of the nucleus magnocellularis of the anterior neostriatum (MAN), which is part of the song control system (*7, 13*), recorded multi-unit responses to auditory stimuli with latencies longer than those in the XIIts nucleus or nerve. Furthermore, a restricted area within the dorsal thalamus that is back-filled by injections of horseradish peroxidase into the lateral MAN showed auditory activity that followed the activity in the nXIIts and preceded that in the lateral MAN. Thus part of the dorsal thalamus and lateral MAN may be components of a recurrent loop carrying information derived from analysis of sound stimuli by the XIIts nucleus.

The telencephalic nuclei that control learned song are several times larger in adult male zebra finches, which sing, than in adult females, which do not (*14*). This sexual dimorphism is mirrored by the distribution of birds with auditory responses in the NXIIts: 53 of 68 male zebra finches and 0 of 12 females showed auditory responses in the ts nerve, which is a significant difference ($\chi^2 = 28.2$, $P < 0.001$). If nXIIts-mediated song perception is related to the potential for song production, then females and males might differ in their perception of song. We do not know whether this is the case for zebra finches, but there are suggestions of such a sexual perceptual dimorphism in other species of songbirds (*15*). Bird song, as well as other animal vocalizations, may only be totally intelligible to a neural system that is capable of producing the same vocalizations. Birds that perceive song as a series of articulatory gestures may have their own particular form of phonetic analysis.

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9. Inhibitory syllables or introductory notes did not evoke multi-unit activity whether they were presented in positions 1, 2, or 3 of a triplet. Syllables that were excitatory or neutral in triplet positions 2 and 3 evoked multi-unit responses when presented in position 1.
10. The mean response levels for the first, second, and third positions within a triplet were calculated for each recording site. The number of positive multi-unit responses to all syllables presented at a single position was divided by the total number of trials. Each syllable was presented at each triplet position for a minimum of ten trials. The mean total response was subtracted from the number of positive responses to the syllable; this difference was then divided by the standard deviation of the total response to yield the response index for the syllable. Negative response indices indicated an inhibitory effect. Response indices that differed from the mean response level by <1.00 standard deviation were ignored.
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Sequence Homology Between Certain Viral Proteins and Proteins Related to Encephalomyelitis and Neuritis

Abstract. *Post-infectious or post-vaccinal demyelinating encephalomyelitis and neuritis may be due to immunological cross-reactions evoked by specific viral antigenic determinants (epitopes) that are homologous to regions in the target myelins of the central and peripheral nervous systems. Such homologies have been found by computer searches in which decapeptides in two human myelin proteins were compared with proteins of viruses known to infect humans. These viruses include measles, Epstein-Barr, influenza A and B, and others that cause upper respiratory infections. Several regions identified in myelin basic protein and P_2 protein can be related to experimental allergic encephalomyelitis or neuritis in laboratory animals*

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Encephalitis, myelitis, and neuritis are well-known complications of certain viral infections and vaccines (*1*), especially vaccinia, measles, infectious mononucleosis, and influenza. The most recent example of such a complication is the Guillain-Barré syndrome (GBS), which followed the national swine flu vaccination program of 1976 (*2*). Experimental allergic encephalomyelitis (EAE) and neuritis (EAN) have provided precise histopathologic models in many species of animals for these post-infectious and post-vaccinal neural complications in humans (*3*). These experimental auto allergic diseases are caused by hypersensitivity to special antigens, myelin basic protein (BP) and P_2 protein, in the target myelins of the central (CNS) and peripheral (PNS) nervous systems, respectively (*4*).

The manner in which a virus could be related to these myelin antigens is open to speculation. Because measles antigens cannot be detected in the CNS in cases of measles encephalitis and sensitization to myelin BP can be detected in many such cases, the suggestion has been made that a nonspecific liberation of BP-sensitive lymphocytes follows the early lymphopenia of measles and that

these lymphocytes then enter the CNS and produce an EAE-like disease (*5*). However, this hypothesis does not explain why only EAE, and not many autoallergic diseases of other organs, results from the release of these lymphocytes. A simpler explanation is that a viral antigenic determinant (epitope) evokes a specific sensitization that cross-reacts with a homologous sequence in the target antigen, BP.

The availability of computer programs (*6*) designed to search for homologous sequences has allowed us to explore the possibility that at least one viral peptide segment is sufficiently similar to a region in the target antigens to evoke EAE or EAN in persons who develop enough hypersensitivity to the viral epitope. Decapeptides were considered to be long enough for an epitope to cause EAE or EAN (*4*).

