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Impaired anti-pneumococcal antibody response in patients with AIDS-related persistent generalized lymphadenopathy

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SUMMARY

Pre- and post-immunization serum antibodies to pneumococcal polysaccharides (PPS) and tetanus toxoid (TT) were measured in 25 patients with persistent generalized lymphadenopathy and serum antibodies to the human immunodeficiency virus (HIV). The increase in post-immunization anti-PPS antibodies was lower than 40% in 16/25 patients. Isotype analysis indicated that the IgM, IgA, IgG2, but not the IgG1 antibody responses were lower in patients that in healthy controls, whereas pre-immunization values were similar. For TT, no difference was found between the patients and the healthy group in total and IgG1 antibody response whereas IgG4 response was lower in patients. No significant association was found between the defect in anti-PPS antibody response and associated thrush or constitutional symptoms or other immunological parameters. These findings suggest that defective response to a thymo-independent polysaccharide antigen is a distinctive consequence of HIV infection.

Keywords AIDS-related lymphadenopathy pneumococcal polysaccharides antibody response

INTRODUCTION

Infection with the human immunodeficiency virus (HIV) is associated with a variety of disorders. The acquired immunodeficiency syndrome (AIDS) includes the more severe manifestations such as opportunistic infections and malignancies (CDC, 1985), and profound immunological abnormalities (Seligmann *et al.*, 1984). Persistent generalized lymphadenopathy (PGL) may be an isolated manifestation, or alternatively be associated with other systemic or local symptoms (CDC 1983; Metroka *et al.*, 1983; Ioachim, Lerner & Tapper, 1983; Abrams *et al.*, 1984). In these cases, the major concern is the possible evolution to full blown AIDS. In this context, we have recently conducted a prospective study in a large series of patients with PGL to identify immunological abnormalities of prognostic value. In addition to other immunological parameters, antigen specific immune responses *in vivo* and *in vitro* were investigated. These included, in a subgroup of patients, both T-independent and T-dependent responses to antigenic challenge *in vivo* (i.e. to pneumococcal polysaccharides (PPS) and tetanus toxoid (TT) respectively). Our data show that the response to

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PPS is abnormal in PGL patients who have no other major AIDS-associated immunologic abnormalities.

MATERIALS AND METHODS

Patients. The 25 patients presented in this paper belong to a group of 147 patients with AIDS-related PGL who were enrolled in a prospective study. Informed consent was obtained from all participants. The tests were done at enrolment.

Immunological evaluation. Immunization with one dose of TT (IPAD T, Institut Pasteur, 30 IU/dose) was performed on the first day of the study (day 0). On the same day, an initial immunological evaluation was done, which included delayed cutaneous hypersensitivity responses, determination of serum immunoglobulin (Ig) levels, lymphocyte membrane phenotypes, proliferative responses to mitogens and antigens, and pre-immunization antibody determinations. Thirty to 60 days later, antitetanus antibody levels and lymphocyte responses to TT *in vitro* were measured, and patients were immunized with a 14 valent antipneumococcal vaccine (Imovax-Pneumo 14, Institut Mérieux). Twenty-four to 60 days later, serum was obtained to determine the level of antipneumococcal antibody. Due to practical difficulties 3/25 patients studied for PPS responses were not completely studied for TT (Nos 13, 18, and 23, see Table 1); for this reason, TT antibody data from three additional randomly chosen patients with PGL were included for statistical analysis of anti-TT antibody responses only.

Control healthy adults in which anti-TT antibody responses were studied in parallel, consisted of twelve 18–50 year old vaccinees studied on day 0 and days 21–35 after booster immunization. Two control groups were studied for anti-PPS antibodies: the first consisted of five non-homosexual healthy adults; the second of five healthy male homosexuals, without detectable anti-HIV antibodies at the time of study. Since no statistical difference was detected between the two groups for anti-PPS antibody responses (for total antibodies, and antibodies of the different isotypes, $P > 0{\cdot}5$), data from both groups were pooled into one control group for statistical analysis.

