Antibodies, lectins, lipoproteins, and other biologically active proteins have been proposed as carriers of drugs and enzymes (*2*). Insulin might have specific advantages for delivering enzymes (and perhaps certain drugs) to muscle tissue because of the high density of insulin receptors on these cells. That other cells, such as hepatocytes and blood cells, also have numerous insulin receptor sites is not a serious problem, since the administered enzyme would not be expected to be toxic to normal tissue.

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15. Muscle-to-plasma ratios of labeled enzyme were approximately eight times higher when insulin was conjugated to the enzyme complex than when it was not. Corrections were made for plasma contamination of muscle tissue. These corrections were important since the counts for control conjugate (no insulin) in muscle tissue were very low. Mice receiving labeled enzyme-albumin-insulin (10^5 count/min) showed 700 count/min per gram of muscle and a maximum blood contamination of 80 count/min per gram. Mice receiving labeled enzyme-albumin (10^5 count/min) showed 115 count/min per gram of muscle and a maximum blood contamination of 60 count/min per gram.
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People with Absolute Pitch Process Tones Without Producing a P300

Abstract. *The P300 is a positive-going component of the event-related potential. In subjects with absolute, or "perfect," pitch, the P300 elicited by the less frequent of two auditory probes is small or absent. In these subjects, visual probes elicit a normal P300. These results support the view of P300 as a manifestation of the updating of working memory.*

Some individuals can name the tones produced by a large variety of musical instruments. People with this "perfect" or "absolute" pitch (AP) are able to label correctly upward of 50 different pitches (*1*), although they do not have superior auditory discrimination skills (*1*). The weight of the evidence suggests that individuals with AP have access to a set of internal "standards" that allows them to fetch the name of a tone without comparing the representation of the tone they have just heard with a recently fetched representation of a standard (*2*). If so, those with AP may not need to maintain, or update, in their working memory the representations of infrequently occurring events.

The P300 is a positive-going component of the event-related brain potential (ERP) that may be a manifestation of the processes of maintaining or updating working memory. It tends to be large at the parietal electrode. It is quite easily obtained in the "oddball" procedure, in which two discrete stimuli (one frequent and one rare) are presented in a Bernoulli sequence; the subject counts the rare stimulus, which elicits a large P300. A consideration of the variables that control the amplitude and latency of P300 has led Donchin and his colleagues (*3, 4*) to suggest that the component is the manifestation of a subroutine invoked whenever there is a need to update the model of the environment in working memory. If AP subjects process acoustic stimuli without reliance on such schema, they should not emit a P300 in response to novel tones. We have confirmed this prediction. We predicted little, if any, difference in the visually elicited P300 of subjects with and without AP; but we predicted that rare auditory stimuli would elicit a much smaller P300 in the AP subjects than in individuals lacking AP.

All subjects were students of music at the University of Illinois (eight males and six females). We assayed their ability to discriminate tones by a method adapted from Lockhead and Byrd (*5*). Each subject heard a series of pure tones generated by a programmable oscillator (*6*). The 81 tone pitches represented the fundamentals of the piano, ranging from 63 to 4186 Hz. The different tones were presented in a random sequence. The subject was instructed to identify the octave number and the name of the pitch (such as B flat or C) associated with each tone. Each tone was sounded until the subject responded. After 500 msec, the next tone was presented. In session 1, ten blocks (with 25 tones per block) were used for practice, and the subject was informed of the correct response after each identification. Ten more blocks were presented without feedback in session 2. The error distributions for session 2 are shown in Fig. 1.

Subjects who described themselves as having the AP skill (AP group) made fewer errors than did those who reported having "normal" pitch discrimination (control group) (Fig. 1). The errors that the AP subjects did make were "octave" errors—that is, they identified the pitch correctly, but they assigned it to a higher

Table 1. Correlation (r) of AP score with ERP measures. For both amplitude and area, the difference between the coefficients was significant ($P < 0.05$).

