Spring, 2026

Thank you for viewing this series of papers; three of them authored by Stan Korsmeyer, himself.

They are presented chronologically to demonstrate how far his field of research in human immunology and the origins of white blood cell cancers has progressed in the years 1975-2025.

Introductory comments before each are to draw attention to the real life and death implications of Stan's - and hundreds of other's- medical and scientific research. May it be allowed to continue.

Wm. P. Hyde, M.D.
BHS, 1968

This paper is from the prestigious New England Journal of Medicine in November,1975. It covers a topic also addressed in the October, 1974 issue of Gastroenterology also by Stan and the same co-authors. The laboratory investigations described in these papers were done by Stan when he spent some months at the University of New Mexico after graduation from the University of Illinois in 1972 or after completing his first year at the U of I School of Medicine in the summer of 1973. This means that Stan was the lead author of two papers published in leading medical journals having completed only his Bachelor's Degree from U of I Champaign-Urbana where he was introduced to and participated in immunology research. This extraordinary accomplishment foretold an exciting and fruitful research career that did indeed come to pass!

Now, some comments on the work itself. In 1973 inflammatory bowel disease (Crohn's disease and ulcerative colitis) was recognized to come about because of heightened immune system reaction occurring in the intestinal lining of those affected. Hence the name, inflammatory bowel disease. The origin and nature of the harmful inflammatory reaction was not precisely known. This study strongly suggested that its origin may lie in the exposure to a common environmental agent (be it chemical or bacterial) plus an inherited genetic predisposition for an altered immune reaction to that agent.

Now, fifty years later, this explanation is still accepted. The many treatments available for these ailments are directed at inhibiting the immune response and the harmful effects there from.

"Antilymphocyte Serum"

LYMPHOCYTOTOXIC ANTIBODY IN INFLAMMATORY BOWEL DISEASE

A Family Study

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Abstract The prevalence of lymphocytotoxic antibody in inflammatory bowel disease is 40 per cent. Twenty-seven of 90 relatives of 23 probands with the disease (30 per cent) demonstrated lymphocytotoxic antibody, as contrasted with only three of 69 control family members (4 per cent) ($P < 0.0001$). Decreased lymphocytotoxicity against lymphocytes from patients with inflammatory bowel disease as compared to normal donor lymphocytes previously demonstrated in the serum of probands was also observed in the serums from family members of the probands. Nineteen of the 48 household contacts of probands (40 per cent) were positive for antibody, whereas eight of 42 nonhousehold contacts (19 per cent) demonstrated it ($P < 0.05$). Eight of 16 spouses (50 per cent) of probands showed antibody. The increased prevalence of lymphocytotoxic antibody in family members of probands and its occurrence mainly in household contacts (consanguineous and non-consanguineous) may indicate the exposure of probands and their family members to a common environmental agent. (N Engl J Med 293: 1117-1120, 1975)

NATURALLY occurring lymphocytotoxic antibodies have recently been described in the serum of patients with Crohn's disease or chronic ulcerative colitis.[1,2] The prevalence of lymphocytotoxic antibodies in both forms of inflammatory bowel disease was 40 per cent.[2] Antilymphocyte antibodies have also been reported in patients with systemic lupus erythematosus,[3-7] and appear in NZB/W mice in which an autoimmune disease similar to human lupus spontaneously develops.[8,9] A wide variety of other conditions involving altered immunologic function is associated with the presence of lymphocytotoxins, including acute and chronic hepatitis,[10] infectious mononucleosis,[11,12] and Hodgkin's disease,[13] and after vaccination against rubella.[14]

The cause of chronic inflammatory bowel disease remains unknown; however, attention has focused upon the possible importance of transmissible agents in Crohn's disease,[15-18] and more recently in ulcerative colitis.[19] The demonstration of a high prevalence of lymphocytotoxic antibody in the non-consanguineous household contacts of probands with systemic lupus erythematosus appears to provide evidence for the possible effect of an environmental agent in the pathogenesis of this disease.[20] Therefore, the present study of the family members of subjects with inflammatory bowel disease was undertaken to determine the frequency and expression of lymphocytotoxic antibody in such families. The findings suggest that an environmental or common agent may exist among family members of patients with either Crohn's disease or chronic ulcerative colitis.

