

## HYPER-IgE SYNDROME WITH RECURRENT INFECTIONS — AN AUTOSOMAL DOMINANT MULTISYSTEM DISORDER

BODO GRIMBACHER, M.D., STEVEN M. HOLLAND, M.D., JOHN I. GALLIN, M.D., FRANK GREENBERG, M.D.,\*  
SUVIMOL C. HILL, M.D., HARRY L. MALECH, M.D., JUDITH A. MILLER, R.N., ANNE C. O'CONNELL, B.DENT.Sc., M.S.,  
AND JENNIFER M. PUCK, M.D.

### ABSTRACT

**Background** The hyper-IgE syndrome with recurrent infections is a rare immunodeficiency characterized by recurrent skin and pulmonary abscesses and extremely elevated levels of IgE in serum. Associated facial and skeletal features have been recognized, but their frequency is unknown, and the genetic basis of the hyper-IgE syndrome is poorly understood.

**Methods** We studied 30 patients with the hyper-IgE syndrome and 70 of their relatives. We took histories, reviewed records, performed physical and dental examinations, took anthropometric measurements, and conducted laboratory studies.

**Results** Nonimmunologic features of the hyper-IgE syndrome were present in all patients older than eight years. Seventy-two percent had the previously unrecognized feature of failure or delay of shedding of the primary teeth owing to lack of root resorption. Common findings among patients were recurrent fractures (in 57 percent of patients), hyperextensible joints (in 68 percent), and scoliosis (in 76 percent of patients 16 years of age or older). The classic triad of abscesses, pneumonia, and an elevated IgE level was identified in 77 percent of all patients and in 85 percent of those older than eight. In 6 of 23 adults (26 percent), IgE levels declined over time and came closer to or fell within the normal range. Autosomal dominant transmission of the hyper-IgE syndrome was found, but with variable expressivity. Of the 27 relatives at risk for inheriting the hyper-IgE syndrome, 10 were fully affected, 11 were unaffected, and 6 had combinations of mild immunologic, dental, and skeletal features of the hyper-IgE syndrome.

**Conclusions** The hyper-IgE syndrome is a multisystem disorder that affects the dentition, the skeleton, connective tissue, and the immune system. It is inherited as a single-locus autosomal dominant trait with variable expressivity. (N Engl J Med 1999;340:692-702.)

©1999, Massachusetts Medical Society.

**T**HE hyper-IgE syndrome (numbers 147060 and 243700 in the Mendelian Inheritance in Man, a catalogue of inherited diseases)<sup>1</sup> is characterized by recurrent staphylococcal skin abscesses, pneumonia with pneumatocele formation, and extreme elevations of serum IgE.<sup>2-4</sup> Reports of more than 200 cases have been published.<sup>5-11</sup> Studies have focused on the immune system; they detected eosinophilia in blood, sputum, and abscesses<sup>6,9,10</sup>; defective granulocyte chemotaxis<sup>4,12-15</sup>; abnormalities in T-lymphocyte subgroups<sup>16,17</sup>; defective antibody production<sup>18-21</sup>; and decreased production of or respon-

siveness to cytokines such as interleukin-4 and interferon- $\gamma$ .<sup>22-25</sup> However, no specific defect in the immune system has been found in all patients.

Several reports have pointed out findings apparently unrelated to the immune system,<sup>7,9-11</sup> including characteristic facial features,<sup>3,5,6,8,26,27</sup> hyperextensibility of joints,<sup>2</sup> multiple bone fractures,<sup>28-31</sup> and craniocostostosis.<sup>15,32-34</sup> The genetic basis of the hyper-IgE syndrome is unclear; most cases are sporadic. A report of two sisters with parents unaffected by the hyper-IgE syndrome suggested autosomal recessive inheritance,<sup>35</sup> but several pedigrees are more consistent with dominant inheritance.<sup>9,10,14,36,37</sup> The hyper-IgE syndrome occurs in persons from diverse ethnic backgrounds and does not seem to be more common in any specific population.

A large cohort of patients with the hyper-IgE syndrome has been followed for more than two decades at the National Institutes of Health, providing an opportunity for the systematic assessment of the features of this syndrome, their incidence, and their development over time. We have found the hyper-IgE syndrome to be a multisystem disorder with variable expression of a specific group of dental, skeletal, and facial as well as immunologic abnormalities. Evaluation of the families in our cohort demonstrated autosomal dominant inheritance with variable expressivity. Recognition of the wide spectrum of phenotypes of the hyper-IgE syndrome will aid diagnosis, management, and genetic-linkage studies of this disorder.

### METHODS

#### Subjects

The 30 patients in our study had been given a diagnosis of the hyper-IgE syndrome on the basis of elevated serum IgE levels; eczematoid rashes; and unusual, severe, recurrent infections such as skin abscesses, candidiasis, and pneumatocele-forming pneumonias in the absence of any other underlying defect in the immune system. We studied these patients and 70 of their relatives under approved protocols at the Warren Grant Magnuson Clinical Center,

From the Genetics and Molecular Biology Branch (B.G., J.M.P.) and the Genetic Disease Branch (E.G.), National Human Genome Research Institute; the Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases (S.M.H., J.I.G., H.L.M., J.A.M.); the Department of Radiology, Warren Grant Magnuson Clinical Center (S.C.H.); and the Clinical Research Core, National Institute of Dental and Craniofacial Research (A.C.O.) — all at the National Institutes of Health, Bethesda, Md. Address reprint requests to Dr. Puck at the Immunologic Genetics Section, GMBB/NHGRI, Bldg. 49, Rm. 3A14, 40 Convent Dr., Bethesda, MD 20892-4442, or at jpuck@nhgri.nih.gov.

\*Deceased.

National Institutes of Health, Bethesda, Maryland. Informed consent was obtained from all subjects or their parents. Some of the patients had been followed for up to 24 years; 14 patients had been followed for more than 10 years (a total of 291 patient-years). Thirteen of the cases were reported in 1983.<sup>6</sup> In 1997, 26 patients were examined, of whom 2 have since died; we also reviewed records of 4 other National Institutes of Health patients, who had died before 1997. The current cohort consisted of 10 male and 20 female patients between 3 and 58 years of age (mean, 26.5) from diverse racial backgrounds (Table 1). Five families had more than one family member who was fully affected by the disorder.

