manner (*5, 8, 14*). Thus, design of a radioactive receptor assay with this system should permit an examination of the molecular basis for interaction of [Nle^4, D-Phe^7]-α-MSH and other melanotropins with its receptor. It may also be possible to use [Nle^4, D-Phe^7]-α-MSH in the detection of human melanoma. Since the labeled melanotropin would presumably bind preferentially to melanoma membrane receptors, radioisotope imaging methods could be used to detect melanoma tumors in skin. It might also be possible, by conjugating adriamycin or other cancer therapeutic agents to [Nle^4, D-Phe^7]-α-MSH, to develop a cell-specific (melanoma cell) drug delivery system; we found previously (*8*) that [Nle^4, D-Phe^7]-α-MSH is nonbiodegradable in serum.

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Myeloma Neuropathy: Passive Transfer from Man to Mouse

Abstract. *Mice were injected daily, for up to 10 weeks, with purified monoclonal immunoglobulin G from patients with myelomatous polyneuropathy or benign gammopathy. The animals developed a demyelinating polyneuropathy with slowed nerve conduction velocities. The putative antinerve factor may be an antibody since injection of Fab fragments from the monoclonal immunoglobulin G produced a similar demyelination. This provides evidence of a circulating factor in the serum of myeloma patients with polyneuropathy that reproduces typical features of the human disease on passive transfer. This disorder is thus distinguished from other neuropathies that occur as remote effects of malignant disease but have no identified pathogenic factors associated with them.*

Peripheral neuropathies (PNP's) have been described in patients with solitary and multiple myeloma (*1*). In this malignant disease of immunocytic origin as well as in other neoplastic conditions the "paraneoplastic" PNP is characterized by demyelination (*2, 3*).

The pathogenesis of myeloma-PNP has long been debated. The finding of immunoglobulins G and M (IgG, IgM) and complement in sural nerve specimens from patients with myeloma-PNP led to the hypothesis that monoclonal immunoglobulins (m-Ig) may play an important pathogenic role (*4, 5*). More recently it was argued that binding of m-IgG to nerves might be an unspecific epiphenomenon since IgG deposition can also be seen in other neuropathies (*6, 7*). Furthermore, it has been speculated that the demyelinating m-Ig could be an antibody against peripheral nerve components (*8*), since (i) myeloma is associated with autoimmune diseases (*9*) and (ii) myeloma cells occasionally produce m-Ig with distinct antibody specificities (*10*).

In this report we demonstrate that m-IgG plays a part in the pathogenesis of PNP in m-IgG–secreting myeloma and we present preliminary evidence of an immunopathologic mechanism. In order to test the direct pathogenic effect of m-IgG we passively transferred human m-IgG to mice. This model system was originally devised for studies on the immune mechanism in myasthenia gravis (*11*). Plasma was obtained from seven patients, six with severe m-IgG–secreting myeloma who had undergone therapeutic plasmapheresis, and one with benign monoclonal gammopathy. Two of the myeloma patients and the one with monoclonal gammopathy had clinical signs of a PNP, whereas three had no clinical evidence of nerve involvement. One patient had died before this study was started and his neurological status was not recorded. Pure IgG was prepared by ion exchange chromatography on DEAE-Sephacel (Pharmacia) as previously described (*12*). The eluates were reduced to a final concentration of 20 mg of IgG per milliliter (Amicon-XM 50), dialyzed against physiological saline, and stored at −70°C until use. All IgG fractions were free of other serum proteins as assessed by standard immunoelectrophoresis with rabbit polyvalent antiserum against such human proteins (Behring-Werke). Polyclonal IgG (p-IgG) from a serum pool of more than ten healthy donors was prepared in the same manner. Immediately before use the material was thawed and sterilized through membrane filtration (Minisart, Sartorius; pore size, 0.2 μm).

Thirty-four female B6D2F1/J inbred mice (Jackson Laboratory) 8 to 11 weeks of age, 20 to 22 g in body weight, were used in these experiments. Each mouse received daily intraperitoneal injections of about 20 mg of m-IgG or p-IgG for 8 to 10 weeks in the initial set of experiments and for 10 to 14 days in the later part of the study.

This dose amounted to IgG concentrations of 15 to 20 g per liter in the mouse plasma and was therefore roughly equivalent to the IgG concentrations in the patients from whom IgG was obtained. Tolerance to human proteins was induced by a single dose of cyclophosphamide 24 hours after the first injection (300 mg per kilogram of body weight) (*13*).

