because of incomplete data. These are a brother of Basex and Dupré's case (1957) and of Kubicz's (1970); family members in various studies (Schamberg, 1960; Degos *et al*, 1969; Scoggins *et al*, 1971; Nazzaro *et al*, 1972); or because of incorrect diagnosis (Moon-Adams and Slatkin, 1955; Aplas, 1956). Two reports on dyskeratosis congenita could not be located (Jacobs and Tromovitch, 1962; Lobo *et al*, 1964). One case of dyskeratosis congenita reported as Fanconi's anaemia (McDonald and Goldschmidt, 1960) is included in Table I.

Clinical features. The disease manifested itself before puberty in all cases except one (case 24); it was noted at birth in four cases (10, 22, 26, 31). The earliest manifestations, in order of frequency, were skin hyperpigmentation, nail dystrophy, leukoplakia of the oral mucosa, epiphora, anaemia, and bullous eruptions of the skin. The first three findings are characteristic of dyskeratosis congenita and they eventually appeared in almost all the cases. Those who did not have this triad were either in a young age group or were incompletely described.

In addition to typical reticulated telangiectatic hyperpigmentation (100%), the other skin changes were atrophic and wrinkled skin over the dorsum of hands, feet, genitalia, and extremities (93%); hyperhidrosis of palms and soles (89%); and hyperkeratosis of palms and soles (72%) causing cracking, fissure, and disappearance of dermal ridges. The bullae often developed (78%) after even a slight trauma. Acrocyanosis was noted in 55% of the patients. Dystrophic change of nails (98%) was not of the same degree in all digits. The fingernails were usually more severely affected than the toenails.

Leukoplakia (87%) could occur anywhere but leukoplakia of the oral mucosa was the most frequent and constant finding. Other sites of leukoplakia were urethra (cases 3, 14), glans penis (case 10), vagina (case 18), rectoanal region (cases 5, 10, 14, 25).

No good description of dental abnormalities was available. This is probably because most of the

Low intelligence	Dysphagia	Hyposthenic build	Small testes and penis	Anaemia	Leukopenia and/or thrombocytopenia	Hepatomegaly	Splenomegaly	Cause of death
	*		+	+	+	+	+	
	+			-	-			M
		+		-	-	-	-	
-	+		+	-	-			
	-	-		+	+			
-		-		-	-			
-		-		+	+			
-		+		-	-			
+				-	-			
+				-	-			
-		+		+	+	-	+	
-		-	-	+	+	-	+	B
				-				I
	+			-	+			
				-				
+	-	+	-	-	-	-	-	I
+	-	-	-	-	-	-	-	
+	-	-	-	-	-	-	-	
+	-	-	-	-	-	-	-	
+	-	+	+	+	+	-	-	I
13/31	10/17	14/29	8/20	24/46	21/43	4/25	12/27	
42	59	48	40	52	49	16	44	

morrhages. All of them were mentally retarded and probably could be classified in the trainable group. The findings that were present only in the propositus but not in his nephews were underweight and short stature; alopecia; sparse eyebrows, eyelashes, and body hair; early dental loss; hypogonadism and aplastic anemia.

patients had lost their teeth by the time they were first seen. Early dental loss or extensive caries were reported in 63% of cases. Wide separation of teeth (cases 10, IV.14, IV.17, and IV.20), malformed teeth (cases 10, 11), crowded teeth (case 32), and hypocalcification (IV.14) may reflect abnormal dental development.

Fifty-one percent of the patients had thin, lusterless hair. The sparse body hair in some cases could be related to hypogonadism. Eyebrows and eyelashes were sometimes absent.

Epiphora resulting from obliteration of punctae lacrimalis by epithelial hyperplasia was found in 78%. Other ocular findings were conjunctivitis, blepharitis, ectropion, and loss of eyelashes. Optic pallor (case 40) and atherosclerotic change of retinal vessels (case 18) were found in one patient each. None of the previously reported cases had retinopathy similar to our propositus.

Thirteen of 31 patients (42%) had subnormal intelligence. The level of mental development is difficult to determine because IQ testing was not generally performed except in cases 5, 9, and 25 whose IQs were 93, 85, and 79, respectively. The IQs in our patients ranged from 55–65. It is of note that there seemed to be an intrafamilial correlation in the mental capability (families of Garb, 1958 [cases 6 and 7], of Bryan and Nixon, 1965 [cases 24–27], of Nazzaro *et al*, 1972 [cases 38 and 39], and of our family).

