

Immunodeficiency and other clinical immunology

Production of factors with B-cell growth and differentiation activities by peripheral blood mononuclear cells from patients with hypogammaglobulinemia

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Background: The maturation of normal B lymphocytes proceeds through a growth phase and a differentiation phase. These two phases appear to be under the influence of mediators released by immune cells, B-cell growth factor(s), which induce proliferation of B cells; and B-cell differentiation factor(s), which induce B-cell differentiation.

Methods: We analyzed the ability of peripheral blood mononuclear cells from patients with hypogammaglobulinemia to produce B-cell growth factor and B-cell differentiation factor activity in comparison with normal peripheral blood mononuclear cells.

Results: Of 27 patients tested, 26 had normal production of B-cell growth factor activity. A quantitative but not absolute defect in B-cell growth factor production was demonstrable in one boy with hypogammaglobulinemia. Interleukin-2 and interleukin-4 levels, as determined antigenically in these supernatants, had a similar distribution pattern from patients' or from control peripheral blood mononuclear cells; that is, undetectable levels of interleukin-2 were produced by cells from 4 of 16 patients tested and from 4 of 13 control subjects, and undetectable levels of interleukin-4 produced by cells from 6 of 16 patients and 4 of 13 control subjects. B-cell differentiation factor activity was absent in only one child tested but present in all other patients. Two patients had quantitatively low secretion of B-cell differentiation factor, but all others were within normal range. The two patients with quantitatively depressed B-cell differentiation factor activity had normal levels of B-cell growth factor activity, interleukin-2, and interleukin-4 produced from their cells.

Conclusion: Peripheral blood mononuclear cells from the majority of patients with hypogammaglobulinemia appear to have the capacity to produce B-cell growth factors and B-cell differentiation factor activity *in vitro*. (*J ALLERGY CLIN IMMUNOL* 1994;93:126-35.)

Key words: Hypogammaglobulinemia, B-cell growth factor, B-cell differentiation factor, IL-2, IL-4, mediator production, concanavalin A stimulation

Patients with hypogammaglobulinemia are at increased risk for chronic or recurrent upper and lower respiratory tract or bowel infections. The respiratory infections can lead to end-stage lung

disease, which can result in right-sided heart failure and death. The etiology of the hypogammaglobulinemia is unknown, but the diverse set of clinical syndromes and the variable cellular func-

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Supported by grants from the Medical Research Council of Canada, the Canadian Arthritis Society, the British Columbia Health Care Research Foundation and Immuno Canada Ltd.

Received for publication July 10, 1992; revised May 18, 1993; accepted for publication May 20, 1993.

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0091-6749/94 \$1.00 + .10 1/1/48853

Abbreviations used

AET:	2-Aminoisothiuronium bromide
BCDF:	B-cell differentiation factor
BCGF:	B cell growth factor
Con A:	Concanavalin A
IFN- γ :	Interferon- γ
IL-2:	Interleukin-2
IL-4:	Interleukin-4
IL-5:	Interleukin-5
PBMCs:	Peripheral blood mononuclear cells
PHA:	Phytohemagglutinin
PWM:	Pokeweed mitogen

tional analyses suggest that hypogammaglobulinemia results from an array of causes.¹

After exposure of the host to an infectious agent, the antigen must be processed and presented by Ia-positive cells to induce an antigen-specific response among a network of T and B lymphocytes. Once macrophages and T lymphocytes are stimulated, they have the capacity to secrete factors that are required in the maturation of appropriately primed (i.e., by antigen) B lymphocytes. The factors are not antigen-specific but induce the proliferation (B-cell growth factor [BCGF]) or differentiation (B-cell differentiation factor [BCDF]) of antigen-primed B cells. Under normal circumstances specific antibody production is the result.²

Several factors are known to have BCGF-like activity. Interleukin-2, -4, and -5 (IL-2, IL-4, and IL-5) are products of T cells that promote growth of primed B cells.²⁻⁴ B cells themselves apparently can secrete a factor that produces BCGF-like activity.³ Similarly, B-cell differentiation can be induced by several different factors including interleukin-6.⁵⁻⁷ Interleukin-6 is also known to be an autocrine factor to B cells,⁸ (Ling et al., unpublished observations). Although these factors have been cloned, identification of each factor within a supernatant containing multiple factors, especially at a functional level, is not always possible. Nevertheless, functional characterization of BCGF-like and BCDF-like activities as related to the two major stages of B-cell maturation, namely, growth and differentiation, is feasible.⁵⁻⁷