In 24 mice we measured nerve conduction velocities in vivo at the mouse tail nerve. Nerve conduction velocities were examined at weekly intervals in the long-term experiments to detect the first signs of nerve damage. In the short-term study at least two measurements were carried out before and after the injection

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Table 1. Morphological results from 34 mice treated with daily intraperitoneal injections of 20 mg of various m-IgG and p-IgG preparations. Plus or minus signs indicate, respectively, presence or absence of structural alterations.

Ig injected	Number of patients	Duration of treatment (weeks)	Demyelination of teased fiber	Electron microscopic examination	Number of mice
		Myeloma			
m-IgG	3* (2 with PNP)	8 to 10	+	+	5
	3* (2 with PNP)	3 to 6	+	+	4
	3* (2 with PNP)	1 to 2	+	+	5
m-IgG	3 (without PNP)	8 to 10	−	−	4
		Benign gammopathy with PNP			
m-IgG	1	2	+	+	1
p-IgG	1	2	−	−	1
		Controls			
p-IgG	Blood donor pool	8 to 10	−	−	5
	Blood donor pool	1 to 6	−	−	5
		IgG fragments			
m-Fab	1 (myeloma with PNP)	2	+	+	1
m-Fc	1 (myeloma with PNP)	2	−	−	1
p-Fab	Blood donor pool	2	−	−	1
p-Fc	Blood donor pool	2	−	−	1

*No neurological findings were recorded in one of these patients.

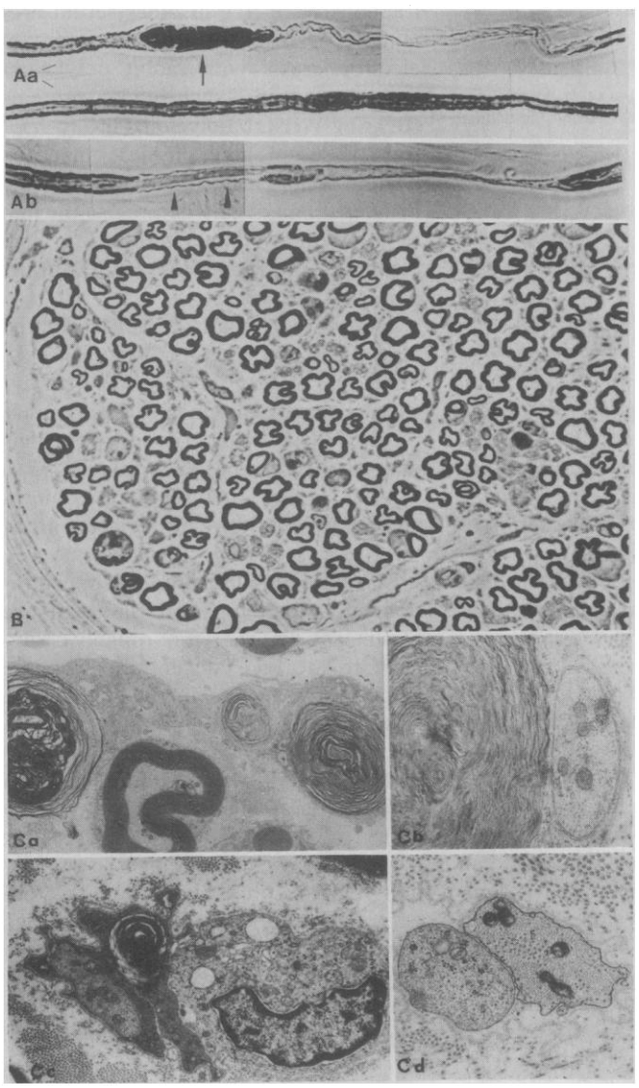

Fig. 1. (Aa and Ab) Teased fibers from sciatic nerve of a mouse treated with monoclonal IgG for 2 weeks. (Aa) Two consecutive regions of a fiber with internodal demyelination and "sausage-like" formation of myelin (*14*) (arrow). (Ab) Another teased fiber with a thin sheath of remyelination (arrow heads) (×400). (B) Semi-thin cross section of a nerve fascicle with scattered damaged nerve fibers (×640). (C) Electron micrographs of some representative findings in one such fascicle. (Ca) Myelin debris (×4900). (Cb) Schwann cell cytoplasm with a concentric array of degenerated myelin and a small axon profile devoid of myelin (×20,500). (Cc) Schwann cell with a demyelinated axon adjacent to another basal membrane-bound cell (×9000). (Cd) Axon sprout and Schwann cell profile with a loosely fitting basal lamina investment (×25,250).

