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# Response of Human Lymphocytes to Measles Virus After Natural Infection

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The lymphoproliferative response to measles, mumps, and vaccinia virus-infected monolayers measured in seropositive adults by thymidine incorporation demonstrated that only 5% of individuals responded well to measles virus (stimulation index, >5). Possible explanations for this occurrence include a lack of sensitization, active suppression, or failure in long-term stimulation. To distinguish among these possibilities, we studied the responses to measles virus in 22 immunocompetent individuals during early convalescence from natural measles infection. Substantial responses occurred (stimulation index, 7.03), particularly in a smaller group which included those individuals with milder cases of the disease. The level of responsiveness declined over a period of weeks. Responder and nonresponder cell mixing showed no active cellular suppression. These studies indicate that the low responses to measles virus found in late convalescence represent a lack of prolonged stimulation of the cell population measured in this assay.

In an earlier study (18), the measurement of the lymphoproliferative responses of seropositive adults to measles, mumps, and vaccinia viruses by [$^3$H]thymidine ([$^3$H]Tdr) incorporation demonstrated that only a small number (5%) of individuals responded well to measles virus (stimulation index [SI], >5), as compared with more substantial responses to mumps (SI, 10.6) and vaccinia viruses (SI, 12.5), and that, in responder individuals, T cells were responsible for the proliferative response to each virus. Cytotoxic T cell responses to measles virus-infected cells have been demonstrated during acute measles infection (12), but relatively few normal individuals appear to generate significant cytotoxic T cell responses during late convalescence (14). In addition, the capacity to generate cytotoxic T cells in response to measles virus in secondary in vitro culture may depend on the capacity of lymphocytes to proliferate in response to viral antigens (C. J. Lucas and H. F. McFarland, submitted for publication). The general degree of unresponsiveness to measles virus in late convalescence may, therefore, be due to a lack of initial sensitization or active suppression or to a failure in long-term stimulation or amplification of T lymphocyte proliferation. To investigate these possibilities, we studied the proliferative response to these viruses during early convalescence from natural measles infection.

## MATERIALS AND METHODS

Diagnosis of acute measles was based on the following criteria: an acute febrile illness (temperature, ≥38.3°C), a characteristic generalized maculopapular rash, and at least one of the following—cough, coryza, conjunctivitis or photophobia, Koplik spots, an immunoglobulin M response to measles virus, and a fourfold rise in measles hemagglutination inhibition titer. A total of 22 individuals with acute measles were studied (mean age, 16.6 years). Of the individuals studied, 5 had no known exposure to measles virus and 17 had been vaccinated previously. Of these individuals, two had been vaccinated with live virus and 14 with killed virus. One individual had been vaccinated with both live and killed vaccines on different occasions. Six exposed but asymptomatic siblings (mean age, 22.6 years) and 10 unexposed control individuals (mean age, 19.2 years) were also studied. All had been exposed to measles virus. Five of the six siblings had been vaccinated with killed virus, and one had had natural measles infection. Five of the control individuals had been vaccinated (three with live and two with killed virus), and four had had acute measles infections.

Initial studies were done 3 to 15 weeks after the onset of rash (mean, 9.4 weeks). Certain individuals and their siblings were restudied 4 to 12 weeks later (mean, 15.1 weeks after the onset of rash).

**Cell suspensions.** Mononuclear cells were obtained from heparinized peripheral blood by Ficoll-Hypaque (Bionetics Medical Laboratories, Kensington, Md.) density gradient centrifugation (1). The cells were either used fresh in the proliferative assay described

below or cryopreserved for later investigation.

