SPECIAL ARTICLE

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Dr. Alfred T. Lane (Stanford University) organized the sixteenth annual meeting of the Society for Pediatric Dermatology, held in Williamsburg, Virginia. The seventh annual Sidney Hurwitz Lecture was delivered by Dr. Rona M. MacKie (University of Glasgow) on "Melanoma: Risk Factors in Dysplastic Nevus Syndrome." President Anne Lucky (Cincinnati, Ohio) welcomed the society members to Williamsburg and introduced the first speaker.

COLONIAL MEDICINE

Dr. Tor A. Shwayder (Henry Ford Hospital) presented a delightful and professional "Character Interpreter Portrayal of Isaac Shwayder, Medical Doctor (circa 1799)." Complete in eighteenth-century costume, including three-cornered hat and silk hose, Dr. Shwayder discussed the art and science of medicine as it evolved in colonial Williamsburg. However, he became distracted from his lecture by the newspaper account he received, dated December 17, 1799, telling of General George Washington's death. We learn the story of General Washington's rapid demise, probably from bacterial infection, hastened by the medical treatments of the day, including frequent and copious blood letting. There was a current saying, "more people died annually from lancets than from swords."

MELANOMA: RISK FACTORS AND DYSPLASTIC NEVUS SYNDROME

Dr. Rona MacKie first discussed risk factors in melanoma, citing several large case control studies carried out in western Canada, Scotland, Scandinavia, and Germany. The frequency of melanoma has doubled each decade in Scandinavia, the United Kingdom, and Germany. The frequency increases with high altitudes, low latitudes, pale skin, outdoor recreation, and total number of banal, nondysplastic nevi. Other risk factors are the tendency to freckle, a history of severe sunburn, three or more clinically atypical nevi, and fair hair. Factors that are associ-

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ated with acquisition of large numbers of banal nevi include one or more years of childhood spent in the tropics, Mediterranean holidays when less than 5 years old, light skin that burns rather than tans, severe sunburn in childhood, and freckling. The working hypothesis is that these early childhood events act as initiating factors that may induce benign melanocytic lesions. Later, further sun exposure may lead to both promotion and progression, with the development of melanoma.

An additional risk factor for the development of melanoma is the presence of clinically atypical and pathologically dysplastic nevi (DN). There is much confusion regarding the use of the term "dysplastic nevus" because experts do not agree on pathologic criteria. Elder's clinical criteria are size greater than 5 mm, irregular outline, "fried egg" profile, variegated pigmentation, and erythema. His pathologic criteria are basilar melanocytic hyperplasia, cytologic melanocytic atypia, fusion of melanocytic nests, lymphocytic infiltrate, lamellar or concentric fibroplasia, and rete ridge elongation.

The four categories of DN according to the NIH Consensus Conference are (A) sporadic; (B) familial nevi with no melanoma; (C) sporadic personal melanoma (not in the family, patient only); (D_1) familial nevi with personal melanoma and one family member with melanoma, and (D_2) familial nevi with personal melanoma and two family members with melanoma. The increased risk of melanoma depending on the type of dysplastic nevus is as follows: type A, 4-fold increase; type B, 7-fold increase; type C, 80-fold increase; type D, 108-fold increase. It was noted that melanoma was extremely rare prepubertally, but in the few patients in whom it has occurred, 50% developed in giant melanocytic nevi.

In Dr. MacKie's current study of melanomas in individuals under age 30 years, a significant association exists between the presence of a nevus since early life and the development of melanoma at that site. This suggests that a portion of congenital or early-onset small nevi have the potential for malignant change. Continuing studies will attempt to establish the rate at which this occurs and guidelines for the management of small congenital nevi. Because these melanomas do not seem to develop prior to puberty—approximately 1 chance in 100 exists that a small congenital nevus will become malignant by 13 years of age—it is reasonable to offer excision of small congenital nevi at puberty. Of 95 patients who developed melanoma at age 30 or less, 44% had evidence of a preexisting, small congenital nevus at the site. The melanomas that developed on these nevi tended to be thick. Dr. MacKie recommended a photographic record of dysplastic nevi in children, and removing those that developed characteristics suggestive of melanoma.

HERPES SIMPLEX INFECTIONS IN CHILDREN

Dr. J. Clark Huff (University of Colorado) discussed the four types of herpes simplex virus (HSV) infection in children: initial (primary) infection; reactivation (recurrent) infection; infection in the immunocompromised host; and herpes-associated erythema multiforme (EM).

Initial or primary HSV infection is most commonly subclinical or unrecognized. Older literature stated that 95% of the United States population was seropositive, but current studies revised this figure to 52% to 65%.

Neonatal HSV infection occurs in about 1 in 1400 live births—that is, 1500 to 2200 affected infants per year in the United States. Seventy percent of the cases are due to HSV-2. Risk factors for neonatal HSV infection are thought to include asymptomatic shedding from the maternal genital tract, especially the cervix, at the time of delivery; recently acquired subclinical first episode infection; reactivation herpes with shedding (although risk is only about 3% in these infants); and the absence of maternal antibodies to HSV-2. Neonatal HSV localized to the skin, eye, or mucous membrane is associated with no mortality. When encephalitis is present, mortality is 15%, and of those who survive, 64% have severe sequelae, usually mental retardation. If the infection is disseminated but no encephalitis is present, mortality is 57% and morbidity at one year is 41%. Treatment is acyclovir 30 mg/kg/day intravenously for 10 days.

An HSV infection in the immunocompromised host is often extremely severe. Treatment is intravenous acyclovir 30 mg/kg/day for 10 days.

