Interferon, Antibody, and Other Host Factors in Herpes Zoster

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ABSTRACT The influence of several factors on the course of herpes zoster was studied in 151 patients. Dissemination of zoster was associated with the presence of a concurrent disease, especially Hodgkin's disease, and/or the use of immunosuppressive therapy. Several host-immune parameters, including quantitative immunoglobulins, circulating lymphocyte counts, delayed hypersensitivity to multiple skin test antigens, and lymphocyte transformation to phytohemagglutinin did not correlate with dissemination of disease. Development of virus-specific complement-fixing antibody (CFA) was delayed in some patients with disseminated disease.

Vesicle interferon (V-IF) titers were low early in the disease in patients with localized and disseminated zoster and then rose, usually abruptly, to a peak value and declined as pustulation and crusting occurred. However, titers in patients with localized disease rose at an earlier time. This could be seen in terms of time to development of intermediate values of V-IF or by the day on which the sharpest rise occurred. In 15 carefully studied patients with disseminated disease, the development of the maximum V-IF response was followed within 48 hr by cessation of dissemination. Half of the patients in this group had no CFA detectable until after dissemination had ceased.

These findings suggest at least two host factors whose interaction might determine host response to zoster; local interferon production (possibly mediated by sensitized lymphocytes) and humoral antibody, acting to prevent or shorten dissemination of an initially local disease.

INTRODUCTION

It is accepted, from epidemiological studies, that herpes zoster is due to the reactivation of latent varicella-zoster (VZ) virus infection, usually acquired years before in childhood and manifested at that time as chicken pox (1–4). Herpes zoster most commonly appears as a localized infection confined unilaterally to a single or adjacent dermatomes served by the nerve distribution of a spinal cord segment or cranial nerve branch. However, sometimes the infection will spread from its localized area and pox appear in distant areas of the skin; visceral involvement may also occur. The reported incidence of dissemination has varied from 2 to 90% (5). Obvious factors influencing this variance include the method of patient followup; i.e., personal experience as opposed to retrospective chart reviews, etc. It has also been suggested that certain underlying diseases and various therapeutic modalities predispose to this complication (5–8).

We have studied and report here, in a current series of patients, the influence on dissemination of associated disease and treatment, as well as several host-immune factors, including humoral immunity, cellular immunity, and interferon production.

METHODS

Patient population. The patient population consisted of 151 patients referred to the Division of Infectious Diseases between July 1969 and April 1971. Patients diagnosed as having herpes zoster had a classical clinical presentation and lesion distribution. Serological confirmation was obtained in 125 cases with serial (two to three specimens) complement-fixing antibody (CFA)[1] titrations and/or simultaneous anti-VZ (varicella-zoster) and anti-herpes simplex virus CFA titrations (9). Serologic studies, demonstration of specific immunofluorescence with monkey anti-VZ serum on vesicle scrapings (10), and/or VZ virus isolation from clinical specimens was obtained in nearly all cases, and in every case in which the clinical presentation was not classical. By these methods several cases of herpes simplex infection in a band-like (pseudozoster) distribution (11) were diagnosed and excluded from this series.

Patients were considered as having disseminated disease if five or more vesicles appeared distant from the primary dermatone or if visceral organ involvement was demon-

[1] *Abbreviations used in this paper:* CFA, complement-fixing antibody; MEM, Eagle's minimum essential medium; PHA, phytohemagglutinin; PPD, purified protein derivative of *M. tuberculosis;* V-IF, vesicle fluid interferon; VZ, varicella-zoster.

strated. Thus three patients with less than five distant vesicles were considered to have "trivial dissemination" and grouped with the patients with localized disease, as was a fourth patient with vesicles appearing anteriorly and posteriorly on both legs but none above the waist (possible autoinoculation). Two patients seen late in their course who had central nervous system involvement attributable to herpes zoster infection, but in whom distant vesicles were not documented, were considered as disseminated. In patients with disseminated disease, each new crop of peripheral vesicles was counted and circled in a different color each day. Generous margins were used to delineate the primary dermatome in counting pox to allow for the variable distribution of somatic nerves.