**Proliferative assay.** A lymphoproliferative assay was employed with virus-infected, fixed tissue culture cells as antigen (17, 18). Vero cell (American Type Culture Collection, Rockville, Md.) monolayers in 96-well microtiter plates (model 3040; Falcon Plastics, Oxnard, Calif.) were infected with one of the following: Edmonston strain measles virus, Kilham strain mumps virus, or the IHD strain of vaccinia virus. Uninfected cells were used as controls. Optimal cytopathic effect was present at 48 h, when the monolayers were fixed with 0.025% glutaraldehyde for 20 min and washed three times with phosphate-buffered saline (PBS). The presence of viral antigens was confirmed by immunofluorescence. Lymphocytes were cultured on the monolayers at a cell concentration of $3 \times 10^5$ cells per well in 0.2 ml of RPMI 1640 medium containing 1% human AB serum. Each 100-ml portion was supplemented with 10,000 μg of penicillin, 10,000 μg of streptomycin, 5 mg of gentamicin, 200 mM glutamine, and 20 mM HEPES (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid) buffer. Each assay was performed in triplicate. The cell cultures were maintained in a humidified atmosphere of 5% $CO_2$ in air at 37°C. At 96 h, the wells were pulsed with 1 μCi of [$^3$H]Tdr for 4 h and harvested on a Multiple Automated Sample Harvester II (Microbiological Associates, Bethesda, Md.). Stimulation was calculated as both the difference in [$^3$H]Tdr incorporation by lymphocytes on infected monolayers from those on uninfected monolayers (Δ cpm) and the ratio of the two (SI). Background [$^3$H]Tdr incorporation of lymphocytes on uninfected monolayers was generally <2,000 cpm.

When cryopreserved mononuclear cells were used in the lymphoproliferative assay, the results did not differ by more than 10% from those obtained when fresh cells were studied.

**Mitogen response.** Mononuclear cells were cultured in microtiter wells at a cell concentration of $3 \times 10^5$ cells per well in RPMI 1640 medium supplemented as described above, with and without the addition of concanavalin A (Miles-Yeda Ltd., Kankakee, Ill.) at a final concentration of 1 μg/ml. At 72 h the wells were pulsed with 1 μCi of [$^3$H]Tdr for 4 h and harvested and counted as described above.

**Radioimmunoassay.** Sera from all individuals were tested for measles antibodies by a modification (K. W. Rammohan, personal communication) of the solid-phase radioimmunoassay previously described (17). Confluent monolayers of MA-160 cells (M. A. Bioproducts, Walkersville, Md.), a human prostate cell line, and MA-160 cells persistently infected with the Mantooth strain of measles virus (MA-160 SSPE) were treated with EDTA 1:5,000 (GIBCO Laboratories, Grand Island, N.Y.), and the single-cell suspensions produced were washed twice with PBS. One milliliter of RIPA buffer (13) was used to solubilize $10^8$ cells. The cell lysates were frozen at −70°C, thawed, diluted with PBS, centrifuged at 1,000 × *g* for 20 min, refrozen, and subsequently used at a 1:20 dilution in PBS. Fifty microliters of lysate per well was incubated overnight at 4°C in polyvinyl chloride microtiter plates (Dynatech Laboratories, Inc., Alexandria, Va.). After three PBS washes, the plates were incubated for 1 h at room temperature with PBS containing 2% fetal calf serum, aspirated, and then incubated further for 1 h with 25 μl of 10-fold dilutions of serum per well (each dilution was assayed in triplicate). Normal mouse serum and serum from a patient with subacute sclerosing panencephalitis were included in each assay as positive and negative controls, respectively. Staphylococcal protein A (Pharmacia Fine Chemicals, Piscataway, N.J.) was radioiodinated as described previously (19) and diluted in PBS containing 2% fetal calf serum to 25,000 cpm per 20 μl; this volume was added to each well after three more PBS washes. The plates were incubated for 30 min, washed again three times, and dried, and the wells were cut and counted individually in a Gamma 4000 counter (Beckman Instruments, Inc., Fullerton, Calif.). Antibody titer was calculated as the $\log_{10}$ of the reciprocal of the highest dilution of antiserum giving a binding (infected/uninfected) ratio of >2.0.