Measurement and isotype characterization of anti-pneumococcal and anti-tetanus serum antibodies. Antibody levels were determined using an indirect enzyme-linked immunoassay (ELISA). Plates were coated with either pneumococcal polysaccharides (14-valent Imovax-Pneumo 14) (5 μg/ml for total and IgA antibody determination, 10 μg/ml for IgM and IgG subclass determination), or TT (2 μg/ml solution, 1050 Lf/mg) (Institut Pasteur), diluted in pH 9·6, 0·1 M carbonate-bicarbonate buffer. After saturating with PBS-Tween, 3% bovine serum albumin (BSA) and washing, 100 μl of each serum dilution in BSA PBS-Tween were incubated in duplicate (4 h at room temperature): (a) total antibodies were detected using beta-galactosidase-coupled sheep $F(ab)_2$ fragments to human heavy and light chains (Amersham International, Amersham, UK; 1:500, incubated for 3 h, 37°C), diluted in 0·5% BSA, 10 mM $MgCl_2$, 1 mM 2-mercaptoethanol PBS-Tween; (b) IgM antibodies were detected using a purified mouse antihuman μ-chain monoclonal (BPA 2, 1:1000, incubated overnight, 4°C) (a kind gift of Dr Guglielmi); (c) IgG antibodies belonging to the IgG1, IgG2, IgG3 and IgG4 subclasses were measured using mouse monoclonal antibodies to human subclasses (ascite fluids; 1:2000, 18 h, 4°C): antiγi (BAM 15, clone NL16); antiγ2 (BAM10, clone GOM1); antiγ3 (BAM 08, clone ZG4); antiγ4 (BAM11, clone RJ4), all obtained from Seward, Bedford, UK) (Lowe *et al.*, 1982; Persson, Hammarstroem & Smith, 1985). Monoclonal binding was measured with sheep anti-mouse Ig-galactosidase linked $F(ab)'_2$ IgG fragments (Amersham, 1:250, 3 h, 37°C). After adding ortho-nitrophenyl-galactopyranoside (0·9 mg/ml, 10 mM $MgCl_2$ (1 mM 2-mercaptoethanol PBS-Tween) at 37°C, and, 30 min later, 50 μl 1M Na_2Co_3, optical density was measured at 405 nm; (d) antibodies of the IgA class were detected using alkaline-phosphatase-coupled goat $F(ab)_2'$ fragments to humanαheavy Ig chain (Tago, Burlingame, CA, USA, 1:2000, 3 h, 37°C), diluted in 0·5% BSA, PBS-Tween, and revealed using para-nitrophenylphosphate (1 mg/ml) in a 10% diethanolamine buffer, pH 9·8 (30 min, 37°C); the reaction was stopped with 100 μl 3 M NaOH.

Antibodies in experimental samples were evaluated by comparing experimental OD values for three dilutions with standard curves obtained from reference samples run on the same ELISA plates

Table 1. Pre-and post-immunization serum antibodies to PPS and TT in 25 PGL patients

	T T(IU/ml)		PPS (AU/ml)	
Patients	Before	After	Before	After
1	0·25	1·45	20	45
2	0·05	0·05	17	26
3	0·15	0·15	66	60
4	2·5	3·5	25	57
5	2·5	2·55	138	160
6	0·25	3·2	61	67
7	0·05	0·5	46	57
8	2·9	3·0	43	45
9	0·4	1·9	55	41
10	0·05	1·9	30	27
11	0·05	0·85	37	41
12	0·05	1·50	42	143
13	ND	1·45	3	2
14	0·20	1·75	10	5
15	0·35	8·0	4	1
16	2·40	32·0	19	11
17	0·1	2·40	3	2
18	ND	ND	15	36
19	0·45	0·10	86	26
20	0·20	6·10	33	45
21	2·00	2·10	15	12
22	0·15	0·15	4	17
23	ND	4·2	17	17
24	0·10	0·95	44	50
25	1·50	14·7	45	62