Dysphagia in dyskeratosis congenita (59%) was ascribed to oesophageal diverticulum (cases 6, 21) and congenital oesophageal stenosis (cases 28, 9, 45) but in five cases the anatomic abnormality could not be determined. One patient (not included in Table I) had suffered from dysphagia and subsequently developed carcinoma of the cervical oesophagus (Schamberg, 1960).

Forty-eight percent of the patients were of hyposthenic build, only case 40 and our propositus (III.20) were also short. 'Sharp', 'pinched' facies, and large 'beaked' nose were described in four patients (cases 3, 10, 28, and 30) as well as in III.20. These findings could very well be secondary to decreased subcutaneous fat.

Although small testes and penis were mentioned in eight patients, hypogonadism was documented in only case 11. Cases 6 and 8 had a small sella turcica but there was no other evidence indicating it to be pathological. Hypopituitarism and hypoadrenalism were mentioned in case 9. Two patients had enlarged thyroid (cases 16, 20). III.20 had secondary hypogonadism.

Additional findings in dyskeratosis congenita were abnormalities of the external ear (case 10) and mid-

dle ear (case 21), minor skeletal anomalies (cases 11, 18, 19, 26), aseptic necrosis of hips (cases 16, 26), deformed joints (cases 10, 43), abnormal ECG (cases 10, 15), and urethral stenosis (cases 10, 43).

Laboratory studies. The cytogenetic studies carried out in nine of the reported cases (16, 21, 24, 25, 26, 27, 28, 42, 44) and in our patients demonstrated no structural abnormality and no increased breaks or gaps. The studies in most cases were in blood lymphocytes, except case 16 and the four patients in this report in which bone marrow and skin fibroblasts were also studied.

The chromosome studies of the peripheral lymphocytes in the family reported by Scoggins *et al* (1971) showed endoreduplications in two patients, one of whom also had chromatid breaks in two out of 27 cells examined (personal communication). Their karyotypes were normal. Morrison (1974) found 20% of chromosomal breaks in one of his patients (case 45) and another patient (case 46) had 10% breakage.

Immunological investigations were reported in only a few patients. Case 16, aged 17, and case 42, aged 10, were found on necropsy examinations to have thymic aplasia and lymphocyte depleted spleen and lymph nodes. All the immunoglobulins were abnormally low in case 42 (Ortega *et al*, 1972) as was the IgM in cases 40 and 41 (Steier *et al*, 1972). The family studied by Scoggins *et al* (1971) was reported to have normal immunoglobulin levels and skin homograft rejection but absence of delayed hypersensitivity response to skin tests.

Aminoaciduria was reported in case 21 but was absent in our family.

Complications. The evidence from the literature indicates that there is a definite increased incidence of solid malignant tumours in the patients with dyskeratosis congenita. Leukaemia has not been reported in any of the cases.

Malignant changes usually developed in the mucous membrane. The sites of the tumours in seven patients (5, 6, 10, 18, 29, 35, 37) were the tongue, buccal mucosa, nasopharynx, rectum, cervix, vagina, and the skin. A patient reported by Schamberg (1960) had carcinoma of the oesophagus. Interestingly, two of the patients had multiple primary tumours (cases 5, 6).

In at least three of these cases (5, 6, 37) the carcinoma was found to originate in the pre-existing leukoplakia. The interval between the time when oral leukoplakia was first noted and the malignant change was approximately 27 years in case 5, 10 years in case 6, and 16 years in case 37.

TABLE II
DEVELOPMENT OF MALIGNANT TUMOURS IN DYSKERATOSIS CONGENITA

Case	Age at Detection (yr)	Location	Type
5 (Cole <i>et al</i> , 1957)	47-50	Tongue	Squamous cell carcinoma
		Rectum	Adenocarcinoma
		Nasopharynx	Squamous cell carcinoma
6 (Garb, 1958; case 2)	35	Buccal mucosa	Epidermoid carcinoma (grade 3)
		Rectum	Mucinous carcinoma (poorly differentiated)
10 (Costello, 1967)	20	Dorsum of hand	Squamous cell carcinoma
18 (Sorrow and Hitch, 1963)	31	Cervix and vagina	Squamous cell carcinoma (moderately well differentiated)
29 (Addison and Rice, 1965; case 2)	24	Buccal mucosa	Squamous cell carcinoma (well differentiated)
35 (Kubicz, 1970)	24	Coral mucosa	Basal-squamous cell carcinoma
37 (Cannell, 1971)	33	Oral mucosa	Anaplastic squamous cell carcinoma
(Not in Table I; Schamberg, 1960)	—	Oesophagus	(Squamous cell) carcinoma

The types and locations of the tumours are shown in Table II. The age in which the tumour was first noted was usually between the third and the fifth decade.

