

SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS

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Abstract Four homosexual men presented with gradually enlarging perianal ulcers, from which herpes simplex virus was cultured. Each patient had a prolonged course characterized by weight loss, fever, and evidence of infection by other opportunistic microorganisms including cytomegalovirus, *Pneumocystis carinii*, and *Candida albicans*. Three patients died; Kaposi's sarcoma developed in the fourth. All were found to have depressed cell-mediated immuni-

ty, as evidenced by skin anergy, lymphopenia, and poor or absent responses to plant lectins and antigens in vitro. Natural-killer-cell activity directed against target cells infected with herpes simplex virus was depressed in all patients. The absence of a history of recurrent infections or of histologic evidence of lymphoproliferative or other neoplastic diseases suggests that the immune defects were acquired. (N Engl J Med. 1981; 305:1439-44.)

CHRONIC ulcerating lesions caused by herpes simplex viruses (HSV) are unusual even in patients with severe immunologic defects. These lesions occur in advanced lymphoproliferative disease, after immunosuppression for organ transplantation, during treatment with high doses of corticosteroids, and in certain primary immunodeficiency disorders.¹⁻⁸ In four previously healthy homosexual men we found chronic perianal ulcers infected with HSV. Immunologic evaluation confirmed the presence of apparently acquired cellular immunodeficiency. The course in these patients was characterized by severe, unrelenting opportunistic infections, leading to death in three patients.

METHODS

Subjects

The four patients were referred to Mount Sinai Hospital or to Memorial Hospital for diagnosis or treatment. Controls were normal male and female volunteers 20 to 50 years old.

Immunologic Studies

Mononuclear cells were obtained from heparinized venous blood and characterized by cell markers as previously described.⁹ Hybridoma-derived reagents defining Leu-1, present on all normal human T lymphocytes, and Leu-2a, characteristic of a suppressor/cytotoxic subset, were kindly provided by Dr. Robert L. Evans.¹⁰ Responses to phytohemagglutinin, concanavalin A, pokeweed mitogen, and antigens from microbial pathogens were measured by cellular DNA synthesis.¹¹ Natural-killer-cell function was determined by comparing the cells' cytotoxicity among uninfected ⁵¹Cr-labeled human foreskin fibroblasts with their cytotoxicity among HSV-infected fibroblasts.¹² Delayed skin hypersensitivity was tested with recall antigens that usually elicited a response in normal adults (*Candida albicans*, streptokinase-streptodornase, mumps, and tetanus toxoid). Immune complexes were detected with a modification of the Raji-cell assay for Patient 1¹³ and precipitation with 3.5 per cent polyethylene glycol for the other three

patients.¹⁴ Specimens for viral culture were transported in Hanks' salts and incubated with a panel of cell types. Cytopathic effects in human embryonic kidney were observed within 24 to 48 hours when a specimen was positive for HSV. Commercial antisera were used to characterize direct immunofluorescence for HSV in biopsy specimens.

PATIENTS

Patient 1

A 26-year-old white homosexual man first noted perianal pain and vesiculation in January 1980. During the following spring, ulcerations gradually developed and fever and weight loss began. At presentation elsewhere the patient was anemic. Results of marrow and liver biopsies were negative. Antibiotics were administered. A large perianal ulcer had formed by July, and hepatosplenomegaly and generalized lymphadenopathy were observed when he was admitted to Memorial Hospital. Cultures taken from the ulcer bed indicated HSV Type 2; sigmoidoscopy revealed proctitis and an anterior anal ulcer. Chest x-ray films showed an infiltrate of the right upper lobe. Skin anergy was noted. Further evaluation for suspected inflammatory bowel disease or lymphoma was negative. By August, the patient had lost approximately half his original weight, and fever and perianal ulceration continued. Exploratory laparotomy with splenectomy and biopsies of the liver, small intestine, and lymph nodes showed only lymphocyte depletion. Satellite ulcers appeared on the buttocks. Parenteral nutritional supplements, transfusions, and antibiotics were given, but without benefit. In October, the chest films were unchanged. Persistently positive cultures for HSV, abnormal liver-function tests, and an enlarging ulcer led to a trial of an experimental antiviral compound 2'-fluoro,5-iodo-aracytosine (FIAC). Rectal bleeding developed; colonoscopy revealed vesicles and ulcers, but biopsies were nondiagnostic and cultures were negative for HSV and other pathogens. Human-leukocyte interferon, broad-spectrum antibiotics, and trimethoprim-sulfamethoxazole (TMP-SMZ) were given for increasing dyspnea with bilateral pulmonary infiltrates. Renal failure and encephalopathy developed, and the patient died in October.