### Clinical Evaluation

For all subjects, we took a complete history, reviewed medical records, performed physical examinations with anthropometric measurements, obtained chest radiographs, and performed laboratory measurements that included complete and differential blood counts and levels of IgE in serum. Patients underwent dental examination and radiography. The status of dental eruption, evaluated clinically, was compared with previously published standards that had been normalized for age.<sup>41</sup> Radiographic assessment of the stage of tooth development was used to calculate dental-development age from standard tables.<sup>42</sup>

### Statistical Analysis

Measurements of each patient's face and body were compared with published standards to determine the patient's z scores.<sup>38</sup> Using the patients' z scores, we derived percentiles, mean z scores of the sample, and the significance of the z scores from the t function or the normal-distribution function. The t-test was used to assess the correlation between eosinophil counts and IgE levels and to evaluate the significance of the delay of tooth eruption for patients, as compared with normal tooth eruption.

## RESULTS

### Dental Abnormalities

Seventy-two percent of the patients with the hyper-IgE syndrome who were older than eight years reported retained primary teeth, noneruption of permanent teeth, or double rows of teeth where permanent teeth erupted adjacent to primary teeth (Fig. 1A and 1B). Shedding of primary teeth, although delayed, did occur in some patients; however, most patients required extraction of eight or more retained primary teeth. The failure of primary teeth to exfoliate on time had not previously been found to be associated with the hyper-IgE syndrome.

Because tooth development and tooth eruption are separate processes,<sup>41,42</sup> both characteristics were assessed in six patients with the hyper-IgE syndrome who were between 8 and 16 years of age. Unlike patients with other systemic diseases, who may have generalized delay in tooth development, patients with the hyper-IgE syndrome had dental-development ages that coincided with their chronologic ages. However, tooth eruption was significantly delayed — by more than 1 SD in five patients and more than 2 SD in one patient with the hyper-IgE syndrome — as compared with standards for age-matched healthy children ( $P < 0.002$ ). Five of 15 patients with the hyper-IgE syndrome who were between 20 and 35 years of age also had striking evidence of delayed exfolia-

tion, with primary teeth still present, permanent teeth still erupting, or both (Fig. 1C). Patient 23 also had five supernumerary mandibular premolars that had not erupted.

For teeth without predecessors (all deciduous teeth and permanent molars), eruption occurred on time. When primary teeth had been extracted in adolescence, permanent teeth erupted normally (Fig. 1C, upper left quadrant of patient's mouth). We consistently found a reduced rate of resorption of the roots of primary teeth; retention of these teeth, in turn, prevented appropriate eruption of the permanent successors.

### Abnormalities of the Head and Face

Distinctive facial characteristics of patients with the hyper-IgE syndrome were found to be universal by the age of 16 years (Table 1). Patients had facial asymmetry with a suggestion of hemihypertrophy; a prominent forehead; deep-set eyes; a broad nasal bridge; a wide, fleshy nasal tip; and mild prognathism (Fig. 2). Facial skin was rough, with prominent pores. The interalar distance was compared with published standard values and with z scores for whites.<sup>38</sup> The percentiles for the 20 patients with the hyper-IgE syndrome for whom interalar distance could be evaluated ranged from the 42nd to >99.9th percentile (Table 1); the mean interalar distance in these patients was above the 98th percentile ( $P < 0.001$ ). In the 24 patients whom we measured, head circumference also tended to be larger than normal (mean z score, 0.326;  $P = 0.06$ ). Craniosynostosis, which had been reported previously,<sup>32-34</sup> was not seen in our patients. Height and other measurements were unremarkable. However, anomalies in midline facial development were observed: a high-arched palate in 71 percent of the patients, a cleft lip and palate in one patient (Patient 28), and midline sagittal clefts in the middle third of the tongue in Patients 9 and 13, who are sisters.

### Skeletal Abnormalities

Although bone fractures were known to occur frequently in patients with the hyper-IgE syndrome, their incidence was unknown.<sup>28-31</sup> In our cohort, 57 percent of the patients had had at least three fractures, which occurred at all ages; the fractures were often due to unrecognized or minor trauma, such as having a diaper changed, carrying luggage, bearing the weight of a leg cast, standing in ocean waves, or line dancing. The fractures occurred in long bones, ribs, and pelvic bones. Some fractures prompted unwarranted investigations for possible child abuse, whereas others were initially unsuspected because of the absence of severe pain. In two patients with multiple fractures, values on densitometry of femoral, radial, and vertebral bones were consistently lower than normal; however, in three others, values were

**TABLE 1.** FINDINGS IN PATIENTS WITH THE HYPER-IgE SYNDROME.

PATIENT No. (FAMILY)	AGE*	SEX	RACE	FINDINGS†												
				ECZEMA	BOILS	PNEUMONIA (PATHOGEN)‡	LUNG CYST	CANDIDIASIS	PEAK IgE§	EOSINO-PHILS¶	CHARACTERISTIC FACIES	INTERALAR DISTANCE	DELAYED DENTAL SHEDDING	BONE FRACTURES**	JOINT HYPER-EXTENSIBILITY	DEGREE OF SCOLIOSIS (CAUSE)††
	yr								IU/ml	per mm <sup>3</sup>						
1	3	F	Mixed	Yes	Yes	Yes	No	Yes	15,375	726	No	NA	NA	No	NA	None
2 (A)	4	M	Asian	Yes	No	No	No	No	3,447	1012	No	NA	NA	No	No	None
3 (B)	4	F	White	Yes	No	No	No	Yes	10,375	940	No	54	NA	No	No	None
4 (B)	8	F	White	Yes	No	Yes	Yes	Yes	19,208	1540	No	92	Yes	Yes	Yes	None
5	11	M	White	Yes	Yes	Yes (Hi)	Yes	Yes	10,210	816	No	72	Yes	Yes	Yes	None
6	16	M	Black	Yes	Yes	Yes (Sa, Hi)	Yes	Yes	53,480	1008	Yes	NA	Yes	Yes	No	10° (idiopathic)
7 (C)	16	F	White	Yes	Yes	Yes	Yes	Yes	10,758	828	Yes	>99.8	Yes	Yes	Yes	10° (idiopathic)
8 (D)‡‡	19	F	White	Yes	Yes	Yes (Sa, Pc)	Yes	Yes	34,676	1146	Yes	95	Yes	Yes	Yes	None
9 (E)	22	F	White	Yes	Yes	Yes	No	No	9,610	820	Yes	>99.9	Yes	No	No	25° (idiopathic)
10‡‡	22	F	White	Yes	Yes	Yes (Pa, Af, Pc)	Yes	Yes	15,458	948	Yes	95	Yes	Yes	Yes	20° (L2 wedge)
11‡‡	24	F	White	Yes	Yes	Yes (Hi, Pa)	Yes	Yes	28,700	1158	Yes	99.9	Yes	Yes	Yes	10° (LLD, Th)
12‡‡	24§§	F	White	Yes	Yes	Yes (Sa, Hi, Af, Pa, Mc)	Yes	Yes	12,800	936	Yes	NA	NA	NA	Yes	10° (idiopathic)
13 (E)	26	F	White	Yes	No	Yes (Pa, Kp)	Yes	Yes	9,600	1712	Yes	90	Yes	No	Yes	30° (idiopathic)
14	27	M	White	Yes	Yes	Yes	No	Yes	14,220	930	Yes	95	Yes	Yes	Yes	10° (idiopathic)
15	27	F	White	Yes	Yes	Yes (Pa, Mc)	Yes	No	15,250	930	Yes	95	Yes	No	Yes	None
16‡‡	27	F	White	Yes	Yes	Yes (Af, Sm)	Yes	Yes	31,380	2034	Yes	42	No	Yes	Yes	45° (idiopathic)
17 (F)‡‡	28	F	White	Yes	Yes	Yes	Yes	Yes	22,402	812	Yes	>99	Yes	Yes	Yes	70° (Th)
18	28§§	F	White	Yes	Yes	Yes (Af, Pa, Sa)	Yes	Yes	38,572	1304	Yes	69	Yes	Yes	Yes	None
19	29	F	White	Yes	Yes	Yes (Pa, Mi)	Yes	Yes	25,058	1060	Yes	98	Yes	Yes	Yes	None
20 (B)	31§§	F	White	Yes	Yes	Yes (Af, Ax)	Yes	Yes	18,867	940	Yes	90	No	No	No	15° (idiopathic)
21	33	M	White	Yes	Yes	No	No	No	32,871	1558	Yes	>99.9	Yes	No	Yes	None
22‡‡	33§§	F	White	Yes	Yes	Yes	Yes	Yes	10,500	800	Yes	NA	No	Yes	Yes	20° (Th)
23‡‡	34	F	Black	Yes	Yes	Yes (Hi, Sp, Ax)	Yes	Yes	54,300	1034	Yes	NA	Yes	No	Yes	45° (T3-5 hemivertebrae)