Laboratory procedures. Quantitative immunoglobulins were determined during the acute illness by radial immunodiffusion (12). Normal adult values (milligrams per 100 milliliters, mean±2 SD) for the laboratory performing this test are: IgG 710–1540, IgA 60–490, IgM (males) 37–204, IgM (females) 42–261. Corresponding childhood normal limits used were as previously published (12). Anti-VZ CFA titrations were performed by the method of Brunell and Casey (13). Vesicle fluid interferon (V-IF) titrations, and studies to determine if the interfering activity had the physicochemical properties of interferon, were performed as described previously (14). All V-IF determinations were performed on pooled vesicle fluid from the primary dermatome area.

Lymphocyte stimulation by phytohemagglutinin (PHA) was performed as follows. 30 ml of blood was drawn into a syringe containing 1.5 ml phenol-free heparin. Gravity sedimentation of the cells was allowed for 2 hr, and the leukocyte-rich supernatant aspirated and counted. This supernatant was then centrifuged at 1000 rpm for 10 min, and a quantity of plasma removed. The cell pellet was then resuspended in the remaining plasma and Eagle's minimal essential medium (MEM) at a cell density of 2×10^6 cells/ml and in a concentration of 10% autologous plasma. Siliconized loosely capped glass tubes were seeded with 2 cc of cell suspension. To three or more tubes, 68 μg of PHA-P (Difco Laboratories, Inc., Detroit, Mich.) was added in 0.1 ml MEM and three or more tubes served as a control (0.1 ml additional MEM added). On a few occasions when the volume of blood obtained was less than 30 ml (child, or adult with difficult venesection) only two PHA and control culture tubes could be initiated. After 6 days at 37°C in a 5% CO_2 environment, 2 μCi of tritiated thymidine in 0.1 ml was added to each tube. After 18 hr the cells were harvested on filter paper, the papers were oven-dried and inserted in vials with toluene-base scintillation counting fluid and counted for 4–10 min in a liquid scintillation counter. Results were scored as the ratio of counts/minute in PHA-treated to control cultures, and analyzed using a 5-fold or greater increment of PHA to control cultures as an acceptable response. Although preliminary experiments showed that the increase in counts in stimulated cultures was slight after 4 days, the longer incubation time was used because of concurrent experiments with other antigens (not reported here) which required the longer periods.

Adults with less than 1000 circulating lymphocytes on each determination during the acute illness were considered lymphopenic, and comparable values for childhood age groups were determined from standard sources (15).

0.1 ml of mumps (Eli Lilly & Co., Indianapolis, Ind.), *Candida* (Hollister-Stier Laboratories, Spokane, Wash.),

intermediate purified protein derivative (PPD) of *Mycobacterium tuberculosis,* histoplasmin, and blastomycin (Parke, Davis & Company, Detroit, Mich), coccidioidin (Cutter Laboratories, Inc., Berkeley, Calif.) 1:100 dilution, skin test antigens were applied to the volar forearm of patients during the acute illness. The mumps test was read at 24 hr and the others at 48 and 72 hr. Erythema $\geqq 1.5$ cm was considered a positive reaction to mumps antigen, and reactions of >5 mm induration were considered positive for the other antigens. Previous studies (16) with similar antigens suggest that $>95\%$ of the general population would react to one or more of these antigens.

Statistical methods. All significance tests for differences between groups were calculated by the chi square method.

RESULTS

Influence of diagnosis and treatment. The patients were divided into three categories: no underlying disease (normal) (79 patients), concurrent Hodgkin's disease (26 patients), and the remainder (Miscellaneous) (46 patients). The diagnoses associated with zoster are given in Table I.