Autopsy revealed herpetic proctitis and colitis, with viral dissemination to the posterior columns of the spinal cord. *Pneumocystis carinii* was present in the lungs. Intranuclear and intracytoplasmic inclusions typical of cytomegalovirus were present in the adrenals, lungs, colonic smooth muscle, and endothelium underlying the ulcerations. Electron microscopy (kindly performed by Dr. Robert A. Erlandson) showed inclusions compatible with either HSV or cytomegalovirus.

Patient 2

A 32-year-old Hispanic homosexual man had perianal vesicular lesions in July 1979; biopsy suggested cytomegalovirus infection. In November, he began to have fever, anorexia, gradual weight loss,

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abdominal pain, and hematochezia. In March 1980, rectal bleeding was severe enough to require transfusion of eight units of blood. Ulceration of the perianal lesion and diffuse lymphadenopathy were noted. The cause of these conditions was not revealed by sigmoidoscopy, gastrointestinal barium studies, examination of stools for bacteria and parasites, abdominal computerized tomography, sonography, or serologic studies; on the basis of inclusions found on rectal biopsy, which suggested lymphogranuloma venereum, tetracycline was given, without effect.

The patient was transferred to the Mount Sinai Hospital in May because of continued fevers and cachexia. He had oral candidiasis, generalized shorty lymphadenopathy, and abdominal tenderness in the left lower quadrant. The perianal ulcer had enlarged to 12 cm. Anemia and leukopenia were noted. Culture and immunofluorescence testing of the ulcer showed only HSV Type 2. Evaluation for lues, gonorrhea, lymphogranuloma venereum, and other pathogens was negative. A biopsy suggested that HSV and cytomegalovirus coexisted in the ulcer. Lymph-node biopsy indicated the absence of germinal centers. Treatment with vidarabine for five days had no effect, nor did a four-day trial of acyclovir (kindly provided by Burroughs-Wellcome). Spiking fevers, rectal bleeding, progressive wasting and lymphopenia did not respond to broad-spectrum antibiotics and transfusions. Terminally, the patient appeared to have a generalized cardiomyopathy; he died on August 8, 1980. Permission for autopsy was denied.

Patient 3

A 28-year-old Colombian homosexual man reported dull pain in the left lower abdominal quadrant and rectal bleeding in May 1980. He was treated surgically for presumed perianal abscess. Postoperative rectal bleeding necessitated transfusions. In June fever (temperature to 40°C) and weight loss began. After additional anal surgery, a perianal ulcer developed and gradually spread. Tetracycline and prednisone were given. However, unrelenting fever, perianal ulceration, and a 12-kg weight loss prompted an extensive but unrevealing evaluation, which included colonoscopy, gastrointestinal contrast studies, marrow biopsy, gallium and liver/spleen scans, abdominal sonography, and standard cultures.

The patient was transferred to the Mount Sinai Hospital in February 1981 because of cachexia and a 20-cm perianal ulcer (Fig. 1). Repeat evaluation for inflammatory bowel disease and lymphoma included exploratory laparotomy and construction of a diverting colostomy. No specific pathologic process was found; node-biopsy specimens were normal. Cultures of the ulcer grew HSV Type 2, which was confirmed by immunofluorescence testing and typical morphologic appearance. Vidarabine was given until central-nervous-system toxicity developed. In April, the patient was transferred to Memorial Hospital for further treatment with interferon and FIAC; however, the ulcer did not regress and cultures remained positive. Bilateral interstitial pneumonitis and encephalopathy led to his death in June.

At autopsy, necrotizing, hemorrhagic bronchopneumonia, hemorrhagic colitis, and cholelithiasis were found. Post-mortem cultures from lung, liver, spleen, lymph nodes, and heart were negative, but herpetic intranuclear inclusions suggestive of cytomegalovirus were seen in the colon, adrenals, stomach, and lungs.