**Proliferative assay of mixed cells.** Frozen mononuclear cells from the first and second bleeds of selected individuals were mixed in various concentrations to examine their capacity to help or suppress the proliferative response. The cells were cultured for 120 h in microtiter wells in RPMI 1640 medium supplemented as described above and harvested.

## RESULTS

The proliferative responses to measles, mumps, and vaccinia virus-infected monolayers of all the individuals studied are shown in Fig. 1. Although a wide range of responses was observed, the mean response of the infected group was significantly different from that of age-matched controls ($P < 0.05$). The level of each response did not correlate with the time that an individual was studied after infection; both vaccinated and unvaccinated individuals were included among those showing good responses. Neither exposed siblings nor age-matched controls showed increased responses to measles virus. Responses to mumps and vaccinia viruses in the acute measles and control groups were not significantly different from each other. In all groups, the levels of mumps and vaccinia responses were relatively higher than were the levels of measles virus responses.

In the acute measles group, there were six individuals whose level of response was >2 standard deviations from that of the age-matched controls (comparison of means: $P < 0.0025$). Five of the six individuals had been vaccinated (four had received killed virus vaccine, and one had received live virus vaccine). Two of these high responders had a different clinical course consisting of a milder illness of fever, rash, and respiratory symptoms. Both of these individuals had received killed virus vaccine.

Differences noted for individual cases were again apparent when the Δ cpm and the SIs of the groups were compared (Table 1). In addition, the acute measles group had radioimmunoassay titers markedly higher than those

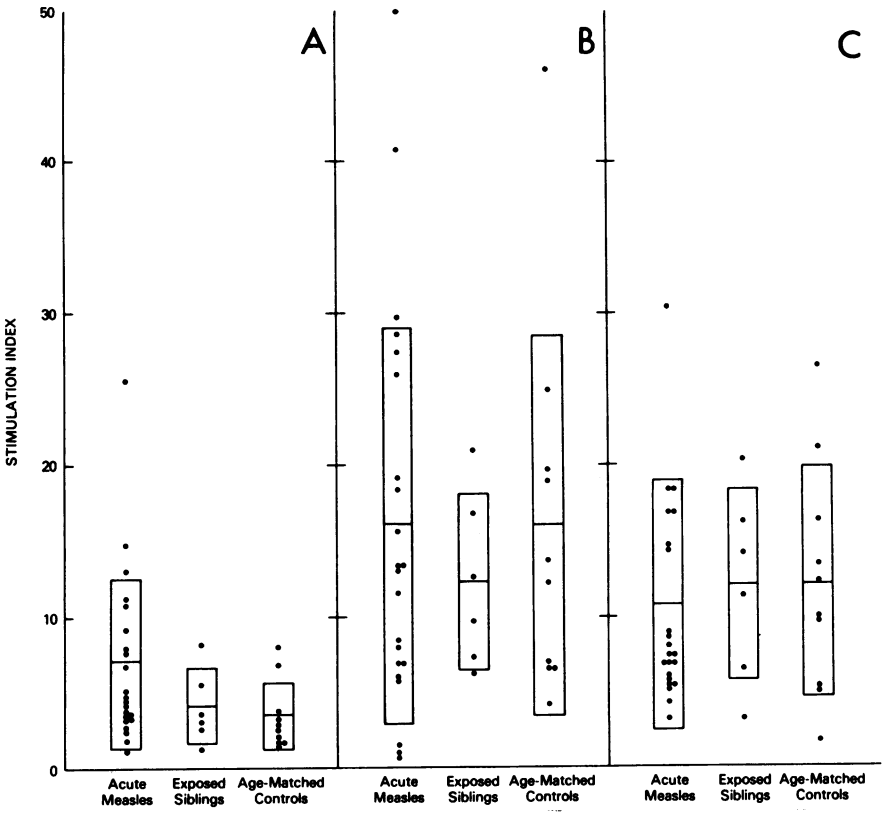


FIG. 1. Proliferative responses to measles (A), mumps (B), and vaccinia (C) viruses of individuals with acute measles and exposed sibling and age-matched controls. The boxed area indicates Mean ± 1 standard deviation.

of the unaffected siblings and controls ($P < 0.005$). The antibody titers for the groups of individuals with either high or low proliferative responses, however, were not significantly different from each other.

