

Antibody responses to protein, polysaccharide, and Φ X174 antigens in the hyperimmunoglobulinemia E (hyper-IgE) syndrome

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To investigate whether an underlying defect in antibody (Ab)-forming capacity could contribute to the infection susceptibility of patients with hyper-IgE syndrome, we evaluated 11 such patients for their responses to bacteriophage Φ X174 (Φ X174), diphtheria and tetanus toxoids, and pneumococcal (Pneumovax) and Hemophilus influenzae vaccines. Three of nine patients immunized with Φ X174 had normal primary and secondary Ab responses, five had accelerated declines in their titers after initially normal primary Ab responses and lower than normal secondary Ab responses, and two of the latter patients failed to switch normally from IgM to IgG Ab production. Only one of 10 patients tested had normal Ab responses to diphtheria toxoid, and postimmunization antitetanus titers were abnormally low in five of the 10 patients tested. Serum Abs to H. influenzae polyribose phosphate were protective in seven of the eight immunized patients. Five of the nine patients administered Pneumovax had poor Ab responses to at least one of the pneumococcal serotypes 7, 9, or 14. Abnormal antipolysaccharide responses did not correlate with IgG₂ deficiency. All patients responded with protective Ab levels to type 3. Thus, patients with hyper-IgE syndrome are heterogeneous with respect to their Ab-forming capacities. Ab deficiency may contribute to infection susceptibility in some of these patients. (J ALLERGY CLIN IMMUNOL 1991;87:803-11.)

Hyper-IgE syndrome is a rare immunodeficiency disorder characterized by recurrent severe staphylococcal abscesses of the skin, lower respiratory tract, and other sites from infancy.¹⁻³ With time, such patients develop recurrent or chronic infections with other bacteria and fungi but rarely with viral agents. Distinctive physical features of this syndrome are the almost uniform propensity of such individuals to form persistent pneumatoceles after staphylococcal pneumonias^{2, 4} and the presence of unexplained osteopenia.^{2,5} Despite extensive investigation, the only consistent laboratory abnormalities in these patients

Abbreviations used

Ab:	Antibody
Hyper-IgE:	Hyperimmunoglobulinemia E
HIB:	<i>Hemophilus influenzae</i> vaccine
Pneumovax:	Pneumococcal vaccine
DT:	Diphtheria and tetanus
Φ X174:	Bacteriophage Φ X174
PRP:	Polyribose phosphate
Pt:	Patient

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have been persistent marked elevations of serum IgE concentrations and of the number of blood eosinophils.^{2, 3} However, the primary cause of the excessive IgE production and its contribution to the recurrent infections and other problems in these patients has yet to be elucidated.

The purpose of this study was to investigate in a comprehensive manner whether an underlying abnormality in Ab-forming capacity is likely to account for the infection susceptibility of these patients. The rationale for this study was the original observation of poor anamnestic Ab responses despite normal serum

TABLE I. Clinical features of 11 patients with hyper-IgE syndrome

Pt No.	Age (yr)	Sites of infection	Organisms responsible	Pneumatocoeles	Serum IgE concentration
1	3	Skin Lungs Ears	<i>S. aureus</i> <i>H. influenzae</i>	Yes	5,800
2	5	Skin Lung Meninges Nails	<i>S. aureus</i> <i>Cryptococcus neoformans</i> <i>C. albicans</i>	Yes	6,200
3	12	Skin Lungs Nails Ears	<i>S. aureus</i> <i>Streptococcus pneumoniae</i> <i>C. albicans</i>	Yes	2,800
4	12	Skin Lungs Ears Sinuses	<i>S. aureus</i> <i>Streptococcus pneumoniae</i> <i>Pseudomonas</i>	Yes	24,000
5	14	Lungs	<i>S. aureus</i> <i>H. influenzae</i> <i>Pseudomonas</i> <i>Klebsiella</i>	Yes	5,150
6	18	Skin Lungs Ears Nails	<i>S. aureus</i> <i>H. influenzae</i> <i>Klebsiella</i> <i>C. albicans</i>	Yes	6,000
7	19	Skin Lungs Ears Sinuses Joints	<i>S. aureus</i> <i>H. influenzae</i> <i>Streptococcus pneumoniae</i> <i>C. albicans</i>	Yes	8,000
8	20	Skin Lungs Sinuses Eyes	<i>S. aureus</i>	Yes	7,000
9	27	Skin Lungs Ears Sinuses Nails	<i>S. aureus</i> <i>H. influenzae</i> <i>C. albicans</i>	Yes	890
10	28	Skin Lungs Sinuses	<i>S. aureus</i>	Yes	12,000
11	46	Skin Lungs Sinuses	<i>S. aureus</i> <i>Candida</i> <i>Mycobacterium avium-intracellulare</i>	Yes	870