The HSV-associated EM is usually a minor form of EM, and follows recurrent HSV by 3 to 21 days. The polymerase chain reaction (PCR) has been used to identify herpes virus DNA in skin lesions of EM. In HSV-associated EM, 100% of lesions had HSV DNA. Fifty percent of patients with idiopathic EM had evidence of HSV DNA in lesions. Prophylaxis includes oral acyclovir 400 to 800 mg/day.

The diagnosis of HSV can be made on culture, which is usually positive in one to two days. A new technique involves culturing for 24 to 48 hours and then fluorescent antibody staining. Tzanck preparation is reliable in new vesicles. Immunocytology,

enzyme-linked immunosorbent assay of blister fluid, and spin amplification techniques are available at some institutions.

NUTRITIONAL DEFICIENCY

Dr. Moise L. Levy (Baylor College) discussed the cutaneous signs of four types of nutritional deficiency: protein-energy malnutrition, vitamin deficiencies, essential fatty acid deficiency, and trace element deficiency. Protein-energy malnutrition is the most common worldwide and is recognized clinically as kwashiorkor or marasmus. Either can follow poor dietary intake, malabsorption, or catabolic state.

The skin in kwashiorkor shows hypopigmentation and diffuse pitting edema. Waxy elevated plaques ("enamel paint") or erosions ("flaky paint") are often seen. In marasmus the skin is dry, wrinkled, and loose, often producing "monkey facies." The hair is reddish and thin in kwashiorkor, and alternating periods of adequate and inadequate nutrition are reflected in alternate bands of color in the hair, the so-called flag sign. In marasmus the hair is also thin and slow growing, and lanugo hair may be seen.

Deficiencies of vitamins A, B, and C also produce skin signs. Vitamin A deficiency produces follicular papules, so-called phrynoderma. Xerosis is prominent, as are ophthalmologic abnormalities including Bitot spots and keratomalacia, with iris prolapse in severe cases.

Vitamin C deficiency produces scurvy, and most cases are due to inadequate intake. Skin manifestations include corkscrew hairs (secondary to decrease in disulfide bonds in the affected hairs), perifollicular hemorrhage, gingival edema and hemorrhage, weakness, depression, diarrhea, and anemia.

Essential fatty acid deficiency occurs in premature infants with inadequate adipose stores. Unsaturated fatty acids that cannot be synthesized by humans are necessary for membrane structure and the production of eicosanoids. Linoleic acid is the primary nutrient for treating or preventing this deficiency. Clinically, alopecia, xerosis, and scaling are present. The infants have retarded growth and show an increased susceptibility to infection.

Trace element deficiency is correctable when the deficiency is in iron, copper, zinc, chromium, manganese, or iodine. Zinc deficiency is caused by inadequate intake, including breast milk deficient in zinc, increased excretion, or a genetic factor. Clinically, acral and periorficial dermatitis occur. Paronychia, angular stomatitis, glossitis, and alopecia often are present. Impaired wound healing, growth retardation, marked irritability, diarrhea, and immune abnormalities may be seen.

COAGULATION DISORDERS

Dr. Hazel Vernon (Medical College of Virginia) discussed three coagulation disorders with manifestations in the skin: protein C deficiency, purpura fulminans, and the Kasabach-Merritt syndrome.

Homozygous protein C deficiency is extremely rare, with only 17 confirmed cases in the United States and Europe. Protein C activity is usually less than 1%, with protein C antigen ranging from less than 1% to 30%. The three major clinical findings in these newborns are the onset of ecchymoses and necrotic lesions within 2 to 12 hours of birth, central nervous system thromboses, and blindness. Hematologic studies show a picture of disseminated intravascular coagulation with decreased platelets and fibrinogens, elevated fibrin split products, and prolonged activated partial thromboplastin and prothrombin times. Protein C levels are low or absent. Histologic examination of a skin biopsy specimen reveals extensive thrombosis with fibrinoid necrosis of vessel walls and hemorrhage into subcutaneous fat, but without vasculitis. Treatment includes fresh-frozen plasma given daily, or protein C and S concentrates. Warfarin may also be given.

Purpura fulminans is characterized by the sudden onset of hemorrhagic necrosis of the skin and disseminated intravascular coagulation, as well as widespread cutaneous thrombosis. It usually arises in the setting of an overwhelming infection due to *Haemophilus influenzae*, or meningococcal, streptococcal, or staphylococcal infection. Tumor necrosis factor is thought to act as a procoagulant, together with bacterial endotoxin. Treatment includes eradicating the infectious cause and supporting the child with platelets and fresh-frozen plasma. Heparin, dextran, steroids, plasmapheresis, and urokinase have been used in the treatment of purpura fulminans.

Kasabach-Merritt syndrome is a localized consumption coagulopathy occurring within a very large hemangioma, most commonly on the extremity. The median age of onset of the syndrome is 5 weeks (range birth–73 yrs). The mortality rate is 21%. Usually the size of the hemangioma increases suddenly, with the development of petechiae or ecchymoses elsewhere, and gastrointestinal bleeding. Laboratory studies show a picture of disseminated intravascular coagulation. Current recommenda-

tions for therapy include high-dose prednisone (2–4 mg/kg/day), expecting improvement within several days. Surgery can be attempted if the lesion is accessible and relatively small. Epsilon-aminocaproic acid (Amicar) can be used to allow the hemangioma to clot and scar, with a response seen after two weeks. Finally, intermittent pneumatic compression can be tried if the hemangioma is in an appropriate location. It is used 24 hours per day until involution begins and then is used nightly.

CLINICOPATHOLOGIC CONFERENCE

Dr. Loren Golitz (University of Colorado) presented clinicopathologic cases submitted by members of the Society. Drs. Lawrence Eichenfield and Paul Honig (University of Pennsylvania) reported a 14-year-old boy with follicular mucinosis. He had developed a scaling, annular plaque above the right eyebrow eight months previously, and hairs were absent within the involved area. The lesion was unresponsive to topical antibiotics and hydrocortisone.