A transient, widespread depression of cell-mediated immunity which occurs during natural measles infection has been described (7, 21, 25). Responses to concanavalin A were therefore measured to eliminate the possibility of the presence of a generalized depression of in vitro immunity in the infected individuals at the time they were first studied. All groups responded well to this mitogen (Table 2). Although wide individual variations occurred, no depressed responses were noted in the measles cases. Specific immune responses, therefore, were measured during a period of immune competence. Conversely, the low degree of responsiveness to measles virus in some of the acute cases must have occurred despite the capacity to respond to the mitogens and to the other viruses.

Twelve individuals were available for repeated study. Proliferative responses to measles virus decreased significantly with time in the nine acute cases ($P < 0.05$), whereas responses remained unchanged in the three sibling controls (Table 3). Further examination of the measles responses after acute infection demonstrated that six of the nine individuals had a decreasing response, whereas two showed relatively little change and a single individual showed moderately increased response. Responses to mumps and vaccinia viruses remained relatively unchanged in all cases.

The decrease in proliferative responses found in the majority of individuals after acute measles infection may relate to the origin of the unresponsive state noted in late convalescence. The most likely mechanisms for this decrease could be either the generation of suppression or the failure to maintain a responsive circulating cell population. To examine the possibility of suppression, we mixed frozen mononuclear cells from the first (high-responder [HR]) and second (low-responder [LR]) bleeds of individuals who showed declines in the levels of their proliferative responses (Table 4). Unmixed HR cells proliferated to a greater degree than did LR cells. When HR cells were added to LR cells, no suppression of the HR proliferative response occurred. Conversely, mixing HR cells with LR

cells did not alter the LR proliferative response. Thus, the decrease in the proliferative response with time does not appear to be due to cellular suppression and probably represents a decrease in the number of circulating lymphocytes capable of proliferation in response to measles virus.

## DISCUSSION

In previous studies of seropositive late convalescents (17, 18) in which a specific, reproducible, and sensitive in vitro proliferative assay was used, a minority of normal individuals were found to respond to measles virus, despite the adequate presence of viral antigens. This situation is unlike that noted for mumps and vaccinia viruses, in which responses occur universally in seropositive individuals. Responsiveness to measles virus was not restricted to the presentation of antigen in the context of appropriate HLA antigens (17) and was mediated in particular by the $T_G$ cell subset (18). Therefore, the general lack of proliferation observed could be due to failure in the initial sensitization of responder T cells or suppression of the acquisition of the response by either viral infection of T cells or induction of antigen-specific suppressor cells. Alternatively, the lack of long-term exposure to antigen or failure to maintain a clonally expanded reactive cell population may explain these findings.

This study was undertaken to investigate whether a proliferative response occurred after natural measles infection and, if so, the nature of any regulatory mechanisms present. We demonstrated that, in early convalescence from acute measles, immunocompetent susceptible individuals are capable of a specific proliferative response to the virus, as measured in this assay. Failure in the initial sensitization to measles antigens, therefore, appears to be an unlikely explanation for a state of unresponsiveness. Recent exposure to viral antigens by infection or inoculation (11) appears to be a requirement for response in normal individuals. Some of the individuals with high responses appeared to have a milder form of the disease, and it is possible that the magnitude of the proliferative response correlates to some degree with a reduction in severity of disease (2, 26). Whether this would also protect against early or late complications of measles is not clear at this time.