Production of factors by patients with hypogammaglobulinemia has not been studied extensively. Saiki et al.⁹ described a woman with hypogammaglobulinemia whose peripheral blood mononuclear cells (PBMCs) did not secrete IL-2 but would produce BCGF-like and BCDF-like activity.⁹ Raziuddin and Teklu¹⁰ reported hypogammaglobulinemia in a man whose PBMCs failed to produce BCGF-like or BCDF-like agents

in response to phytohemagglutinin (PHA). Recently our laboratory described a boy with hypogammaglobulinemia who had no detectable BCDF-like activity.¹¹ Sneller and Strober demonstrated depressed levels of messenger RNA expression for IL-2, IL-4, IL-5, and interferon- γ (IFN- γ) by T lymphocytes from four patients with hypogammaglobulinemia.¹² We report our findings related to the production of BCGF-like and BCDF-like activities, and IL-2 and IL-4 by PBMCs from a group of 27 patients with hypogammaglobulinemia.

METHODS

Patients

Thirteen patients with hypogammaglobulinemia were studied from one center in Calgary, Alberta (patient group 1), and 14 from another center in Vancouver, British Columbia (patient group 2). They ranged in age from 4 to 57 years. IgG levels were less than 3.5 gm/L before therapy in all but two patients, who had IgG levels between 4 and 5 gm/L. One patient had significant hypogammaglobulinemia that antedated the diagnosis of chronic lymphocytic leukemia. All patients were receiving Ig replacement, all by intravenous routes. Blood samples were drawn within the last week of the patients' three or four weekly infusion cycles.

In each assay PBMCs from a normal person were studied concomitantly. Ages of control subjects ranged from 20 to 44 years. Samples from most patients were assayed on more than one occasion to assess reproducibility. The mean activity is shown in the figures. All mediator production assays were established within 24 hours of blood sampling.

Mitogenesis and Ig secretion assays

All patient PBMCs were assayed in a service laboratory for proliferative responses to T-cell mitogens, phytohemagglutinin (PHA) (Can Lab), Pokeweed mitogen (PWM) (Can Lab) and concanavalin A (Con A) (Baie d'Urf, Quebec) with assays as previously described.¹¹ PWM was used to stimulate Ig secretion from PBMCs, and the IgG and IgM were quantified by ELISA after 12 days in culture.¹¹ Details of the patients' chemical manifestations, *in vitro* Ig secretion, and mitogen responses are described in Tables I and II.

BCDF and BCGF production

These techniques were previously reported.¹¹ In brief, PBMCs from patients or control subjects were cultured in tubes, 1.5×10^6 cells/ml in RPMI-1640 supplemented with 1% fetal calf serum (Gibco, Burlington, Ontario, Canada) and 300 μ g Con A, a T-cell mitogen, in a 37° C humidified atmosphere of 5% carbon dioxide. Supernatants were recovered after 3 days and frozen for later analysis of factors. By comparison with PHA, PWM, and *Staphylococcus aureus* Cowan strain I, we found that Con A gave the best production of BCGF-like and BCDF-like activity from

TABLE I. IgG and IgM production by PWM stimulation of PBMCs of patients with hypogammaglobulinemia (group 1) and normal control subjects

Patient			PWM Ig secretion (ng/ml)	
Number	Age (yr)	Clinical manifestations	IgG	IgM
1	34	Pneumonia, malabsorption	124	216
2	25	Pneumonia	1057	230
3	21	Pneumonia, sinusitis	1721	4711
4	61	Pneumonia	1627	4010
5	39	Pneumonia, neurologic dysfunction	346	720
6	34	Pneumonia, lymphocytic infiltrate of bone marrow, liver	216	396
7	35	Pneumonia, sinusitis	2062	5042
8	57	Pneumonia	3764	8327
9	35	Pneumonia, malabsorption	46	< 39
10	4	Pneumonia, chronic gastroenteritis with malabsorption, mental retardation	103	164
11	28	Pneumonia, heart-lung transplant		
12	36	Pneumonia		
13	55	Pneumonia, deep vein thrombosis		
Normal control subjects (<i>n</i> = 8)			3446 ± 1245 (1572-5516)*	6526 ± 1427 (4392-9274)*

Supernatants were analyzed by standard ELISA technique. Supernatants from Con A-stimulated PBMCs were assayed for IL-2 and IL-4 with a commercial ELISA kit. PBMCs from patients were assessed for response to T-cell mitogen (PHA) and B-cell mitogen (SAC). Blank cells indicate samples that were not analyzed.