Follicular mucinosis causes grouped, follicular papules, nodules, or patches of hair loss. Mycosis fungoides (MF) occurs in 15% or less of patients but has never been reported in an individual less than 20 years of age. It was noted that three reports described children with follicular mucinosis who later developed Hodgkin disease.

Drs. Andrea Dominey, Moise Levy, and H. Hawkins (Texas Children's Hospital) submitted a case of congenital neuroblastoma. A newborn had numerous cutaneous nodules that rapidly increased in size, as well as an intraabdominal mass and hepatomegaly. Examination of bone marrow and skin biopsies revealed a round cell tumor consistent with neuroblastoma. The infant underwent exploratory laparotomy, at which time a nonresectable retroperitoneal tumor was found, with hepatic involvement but no adrenal gland involvement.

Congenital neuroblastoma is the most common malignant tumor in neonates and represents 8% to 10% of all cancers in children up to 15 years of age. In neonates, cutaneous metastases may produce a "blueberry muffin" appearance. Because one-third of children have metastases at the time of diagnosis, the prognosis is poor. Neuroblastoma is the prototype of small, round, blue cell tumors, the others being rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. Marker studies in neuroblastoma usually are negative for B and T cells and positive for neuron-specific enolase. Dense core granules (neurosecretory granules) are seen on electron microscopy. Good prognostic factors include age less than 1 year, stage I or IV-S tumors, location above the diaphragm (not involving adrenal glands), and well-differentiated morphology (all markers present). Polyploidy by DNA flow cytometry is associated with a poor prognosis, whereas aneuploidy is associated with increased survival. Genomic amplification of the N-myc oncogene is associated with rapid tumor progression.

Dr. Julie Francis (University of Washington) discussed a white newborn boy who, after a vacuum extraction delivery, was noted to have a large cephalohematoma on the left parietal scalp. All scalp hair was present and no erosions were noted. At 4 days of age, erosions with yellow crusting developed and continued to enlarge. At 2 months of age, a raised, flesh-colored plaque developed peripherally around the erosions, and the erosions continued to heal. At the present time, the plaque measures 3 × 3 cm with central atrophy, peripheral flesh-colored papules, crusting, and complete hair loss within the scarred area. Bacterial and herpes cultures were negative, as were maternal ANA and SSA. Examination of skin biopsy specimens showed fibrosis consistent with scar and a large foreign body granuloma reaction to keratin remnants of hair follicles. Hair follicles were decreased in number as well, suggesting a diagnosis of aplasia cutis congenita. In the discussion, Dr. Wesley Galen (New Orleans) reported that she has seen six similar cases after vacuum extraction with a defective machine by the same obstetrician. She thinks these are secondary to trauma and resulting cellulitis, and not to aplasia cutis congenita.

CASES OF THE YEAR

The presentation of cases of the year was organized by Dr. Samuel Weinberg (New York University). Drs. Teresita Laude (SUNY-Brooklyn) and Brad Singman (Staten Island, New York) discussed twin boys born at 34 weeks with anhydrotic ectodermal dysplasia. They had large square foreheads with bossing, beaked nose, increased scalp vascularity, and decreased eccrine glands on skin biopsy. Anhydrotic ectodermal dysplasia is an X-linked recessive disorder characterized by anhydrosis, abnormal dentition, and hypotrichosis.

Dr. Rhonda Schnur (Children's Hospital of Philadelphia) discussed a child with hypohidrotic ectodermal dysplasia who had minimal sweating ability, hypoplastic nipples, and hypotrophic dentition, and whose mother had small breasts and abnormal teeth and nails. Because of recent advances in molecular

genetics, DNA analysis of linked RFLPs may be a useful adjunct for genetic counseling in some of the ectodermal dysplasias.

Dr. Maureen Rogers (The Children's Hospital, Camperdown, Australia) presented a case of Netherton syndrome in an infant girl who at birth had erythema and scaling resembling congenital ichthyosiform erythroderma. Her hair, including eyebrows, failed to grow until she was 7 month old, at which time examination of a hair pluck showed the typical "ball in a cup" (bamboo hair) picture of Netherton syndrome. The disorder is autosomal recessive, with skin manifestations most commonly of ichthyosis linearis circumflexa, and occasionally of ichthyosiform erythroderma, as in this child. Atopic dermatitis may be present, and hypernatremia has been reported. Because the hair often does not grow until later, diagnosis is often delayed. The point was made that if present, an eyebrow hair can be plucked and the characteristic changes found there as well.

Dr. Lawrence Eichenfield reported a case of aplasia cutis congenita (ACC) in association with fetus papyraceous. Fetal death of a twin occurred at 13 weeks, and the mummified fetus was noted at birth. The viable twin was born with a scalp lesion of ACC as well as linear lesions on the arms and flank. The disorder in association with fetus papyraceous or placental infarct is classified as group V ACC. One theory of pathogenesis is that embolic or thromboplastic material is transferred from the dead fetus through the placenta to the surviving twin. It is unclear why lesions are symmetric.

Drs. Lynn Williams and Linda Rabinowitz (Thomas Jefferson University) discussed a case of tyrosinemia II (Richner-Hanhart syndrome). The patient was born at 35 weeks and throughout infancy refused to eat meats. He developed photophobia and tearing at an early age, and at 2 years of age developed painful plantar keratoderma. The diagnosis of tyrosinemia II was made by finding a high tyrosine level on plasma amino acid screening. Urinary tyrosine metabolites were also increased. Tyrosinemia II is due to deficiency of the hepatic cytosolic enzyme tyrosine aminotransferase. This patient was treated with avoidance of all dairy products, and showed improvement in the eye and skin symptoms within two weeks. A low-tyrosine, low-phenylalanine diet in infancy is beneficial, and older children may be maintained on a low-protein diet if tyrosine levels do not exceed 10 mg/dl.

