Dyskeratosis Congenita: Relationship to Fanconi’s Anemia

By William Steier, G. Arthur Van Voolen, and Victor J. Selmanowitz

Dyskeratosis congenita and Fanconi’s anemia share impressive features in common: primary refractory pancytopenia; bone marrow hyperplasia (cuboidal phase) and megaloblastosis, eventuating in severe hypoplasia of the marrow; cutaneous melanotic dyschromia; lacrimal duct blockage and a host of other minor abnormalities, in addition to mental retardation and generalized impairment of growth. Evaluation of two brothers with dyskeratosis congenita, and review of previous reports, indicate the following to be more prominent in dyskeratosis congenita than in Fanconi’s anemia: cutaneous telangiectatic erythema and atrophy; exocrine, ungual, and dental dysplasias; mucosal leukoplaikia, carcinomatosis, and stenosis; and esophageal diverticula. Prominent in Fanconi’s anemia but not dyskeratosis congenita are the renal and particular skeletal anomalies. Possible transition cases are discussed. The proband studied suffered from progressive refractory pancytopenia, fevers, abdominal pains, malabsorption syndrome, and finally subarachnoid hemorrhage. Cultured leukocytes had normal-appearing karyotypes. The proband’s brother had cutaneous alterations of dyskeratosis congenita, but a hemogram revealed only mild thrombocytopenia and macrocytosis. Both brothers had elevated levels of hemoglobin F, leukocyte alkaline phosphatase, serum IgG, and thyroglobulin antibody, and both had reduced levels of serum IgM and vitamin B12.

The earliest descriptions of dyskeratosis congenita (Zinsser-Engman-Cole syndrome, Cole-Rauschkolb-Toomey syndrome) were those of Zinsser (1906), Engman (1926), and Cole, Rauschkolb, and Toomey (1930). This genetic and ultimately lethal disorder has been recognized on the basis of mucocutaneous and hematopoietic derangements. Fewer than 30 cases have been reported to date, mostly in the dermatologic literature. Ectodermal findings include cutaneous atrophy, telangiectasia, and hyper- and hypomelanosis in a reticulated pattern; alopecia of scalp and eyelids; ungual, exocrine, and dental dysplasias; and mucosal leukoplaikia with neoplastic consequences. A list of features is provided in Table 1.

The onset is first observed in childhood and survival has been curtailed to between the second and fifth decades. The lethal consequences have been attributed to the general debilitation, severe pancytopenia with progressive bone marrow hypoplasia, susceptibility to infection (bronchopneumonia, meningitis), and carcinomatosis usually arising from mucosal primary sites, and, less often, cirrhosis and bleeding diathesis.
Table 1. Nonhematologic Features of Dyskeratosis Congenita*

<table>
<thead>
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<th>General</th>
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<tr>
<td>Skeletal: growth retardation and frailty</td>
<td>Fanconi's anemia</td>
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<tr>
<td>Facies: telangiectatic, erythematous, sharp-featured</td>
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<td>Psyche: mental retardation</td>
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<td>Endocrine: Genital hypoplasia and other anomalies, thyromegaly</td>
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| Dermatologic                        |          |
| Skin: Hyper- and Hypomelanosis       |          |
| Hair: Hypotrichosis, premature canities |          |
| Nails: Ungual hypoplasia and dystrophy |          |
| Exocrine: Palmoplantar hyperhidrosis, generalized hypohidrosis elsewhere |          |

| Mucosal                              |          |
| Leukoplakia, bullae, erosion, ulceration, atrophic lingual papillae |          |
| Carcinomas: buccal, lingual, nasopharyngeal, pulmonary, esophageal, cervicovaginal, anorectal |          |
| Atrophy, stenosis or fissures: esophageal, anal, urethral, ureteral, vaginal |          |
| Esophageal dysfunction and/or diverticulae |          |

| Dental                               |          |
| Gingivitis, periodontitis, dental dysplasia and early carious degeneration |          |

| Ocular                               |          |
| Obliteration of puncta lacrimalis, ectropion, absence of cilia, squamous blepharitis, conjunctivitis (bullous) |          |

*Italicized features are relatively frequent in Fanconi's anemia. Hematologic features and carcinomatosis in Fanconi's anemia are discussed in the text.

Going by reported cases, dyskeratosis congenita would seem to be expressed predominantly in white males. One affected black and a few Orientals have been reported. Two females have had the disorder, and three additional females may have had an atypical form.