IgG, IgA, and IgM concentrations in the first two patients described with this syndrome¹ and two recent studies of impaired Ab-forming capacities in such patients.^{6,7} Our results indicate that patients with hyper-

IgE syndrome are heterogeneous with respect to their ability to form Abs to a spectrum of vaccines containing protein, polysaccharide, and/or viral (phage) DNA antigens. Ab deficiency may contribute to the

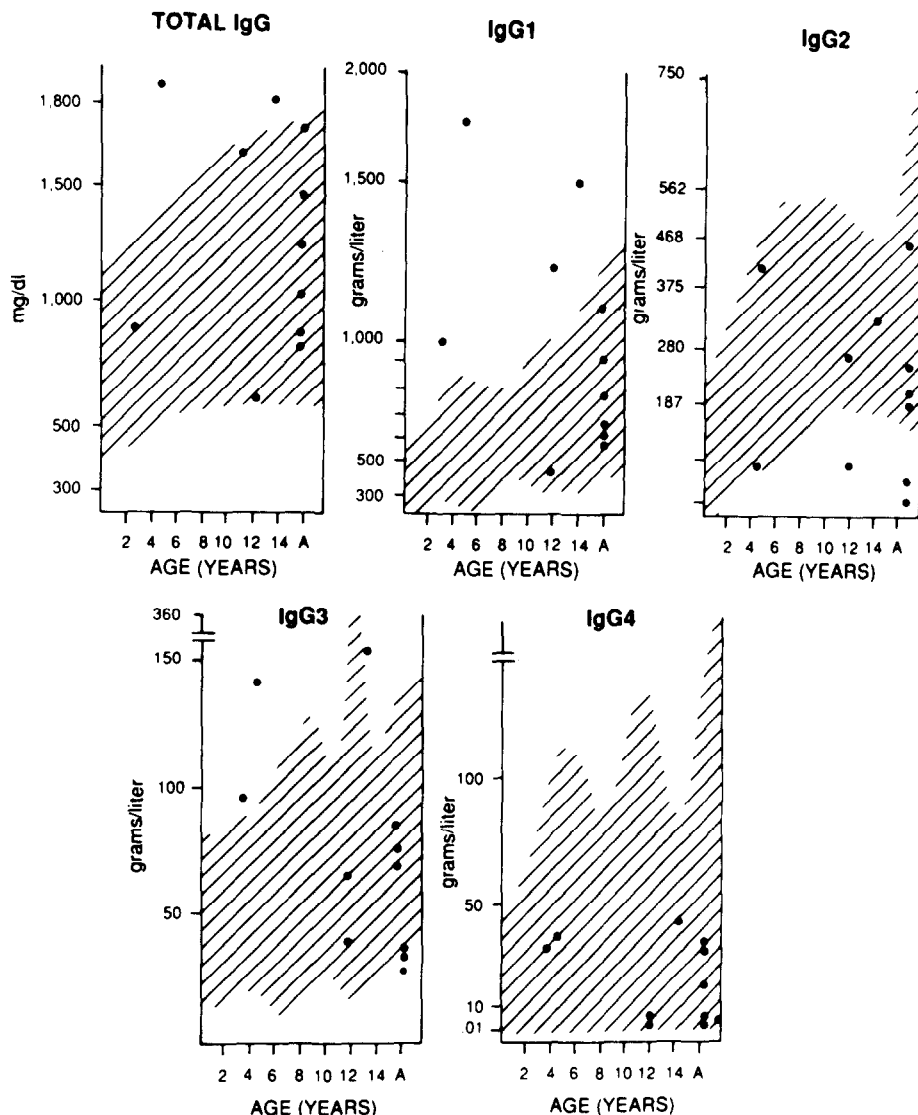


FIG. 1. Serum IgG and IgG subclass concentrations of 11 patients with hyper-IgE syndrome. *Hatched area* indicates normal values for age. (IgG values from Buckley RH et al.¹²; IgG subclass levels from Oxelius VA. *Acta Paediatr Scand* 1979;68:23-7.)

infection susceptibility of some patients with hyper-IgE syndrome.

MATERIAL AND METHODS

Subjects

Eleven patients with the classic features of hyper-IgE syndrome were studied (Table I). All studies reported were approved by the Duke University Committee on Human Investigations. Ten patients were male and one was female. Patients ranged in age from 3 to 49 years. All patients had increased serum IgE concentrations (890 to 24,000 IU/ml). All patients had lifelong histories of staphylococcal abscesses and recurrent staphylococcal pneumonia; 10 patients had developed persistent pneumatoceles. Six patients had recurrent or chronic sinusitis; two had had septic arthritis,

two had had sepsis (one pneumococcal; one staphylococcal), one patient had developed cryptococcal meningitis, one patient died of pulmonary infection with *Mycobacterium avium-intracellulare* (Pt 11), and one patient succumbed to a Burkitt's lymphoma (Pt 1).⁸ None of the patients was receiving immunoglobulin replacement therapy, nor had they received this therapy or any other blood product before the time of their evaluation.