Twenty-four patients (52%) developed anaemia as the result of bone marrow failure. Nineteen of the patients also had leukopenia and/or thrombocytopenia. One patient (case 44) had only thrombocytopenia at the time of the report.

Infection and/or gastrointestinal bleeding led to the fatal outcome in eight cases (5, 7, 11, 15, 16, 23, 42, 43), usually in their second decade. Deaths in the family reported here also occurred at an early age. II.13 and II.19 (not included in Table I) died from respiratory tract infections of unknown aetiology at which time II.13 was said to have 'anaemia', and II.19 'aplastic anaemia'.

The immediate causes of death in IV.11 and the propositus were, however, not related to haematological complications. IV.11 died at age 17 from *Pneumocystis carinii* pneumonia at which time the peripheral blood counts showed no evidence of bone marrow failure. The propositus, although he had suffered from aplastic anaemia for at least 2 years with occasional minor bleeding episodes, died from cytomegaloviral infection at 31 years of age. (Detailed pathological findings in these two patients will be reported elsewhere.)

Mode of inheritance. Although dyskeratosis congenita has been generally accepted to be hereditary, the mode of inheritance was still considered as 'unknown' or 'unclear' by several authors, even in the more recent reports. There has in the past been strong supportive evidence for an X-linked

recessive mode of inheritance; however, both autosomal recessive and autosomal dominant transmissions have also been suggested. We have accumulated the pedigree data from the published papers to determine whether the segregation of the disease supports the X-linked recessive mode of inheritance, or if, in fact, there is genetic heterogeneity.

Dyskeratosis congenita has been reported in several ethnic groups: Caucasian American, American Negro, Jewish American, Brazilian, German, French, Dutch, Italian, Polish, Australian, Japanese, and African. Of 51 patients reported in the literature, only five were females giving M:F sex ratio of 10:1; 22 cases came from 11 families and the rest were sporadic cases.

The preponderance of affected males together with the occurrence of the disease in eight sets of male sibs (Zinsser, 1910; Engman, 1926; Garb and Rubin, 1944; Koszewski and Hubbard, 1956; Basex and Dupré, 1957; Kubicz, 1970; Nazzaro *et al*, 1972; Steier *et al*, 1972) suggest an X-linked recessive trait. The supportive evidence for X-linked recessive transmission came from Bryan and Nixon's family (1965), where the disease was transmitted through the females in three generations, with a total of five affected males. There was one opportunity for male-to-male transmission which did not occur. The inheritance pattern in the family reported here also indicates dyskeratosis congenita to be X-linked recessive trait. In three generations, nine affected males received the defective gene through their mothers.

However, the relationship between this seemingly X-linked recessive disease and the affected females

TABLE III
SEGREGATION ANALYSIS OF 14 FAMILIES FROM THE LITERATURE

Case(s)	Observed									Expected				
	Total No. in sibship	Affected sibs	Non-affected sibs	Total males	Affected males	Non-affected males	Total females	Affected females	Non-affected females	Autosomal Recessive			X-linked	
										Total number in sibship (= 1)	Affected sibs (= 0.25)	Non-affected sibs (= 0.75)	Total males (= 1)	Affected males (= 0.5)
1, 2	6	2	4	2	2	0	4	0	4	6	1.5	4.5	2	1
5	4	1	3	1	1	0	3	0	3	4	1	3	1	0.5
6, 7	4	2	2	3	2	1	1	0	1	4	1	3	3	1.5
11, 12	6	2	4	4	2	2	2	0	2	6	1.5	4.5	4	2
13	3	2	1	3	2	1	0	0	0	3	0.75	2.25	3	1.5
15	7	1	6	—	—	—	—	—	—	7	1.75	5.25	—	—
16	4	1	3	2	1	1	2	0	2	4	1	3	2	1
19	2	1	1	2	1	1	0	0	0	2	0.5	1.5	2	1
20	2	1	1	1	1	0	1	0	1	2	0.5	1.5	1	0.5
21	3	1	2	2	1	1	1	0	1	3	0.75	2.25	2	1
22	5	1	4	3	0	3	2	1	1	5	1.25	3.75	3	1.5
35	6	2	4	—	—	—	—	—	—	6	1.5	4.5	—	—
37	3	1	2	2	1	1	1	0	1	3	0.75	2.25	2	1
40, 41	3	2	1	2	2	0	1	0	1	3	0.75	2.25	2	1