↓, slightly depressed; ↓ ↓, moderately depressed; ↓ ↓ ↓, severely depressed; ND, not detectable; SAC, *S. aureus* Cowan strain I.

*Values expressed as mean ± SD (range).

normal PBMCs (data not shown). Normal control cells were cultured each time a patient sample was processed.

BCGF assay

BCGF-like activity was assessed in a costimulator assay as previously described.¹¹ In brief, tonsillar lymphocytes were twice depleted of T cells by a 2-aminoisothiuronium bromide (Sigma Chemical Co., St. Louis, Mo.) rosetting technique and the macrophages were removed from the enriched B-cell population by adherence to plastic. The B lymphocyte-enriched cells were then cross-linked with 15 µg of insolubilized anti-µ antibody on Sepharose beads (Biorad, Mississauga, Ontario, Canada) in microtiter wells containing 10⁵ cells. Serial dilutions of the Con A supernatants were added, and the proliferative activity was assessed after 3 days by tritiated thymidine incorporation. In each experiment the supernatant of the control subject was similarly assayed, as was an in-house standard crude supernatant. The in-house standard was prepared in the same manner as the patient samples except in large quantities with normal PBMCs.

BCDF assay

Two assays were used to assess BCDF-like activity. This first assay was previously described¹¹ and is based

on the BCDF-reactive lymphoblastoid cell line, CESS.⁶ Briefly, 10⁴ CESS cells per well were incubated with serial dilutions of the Con A supernatant and the amount of IgG secreted was determined by ELISA after 3 days in culture. The second assay used the IL-6-dependent cell line B9, kindly provided by Dr. P. Lansdorp (Terry Fox Laboratories, Vancouver, British Columbia, Canada).⁷ These cells proliferate in supernatants containing IL-6. Five thousand cells per well were added to serial dilutions of supernatant, and the proliferative response of the B9 cells was assessed after 3 days by tritiated thymidine incorporation. All patients and control subjects from each of the two groups were assessed in one laboratory for production and analysis of mediators. Both patient and control groups were analyzed by the identical BCGF-like assay, whereas the BCDF-like activity of group 1 patients and control subjects was assessed by the CESS assay and that of group 2 patients was assessed by the B9 assay. The results of the analysis by functional assays from groups 1 and 2 are therefore presented separately.

IL-2 and IL-4 assays

Commercial kits were purchased from Genzyme, distributed by Intermedico, Markham, Ontario, Canada, and the supplier's instructions were followed to assess the IL-2 and IL-4 level in the supernatants.

Levels in Con A-stimulated supernatant					
1/4 maximum values				PBMC response	
BCGF	BCDF	IL-2 (pg/ml)	IL-4 (pg/ml)	PHA	SAC
17	99	885	63	↓↓↓	↓↓↓
84	14			Normal	↓↓↓
72	58	ND	ND	Normal	Normal
53	73	1123	ND	↓	Normal
71	71	1776	50	↓	↓
63	104			↓	↓
32	75	1169	62	↓	Normal
33	40	530	61	↓	Normal
36	105	ND	50	Normal	Normal
30	0	1162	ND	Normal	Normal
17	11			↓	↓↓
49	118	1984	62	↓	Normal
64	75			↓	↓↓
See Fig. 1	See Fig. 2	See Fig. 3	See Fig. 4		

Calculation of BCGF/BCDF activity

Calculation of BCGF and BCDF activity was performed by a computer program written to interpolate half maximum or one fourth of maximum values for each dilution curve of logarithmically transformed data (i.e., tritiated thymidine incorporation for BCGF-like assay and B9 cells or IgG levels for CESS cells). One unit of activity was defined as the dilution required to achieve one fourth of the maximum response. Comparisons were always made to supernatants from normal control subjects. The mean and SD were calculated from the log of the unit values and plotted on a logarithmic scale.