In much of the literature on dyskeratosis congenita, the condition has been proposed as a variant of Fanconi's anemia. Both disorders commonly manifest primary refractory pancytopenia; bone marrow hyperplasia and megaloblastosis, going on to severe hypoplasia and replacement by fat, and cutaneous dyschromia and retardation of growth (Table 1).

CASE REPORT

The proband, a 21-yr-old Jewish male, was hospitalized for severe anemia. Moderate anemia was first noted at age 9 and treated to no avail with iron, vitamin B12, and folic acid. Neutropenia and splenomegaly were discovered at age 13 during a hospitalization for abdominal right lower quadrant pain. Appendectomy did not reveal appendicitis. At 17 yr of age, easy bruisability, bleeding gums, and prolonged bleeding from minor cuts were noticed. Four months prior to hospitalization, the patient developed progressive weakness and fatigue. There was no history of jaundice, exposure to toxins, or recent infection.

The record of medical abnormalities dated back to age 4 when cutaneous dyschromic changes were observed. Four years later he developed bilateral lacrimal duct blockage and dystrophic changes of the finger- and toenails. Between ages 12–14 he experienced puberty, lost most of his lower eyelashes, began to develop male pattern alopecia, and noticed a
generalized sweating deficiency, except for the palms which were hyperhidrotic. At 15, a meatotomy was performed to relieve urethral stenosis. Periodontitis and loss of several teeth occurred at age 16; the following year the remaining teeth required extraction.

Physical examination revealed a 157 cm (62 in) tall, 101 lb, normally proportioned but frail individual. The skin was altered in a widespread manner by small, hypopigmented, and liminally atrophic macules of various shapes. The areas interspersed between and surrounding the hypopigmented spots were brownish-tan in hue, giving a reticulated appearance. Histologic examination of biopsy specimens of hyper- and hypopigmented skin revealed thin, flattened epidermis with "washing out" of the basal layer, a constant granular layer one to two cells thick and relative hyperkeratosis. A sparse lymphocytic infiltrate was located in the superficial dermis. In the section from hyperpigmented skin there were, in addition, increased epidermal melanization and pigment-laden melanophages in the superficial dermis.

The face, especially the upper half, and the neck and upper portion of the chest were erythematous and telangiectatic, this being superimposed on the pigmented disturbance (Figs. 1 and 2). The patient had a seborrheic countenance, squamous blepharitis, scaly grayish-white plaques on the scalp, and advanced male-pattern alopecia. Axillary and pubic hair-distribution was normal. The skin of the hands and feet was wrinkled, atrophic, erythematous, and shiny. Palms, soles, elbows, and knees exhibited scaly patches. All nails were hypoplastic, longitudinally ridged, and tapered (Fig. 3). There was absence of the distal portions of the nail plates. Digital dermatoglyphic ridges were flattened and nearly absent (Fig. 3). The starch-iodine sweat test with heat stimulation indicated absence of sweating on the forehead.

Ophthalmologic examination disclosed bilateral optic nerve pallor. The retinal blood vessels and maculae appeared normal. Oculomotility was intact. Eyelashes were sparse, some cilia directed inwards towards the globe. Lacrimal papillae were present but the puncta lacrimalia were blocked, resulting in bilateral epiphora. Inspection of the mouth revealed atrophic lingual papillae, anodontia, and buccal leukoplakia. The thyroid gland was not palpable. There was no peripheral lymphadenopathy. Cardiopulmonary findings, including electrocardiographic results, were within normal limits. Blood pressure was 118/80 mm Hg. The spleen was palpable 2 cm below the left costal margin. There was no hepatomegaly or unusual abdominal masses. Sigmoidoscopy revealed friable rectal mucosa with diffuse bleeding points. Neurologic examination, including electroencephalography and brain scan, disclosed no idiosyncrasies. Intelligence was average.

No abnormalities were visualized in the following roentgenographic studies: chest P-A and lateral views, intravenous pyelogram, esophagogram, and upper GI and small bowel series. A barium enema revealed the colon to be somewhat small in caliber. Roentgenograms of the cranial sinuses revealed a clouded right maxillary sinus. A bone survey showed sclerosis of the lumbar spine and generalized demineralization.