Dissemination was most common in patients with Hodgkin's disease and least common in patients with no underlying disease (Table IIA).[a] Although the most

TABLE I

List of Diseases Associated with Herpes Zoster*

Hodgkin's disease (26)	Alcoholic cardiomyopathy
Carcinoma (7): breast (3), lung (2), nasopharyngeal, endometrial	Serum hepatitis
Lymphoma (6): histiocytic (2), lymphosarcoma (2), lymphocytic, reticulum cell sarcoma	Rheumatoid arthritis
	Acute lymphocytic leukemia
	Cirrhosis and hepatic coma
Systemic lupus erythematosus (6)	
Chronic lymphocytic leukemia (3)	Myeloma
Diabetes mellitus (3)	Myeloid metaplasia
Ulcerative colitis (2)	Wilms' tumor
Chronic obstructive lung disease (2)	Arsenic poisoning
Sarcoma (2): osteogenic, hemangiopericytoma	Multiple sclerosis
	Renal transplant
Hydronephrosis, bilateral	Psoriasis
Heart transplant	Benign lymphoproliferative disease

* Number in parenthesis indicates number of patients with each type of disease if greater than one.

[a] The incidence of dissemination in these diagnostic categories is that seen at a university medical center, where immunosuppressive therapy for various diseases is common. Despite frequent referrals of patients with zoster from the San Francisco Bay area for study and for preparation of zoster-immune globulin, it is likely that cases with complications are referred in a higher proportion than uncomplicated ones. For the Hodgkin's disease group, how-

TABLE II

Relationship of Dissemination to Diagnosis, Stage, and Therapy

A. Dissemination in herpes zoster

	Patient category		
	Hodgkin's disease	Miscel-laneous	Normal
Number of patients	26	46	79
Dissemination, %	73	30	11
Duration of dissemination, Mean *days**	3.9	6.9	4.7

B. Dissemination within miscellaneous category

	Dissemination rate‡	
	All patients	Patients with immuno-suppressive therapy§ only
Malignancy	10/21	9/19
No malignancy	4/25	4/14

C. Dissemination in Hodgkin's disease, by stage

	Dissemination rate‡
Stage I	1/2
Stage II	4/6
Stage III	3/3
Stage IV	11/15

* Minimum number, because cytosine arabinoside given intravenously for severe disease in a few patients may have abbreviated the course, and because four patients died during disseminated disease.

‡ Patients with disseminated disease/total patients (for whom information available).

§ Radiotherapy or chemotherapy with corticosteroids or cytotoxic drugs.

severe dissemination was seen in patients with associated diseases, the mean number of days in which new distant lesions were seen was not strikingly different in the three categories.

Although dissemination was more common in patients with a malignancy (even if Hodgkin's disease was excluded), this association appears more closely related to the effect of therapy rather than diagnosis (Table IIB). Within the Miscellaneous category, the dissemination rate was similar in patients with or without malignancy when only patients receiving immunosuppressive therapy were compared.

ever, the incidence of dissemination may accurately reflect that in a group of patients treated extensively (17) (radiotherapy with curative intent, splenectomy at time of staging laparotomy, and/or quadruple chemotherapy in many patients). This is because most of these patients were referred to us with the disease still localized, and the possibility of dissemination was evaluated by frequent careful examinations.

The correlation between dissemination and the different modalities of therapy is presented in Table III. In the Miscellaneous category there appears an increased association of dissemination with cytotoxic drugs rather than with steroids, apparently unrelated to diagnosis. Although all the patients receiving steroids alone did not have a malignancy and dissemination of disease was rare, two of the five patients receiving only cytotoxic drugs in whom dissemination occurred did not have a malignancy.

In patients with Hodgkin's disease and zoster, there was a preponderance of zoster cases in advanced lymphoma (Table IIC). This distribution of Hodgkin's-zoster cases by stage contrasts sharply with the incidence of these stages in the total Hodgkin's disease population (17) as Stanford. However, dissemination was frequent regardless of the stage of disease.