RESULTS

In group 1 the BCGF-like activity produced from unstimulated PBMCs may be higher in two patients than in the normal control subjects (Fig. 1). However, this was not evident in group 2. Once stimulated by Con A, the production of BCGF-like activity by PBMCs from the majority of patients was equivalent to that from the normal PBMCs. Only one patient in group 2 had a BCGF-like production that was less than 2 SDs below the means for the normal PBMCs.

Given that IL-2 and IL-4 have BCGF activities, they were assessed in the supernatants. The distribution of levels of IL-2 and IL-4 were similar for the patients' and the normal supernatants (Figs. 2 and 3). Some samples from each group

had IL-2 or IL-4 levels less than detectable limits in the assay. In 4 of 16 patient samples and 4 of 13 control samples IL-2 was undetectable, and in 6 of 16 patients and 4 or 13 control subjects IL-4 levels were undetectable. The means were not significantly different between the groups.

Unstimulated cells produced BCDF-like activity (Fig. 4, *A*) and IL-6 (Fig. 4, *B*) in the majority of cases. IL-6 activity increased somewhat on exposure to Con A for patients and control subjects (Fig. 4, *B*) but not for BCDF-like activity assessed within the CESS assay. This could suggest that the two assays may measure different mediators or may be inhibited by different substances. However, in both *A* and *B* of Fig. 4 there is no marked defect in the majority of patients compared with control subjects. The one patient in Fig. 4, *A*, whose Con A-stimulated PBMCs produced less than 1 unit of BCDF-like activity was a boy with hypogammaglobulinemia who has been described elsewhere.¹¹ Two patients and one control subject from group 1 and one control subject from group 2 had marginally depressed BCDF-like activity when the Con A-stimulated PBMCs were compared. The two patients with lower than normal BCDF-like activity levels had normal BCGF-like activity, and IL-2 and IL-4 levels.

There was no correlation between the production of BCGF-like or BCDF-like activities with

TABLE II. IgG and IgM production by PWM stimulation of PBMCs of patients with hypogammaglobulinemia (group 2) and normal control subjects

Patient			PWM Ig secretion (ng/ml)	
Number	Age (yr)	Clinical manifestations	IgG	IgM
1	31	Sinusitis, pneumonia	83	1567
2	29	Sinusitis, pneumonia	107	364
3	46	Pneumonia, arthralgia	369	4318
4	16	Pneumonia	< 30	< 39
5	28	Pneumonia, endocrine dysfunction	< 30	601
6	32	Prior bone marrow transplant		
7	33	Pneumonia	< 30	196
8	20	Steatorrhea, otitis media	< 30	
9	11	Pneumonia	< 30	
10	14	Otitis media	< 30	
11	3	Otitis media, pneumonia		
12	14	Otitis media	< 30	333
13	34	Otitis media, sinusitis	402	12,622
14	28	Pneumonia	377	799
Normal control subjects			4023 ± 3827	6391 ± 1756
(n = 7 for IgM, n = 10 for IgG)			(1095-13313)*	(3966-8253)*

Supernatants were analyzed by standard ELISA technique. Supernatants from Con A-stimulated PBMCs were assayed for IL-2 and IL-4 with a commercial ELISA kit. PBMCs from patients were assessed for response to T-cell mitogen (PHA) and B-cell mitogen (SAC). Blank cells indicate samples that were not analyzed.

↓, Slightly depressed; ↓ ↓, moderately depressed; ↓ ↓ ↓, severely depressed; ND, not detectable; SAC, *S. aureus* Cowan strain I. *Values expressed as mean ± SD (range).

T-cell functioning assessed by proliferative response to PHA, Con A, and PWM. Eight patients with significant T-cell proliferative defects had normal BCGF-like and BCDF-like production, and the patient with the markedly defective BCDF-like activity had normal T-cell proliferation to mitogens.¹¹ Similarly, the majority of patients in group 1 and in group 2 had impaired Ig secretion in vitro compared with control subjects, when their PBMCs were cultured for 12 days with PWM (Tables I and II); that is, in in vitro production of BCGF-like activity, IL-2, IL-4, and BCDF-like activity appear to be normal even though most patients had depressed secretion of Ig in vitro.