is not clear. Four of the five female patients were sporadic cases and one had an affected brother (Addison and Rice, 1965). One explanation may be the Lyonization effect of the gene in the female heterozygotes. Steier *et al* (1972) reported 'mild dyschromic cutaneous changes' in the mother and the sister of his two male patients. But none of the females, including the obligate carriers, in Bryan and Nixon's family (1965) or in the family reported here showed any sign of the disease.

Another possible explanation might be that autosomal forms of dyskeratosis congenita also exist. One instance of parental consanguinity was reported (Costello and Buncke, 1956); there was one male offspring but the total number of sexes of the offspring was not provided. Using the Chi-square test, pedigree analysis of 14 families (in which the disease was present in only one sibship and the family history was considered adequate for analysis purpose) showed the probability to be 0.9999 for X-linked recessive and 0.75 for autosomal recessive transmission (Table III).

In three families, the disease was said to be autosomal dominant. One reported by Scoggins *et al* (1971) is a Negro family in which the proband, his father, his three sisters, and his daughter have evidence of dyskeratosis congenita (R. B. Scoggins,

personal communication). Degos *et al* (1969) reported an affected woman whose sister, father, uncle, and paternal grandmother were probably affected also. Nazzaro *et al* (1972) in their report of two brothers mentioned that there were five other affected members, two of whom were females. The authors suggested that the pattern fits incomplete dominant transmission. The exact relationship of the affected family members was not reported.

Linkage study in the present family. The red blood cell G6PD electrophoresis was done on all family members seen by us and colour vision test was performed with HRR pseudochromatic plate in the male members. The G6PD electrophoresis showed all to be type A. The colour vision test was normal in all males except the proband whose colour vision defect may be secondary to the severe retinal pathology rather than hereditary X-linked colour blindness. Therefore these two X-linked markers are not informative.

The Xg^a blood group is, however, informative in this family (see Fig. 1). III.11 is an Xg^a heterozygote. The Xg^a blood types of III.15 and III.17 indirectly indicate that II.1 was also heterozygous. Xg^a type could not be determined in the proband because he also had a positive direct Coombs test.

Recessive				$\chi^2 = \sum \frac{(\text{Obs} - \text{Exp})^2}{\text{Exp}}$	
Non-affected males (=0.5)	Total females (=1)	Affected females (=0)	Non-affected females (=1)	Autosomal Recessive	X-linked Recessive
				χ^2 v = 1	χ^2 v = 3
1	4	0	4	0.2222	2.0
0.5	3	0	3	0	1.0
1.5	1	0	1	1.3333	0.3333
2	2	0	2	0.2222	0
1.5	0	0	0	2.7777	1.3333
1	1	1	1	0.4285	—
1	2	0	2	0	0
1	0	0	0	0.6666	0
0.5	1	0	1	0.6666	1.0
1	1	0	1	0.1111	0
1.5	2	1	1	0.6666	(3.5)*
1	1	1	1	0.2222	—
1	1	0	1	0.1111	0
1	1	0	1	2.7777	2.0
				$\chi^2 = 10.2063$	$\chi^2 = 7.6666$
				V = 14	V = 33
				p = 0.75	p = 0.9999

The data from this family indicate no close linkage between dyskeratosis congenita and Xg^a blood group.

Dyskeratosis congenita and Fanconi's anaemia. Although dyskeratosis congenita and Fanconi's anaemia are different in many ways and are caused by different genes, their similarities, especially the hyperpigmented skin and aplastic anaemia, are very striking and have led to some confusion in the literature. McDonald and Goldschmidt (1960), in their report of Fanconi's anaemia, described a boy who, in addition to aplastic anaemia, also had rough and dry skin, dystrophic finger and toe nails, and bilateral epiphora. In retrospect these findings are more suggestive of dyskeratosis congenita than Fanconi's anaemia. Several investigators suggested that Fanconi's anaemia and dyskeratosis congenita are probably related or are variants of the same disease, for which Bodalski *et al* (1963) proposed the name Fanconi-Zinsser syndrome. Steier *et al* (1972) felt that some of the case reports possibly represent 'transition cases' between dyskeratosis congenita and Fanconi's anaemia; however, they admitted this was quite conjectural.