Patient 4

A 22-year-old Hispanic homosexual man had fever (38.5°C) and night sweats in July 1980. Gradual weight loss began. Oral candidiasis was noted in September. By December, an 8-kg weight loss, generalized lymphadenopathy, splenomegaly, anemia, and leukopenia were observed. Chest films showed an infiltrate in the right upper lobe. Evaluation for underlying disease, including gastrointestinal roentgenography, liver biopsy, gallium scanning, abdominal sonography, and colonic and lymph-node biopsies, gave non-specific or normal results. In January 1981, perianal vesicular lesions first appeared; cultures showed HSV Type 2. Spiking fever, lethargy, anorexia, and weight loss continued, and the perianal lesions formed a gradually enlarging ulcer; ulcerative lesions, from which HSV was cultured, also appeared on the nasolabial fold (Fig. 2A). By April, the patient had lost 22 kg and had severe oral candidiasis. Treatment with amphotericin led to some reduction in the

candidal infection; klebsiella bacteremia resolved with antibiotics. Treatment with vidarabine for two weeks did not affect the lesions or other symptoms, but in May acyclovir (Burroughs-Wellcome) given for 10 days led to defervescence and gradual healing of the ulcers (Fig. 2B). The marked lymphopenia and lymphoid dysfunction (Fig. 2B). The marked lymphopenia and lymphoid dysfunction that had characterized the disease (see Results) were not altered. TMP-SMZ was given in low doses to prevent pneumocystosis. In July, the ulcers recurred and HSV was again cultured. During successful retreatment with acyclovir, bluish nodules on the back and penile shaft were noted. On biopsy, a diagnosis of Kaposi's sarcoma was made.

RESULTS

Serologic data are summarized in Table 1. Patient 1 never had detectable complement-fixing antibodies against HSV. Patients 2 and 4 had unchanging titers, against HSV. Patients 2 and 4 had a fourfold increment in titer. Sero- and Patient 3 had a fourfold increment in titer. Serologic evidence of active cytomegalovirus infection was present only in Patient 2. Patient 4 had complement-fixing antibody titers of 1:8 and less than 1:8. There was no evidence of acute or recent infection with varicella-zoster or Epstein-Barr viruses, lymphogranuloma venereum, or toxoplasmosis. Antibody to hepatitis B virus was present in two patients, and hepatitis B surface antigenemia developed late in Patient 1. Other serologic studies, particularly in Patient 1, failed to

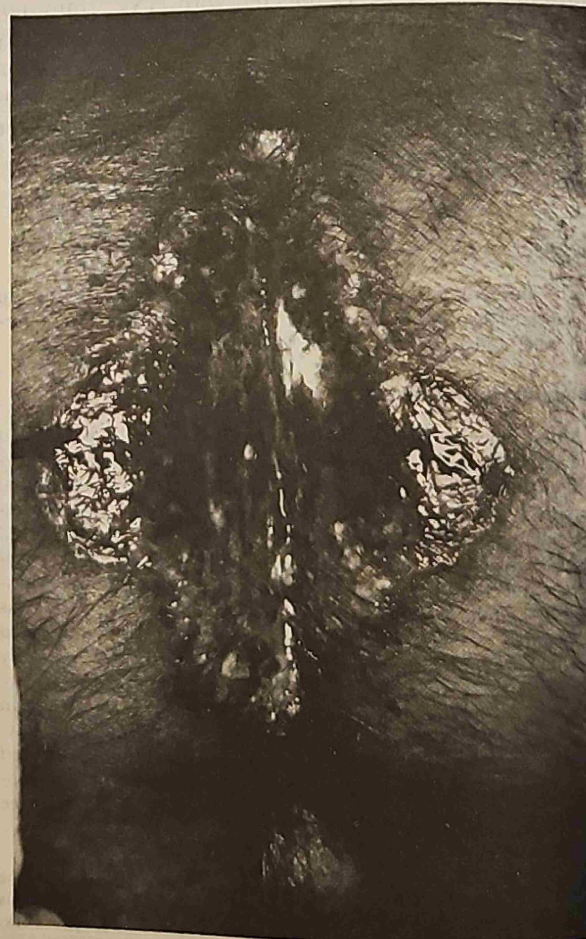


Figure 1. Perianal Ulceration of Patient 3, before Therapy with Vidarabine. The appearance of the lesion did not change during or after this treatment.