MATERIALS AND METHODS

Patient Material

Serums from 90 members of 23 families each containing a subject with inflammatory bowel disease were collected in Albuquerque and Minneapolis. Eighteen families contained a proband with Crohn's disease, and five a proband with ulcerative colitis. First-degree relatives were defined as parents, children, and siblings of the proband, whereas second-degree relatives were twice removed from the proband (i.e., grandparent, uncles, or aunts). Family members were further subdivided into household contacts who lived with the proband, and nonhousehold contacts. Of the 90 family members studied 59 were first-degree relatives, 15 were second-degree relatives, and 16 were spouses of the probands. Forty-eight of the 90 family members were classified as household contacts whereas 42 were nonhousehold contacts. The 48 household contacts included 32 first-degree relatives and all 16 spouses of the probands. None of the 15 second-degree relatives studied had close household contact with the probands. Sixty-nine control serum specimens from the members of 15 families of medical-center personnel were collected in Albuquerque and Minneapolis. These controls closely matched the patients' family members in age, sex, parity, and ethnic background (Table 1). For each family member studied a history of pregnancy, blood transfusion, previous hepatitis or infectious mononucleosis, and possible recent acute viral illness was carefully recorded. There was no difference in the frequency of the above features between family members of patients with inflammatory bowel disease and control family members.

The presence of lymphocytotoxic antibody was detected by the microcytotoxicity method of Terasaki and McClelland.[21] With this technic 1 μliter of serum and 1 μliter of whole lymphocytes at 1×10^6 cells per milliliter were incubated at 15°C for 15 minutes, when 5 μl of rabbit complement was added. After further incubation at 15°C for three hours, 3 μl of Eosin Y dye and 8 μl of 40 per cent formalin were added sequentially to each well. The percentage of killing was determined by dye exclusion with use of an inverted phase contrast microscope. Target lymphocytes were obtained from Ficoll-Hypaque gradient separation of peripheral

Table 1. Comparative Analysis of Families of Subjects with Inflammatory Bowel Disease (IBD) and Control Family Members Studied.

GROUP	IBD FAMILY MEMBERS	CONTROL FAMILY MEMBERS
Families studied	23	15
Total subjects studied	90	69
Mean age (yr)	33	28
Sex:		
Male	36 (40%)	34 (49%)
Female	54 (60%)	35 (51%)
Multiparous females	25 (28%)	15 (22%)
Ethnic origin:		
Anglo-American	85	64
Spanish-American	5	5

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blood from 16 normal adult subjects representing a panel of widely differing HL-A phenotypes.

An individual test with a given serum was considered positive if 20 per cent or more of the target lymphocytes were killed. Serum from a given subject was considered to be positive for lymphocytotoxic antibody only if it killed 20 per cent or more of the target lymphocytes from at least half the donors in the panel. These criteria, selected at the onset of the study and before analysis of the data, are the same as those used in earlier studies[1,2,20] and were chosen to identify only serum specimens with broad cytotoxic activity against lymphocyte antigens of non-HL-A identity. Normal serum known to give <10 per cent target cell killing and human serum albumin were tested simultaneously with the serum from control family members, or family members of patients with inflammatory bowel disease. These controls for spontaneous cell death consistently showed <10 per cent target cell killing. All tests including those from controls as well as family members of patients were read in co-blind fashion by one investigator (S.J.K.).