Although some of the differences between dyskeratosis congenita and Fanconi's anaemia have been

previously pointed out, we feel that it would be appropriate to include the comparison (Table IV) between the two diseases here. The frequencies of the findings are given where available.

Dyskeratosis congenita, immune deficiency, chromosome instability, and neoplasia. Further data are necessary before a conclusion can be made as to whether immunological defect and/or chromosomal instability are integral parts of dyskeratosis congenita.

Deaths in two of our patients were caused by opportunistic infections; one died from *Pneumocystis carinii* and one from cytomegalic inclusion disease. These two diseases are rare in normal healthy individuals but are found in immunosuppressed or immunological deficiency states (Merigan and Stevens, 1971; Walzer *et al*, 1974). The fact that neither of our patients received an immunosuppressive drug strongly suggests a defect in their immune system. The absence of delayed skin hypersensitivity in the family reported by Scoggins *et al* (1971) and the family in this report, together with thymic aplasia in the patients of Ortega *et al* (1972) and Inoue *et al* (1973) seem to support that there is a defect in the cell mediated immune system. The low levels of immunoglobulins in the patients of Steier *et al* (1972) and of Ortega *et al* (1972) indicates that the antibody producing system is also defective in certain patients with dyskeratosis congenita.

The evidence for chromosomal instability in dyskeratosis congenita is still minimal. So far there have been only two reports (out of nine reports in which chromosomal studies were done) that seem to point in this direction (Scoggins *et al*, 1971; Morrison, 1974). The poor lymphocyte response to PHA in our propositus, probably reflecting T-cell defect, and the low number of mitosis in the marrow cells precluded an opportunity for proper cytogenetic studies in this case. If chromosomal abnormality is indeed part of this disease, the normal chromosomal findings in the three nephews could possibly be explained on the basis of the relatively early stage of the disease, that the cytogenetic abnormality is inconstant, or that it is not detected in all patients. An answer to the above could probably be derived from longitudinal chromosomal studies which are currently underway.

The relation between neoplasia and immunodeficiency state has been extensively discussed in several recent publications (Gatti and Good, 1971; Good, 1972; Waldmann *et al*, 1972). The concept of immune surveillance as a defence mechanism against cancer has been supported by evidence from

TABLE IV
COMPARISON BETWEEN DYSKERATOSIS CONGENITA AND FANCONI'S ANAEMIA

	Dyskeratosis Congenita	Fanconi's Anaemia*
Mode of inheritance	Usually X-linked recessive; can be autosomal recessive or dominant	Autosomal recessive
M:F sex incidence	10:1	2:1
Birth weight	Normal in most cases	Low (56% weighed less than 2.5 kg)
Microcephaly	Absent	Present (40%)
Eye abnormalities	Epiphora and/or stenosis of punctae lacrimalis (78%)	Strabismus (22%), microphthalmia (16%)
Leukoplakia	Present (87%)	Absent
Alopecia	Present (51%)	Absent
Hyperpigmentation	Present (100%)	Present (77%)
Nail dystrophy	Present (98%)	Absent
Skeletal malformations	Rare	Present (66%), especially of the upper limbs
Internal abnormalities	Oesophageal diverticulum or stricture; dysphagia (59%)	Renal anomalies (28%)
Stature	Hyposthenic build (54%)	Short (60%), usually below 3rd centile
Mental deficiency	Present (42%)	Present (17%)
Hypoplasia of the bone marrow	Present (52%)	Present (100%)
Malignancy	Solid tumours (17%); no leukaemias reported	Solid tumours reported in at least 7 cases; (Bernstein <i>et al</i> , 1971; Swift <i>et al</i> , 1971) leukaemia reported in at least 8 cases (Dosik <i>et al</i> , 1970)
Chromosomal breakage and rearrangement	Probably absent	Present in lymphocytes, bone marrow, and fibroblasts (Dosik <i>et al</i> , 1970; German, 1971)
Immunological defect	Present	Absent

* Reference: Gmyrek and Syllm-Rapoport (1964) unless otherwise indicated.

both clinical and laboratory studies. Several genetic disorders are known to be associated with immunodeficiency and an increased incidence of malignancy. These include ataxia-telangiectasia, Wiscott-Aldrich syndrome, Bruton agammaglobulinemia (Waldmann *et al*, 1972), and Bloom's syndrome (German, 1969).