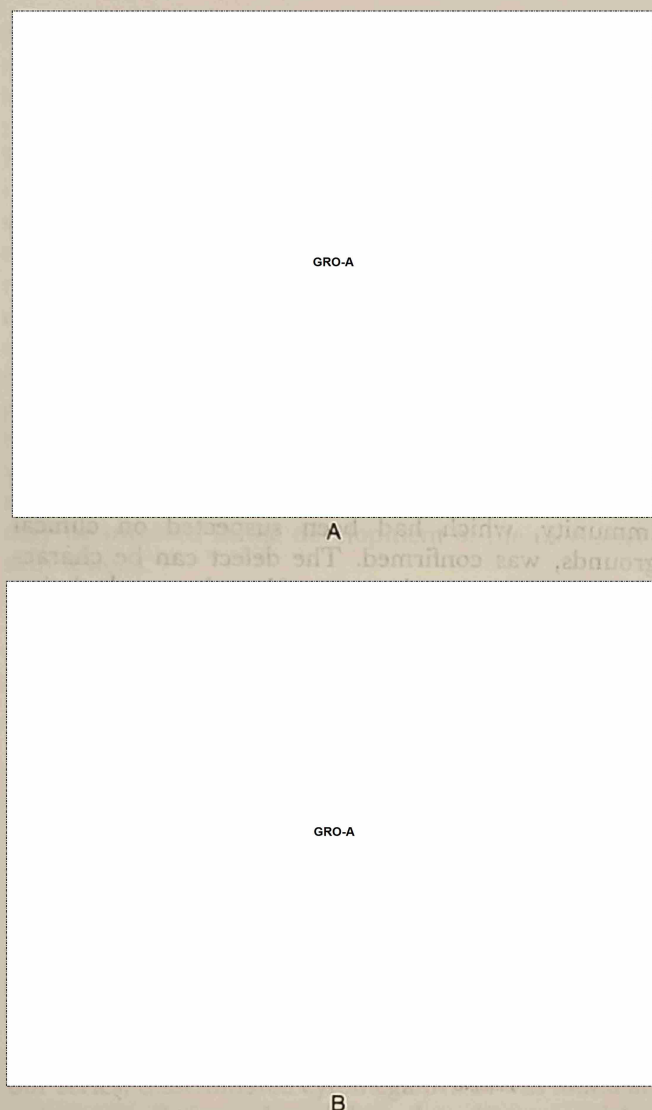


Figure 2. Nasolabial Lesion of Patient 4.

Panel A shows lesion (completely obstructing both nares) before therapy with acyclovir, and Panel B shows healing three days after treatment.

suggest infection with legionella species, cryptococcosis, histoplasmosis, *Entamoeba histolytica*, toxoplasma, respiratory syncytial viruses, or rubeola virus. Serologic testing for syphilis was negative in all patients.

Skin anergy to recall antigens was present in all subjects (Table 2). Total lymphocyte counts were regularly depressed. Except for a single determination (Patient 1, July 1980), counts did not exceed 1000 and averaged from 200 to 600. The severe lymphopenia limited the studies that could be done. The proportion of cells with T-cell characteristics ranged from normal to depressed in various determinations. The proportion of sheep rosettes tended to be lower than the proportion of cells demonstrable with use of hybridoma-derived antibodies to T cells (anti-Leu-1). Although this finding suggests that a serum inhibitor of rosette formation was present, none was found in Patients 3 or 4. The proportion of T cells exhibiting a

suppressor/cytotoxic cell phenotype (Leu-2a) was increased in Patient 3 but not in Patients 2 or 4. Lymphocyte responses to plant lectins were moderately diminished in Patient 1, more severely so in Patients 2 and 3, and progressively depressed in Patient 4. Only Patient 4 had a response to phytohemagglutinin that was within the normal range when he was first studied. Responses to pokeweed mitogen were relatively preserved. In Patient 1, despite only moderate depression of mitogen-induced proliferation, transformation responses to all antigens tested, including HSV and cytomegalovirus, were absent.