Staphylococcus aureus was the primary pathogen causing these illnesses; however, the patients also had had serious infections with other organisms, including *Hemophilus influenzae*, *pseudomonas*, pneumococcus, *Klebsiella pneumoniae*, *M. avium-intracellulare*, and *Cryptococcus neoformans*. Cutaneous candidal infection was also a significant problem for many patients (Table I). Viral infections were not common.

TABLE II. Pre- and postimmunization Ab titers in 11 patients with hyper-IgE syndrome

Pt No.	Diphtheria*		Tetanust	
	Before	After	Before	After
1	Neg	Neg	Neg	1:243
2	1:6561	1:6561	1:6561	1:19683
3	Neg	1:27	1:243	1:729
4	Neg	—	1:81	—
5	Neg	Neg	1:27	1:531441
6	1:9	1:243	1:81	1:59049
7	Neg	1:3	Neg	1:27
8	Neg	Neg	1:2187	1:531441
9	Neg	Neg	1:3	1:243
10	Neg	Neg	1:6561	1:19683
11	1:27	1:243	1:2187	1:6561

—, Not done.

*Normal postimmunization titer >1:2000.

†Normal postimmunization titer >1:10,000.

‡Expressed as nanograms per milliliter; protective levels are 100 to 150 ng/ml.

§Expressed as nanograms per milliliter; protective levels are 200 to 300 ng/ml.

||Abnormal values are in **boldface**.

Vaccines

Adult patients received the following vaccines in the specified doses: 0.5 ml of HIB (Lederle Laboratories, Wayne, N.J.), 0.5 ml of Pneumovax (Merck Sharpe & Dohme, West Point, Pa.), and/or 0.5 ml of DT toxoid (Wyeth-Ayerst Laboratories, Philadelphia, Pa.).

Children received the same vaccines at doses appropriate for age. Patients received 0.02 ml/kg of primary and secondary Φ X174 immunizations, as outlined by Ochs et al.⁹

Serum immunoglobulin and IgG subclass concentrations

Serum IgD and IgE concentrations were determined by a modification of the double-Ab radioimmunoassay of Gleich et al.¹⁰ as previously described.¹¹ Serum IgG, IgA, and IgM were quantified by single radial immunodiffusion, with isotype-specific goat and rabbit antihuman immunoglobulin antisera, reference standards, and age-appropriate normal values developed in this laboratory.¹² Serum IgG subclass concentrations were determined by an ELISA (The Binding Site, Inc., San Diego, Calif.).