There was no correlation between the level of proliferative response and the antibody titer in individual cases. These findings are in agreement with those of an earlier study (18) in which no correlation was found between the level of proliferation and the antibody titer. This would suggest that antibody production is neither dependent on nor regulated by a proliferating cell

TABLE 1. Proliferative response of lymphocytes to measles, mumps, and vaccinia virus-infected monolayers

| Group (no.) | Monolayer infection[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Measles | | | Mumps | | Vaccinia | | |
| | Δ cpm | SI | RIA[b] ($log_{10}$ titer) | Δ cpm | SI | Δ cpm | SI | |
| Acute measles (22) | 4,416 ± 3,384 | 7.03 ± 5.57[c] | 5.27 ± 1.20[d] | 11,629 ± 9,725 | 15.90 ± 13.02 | 7,684 ± 6,378 | 10.70 ± 8.21 | |
| Exposed siblings (6) | 2,951 ± 2,801 | 4.20 ± 2.51 | 2.86 ± 0.69 | 9,681 ± 4,612 | 12.18 ± 5.69 (NS) | 10,014 ± 5,879 (NS) | 12.02 ± 6.33 | |
| Age-matched controls (10) | 2,819 ± 1,700 | 3.52 ± 2.25 | 2.40 ± 1.17 | 15,416 ± 7,075 | 15.90 ± 12.58 | 14,509 ± 10,974 | 12.19 ± 7.59 | |

[a] All data expressed as mean ± SD.
[b] RIA, Radioimmunoassay.
[c] $P < 0.05$, Student $t$ test; comparison with age-matched controls.
[d] $P < 0.0005$, Student $t$ test; comparison with age-matched controls.

TABLE 2. Proliferative response of lymphocytes to concanavalin A

| Group (no.) | Stimulation (mean ± SD) calculated as: | |
|---|---|---|
| | Δ cpm | SI |
| Acute measles (18) | 107,230 ± 39,553 | 102.98 ± 55.80 |
| Siblings (6) | 105,875 ± 28,597 | 168.83 ± 92.44 |
| Controls (8) | 70,265 ± 21,304 | 124.14 ± 71.18 |

population. The fact that circulating antibody remains for prolonged periods of time after measles infection, whereas the proliferative response is extremely low, would also support the concept of differential regulation of these two responses (5, 9).

Transient, widespread depression of cell-mediated immunity occurs during the acute phase of measles infection (4, 7, 20, 21, 25). In particular, mitogen- and antigen-induced proliferation of lymphocytes are suppressed (4, 20). These findings are most likely due to acute infection of circulating lymphocytes during this phase (4, 20). It is conceivable that measles virus persists in lymphocytes beyond the acute stage of infection and that this virus has a more selective inhibitory effect on activated lymphocytes (particularly in those responding against measles virus) than the more widespread effects observed earlier. In preliminary studies in which in situ hybridization is used (6; unpublished observations), however, the presence of the measles virus genome has not been demonstrated in individuals with either high or low proliferative responses. It appears unlikely, therefore, that activation of persistent virus with selective inhibition of proliferation would account for the relatively low responses to measles virus at the times studied here. The extent to which proliferation is suppressed in infected lymphocytes in vitro is partly related to variables such as the multiplicity of infection and the time and dose of mitogen added (15, 22, 27). Mitogen stimulation is required for the optimal production of viral polypeptides (W. J. Bellini, G. D. Silver, D. E. McFarlin, and H. F. McFarland, submitted for publication) and particles (15, 23) in infected lymphocytes in vitro; this occurrence is the very event which blocks cellular proliferation. Although macrophages and T and B cells can be infected by measles virus, T cells appear to have a greater susceptibility to infection by measles virus than either macrophages or B-cells (10, 23, 27). This may relate in part to the availability of receptors for the virus (8, 24) as well as to other metabolic factors (10, 16, 23, 27). These factors in the virus-host interaction may modulate the level of the specific proliferative response to measles virus during the acute phase of infection, but they do not appear to abrogate it. They may, conceivably, also relate to the failure to maintain a higher long-term degree of responsiveness to the virus.