**Laboratory Data**

On admission, hemoglobin level was 4.9 g/100 ml and hematocrit was 15%. Peripheral blood film revealed anisocytosis, poikilocytosis, slight hypochromasia, and macrocytosis of red blood cells. The reticulocyte count was 1.0%; direct Coombs test was negative, and red blood cell osmotic fragility and autohemolysis were normal. The alkaline resistant hemoglobin was 6.6% (normal, under 2%). Hemoglobin electrophoresis did not disclose further abnormalities. The white blood cell count was 2000/cu mm with a differential count of 45 neutrophils, 14 bands, 23 lymphocytes, and 18 monocytes. Leukocyte alkaline phosphatase scores were 376 and 380 (normal 15-100) on two determinations. The platelet count was 40,000/cu mm.

Sternal and posterior iliac crest bone marrow aspirates revealed hypoplasia; myeloid:erythroid ratio of 1:1; megaloblastic hemopoiesis; and a relative increase in numbers of promyelocytes and myelocytes (Fig. 4). Iron was present. Posterior iliac crest biopsy examination confirmed the hypoplastic nature of the marrow and revealed fat replacement (Fig. 5). There was no myelofibrosis (Masson trichrome stain).

Serum levels of iron and total iron binding capacity were normal. Serum vitamin B12...
level\textsuperscript{28} was 128 pg/ml (normal 200–900 pg/ml) and serum folate level\textsuperscript{29} was so low as to be undeterminable (normal 7–16 ng/ml). Urinary formiminoglutamic acid excretion\textsuperscript{30} was 4.7 mg/hr (normal 2 mg/hr). There was a normal concentration of gastric intrinsic factor, no intrinsic factor antibodies\textsuperscript{31} and normal level of serum folic acid reductase.

On two occasions, chromosome preparations from peripheral blood leukocytes revealed normal-appearing 46 XY karyotypes. No increased incidence of chromatid breaks, gaps, constrictions or rearrangements was observed.

The following determinations yielded normal results: routine urinalysis; urinary amino acid chromatography; urinary hemosiderin; 24-hour urinary 17-ketosteroids, 17-hydroxycorticoids, testosterone, and creatinine; ACTH stimulation and metyrapone tests; sucrose hemolysis test; acid hemolysis test; thrombin time; prothrombin time; partial thromboplastin time; antinuclear factor antibody; L. E. cell preparations; latex fixation; VDRL; and BUN. There were normal serum levels of creatinine, electrolytes, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, alkaline phosphatase, total bilirubin with fractionation, \( \beta \)-carotene, cholesterol, total protein, albumin, globulin, amylase, calcium, phosphorus, uric acid and C3 component of complement.

Hospital Course

The patient was symptomatically managed with bimonthly packed red blood cell transfusions and periodic platelet transfusions. Therapeutic attempts with the following hematins in pharmacologic doses, for periods of at least 2 wk each, were to no avail: folic acid; citrovorum factor; vitamins B\(_1\), B\(_2\), B\(_6\), and C; and prednisone. Fluoxymesterone was tried for 4 mo, also without benefit.

Hospitalization was required 8 times during the next 15 mo because of severe anemia, unexplained acute abdominal pain and tenderness mainly in the left upper quadrant area, rectal bleeding, diarrhea, and fever. During the abdominal crises there was no elevation of serum or urinary amylase or lipase, or urinary porphobilinogen or \( \Delta \)-aminolevulinic acid. Stools were foul-smelling and oily and intermittently positive for occult blood. Institution of a gluten-free diet was associated with temporary cessation of diarrhea.

Blood, urine, and stool cultures failed to demonstrate bacterial or mycotic pathogens. FEVERS of 104–105\( ^\circ\) F did not respond to antibiotics such as cephalothin and kanamycin. The fever dropped within 24 hours of instituting prednisone 100 mg/day orally followed by dexamethasone 15 mg/day, but rapidly recurred when doses were lowered. The urinary etiocholanolone level was too low to be measurable.

When recurrent symptoms and fever did not respond to the reinstitution of high doses of steroids, the patient was transfused and exploratory laparotomy and splenectomy were performed. The spleen weighed 147 g; microscopic examination revealed only congestion. Histologic study of a specimen of liver revealed hemosiderosis and mild fibrosis. Symptoms subsided postoperatively and 3 wk postsurgery he was discharged on fluoxymesterone and prednisone. A bone marrow aspirate at this time showed megaloblastic maturation and marked erythroid hypoplasia, most of the cells present being promyelocytes and myelocytes. Megakaryocytes were rare.