In view of our previous findings of decreased lymphocytotoxicity when serums in Crohn's disease were tested against lymphocytes of patients with Crohn's disease,[1] 23 of the lymphocytotoxic serums from family members of patients with inflammatory bowel disease were also tested against a panel of target lymphocytes obtained from six patients with Crohn's disease. Unfractionated whole lymphocytes derived from Ficoll-Hypaque separation of whole blood, as well as a relatively enriched T-cell preparation obtained by passage of lymphocytes over Degalan anti-immunoglobulin columns were used as target cells in these determinations.[22] Either chi-square analysis or Student's t-test was used in all statistical comparisons between various groups.

Results

Lymphocytotoxic antibody was detected in the serums of 24 of 80 family members of patients with Crohn's disease, and in three of 10 family members of patients with ulcerative colitis. The overall prevalence of the antibody in the 90 family members of combined probands with inflammatory bowel disease was thus 30 per cent, whereas only three of 69 members of control families (4 per cent), demonstrated antibody ($P < 0.0001$) (Table 2). No clear sex difference was apparent in the occurrence of antibody among the family members of patients with inflammatory bowel disease. None of the 15 multiparous women in the control families were positive for lymphocytotoxic antibody by the criteria used in this study. Ten of the 23 probands themselves were positive for antibody (44 per cent) at the time their family members were studied (Table 2).

Table 2. Prevalence of Lymphocytotoxic Antibody (LCA) in Probands with Inflammatory Bowel Disease (IBD), Family Members of Probands and Control Families.

Group	No. of Serums Tested	No. LCA Positive	% LCA Positive	
Control family members	69	3	4	
				P<0.0001
Total IBD family members	90	27	30	
Household contacts	48	19	40	
				P<0.05
Nonhousehold contacts	42	8	19*	
Consanguineous IBD relatives	74	19	26	
1st degree	59	16	27	
2d degree	15	3	20	
Non-consanguineous IBD relatives	16	8	50†	
IBD probands	23	10	44	

*P<0.025 compared to prevalence in controls.

†P<0.05 compared to prevalence in consanguineous relatives.

Since the occurrence of the antibody in the families of patients with Crohn's disease and ulcerative colitis was essentially the same, the data were combined in the analysis of the subgroups of family members of subjects with inflammatory bowel disease.

A significantly ($P < 0.05$) higher prevalence of lymphocytotoxic antibody was noted in the 48 family members who had household contact with the proband with inflammatory bowel disease (40 per cent) as compared to the 42 relatives without household contact (19 per cent) (Table 2). A similar trend was observed when the prevalence of antibody in the 32 first-degree relatives with (34 per cent) was compared to that in the 27 first-degree relatives without household contact (18 per cent) although this was not a significant difference ($P < 0.1$). Lymphocytotoxic antibody was detected in three of 15 (20 per cent) second-degree relatives, all of whom were nonhousehold contacts (Table 2). The 19 per cent prevalence of antibody in the 42 relatives (first and second degree) who were nonhousehold contacts at the time of study was significantly ($P < 0.025$) higher than that observed in control families (4 per cent) (Table 2). However, the importance of household contact with the proband with inflammatory bowel disease for the expression of lymphocytotoxic antibody is further illustrated by the occurrence of antibody in eight of 16 (50 per cent) non-consanguineous relatives (all spouses of the probands with inflammatory bowel disease). This prevalence among non-blood relatives was significantly ($P<0.05$) higher than that in consanguineous (first-degree and second-degree) relatives (Table 2).

Table 3. Average Lymphocytotoxicity of the Serums Tested.

Average Cytotoxicity (%)	23 Probands	48 Household Contacts	42 Nonhousehold Contacts	90 Total Family Members	69 Control Family Members
0-4	0	0	0	0	0
5-9	3*	11	13	24	27
10-14	9	16	15	31	35
15-19	1	8	5	13	4
20-24	3	5	2	7	2
25-29	0	2	1	3	0
30-34	1	8	0	8	0
35-39	2	1	2	3	1
40-44	1	0	0	0	0
45-49	1	0	0	0	0
50-54	1	0	0	0	0
55-59	1	1	0	1	0

*No. of serums showing average cytotoxicity in range indicated.