Assays for serum Abs

DT Ab titers were determined in this laboratory by tanned-cell hemagglutination, as previously described,¹³ 2 weeks after booster immunization with DT toxoid; all subjects had been immunized earlier with the recommended number of diphtheria-pertussis-tetanus immunizations. *H. influenzae* and pneumococcal Ab concentrations were measured by Specialty Laboratories, Inc. (Los

Angeles, Calif.), by an enzyme immunoassay and radioimmunoassays, respectively. Sera were collected 4 weeks after immunization with HIB and Pneumovax. Φ X174 Ab was titered by in vitro phage neutralization in the laboratory of Drs. Hans Ochs and Ralph Wedgwood at the University of Washington in Seattle.⁹

RESULTS

Serum immunoglobulin and IgG subclass concentrations

All patients had total serum IgG, IgG1, and IgG4 concentrations within or above the expected range for age (Fig. 1). Three patients (Pts 3, 7, and 9) had serum IgG2 concentrations significantly below the normal range for age. None had complete absence of IgG2. Two patients (Pts 6 and 11) had a minimal decrease in serum IgG3. Serum concentrations of IgA and IgM were within the normal range for age. Serum IgD concentrations were often elevated (data not presented).

Antibody responses to protein antigens

Only one (Pt 2) of 10 patients who received DT toxoid boosters responded with a normal rise in diphtheria Ab titers 2 weeks later (Table II; Fig. 2). Five patients (Pts 1, 3, 7, 9, and 11) also failed to produce antitetanus Ab, normally (Table II; Fig. 2), one of these (Pt 1) patients despite three DT toxoid booster immunizations.

Antigens									
<i>H. influenzae</i> †		Pneumococcal (serotype)§							
		3		7		9		14	
Before	After	Before	After	Before	After	Before	After	Before	After
—	75	—	—	—	—	—	—	—	—
—	—	—	>2000	—	151	—	355	—	139
—	1049	109	2000	42	77	43	139	33	117
>5000	>5000	82	387	40	363	106	764	89	81
Neg	>5000	—	1200	—	711	—	407	—	1270
3640	3740	129	1152	38	75	33	53	710	523
>5000	>5000	574	>2000	770	1190	77	273	189	245
—	—	—	—	—	—	—	—	—	—
—	—	—	883	—	504	—	226	—	134
1872	1716	550	>2000	413	1615	380	878	198	210
3640	>5000	60	>2000	169	866	101	>2000	>2000	>2000

Ab responses to polysaccharide antigens

Five (Pts 2, 3, 4, 6, and 9) of the nine patients failed to develop protective Ab concentrations to one or more of the pneumococcal polysaccharide serotypes 7, 9, and/or 14 after Pneumovax immunization (Table II; Fig. 3). Two of these five patients responded poorly to types 7 and 9, and two additional patients of these five had low Ab responses to type 14 only. Most patients had excellent responses to type 3 pneumococcal polysaccharide, considered the most immunogenic serotype. However, one patient (Pt 3) required a booster Pneumovax immunization to induce protective levels of type 3 Ab. He also failed to respond to the other serotypes.

Of the eight patients who received HIB, six (Pts 1, 3, 5, 6, 10, and 11) received unconjugated HIB. Five of these six patients who made Ab responses to PRP thus made true responses to the polysaccharide antigen (Table II; Fig. 3). One of the six (Pt 7) patients failed to generate a protective level. Two of the six (Pts 6 and 10) patients had protective preimmunization anti-PRP Ab titers; however, they failed to increase their response after immunization. Both patients (Pts 4 and 7) who received conjugated HIB produced Ab to PRP, normally.

Correlation of IgG2 concentration and Ab responses

IgG2 subclass concentrations did not predict abnormal Ab responses. Patients with normal and abnormal IgG2 concentrations failed to respond to both protein (data not presented) and polysaccharide anti-

gens (Fig. 4). The only patients in our series who did not respond to unconjugated HIB (Pt 1) with protective levels or failed to increase their Ab titers after immunization (Pts 6 and 10) with HIB had normal serum IgG2 concentrations. Similarly, three (Pts 2, 4, and 6) of the six patients with normal IgG2 concentrations failed to generate a protective Ab response to one or more of the pneumococcal serotypes 7, 9, and/or 14 after immunization with Pneumovax.