DISCUSSION

Numerous factors are involved in B-cell growth and differentiation, and they can influence Ig secretion in various in vitro model systems. Nevertheless, it appears that few patients with hypogammaglobulinemia have their disease(s) as a result of defective production of BCGF-like or BCDF-like activities. Only one patient had an absolute defect in BCDF-like production¹¹ (Fig. 2), one patient had a quantitative defect in

BCGF-like secretion (Fig. 1), and two patients and two control subjects had quantitative defects in BCDF-like production (Fig. 2). Expressed alternatively, 26 of 27 patients with hypogammaglobulinemia had PBMCs that would produce BCGF-like and BCDF-like activity when cultured with Con A, although for three of the 26 patients the level of BCGF-like or BCDF-like activity was below the normal range.

Literature reports of the hypogammaglobulinemia with factor deficiencies are rare. Of patients with hypogammaglobulinemia, our laboratory described a child with a BCDF-like functional defect,¹¹ Saiki et al.⁹ published a case of IL-2 deficiency in a woman, and Raziuddin and Teklu described a man with a BCGF-like and BCDF-like secretory defect.¹⁰ The report of Sneller and Strober¹² is interesting and has results that conflict with ours. They contend that BCGF-like activity is decreased, as are IL-2, IL-4, IL-5, and IFN-γ gene production, and IL-2 and IFN-γ protein production, in four patients studied with common variable immunodeficiency. Our data, however, suggest that the distribution of IL-2 and IL-4 production resulting from Con A is the same for normal subjects for patients. Although some

Levels in Con A-stimulated supernatant					
BCGF (pg/ml)	BCDF (pg/ml)	1/4 maximum values		PBMC response	
		IL-2	IL-4	PHA	SAC
38	1750			Normal	Normal
15	3100			↓ ↓	↓ ↓
62	26,000			↓ ↓	Normal
48	32,000			↓ ↓ ↓	↓ ↓ ↓
60	4295			Normal	↓ ↓ ↓
56	6250	ND	ND		Normal
24	8750	196	354		
43	2431			Normal	Normal
47	6500	1392	130	Normal	Normal
6	7000	1314	ND	Normal	Normal
22	8000	ND	ND	Normal	Normal
47	3160	1138	62	Normal	Normal
14	8000	484	68		
44	4750				
See Fig. 1	See Fig. 2	See Fig. 3	See Fig. 4		

samples have levels of IL-2 or IL-4 less than the detectable limit of the assays, all but one patient with low IL-4 had normal levels of BCGF-like activity. Debate does exist in the literature, however. Recent reports suggested that the majority of PBMCs from patients with hypogammaglobulinemia have normal lymphokine activity,¹³ whereas others claim that the majority have defective BCDF-like activity.¹⁴ Each of these reports appears to have used different inducers of T cells, namely, PHA with phorbol myristate acetate or PHA, respectively, whereas our data are based on Con A stimulation of cells. This discrepancy in the literature may reflect that different inducers initiate different pathways of cell activation and hence require further study of the mechanisms of activating cells from patients with hypogammaglobulinemia. We found Con A to be a better inducer of BCGF-like activities (data not shown), but on the other hand, neither Con A nor PHA may have any relevance in the mechanism of in vivo induction of factors. Clearly if IL-2, IL-4, IL-5, and IFN- γ are not the major inducers of BCGF-like activity, then these findings would require considerably greater assessment to explain the apparent contradictory results. There have been few studies of patients with hypogammaglobulinemia beyond these case reports and to our knowledge no published reports of large numbers of patients.

From the perspective of IL-6, Adelman et al.¹⁵ demonstrated elevated serum IL-6 levels in 13 of 17 patients with hypogammaglobulinemia. Similar to our data, their findings included elevated spontaneous IL-6 production in vitro and, further, normal lipopolysaccharide-induced IL-6 production by PBMCs from patients. Some other studies have shown some inability of the PBMCs of patients with hypogammaglobulinemia to respond by proliferation or differentiation to exogenous factors in vitro.¹⁵⁻²⁰ Saxon et al.¹⁶ showed that B cells did not demonstrate the development of normal cell surface markers when they were stimulated by T-cell-replacing factors. Pastorelli et al.¹⁷ demonstrated that IL-4 is inhibitory to Ig secretion by PBMCs from patients with hypogammaglobulinemia. A recent review by Spickett and Farrant¹⁸ reinforced the concept that, given abnormal responsiveness to various mediators and supernatants, the B-cell unresponsiveness to signaling by mediators and the resultant failure to undergo differentiation may explain many of the causes of hypogammaglobulinemia.