normal or nearly normal. Three of four additional patients without recurrent fractures also had low bone-density values.

Seventy-six percent of the patients with the hyper-IgE syndrome who were 16 or older had scoliosis with maximal curvature of 10 degrees or more, and 32 percent had curvature of 20 degrees or more (Table 1). In 10 patients, scoliosis was idiopathic. Seven others had scoliosis accompanied by leg-length discrepancy or received a diagnosis of scoliosis after undergoing thoracotomy for lung-cyst removal. In addition,

two patients had congenital spinal abnormalities: a wedge-shaped L2 vertebra (Patient 10) and hemivertebrae at T3 to T5 (Patient 23). Four women required surgical stabilization of scoliosis between the ages of 17 and 23. Other skeletal abnormalities, each seen once, were occult spina bifida, bifid rib, and pseudarthrosis of the rib.

Hyperextensible joints, including fingers, wrists, shoulders, hips, and knees, were found in 68 percent of the patients, and three patients (Patients 7, 11, and 29) had genu valgum.

HYPER-IgE SYNDROME WITH RECURRENT INFECTIONS

TABLE 1. CONTINUED.

PATIENT No. (FAMILY)	AGE*	SEX	RACE	FINDINGS†												
				ECZEMA	BOILS	PNEUMONIA (PATHOGEN)‡	LUNG CYST	CANDIDIASIS	PEAK IgE§	EOSINOPHILS¶	CHARACTERISTIC FACIES	INTERALAR DISTANCE	DELAYED DENTAL SHEDDING	BONE FRACTURES**	JOINT HYPEREXTENSIBILITY	DEGREE OF SCOLIOSIS (CAUSE)††
				yr				IU/ml	per mm <sup>3</sup>	percentile						
24‡‡	35	M	White	Yes	Yes	Yes (Hi, Af)	Yes	Yes	4,000	836	Yes	>99.7	No	Yes	No	18° (LLD, Th)
25‡‡	38	M	Black	Yes	Yes	No	No	No	17,815	932	Yes	NA	No	No	No	None
26 (A)‡‡	38	M	Asian	Yes	Yes	Yes	Yes	Yes	20,700	1130	Yes	NA	No	No	No	10° (idiopathic)
27 (D)‡‡	41	F	White	Yes	Yes	Yes (Sa, Hi, Af, Pa, Sp)	Yes	Yes	58,200	1310	Yes	95	Yes	Yes	Yes	10° (idiopathic)
28‡‡	43§§	M	White	Yes	Yes	Yes	Yes	Yes	1,875	910	Yes	NA	NA	NA	NA	10° (LLD)
29 (C)‡‡	46	M	White	Yes	Yes	Yes (Hi)	Yes	Yes	2,392	1032	Yes	98	Yes	Yes	Yes	10° (Th)
30‡‡	58§§	F	White	Yes	Yes	Yes (Af, Pa)	Yes	Yes	11,196	712	Yes	NA	No	No	No	20° (Th)
				INCIDENCE												
				percent												
				100	87	87	77	83	97 (>2,000 IU/ml)	93 (>2 SD above the mean for normal subjects)	83 (100 for patients ≥16 yr)	80 and 65 (≥1 SD and ≥2 SD above the mean for normal whites)¶¶	72¶¶	57¶¶	68¶¶	63 (76% for patients ≥16 yr)

\*The patient's age in 1997 or at the time of death is shown.

†NA denotes not available. The patient was too young for the determination to be made or had died.

‡The pathogens listed were isolated between 1992 and 1997. Hi denotes *Haemophilus influenzae*, Sa *Staphylococcus aureus*, Pc *Pneumocystis carinii*, Pa *Pseudomonas aeruginosa*, Af *Aspergillus fumigatus*, Mc *Moraxella catarrhalis*, Kp *Klebsiella pneumoniae*, Sm *Stenotrophomonas maltophilia*, Mi *Mycobacterium intracellulare*, Ax *Alcaligenes xylosoxidans*, and Sp *Streptococcus pneumoniae*.

§A normal serum level of IgE in adults is less than 130 IU per milliliter. To convert values to micrograms per liter, multiply by 2.4.

¶The values for 2 SD above the mean in our laboratory are 780 per cubic millimeter for female subjects and 810 per cubic millimeter for male subjects. The values shown were obtained at the same time as, or as close as possible to the time when, the highest level of IgE was measured.

||Percentiles are for a normal population of white males and females.<sup>28</sup>

\*\*"Yes" indicates that the patient had had three or more bone fractures resulting from minimal trauma.

††The degrees indicate maximal spinal curvature; possible contributing factors are as follows: LLD, denoting leg-length discrepancy, and Th, denoting thoracotomy to remove lung cyst. Spinal locations are denoted by L (lumbar) and T (thoracic).