Dr. Susan Mallory (St. Louis Children's Hospital) described a newborn with blisters thought to have HSV and treated with acyclovir. All cultures and Tzanck preparations were negative, but examination of a skin biopsy specimen was reported as "viral infection." As blistering continued, a repeat biopsy was performed at age 11 days and interpreted as erythema multiforme. Oral prednisone was begun and the blistering ceased. The pattern of peripheral blisters around a central bulla ("crown of jewels") was noted and a skin biopsy specimen was sent for DIF. Examination revealed linear IgA at the basement membrane zone. The child was treated with dapsone and by 6 months of age had only residual mild scarring of the skin with milia, but severe eye sequelae and blindness. The two points to be learned from this case are first, immunobullous disease can occur in the neonate; and second, the younger the age at onset of chronic bullous disease of childhood, the more significant the sequelae tend to be.

Dr. Allison Holm (Batavia, New York) presented a case of rash with Epstein-Barr virus (EBV) infection and amoxicillin therapy. An 8-year-old boy developed fever, lymphadenopathy, hepatomegaly, and jaundice. He had been treated with amoxicillin two weeks earlier and developed a diffuse morbilliform eruption. The mono spot test was negative, and a broad differential diagnosis was considered, including Kawasaki disease and leptospirosis. The child was suspected of having virus-associated hemophagocytic syndrome or X-linked lymphoproliferative syndrome; however, he recovered with VP-16 and intravenous gammaglobulin. It is important to remember that in childhood mononucleosis, the mono spot test is frequently negative and EBV-specific serologies must be obtained.

Tuesday, July 2, 1991
RESEARCH AWARD

The Resident/Fellow Pediatric Dermatology Research Award was presented to Steven Shpall, M.D. (University of California, San Francisco) for his study, "The Risk of Melanoma in Black Patients." He found that the number of blacks with at least one congenital nevocytic nevus (CNN) was 1.8%. Malignant transformation was strongly age dependent. For those under 15 years old, the risk was 1 in 10,000 (0.01%), and for the group age 15 to 35 years it was 1 in 3700 (0.027%). The overall risk was 0.61%. These data assume that all melanomas arise in CNN and, therefore, may overestimate the risk by 10- to 100-fold. Dr. Shpall concluded that removal of CNN is not recommended in black patients, especially those under age 35.

CASES IN SEARCH OF A DIAGNOSIS

Dr. William Weston (University of Colorado) presented four "Cases in Search of a Diagnosis." The first, from Dr. Maureen Rogers, was a 6-year-old with unusual annular erythema beginning at 1 hour of age and consisting of intensely pruritic rings within rings, largely on the trunk. The child's general health has been unaffected. Results of exhaustive laboratory studies were unremarkable; a biopsy specimen showed an infiltrate with a predominance of eosinophils and neutrophils, with distinct flame figures as seen in Well syndrome. Spirochetes present on one specimen stained with Warthin-Starry could not be found in subsequent specimens. The long list of treatments that failed included prednisone, cromolyn, antihistamines, antibiotics, dapsone, phototherapy, and elimination diet. Members of the audience mentioned three separate cases with similar lesions. These children went on to have severe liver and renal disease, but no diagnosis. Because the lesions in Dr. Rogers' patient cleared only with fever, the use of alpha-interferon was suggested.

Dr. Elaine Siegfried (University of Iowa) discussed an unusual port-wine stain present at birth with extensive localized loss of subcutaneous fat. Biopsy was unremarkable. Diagnosis of atypical cutis marmorata telangiectatica congenita or atypical lipodystrophy was proposed. Dr. Anne Lucky noted that in similar cases, the atrophic component gradually resolved without treatment.

A second case from Dr. Siegfried was that of a child with acquired erythema of one cheek after a four-day febrile illness. Biopsy showed an exuberant lichenoid infiltrate extending deeply into fat. On direct immunofluorescence, there was granular IgM at the basement membrane zone. Remarkable laboratory study results included erythrocyte sedimentation rate 72, platelets 607,000, and negative ANA and Ro antibodies. Numerous treatments from topical steroids to laser yielded nothing. Audience members suggested Jessner benign lymphocytic infiltrate, foreign body reaction (e.g., fiberglass), connective tissue disease, and panniculitis as possible diagnoses.

For the last case, Dr. Amy Paller (Northwestern University) asked, "What's this syndrome?" Born prematurely, the child had microcephaly, unusual facies, abnormal tooth enamel, mental retardation, absence of the corpus callosum, retinitis pigmentosa, strabismus, deafness, renal failure, and hypertension. Cutaneous findings included facial erythema (increased with heat), eczema, unilateral café au lait macules, and one axillary freckle. The family history was unremarkable, and results of chromosome studies were normal. The consensus of the audience was that this most likely represented a chromosomal abnormality not yet identified by gene mapping.

ATOPIC DERMATITIS

In her lecture on atopic dermatitis, Dr. Rona MacKie focused on European research and experience. She cited a 1989 study by Cookson at Oxford that linked IgE to chromosome 11q, and showed that specific allergic responses are linked to the major histocompatibility complex. The abnormal regulation and overproduction of IgE is secondary to a preferential expansion of a subset of T helper cells with a relative reduction of gamma-interferon-producing T helper cells. Basic research has shown that the mononuclear cells in atopic patients are defective in controlling production of interleukin (IL)-4. A high level of IgE is the result of IL-4 overproduction. Thus, in atopic dermatitis the cytokine-mediated immune response is distorted.