The average lymphocytotoxicity of each serum tested with the entire panel of target lymphocytes obtained from 16 normal donors is shown in Table 3. The probands with inflammatory bowel disease tended to show higher average lymphocytotoxicity than their relatives, who in turn showed higher lymphocytotoxicity than control family members. In addition, the household contacts of the probands showed somewhat higher average lymphocytotoxicity than the nonhousehold contacts. With use of the Kolmogorov–Smirnov two-sample test,[23] the distribution of average lymphocytotoxicity among family members of probands was significantly different from that in control families ($D=0.287$, $P<0.01$).

The pedigree of a representative family of a proband is presented in Figure 1. Both the spouse and the daughter in this family were positive for lymphocytotoxic antibody, whereas none of the proband's siblings demonstrated it.

When the serum specimens of 23 family members with antibody were tested against target lymphocytes obtained from subjects with Crohn's disease, a marked diminution in lymphocytotoxicity was noted in 15 of the specimens tested (Table 4). The mean (± 1 S.D.) per cent cytotoxicity in serum of these 23 family members against unfractionated normal donor lymphocytes was 28 ± 9, and that against the panel of lymphocytes from subjects with Crohn's disease was 14 ± 7. This difference was significant ($P < 0.001$).

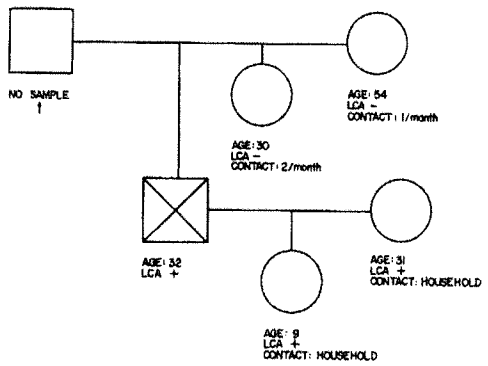

Figure 1. Crohn's Disease Family 15 Containing the Proband, Identified by the X-Marked Square, Who Was Positive for Lymphocytotoxic Antibody (LCA), Two Household Contacts Who Were Also Positive, and Two Tested Nonhousehold Relatives Who Were Negative.

Discussion

The present study has demonstrated an increased prevalence (30 per cent) of naturally occurring lymphocytotoxic antibody in the family members of probands with Crohn's disease or ulcerative colitis in comparison to that observed in a matched normal population (4 per cent). Since these family members displayed no higher prevalence of other pathologic states or conditions associated with lymphocytotoxic antibody than the controls, we conclude that the familial association with patients who have inflammatory bowel disease is the most reasonable explanation for the high rate of antibody among these family members. An additional finding in the present study was the significantly greater prevalence of the antibody in household contacts of the probands (40 per cent) as compared to nonhousehold contacts (19 per cent). This observation, together with the finding of a significantly higher antibody frequency in the non-consanguineous relatives of the probands (50 per cent) as compared to that in consanguineous relatives (26 per cent), is indicative of a relatively horizontal pattern in the expression of lymphocytotoxic antibody. However, the significantly increased rate of antibody in the relatives without household contact over that observed in control families is consistent with the possible involvement of genetic factors in the expression of this antibody. Since many of the currently non-

Table 4. Lymphocytotoxic Activity (per Cent Killing) of Serums of 15 Family Members of Probands with Inflammatory Bowel Disease (IBD) against Normal and Crohn's-Disease Target Lymphocytes.