‡‡This patient was included in a previous report.<sup>6,36,39,40</sup>

§§The age at death is shown.

¶¶The incidence rate was calculated for all patients for whom presence or absence of the finding could be ascertained.

Immunologic Features and Infections

Eczema, abscesses, candidiasis, pneumonia, eosinophilia, and elevated serum levels of IgE were the most common manifestations of immune dysfunction in patients with the hyper-IgE syndrome (Table 1). Moderate-to-severe eczematoid rashes were universal in early life, but boils and pneumonia occurred less frequently in youth, particularly in children maintained on antibiotic prophylaxis. As is characteristic of hyper-IgE syndrome,<sup>43</sup> pneumonia led to the formation of pneumatoceles in 77 percent of the patients.

Pathogens that were cultured from pulmonary specimens during the period from 1992 through 1997 are shown in Table 1. Acute pneumonia was caused most frequently by *Staphylococcus aureus* or *Haemophilus influenzae*; in contrast, superinfections of pneumatoceles were associated with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. Fifteen patients required thoracotomy for removal or drainage of infected pneumatoceles.

Other systemic infections were recurrent bacterial arthritis and staphylococcal osteomyelitis at fracture



**Figure 1.** Failure of Dental Exfoliation in Patients with the Hyper-IgE Syndrome.

Panel A shows the lower canines of Patient 8 (age, 11 years), and Panel B shows the upper central incisor of Patient 4 (age, 8 years) and a high palate. Persistent deciduous teeth required extraction in both subjects. Panel C shows a panoramic radiograph of Patient 11 (age, 23 years), revealing retention of five primary teeth with unresorbed roots. The eruption of four upper and lower premolars has been blocked by retained primary teeth, and a retained deciduous right lower canine can be seen behind and lateral to its erupted permanent counterpart. In contrast, timely removal of unshed primary teeth in the upper left quadrant of the patient's mouth (upper right) allowed normal eruption of the premolars.

sites. Six patients (Patients 6, 12, 13, 16, 22, and 30) had episodes of bone pain; the findings on radioactive technetium scanning and magnetic resonance imaging were consistent with a diagnosis of osteomyelitis,<sup>44</sup> but the cultures were negative. These patients received antibiotics, and the lesions resolved.

Chronic candidiasis of mucosal sites and nail beds affected 83 percent of the patients with the hyper-IgE syndrome, including children who had not yet had pneumonia or skin abscesses. Two patients had median rhomboid glossitis, which is a chronic form of candidiasis,<sup>45</sup> and two had *Pneumocystis carinii* pneumonia. Tissue-invasive fungal infections also occurred. Patient

18 had a pulmonary cyst chronically colonized with aspergillus and died of a mycotic (*A. fumigatus*) aneurysm of the brain; Patient 13 had osteomyelitis of the femoral neck caused by yeast; Patient 23 had lymphatic and visceral candidiasis; and Patient 29 had invasive esophageal *Cryptococcus neoformans* infection.<sup>45</sup>

Substantial fluctuations in serum IgE levels were noted over time. The highest values recorded for each patient are shown with concurrent eosinophil counts in Table 1. IgE levels higher than 2000 IU per milliliter (4800  $\mu\text{g}$  per liter)<sup>6,9,10</sup> were documented in all but Patient 28, who enrolled at the age of 34 years with an IgE level of 1875 IU per milliliter



**Figure 2.** Characteristic Facial Appearance of Men and Women of Different Races with the Hyper-IgE Syndrome.

(4500  $\mu\text{g}$  per liter). An unexpected finding in six otherwise typical patients, each followed for more than five years, was a decline in the IgE level; IgE levels fell to less than 2000 IU per milliliter in five patients and fell to the normal range (less than 130 IU per milliliter [312  $\mu\text{g}$  per liter]) in three of the five (Fig. 3). Although eosinophil counts at least 2 SD above normal values were found in 93 percent of the patients, there was no correlation between the number of eosinophils and level of IgE in serum ( $r=0.27$ ,  $P>0.05$ ).

#### Additional Findings

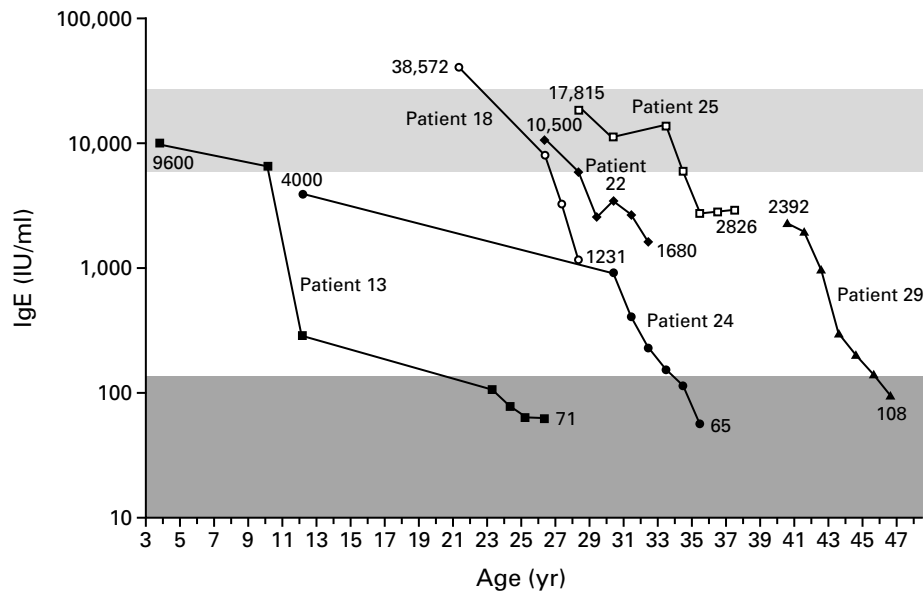
Medical diagnoses not previously reported in patients with the hyper-IgE syndrome included apparently noninfectious vascular events in the central nervous system in three women. Patient 23 had an occlusion of the central retinal artery at the age of 18, and at the age of 34 a leaking berry aneurysm and bilateral aneurysms at the internal carotid bifurcations were diagnosed. Patient 13 had a left cerebral embolus at the age of 18 during an episode of transient cardiomyopathy, and Patient 30 had a throm-

botic stroke of the left posterior inferior cerebellar artery at the age of 54. No consistent risk factors were identified in these patients.

Patient 25, who was uncharacteristically free of pneumonia, had double rows of eyelashes and lymphedema (this syndrome, distichiasis lymphedema syndrome, is frequently an autosomal dominant condition, but it was absent in other members of his family); Patient 28, a nonsmoker, died of squamous-cell carcinoma of the tongue at the age of 43. Patients 20, 22, and 30 died of respiratory failure, and Patient 12 died in an accident. Lupus erythematosus,<sup>46</sup> autoimmune vasculitis,<sup>47</sup> and lymphoma,<sup>48-50</sup> all of which have been reported in the hyper-IgE syndrome, have not developed in any of the patients in our study.