In studies of dust mite allergy Dutch researchers have shown the likely role for allergen-specific T helper response. The importance of Langerhans cells in trapping IgE-antigen complexes and antigen presentation was stressed.

Dr. MacKie reviewed several treatment modalities for atopic dermatitis. Work in her own laboratory has centered on the role of *Staphylococcus aureus* in initiating and perpetuating atopic dermatitis lesions. Although other microorganisms are not significant, the number of *S. aureus* organisms (especially phage type III) have a quantitative relationship to disease activity. Based on these observations, studies of topical mupiricin were the next step and yielded highly statistically significant reduction in *S. aureus* colonization and significant clinical improvement.

Unpublished information on the use of Chinese herbal medicine included a study of 47 children, which showed improvement in 51% of atopics with no effect on asthma or IgE levels. Until analysis of the herbs is completed, concern over the safety of this therapy remains. Finally, Dr. MacKie discussed the striking clinical improvement noted with subcutaneously injected gamma-interferon. It is hypothesized that gamma-interferon controls IgE production by its action on mononuclear cells.

SCLERODERMA AND MORPHEA

Dr. Jouni Uitto (Thomas Jefferson University) discussed scleroderma and morphea in children. He reported that at least 14 different collagens are classified and that five new genetically distinct ones have recently been discovered, all with alpha chains. In reviewing fibrotic diseases, Dr. Uitto stressed that the common pathway and hallmark of these conditions are connective tissue deposition and primary collagen accumulation, respectively.

In his research using abundantly available tissue of keloid scars as a model, Dr. Uitto has shown that mRNA of types I and IV collagen is increased. Transforming growth factor-beta increases collagen deposition. Its origin is probably vascular, either from platelets or endothelial cells.

Turning to treatment, Dr. Uitto discussed several drugs. Penicillamine is believed to prevent intramolecular cross-linking. It is effective in progressive systemic sclerosis and linear morphea, but takes six to eight months to work and must be started early in the disease course. Side effects are abundant. Corticosteroids probably act by increasing collagenase activity and reducing cross-linking. Although their systemic use has been disappointing, topical steroids are useful in softening lesions. Gamma-interferon antagonizes transforming growth factor-beta activity. Preliminary data indicate that it may be useful. In anecdotal reports, phenytoin improved linear morphea, but Dr. Uitto is not impressed with its effectiveness. In the United States, penicillin is administered only to patients with increased *Borrelia* titers, but in Europe all patients with morphea or systemic sclerosis are treated with high dosages. Photopheresis may be worth a try in rapidly progressive SS but studies to date have not been convincing.

IMAGING NEUROCUTANEOUS SYNDROMES

Dr. Rich Towbin (Pittsburgh Children's Hospital) spoke on imaging studies in neurocutaneous syndromes. In deciding whether to use computerized tomography (CT) or magnetic resonance imaging (MRI), he stressed that CT is still an excellent method and costs one-third of what MRI does. The latter is particularly useful for posterior fossa lesions, craniocervical junction, leukoencephalopathy, temporal lobe lesions, and spinal cord lesions. However, it is somewhat problematic in children due to the extended time required and the confining nature of the equipment.

Controversy remains over the desirability of baseline studies in neurofibromatosis type 1 (NF-1). Traditionally, CT has been weak, whereas MRI finds "too much." Unidentified bright objects pose a dilemma for the radiologist. These probably represent hamartomas in most cases and, in general, require intervention only if there is a mass effect. In NF-2 MRI is definitely superior to CT, and very important in identifying tumors of the eighth nerve. In diagnosing tuberous sclerosis, CT is a good tool for identifying cerebral calcification; MRI is helpful in detecting malignant transformation. In addition, CT is the best method for detecting the characteristic serpiginous train-track calcifications of Sturge-Weber syndrome. For the classic hemangioblastoma of von Hippel-Lindau, angiography has been replaced by MRI.

VASCULITIC DISEASES

Vasculitic diseases of childhood were addressed by Dr. Thomas Lehman (Cornell University). In his broad overview he stressed that many specialists may be required to diagnose and care for these children, who may not fit into any neat category. Key points included the fact that children with linear scleroderma en coup de sabre may have vasculitis in the underlying brain. Also, en coup de sabre may be easily confused with Parry-Romberg syndrome (progressive facial hemiatrophy). The latter is distinguished by tongue involvement.

In summation, Dr. Lehman gave the following take home messages: (1) disease expression is a direct consequence of the size of the vessel involved; (2) each vessel type has its own characteristics with regard to pressure, flow, cellular makeup, and anatomic distribution; and (3) disease manifestations are influenced by the size (and several other characteristics) of the antigen or inciting agent, and the host's genetic makeup.

NEUROFIBROMATOSIS

In the first of two lectures, Dr. Vincent Riccardi (Alfigen, Pasadena, California) gave a fascinating review of new developments and important characteristics of neurofibromatosis (NF). Based on his observations of hundreds of patients, he had many clinical pearls. The macromelanosomes of café au lait macules (CALM) are not helpful in diagnosis due to their presence in healthy subjects and the great difficulty in identifying them in children and all black patients. He maintains that there is no reason to biopsy patients to make the diagnosis of NF. Axillary freckling, which occurs early in NF, must

be a cluster of at least 10 or 12 to be diagnostic. Acquired freckling in NF is a different phenomenon, occurring in areas of friction (e.g., neck, axillae) due to environmental factors, not genetics.