Ab responses to Φ X174

Immunization of nine patients with Φ X174 resulted in a heterogeneous Ab response pattern (Table III; Fig. 5). All patients cleared Φ X174, normally. Five (Pts 1, 2, 4, 8, and 9) patients had an atypical pattern characterized by a normal primary response at 1 week but an accelerated decline in anti- Φ X174 Ab during the following 3 weeks; all of these five patients also had poor secondary Ab responses. Two of the latter (Pts 1 and 2) patients also failed to switch normally from IgM to IgG antibody, producing only 17% and 1% anti- Φ X174 IgG antibody, respectively, after the secondary immunization (Table III). One patient (Pt 6) had a normal Φ X174 antibody titer measured 3 months after his primary immunization (Kv, 5.62). Although serum samples were not collected at the specified time after immunization, this late post-immunization Ab value, as well as a normal secondary Ab response, suggests that he may have had a normal primary response. Two patients (Pts 3 and 7) had normal primary and secondary Ab responses and normal isotype switching. One other patient (Pt 11) had

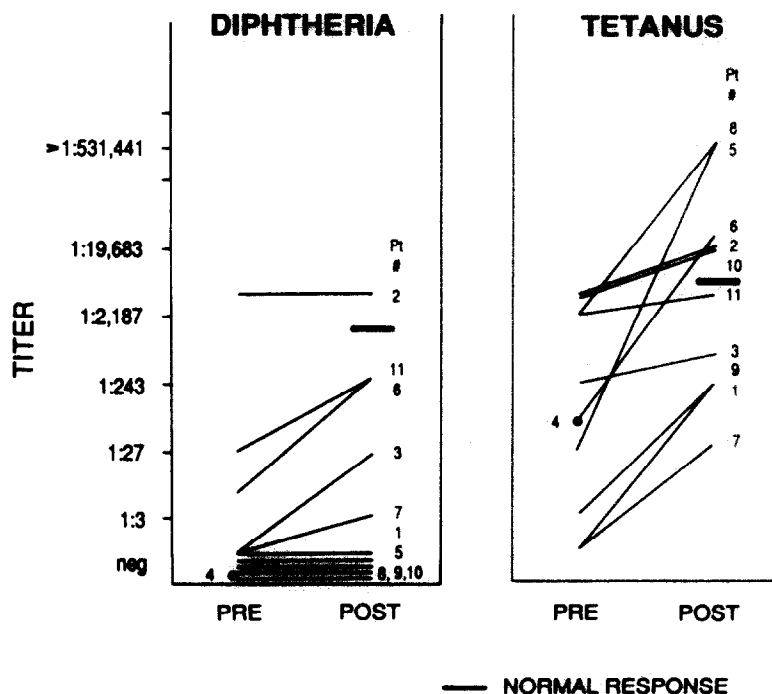


FIG. 2. Ab responses of patients to immunization with DT toxoid. Each line represents a single patient's pre- to postimmunization rise in antibody titer; normal tanned cell hemagglutination Ab titers after immunization (—): diphtheria, $>1:2000$; tetanus, $>1:10,000$.

TABLE III. Primary and secondary Ab responses to ϕ X174

Pt No.	Peak Kv		% IgG
	Primary	Secondary	
1	9.87*	79.3 †	17
2	6.86*	6.5	1
3	197.00	651.0	30.2
4	8.70*	159.0	39
6	—	1533.0	68
7	19.80	153.0	93
8	10.00*	9.9	68
9	57.00*	50.5	53
11	480.00	—	—

—, Data not available.

*Kv normal at 1 week and then decreased.

†Abnormal values are in **boldface**.

‡Borderline.

an increased primary response. She died before completion of the secondary immunization series.