Measure	Auditory	Visual
Amplitude	−0.63*	−0.11
Area	−0.64*	−0.13

*$P < 0.05$.

or lower octave than that of the actual stimulus. The considerable individual differences that existed were indexed by the percentage of correct pitch identifications, regardless of the correctness of octave identification (*7*).

Each subject was presented with a visual and an auditory oddball test. The auditory stimuli were 1000- and 1100-Hz sinusoidal tones presented with a rise-fall time of 10 msec and a duration of 60 msec. The visual stimuli were the characters H or S presented for 60 msec on a screen. The characters subtended a visual angle of 1.3°. Within any given sequence of stimuli the interval between successive stimuli was either 1600 or 3000 msec (*8*). Each subject was presented with 20 blocks of visual and 20 blocks of auditory stimuli. In each block of 100 stimuli, one of the two stimuli appeared with a probability of 0.20. The subject was instructed, in each block, to count the rarer of the two stimuli. The order in which blocks in the two modalities were used and the selection of the rare stimulus were counterbalanced in a Latin square design.

The ERP's obtained from all subjects (*9*) are displayed in Fig. 2. The control subjects showed standard ERP's in both visual and auditory modalities. The ERP elicited by the rare events was characterized by a large, positive-going component with a latency of about 400 msec. Similar data were recorded from the AP subjects in the visual modality. However, the ERP's elicited by rare auditory events in the AP subjects differ from those elicited by rare visual events: for most of the seven AP subjects, the auditory P300 was smaller than that elicited in the same subjects by the visual stimuli and in control subjects by rare stimuli in both modalities. Pooled data are consistent with individual data.

These inferences were corroborated by an analysis of the amplitude and area of the P300 to the rare stimulus. The amplitude was defined as the maximum positivity (at the parietal electrode) in the interval between 300 and 600 msec after the stimulus. The area of the P300 was computed by integrating the data over the same interval. An analysis of variance of both amplitude and area scores revealed an interaction between AP ability and modality of the stimuli [$F(1, 12) = 7.04$, $P < 0.05$, and $F(1, 12) = 8.01$, $P < 0.05$, respectively]. The mean amplitude of the P300 elicited by rare auditory probes was 7.33 μv in the control subjects and 3.33 μv in the AP subjects [$F(1, 12) = 9.38$, $P < 0.05$]. The difference between amplitude of P300 elicited by visual probes in the controls (9.13 μv), and the AP subjects (6.53 μv), was not statistically significant [$F(1, 12) = 0.48$].

The differences in the AP skill within the two groups suggested a possible relationship between the amplitude of P300 in the two modalities and the subject's