Further work-up obtained during the eight hospitalizations yielded normal results for the following: erythrocyte glucose-6-phosphate dehydrogenase and glutathione reductase; splenic sequestration studies performed with \(^{51}\)Cr, stool fat and fatty acid concentration, serum protein bound iodine level, RA\textsuperscript{131}I thyroid uptake and scan; and serum IgA level.

Detected abnormalities included the following. There was progressive hypocellularity of the bone marrow. Erythrocyte pyruvate kinase was 3.3 I.U. (normal 4.2–10.1 I.U.). The Schilling test yielded 5% excretion of \(^{60}\)Co-labeled vitamin B\(_12\) with and without intrinsic factor. Ferrokinetic studies with \(^{59}\)Fe showed a delayed plasma iron clearance, decreased and delayed uptake of iron into the marrow, and abnormally slow release from the marrow, findings usually seen in hypoplastic anemia. There was no increased iron uptake over the liver, spleen or tibia, but it was slightly excessive over the femur, suggesting hematopoietic activity in that one area. The red cell T\(_{1/2}\) determined with \(^{51}\)Cr was 15 days during a period of occult blood loss rectally. The following quantitative serum immunoglobulin abnormalities were found (Hyland): IgG 2500 mg/100 ml (normal 600–1200 mg/100 ml) and
IgM 23 mg/100 ml (normal 51–109 mg/100 ml). Weakly-reacting thyroglobulin antibody (Hyland) was detected. Carbohydrate studies revealed a glucose tolerance test curve of the diabetic type; a flattened lactose tolerance test curve with the maximum sugar rise being 10 mg/100 ml; and a low urinary excretion of 2.5 mg D-xylose in 5 hr after a standard (25 g) loading dose. The urinary FSH level (Bioscience) was 50–100 mouse U (normal 6–50 mouse U).

The patient’s final admission was necessitated by the onset of severe headache and hematemesis. Shock supervened and multiple areas of petechiae and ecchymosis were observed. Despite blood transfusions, the patient quickly expired. Permission was unobtainable for postmortem examination.

Family History and Case Studies

The parents were nonconsanguineous, American-born, and descended from Ashkenazic Jews. On the maternal side an aunt had polycythemia vera, an uncle had Buerger’s disease, and a grandmother had hyperpigmented skin and loss of nails.

The proband’s 18-yr-old brother had cutaneous manifestations and onychodystrophy typical of dyskeratosis congenita (Fig. 6). His alopecia was less advanced than the proband’s and consisted of early recession of the frontal hairline. His hands were wrinkled, erythematous, atrophic, and shiny, but the palms as well as the elbows, knees, and soles were not as desquamative as those of the proband. Psychiatric history indicated that he had psychopathic traits. The mother, age 42, and a sister, age 8, had mild dyschromic cutaneous changes of probable significance.

In the parents and siblings of the proband, the following determinations yielded normal results: direct Coombs test; concentration of erythrocytic glucose-6-phosphate dehydrogenase; C3 level of serum complement; latex fixation test; serum iron level and total iron-binding capacity; blood urea nitrogen level; serum levels of glutamic oxalacetic acid transaminase, lactic dehydrogenase, alkaline phosphatase, total bilirubin, calcium, phosphorus, and uric acid. The following tests yielded normal results except as indicated: complete blood count (the brother had macrocytosis and a platelet count of 102,000/cu mm); fetal hemoglobin level (2.5% in the brother); leukocyte alkaline phosphatase (222 in the brother); serum vitamin B12 level (120, 36, and 164 pg/ml, respectively, in the mother, brother and sister); fasting blood sugar (215 mg/100 ml in the father); serum cholesterol (260 and 325 mg/100 ml, respectively, in father and mother); immunoglobulin levels (serum IgG value of 2800 mg/100 ml in the brother, and serum IgM values of 44 and 46 mg/100 ml, respectively, in the mother and sister); thyroglobulin antibody (strongly positive in the brother).