Measurements of serum immunoglobulin and immunoelectrophoresis indicated polyclonal hyperimmunoglobulinemia, particularly of IgA. Despite this finding, serum antibody titers were generally low. The proportions of B cells were normal in all subjects. Absolute numbers of B cells, as well as of T cells, were depressed.

We considered the results of the assay of natural-killer-cell function in two ways. (1) HSV-specific natural-killer activity in lytic units per million mononuclear cells was determined directly from the lytic system. The calculation, which is based on a range of ratios of killer cells to target cells, considers all cells isolated from blood.¹² According to this standard, natural-killer activity was normal in Patients 1 and 4; it was initially very depressed, in Patient 3, but later gradually became normal. (2) Because of the severe deficiency of mononuclear cells, calculation of the lytic units per milliliter of blood, based on cell yields, was also made (Table 2). By this criterion, all subjects had severely depressed natural-killer function; Patient 2 had no measurable activity.

DISCUSSION

Ulcerative lesions caused by HSV are usually observed only in patients with severe deficits of cellular immunity associated with another underlying disease.¹⁻⁸ That four patients who were believed not to have been previously immunocompromised had such skin lesions (with three dying after an inexorably downhill course) suggests that some factor common to all the patients was operative. The fact that all were homosexual men was striking. Reports of Kaposi's sarcoma and opportunistic infections similar to those that we observed (e.g., *P. carinii*, *Cryptococcus neoformans*, and cytomegalovirus) suggest that our findings are part of a nationwide epidemic of immunodeficiency among male homosexuals.^{15,16}

The most prominent and so-far unexplained immunologic finding in these four men was profound lymphopenia. Many of the immunologic deficits that we measured could be attributed to this state of apparent lymphocyte depletion. Skin anergy was present in all subjects. When the responses to in vitro stimulation with plant lectins and antigens could be determined, they showed moderate to marked depressions in lymphocyte proliferative ability. Difficulty in interpretation of these data arises because of the paucity of available lymphoid cells and their dilution

Table 1. Evidence of Ulcerative Herpes Simplex and Other Infections among Four Homosexual Men.

EVIDENCE	INFECTION *						
	HSV	CMV	HBsAg	HBsAb	<i>Candida albicans</i>	<i>Pneumocystis carinii</i>	ADENOVIRUS
	no. of patients positive/no. tested						
Positive culture	4/4	0/4	†	†	2/4	†	1/4
Morphologic (active infection)	4/4	3/4	†	†	2/4	1/4	1/4
Serologic							
Prior exposure	3/4	2/4	0/4	2/4	†	†	0/1
Active infection (titer rise)	1/4	1/4 ‡	1/4	0/4	†	†	0/1

*HSV denotes herpes simplex virus, CMV cytomegalovirus, HBsAg hepatitis B surface antigen, and HBsAb antibody to HBsAg.

†Study was either inappropriate or not performed.

‡Another patient (Patient 4) had a cytomegalovirus titer below 1:8 on complement fixation when first studied; on a repeat study two weeks later the titer was 1:8.

by monocytes in the mononuclear-cell isolates. Relative monocytoysis in mononuclear-cell preparations is known to lead to poor in vitro proliferative responses.¹⁷ Among the lymphoid cells present, there was specific depression of cells forming sheep-erythrocyte rosettes in two patients and a relative rise in cells bearing the Leu-2a phenotype in one patient. The relative rise implies an increase in the ratio of suppressor to helper cells among the lymphoid-cell populations — a finding that we (unpublished data) and others¹⁸ have observed in cases of infectious mononucleosis. Attempts to rectify the lymphoid-cell responses of one patient in vitro by means of thymic humoral factors¹⁹ were unsuccessful. When these findings were taken together, a severe defect in cellular

immunity, which had been suspected on clinical grounds, was confirmed. The defect can be characterized as a progressive state of lymphocyte depletion and consequent dysfunction, in which cellular immunity is principally affected.

The specific host defense against HSV is poorly understood. Although patients with depressed lymphocyte counts or T-lymphocyte-macrophage dysfunction might be expected to have severe illness secondary to HSV, the vast majority of such patients do not. Consequently, it is suspected that other factors play an important part in HSV-specific host defense. The group of patients most frequently reported to be susceptible to ulcerative HSV are those who have had immunosuppression for organ transplantation. Re-

Table 2. Immunologic Findings in Patients and Controls.