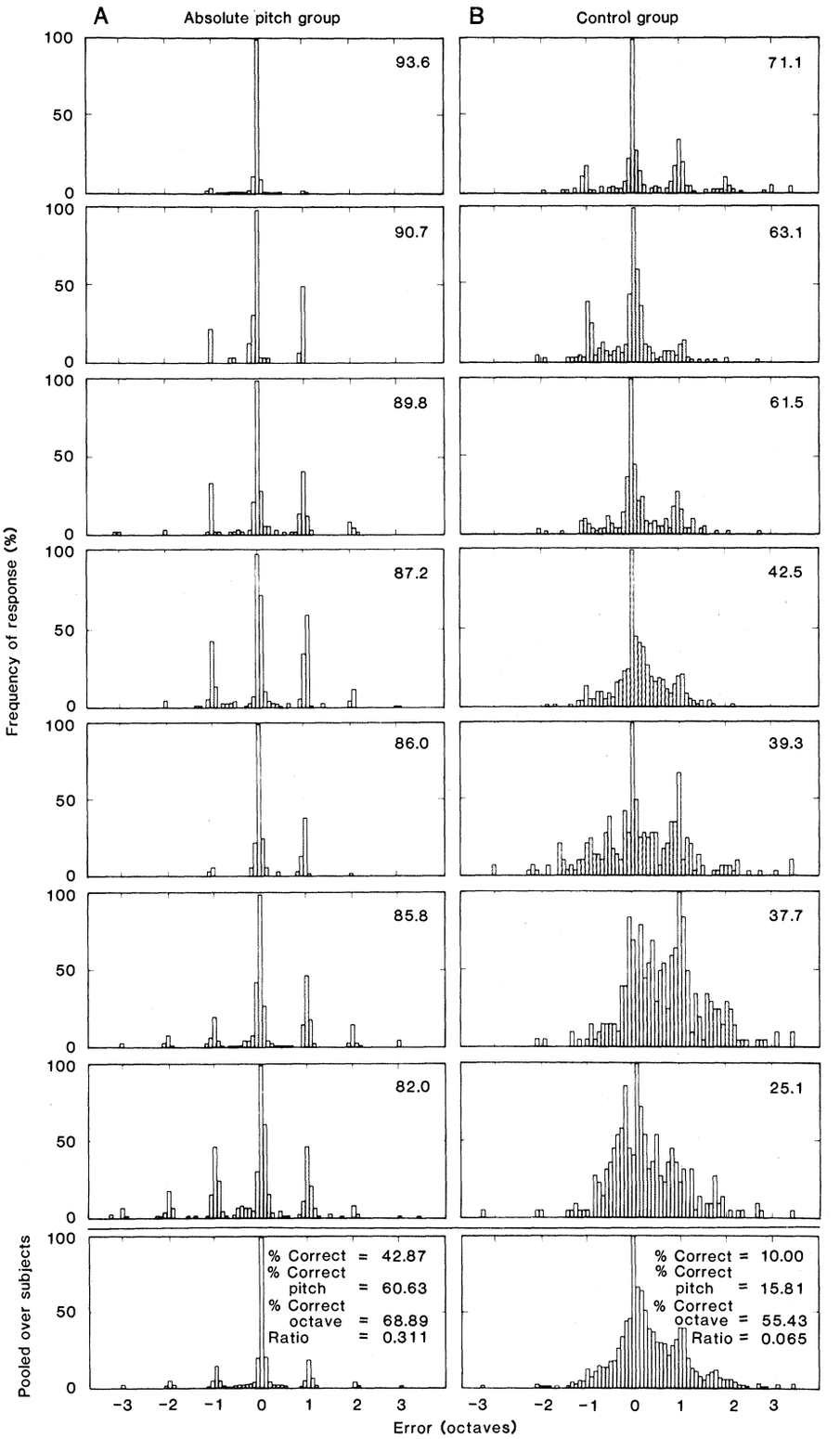

Fig. 1. The frequency distribution of each subject's errors in the AP ability test. The histograms show the frequency of the subject's responses as a function of the distance along the pitch dimension between the stimulus actually presented and the response. Values for the response that occurred most frequently are set to 100 percent. Values for other responses are adjusted accordingly. The score shown in the upper right corner of each histogram is the percentage of correct responses exclusive of octave and semitone errors (*7*).