DISCUSSION

The precise host defect leading to recurrent staphylococcal abscesses in patients with hyper-IgE syndrome is unknown. During the past two decades, several highly variable immunologic aberrations have been reported in patients with this condition, including

high titers of IgE Abs to staphylococcal antigens,¹⁴⁻¹⁵ a deficiency of suppressor T cells,¹⁶ and chemotactic defects.¹⁷⁻¹⁹ In most cases, however, no deficiency of suppressor T cells has been found. Chemotactic abnormalities have rarely been found and have been inconsistent, even in the same patient.²⁻³ Lymphocyte phenotypes and responsiveness to mitogens have usually been normal.² Approximately one half of patients have had decreased delayed hypersensitivity responses

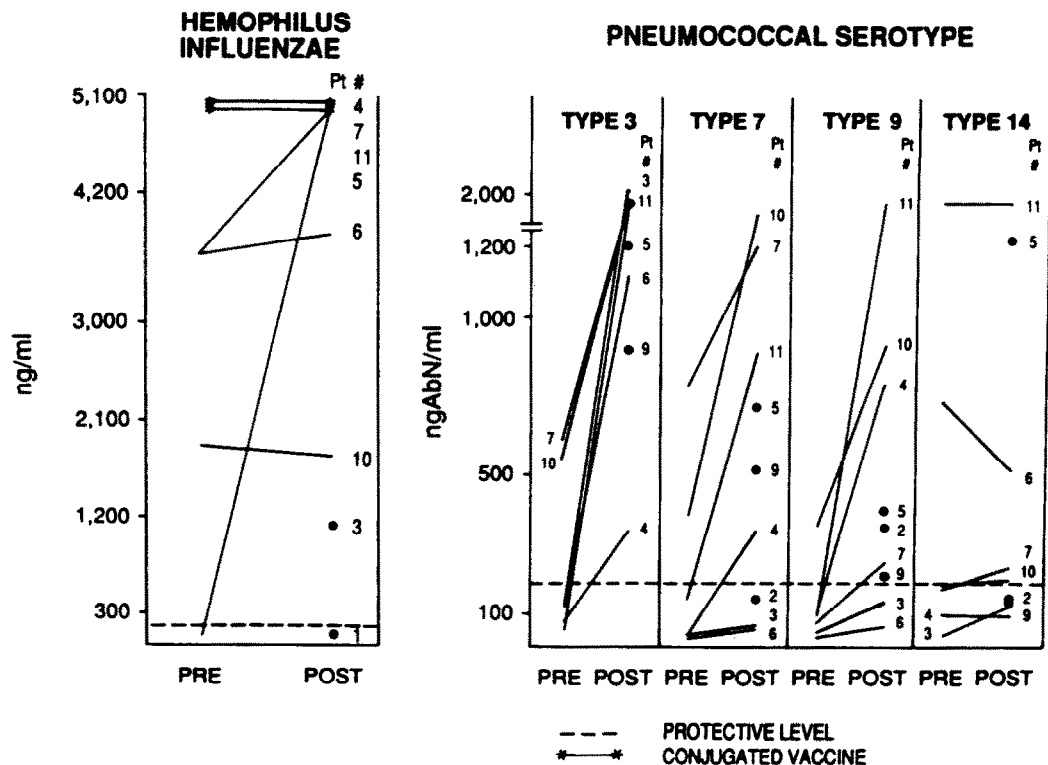


FIG. 3. Ab responses of patients to immunization with Hib and Pneumovax. Each line represents a single patient's pre- to postimmunization rise in Ab titer. Isolated dots (●) represent patients who had only postimmunization titers; protective Ab concentration (---): Hib, >100 to 150 ng/ml; Pneumovax, >200 to 300 ng/ml.

to intradermal testing with *Candida* and tetanus antigens and/or poor lymphocyte proliferative responses to antigens in vitro.²