Immune factors and dissemination. Quantitative immunoglobulins, circulating lymphocyte counts, delayed hypersensitivity to six skin test antigens, and lymphocyte stimulation by PHA were compared for localized and disseminated zoster in the three patient categories (Table IV). There was no significant ($P < 0.05$) association of any of the first three parameters with disseminated disease, with the exception of a high incidence of hypogammaglobulinemia in disseminated patients in the Miscellaneous category. This could not be associated with any particular disease, as all four disseminated patients in this category had different diagnoses. There was

TABLE III

Relationship of Dissemination to Therapy

Therapy	Patient category	
	Miscel-laneous	Hodgkin's disease
Radiotherapy alone*	0/1‡	4/9
Chemotherapy alone		
Corticosteroids	1/7	—
Cytotoxic drugs§	5/6	—
Both corticosteroids and cytotoxic drugs	3/7	4/4
Both chemotherapy and radiotherapy		
Radiotherapy, corticosteroids	0/1	2/2
Radiotherapy, cytotoxic drugs	3/6	3/3
Radiotherapy, corticosteroids, cytotoxic drugs	1/4	6/7

* Radiotherapy in preceding 12 months.

‡ Patients with disseminated disease/total patients.

§ Therapy in preceding 6 months with one or more of: cyclophosphamide, 6-mercaptopurine, L-asparaginase, chlorambucil, nitrogen mustard, melphalan, hydroxyurea, busulfan, methotrexate, azathioprine, vinblastine, vincristine, procarbazine, 5-fluorouracil.

TABLE IV

Correlation of Impairment of Host Immunity and Dissemination

| | Patient category | | |
Immune deficiency	Normal	Miscel-laneous	Hodgkin's disease
Lymphopenia in:			
Localized zoster	0/19*	15/27	5/7
Disseminated zoster	1/9	5/13	12/17
Anergy in:			
Localized zoster	7/12	8/10	4/4
Disseminated zoster	0/4	3/4	11/12
Depressed IgG, IgA, or IgM in:			
Localized zoster	4/35	2/18	3/5
Disseminated zoster	1/7	4/7	3/9
Depressed lymphocyte transformation to phytohemagglutinin in:			
Localized zoster	1/15	7/16	3/5
Disseminated zoster	0/6	2/5	6/12

* Fractions are number of patients in category with immune deficiency/total patients in category assayed for this immune parameter. See Methods for criteria used. The sample of patients assayed for any parameter is believed representative of the total population in that category.

also no association with a particular immunoglobulin class; of the eight disseminated hypogammaglobulinemic patients, decreased levels of IgG, IgA, and IgM were present in five, four, and seven patients respectively.

No relationship between dissemination of zoster and diminished lymphocyte transformation by PHA was found. However, in some groups we had but few patients.

Patients (both with localized and disseminated zoster) in the Hodgkin's and Miscellaneous categories had, in general, lower transformation than normal individuals. This depression has been noted in earlier studies in Hodgkin's disease, and in other patients receiving anti-tumor therapy, in the absence of zoster (18-22). To rule out the effect of the acute concurrent viral disease on lymphocyte transformation, 9 patients were assayed a second time months after the acute zoster. This group included patients from all three patient categories, with localized and disseminated disease and with high and low initial values. There were no significant changes in transformation on retesting these patients.