#### Genetics of the Hyper-IgE Syndrome

Eleven of the patients with the hyper-IgE syndrome came from families that had more than one affected member (five families altogether) (Fig. 4, Families A through E, solid symbols). Four pedigrees demonstrated parent-to-child transmission consistent with



**Figure 3.** Serum IgE Levels in Patients with the Hyper-IgE Syndrome Whose Levels Declined.

The normal IgE level is less than 130 IU per milliliter, as indicated by the dark shading; the mean ( $\pm$ SD) IgE levels of patients with the hyper-IgE syndrome in this study are indicated by light shading. To convert values for IgE to micrograms per liter, multiply by 2.4.

dominant inheritance; in Family A, transmission from father to son excluded X-chromosome linkage. Five of eight offspring of patients with the hyper-IgE syndrome were fully affected.

To evaluate further the mode of transmission, we examined 70 relatives of patients with familial and sporadic hyper-IgE syndrome to identify features of the hyper-IgE syndrome in the immune, skeletal, and dental systems. Characteristic findings in two or more of these systems plus at least one highly specific feature were considered to indicate a substantial probability of having inherited a genotype for the hyper-IgE syndrome, because these features are sufficiently uncommon in the general population that they would rarely occur together in one person by chance alone. Eight relatives of affected patients who had multiple findings consistent with the hyper-IgE syndrome were identified in Families C, D, and E and also in a sixth family, Family F (Fig. 4, cross-hatched symbols; the phenotypic features are listed below each symbol).

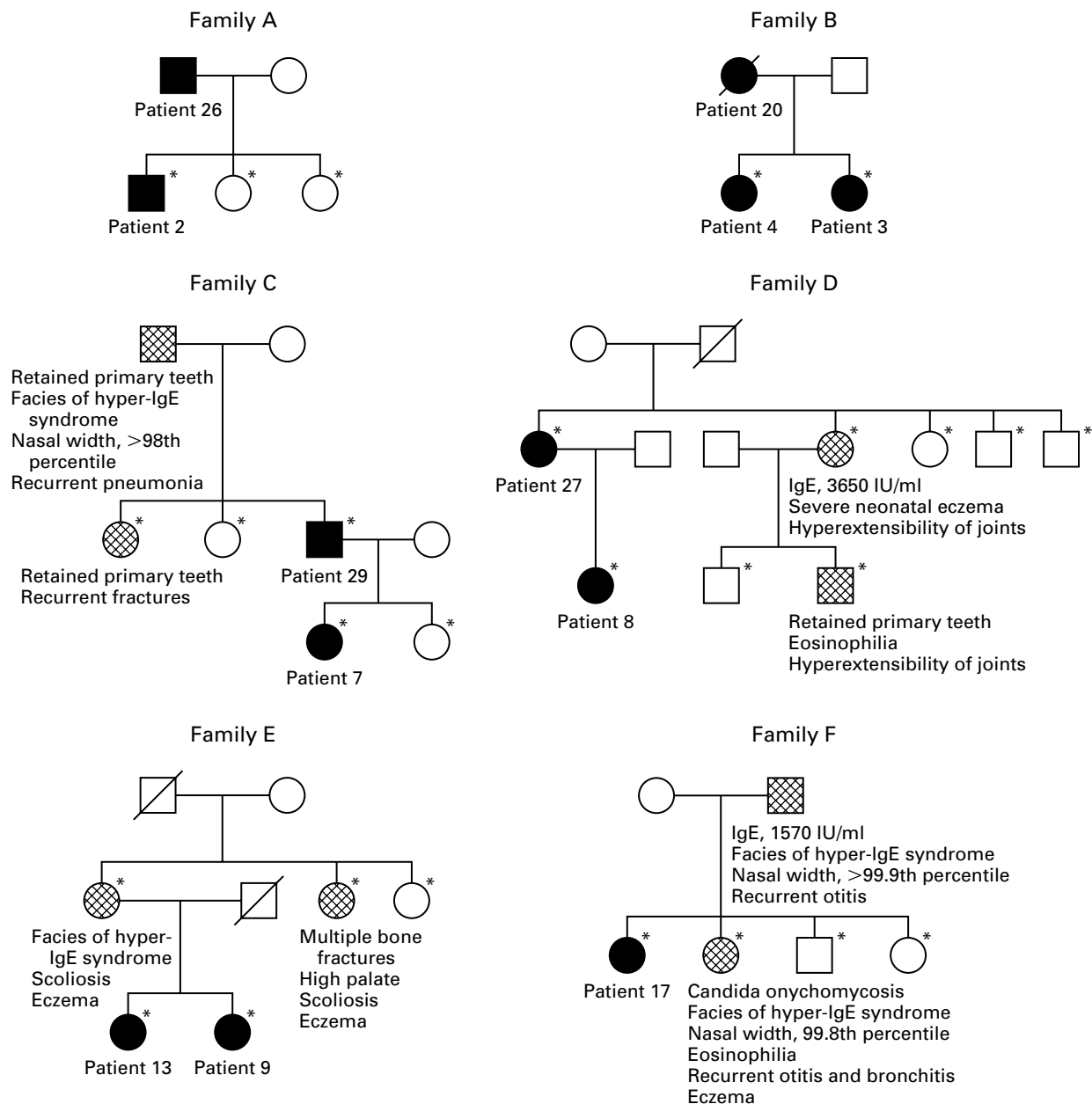
Six other relatives of patients with the hyper-IgE syndrome had one or two immunologic features that are consistent with the hyper-IgE syndrome but are also common in the general population (e.g., moderate eczema, frequent respiratory infections, and eosinophilia); their genotypes were considered indeterminate (data not shown). The remaining relatives had no features consistent with the hyper-IgE syndrome and were judged unlikely to have a genotype for the syndrome. Under a model of single-locus autosomal dominant inheritance with varying expressivity, the

persons represented in Figure 4 by a symbol marked with an asterisk would be at 50 percent risk for inheriting a genotype for the hyper-IgE syndrome, although grandparental origin could not be distinguished from origin from a new mutation in Families D and E. Of the 27 at-risk relatives, 10 were fully affected by the hyper-IgE syndrome, 11 had no features of the syndrome, and 6 had multiple immunologic, skeletal, or dental findings consistent with a phenotype of mild hyper-IgE syndrome.