Deficient Ab responses to DT toxoids,^{1,7} *H. influenzae*,⁷ and *S. aureus* teichoic acid^{6,7} have been previously reported in patients with hyper-IgE syndrome. Four of the seven patients with hyper-IgE, evaluated by Leung et al.,⁷ also had low serum IgG2 concentrations. Dreskin et al.⁶ found patients with hyper-IgE to have an excess of anti-*S. aureus* IgE and IgM without an excess of anti-*S. aureus* IgG. Those same patients had a deficiency of serum and salivary anti-*S. aureus* IgA. In those patients, the incidence of infection at mucosal surfaces and adjacent lymph nodes was inversely proportional to the quantity of serum anti-*S. aureus* IgA and related to the elevated quantities of serum anti-*S. aureus* IgE, total serum IgE, and IgD.⁶ These observations, in their aggregate, have suggested that patients with the hyper-IgE syndrome may have one or more humoral immunodeficiencies. However, none of the abnormalities reported has been present in all such patients.

This evaluation was designed to explore in a comprehensive manner the question of whether de-

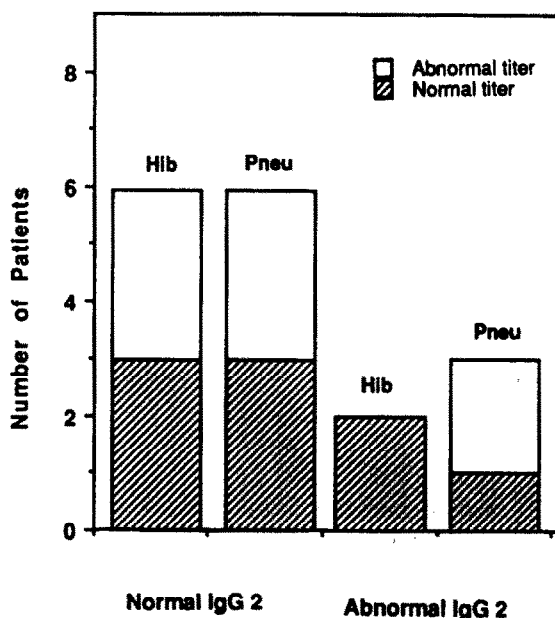


FIG. 4. Comparison of serum IgG2 concentration and Ab response to immunization with polysaccharide antigens, Hib, and Pneumovax. Serum IgG2 concentration was unable to predict which patients would have normal (▨) or abnormal (□) Ab concentrations after immunization.