DISCUSSION

Expressivity

Hematopoietic deficiency has been reported in over half the cases of dyskeratosis congenita. The kindred reported here demonstrates variable degrees of severity, the younger brother’s condition being less advanced than the proband’s. Eventually, he may not be exonerated from pancytopenia. In the one black patient reported with dyskeratosis congenita,20 the hemoglobin level dropped from 14.9 g/100 ml to 11.9 g/100 ml in the patient’s 44th year of life. Other patients have also shown changes from normal to abnormal values with regard to hemoglobin,22 white blood cell counts,10,22 or platelet counts.10 Our proband’s sister and mother both had cutaneous dyschromia and slightly decreased levels of serum vitamin B12 and IgM. In another example of intrafamilial variance, the cases of Addison and Rice,21 a 24-yr-old woman with dyskeratosis congenita died from metastatic squamous cell carcinoma originating from the buccal mucosa, whereas her 22-yr-old brother suffered major hazards from his hematopoietic fault.
Abdominal Findings

The proband manifested a triad of sharp abdominal pain, diarrhea, and fever. Abdominal pain and diarrhea are mentioned in other reported cases,\textsuperscript{10,14} though constipation also has been recorded.\textsuperscript{5,6} The causes for the pain and fever were not found. Koszewski and Hubbard's\textsuperscript{10} patient also had abdominal pain and did not have raised levels of urinary uro- or-coproporphyrins. The diarrhea could be explained by the presence of a malabsorption syndrome that was demonstrated by low serum vitamin B\textsubscript{12} and folate levels, an abnormal Schilling test both with and without intrinsic factor, impaired D-xylose absorption, and flat lactose tolerance test. Thrombocytopenia precluded small bowel biopsy.

Portal fibrosis of the liver,\textsuperscript{10,13} cirrhosis and portal hypertension,\textsuperscript{14,22} and hepatosplenic and cutaneous hemosiderosis\textsuperscript{10,14} have occurred rather commonly considering the small number of patients reported with dyskeratosis congenita. Transfusions account for iron deposition; however, hemosiderosis has been described in a patient who had not been transfused.\textsuperscript{10} Furthermore, hemosiderin deposits are characteristically found with other varieties of chronic hypoplastic anemia (including the Fanconi type). Serum iron levels have been in the normal-to-elevated range in previously reported patients with dyskeratosis congenita.\textsuperscript{10,21,22}

Blood Cell Enzymes and Serum Immunoglobulins

The proband’s erythrocytes had normal concentrations of glucose-6-phosphate dehydrogenase and glutathione reductase and slightly diminished pyruvate kinase. Leukocyte alkaline phosphatase activities were elevated in the proband and his brother.

Immunoglobulin abnormalities have not been reported to be prominent or consistent in dyskeratosis congenita,\textsuperscript{21} yet both our proband and his brother had thyroglobulin antibodies, broad elevations of IgG, and a decrease in IgM. Two previous patients with dyskeratosis congenita had thyroid enlargement.\textsuperscript{16,18}

Relationship to Fanconi’s Anemia

Clinical Findings: Some of the remarkable similarities shared by dyskeratosis congenita and Fanconi’s anemia were previously listed. Unexplained abdominal pain and fever,\textsuperscript{32,33} hemosiderosis and cirrhosis have also been recorded in Fanconi’s anemia.\textsuperscript{32-38} The onset of severe hematologic symptoms in Fanconi’s anemia is usually in childhood but occasionally in adulthood,\textsuperscript{32-38} and the 5-yr survival rate is low due to infection or hemorrhage.\textsuperscript{39} Swift et al.\textsuperscript{33} stated that there is no way of telling at the present time whether the same inherited metabolic abnormality is present in all cases, child or adult, of Fanconi’s anemia, though the characteristic cytogenetic abnormalities are found at both age levels. In dyskeratosis congenita, the usual progression is: ectodermal dystrophy appearing in the first decade of life, hematopoietic peril in the second and third decades, and carcinomatosis supervening in the third, fourth, and fifth decades.
Clinical evaluation of the two brothers we studied, plus a review of the literature, indicate the following to be prominent in dyskeratosis congenita but infrequent in Fanconi’s anemia: telangiectatic erythema of face, neck, upper portion of the chest, hands, and feet; notable atrophy of the skin of the hands and atrophic spots elsewhere on the body; exocrine disturbances; ungual and dental dysplasias; mucosal leukoplakia, carcinomatosis, and stenosis; dysphagia and esophageal diverticula. In dyskeratosis congenita, there is greater emphasis in the ectodermal realm. The degree of telangiectatic erythema varies among cases. The patient of Addison and Rice was described as being “pale” (as are patients with Fanconi’s anemia) but, in Costello and Buncke’s patient, the facial erythema was pronounced and “burgundy wine red.”