The use of Con A as the mitogenic stimulus can be questioned. In our hands it was the most potent of the lectins in inducing BCGF-like and BCDF-like activity from normal PBMCs and hence was chosen to test maximal production (data not shown). However "maximal production" may not be relevant in vivo. An alternate "phys-

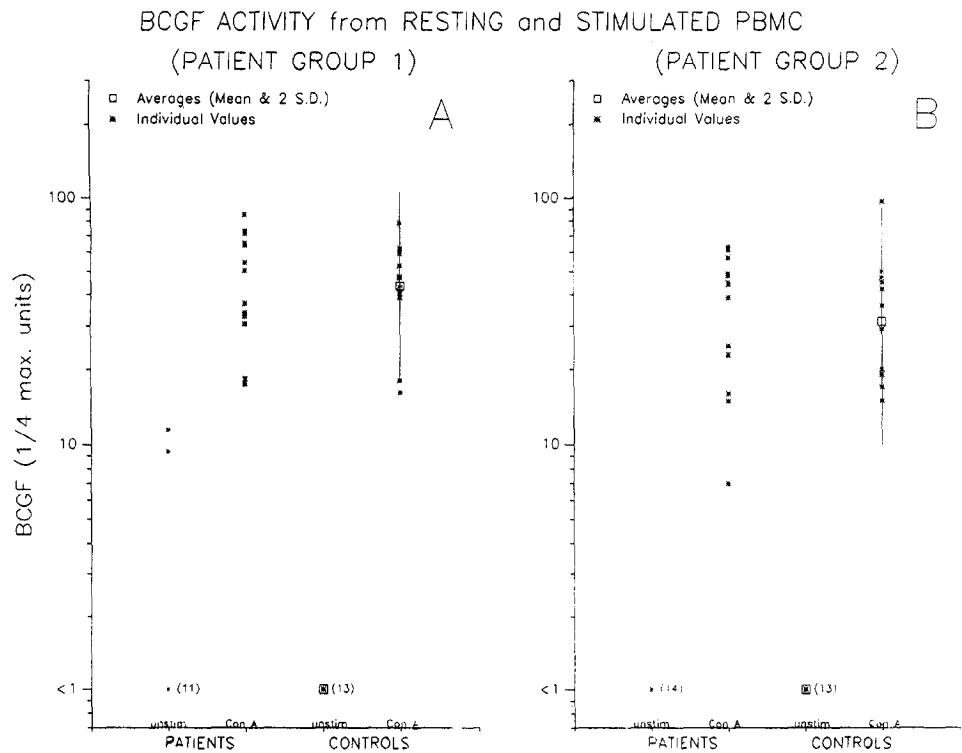


FIG. 1. BCGF-like production by PBMCs is shown for patients with significant hypogammaglobulinemia compared with normal control subjects. Two groups of patients in **panels A and B** are from two different centers. Specific responses are illustrated by *asterisk*, and the *box* and the *line* represent mean and 2 SDs from the mean of normal control results. Results are expressed as one fourth maximum units.