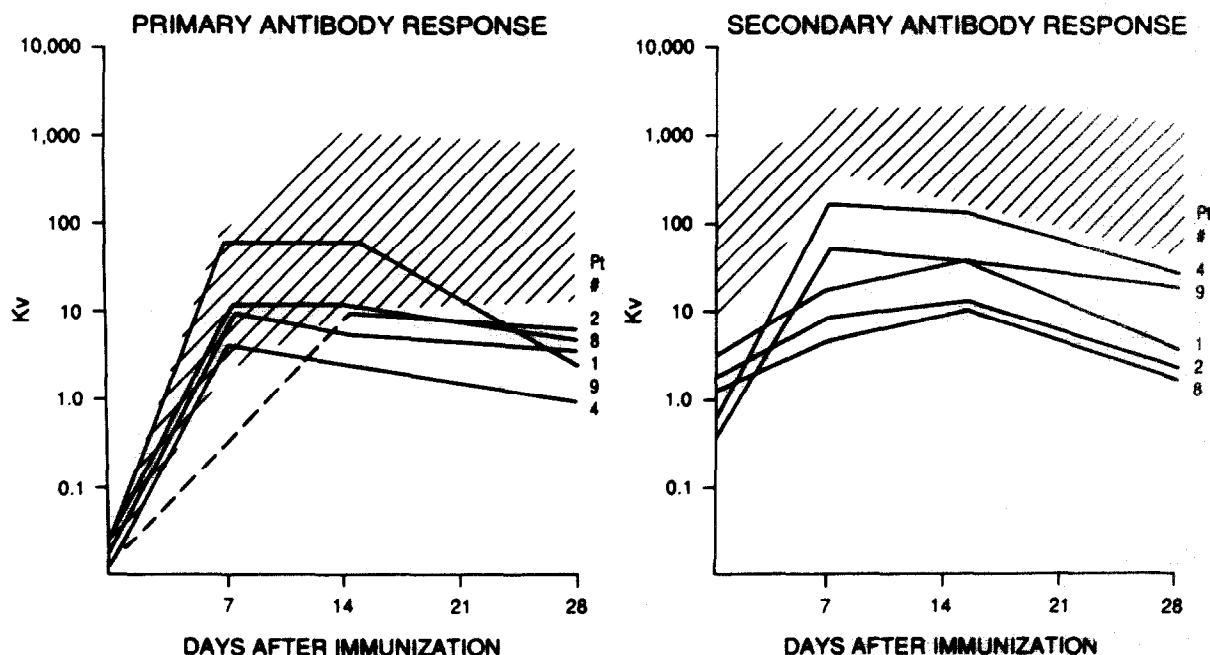


FIG. 5. Atypical anti- Φ X174 Ab responses in five patients with hyper-IgE syndrome; sample not available, data extrapolated (—). Hatched area indicates normal values. (From Ochs et al.⁹)

fective humoral immune responsiveness might account for the infection susceptibility of a group of well-characterized patients with this syndrome. We chose protein, polysaccharide, and viral (phage) DNA as immunogens. Results of Φ X174 immunization have not been previously reported in patients with hyper-IgE syndrome. We selected this immunogen because it allowed us to evaluate primary and secondary Ab responses to a neoantigen in these patients. Φ X174 does not infect mammalian cells and thus may not be processed and presented to human T and B cells in exactly the same way that viruses, which infect human cells, are presented. However, it is known to be an extremely potent immunogen, even in premature infants.⁹ It also permitted us to examine the capacities of our patients to switch from IgM Ab production after primary immunization to IgG Ab production in the secondary immune response. Five of the nine immunized patients had abnormal responses to Φ X174. Although these five patients had a normal initial primary response, they experienced rapid declines in Ab titers. None of the five patients had quantitatively normal secondary Ab responses. Two patients failed to switch from IgM to IgG antiphage Ab production after the second immunization. These deficient secondary Ab responses suggest that patients with hyper-IgE syndrome may have difficulty with immunologic memory. Our findings extend and confirm findings of ours¹ and other investigators^{6,7} that defective Ab formation may be a feature of some patients

with the hyper-IgE syndrome. However, in our study, there was no uniform pattern to the Ab deficiencies noted. No patient had completely normal Ab responses. Three patients (Pts 1, 3, and 9) failed to generate appropriate Ab titers to both protein and polysaccharide antigens; two of these (Pts 1 and 9) patients also had an abnormal or atypical response to Φ X174. Of the three patients with normal Ab response to Φ X174 (Pts 3, 6, and 7), one patient (Pt 3) failed to generate Abs after tetanus (protein) immunization, and two patients (Pts 3 and 6) failed to respond with protective Ab concentrations to one or more of the pneumococcal serotypes 7, 9, and/or 14 after Pneumovax (polysaccharide) immunization. Our demonstrated lack of correlation of IgG2 subclass concentration and antipolysaccharide Ab responses emphasizes the lack of value of measuring IgG subclass concentrations alone in determining the immune status of these or any other patients. Clearly, Ab responses after immunization provide much more relevant information.

Thus, patients with the hyper-IgE syndrome appear heterogeneous with respect to their ability to form Abs. Impaired Ab-forming capacity may contribute to infection susceptibility in some patients, but not all, of these patients. All patients with hyper-IgE should have evaluation of their humoral immune status to include not only total serum immunoglobulins and IgG subclasses but, more importantly, Ab responses to both protein and polysaccharide antigens. If sig-

nificant Ab deficiency is present, the patient may benefit from monthly treatment with intravenous immunoglobulin.

Like many of the other immunologic abnormalities reported in patients with hyper-IgE syndrome, the pattern of impairment in Ab-forming capacity is not consistent. However, these defects in antigen-specific humoral responses could be related to the previously noted² abnormal antigen-specific lymphocyte proliferative responses in many of these patients. These observations, coupled with the uniform marked elevations in serum IgE and eosinophilia in these patients, make it attractive to postulate that the primary lesion in such patients may be in one or more subpopulations of helper T cells.

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