CFA studies. Fig. 1 shows the CFA results in the first 40 days after onset in patients with localized and disseminated disease. It is apparent from this figure that there are proportionately more negative determinations in the first 10 days after onset in patients with dissemination, and several negative determinations after 10 days. If the first 15 days after onset are subdivided and studied further (Table V) we note that for each 5 day interval more patients with localized disease have antibody. For this analysis, patients who were seronegative on their initial determination were considered to be also negative at any 5-day intervals which preceded that determination. Likewise, after presence of antibody was demonstrated in a serum specimen, that patient was counted as sero-positive in any succeeding 5-day intervals (even though no further determinations may have been performed on that patient). The validity of these assumptions was confirmed by serial follow-up of many individual patients. In all, once CFA was present, it could always be demonstrated in serum specimens collected for at least 100 days thereafter. The relationship of CFA titer to time in individual patients presented previously (23) was
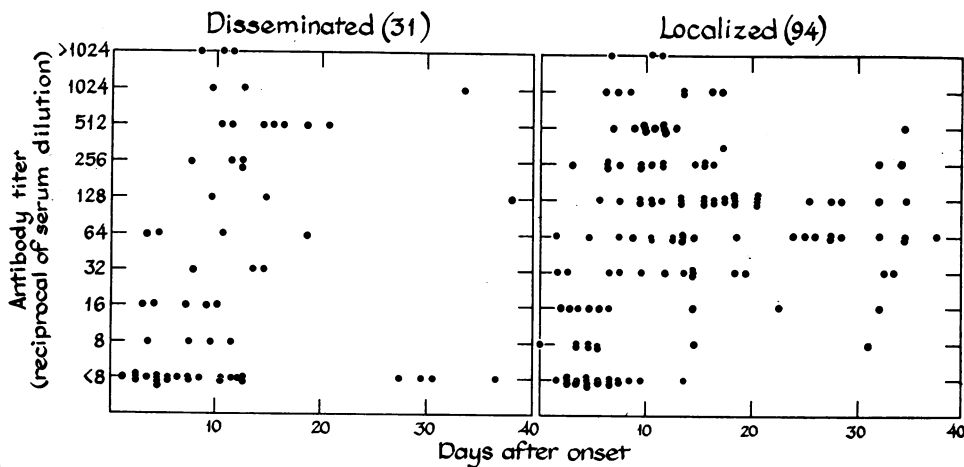

FIGURE 1 Time-course of complement-fixing antibody titers in disseminated (31 patients) and localized (94 patients) zoster.

TABLE V

Per cent of Patients with Complement-Fixing
Antibody at Selected Time Intervals

	Time interval, days after onset		
	0–5	6–10	11–15
Localized zoster	50% (26)	79% (47)	98% (64)
Disseminated zoster	26% (19)	55% (22)	77% (26)

Per cent, No. of patients with antibody titer >1:8/total patients (number in parenthesis) for whom data available × 100. The sample of patients assayed for any parameter is believed representative of the total population in that category.

confirmed in our patients. The four negative determinations after 15 days after onset were contributed by 2 hypogammaglobulinemic patients. These patients were considered to have failed to produce CFA and excluded from the above analysis.

This difference in antibody kinetics between localized and disseminated zoster appears not merely due to the presence of more patients with associated diseases in the disseminated group. Patients with localized zoster with and without an associated disease had the same kinetics of antibody response in this 15 day interval. Also, in the Miscellaneous category, where there were sufficient numbers of both kinds of patients (localized and disseminated) for comparison, these differences in time of antibody appearance were indeed statistically significant ($P < 0.05$).

Although the timing of CFA appearance in patients with localized and disseminated disease appears different, the mean peak CFA titer eventually reached by both groups was the same (Fig. 1).

Although 11 patients with disseminated zoster were seronegative at the time dissemination began, 2 patients (as well as an additional 2 patients studied since April 1971) began to form antibody before dissemination occurred. This group included a patient with a CFA titer of 1:128 4 days before dissemination began. Thus presence of CFA alone is not reliable in predicting whether dissemination will occur.

Vesicle fluid interferon. The kinetics of vesicle fluid interferon appearance was studied with serial specimens. We found both patients with localized and disseminated disease began with low levels (< 1000 units/4 ml, and commonly < 100 units/4 ml) which then later rose, usually abruptly over a 1-2 day period, to a peak value. V-IF then declined as pustulation and then crusting occurred. Summarized data on the time course of V-IF in localized and disseminated disease are presented in Fig. 2. At 5 days V-IF levels in patients with localized disease have begun to rise and by 9 days all have done

so. Patients with disseminated disease as a group lag behind patients with localized disease in development of V-IF levels, whether 1000 units (U) or 2000 U is compared, at the time intervals shown. The differences between these two groups of patients at either of these V-IF levels at 5, 7, and 9 days are significant ($P < 0.05$).