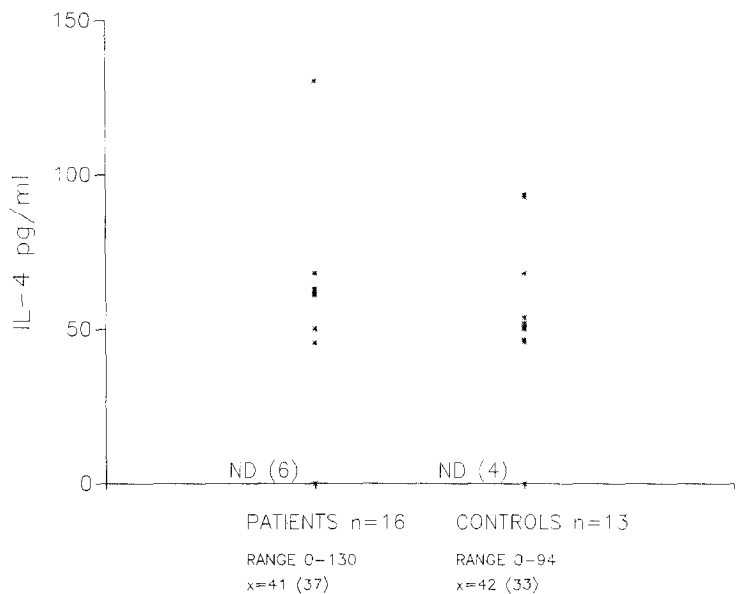


FIG. 2. IL-2 content in Con A supernatants was analyzed for patients and normal control subjects. No IL-2 was detected (*ND*) in four supernatants from patients and five from control subjects. The lower limit of detection of IL-2 by this assay is given as 150 pg/ml. Range, mean ($\bar{x}$), and SD (in *parentheses*) are given.

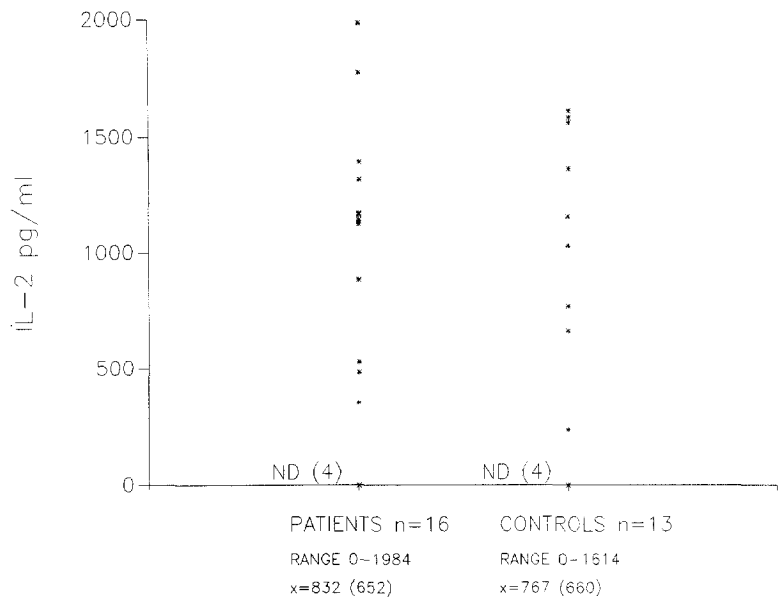


FIG. 3. IL-4 content in Con A supernatants was analyzed for patients and normal control subjects. No IL-4 was detected (*ND*) in six supernatants from patients and four from control subjects. Lower limit of detection of IL-4 by this assay was 45 pg/ml. Range, mean (*X*), and SDs (in *parentheses*) are given.