STUDY	FINDING *							
	PATIENTS				CONTROLS			
	1	2	3	4	mean \pm S.D.			
Delayed-type skin response	Absent	Absent	Absent	Absent	Present			
Mean lymphocyte count	657	435	316	360	1000-4800			
T cells (per cent)								
Sheep rosettes	70	59, 79	28	69, 55	80 \pm 7			
Leu-1	ND	89	53	65	78 \pm 5			
Leu-2a	ND	20	62	29	32 \pm 9			
Mitogen responses (net cpm †)								
Phytohemagglutinin	11,852	1,509	1,313	613	23,100	968	475	29,000 \pm 4,400
Concanavalin A	1,683	1,767	674	386	1,372	767	478	21,000 \pm 6,200
Pokeweed mitogen	5,635	1,148	3,887	766	4,136	1,067	132	15,800 \pm 5,100
Antigen responses in vitro	Absent	QNS	QNS	QNS	Positive			
Mixed leukocyte reaction (net cpm †)	1,505	QNS	QNS	QNS	>5000			
Natural killing of HSV-infected target cells ‡	8.2, 1.4	0	0.2-21.7	15.7	111 (52-239)			
Serum immunoglobulin (mg/dl)								
IgG	864-1394	2360	1660	1370-1710	500-1500			
IgA	322-375	445	435	420-1431	40-300			
IgM	133-300	90	230	55-275	40-200			
Isohemagglutinin								
Reciprocal								
Titers (anti-A/B)	-/8	8/-	32/8	4/0	>4			
B cells (per cent IgM-positive)	0	QNS	8	8	6 \pm 2			
Immune complexes	0	0.20	0.20	0.04	0.04	<0.12		

*ND denotes "not determined," and QNS "quantity not sufficient [for determination]."

†Net cpm = (cpm stimulated) - (cpm unstimulated control), where cpm = counts (per minute) of tritiated thymidine incorporated after three days' culture (five days for mixed leukocyte reaction).

‡Killing = (cytotoxicity toward infected targets) - (cytotoxicity toward uninfected targets), expressed as lytic units per milliliter of blood. Normal range = \pm 2 S.D. on long-transformed data.¹²

cently, cells that confer "natural" immunity and do not require prior exposure to their specific target cells have been described. Certain natural-killer cells are thought to be involved in the host defense against HSV in mice and in human beings.^{12,20} Overwhelming disseminated HSV infection in neonates and in some adults is associated with depressed natural-killer activity of this sort.¹² We measured this type of natural-killer cell in our patients because of their unusual HSV lesions. On a "per-cell" basis, the natural-killer cells in two of the four patients were abnormally hyporesponsive. Moreover, in view of the paucity of mononuclear cells present per unit of blood, the calculated herpes-directed natural-killer activity was severely depressed in all patients. Thus, a common absence of HSV-directed natural-killer activity may be involved in the development of the ulcerative skin lesions.

The cause of the immunodeficiency disorder that we observed is undoubtedly complex. Viral infection, especially in unusually heavy inoculum transmitted by enteric routes, may be an important initiating factor.

Infection by a great many viruses such as measles or rubella can result in depressed delayed-type hypersensitivity.²¹ Primary cytomegalovirus infection has been associated with a particularly prolonged cellular immunodeficiency state.^{22,23} Exposure to cytomegalovirus is known to be particularly heavy within the homosexual community; a 94 per cent prevalence has been defined by anticomplement immunofluorescence.²⁴ A series of four previously healthy homosexual men with active cytomegalovirus infections complicated by *P. carinii* pneumonia has been reported.¹⁵ In our series, disseminated cytomegalovirus was found at autopsy in Patients 1 and 3, and on biopsy and by seroconversion in Patient 2. Cytomegalovirus must be considered a candidate initiator of the immune defects observed.