with (a) a pool of 5 high titre anti-PPS sera from healthy individuals recently immunized; (b) an anti-TT IgM rich serum for IgM antibodies to TT; (c) a standard Ig preparation of known antitoxic activity (CNTS, 125 IU/ml) for total and IgG anti-TT antibody evaluation. Experimental concentrations were calculated for OD in the quasi-linear portion of the interpolated sigmoid standard semi-log curve constructed from dilutions of standard preparations. For total anti-TT antibodies, results were expressed in IU by direct reference to the standard preparation. For other antibody estimations, the OD values of serial dilutions of standard preparations added in antigen-coated wells were compared with OD values generated by interacting the same anti-Ig antibodies with known amounts of Ig coated to plates (i.e. dilutions of a pool of sera from 100 healthy adults in which IgM, IgA and IgG levels; and IgG1, IgG2, IgG3 and IgG4 levels had been measured in a Mancini technique, and in a competitive immunoenzymatic assay, respectively; Aucouturier *et al.*, 1984). In preliminary experiments, coating efficiency to microplates of Ig (i.e. known concentrations of Ig present in dilutions of the pool) was assessed in an antibody competition assay: anti-Ig antibodies which had first reacted with Ig were transferred into Ig-coated microplates, in which the remaining free anti-Ig antibody was allowed to bind to coated Ig. Coating efficiency of Ig to plates was estimated by comparing the amounts of anti-Ig bound to plates with and without addition of Ig in the first stage of the reaction. From experiments performed with several anti-Ig antibodies and coated Ig ranging from 20 ng to 12 μg per well, an average coating efficiency of 37% ($\pm$ 1 s.d. = 5%) was calculated. Since ELISA results may be influenced by several additional parameters, such as antibody affinities (Steward & Lew, 1985), serum concentrations of antibodies estimated in μg/ml using this method were expressed as arbitrary units (one AU = 1 μg/ml).

Measurement of serum immunoglobulin levels and of blood lymphocyte subsets. Serum Ig levels

were quantified with the Mancini technique. T3, T4 and $T8^+$ cells were counted using monoclonal antibodies in an indirect immunofluorescence assay.

In vivo *and* in vitro *T-dependent lymphocyte responses.* Sensitization and secondary response to dinitrochlorobenzene were studied as previously described (Preud'homme & Depuy, 1968). Skin tests with phytohaemagglutinin and antigens were performed on the forearm skin by intracutaneous injection of 0·1 ml of phytohaemagglutinin (10 μg/ml) PHA HA (Welcome, Beckenham), tuberculin (TUB) (10 IU/0·1 ml, Institut Pasteur), candidin (CDD) (1:1000, Institut Pasteur). Forty-eight hours later, a mean size of induration of over 3 mm was considered positive. Proliferative lymphocyte responses were measured to: (a) phytohaemagglutinin, PHA-P (Difco), 1:600 of stock solution; (b) pokeweed mitogen (Lederle) 1:30 of stock solution; (c) concanavalin A (Sigma; 10 μg/ml), (d) TT (1050 Lf/mg); streptokinase-dornase (SKSD, Varidase (Lederle) 100 μg/ml); (f) CDD, 1:4000; Cytomegalovirus antigen (a kind gift from Dr Harzic, 3 μg/ml); (g) TUB PPD (Institut Mérieux; 250 IU/ml). Results are expressed as Δ ct/min/$0{\cdot}2 \times 10^6$ cells i.e. (incorporation (ct/min) in stimulated cultures) minus spontaneous incorporation (ct/min) in unstimulated cultures).