The macules are highly variable: they may be two-tone or spotted, ragged or smooth in outline, of huge size, and darken with sun exposure. In general, the darker the background skin, the darker the CALM. The "Riccardi sign" is the presence of an abnormal hair whorl overlying the spine in NF-1, indicating the presence of either vertebral dysplasia or plexiform neurofibroma underneath. This finding is significant because it shows that NF-1 is a defect with onset in embryonic development. The presence of juvenile xanthogranuloma is an important sign of NF-1 in young children, present in up to 1%. This lesion may lead the child to the dermatologist, with eventual discovery of NF. Another important association is chronic myelogenous leukemia, seen in 0.5% of children with NF. Dr. Riccardi believes that almost all children with NF-1 can be diagnosed on clinical grounds by age 1. Infants with CALM should simply be followed closely and considered as having presumptive NF-1 until proved otherwise.

CLINICOPATHOLOGIC CONFERENCE

Concluding the day's program, Dr. Loren Golitz presented the CPC with cases of blue rubber bleb syndrome, Sweet syndrome, and non-X histiocytosis.

Wednesday, July 3, 1991
CONTROVERSIES IN PEDIATRIC DERMATOLOGY

Dr. Alvin Jacobs (Stanford University) reviewed the epidemiology, natural history, clinical features, and treatment of hemangiomas. With many superb illustrations from his own practice, he demonstrated the complete regression of many untreated lesions. He cautioned those who embark on new therapies to remember the dictum of *primum non nocere*. When he sees an infant whose hemangioma will spontaneously regress without treatment, he spends additional time reassuring the parents by showing them examples of others that involuted spontaneously. He photographs the infant's hemangioma and schedules frequent follow-up visits to illustrate to the parents the progress of the lesion.

Dr. Karen Rothman (Westboro, Massachusetts) discussed the experimental use of the pulsed-dye laser for treatment of hemangiomas. She emphasized the need for controlled studies to determine the efficacy and safety of this treatment. She outlined the collaborative study she has begun in order to answer these questions.

ECTODERMAL DYSPLASIA: DIAGNOSIS AND MANAGEMENT

Dr. Virginia Sybert (University of Washington) outlined an approach to the ectodermal dysplasias. These are defined as disorders in which there are two or more abnormalities in ectodermal derivatives: hair, teeth, nails, sebaceous glands, sweat and mucous glands, and lens and conjunctiva of the eye. One system of classification used by Freire-Maia and Pinheiro in their textbook *Ectodermal Dysplasia* numbers the ectodermal structures: 1, trichodystrophy; 2, dental defects; 3, onychodystrophy; 4, dyshidrosis; and 5, other abnormalities.

Hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome) was reviewed. It is an X-linked recessive disorder. The mutation is located on the proximal portion of the long arm of the X chromosome. It affects approximately 1 in 100,000 males born. Affected individuals have sparse to absent scalp and vellus body hair, hypodontia or adontia, a paucity of sweat glands, and decreased mucus production in the respiratory tree. Although previously referred to as anhidrotic, patients have some ability to sweat. The nails are normal. Patients may suffer from eczema, frequent upper respiratory tract infections, and difficulty lacrimating. They have characteristic facies with a saddle nose, midfacial hypoplasia, and periorbital hyperpigmentation. The diagnosis in newborns may be difficult to make if there has been no prior family history. One clue is the presence of peeling skin that may be mistaken for a collodion membrane. If the diagnosis is missed at birth, the infant often experiences bouts of unexplained fever due to inability to sweat. A dental panoramic x-ray demonstrates the absent primary teeth and peg-shaped incisors. By puberty many patients develop some ability to sweat and also acquire secondary sexual hair. In their management, it is important to have them fitted for dentures by 3 to 5 years of age.

Other forms of ectodermal dysplasia include the Clouston syndrome, which is known as the hidrotic form. It is an autosomal dominant disorder characterized by normal sweating and normal teeth, but abnormal nails, hair, and mucous glands. Rapp-Hodgkin ectodermal dysplasia is an autosomal dominant condition with hypotrichosis, hypohidrosis, onychodystrophy, and cleft lip and palate.

Ankyloblepharon-ectodermal dysplasia-cleft lip and palate (AEC) and ectrodactyly-ectodermal dysplasia-cleft lip and palate (EEC) are two other autosomal dominant conditions. The former may develop pyogenic granuloma-like lesions in the scalp.

Information for patients and their physicians is available from the National Foundation for Ectodermal Dysplasias, 219 East Main Street, Mascouteh, IL 62258.

HERITABLE DISORDERS OF CONNECTIVE TISSUE

Dr. Jouni Uitto reviewed the biochemistry of the collagen molecule. Functional alterations in collagen affect the cornea, tendon, cortical bones, cartilage, lungs, and liver. Molecular defects in collagen molecules give rise to the various clinical phenotypes of Ehlers-Danlos disease (ED). The 11 distinct forms show a wide spectrum of involvement, although some overlap is seen among them. Clinically, ED is characterized by loose-jointedness, hyperextensible skin, and eye problems including strabismus and fragile corneas. The inheritance in the various forms of ED may be autosomal dominant, autosomal recessive, or X-linked recessive. Fifty percent of patients cannot be easily classified into a specific type. The prevalence of these disorders depends on the sensitivity of the diagnostic criteria.

Types IV, VI, VII, IX have been characterized biochemically as collagen defects. Type IV ED is due to a deficiency of type 3 collagen, which is abundant in skin and vascular connective tissue. This explains the increased frequency of major gastrointestinal or aortic rupture in these patients. It is important to establish an accurate diagnosis. This can be done by analyzing the collagen in a skin biopsy specimen.