## DISCUSSION

The hyper-IgE syndrome has been considered primarily an immunodeficiency disease because it causes frequent abscesses, persistent eczematoid rashes, and extreme elevations of IgE in serum. Our study shows that abnormalities in dentition, bones, and connective tissue are as common in the hyper-IgE syndrome as immunologic abnormalities and establishes that the hyper-IgE syndrome is a multisystem disorder.

The failure to shed primary teeth, not previously recognized as a feature of the hyper-IgE syndrome, occurred in 72 percent of patients old enough for evaluation. This characteristic contrasts with the early loss of primary teeth as a result of periodontal infection in other disorders of host defenses, most notably defects in leukocyte adhesion. Retention of individual primary teeth is not rare in the general population, but in our cohort the condition affected all primary teeth and caused impaction of the succedaneous teeth. Tooth development and the eruption of permanent



**Figure 4.** Pedigrees of Six Families with the Hyper-IgE Syndrome.

Squares represent male family members, and circles female family members. A slash indicates that the person has died. Open symbols represent healthy persons, solid symbols patients with the hyper-IgE syndrome, and cross-hatched symbols persons with groups of findings associated with the hyper-IgE syndrome that are uncommon in the general population. In this model, based on autosomal dominant inheritance, asterisks indicate persons at 50 percent risk for inheriting a genotype for the hyper-IgE syndrome. To convert values for IgE to micrograms per liter, multiply by 2.4.

molars occurred on time, suggesting impaired resorption of primary teeth rather than defective eruption. The latter has been implicated in cleidocranial dysplasia, which results from autosomal dominant mutations in the transcription factor CBF1A1.<sup>51</sup> Characteristics of cleidocranial dysplasia are alveolar bone abnormalities, impaired dental exfoliation, supernu-

merary teeth, and lack of cementum in roots.<sup>52</sup> Cleidocranial dysplasia thus superficially resembles the hyper-IgE syndrome, but the dental and skeletal abnormalities of cleidocranial dysplasia — short stature, absent or hypoplastic clavicles, and depressed nasal bridge — are distinct, and cleidocranial dysplasia is not associated with immunologic dysfunction.

The factors that control physiologic dental-root resorption are undefined but may involve the activation of osteoclasts, macrophages, or both by cytokines, which also mediate local inflammation. We suspect that delayed resorption of the roots of primary teeth in the hyper-IgE syndrome may be a manifestation of the same defect that results in ineffective inflammatory responses and the formation of pneumatocetes.

Additional abnormalities of bone and connective tissue caused substantial morbidity in our patients with the hyper-IgE syndrome. Their unexpectedly frequent fractures may reflect a higher-than-normal level of cytokine-mediated bone resorption<sup>31</sup>; indeed, overexpression of interleukin-4 in mice causes osteoporosis.<sup>53</sup> However, we documented fractures in subjects with normal bone density. Moreover, fracture sites commonly associated with osteoporosis are the vertebral bodies and femoral neck, but our patients' fractures were in the long bones, pelvis, and ribs. Whether bone fragility in the hyper-IgE syndrome is due to decreased mineralization or to other abnormalities remains to be determined.

More than three quarters of the patients with the hyper-IgE syndrome who were older than 11 years had 10 degrees or more of scoliosis, and one third had 20 degrees or more — far higher rates than are reported in unselected adolescents (of whom 1.5 percent had scoliosis of 10 degrees or more, and 0.5 percent had 20 degrees or more).<sup>54-56</sup> More than half the cases of scoliosis in our patients were idiopathic, suggesting an intrinsic susceptibility to scoliosis in patients with the hyper-IgE syndrome. Generalized hyperextensibility of joints was recognized in the initial description of the disease,<sup>2</sup> but the 68 percent incidence in our patients is higher than previously reported.

The unusual facial phenotype of the hyper-IgE syndrome had also been noted previously, in both early and recent reports.<sup>2,27</sup> Our anthropometric evaluations confirmed strikingly large nasal interalar distance and suggested larger-than-average head circumference in addition to a specific combination of variations in craniofacial development that were independent of race and sex. Because of the associated developmental variations of the tongue, spine, and ribs and the high incidence of palatal elevation in our patients with the hyper-IgE syndrome, and because of reports of craniosynostosis in the literature,<sup>15,32-34</sup> the hyper-IgE syndrome can be defined as a syndrome of congenital anomalies.

In our study, fluctuations in the patients' IgE levels and eosinophil counts were not correlated and were not related to infections or eczema; this finding had been suggested previously.<sup>57</sup> We also saw no correlation between patients' IgE levels and their interleukin-4-receptor allotype,<sup>58</sup> although such an association has been reported in persons with atopic dermatitis.<sup>59</sup> In some of our patients, IgE levels fell over

time. Although IgE levels exceeded 2000 IU per milliliter in our patients younger than 12, a normal IgE level should not exclude the presence of the hyper-IgE syndrome in an adult. Taken together, these data suggest that eosinophilia and IgE production are influenced by additional factors, beyond those that underlie the pathogenesis of the hyper-IgE syndrome.

Another autosomal dominant disorder with variably expressed anatomical and immunologic abnormalities is the DiGeorge velocardiofacial syndrome. The immunodeficiency associated with this syndrome is due to maldevelopment of the thymus; the prevalence of midline facial and congenital heart defects varies, even among affected members of the same family. Inherited deletions of chromosome 22q11 underlie most cases.<sup>60,61</sup> Although the DiGeorge syndrome differs from the hyper-IgE syndrome in its specific manifestations, it exemplifies the potential for a genetic approach to provide a unified definition of a syndrome and to provide important information to patients and their families about the risk of recurrence in future offspring.

The hyper-IgE syndrome may be caused by the mutation of a single gene, mutations in different genes in different families (indicating genetic heterogeneity), or the deletion of contiguous genes in a short chromosomal region. Although most of our patients were female, large published series show equal distribution between the sexes.<sup>79</sup> Because the genetic backgrounds of our patients were diverse and because survival of patients with this syndrome to reproductive age before the advent of antibiotics was unusual, a founder effect in the hyper-IgE syndrome is unlikely. Therefore the syndrome is expected to result from many independently arising mutations.

All the families in our study reported that there were no features compatible with the hyper-IgE syndrome in generations older than those shown in Figure 4. The apparently greater severity of cases in younger generations may suggest genetic anticipation, as associated with expansion of repetitive DNA motifs, but analysis of more families would be needed to substantiate this possibility. Characterization of the manner of inheritance and the extended phenotypic spectrum of the hyper-IgE syndrome now makes possible a search for genetic linkage and, ultimately, for the gene or genes in which defects produce this combination of immunologic, dental, and skeletal abnormalities.