Statistical analysis. Antibody responses were measured by taking the mean differences of the logarithms of pre- and post-immunization values (equivalent to the logarithms of the geometric mean), assuming a normal distribution in lin-log scale, a feature generally observed for serum antibody distributions (Siber & Ransil, 1983). Variance comparisons between patients and healthy groups and evaluation of the significance of correlations were performed using Student's *t*-tests and *r* coefficients, respectively.

RESULTS

Clinical features. The age of patients ranged from 20 to 54 years (mean: 30·7 years). The time interval between the first clinical manifestations and the immunological study ranged from 3 to 48 months (mean: 12·5). Twenty-two out of 25 patients were homosexual or bisexual males (patients No. 8, and 24 in Tables 1 and 2 were heterosexual males and patient No. 5 was a woman). Two patients (Nos. 9 and 24) were of Caribbean, and three (Nos 5, 10, 19) of North-African descent. None was addicted to intravenous drugs. Two (Nos 5 and 18) were contacts of patients with AIDS. In addition to lymphadenopathy, 6/25 patients exhibited oral thrush, or systemic constitutional symptoms, including intermittent or continuous fever, debilitating fatigue and persistent diarrhoea (Nos 6 and 21; and Nos 7, 17, 21, and 23, respectively). One (No. 20) had a thrombocytopenia. All patients had anti-HIV serum antibodies (titres over 1:40 in ELISA (Brun-Vézinet *et al.*, 1984). None of the patients was receiving therapy during the time of the study. Since the study, one of the patients (No. 7) has progressed to AIDS within a year of the first visit.

Anti-pneumococcal antibodies. Preimmunization anti-pneumococcal antibody levels were not significantly different in the PGL and the healthy group (geometric mean of total antibodies: 29·3 AU/ml in patients, and 50·8 AU/ml in controls; ($P > 0{\cdot}1$). Only 9/25 patients showed a post-immunization increase in anti-PPS antibodies over 40% of the initial value (Table 1), whereas in controls, 10/10 had a post-immunization increase over 40%. In several patients, a trend to a post-immunization decrease in anti-PPS antibody values was observed (see for instance No. 19). The rise in geometric mean-fold (Fig. 1) in PGL patients (1·09-fold) was significantly lower than that of controls (2·60-fold) ($P < 0{\cdot}001$). The post-immunization increase of anti-PPs antibodies was due predominantly to IgM, IgA and IgG2 isotypes (Fig. 1). Preimmunization geometric mean values (AU/ml) for anti-PPS IgM, IgG1, IgG2, IgG3 and IgG4 antibodies were 8·4, 7·3,6·7, 12·1, 1·3, < 1; and 4·7, 5·3, 8·3, 25·6, 1·1, and < 1 in the PGL and control group respectively. In PGL patients, mean increases were lower than in the control group for IgM, IgA and IgG2 isotypes ($P < 0{\cdot}002$; $P < 0{\cdot}002$; and $P < 0{\cdot}05$, respectively) whereas the difference was not significant for IgG1 ($P > 0{\cdot}5$).

Antibody response to tetanus toxoid. Due to differences in the time interval between previous immunization, no valid conclusion could be drawn from the pre-immunization values for TT (geometric means: 0·24 IU/ml and 2·5 IU/ml in the patients and the normals, respectively). Interestingly, a marked heterogeneity in anti-TT responses was observed in the PGL group; 6/26

Table 2. Blood lymphocyte counts, serum immunoglobulin levels, delayed skin responses to DCNB and *in vitro* proliferative lymphocyte responses to antigens in patients with PGL.