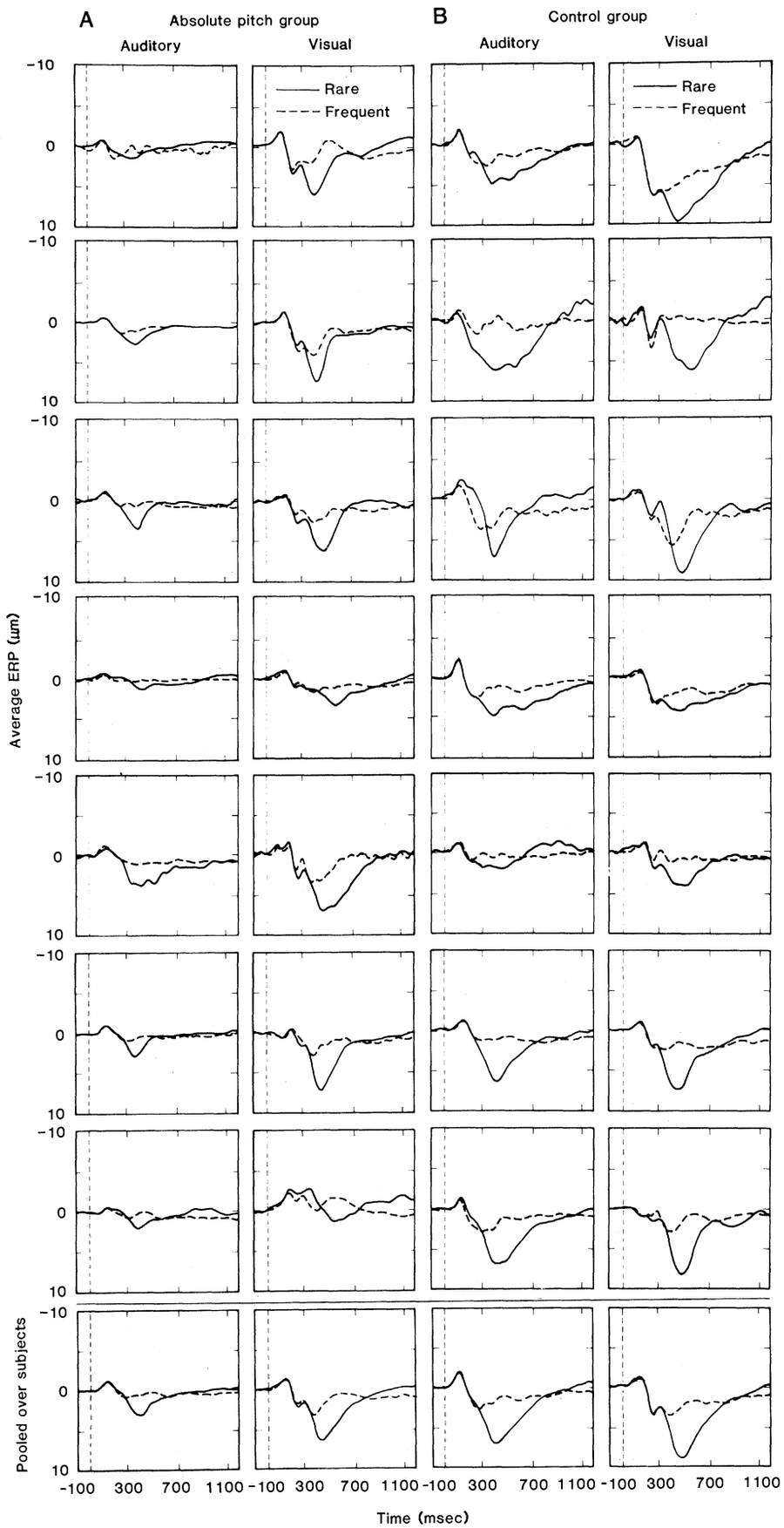

Fig. 2. Average ERP's (at the parietal location) elicited by rare (counted) and frequent visual and auditory stimuli for each subject and pooled within groups.

performance in the AP test. We correlated the amplitude and area of P300 with the percent of correctly identified tones by each of the subjects in the AP test (Table 1). The better the subject's performance in the auditory discrimination task, the smaller the P300 elicited by rare auditory stimuli. No such relationship was observed for the visual stimuli.

These data confirm our prediction. Subjects with the AP skill did not engage in the processing activities manifested by the P300 in the standard manner. This difference was specific to the auditory modality (*10*). When required to make visual discriminations these subjects' P300 did not differ significantly from that elicited in control subjects. Furthermore, the smaller auditory P300 in the AP subjects cannot be attributed to a failure on their part to attend to the auditory stimuli or an unwillingness to perform the task. All subjects counted all rare events with equal accuracy.