Cytogenetic abnormalities have been observed in several human neoplasias (Sandberg and Hossfeld, 1970). In addition, chromosomal instability has been demonstrated in somatic cells of patients with Bloom's syndrome, Fanconi's anaemia, ataxia-telangiectasia, and xeroderma pigmentosum which are genetic diseases with a predisposition to cancer (German, 1971). The significance of chromosomal changes in cancer is still not known. German (1971) was of an opinion that a clone of cells, derived from a single progenitor cell containing marker chromosome(s), once having undergone a certain mutation becomes susceptible to conversion to cancer by some oncogenic factors.

The tendency to develop malignant tumours in

the patients with dyskeratosis congenita could very well result from immunological defect. A predisposition to chromosomal abnormality, if substantiated, could also play a role in the development of cancer.

Primary defect in dyskeratosis congenita.

The interrelation between the multiple system abnormalities in dyskeratosis congenita is yet to be determined. There are two possibilities regarding the relation between aplastic anaemia and immune deficiency in this disease. Since the lymphocyte precursors arise from primitive pluripotent cells located in the bone marrow (McGregor, 1968), a disorder of stem cells can, therefore, give rise to the abnormalities of both T and B lymphocytes as well as to the three cell lines of the bone marrow. Another possible explanation is that the abnormality in the mesoderm, as evident in the bone marrow, may lead to the abnormal development of the thymus gland. It has been shown that epitheliomesenchymal interaction is

necessary in the development of the thymus *in vitro* (Auerbach, 1960), and Peterson *et al* (1964) suggested that the abnormality of the mesoderm will explain the thymus disorder in ataxia telangiectasia. These reasonings, however, do not explain cutaneous manifestations and mental deficiency which are also manifestations of dyskeratosis congenita.

It seems that the basic defect in dyskeratosis congenita may be at the level of cell division. The abnormality in one of the enzymatic steps essential to normal cell division, for example DNA polymerase II whose activity correlates positively with the rate of tissue regeneration (Baril *et al*, 1973), can lead to hypoproliferation or impaired regeneration of the skin, nails, bone marrow, and neurones in dyskeratosis congenita. An example analogous to this may be the defect in deoxyribonuclease which is essential for DNA repair in xeroderma pigmentosum (Robbins *et al*, 1974). Tritiated thymidine incorporation by the lymphocytes and skin fibroblasts may be one way to study the DNA synthesis in this disorder. If this is shown to be abnormal, it will be interesting to look further for any abnormality at the different steps of cell division.

We are grateful to Dr J. Vidgoff for the translation of several articles, Mrs P. Evans for typing the manuscript, Drs G. A. Brooksby and R. G. Weleber for ophthalmological examinations, Dr W. E. Gibson for dental evaluations, and Dr D. Linder for reviewing the pathology slides. We thank Dr B. K. McCaw and Miss C. L. Olson for cytogenetic studies, Miss S. I. Rowe and Miss S. M. Hazard for genetic marker studies, and Dr R. Vlietinck for helping with statistical analysis. We wish to thank also Drs E. W. Lovrien, R. D. Koler, and F. Hecht for their advice, Dr F. J. Storrs for reviewing the manuscript, and Drs R. L. Dimond and S. A. Ebert for referring the *propositus* to us.

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Notice

Symposium on the Pathology of Pregnancy

The Royal College of Pathologists are holding a symposium on the pathology of pregnancy on 12 and 13 February 1976, at the Royal College of Physicians. The following subjects will be covered in the two-day meeting. Fetoplacental function: its nature and assessment; haematological problems; hypertension and renal disease; infections; trophoblastic tumours; and congenital abnormalities.

The symposium is open to workers in all disciplines connected with the subject. The registration fee is £12 (sterling), which includes coffee, lunch, and tea on the two days and a copy of the papers to be published as a special supplement to the *Journal of Clinical Pathology*. Those wishing to attend the symposium dinner on Thursday evening, 12 February, should send with their application form the additional fee of £8 (sterling) which includes drinks before and with the dinner. The final programme will be sent out in February 1976. Application forms can be obtained from The Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF.