

The Hyper-IgE Syndrome

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Introduction

The hyper-IgE syndrome is a primary immunodeficiency disorder first described in 1972 (1) characterized by recurrent staphylococcal abscesses and markedly elevated serum IgE concentrations. Those affected have lifelong histories of severe recurrent staphylococcal abscesses involving the skin, lungs, joints, and other sites. In addition, there is a unique tendency of these patients to form persistent pneumatoceles following staphylococcal pneumonias. Although there usually is a history of a pruritic dermatitis, it is not typical atopic dermatitis, and respiratory allergic symptoms are usually absent.

Since the first two patients with this disorder were reported by me and my associates, I have evaluated a total of 40 patients with similar clinical and immunologic findings (2–4). Patients with this syndrome have also been reported by others (5–13).

Clinical Manifestations

Some general features of the 40 patients with the hyper-IgE syndrome I have evaluated are listed in Table 1. They ranged in age from 1–44 yr at the time of initial evaluation; 26 were male, 14 were female, 12 were black, and 28 were white. They came from a wide geographic area. The hyper-IgE syndrome is a rare disorder, and those affected are not merely individuals with atopic eczema who have repeated superficial infections of their skin lesions. They invariably had had recurrent severe bouts of furunculosis and pneumonia secondary to *Staphylococcus aureus* from early infancy, some from d 1 of life, and persistent pneumatoceles developed in a majority of the patients as a result of their recurrent pneumonias (Fig. 1) (13a,14). Nine of the author's pa-

Table 1
General Features of 40 Patients with the Hyper-IgE Syndrome

Patient	Age	Sex	Race	Age of First Infection	Dermatitis	Wheezing	IgE (IU/mL)
BS	14	M	W	6 wk	+	-	22,300
RB	14	M	W	Newborn	+	-	6,600
AY	16	M	B	Newborn	+	-	40,000
CC	13	M	W	18 mo	+	-	6,400
aTF	11	M	W	Newborn	+	-	9,000
AT	6	M	W	Infancy	+	-	5,000
LH	12	M	B	10 mo	+	-	22,000
JB	2	M	W	1 d	+	-	11,600
DS	17	M	W	Infancy	+	-	46,000
SE	12	M	W	Infancy	+	+	26,500
EN	31	F	B	Infancy	+	+	15,600
VD	11	F	W	1 mo	+	-	38,400
PD	7	F	B	Newborn	+	-	25,600
GD	13	F	B	Infancy	+	-	2,150
FD	3	M	B	4 mo	+	-	2,788
FK	22	M	W	Infancy	+	-	12,362
JM	2	F	W	Infancy	+	-	5,000
AC	10	F	B	Infancy	+	-	51,200
RTo	7	M	W	1 d	+	-	33,000
CH	5	F	B	3 wk	+	-	24,000
JW	7	M	W	6 mo	+	+	39,500
RTel	5	M	W	2 wk	+	-	5,800
PM	22	F	W	8 mo	+	+	130,000
MS	13	F	W	3 wk	+	+	70,800
KSt	1	F	W	Infancy	+	-	320
KSw	18	F	W	6 mo	+	-	3,550
TSw	21	F	W	3 mo	+	-	210
CT	13	F	B	4 mo	+	+	15,500
WW	44	F	W	19 mo	+	-	886
LA	2	M	W	1 d	+	-	23,300
TB	10	M	B	Infancy	-	-	5,150
RA	10	M	W	3 mo	+	-	24,500
TC	1	M	W	1 mo	+	-	577
BK	13	M	W	3 day	+	-	18,700
AM	24	M	W	6 mo	+	-	890
CJM	12	M	W	1 d	+	-	2,800
ES	1	M	W	3 wk	+	-	3,060
WS	44	M	W	Infancy	+	-	4,800
JS	4	M	B	2 yr	+	-	15,600
TW	4	M	B	3 d	+	+	5,820

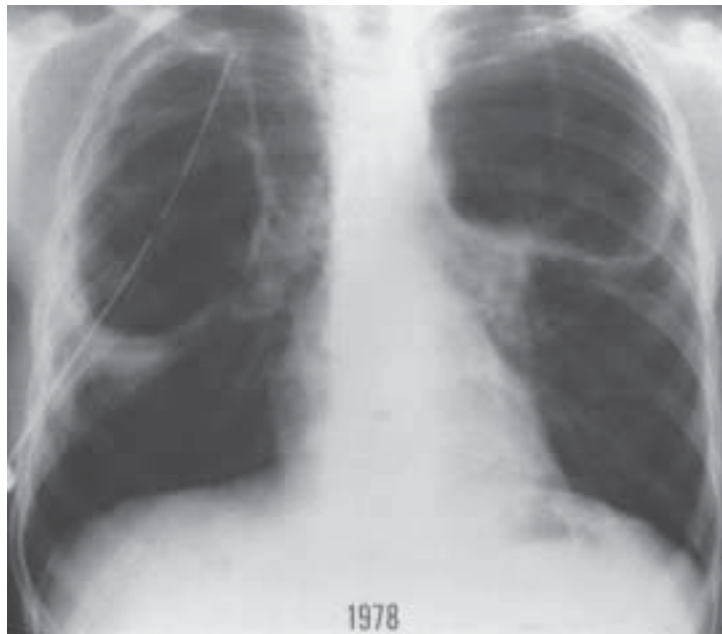


Fig. 1. Chest roentgenogram of 12-yr-old boy with hyper-IgE syndrome. Giant pneumatoceles were present for more than 1 yr. A putrid abscess owing to *Enterobacter cloacae* led to chest tube insertion on the right. Left cyst required emergency excision because of massive hemoptysis and was found to contain an aspergilloma. Adapted with permission from ref. (13a).

tients required thoracic surgery because of giant persistent pneumatoceles that became chronically infected—nine had lobectomies and two underwent complete pneumonectomies because of lung abscesses, one had an empyema, and one had an anterior mediastinal *Candida* granuloma.

As shown in Table 2, all patients have been plagued by infections with *Staphylococcus aureus*, but some also had recurrent *Hemophilus influenzae*, pneumococcal, group A streptococcal, gram-negative, and fungal infections. The sites of infections are listed in Table 3. Infections of the skin and lungs predominated, but the ears, eyes, oral mucosa, sinuses, joints, blood, and even viscera were also involved. A peculiar tendency of the abscesses to localize about the scalp, face, and neck was observed in infants and younger children. Sites that were not foci of infections included the urinary and gastrointestinal (GI) tracts, and the bones (except for mastoids). Cryptococcal meningitis has been observed in one of the author's patients and this complication has also occurred in three patients evaluated by others; bacterial meningitis has not been reported.

Table 2
Organisms Associated with Infection in 40 Patients with Hyper-IgE Syndrome

Organisms	# of Patients Infected
<i>Staphylococcus aureus</i> , coagulase positive	40/40
<i>Candida albicans</i>	20/40
Miscellaneous gram-negative organisms	11/40
<i>Haemophilus influenzae</i>	9/40
Pneumococci	9/40
Streptococci, group A	4/40
Aspergillus species	4/40
Trichophyton species	2/40
<i>Cryptococcus neoformans</i>	1/40
<i>Pneumocystis carinii</i>	1/40
<i>Mycoplasma hominis</i>	1/40

All but one of these 40 patients either had dermatitis at the time of evaluation or, more often, a history of pruritic dermatitis earlier in life (Table 1). Although the lesions resembled those of an eczematoid dermatitis with lichenified skin, the distribution and characteristics of the lesions were not those of typical atopic eczema. None of the patients had histories of allergic rhinitis and only seven were noted to wheeze; even in these, wheezing was not a prominent symptom. Two patients without a history of wheezing were given methacholine inhalation challenges without a significant drop in pulmonary function. Thus, there was minimal evidence of respiratory allergy in these patients. None had a history or clinical evidence of parasitic infestation. Several patients were growth-retarded, predominately those with chronic lower-respiratory tract disease.

Although some features of hyper-IgE patients resemble those present in chronic granulomatous disease (CGD), there are several distinguishing clinical features. Unlike CGD patients, hyper-IgE patients may have infections with catalase-negative organisms, such as streptococci and pneumococci. Further, although patients with CGD also have frequent staphylococcal pneumonias, they rarely have persistent pneumatocoeles such as those that occur in hyper-IgE patients (14). Finally, unlike CGD patients, hyper-IgE syndrome patients rarely have osteomyelitis, urinary tract infections, diarrhea, or intestinal obstruction.

Most abscesses in our patients have been tender and warm, although many of the patients, despite having large deep-seated abscesses, had minimal systemic toxicity. Two girls with red hair, fair skin, and hyperextensible joints were described in 1966 (15), prior to the discovery of IgE, as having "cold," nontender cutaneous abscesses. The

Table 3
Sites of Infections in 40 Patients with Hyper-IgE Syndrome

Sites of Infection	Number of Patients Affected
Skin	39/40
Abscesses	39/40
Deep cellulitis	3/40
Lung	39/40
Pneumatocoeles	24/40
Resection of lobes	9/40
Total pneumonectomy	2/40
Ears	30/40
Mastoidectomy	2/40
Oral mucosa	20/40
Sinuses	18/40
Eyes	15/40
Viscera	10/40
Joints	6/40
Blood	4/40

authors called the condition "Job's syndrome" after the biblical Job, who was smitten with boils. Serum IgE concentrations were later found to be elevated in those two patients and in two more (6).

Nonimmunologic Features

Coarse facial features were noted in the first two patients (1), and this has been a consistent feature of all of the patients I have evaluated with this syndrome (Figs. 2 and 3) (1,15a). Hyper-IgE syndrome patients look very different from their nonaffected family members. Distinctive facial characteristics were again pointed out recently by Grimbacher and his associates (Table 4) (16). Among the findings reported were a prominent forehead, deep-set eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy. They also found that the mean nasal interalar distance in these patients was above the 98th percentile ($p < 0.001$). These findings were present in all patients in that study by age 16 yr (16). High incidences of scoliosis and hyperextensible joints were also noted. An interesting observation in that group of patients that had not been previously reported was a 72% incidence of failure or delayed shedding of the primary teeth, owing to lack of root resorption (16). However, only 77% of the patients in that study had the clinical diagnostic criteria of abscesses, pneumonias with pneumatocoeles, and elevated IgE. Because there is no distinctive laboratory test for this condition, it is unclear whether all of the patients had the hyper-IgE syndrome.



Fig. 2. Patient with hyper-IgE syndrome, showing multiple abscesses of face and neck and coarse facial features. Adapted with permission from ref. (1).

Unexplained osteopenia is also present in most patients with the hyper-IgE syndrome, many of whom have problems with recurrent fractures from even minor trauma (16,17). This problem, which is not correlated with the patient's state of activity or accompanied by any detectable abnormalities in calcium or phosphorus metabolism, was so severe in 1 of 40 patients that collapses of most vertebral bodies occurred (1). Reduced bone density has been found in patients with this syndrome (16,18). Peripheral blood monocytes from hyper-IgE patients have been found to resorb bone to a greater extent than normal monocytes and to release spontaneously abnormally high levels of prostaglandin E_2 (PGE_2) (1,16,18,19).

Inheritance

Fourteen instances of the familial occurrence of the hyper-IgE syndrome have been noted among 8 families in the group of 40 patients

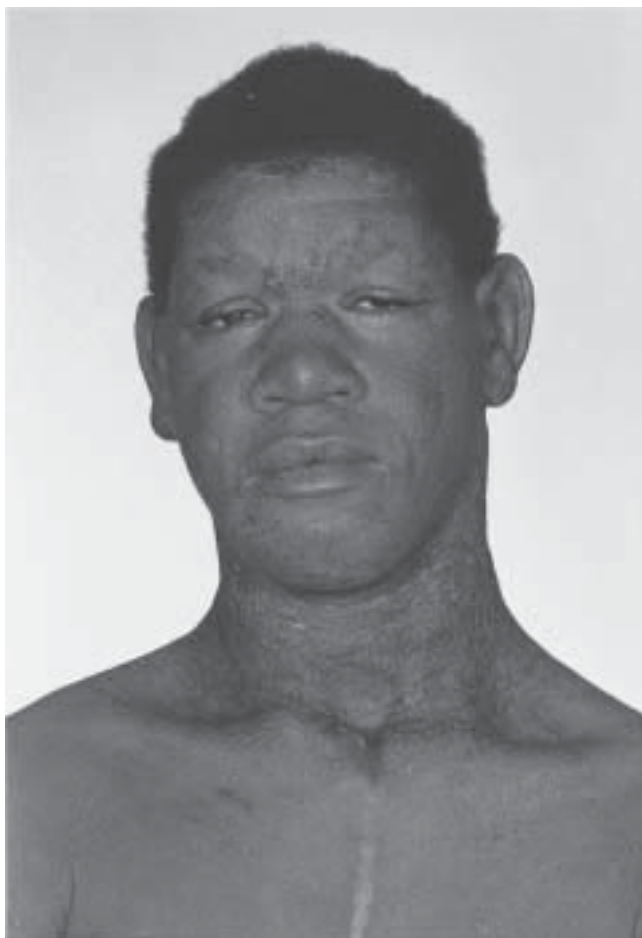


Fig. 3. Patient with hyper-IgE syndrome, again illustrating coarse facial features. Scar over the upper chest is from excision of a *Candida* granuloma of the mediastinum. Adapted with permission from ref. (15a).

Table 4
Nonimmunologic Features of 30 Patients with Hyper-IgE Syndrome^a

Failure or delayed shedding of the primary teeth owing to lack of root resorption	72
Recurrent fractures owing to minor trauma	57
Hyperextensible joints	68
Scoliosis	76
Facial asymmetry: ? Hemihypertrophy, prominent forehead, deep-set eyes, broad nasal bridge, wide fleshy nasal tip, and mild prognathism.	Present in all by age 16.

^a Adapted from ref. (16)

Table 5
Clinical Features of 40 Patients with Hyper-IgE Syndrome

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- Severe infections of the skin and lower respiratory tract from infancy. All have had *furunculosis* and staphylococcal *pneumonia*, and over half have had persistent *pneumatocoles*; 11 have required lung surgery. Most have also had infections of ears, sinuses, eyes, and oral mucosa. Fewer have had infections of joints, viscera, or blood.
 - *Staphylococcus aureus*, coagulase-positive, has caused infections in all. *Candida albicans*, *Haemophilus influenzae*, pneumococci and streptococci, group A isolated in 25–50%, miscellaneous gram-negative rods, and other fungi in some.
 - Pruritic dermatitis chronically or (more often) in past, little or no respiratory allergy. Rash is not typical atopic eczema.
 - Both sexes affected (26males, 14females); 28 were white, 12 were black.
 - Familial occurrence in 14/40 patients in 8 families; IgE normal in non-affected relatives. Pattern in families suggests autosomal dominant trait with incomplete penetrance. No increased frequency of any HLA-A or HLA-B locus antigens.
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evaluated by the author, and there are several additional familial reports (7,16,20). The fact that both males and females have been affected, as well as members of succeeding generations, suggested an autosomal dominant with incomplete penetrance form of inheritance. This proposed mode of inheritance was recently supported by a report from the National Institutes of Health (NIH) in which 11 out of 30 patients came from 5 families in which there was more than one affected member. The pattern was again consistent with autosomal dominant inheritance with incomplete penetrance (16).

A summary of the clinical features of this syndrome is presented in Table 5.

Laboratory Findings

Hematologic Studies

Eosinophilia of blood and sputum has been a consistent finding in all patients. Peripheral eosinophilia as high as 55–60% may occur in some infants. In most patients, both the percentage and absolute number of eosinophils exceeded those seen in the average atopic patient. Total white blood cell counts have ranged from normal to markedly elevated (50,000–60,000/mm³), but no patients were neutropenic or lymphopenic. Anemia was not uncommon in those with chronic lower respiratory infections but was not present when infection was controlled.

Humoral Immunity

Investigations of humoral immunity consistently showed serum IgE concentrations to be exceedingly high, ranging from 3–82 times above the upper limit of normal for our laboratory (Table 1). In addition, serum IgD levels were elevated in a majority, with 14 having values greater than 10 mg/dl and some having levels of 50–159 mg/dl (21). Serum concentrations of one or more of the other three immunoglobulin isotypes were slightly low or elevated in some patients, but more often they were normal (Table 6). Serum IgE concentrations were measured in first-degree unaffected relatives of nine patients, and all the values were normal.

Poor anamnestic antibody responses to diphtheria and tetanus were noted in the first two patients (1), and they failed to respond to the neoantigen keyhole limpet hemocyanin (KLH). To investigate further whether an underlying antibody deficiency could account for the infection-susceptibility of these patients, we evaluated 11 additional patients with the hyper-IgE syndrome for their responses to bacteriophage Φ X174, diphtheria and tetanus toxoids, and pneumococcal (Pneumovax) and *H. influenzae* vaccines (3). Three of nine patients immunized with Φ X174 had normal primary and secondary antibody responses, five had accelerated declines in their titers (after initially normal primary antibody responses) and lower than normal secondary antibody responses, and two of the latter patients did not show normal switching from IgM to IgG antibody production (Table 6). Only 1 of 10 tested had normal responses to diphtheria toxoid, and postimmunization anti-tetanus titers were abnormally low in 5 of the 10 patients tested. Serum antibodies to unconjugated *H. influenzae* polyribose phosphate were protective in seven of the eight immunized patients. Five of the nine who were given Pneumovax immunizations had poor antibody responses to at least one of the serotypes 7, 9, or 14; all patients responded with protective antibody titers to type 3. Abnormal polysaccharide antibody responses did not correlate with IgG2 levels.

Serum antibodies to staphylococcal and *Candida* organisms were detected in the serum of one of the first two patients evaluated (1). Dreskin and colleagues (22) found normal quantities of IgG and elevated IgM antibodies but a deficiency of IgA antibodies to *S. aureus* in 10 patients with the hyper IgE syndrome. The titer of IgA anti-*S. aureus* present correlated inversely with the incidence of infection at mucosal surfaces and in adjacent lymph nodes, suggesting a role for a deficient IgA response in their infection susceptibility. This heterogeneity in their antibody-forming capacities suggests that antibody deficiency may contribute to the infection-susceptibility of some hyper-IgE syndrome

Table 6
Summary of IgG Concentrations and Postimmunization
Antibody Responses in Patients with Hyper-IgE Syndrome^a

Immunologic parameter	No. of patients with abnormal value
Total IgG concentration	0/11 low
IgG1 concentration	0/11 low
IgG2 concentration	3/11 low
IgG3 concentration	2/11 low
IgG4 concentration	0/11 low
Diphtheria antibody titer	9/10 low
Tetanus antibody titer	5/10 low
<i>H. influenzae</i> antibody titer	1/8 nonprotective
Pneumococcus type 3 titer	0/9 nonprotective
Pneumococcus type 7 titer	3/9 nonprotective
Pneumococcus type 9 titer	2/9 nonprotective
Pneumococcus type 14 titer	4/9 nonprotective
Bacteriophage M X 174: primary	5/10 low
Bacteriophage M X 174: secondary	5/10 low
Bacteriophage M X 174: IgG antibody	2/10 low

^a Adapted from ref. (3).

patients, but the fact that it is not present in all patients indicates that antibody deficiency alone is not the fundamental problem in these patients.

IgE isolated from the serum of one of the first two patients in this group contained both kappa (κ) and lambda (λ) chains, excluding the possibility that the IgE was monoclonal. In keeping with their markedly elevated total serum IgE concentrations, but in contradistinction to their negative histories of allergies, the patients had strongly positive immediate wheal and flare reactions to a number of inhalant, food, and pollen allergens as well as to *Candida*, staphylococcal, and other bacterial and fungal antigens (2). Schopfer and associates (23) and Dreskin and coworkers (22) reported detection of high titers of IgE antibodies to *S. aureus* antigens in hyper-IgE syndrome patients and proposed that such antibodies may have a pathogenic role in their special susceptibility to staphylococci. However, similar antibodies were found in patients with eczema and other atopic diseases who were not susceptible to abscess formation (24,25). Moreover, Schmitt and Ballet (26) and Berger and colleagues (27) found high titers of IgE antibodies to tetanus and *Candida* antigens in patients with the hyper-IgE syndrome, suggesting that such antibodies are a consequence of these patients' abnormal IgE regulation.

Cellular Immunity

Although delayed cutaneous anergy to ubiquitous antigens, such as *Candida* and streptokinase-streptodornase, was found in the first two patients described (1), this was a feature in only 50% of the patients tested. Blood lymphocytes from hyper-IgE patients were reported by Geha and associates (28) to be deficient in CD8+ T cells. However, our studies and other reports have revealed normal percentages of CD3+, CD4+, and CD8+ lymphocytes and IgE-bearing B lymphocytes. I found a deficiency of CD3+ T cells bearing the CD45RO isoform (memory T-cell phenotype) in all but 2 of 20 patients with the hyper-IgE syndrome evaluated for this characteristic (29). In mice, Luqman and colleagues (30) have shown this isoform to be present on T_H1 but not T_H2 cells. Whether these observations are relevant to these patients' abnormal anamnestic humoral and cellular responses or excessive IgE production is unknown.

In vitro studies of lymphocyte responses to the mitogens, phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM), have been normal in most patients with the hyper-IgE syndrome. By contrast, lymphoproliferative responses to the antigens *Candida albicans* and tetanus toxoid have been absent or low. Because antigen-induced proliferation of blood lymphocytes is primarily a T-cell response, mixed leukocyte culture (MLC) studies were conducted in nine patients. Six of nine patients' T lymphocytes did not show proliferation in MLC's containing mononuclear cells (MNCs) from one or more genetically different family members. By contrast, T lymphocytes from five of the six patients exhibiting unresponsiveness in intrafamilial MLC reactions proliferated vigorously when stimulated by unrelated subjects' MNCs. HLA-A and HLA-B locus typing done on nine of our patients and their first-degree relatives revealed no unusual antigens and no significant increase or decrease in any antigen frequencies (2).

Regulatory T-Cell Studies

Because of the apparent abnormal regulation of IgE synthesis in such patients, we and others have searched for evidence of a regulatory T-cell defect. The inability of PWM and other polyclonal B-cell activators, such as *Staphylococcus* Cowan 1 organisms to stimulate the production of IgE by human blood B cells in in vitro severely limited studies of human IgE regulation for more than a decade (31–33). However, we observed that Iscove's modified Dulbecco's medium (containing human transferrin, bovine insulin, serum albumin, oleic, palmitic

and linoleic acids, and 10% fetal calf serum [FCS]), supported the synthesis of nanogram quantities of IgE induced by very small concentrations (2.5–5 ng/mL) of IL-4 (31,32), thus providing a reproducibly positive *in vitro* system for assessing human IgE synthesis. Surprisingly, we found that B cells from hyper-IgE patients were relatively refractory to stimulation with interleukin 4 (IL-4) *in vitro* (Fig. 4); this suggested that they may have already been stimulated with excessive endogenous IL-4 *in vivo* (4). It has been difficult to prove, however, that patients with the hyper-IgE syndrome produce excessive IL-4, because IL-4 cannot be measured in body fluids as a result of its short half-life.

Del Prete and associates (34) reported defective interferon (IFN- γ) and tumor necrosis factor α (TNF- α) production by T cells from four patients with the hyper-IgE syndrome stimulated with mitogens *in vitro*. Paganelli and coworkers (35) reported severely reduced or undetectable IFN- γ in supernatants of MNCs from five hyper-IgE patients after stimulation with mitogens or phorbol esters and calcium ionophores. Del Prete and colleagues (34) found that the precursor frequency of T cells able to produce IFN- γ and TNF- α is markedly reduced when compared to controls but that the precursor frequency of T cells producing IL-4 is normal. Neither Vercelli and associates (36) nor our studies (unpublished results) found deficient IFN- γ production by hyper-IgE patients' T cells. Thus, there is as yet no clearly defined T-cell abnormality in the hyper-IgE syndrome. If such a deficiency is found, it is likely to be one of T_H1 cells or cytokines. However, abnormal IgE regulation does not explain the infection-susceptibility of these patients, because equally high levels of IgE are found in many patients with atopic dermatitis who have no susceptibility to abscess formation (37,38).

Chemotactic Studies

The defective polymorphonuclear (PMN) chemotaxis reported in some cases of the hyper-IgE syndrome was suggested to be the basis for the patients' infection susceptibility (39). Such chemotactic abnormalities, however, were found to be highly variable and infrequent. Indeed, Rebuck skin window studies in our first two patients showed normal PMN influx. Fluids from sites of infection in these patients contained numerous PMNs, and a brisk PMN leukocytosis occurs in the presence of infection. Only three of nine of our patients showed consistent depression of either PMN or mononuclear chemotaxis (one of each type and one with both) (2). In most patients with defective chemotaxis, repeated studies were normal. We found no correlation among chemotactic defects, medications, or the presence or absence of infec-

tion. The inconstancy of PMN chemotactic defects in this syndrome makes it highly unlikely that they are the basis of the extreme infection susceptibility seen in these patients.

Complement and Phagocytic Studies

Serum hemolytic complement activity has been normal in all patients tested. The first two patients had normal levels of each of the nine complement components. Their sera were also capable of generating C5a chemotactic factor normally.

PMN phagocytosis, metabolism, and killing have been normal in the author's patients and in others' studies. Because the clinical history in the hyper-IgE syndrome resembles that in CGD, phagocytic cell functional studies are often among the first performed. The granulocytes have normal phagocytic mechanisms, bacterial killing, and oxidative metabolism; the normal oxidative metabolism is indicated by normal respiratory burst studies.

Histologic sections of lymph nodes, spleen, and lung cysts obtained at surgery have demonstrated a striking degree of tissue eosinophilia. This was particularly true in the spleen of a boy who underwent splenectomy following trauma, and in the wall of a giant lung cyst excised from another patient (2). Thus, it is possible that eosinophils or their products, such as eosinophil major basic protein, play a role in the tissue destruction leading to formation pneumatoceles. Normal thymic architecture, including that of Hassall's corpuscles, was observed at the postmortem examination of one patient.

A summary of the major immunologic features of hyper-IgE cases is presented in Table 7.

Treatment

Because the primary defect in the hyper-IgE syndrome is unknown, no definitive therapy is available. The most successful treatment is lifelong continuous antistaphylococcal antibiotic therapy to prevent staphylococcal infections (40). If pneumatoceles persist for more than 6 mo, surgical excision should be strongly considered because the cysts may enlarge and compress adjacent normal lung, become infected with other organisms, or predispose to fungus-ball formation. Although abscesses are unusual when patients are receiving antistaphylococcal antibiotics regularly, their occurrence may necessitate incision and drainage.

Although immunostimulants (e.g., transfer factor, levamisole) had been used in some patients prior to their referral to our institution, none experienced any clinical benefit, and deterioration often occurred be-

Table 7
Major Immunologic Features of 40 Patients with Hyper-IgE Syndrome

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- Markedly elevated IgE; IgD also elevated in a majority; other immunoglobulins may be modestly low or elevated but are usually normal.
 - Positive immediate wheal and flare reactions to a variety of food, inhalant, bacterial, and fungal antigens.
 - Marked eosinophilia in blood and sputum.
 - Impaired anamnestic (IgG) antibody responses and poor responses to neonatogens.
 - Depressed cell-mediated immunity to ubiquitous antigens in vivo in half and to specific antigens in vitro in a majority. Responses to mitogens are normal, as are percentages of CD4 and CD8 lymphocyte subpopulations.
 - Abnormal intrafamilial mixed leukocyte responses.
 - Decreased proportion of CD45RO positive CD3+ T cells.
 - Highly variable chemotactic abnormalities (not present in most).
 - Impaired IgE production in response to IL-4 in vitro.
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cause of antibiotic discontinuance or delay of surgery. Levamisole was inferior to placebo in a controlled study in hyper-IgE patients (41).

Based on the observation by Coffman and Carty (42) that IFN- γ inhibits murine IL-4-induced IgE synthesis and on confirmation of these findings in humans (43), King and colleagues (44) administered recombinant human IFN- γ to five patients with the hyper-IgE syndrome in an open clinical trial in doses of 0.05 and 0.1 mg/M² three times weekly for 2 and 6 wk, respectively. There was a decline in the serum IgE level in two of five patients on the higher dose. Although no adverse effects were noted, there was no obvious clinical benefit.

Prognosis

If the hyper-IgE syndrome is recognized early in life and the patient is kept on chronic antistaphylococcal antibiotic therapy, the prognosis is good. Many such patients have reached maturity, indicating that the defect is compatible with prolonged survival. If the diagnosis is delayed, chronically infected giant pneumatoceles may develop and lung infections with agents other than staphylococci, such as *H. influenzae*, *Candida*, and *Aspergillus*, may occur. Putrid pyogenic secondary infections may develop within persistent pneumatoceles, and aspergilloma formation with severe hemoptysis may occur. The latter can lead to sudden death. In one of our patients, Hodgkin's disease developed at age 19. In another patient, Burkett's lymphoma developed at age 7 (45). These are the only known cases of malignancy in this syndrome. Ten of the 40 patients evaluated by the author are deceased, 6 from lung disease, 2 from lymphomas, 1 from a myocardial infarction,

and 1 from peritonitis that developed when his esophagogastric junction separated following an injury.

It is important to point out that, 29 years after the initial report of this syndrome (1), neither the precise host defect nor the fundamental biologic error underlying this condition has been found. The combination of elevated serum IgE and osteoporosis is also a feature of IL-4 transgenic mice, suggesting one possible mechanism for the co-existence of these two features (46). Such mice also had abnormalities in thymic selection (47). The hyper-IgE syndrome has recently been mapped to chromosome 4, but a candidate gene has not yet been identified (48). It is hoped that the resources available to the National Genome Research Institute will eventually permit identification of the faulty gene causing this syndrome.

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