period. At the end of an experiment the mouse was anesthetized with Nembutal (60 mg per kilogram of body weight) and the tail and sciatic nerves were rapidly dissected under a stereomicroscope. Parts of the sciatic nerves were immersed and fixed in 2 percent osmium tetroxide in phosphate-buffered saline (*14*). More than 80 single fibers with over 400 internodes were teased and examined for demyelination under a Leitz phase-contrast microscope.

The remaining specimens were prepared for standard electron microscopy by fixation in 2.5 percent glutaraldehyde in phosphate-buffered saline, dehydration, and embedding in Epon. Ultrathin sections were studied on a Zeiss EM 9A and EM 10.

In all animals treated with m-IgG from three of the six individual myeloma patients we found signs of nerve damage in sciatic and tail nerves indicating PNP. In all animals, teased fiber preparations showed nodal widening, paranodal demyelination, and segmental loss of myelin (Fig. 1A). The severity of the changes was correlated only loosely with the duration of treatment. Semi-thin cross sections of nerve fascicles showed damaged nerve fibers in a scattered distribution (Fig. 1B). By electron microscopy we were able to demonstrate demyelination without any alterations in Schwann cells or endoneurium. Wallerian-like degeneration was also observed (Fig. 1C, a to d). Two of the three myeloma patients whose IgG induced nerve lesions on passive transfer of their m-IgG to mice also had clinical evidence of PNP. In none of the animals treated with m-IgG from the remaining three patients (without clinical signs of PNP) or with p-IgG from control plasma did we find pathological alterations (Table 1). It is therefore unlikely that our findings were due to unspecific nerve damage by human immunoglobulins. In one patient with benign monoclonal gammopathy and PNP we were able to passively transfer the m-IgG and the p-IgG in separate experiments after chromatographic separation. Only the mouse treated with the m-IgG showed demyelination; the p-IgG–injected animal was normal.

The nerve conduction velocities were significantly reduced in those mice that showed signs of PNP after passive transfer when compared with pretreatment values (Fig. 2). During serial measurements gradual slowing could be observed within the fourth week. None of the animals showed definite signs of clinical weakness or anorexia with profound weight loss.

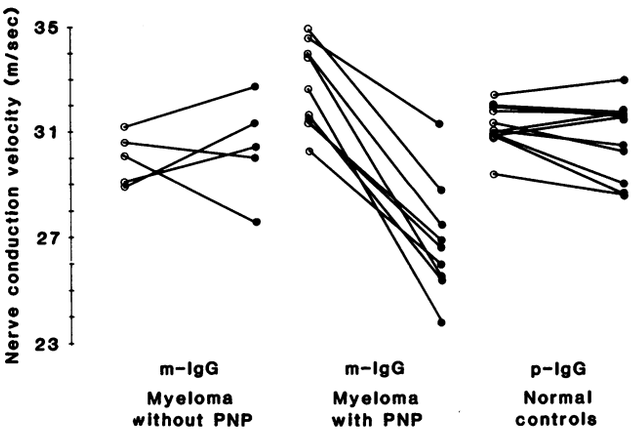

Fig. 2. Nerve conduction velocities in 24 mice treated with daily intraperitoneal injections of monoclonal IgG (*m-IgG*) and polyclonal IgG (*p-IgG*). Each symbol represents a single mouse, measured before (○) and after (●) the treatment period (*20*). The differences of the nerve conduction velocities in the animals treated with monoclonal IgG from patients with myeloma and PNP before and after passive transfer were significant at $P < .01$ (Wilcoxon's nonparametric test for paired differences).

The reproduction of typical features of myeloma PNP in mice by passive transfer of human m-IgG indicates that these immunoglobulins are indeed pathogenic in this disease.