It is plausible to interpret these data as providing additional support for the hypothesis that the P300 is a manifestation of processing activities that are involved in the maintenance of representations of external events over relatively brief time periods. The collection of such representations is referred to as "working memory." Several accounts of the AP phenomenon suggest that subjects with this skill have access to permanently resident representations of the tones, so that they do not need, as the rest of us do, to fetch and compare representations for novel stimuli (*11*). Our data are consistent with the interpretation that the P300 is a manifestation of such comparisons.

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7. A response in which the subject correctly identified the pitch name but incorrectly identified the octave would thus be considered to be a correct response. This score is used because AP subjects differ from control subjects of equal musical experience primarily in pitch identification, not in octave identification. Semitone errors are also ignored in deriving this score because of limits in the pitch resolution of the generator at low frequencies.
8. The study was run with two different interstimulus intervals of 1.6 and 3.0 seconds. Since there were no significant interactions involving interstimulus interval, we omitted its discussion from this report.
9. The electroencephalogram was recorded with Ag-AgCl electrodes placed on the midline at frontal, central, and parietal locations (Fz, Cz,

and Pz; 10-20 International system). The grounding electrode was attached to the forehead. Eye movements were recorded by electrodes placed above and to the right of the right eye. Trials with excessive eye movements or blinks were rejected before being analyzed. Electrode impedance did not exceed 5 kilohm. The signals were amplified by a Grass 7P122 amplifier, with a time constant of 8.0 seconds and an upper half-amplitude cutoff of 35 Hz. The data were digitized at a rate of 100 samples per second over an epoch of 1280 msec, beginning 100 msec before stimulus onset. The digitized data were filtered so that the upper half-amplitude cutoff was reduced to 6.29 Hz. The data were averaged so that for each subject, and for each condition, we had the ERP associated with the rare and frequent stimuli.

10. Even though not statistically significant, there is an apparent difference between the amplitudes of the P300 elicited by visual stimuli in the two groups. The data do not allow us to determine whether the AP subjects use a different processing strategy in both modalities.
11. The characters H and S could be labeled by all subjects with the same facility that the AP subjects labeled the tones. As the P300 component is present in the visual task, it seems reasonable to question the assumption that characters are recognized with automatic facility. Since characters can be presented in an infinity of fonts and shapes, considerable processing may be required for character recognition.
12. Supported by Air Force Office of Scientific Research contract F49620-79-C-0233. We are grateful for the support of A. Fregly. D. Karis, A. Kramer, and A. Mane made many helpful comments on a previous version of this report.

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Transfusion-Associated AIDS: Serologic Evidence of Human T-Cell Leukemia Virus Infection of Donors

Abstract. *An assay for antibodies to membrane antigens of cells infected by human T-cell leukemia virus was used to examine serum from persons who donated blood to 12 patients with acquired immunodeficiency syndrome (AIDS) associated with blood transfusions. The occurrence of positive results in the assay was significantly greater among donors to the AIDS patients (9 of 117; 7.7 percent) than among random donors (1 of 298; 0.3 percent). Of 12 sets of donors examined, 9 sets included a donor whose serum gave positive results for the presence of the antibodies. In six of these nine sets, the seropositive donor was an individual who was also identified as a possible source of AIDS transmission when epidemiologic and immunologic criteria were used.*

The acquired immunodeficiency syndrome (AIDS) is a recently recognized human disease whose incidence in the United States has been rapidly increasing (*1, 2*). Patients with AIDS suffer from at least one type of malignancy, Kaposi's sarcoma, and various life-threatening opportunistic infections, the most common of which is *Pneumocystis carinii* pneumonia. The disease is characterized by diverse immunologic abnormalities, including lymphocyte dysfunction and depletion of the T-helper subpopulation of lymphocytes (*3*).