Type VI ED is an autosomal recessive disorder characterized by scleral fragility leading to blindness, marked hyperextensible skin, and musculoskeletal deformities. It is due to a deficiency of lysyl hydroxylase. This can be confirmed by measuring hydroxylysine in a skin biopsy specimen. Some patients have altered ability to use the cofactor ascorbic acid. The deficiency can be overcome by treatment with high amounts of ascorbic acid in the range of 2 to 4 g/day.

Type VII Ehlers-Danlos is characterized by defective conversion of the precursor molecule procollagen to a mature product.

Type IX disease is caused by a deficiency in lysyloxidase. The primary defect is the altered copper metabolism, since copper is a cofactor for the enzyme. Diagnosis is made by measuring copper levels.

Abnormalities of elastic fibers were reviewed. Elastic fibers are a minor constituent of normal skin, making up 2% to 4% of the extracellular matrix. They are composed of two components: elastin, an amorphous-appearing protein, and a distinct microfibrillar protein. The gene for elastin is on a chromosome that was recently cloned. It is very complex and susceptible to deletions. Elastin undergoes posttranslational modification by cross-linking of molecules mediated by lysyloxidase, a copper-dependent enzyme.

Heritable diseases in which elastic structures are structurally abnormal include pseudoxanthoma elasticum, Buschke-Ollendorff syndrome, cutis laxa, alpha$_1$-antitrypsin deficiency, Ehlers-Danlos type IX, Menkes syndrome, and Marfan syndrome. In alpha$_1$-antitrypsin deficiency there is a deficiency in the inhibitor of elastase. Elastic structures are destroyed in the lung. Both Menkes syndrome and type IX ED show low copper levels but have significantly different outcomes. An abnormal microfibrillar component of the elastic fiber recently was shown in Marfan syndrome.

Cutis laxa, characterized by loose skin, with variable inheritance can also be an acquired condition, as seen in severe drug eruption or sun damage. Skin biopsy specimens show a loss of elastin. The mechanism of the inherited disorder is unknown. Possibilities include reduced synthesis, nonfunctional fibers, defective cross-linking, and increased degradation.

INTERVENTIONAL RADIOLOGIC TREATMENT OF VASCULAR MALFORMATIONS

Dr. Rich Towbin chronicled the advances in radiologic imaging and in biosynthetic material that have created a new role for embolotherapy. Patients with vascular malformations that include arteriovenous malformations and fistulas, who are symptomatically at risk, can be offered treatment that may achieve palliation. The biosynthetic materials include polyvinyl alcohol (Ivelon), dehydrated alcohol, gel foam, and glues. Several types of coils for occlusion can be introduced by variable-stiffness microcatheters that are soft and spaghetti-like. These procedures are mostly used in vascular malformations of the head and neck. In their preselected group of patients they successfully obtained palliation in all and cures (five yrs without recurrence) in 25%. The other area of use is in vascular

tumors prior to surgery to control blood loss. These procedures are not without complications, such as stroke, facial weakness, pain, and revascularization.

BIOLOGIC BASE OF ICHTHYOSIS

Dr. Joseph McGuire (Stanford University) reviewed the events in terminal differentiation of the epidermis. It has been known for some time that cell division is accelerated in some forms of ichthyosis. Although much effort has been expended in studying the synthesis of keratin, it does not appear to play much of a role in the ichthyoses. Filaggrin is an important molecule that probably is involved in ichthyosis vulgaris and the retention of scale. In one theory, as the keratinocyte matures it loses organelles. The filaggrin (stratum corneum basic protein) disease is included. Little is known of the basic abnormalities in the most common ichthyoses such as ichthyosis vulgaris.

Lamellar ichthyosis, which often is manifested as a collodion baby, is a heterogeneous group that has also remained an enigma. On the other hand, X-linked ichthyosis provided the major breakthrough for experimental biologists with the discovery of the steroid sulfatase deficiency in this disorder. The scale of patients with X-linked ichthyosis contains increased cholesterol sulfate that has been circumstantially linked to the delay in cell separation. Other lipid disorders have been associated with ichthyosis. Another exciting discovery has been the identification of a defect in fatty alcohol oxidoreductase in Sjögren-Larsson syndrome, an autosomal recessive condition with ichthyosis, spastic quadriplegia, seizures, mental retardation, and glistening retinal spots. Patients improve when they receive medium-chain lipids. Dorfman described a disorder of neutral lipid storage associated with ichthyosis, myopathy, neurosensory deafness, cataracts, and a fatty liver. Refsum syndrome includes ichthyosis, cerebellar ataxia, and retinitis pigmentosa. It is due to a deficiency of phytanic acid oxidase. If dietary phytanic acid is restricted, the ichthyosis improves.

NEUROFIBROMATOSIS IN CHILDHOOD

Dr. Vincent Riccardi continued his review of the clinical manifestation of neurofibromatosis by discussing some of the peculiarities in the location of neurofibromas. The lesions have a proclivity to develop on the areolae and nipples of 90% of adult women with neurofibromatosis and 10% of males. He feels that this is not necessarily due to an estrogen effect, but may have something to do with the presence of erectile tissue or highly vascular tissue. Neurofibromas are rarely seen over the shins, glans penis, and upper lip. This may be due to lack of fat in these areas and the associated change in temperature. Another peculiarity of location was demonstrated in a patient with extensive neurofibromas who had no lesions in an area of motor and sensory deficit. The last example was a patient who developed numerous lesions in the area of a donor site for a skin graft.

Patients with NF-2 have findings that may mimic other disorders. They do not all have café au lait macules. If skin tumors are present, they are schwannomas and may have overlying hyperpigmentation and hypertrichosis. Four cases of NF-2 have been discovered in patients who had nasolabial neurofibromas. This appears to be an important pathognomonic sign. Patients should be cautioned to avoid swimming or diving alone since they are at risk of becoming disoriented under water from the vestibular schwannomas.