Patient	Blood lymphocyte counts (per mm3)			Serum imunoglobulins (mg/ml)			Delayed type cutaneous response to DCNB	*In vitro* proliferative lymphocyte response to antigens Δ ct/min/0·2 × 10^6 cells)				
	T3	T4	T8	IgG	IgA	IgM		TT*	TUB	CMV	CDD	SKSD
1	2089	1020	1117	16·2	1·95	1·7	ND	ND	58725	800	119090	1640
2	1170	150	945	26·2	5·7	2·6	–	30	30	30	822	ND
3	1156	935	272	7·0	1·2	2·3	–	56019	20092	ND	72531	90100
4	2315	781	1478	26·2	1·5	1·8	+	45890	11457	790	76945	177021
5	1368	900	378	20·4	1·5	3·1	+	4998	3174	30	103068	55393
6	1894	947	768	10·7	3·6	2·0	+	833	76995	30	44958	108635
7	1710	270	1380	21·9	5·2	3·3	–	50	30	2698	30	7192
8	2077	1488	674	17·1	1·1	2·8	ND	13712	7936	30	3405	548
9	1398	828	552	22·4	1·6	2·8	+	40517	55956	916	90775	28545
10	1759	1212	523	11·3	1·0	2·2	+	ND	37613	23880	38413	1700
11	1544	633	891	16·0	1·7	1·7	+	3297	17735	1258	10014	40956
12	5330	1460	3870	36·5	1·6	6·3	ND	5276	3973	ND	19886	1559
13	1294	405	858	26·2	1·0	1·0	ND	1300	30	2090	16013	2090
14	1357	458	863	13·7	1·1	0·77	+	3780	76402	35081	32960	16585
15	899	365	562	15·6	3·0	1·75	ND	2233	19072	6830	101457	110785
16	2093	807	1226	—	1·9	3·2	+	2973	1800	19161	25110	24238
17	1610	680	920	23·8	2·5	1·6	–	16583	10725	13776	50140	735
18	1650	1000	586	16·0	2·7	1·85	+	30270	7930	80276	80494	56445
19	1452	550	990	13·7	3·1	3·1	+	5360	51390	1205	19525	ND
20	921	545	315	16·9	3·4	2·0	ND	54278	2985	ND	45715	23990
21	2050	725	1000	14·0	1·4	1·8	ND	17738	33730	2433	78000	14472
22	839	524	341	11·1	2·4	2·7	+	400	84900	2215	40125	7942
23	1300	455	937	17·0	6·4	3·0	ND	1555	10905	ND	43010	2736
24	1716	330	880	—	7·7	6·5	–	30	64695	ND	15563	125
25	728	119	549	21·0	2·4	2·1	–	ND	4190	155	551	ND
Mean				17·7	2·8	2·4						
1 s.d.				5·4	1·8	1·1						

* Measured following booster immunization.
ND, not done
† Presence of a monoclonal component.

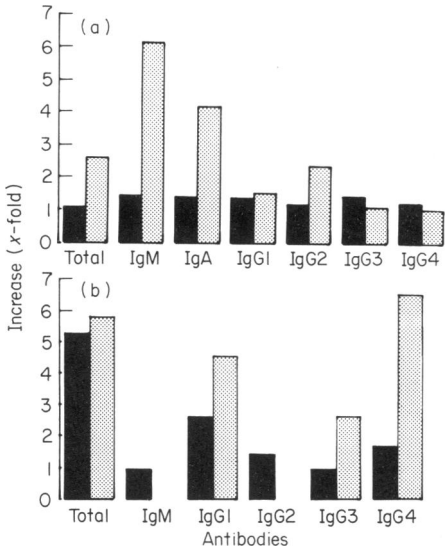

Fig. 1. Post-immunization increase of antibody levels in patients with PGL and healthy control individuals. (■) Patients with PGL; (▨) healthy control individuals. Results expressed as post-immunization/pre-immunization rise of the geometric mean serum antibody level.