In further experiments we examined the possibility that the interaction of m-IgG and nerve tissue might be antibody-mediated. To show this we first prepared the monovalent Fab and Fc fragments from one "active" m-IgG by enzymatic cleavage with Mercuripapain (Sigma) according to a modified Porter procedure (*12*). Briefly, fragments were isolated by ion exchange chromatography on DEAE-Sephadex A 50 (Pharmacia), and the absence of proteinase activity was checked by an enzymatic test originally devised for chymotrypsin. For control experiments Fab and Fc fragments were purified from a p-IgG in the same manner. Fab and Fc fragments were then injected into four mice in the same way as with native IgG. The doses were roughly equivalent to the relative amounts of putative antigen-binding sites on the IgG molecule.

Only the Fab fragments of the "active" m-IgG induced segmental demyelination; the Fc fragments of the same m-IgG and the fragments from the control IgG did not passively transfer a PNP. Since only Fab fragments bear the antigen-binding determinants and carry the variable region, these findings support the hypothesis of an immunopathologic mechanism operative in myeloma PNP.

If this were true the "active" m-IgG should have a special affinity for peripheral nerve components. In order to examine this we carried out direct immunofluorescence tests on sciatic nerve cryosections taken from mice with passively transferred PNP and from p-IgG–injected control animals. Fluorescein isothiocyanate (FITC)–conjugated rabbit antiserum to human IgG (Behring-Werke) was incubated with the 5-μm sections for 30 minutes, rinsed with phosphate-buffered saline, and studied on a Zeiss Axiomat fluorescence microscope.

In these preparations IgG was clearly identified. In the nerves from animals treated with m-IgG, fluorescence was much more intense than in the control sections, and in the former the stain was in closer proximity to the myelin sheath (Fig. 3). These findings suggest specific binding of m-IgG to nerve, but the possibility that some of the IgG binding was secondary to the demyelinating process cannot be excluded, since this occurs in human neuropathies of nonmyeloma origin (*6, 7*).

We then examined the possibility that the "active" m-IgG cross-reacts with other antigens. A series of indirect immunofluorescence tests was carried out according to standard methods with a panel of human organ sections (*15*). In addition, nonorgan specific antibodies were tested, including antibodies to nuclear protein, rheumatoid factor and antibodies to single-stranded DNA. Two of the four "active" m-IgG fractions but none of the controls showed antibody activity against smooth muscle tissue on indirect immunofluorescence.

Our results provide evidence that patients with IgG-secreting myeloma and neuropathy possess a factor in their monoclonal IgG fractions that demyelinates mouse nerves in vivo and thereby reproduces typical features of the human disease after passive transfer. We suggest that this factor is an antibody directed to an undetermined antigen in peripheral nerve tissue. The fact that two of the four demyelinating m-IgG's cross-reacted with smooth muscle antigens suggests that the putative antibody is not highly organ-specific.

The passive transfer of PNP by the m-IgG but not the p-IgG fraction from the patient with benign monoclonal gammopathy strongly supports the hypothesis that the putative antibody is an m-IgG. Though it seems unlikely, the possibility cannot be excluded that a distinct second autoantibody is present in the small amounts of p-IgG contaminating the m-IgG preparations from the three myeloma patients.

The role of the complement system remains to be elucidated by experiments with complement-deficient mice. Since monovalent Fab fragments do not activate complement (*16*) the demyelinating activity of Fab in one of our experiments

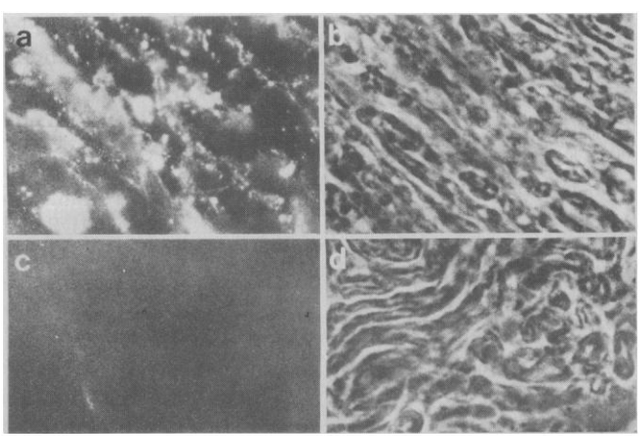

Fig. 3. Cryosections (5 μm) of mouse sciatic nerves after passive transfer of monoclonal (a and b) and polyclonal (c and d) IgG. (a and c) Direct immunofluorescence preparations [FITC-conjugated rabbit antiserum to human IgG (Behring-Werke, West Germany), dilution 1:32]. (b and d) Phase-contrast micrographs of the corresponding serial sections (×450).

strongly suggests that complement is not crucial in bringing about the nerve lesion. The demonstration of a potentially pathogenic role of m-IgG in myeloma neuropathy may have implications for the management of patients with this disorder (*17*).