Tables 1 and 2 summarize the comparisons of encephalomyelitis-related human BP and neuritis-related human P_2 protein with various proteins from viruses associated with post-infectious and post-vaccinal neurological complications. Homologous sequences can be found in many viral proteins and many regions of BP and P_2 protein. Several of the epitopes in BP have been well localized, including sequences 22 to 31, 36 to 45, 66 to 75, 91 to 100, 111 to 120, and 126 to 135 (Table 1), which are included in epitopes that cause EAE in rats, rabbits, guinea pigs, and monkeys or that react with monoclonal antibodies (*4, 7*). The epitopes in P_2 protein are not yet well localized, but a portion of the one sequence (residues 66 to 78) which has produced EAN in Lewis rats is represented by the nucleocapsid proteins of measles and canine distemper viruses (*8*), as shown in Table 2. In rabbits, however, this peptide is much less able to induce neuritis, almost equal activity being present among all three of the major cyanogen-bromide peptides, residues 1 to 20, 21 to 113, and 114 to 131 (*9*). Thus, the neuritis-inducing activity of several influenza vaccines in rabbits (*10*) may be caused by the two homologous decapeptides of influenza A proteins in sequences 114 to 123 and 121 to 130 of P_2.

The BP-homologous sequences in measles C and nucleocapsid proteins (*8*) may account not only for encephalomyelitis in humans (*1*) but also for cross-reactions detected by delayed skin tests with BP in measles-sensitized guinea pigs (*11*). We suggest that similar sequences in swine influenza proteins will be found to be homologous with chicken P_2 protein and to account for the "anti-P_2" antibodies reported in postvaccinal GBS patients (*12*).

Chemical similarity of amino acid residues is a necessary, but not a sufficient, criterion for antigenic similarity. Secondary or tertiary structural considerations can create epitopes quite different from those defined only by a linear sequence of residues. However, as the human epitopes have not yet been defined, at least some of the ones identified in Tables 1 and 2 might be considered, as a first approximation, to be involved in para-infectious encephalomyelitis and neuritis. By analogy with the different sequences in BP that can cause encephalitomyelitis in different strains of inbred mice or other animals, it seems likely that humans who are genetically heterogeneous will react to several different epitopes, at least as different as those to which noninbred monkeys and rabbits react (*4*).

One difference between post-infectious and post-vaccinal neuroallergic complications should be noted. Although RNA segment 8 in influenza viruses codes for the two nonstructural proteins NS_1 and NS_2, these proteins are found in the infected host and not in the mature virion (*13*). Therefore, they would not occur in a vaccine.

Most of the proteins analyzed here are

Table 1. Homologous decapeptides in human BP and certain viral proteins. Abbreviations for amino acids are as defined (*15*).

First BP residue number-sequence	Virus		
	Name	Protein	First residue number-sequence
22-DHARHGFLPR	Adenovirus 2,5	Late 100K	667-NKARQEFLLR
24-ARHGFLPRHR	Adenovirus 2	B-137	80-GRPGFEPRIR
36-GILDSIGRFF	Influenza A/NT/60/68	NP	31-KMIDGIGRFY
36-GILDSIGRFF	Influenza A/WSN/33	P_1	458-GIGAGVNRFY
36-GILDSIGRFF	Canine distemper	Nucleocapsid	62-GILISILSLF
37-ILDSIGRFFG	Influenza A/PR/8/34	NP	32-MIGGIGRFYI
66-TAHYGSLPQK	Adenovirus 7	Terminal	604-RAGYQNLPAR
91-KNIVTPRTPP	Adenovirus 2,5	Late 100K	132-RHLFSPRVPP
91-KNIVTPRTPP	Adenovirus 7	Maturation pIVa2	341-MHISSPRMHP
91-KNIVTPRTPP	Respiratory syncytial	Matrix	60-KQISTPKGPS
92-NIVTPRTPPP	Adenovirus 2,5	72K DNA-binding	62-DALVPRTPSP
107-RGLSLSRFSW	Epstein-Barr	EC-RF_2	432-RHGELFRFIW
110-SLSRFSWGAE	Adenovirus 2,5	Early 21K	26-WFWRFLWGSS
110-SLSRFSWGAE	Influenza A/Udorn/72	NS_1	197-TLQRFAWGSS
110-SLSRFSWGAE	Influenza B/Lee/40	NS_1	30-CYERFSWQRA
111-LSRFSWGAEG	Influenza A/Udorn/72	NS_1	198-LQRFAWGSSN
111-LSRFSWGAEG	Measles	C	1-MSKTEWNASQ
111-LSRFSWGAEG	Adenovirus 2,5	Early 21K	27-FWRFLWGSSQ
112-SRFSWGAEGQ	Measles	Nucleocapsid	142-SRFGWFENKE
120-GQRPGFGYGG	Adenovirus 2,5	Late 100K	734-SGRGGFGRGG
126-GYGGRASDYK	Epstein-Barr	EC-LF_2	194-GYGNHAGDYH
136-SAHKGFKGVD	Influenza A/Japan/305/57	HA	380-STQKAFDGIT
153-IFKLGGRDSR	Measles	Nucleocapsid	429-LPRLGGKEDR

Table 2. Homologous decapeptides in human P_2 protein and certain viral proteins. Amino acid abbreviations are as defined (*15*).