Prominent in Fanconi’s anemia but not dyskeratosis congenita are: specific skeletal and renal anomalies, hyperreflexia, strabismus, microphthalmia, and possibly deafness. In 129 cases of Fanconi’s anemia reviewed by Gmyreck and Syllm-Rapoport, 66% had skeletal malformations in various combinations: aplasia or hypoplasia of the thumb (48%), aplasia or hypoplasia of the radius (15%), reduced number of carpal bones (33%), and syndactyly (12%); 28% had renal malformations (aplasia, reduplications, cysts, ectopia, horseshoe kidneys, vascular anomalies); 22% had strabismus; 19% had hyperreflexia, and 7% deafness. While it is possible that in studies of dyskeratosis congenita strabismus and hyperreflexia may have been overlooked, the absence of the renal and particular skeletal malformations (of Fanconi’s anemia) cannot be dismissed and remain important differentiating features. In dyskeratosis congenita, less specific skeletal abnormalities have been detected: scoliosis, incomplete closure of vertebral arches, rudimentary spinous processes, and osteoporosis. The patient of Costello and Buncke had ankylosed metacarpal flexural deformities of the hands. In a kinship with classical dyskeratosis congenita studied by Bryan and Nixon, shortened terminal phalanges of the thumbs occurred in two otherwise unaffected females.

The cutaneous hyperpigmentation commonly observed in Fanconi’s anemia may be diffuse, widespread, or more pronounced in certain areas of predilection: sides of the neck, axillae, antecubital fossae, and pelvic region (perianogenital, lower abdomen, buttocks, and thighs). Usually the melanosis is not intense in hue except in the perineum. The skin may appear mottled or else discolored by large hyperpigmented patches with diffuse boundaries within which small guttate hypopigmented macules are interspersed. It is uncertain whether the dermatoses of Fanconi’s anemia and dyskeratosis congenita are causally related, though the melanotic alterations show surface similarity.

Two sisters and their female cousin, described by Moon-Adams and Slatkin, had widespread melanosis from infancy that showed predilection and emphasis in the same sites as in Fanconi’s anemia. In adulthood, guttate hypopigmented spots developed, interspersed in the melanodermic skin. These patients had onychodysplasia as occurs in dyskeratosis congenita but did not manifest erythema, leukoplakia, dental dysplasia, exocrine disturbances, gas-
Fig. 1. Reticulated and spotty pigmentary alterations, sharp-featured facies and sparsity of cilia of eyelids. The forehead was erythematous.

Fig. 2. Telangiectatic erythema of the neck and upper portion of the chest superimposed on the changes in melanization.

Fig. 3. The skin of the fingers was wrinkled, shiny, and atrophic. All of the nails were hypoplastic, ridged, and foreshortened.

Fig. 4. Posterior iliac crest marrow aspirate exhibiting megaloblastic hemopoiesis. Wright-Giemsa. × 600.

Fig. 5. Posterior iliac crest biopsy specimen showing hypocellularity and fat replacement. Hematoxylin and eosin. × 100.

Fig. 6. Generalized pigmentary disturbance in proband’s brother. There are early recession of frontal hairline and sparsity of the cilia of the eyelids. Eyebrows, however, are luxuriant.
Internal abnormalities, or hematopoietic aberrations. The younger sister had unexplained abdominal pain, mostly in the right lower quadrant. Moon-Adams and Slatkin proposed that these patients might have an atypical form of dyskeratosis congenita.

On consideration of the distinguishing criteria in the diagnosis of Fanconi’s anemia vs. dyskeratosis congenita, it sometimes becomes necessary to re-evaluate the past medical literature. For example, case 5 of McDonald and Goldschmidt had been cited as an example of Fanconi’s anemia manifesting dystrophy of the finger- and toenails. From the information given, the condition is compatible with dyskeratosis congenita.

Transition Cases: Among aforementioned cases, the kinds of skeletal defects in the patient of Costello and Buncke and in the kinship of Bryan and Nixon, and the distribution of the pigmentary alterations in the patients of Moon-Adams and Slatkin, may hint towards transition features between dyskeratosis congenita and Fanconi’s anemia. Admittedly, this is quite conjectural.