As in myasthenia gravis (*18*), a humorally mediated autoimmune disease of the neuromuscular junction, antibody depletion therapy by plasma exchange might prove beneficial.

Note added in proof: After submission of this manuscript, Latov *et al.* (*19*) described a human monoclonal antibody to peripheral nerve myelin in a patient with IgM_{Kappa}-monoclonal gammopathy. The patient's polyneuropathy improved after treatment with plasma exchange, steroids, and cytotoxic drugs. As in the mice used in our experiments, the patient's nerves showed segmental demyelination.

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20. Nerve conduction velocity of the tail nerve was measured in a paraffin bath maintained at 30°C by a pair of subcutaneous tungsten microelectrodes at the proximal end of the tail. Supramaximal stimuli of 0.1-msec duration were applied at the distal end of the tail by another pair of electrodes with a Grass S 88 stimulator connected to SIU 5. The distance between stimulating and recording electrodes was measured by caliper and was 5 to 6 cm. Recordings were made with a differential amplifier, displayed on a Tektronix 5103 N storage oscilloscope, and photographed by Polaroid film. All measurements were made at least three times on the same day with different electrode positions. The coefficient of variation of these multiple measurements ranged from 1.5 to 6.4 percent in individual mice.
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Periodicity of Sleep States Is Altered in Infants at Risk for the Sudden Infant Death Syndrome

Abstract. *The normal succession of sleep and waking states through a night is disturbed in infants at risk for the sudden infant death syndrome. Compared with normal infants, siblings of the sudden infant death syndrome victims have longer intervals between active sleep epochs at particular times during the night in the newborn period and a decreased tendency to enter short waking periods at 2 and 3 months of age. The latter finding is interpreted as an increased tendency to remain asleep, or a relative failure to arouse from sleep in infants at risk.*

Sleep is a focal point for studies of the sudden infant death syndrome (SIDS), since victims of this syndrome succumb at times when they would be expected to be asleep (*1*). We report here that the organization of sleep states is disturbed in infants at risk for SIDS. Sleep in the infant is composed of two distinct states: a quiescent, or quiet sleep (QS) state, characterized by regular respiration and a slow wave encephalographic (EEG) pattern, and an active sleep (AS) state, accompanied by irregular respiration, activated EEG, and phasic muscle activity (*2*). Episodes of QS and AS, intermixed with waking (AW) periods, follow each other in succession throughout the night. This temporal sequencing, rather than the total amount of time spent in each state, is disturbed in infants at risk for SIDS. The importance of this finding is that arousal from sleep may be necessary to restore respiration after certain challenges to the infant (*3*), and an inability to switch from sleep to waking might lead to total respiratory failure.

Twenty neurologically normal infants and 20 infants who were subsequent siblings of SIDS victims (SSIDS) participated in this study. All infants were of conceptional ages between 37 and 44 weeks, and all had 1-minute Apgar scores between 8 and 10. Subsequent siblings of SIDS victims were chosen as a risk group since they have a three- to fourfold higher risk for SIDS than the general population does (*4*). The SSIDS and normal infants were matched according to the educational level of their parents in order to equate for socioeconomic background. Birth weights ranged from 2878 to 4111 g for the normal infants and from 2301 to 4593 g for the higher risk infants. Each infant was admitted to the sleep laboratory at 1700 hours for an all-night monitoring session (range, 10 hours and 40 minutes to 12 hours) during the first week of life and subsequently at 1, 2, 3, 4, and 6 months of age (*5*). The parents were informed of the nature and objectives of the study, and written permission was obtained before participation.

Successive minutes of each record were classified QS, AS, or AW according to criteria described elsewhere (*6*). Sleep scores for each state were then transformed into a binary sequence of 0's and 1's, with 0 representing the absence of a given state and 1 representing the presence. In this manner, 640- to 720-point binary series for QS, AS, and AW were compiled and used to describe the presence or absence of each state in a 12-hour recording. Because of the abrupt transitions associated with binary elements, these three time series for each individual at every age were subjected to a three-term moving filter to reduce high-frequency components (*7*). The smoothed series was then submitted to a fast Fourier transform program to esti-

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