Sufficient serial samples were available from 26 patients to determine on which day the sharpest rise in V-IF began, and this information demonstrated also the earlier rise of V-IF in patients with localized disease. All of 11 patients with localized disease had begun their sharpest increase within 8 days (mean 5.4, range 1-8 days) after onset, whereas only 7 of 14 patients with disseminated disease had done so (mean 9.6 days, range 4-32 days) ($P < 0.05$). There thus appear to be two types of patients with disseminated disease with regard to V-IF. In one group V-IF rises about 6 days (±2 days) after onset (as do most patients with localized disease). In a second group of patients with disseminated disease V-IF sharply rises at 11±2 days after onset. The duration of dissemination was longer in this second group (mean 8.1 days *versus* mean 4.5 days for the first group). The group of patients with disseminated disease and a late V-IF rise also began their dissemination at a later time (mean 7.1 days after onset, range 2-12 days) than the group of patients with disseminated zoster and an early V-IF rise (mean 4.3 days after onset, range 3-6 days). If this were not the case, the differences in duration of dissemination might have been even greater.

The absolute increase in V-IF (i.e. from the lowest to the peak determination) was similar in patients with localized and disseminated disease. This increase in V-IF in patients with localized zoster ranged from 760-22,700
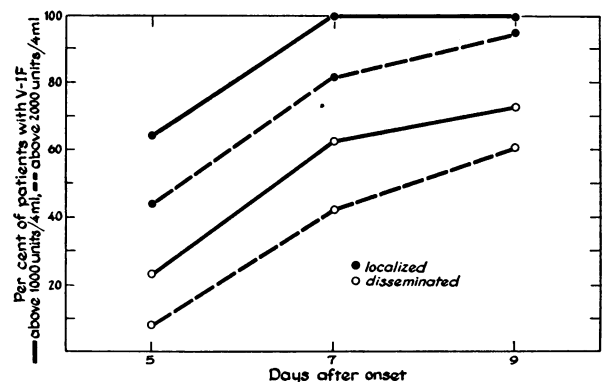

FIGURE 2 Differences in V-IF appearance in 25 localized and 22 disseminated cases of zoster as shown by time of development of intermediate (1000–2000 U/4 ml) V-IF levels. Differences between localized and disseminated zoster at both levels at 5, 7, and 9 days are significant at $P < 0.05$.

U (mean 7519 U), and in patients with disseminated zoster, 1090-34,900 U (mean 11,059 U).

The observed differences between localized and disseminated patients in timing of V-IF appearance appeared independent of any of our three patient categories. First, the localized and disseminated groups studied were similar in composition with regard to patient category. For example, only 3 of the 11 patients with localized disease discussed, in whom days from onset to sharpest rise could be calculated, had no underlying disease. This is largely because the patients with no underlying disease had smaller vesicles which evolved rapidly, thus making serial sampling difficult (see also footnote 3 in Discussion). Also, within the localized and disseminated groups, there was no correlation between presence or absence of associated disease and day of onset of rise.

The cessation of dissemination closely correlated with the development of peak V-IF levels. In all of 15 patients with adequate serial specimens and close followup with circling and counting of lesions, dissemination ceased within 48 hr after peak V-IF titers were reached, regardless of the number of days after onset or the number of days of dissemination which had elapsed. This information is summarized in Table VI. Two of these