Although the etiology of AIDS is unknown, epidemiologic observations suggest that it is caused by an infectious agent transmitted sexually and, less commonly, through parenteral exposure to blood or blood products (*4*). In the United States, about 94 percent of patients reported to have AIDS belong to one or more of the following groups: homosexual or bisexual men, abusers of intravenous drugs, persons born in Haiti, and persons with hemophilia (*2*). Another 1 percent of AIDS patients do not belong to any of these groups but received transfusions of blood or blood components within 5 years before the onset of their illness. These cases are classified as transfusion-associated AIDS and have been described in detail elsewhere (*5, 6*).

Among the agents studied as a possible cause of AIDS are retroviruses, including the human T-cell leukemia virus (HTLV) (*7*). Compared with control individuals, AIDS patients have a higher prevalence of antibodies directed against membrane antigens of HTLV-infected cells (HTLV-MA) as measured by indirect membrane immunofluorescence and radioimmunoprecipitation techniques (*8*). In studies in which serum from Japanese T-cell leukemia patients and asymptomatic carriers was used, the major antigens detected by antisera to HTLV-MA have been defined (*9*). They include two glycoproteins, designated gp 61 and gp 45, that are encoded by the *env* gene of HTLV (*9*). The prevalence of antibodies to HTLV-MA is also increased in homosexual men with chronic, generalized lymphadenopathy (*8*), an illness that has been associated with AIDS (*10*). Human T-cell leukemia virus has been isolated from the lymphocytes of AIDS patients, both American (*11*) and Japanese (*12*), and DNA sequences that hybridized with a cloned HTLV DNA probe were detected in two other patients (*13*). A retrovirus thought to be related to HTLV has also been isolated from a lymph node of a French homosexual man with chronic lymphadenopathy (*14*). Whether these findings reflect an etiologic role for a retrovirus in AIDS or are simply a consequence of these viruses infecting AIDS patients opportunistically is unknown.

In an attempt to evaluate further the serologic relationship of HTLV or a related virus to AIDS, we have studied patients with transfusion-associated AIDS and the persons who donated blood or blood components to these patients. As of 1 January 1984, the Centers for Disease Control (CDC) had received reports of 32 adults with transfusion-associated AIDS. An additional patient (patient 5), a 69-year-old man with Kaposi's sarcoma, whose age exceeds the limit of 60 years specified for Kaposi's sarcoma patients in the CDC surveillance definition for AIDS (*4*), is included in this report because his abnormal immunologic studies and rapidly fatal clinical course suggest that he did, in fact, have AIDS. For 12 of these 33 cases, donor investigations have been completed. An investigation is considered complete when all available donors (i) have been interviewed regarding risk factors for AIDS, (ii) have been examined for physical findings suggestive of AIDS, and (iii) have provided a blood sample.

Several classes of serum were obtained to serve as controls. These included 298 randomly selected specimens collected during 1979 and 1980 from volunteer blood donors in Philadelphia, Pennsylvania (100 specimens), Madison, Wisconsin (99 specimens), and Tucson, Arizona (99 specimens). Also included for comparison were 81 previously tested serum samples collected in 1981 from homosexual men matched by age, race, and residence to a sample of AIDS patients (*8, 15*) and 45 samples obtained in 1982 from homosexual men in Ithaca, New York.

Serum specimens from patients with transfusion-associated AIDS, donors to these patients, and control subjects were coded and sent frozen to Boston to test for antibodies to HTLV-MA by a method that has been described (*8, 16*). Briefly, a 1:4 dilution of serum was added to two HTLV-I-infected cell lines, Hut 102 and MT 2; the cells were washed; and a fluorescein-conjugated $F(ab')_2$ fragment of goat antibody to human immunoglobulins G, A, and M was added. The cells were washed again, and the proportion of cells having fluorescence was determined for each cell line. Samples with 40 percent or more of the cells having fluorescence on either cell line were considered positive. Positive samples were tested on uninfected lymphoid cell lines to exclude nonspecificity. A negative and a positive control serum