First P_2 residue number-sequence	Virus		
	Name	Protein	First residue number-sequence
3-KFLGTWKLVS	Adeno-associated 2	Coat 1,2	62-DFLTEWRRVS
11-VSSENFDDYM	Adenovirus 2	Hexon	652-TNDQSFNDYL
29-TRKLGNLAKP	Epstein-Barr	EC-LF_1	473-NRMLGDLARA
56-TFKNTEISFK	Adenovirus 2	Hexon	731-TFKKVAITFD
64-FKLGQEFEET	Measles, canine distemper	Nucleocapsid	362-FRLGQEMVRR
89-GSLNQVQRWN	Epstein-Barr	EC-RF_1	176-GLLNLLSRWQ
89-GSLNQVQRWN	Adenovirus 2,5	Maturation pIVa2	430-RTLNDRDRWS
96-RWNGKETTIK	Epstein-Barr	EC-LF_2	649-SWLAKRKAIK
114-VAECKMKGVV	Influenza A/WSN/33	HA	56-GKLCKLKGIA
117-CKMKGVVCTR	Adenovirus 2,5	Early 55K	287-CCWKGVVCRP
121-GVVCTRIYEK	Influenza A (8 strains)	HA	479-GNGCFKIYHK
121-GVVCTRIYEK	Adenovirus	Early 16K	136-ALVCTLLYLK

of influenza A or adenoviral origin. This may stem from the fact that these proteins have been extensively studied and are disproportionately represented in the computer library. Because of the lack of sequences available for vaccinia, measles, and swine flu proteins, the probability that the correct proteins have been sequenced is less than 10 percent. As more information becomes available on these viral proteins, we expect to find additional homologies with myelin proteins (*14*).

Our investigation suggests that spontaneous mutations in the continuously evolving viral proteins could result in fluctuations in the immunogenicity of the epitopes. This, in turn, would account for the variations in incidence of neural complications observed from year to year.

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10. D. W. Ziegler *et al.*, *Infect. Immun.* **42**, 824 (1983). Review of the original histological preparations indicates that EAE was produced, rather than EAN. Repetition of the computer searches of all the peptides, synthetic or native, in the three regions of BP that are related to encephalomyelitis in rabbits revealed only one [FILGGRDSR: F. C. Westall and M. Thompson, *Immunochemistry* **15**, 189, 1978)] that had homology with three regions in two proteins of influenza A viruses: sequences 384 to 392 and 694 to 702 in polymerase 3 and sequence 349 to 357 in the hemagglutinin. Sequence 469 to 477 in the hemagglutinin of influenza C virus was also identified as homologous, but only vaccines containing influenza A and B viruses were tested by Ziegler *et al.* Furthermore, vaccinia's 42K protein sequence 253 to 261 becomes homologous with another synthetic peptide (FKLAGRDSR) that can induce encephalomyelitis. Such homology could account not only for post-vaccinal encephalomyelitis in humans (*1*) but also for antibodies reacting with myelin and oligodendroglia [A. J. Steck *et al.*, *J. Neuroimmunol.* **1**, 117 (1981)].
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14. Since the submission of this manuscript, R. S. Fujinami and M. B. A. Oldstone [*Fed. Proc.* **44**, 1921 (1985)] have reported the production of EAE in a rabbit sensitized with a synthetic octapeptide containing six residues (YGSLPQ) that are identical in DNA polymerase of hepatitis B and one of the three regions in BP known to induce encephalomyelitis in rabbits [R. Shapira, F. C-H. Chou, S. McKneally, E. Urban, R. F. Kibler, *Science* **173**, 736 (1971)].
15. The single letter code of abbreviations for amino acids is as follows: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

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Choline Acetyltransferase Activity in Striatum of Neonatal Rats Increased by Nerve Growth Factor

Abstract. *Some neurodegenerative disorders may be caused by abnormal synthesis or utilization of trophic molecules required to support neuronal survival. A test of this hypothesis requires that trophic agents specific for the affected neurons be identified. Cholinergic neurons in the corpus striatum of neonatal rats were found to respond to intracerebroventricular administration of nerve growth factor with prominent, dose-dependent, selective increases in choline acetyltransferase activity. Cholinergic neurons in the basal forebrain also respond to nerve growth factor in this way. These actions of nerve growth factor may indicate its involvement in the normal function of forebrain cholinergic neurons as well as in neurodegenerative disorders involving such cells.*

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Trophic factors are soluble molecules that influence the survival and differentiation of neurons in developing animals (*1, 2*). It has been suggested that abnormalities in the synthesis or utilization of trophic factors result in the dysfunction or death of specific neuronal populations which occurs in certain degenerative diseases of the central nervous system (CNS) (*1, 3*). A test of this hypothesis requires identification and characterization of trophic factors for the neurons of interest. Nerve growth factor (NGF) is a protein molecule whose neuronotrophic effects have been detailed in many investigations of the peripheral nervous system (PNS) (*4*). Recent studies of neonatal and adult rats showed that cholinergic neurons of the basal forebrain also respond to NGF (*5–8*). To determine whether a different population of forebrain cholinergic neurons, those of the corpus striatum, would also respond to a highly purified preparation of NGF, we measured the activity of choline acetyltransferase (ChAT), an enzyme that is