An awareness of the diverse features of the hyper-IgE syndrome will facilitate the diagnosis of sporadic cases, make genetic counseling possible, and improve patient care.<sup>62</sup> Patients benefit from aggressive antibiotic treatment to minimize infectious complications. They should also receive full evaluations for fractures after even minor trauma, should be monitored vigilantly and treated for scoliosis, and should have retained primary teeth removed.

Supported by a grant (GRI718/1-1) from Deutsche Forschungsgemeinschaft (to Dr. Grimbacher).

*We are indebted to Marc Conte for help with data analysis and presentation, Alejandro Schaffer for statistical consultation, Dr. James Reynolds for bone densitometry, Drs. Rebecca Buckley and Max Muenke for helpful discussions, and all the patients and their families who joined in our research.*

## REFERENCES

- McKusick VA. Mendelian inheritance in man. Catalogs of human genes and genetic disorders. 12th ed. Baltimore: Johns Hopkins University Press, 1998.
- Davis SD, Schaller J, Wedgwood RJ. Job's syndrome: recurrent, "cold," staphylococcal abscesses. *Lancet* 1966;1:1013-5.
- Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics* 1972;49:59-70.
- Hill HR, Ochs HD, Quie PG, et al. Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent "cold" staphylococcal abscesses. *Lancet* 1974;2:617-9.
- Däumling S, Buriot D, Huu Trung P, Griscelli C, Lalama MC, Belohradsky BH. Das Buckley-Syndrom: Rezidivierende, schwere Staphylokokkeninfektionen, Ekzem und Hyperimmunoglobulinämie E. *Infection* 1980;8:Suppl 3:S248-S254.
- Donabedian H, Gallin JI. The hyperimmunoglobulin E recurrent-infection (Job's) syndrome: a review of the NIH experience and the literature. *Medicine (Baltimore)* 1983;62:195-208.
- Belohradsky BH, Däumling S, Kiess W, Griscelli C. Das Hyper-IgE-Syndrom (Buckley- oder Hiob-Syndrom). In: *Ergebnisse der Inneren Medizin und Kinderheilkunde*. Vol. 55. Berlin, Germany: Springer-Verlag, 1987:1-39.
- Gahr M, Allgeier B, Speer CP. Das Hyper-IgE-Syndrom. *Monatsschr Kinderheilkd* 1987;135:329-35.
- Stichm ER, ed. Immunologic disorders in infants and children. 4th ed. Philadelphia: W.B. Saunders, 1996:413-22.
- Buckley RH, Sampson HA. The hyperimmunoglobulinemia E syndrome. In: Franklin EC, ed. *Clinical immunology update: reviews for physicians*. New York: Elsevier North-Holland, 1981:147-67.
- Holland SM, Gallin JI. Disorders of granulocytes and monocytes. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., eds. *Harrison's principles of internal medicine*. 14th ed. Vol. 1. New York: McGraw-Hill, 1998:351-9.
- Hill HR, Quie PG. Raised serum-IgE levels and defective neutrophil chemotaxis in three children with eczema and recurrent bacterial infections. *Lancet* 1974;1:183-7.
- Van Epps DE, El-Naggar A, Ochs HD. Abnormalities of lymphocyte locomotion in immunodeficiency disease. *Clin Exp Immunol* 1983;53:678-88.
- Van Scoy RE, Hill HR, Ritts RE, Quie PG. Familial neutrophil chemotaxis defect, recurrent bacterial infections, mucocutaneous candidiasis, and hyperimmunoglobulinemia E. *Ann Intern Med* 1975;82:766-71.
- Gahr M, Muller W, Allgeier B, Speer CP. A boy with recurrent infections, impaired PMN-chemotaxis, increased IgE concentrations and cranial synostosis — a variant of the hyper-IgE syndrome? *Helv Paediatr Acta* 1987;42:185-90.
- Buckley RH, Schiff SE, Hayward AR. Reduced frequency of CD45RO+ T lymphocytes in blood of hyper IgE syndrome patients. *J Allergy Clin Immunol* 1991;87:Suppl:313. abstract.
- Geha RS, Reinherz E, Leung D, McKee KT Jr, Schlossman S, Rosen FS. Deficiency of suppressor T cells in the hyperimmunoglobulin E syndrome. *J Clin Invest* 1981;68:783-91.
- Buckley RH, Becker WG. Abnormalities in the regulation of human IgE synthesis. *Immunol Rev* 1978;41:288-314.
- Dreskin SC, Goldsmith PK, Gallin JI. Immunoglobulins in the hyperimmunoglobulin E and recurrent infection (Job's) syndrome: deficiency of anti-Staphylococcus aureus immunoglobulin A. *J Clin Invest* 1985;75:26-34.
- Dreskin SC, Goldsmith PK, Strober W, Zech LA, Gallin JI. Metabolism of immunoglobulin E in patients with markedly elevated serum immunoglobulin E levels. *J Clin Invest* 1987;79:1764-72.
- Vercelli D, Jabara HH, Cunningham-Rundles C, et al. Regulation of immunoglobulin (Ig)E synthesis in the hyper-IgE syndrome. *J Clin Invest* 1990;85:1666-71.
- King CL, Gallin JI, Malech HL, Abramson SL, Nutman TB. Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon- $\gamma$ . *Proc Natl Acad Sci U S A* 1989;86:10085-9.
- Paganelli R, Scala E, Capobianchi MR, et al. Selective deficiency of interferon-gamma production in the hyper-IgE syndrome: relationship to *in vitro* IgE synthesis. *Clin Exp Immunol* 1991;84:28-33.
- Rousset F, Robert J, Andary M, et al. Shifts in interleukin-4 and interferon- $\gamma$  production by T cells of patients with elevated serum IgE levels and the modulatory effects of these lymphokines on spontaneous IgE synthesis. *J Allergy Clin Immunol* 1991;87:58-69.
- Claassen JJ, Levine AD, Schiff SE, Buckley RH. Mononuclear cells from patients with the hyper-IgE syndrome produce little IgE when they are stimulated with recombinant human interleukin-4. *J Allergy Clin Immunol* 1991;88:713-21.
- Geha RS, Leung DYM. Hyper immunoglobulin E syndrome. *Immunodef Rev* 1989;1:155-72.
- Borges WG, Hensley T, Carey JC, Petrak BA, Hill HR. The face of Job. *J Pediatr* 1998;133:303-5.
- Kirchner SG, Sivit CJ, Wright PF. Hyperimmunoglobulinemia E syndrome: association with osteoporosis and recurrent fractures. *Radiology* 1985;156:362.
- Brestel EP, Klingberg WG, Veltri RW, Dorn JS. Osteogenesis imperfecta tarda in a child with hyper-IgE syndrome. *Am J Dis Child* 1982;136:774-6.
- Lallemant D, Kalifa G, Buriot D, Sauvegrain J, Griscelli C. Anomalies osseuses constitutionnelles dans les déficits immunitaires congénitaux. *Ann Radiol (Paris)* 1979;22:108-18.
- Leung DY, Key L, Steinberg JJ, et al. Increased *in vitro* bone resorption by monocytes in the hyper-immunoglobulin E syndrome. *J Immunol* 1988;140:84-8.
- Cohen MM Jr. Craniosynostosis update 1987. *Am J Med Genet Suppl* 1988;4:99-148.
- Hoger PH, Boltshauser E, Hitzig WH. Craniosynostosis in hyper-IgE syndrome. *Eur J Pediatr* 1985;144:414-7.
- Smithwick EM, Finelt M, Pahwa S, et al. Cranial synostosis in Job's syndrome. *Lancet* 1978;1:826.
- Bannatyne RM, Skowron PN, Weber JL. Job's syndrome — a variant of chronic granulomatous disease: report of a case. *J Pediatr* 1969;75:236-42.
- Dreskin SC, Gallin JI. Evolution of the hyperimmunoglobulin E and recurrent infection (HIE, JOB's) syndrome in a young girl. *J Allergy Clin Immunol* 1987;80:746-51.
- Blum R, Geller G, Fish LA. Recurrent severe staphylococcal infections, eczematoid rash, extreme elevations of IgE, eosinophilia, and divergent chemotactic responses in two generations. *J Pediatr* 1977;90:607-9.
- Farkas LG. Anthropometry of the head and face in medicine. 2nd ed. New York: Raven Press, 1994:242-346.
- Hall RA, Salhany KE, Lebel E, Bavaria JE, Kaiser LR. Fungal pulmonary abscess in an adult secondary to hyperimmunoglobulin E (Job's) syndrome. *Ann Thorac Surg* 1995;59:759-61.
- Jacobs DH, Macher AM, Handler R, Bennett JE, Collen MJ, Gallin JI. Esophageal cryptococcosis in a patient with the hyperimmunoglobulin E-recurrent infection (Job's) syndrome. *Gastroenterology* 1984;87:201-3.
- Hurme VO. Ranges of normalcy in eruption of permanent teeth. *J Dent Child* 1949;16:11-5.
- Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. *Hum Biol* 1973;45:211-27.
- Merten DE, Buckley RH, Pratt PC, Effmann EL, Grossman H. Hyperimmunoglobulinemia E syndrome: radiographic observations. *Radiology* 1979;132:71-8.
- Andrich MP, Chen CC, Gallin JI. Abnormal bone scintigraphy before clinical symptoms in a patient with defective phagocyte function. *Clin Nucl Med* 1993;18:153-4.
- Wright BA. Median rhomboid glossitis: not a misnomer: review of the literature and histologic study of twenty-eight cases. *Oral Surg Oral Med Oral Pathol* 1978;46:806-14.
- Schopfer K, Feldges A, Baerlocher K, Parisot RF, Wilhelm JA, Matter L. Systemic lupus erythematosus in Staphylococcus aureus hyperimmunoglobulinemia E syndrome. *BMJ* 1983;287:524-6.
- Kimata H. High-dose intravenous  $\gamma$ -globulin treatment for hyperimmunoglobulinemia E syndrome. *J Allergy Clin Immunol* 1995;95:771-4.
- Bale JF Jr, Wilson JF, Hill HR. Fatal histiocytic lymphoma of the brain associated with hyperimmunoglobulinemia-E and recurrent infections. *Cancer* 1977;39:2386-90.
- Einsele H, Saal JG, Dopfer R, Niethammer D, Waller HD, Müller CA. Hochmalignes Non-Hodgkin-Lymphom bei Hyper-IgE-Syndrom. *Deutsch Med Wochenschr* 1990;115:1141-4.
- Gorin LJ, Jeha SC, Sullivan MP, Rosenblatt HM, Shearer WT. Burkitt's lymphoma developing in a 7-year-old boy with hyper-IgE syndrome. *J Allergy Clin Immunol* 1989;83:5-10.
- Mundlos S, Otto F, Mundlos C, et al. Mutations involving the transcription factor CBF1A1 cause cleidocranial dysplasia. *Cell* 1997;89:773-9.
- Jensen BL, Kreiborg S. Development of the dentition in cleidocranial dysplasia. *J Oral Pathol Med* 1990;19:89-93.
- Lewis DB, Liggitt HD, Effmann EL, et al. Osteoporosis induced in mice by overproduction of interleukin 4. *Proc Natl Acad Sci U S A* 1993;90:11618-22.
- Bunch WH, Patwardhan AG. Scoliosis: making clinical decisions. *St. Louis: C.V. Mosby, 1989:44-8.*