The cell mixing experiments do not provide evidence for the existence of a suppressor cell population in early convalescence. Identical mixing experiments in late-convalescent responder and nonresponder individuals, haploidentical for the major histocompatibility complex, have provided similar results (J. I. Greenstein, D. E. McFarlin, and H. F. McFarland, Fed. Proc. **40**:1044, 1981). It is conceivable that suppressor cells are transiently induced after infection and modulate the level of response but that they subsequently become undetectable. This occurrence, however, still would not explain a later decline in the proliferative response measured in this study, unless such early events could exert a longer-term regulatory effect.

A more likely explanation for the decline in the level of proliferative response to measles virus in normal individuals with the lapse of time after acute infection is the failure to maintain an expanded circulating population of cells capable of a proliferative response. This could be accounted for by the following course of events.

TABLE 3. Proliferative response of lymphocytes to measles, mumps and vaccinia virus-infected monolayers after acute infection

| Group (no.) | Mean SI ± SD of monolayer infection | | | | | |
|---|---|---|---|---|---|---|
| | First bleed[a] | | | Second bleed[b] | | |
| | Measles | Mumps | Vaccinia | Measles | Mumps | Vaccinia |
| Acute measles (9) | 8.58 ± 3.98 | 20.71 ± 10.59 | 8.66 ± 4.65 | 5.59 ± 2.47[c] | 18.62 ± 11.50[d] | 9.84 ± 3.91[d] |
| Siblings (3) | 5.77 ± 2.60 | 16.70 ± 4.10 | 13.97 ± 2.46 | 5.67 ± 1.96 | 17.47 ± 2.90 | 10.93 ± 4.65 |

[a] Mean at 9.4 weeks after onset of rash.
[b] Mean at 15.1 weeks after onset of rash.
[c] $P < 0.05$, Student $t$ test; comparison of mean SI of first and second responses to measles virus.
[d] Not significant (Student $t$ test); comparison of mean SI of first and second responses to mumps and vaccinia viruses.

TABLE 4. Effect of mixing HR and LR lymphocytes on the proliferative response to measles virus

| Starting cells[a] | Cells added and no. per well | Monolayer infection (Δ cpm) | |
|---|---|---|---|
| | | Measles | Mumps |
| HR | HR | | |
| | $1 \times 10^4$ | 5,383 | 40,205 |
| | $2 \times 10^4$ | 12,242 | 51,292 |
| | $5 \times 10^4$ | 24,251 | 54,247 |
| HR | LR | | |
| | $1 \times 10^4$ | 13,444 | 21,737 |
| | $2 \times 10^4$ | 16,458 | 44,660 |
| | $5 \times 10^4$ | 18,234 | 58,633 |
| LR | LR | | |
| | $1 \times 10^4$ | 7,435 | 16,132 |
| | $2 \times 10^4$ | 11,729 | 22,088 |
| | $5 \times 10^5$ | 10,737 | 25,191 |
| LR | HR | | |
| | $1 \times 10^4$ | 8,141 | 28,972 |
| | $2 \times 10^4$ | 7,126 | 28,395 |
| | $5 \times 10^4$ | 10,084 | 38,306 |

[a] A total of $1.5 \times 10^5$ per well for all cell types.

Infection of both measles-specific precursor cells and other lymphocytes may occur during the course of acute measles, but the inhibitory effects of viral infection on lymphocyte proliferation are likely to be greatest on the cells activated in vivo at this time only. This inhibition would involve cells responding especially to measles virus. Inhibition of proliferation is also likely to have a significantly greater effect if it occurs during the early stages of clonal expansion of an antigen-specific cell population. In addition, optimal generation of cytotoxic T cell responses appears to require amplification and differentiation signals dependent on lymphocyte proliferation and lymphokine production (3). One consequence, therefore, of the decreased capacity of lymphocytes to proliferate in response to measles virus would be a diminished capacity to generate cytotoxic T cell activity, impairing this potentially protective effector mechanism.

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