patients, because of the severity of their zoster, were receiving intravenous cytosine arabinoside concurrently in the 48 hr preceding cessation of dissemination. We did not know the V-IF levels at the time this therapy was instituted. In several patients CFA did not appear until after dissemination had ceased. In two patients, with hypogammaglobulinemia, CFA was never detected —yet dissemination in these patients stopped, primary lesions healed, and the patients survived. Thus peaking of V-IF was the only factor common to this group of 15
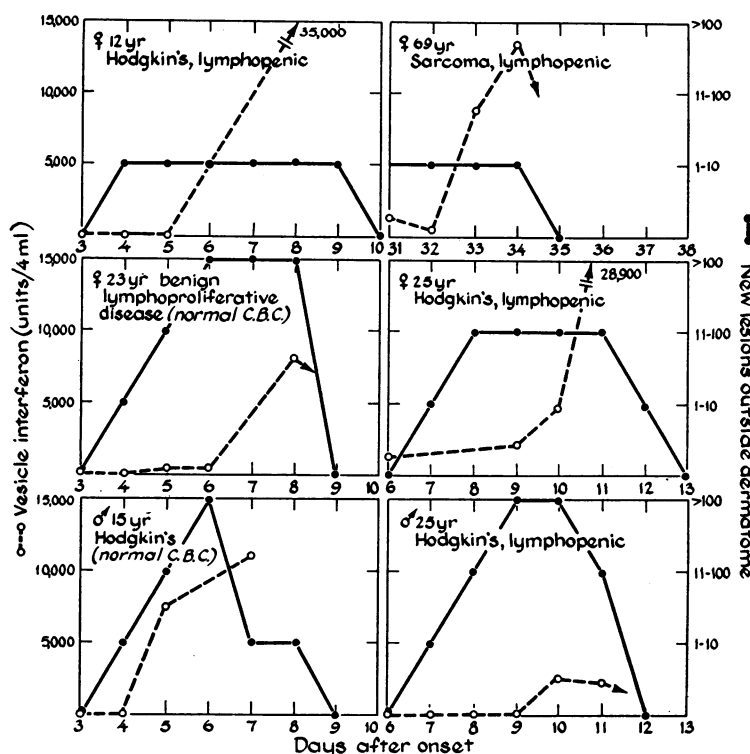

FIGURE 3 Relationship of dissemination of herpes zoster to V-IF. Dissemination phase of illness in six representative patients is shown. V-IF curve shown to development of peak titer; in some cases beginning of decline during crusting phase is shown (descending arrow).

patients in this 48 hr period. The inverse relationship of V-IF to lesion formation is illustrated in six of these patients in Fig. 3. The shape of the curve of V-IF appearance in some typical individual patients can also be seen.

In three patients we were able to sample two individual vesicles in the same patient on the same days of illness. The V-IF titer was the same in both vesicles at each time sampled. To rule out the possible presence of interferon antagonists or inhibitors of interferon action, i.e., stimulon (24), which could also explain low V-IF values, the following experiment was performed. Equal amounts of diluted vesicle fluid from a patient, taken from different days when low and later high interferon levels had been found, were mixed. The V-IF level in this pooled sample accurately reflected the dilution by the sample which had a low V-IF level, with no further drop in titer as would be expected if substances antagonizing interferon action were present in the low interferon sample.

Interferon was rarely demonstrable in the sera of any patients. In a few patients with localized disease sampled in the first few days and in a few patients with disseminated disease at the time that V-IF peaked, low levels of serum interferon (10-30 U/4 ml) were present for 1 day.

Are the delays in V-IF and CFA present in the same patients? Attempts to correlate delay in CFA production with timing of V-IF response (by day on which the abrupt V-IF rise occurred, or absolute level at 5, 7, and 9 days) in individual patients were made. These revealed an association between the timing of these two parameters, but no statistically significant correlations could be made.

DISCUSSION

Earlier studies of a small group of lymphopenic patients with neoplasia (14) suggested localized and disseminated herpes zoster infection could be distinguished by V-IF level, as patients with disseminated disease had levels < 100 U/4 ml. This does not appear to be the case as we find that patients with localized or disseminated zoster, if studied serially, begin with low V-IF levels which then rise, to the same extent in both groups, to high levels. A few patients with intermediate levels (about 1000 U/4 ml but < 2000 U/4 ml) also had dissemination but this ceased as V-IF levels continued to rise. To date, we have not observed any patients with localized zoster with a V-IF titer over 2000 U/4 ml whose disease subsequently disseminated. Dissemination also occurred in the absence of lymphopenia or neoplasia.