patients showed a post-immunization increase of anti-TT antibodies of under 10%, whereas the increase averaged 460% in controls. However, using geometric means (thus assuming a unimodal distribution for both groups), no difference in post-immunization was found between the PGL and the control groups (5·25-fold versus 5·8-fold respectively; $P > 0{\cdot}5$). For IgM anti-TT antibodies, no increase was detected in the PGL group and no comparison with a normal group was performed. The post-immunization IgG anti-TT antibodies in PGL patients, like controls, were predominantly of the IgG1 subclass (1·42-fold increase versus 4·5-fold from pre-immunization values (AU/ml) of 9·6 and 46·3 respectively, Fig. 1); this difference was not significant ($P > 0{\cdot}5$). For IgG4, geometric mean pre-immunization level was 1·1 and 4·8 in the PGL and normal group respectively. The geometric mean rise was lower in patients than in normals (Fig. 1) ($P < 0{\cdot}002$). There was no correlation in patients between total antibodies or antibodies of all isotypes with anti-PPS and anti-TT antibody responses after immunization ($P > 0{\cdot}5$).

Relationship between antibody responses and other clinical and immunological parameters. The limited number of patients with constitutional symptoms or thrush precluded any conclusion on a possible correlation between clinical symptoms associated with lymphadenopathy and defects in antibody response. Delayed skin responses to PHA were negative in 4/15 patients tested. T3 positive blood lymphocyte counts were under 1000/mm^3 in 4/25 patients, and the number of T4$^+$ lymphocytes was under 400/mm^3 in 4/25 patients. T8$^+$ lymphocytes averaged 902/mm $\pm$ 667, and were over 1200/mm^3 in 4/25 patients. A lymphocyte proliferative response to the lectins PHA, PWM and Con A was seen in all patients (Table 1).

Responses to specific antigens were tested *in vivo* and *in vitro*. As shown in Table 2, a delayed hypersensitivity primary reaction to DNCB was negative in several patients tested. For the recall antigens CDD and TUB, negative skin tests were observed in about half of the patients tested. Significant lymphocyte responses *in vitro* to the antigens CMV, TUB, SKSD and CDD were detected in the majority of patients (Table 2). No association was found between antibody responses and all immunological parameters studied.

DISCUSSION

In a group of 25 patients with PGL, a profound defect in post-immunization antibody responses to

PPS was observed in most patients. This defect was not linked to other immunological parameters.

Preimmunization anti-PPS antibodies are probably a useful indication of the previous integrity of humoral immunity; our finding in the PGL group of mean values similar to that of controls suggests that, in contrast with AIDS patients (Ammann *et al.*, 1984), PGL patients can maintain significant 'spontaneous' anti-PPS antibody production. In healthy individuals, immunization with PPS elicited an increase in total serum antibodies within ranges in agreement with previous studies (Schiffman *et al.*, 1980; Landesman & Schiffman, 1981). The response involved predominantly IgM, IgA, and IgG2 isotypes (Eisenberg *et al.*, 1985; Freijd *et al.*, 1984; Hammarstroem, Perrson & Smith, 1985). Post-immunization antibody responses to PPS were severely impaired or absent in the majority of PGL patients. A response was observed in some with an isotype pattern resembling that of healthy individuals (i.e. IGM, IgG2 and IgA), whereas in patients with a diminished response, there was no 'compensation' by the IgG1, IgG3 or IgG4 isotypes.

This profile differed from that observed with the polypeptide antigen TT. The wide range of pre-immunization anti-TT values in both groups presumably reflected the time interval since last immunization (Ballet *et al.*, 1983). It is noteworthy that several patients did not produce a significant post-immunization antibody response, an observation confirmed in other patients in our prospective study. However, the mean anti-TT rise in the PGL group did not significantly differ from that of the control group studied in parallel, or of a larger series reported previously (Ballet *et al.*, 1983). In the responder PGL patients, the IgG response consisted essentially of IgG1. In controls, booster with TT elicited a response predominantly to IgG1, to a lesser extent, IgG4 (Seppala *et al.*, 1984; Bird *et al.*, 1984). The increase in IgG4 antibody was lower, on average, in the PGL group as compared to the control group. Further analyses identifying patients at risk for AIDS should focus on non-responder patients with PGL, since most normal individuals do respond to booster immunization with TT.