Family-Member Serum	Unfractionated Lymphocytes from 16 Normal Adult Donors	Unfractionated Lymphocytes from 6 Subjects with Crohn's Disease	T-Cell Preparations from 6 Subjects with Crohn's Disease
1	33	8	8
2	26	12	9
3	21	4	7
4	26	11	7
5	34	10	11
6	31	14	14
7	33	22	11
8	25	11	6
9	37	26	26
10	23	11	9
11	51	34	35
12	22	8	3
13	38	15	18
14	31	16	13
15	30	18	16

household relatives had had extended periods of household contact with the probands in the past, the finding of an increased incidence of antibody in this subgroup of relatives offers no strong evidence favoring either genetic or environmental factors in the expression of lymphocytotoxicity.

The observation that lymphocytotoxic antibody in family members of probands demonstrated markedly less cytotoxicity for lymphocytes from subjects with Crohn's disease themselves mirrors the finding previously noted with serum from patients with inflammatory bowel disease.[1] This finding may indicate the similar specificity of lymphocytotoxic antibody detected in patients and their families. The exact nature of such reactivity remains to be determined.

Characterization of lymphocytotoxic antibody has previously been undertaken by several groups of investigators. The dependence of cytotoxic activity on a nonphysiologic temperature (15°C) suggested that immunoglobulins other than monomeric IgG might be implicated. Lymphocytotoxic activity has been localized in fractions of high-molecular-weight IgG aggregates,[24] as well as in cold-reacting IgM fractions.[7,25] Considerable work particularly with lymphocytotoxic serum from patients with systemic lupus erythematosus, has failed to reveal any specificity for known cell-surface antigens. The fact that these lymphocytotoxic antibodies react with lymphocytes from normal subjects of widely differing HL-A phenotype deserves emphasis. Synthesis of this type of antibody, which is capable of reacting with normal lymphocyte surface antigens, may indicate a loss of normal tolerance mechanisms. It has repeatedly been demonstrated that the recruitment of functioning helper T cells during the response to new foreign antigens may result in the loss of tolerance to closely neighboring host antigens.[26,27] Thus, one conceivable explanation for the appearance of antibodies reactive against normal lymphocytes is that new antigens expressed on the surface of lymphocytes as a result of viral infection could lead to the loss of tolerance to

neighboring normal cell antigens. A dramatic example of the expression of a new surface antigen on T cells as a result of virus infection has been described by Obota et al.[28]

The possible involvement of transmissible agents in the pathogenesis of inflammatory bowel disease has gained support from experiments in which tissue homogenates from human subjects with Crohn's disease have been inoculated into foot pads of CBA mice,[15-18] or into the ileum of New Zealand white rabbits.[16] A number of the animals receiving homogenates showed granulomatous changes complete with epithelioid cells and occasional giant cells. However, other investigators have reported negative findings with use of similar technics in a different strain of mice.[17] The fact that the lesion can only be transmitted in certain animal species and strains suggests the importance of host factors in the induction of these granulomatous lesions. The nature of such host factors is unknown, but genetic variation in the immune response through IR gene influence is one possibility. Clinical studies[29,30] have indicated a significantly increased familial occurrence of inflammatory bowel disease, and one study[31] has recorded a significantly increased rate of serum antibodies to colon and to *Escherichia coli* 0:14 antigen in first-degree female relatives of probands with ulcerative colitis as compared to age-matched and sex-matched controls.

A decrease in cell mediated immunity in human subjects with Crohn's disease is supported by the demonstration of decreased numbers of peripheral blood T cells,[32] decreased lymphocyte responsiveness to mitogen stimulation,[33,34] and decreased blast transformation in the mixed lymphocyte reaction.[35] It is still uncertain whether these changes are secondary to the disease or reflect a primary immune defect in Crohn's disease. The presence of lymphocytotoxic antibody in subjects with inflammatory bowel disease and in their unaffected family members, particularly those with close household contact, may indicate an exposure of the patients and their families to a common environmental agent. The possibility that such exposure in combination with a specific genetic defect of immune responsiveness is involved in the pathogenesis of inflammatory bowel disease clearly deserves further investigation.

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