A distinguishing feature of the V-IF response, separating patients with localized and disseminated disease, is the later rise of V-IF in the latter group Although there was some overlap in timing of the V-IF response between these two groups there were significant differences. This could be seen by comparing the elapsed time before intermediate V-IF levels (1000 and 2000 U/4 ml) were reached, and, in patients in whom an abrupt rise could be demonstrated, for the time when the abrupt rise occurred.[3]

Of great interest also was the relationship of cessation of dissemination to the peaking of the V-IF response. Of the factors studied in these patients, this parameter alone had a consistent relationship with cessation of new lesion formation. We also noted that, although the vesicles had contained clear fluid until that time, within 24-48 hr after dissemination ceased, clouding of the vesicle fluid peripherally and in the primary dermatome occurred (pustulation). Drying and crusting began shortly thereafter, and the local disease resolved.

Several lines of evidence suggest the V-IF levels are not merely a reflection of the amount of local virus replication. Particularly in patients with associated diseases, big enlarging vesicles, and a protracted course, the absent or low interferon levels for several days (at a time when virus-induced pathology was obvious and tissue destruction increasing) are against this possibility. In some of these patients high V-IF levels did not appear until the 2nd wk of infection. In addition, several workers (25, 26) have documented that virus is present in the first few days after vesicle formation in herpes zoster.

We can only speculate that high V-IF titers are causally related to cessation of dissemination, but we have not observed any patients whose zoster ceased disseminating without a rise in V-IF, and the timing of these two events is appropriate for such a hypothesis. A local interferon response, perhaps mediated by sensitized lymphocytes migrating into the skin, may be critical in halting virus replication and thus preventing viremia. That sensitized lymphocytes release interferon in response to nonviral antigens has been shown (27) in vitro, and it has been demonstrated that lymphocytes may be the critical effector cell in interferon production in some

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[3] The differences in V-IF response between patients with localized and disseminated disease may be even greater than suggested here. To obtain serial samples from patients with localized disease we select for patients with larger primary involvement and longer duration of lesions, patients with localized disease likely to be deficient in the parameters under study. Thus, those patients, usually with no underlying disease, who had tiny vesicles which rapidly resolved would shift the development of high V-IF levels to an even earlier mean time for the localized disease group. Indeed, we did find high levels in the few patients with small, rapidly resolving disease in whom we were able to obtain single or multiple determinations in the first 3 days after onset.

animal models of virus infection (28). Cessation may of course occur as a result of change in another variable, not sampled, which parallels V-IF development or acts in conjuction with it. Such a variable could be another type of antibody other than CFA (e.g., neutralizing antibody), or a contribution of the cellular immune system.

Why does dissemination of herpes zoster occur in some patients while in others it remains localized? In comparison with patients with localized disease, some patients with disseminated zoster have a delayed V-IF response, some have a delayed CFA response, and a few have a delay in both. The overlap in time of appearance of V-IF and CFA in patients with localized and with disseminated disease suggests that the interaction of several factors may be important in containment of local disease. Our data also suggest a potentially important role for local interferon in host defense against viral infections.

We hypothesize that if an individual can mobilize a prompt systemic anamnestic humoral response, perhaps demonstrable by neutralizing antibody levels, as well as a local response in the primary dermatome mediated by sensitized lymphocytes and their effector molecules, he will contain the infection despite any associated disease or immunosuppressive therapy. This interpretation of our findings indicates further immunological studies which will be needed, and has implications for therapeutic intervention in this disease. Possible therapeutic approaches relevant to the compromised host include passive antibody or exogenous interferon, stimulation of endogenous interferon by a non-toxic inducer, or passive transfer of cell-mediated immunity through lymphocyte transfusion or the use of transfer factor.

Addendum. Since our report was prepared for publication, another paper has come to our attention in which a delay in the appearance of the CFA response was noted in patients with disseminated zoster (29). These authors commented that as this delay was seen in only two of the five patients they studied, it may be but a single manifestation of a more profound immunologic defect in patients who have disseminated disease.

ACKNOWLEDGMENTS

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