55. Ohtsuka Y, Yamagata M, Arai S, Kitahara H, Minami S. School screening for scoliosis by the Chiba University Medical School screening program: results of 1.24 million students over an 8-year period. *Spine* 1988;13:1251-7.
56. Soucacos PN, Soucacos PK, Zacharis KC, Beris AE, Xenakis TA. School-screening for scoliosis: a prospective epidemiological study in north-western and central Greece. *J Bone Joint Surg Am* 1997;79:1498-503.
57. Dreskin SC, Kaliner MA, Gallin JI. Elevated urinary histamine in the hyperimmunoglobulin E and recurrent infection (Job's) syndrome: association with eczematoid dermatitis and not with infection. *J Allergy Clin Immunol* 1987;79:515-22.
58. Grimbacher B, Holland SM, Puck JM. The interleukin-4 receptor variant Q576R in hyper-IgE syndrome. *N Engl J Med* 1998;338:1073-4.
59. Hershey GKK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA. The association of atopy with a gain-of-function mutation in the  $\alpha$  subunit of the interleukin-4 receptor. *N Engl J Med* 1997;337:1720-5.
60. Gottlieb S, Emanuel BS, Driscoll DA, et al. The DiGeorge syndrome minimal critical region contains a goosecoid-like (GSCL) homeobox gene that is expressed early in human development. *Am J Hum Genet* 1997;60:1194-201.
61. Driscoll DA, Sullivan KE. DiGeorge syndrome: a chromosome 22q11.2 deletion syndrome. In: Ochs H, Smith CIE, Puck JM, eds. *Primary immunodeficiencies: a molecular and genetic approach*. New York: Oxford University Press, 1998:198-208.
62. Hochreutener H, Wuthrich B, Huwylar T, Schopfer K, Seger R, Baerlocher K. Variant of hyper-IgE syndrome: the differentiation from atopic dermatitis is important because of treatment and prognosis. *Dermatologica* 1991;182:7-11.