Serum immunoglobulins were increased. The consistent elevation of serum IgA levels could reflect the importance of gut-associated lymphoid tissue as a primary site of immunization in this disorder. Battisto and Chase described a state of antigen-specific hyporesponsiveness occurring after oral immunization²⁵ that has recently been reported to result from the seeding of suppressor cells to non-gut-associated lymphoid tissue.²⁶ The immune deficit that we observed could likewise result, in part from the route of exposure to viral pathogens.

Since these cases are certainly rare, even among homosexuals, additional factors must be involved in susceptibility. A group may be specifically hyporesponsive to HSV, perhaps because of their genetic background — e.g., HLA-D-linked immune-response genes. Heavy exposure to HSV could lead to chronic infection, and secondary immunodeficiency could then result. At present, no group has been defined that is genetically susceptible to HSV.

Still another possibility is that among men who are homosexual, some have a latent, broad-based cellular

immunodeficiency that becomes clinically manifest only because of heavy exposure to certain pathogens in particular combinations. For example, a homosexual male nurse whom we studied recovered from pneumocystis pneumonia but eventually died at another hospital of recurrent pneumocystis and cytomegalovirus pneumonia. He had markedly depressed cellular immunity in vitro and increased proportions of Leu-2a-positive cells among his T lymphocytes. Extensive history taking by one of us (B.R.A.) indicated susceptibility to a variety of infectious agents over the previous 20 years, suggesting a low-grade cell-mediated immunodeficiency.

Severe malnutrition probably accentuated the immune deficits that we observed.²⁷ By the time these patients came under study, all were anorectic and cachectic and had been chronically ill for many months. Because of the specific immunosuppressive effects of zinc deficiency,²⁸ plasma zinc levels were determined; they were found to be normal in all four patients, but three were nevertheless given zinc salts empirically. In addition, efforts were made to improve overall protein-calorie intake through oral and parenteral nutritional supplements. Neither of these approaches seemed to alter the patients' clinical courses appreciably.

In view of the relative preservation of immunologic functions early in the course of the illness in Patient 4, immune deficits like those we observed appeared to be progressive with time. It seems possible that earlier recognition and prospective study of such patients will reveal an anomaly in host defense that could illuminate the pathogenesis of this disorder.

There was no obvious contact between the four men. To ascertain whether there was any epidemiologic relation among the viral strains isolated, we submitted samples of the viruses for restriction-enzyme mapping²⁹ (by Dr. Bernard Roizman, University of Chicago). The isolates, all Type 2, were found to be unrelated.

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Note added in proof: We recently studied a fifth patient, a 45-year-old homosexual man with a nine-month history of hepatitis, gradual wasting, eventual intergluteal herpes simplex ulcers, and probable herpes encephalitis. During the period of study, lymphoid function was initially normal, but it later deteriorated. Lymphopenia developed only late in the course. Natural-killer-cell activity studied while the patient had normal lymphocyte counts was very depressed.

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MEDICAL PROGRESS

CAMPYLOBACTER ENTERITIS

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IN less than a decade, *Campylobacter jejuni* has emerged from obscurity as a veterinary pathogen¹ to recognition as a leading cause of enteritis in human beings.²⁻⁶ When proper culture techniques are used, *C. jejuni* is isolated in North America and Europe from patients with diarrhea at least as often as salmonella or shigella species. Moreover, *C. jejuni* has been found in virtually every country in which it has been sought. It seems appropriate, therefore, to give the background that led to documentation of the importance of *C. jejuni* in disease in human beings and to review what is known about campylobacter enteritis.

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HISTORICAL BACKGROUND

Campylobacter species have been known to cause abortion in cattle and sheep since the initial isolation of *Vibrio* (now *Campylobacter*) *fetus* in 1909.⁷ In 1947, *V. fetus* was first cultured from a person,⁸ and over the next 10 years these organisms were occasionally isolated from blood, cerebrospinal fluid and other body fluids, and from abscesses.⁹ Most of the affected patients were elderly or were debilitated by alcoholism, malignant disease, diabetes mellitus, or cardiovascular disease.^{9,10} Because *V. fetus* caused systemic illness predominantly in compromised hosts, it was considered an opportunist. In 1957, however, Elizabeth King recognized that there were two groups of *V. fetus* isolates, each with distinct serologic and biochemical characteristics. She called the organisms that grew best at 42°C "related vibrios" and noted that although the organisms were isolated from blood cul-