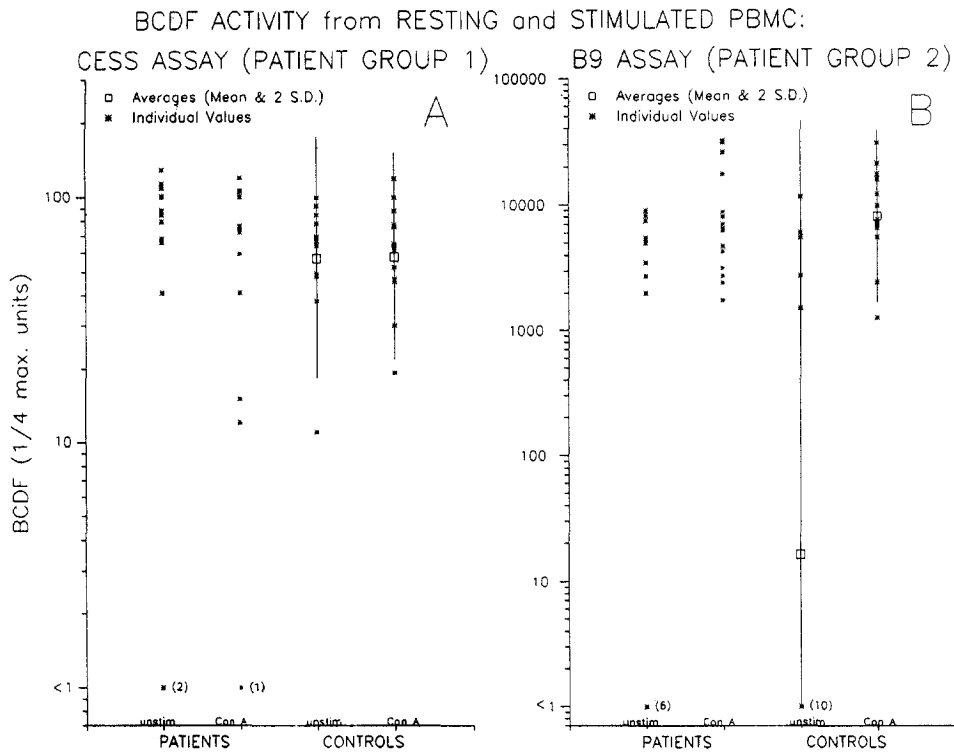


FIG. 4. BCDF-like production by PBMCs of patients with hypogammaglobulinemia and normal control subjects is shown. Panels represent patients from two different centers, in which BCDF-like activity was induced the same way but analyzed differently. **Panel A**, Supernatants from patients in group 1 were analyzed according to induction of IgG secretion by indicator cell line CESS. **Panel B**, Supernatants from patients in group 2 were analyzed by induction of proliferation of IL-6-dependent cell line B9. The *box* and the *line* represent the mean and 2 SDs of the mean in normal control results. Results are expressed as one-fourth maximum units.

biologic" stimulus such as anti-CD3 or specific antigen could be preferred. Nevertheless, the Con A system appears to assess the ability of PBMCs at near-maximum stimulation and hence should be useful in detecting any patients who have absolute defects in BCGF-like or BCDF-like activities. Clearly, quantitative defects that appear with the use of maximal stimulation with Con A or other lectins must be interpreted with caution.

Interestingly, neither BCGF-like nor BCDF-like production correlated with T-cell mitogen responses or with IL-2 or IL-4 levels in the supernatants. This could suggest that production of IL-2, and BCGF-like and BCDF-like activities, are controlled by separate mechanisms, a theory that has been suggested elsewhere.^{9, 11} Because IL-6, which is a major BCDF, is produced by several types of cells other than T cells,² this is not surprising. But IL-4, which is a major BCGF, is secreted largely by T cells, and therefore one might expect that both IL-4 and BCGF-like activity could be depressed concomitantly. However, BCGF-like activity, as defined by the biologic assay, may reflect the function of more than one mediator. For instance, IL-2, IL-4, IL-5, and B cell-derived BCGF can induce B-cell proliferation.^{2, 4} Hence clear interpretation of which mediator may be inadequately produced is not readily possible. Similarly, it is feasible that a low production of one mediator could be masked because of the activity of another mediator with similar BCGF-like or BCDF-like activity. Nevertheless, it is legitimate to conclude that impaired T-cell mitogen responses do not imply defective BCGF-like or BCDF-like production. Similarly, neither can the secretion of Ig in vitro as a result of PWM stimulation predict BCGF-like or BCDF-like production, because the majority of the patients had depressed Ig production caused by PWM.

The fact that very few patients have evidence of defective mediator production is important therapeutically. Correction of the defect by mediator replacement as a therapeutic modality is unlikely. Given the complexity of B-cell maturation and the multiplicity of steps involved, it is probable that multiple causes of hypogammaglobulinemia will be found. Therapy may then have to be individualized.

These data therefore suggests that a defect in BCGF-like or BCDF-like production in vitro does not account for the failure to produce antibody in most patients with hypogammaglobulinemia. Our

laboratory has documented only one exception (Fig. 4),¹¹ but with the assessment of the large number of patients in this study, defective mediator production appears to be a rare event. This study includes the largest number of patients we have found in the literature. Perhaps given the intricacies of the B-cell differentiation pathway and the multitude of steps required to provide complete B-cell maturation, several potential mechanistic abnormalities are feasible.¹ Our data, together with those of many other investigators, suggest that defects in most patients with hypogammaglobulinemia may be in the B cell rather than the T cell and may be related to impaired differentiation.⁹⁻²⁰

We thank Marian Schaumleffel and Susann Dagenais for typing the manuscript, and Ian Mitchell for the data analysis and graphic displays.

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