Dr. Riccardi briefly discussed his management of children with neurofibromatosis and outlined a yearly screen that includes cranial imaging in the asymptomatic patient. He admitted that this was controversial.

The molecular biology of the disease was discussed. The genes for NF-1 and NF-2 have been localized to the long arm of chromosomes 17 and 22, respectively. The NF-1 gene has been cloned. It is a large gene with 300,000 KB. In a study of 300 patients with NF-1 the exact mutation was recognized in only 3%. Buried in the NF gene are three other genes. Two of them are known as EVIS (equotropic viral insertion site) and are associated with murine chronic myelogenous leukemia (CML). This may be important since 0.5% of patients with NF develop CML. Another gene buried within the NF gene is the OMGP (oligodendrocyte myelin glycoprotein). Some patients with NF-1 develop a polyneuropathy that might relate to aberrant expression of this buried gene. In addition, the NF-1 gene is an activating protein for guanosine triphosphatase, affecting growth control through RAS and with a number of other oncogenes. The NF-2 gene is probably a tumor-suppressor gene. Dr. Riccardi speculated that the target area of this mutant gene may be the secretory processes of the internal cell membranes. Evidence for this may be found in the giant melanosomes of neurofibromatosis arising from the Golgi apparatus and the endoplasmic reticulum.

ALOPECIA AREATA IN CHILDHOOD

Dr. Eleanor Sahn (Medical University of South Carolina) reviewed the clinical manifestations of alopecia areata in childhood. She cited a frequency of 17 cases per 1,000,000, with 63% having onset before age 20. Five percent of patients advance to alopecia totalis and 1% to alopecia universalis. She discussed the heredity, with a positive family history in up to 27% of patients, the association with atopy in 18% of children, and the 5% association of autoimmune disorders such as vitiligo and thyroid disease in alopecia areata. The various theories of pathogenesis include infection, neurologic factors, vascular changes, and immune dysfunction. Immune dysfunctions that have been cited are the presence of autoantibodies, decreased T cell counts, anergy, and decreased mitogen response. Therapy was reviewed, such as corticosteroids (topical, intralesional, systemic), anthralin, topical immunotherapy with diphencyprone, PUVA, cyclosporin, thymopentin, minoxidil, inosoplex, isotretinoin, and the use of wigs and psychologic support. The address of the National Alopecia Areata Foundation is 714 C Street, Suite 216, San Raphael, CA 94901; telephone (415) 456-4644.

CASES OF THE YEAR

Dr. Ilona Frieden (University of California, San Francisco) reported a newborn with macrocephaly who on day 6 of life developed macular erythema over the left side of the face. A CT examination showed hydrocephalus consistent with a Dandy-Walker cyst. At 5 weeks of age the vascular lesion had developed into an ulcerated hemangioma that required systemic steroids. An additional finding was a choroidal angioma of the eye. A review of the literature revealed 18 other cases of facial hemangiomas, abnormalities of the posterior fossa, and abnormal eye findings.

Dr. Bernard Cohen (Johns Hopkins University) described a child with blue rubber bleb nevus syndrome who had repeated episodes of acute anemia requiring several transfusions. The anemia was not due to gastrointestinal blood loss but seemed to be due to a hemolytic anemia with a localized disseminated intravascular coagulation.

Dr. Steven Resnick (University of North Carolina) described a newborn who had a large, tense nodule on the buttock thought to be a hemangioma. When it began to hemorrhage, it was excised. The pathology revealed a spindle cell neoplasm with small, spindle-shaped, vascular spaces. There have been two different interpretations: neurogenic sarcoma and congenital fibrosarcoma.

Dr. Andrea Dominey reported two infants with congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease). They had ulcerated lesions appearing at birth, resolving spontaneously over several months. Their skin biopsy specimens were typical, with histiocytic infiltrates surrounded by reticulum fibers. Electron microscopy revealed Birbeck granules and laminated dense bodies.

Dr. Robert Silverman (Annandale, Virginia) discussed a 29-year-old man with Down syndrome who had generalized syringomas that became more prominent with anxiety or activity. He cited an earlier study that found syringomas in 18% of those with Down syndrome.

Dr. Karen Wiss (Boston Children's Hospital) described a 5-month-old who was born with yellowish red plaques and nodules involving the nose, forehead, and cheeks, spreading to the extremities. Lesions over the extremities were covered with an increased density of hair. Except for hoarseness and nasal stuffiness the child was well. Laboratory studies showed only an elevated sedimentation rate and a mild microcytic anemia. Ear, nose, and throat examination revealed an enlarged uvula. The family history was significant in that the patient's father, brother, paternal aunt, and cousin had similar lesions at birth that resolved spontaneously. Only a paternal uncle has persistent lesions. He has a diagnosis of sarcoidosis. A skin biopsy specimen from the patient revealed sheets and nodular aggregates of histiocytoid cells. Macrophage markers were markedly positive, and Langerhans cell markers were focally positive. Electron microscopy showed no true Birbeck granules. Invaginations of the plasma membrane appeared to represent incompletely formed Birbeck granules. The whole picture was interpreted as an indeterminate cell proliferation. Because of progressive deformity of the skin, the child was treated with topical steroids, topical nitrogen mustard, and vinblastine, with no response.

Maira Alvarez-Franco (Children's Memorial Hospital, Chicago) discussed a *Fusarium* infection in an 18-year-old leukemic that caused oral lesions and a lip ulceration. Within several days a generalized rash developed. A biopsy specimen showed fungal hyphae and cultures grew *Fusarium*. The patient died despite treatment with amphotericin.