No conclusion could be reached on an association between antibody responses and constitutional symptoms in our patients. There was no correlation between antibody responses and other immunological features, including serum Ig levels. It is notable that very few individuals had associated clinical symptoms or immunological abnormalities in contrast to some other series in the literature (Ioachim *et al.*, 1983; Klein *et al.*, 1984; Murray *et al.*, 1985) where low T cell counts, defects in delayed skin reactions and lymphocyte responses *in vitro* to lectins and foreign antigens have been reported (Klein *et al.*, 1984). In a recent report, the predominant defects were abnormal lymphocyte proliferation and immune interferon production in response to soluble antigens; interestingly, they were associated with the presence of constitutional symptoms or thrush and the further appearance of opportunistic infections (Murray *et al.*, 1985). In our patients, with the exception of DNCB skin reactions, *in vivo* and *in vitro* antigen specific responses were generally preserved. In this context, abnormal anti-PPS antibody responses appear to be a distinctive immunological abnormality and may be an early consequence of infection by HIV. Follow-up will determine whether this abnormality has any predictive value for AIDS. Whereas previous data, and our own indicate that HIV infection and PGL are compatible with the preservation of significant T cell mediated responses, full-blown AIDS is characterized by the inability of helper/inducer $T4^+$ lymphocyte to recognize and respond to soluble protein antigens such as TT (Lane *et al.*, 1985).

In AIDS-related conditions, hypergammaglobulinaemia and an increase in circulating Ig secreting cells presumably reflects polyclonal B cell activation, responsible for the refractoriness *in vitro* of B cells to activators (Lane *et al.*, 1983; Zolla-Pasner, 1984). In homosexuals with PGL, but without manifestations of AIDS, the responses of B cells *in vitro* to polyclonal stimulators and antigen were impaired (Pahwa *et al.*, 1984). In this context, our finding of abnormal anti-PPS response is interesting since it demonstrates a defect of B cell function *in vivo* (Schiffman, 1983), contrasting with preserved T cell functions in most of these patients. This is consistent with the independence of human anti-PPS responses to T cells which, although less well established than in mice, is supported by some evidence, such as the lack of T cell proliferative response to soluble polysaccharide antigens (Kehrl & Fauci, 1983).

The destruction of the B lymphocyte corona around damaged germinal centres histologically observed in lymph nodes of PGL patients (Janossy *et al.*, 1985) is consistent with a defect in antibody responses. Although primary antibody responses to polysaccharides may involve spleen

cells (Amlot & Hayes, 1985), secondary stimulation with PPS presumably generates B cells in germinal centres analogous to those found in blood following anti-PPS vaccination (Kehrl & Fauci, 1983).

The restriction of anti-PPS antibody production (or its control) to B cell subsets, possible human counterparts of murine B cells responsive to class 2 thymo-independent antigens (Scher, 1982), may explain the anti-PPS antibody defect in PGL patients. These B cells may be more sensitive to consequences of HIV infection, than those which respond to the polypeptide antigen TT. Whether they are preferentially infected by HIV (Montagnier *et al.*, 1984) or a target for its products (Pahwa *et al.*, 1985) is not clear.

Pneumococcal bacteraemia was found more commonly in patients with AIDS than in the general hospitalized population (Simberkoff *et al.*, 1984). In our PGL patients, anti-PPS antibody was presumably acquired before HIV infection, and was maintained at levels considered to be protective (Landesman *et al.*, 1981). The failure of PGL patients to raise their antibody levels normally after vaccination may explain the predisposition to pneumococcal infection in HIV-infected children, who may not have been previously exposed to these organisms (Shannon & Ammann, 1985). Our data suggest that passive rather than active immunoprophylaxis could be useful in these patients.

The results reported here point out the importance of abnormalities in B cell function as revealed by defective responses to T-independent polysaccharide antigens in patients with PGL. They point to further evaluation of B cell interactions with the virus and to the study of immune responses to polysaccharide antigens in healthy HIV carriers.

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