A stronger case can be made for the series of patients reported by Swift et al. and by Esparza and Thompson. These patients, young adult women with the distinguishing clinical and karyotypic abnormalities of Fanconi’s anemia had, in addition, a high frequency of squamous cell carcinomas at various mucosal sites (gingiva, esophagus, vulva, anus). The maternal grandfather of one of the patients died of a squamous cell carcinoma of the base of the tongue which had spread locally and metastasized to the lung. Though Swift et al. suggested that the putative gene for Fanconi’s anemia predisposed these individuals to solid tumors as well as leukemias, the phenomenon of mucosal carcinomatosis so characteristic of dyskeratosis congenita is also suggestive of a transition phase. The preponderance of the female sex in the proposed transition cases is noteworthy.

Karyotypes: In Fanconi’s anemia, the abnormally high incidence of chromatid gaps, breaks, constrictions, and rearrangements in cultured peripheral leukocytes and cutaneous fibroblasts is now well recognized. In addition to karyotype studies in our proband, three patients with dyskeratosis congenita and their mother reported by Bryan and Nixon, a patient of Addison and Rice, and the black patient with dyskeratosis congenita reported by Milgram et al. were reported as having normal-appearing karyotypes.

At first we were tempted to conclude that the karyotypic divergency proved that dyskeratosis congenita and Fanconi’s anemia are different and unrelated. We have relented from such a definite stand for the following reasons: (1) The overlap of other features remains impressive. (2) There are evidences of transition cases. (3) It is possible that the visualized karyotypic changes in Fanconi’s anemia are induced by extraneous factors (such as viruses) to which these patients show greater susceptibility as part of the Fanconi’s anemia variation. (4) There may be an increased familial incidence of leukemia in dyskeratosis congenita as in Fanconi’s anemia and other disorders in which cytogenetic abnormalities have been visualized (e.g., Bloom’s Syndrome).

General Hematologic Findings: These findings are basically the same in dyskeratosis congenita and Fanconi’s anemia. The hematopoietic fault leading
DYSKERATOSIS CONGENITA

To pancytopenia may affect certain stem cell populations more than others, so that severe anemia or thrombocytopenia may prevail. The pancytopenia is reflected by general debilitation and weakness, susceptibility to infections and bleeding diathesis.

During certain phases, the bone marrow is hyper- or normocellular. During the patient’s downhill course, the marrow becomes progressively and profoundly hypocellular in terms of blood cell precursors, and replacement by fat cells and fibrosis is observed. The marrow’s red blood cell precursors can be normoblastic but there is also a tendency for megaloblastic maturation. Diminished or total absence of megakaryocytes has been repeatedly commented on.

The red blood cells may be hyper-, or hypochromic, and also tend to be anisocytotic, poikilocytic, and macrocytic. In Fanconi’s anemia, vitamin B₁₂ may be insufficiently utilized in the synthesis of nucleotides. In our kinship with dyskeratosis congenita there was also evidence of a biochemical defect in DNA synthesis. In the proband, despite decreased serum vitamin B₁₂ and folate levels, and elevated urinary excretion of formiminoglutamic acid (presumably due to poor gastrointestinal absorption), no hematologic improvement followed pharmacologic doses of vitamin B₁₂ and folic acid. The marrow remained megaloblastic, indicating impaired utilization.

The presence of pancytopenia and inconstant splenomegaly led to the conjecture that hypersplenism might be operative. In dyskeratosis congenita, splenectomy has not resulted in pronounced or prolonged hematologic improvement. The same holds for Fanconi’s anemia in general, however, significant improvement has occasionally been noted.

Hemolysis is not of major significance in either disorder. The direct Coombs test result and osmotic fragility are generally normal and reticulocyte counts are usually normal or low. Occasionally a minor hemolytic component has been detected. Red blood cell antibodies against donor erythrocytes undoubtedly contribute to shortened survival of cells subsequently transfused. Extramedullary hematopoiesis is of minor degree in both dyskeratosis congenita and Fanconi’s anemia.

Alkali resistant hemoglobin (fetal hemoglobin) is elevated in dyskeratosis congenita and Fanconi’s anemia, as well as in other varieties of aplastic anemia. It is possible that the appearance of hemoglobin F is not due to a primary genetic defect, but rather is the consequence of stressed erythropoiesis. Alkali resistant hemoglobin may be elevated in nonanemic siblings of patients with constitutional aplastic anemia who subsequently become anemic, so that elevated hemoglobin F may be regarded as an early biochemical abnormality. It will be interesting to follow the blood picture of our proband’s brother who has a slight elevation at this time.

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