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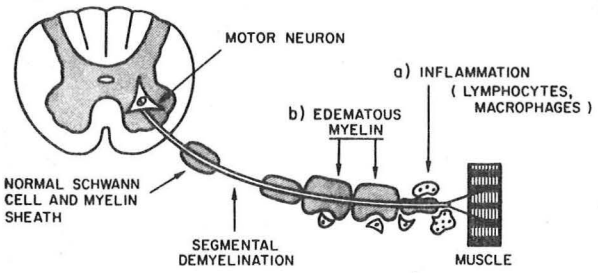
Neurol.

DEPARTMENT OF INTERNAL MEDICINE GRAND ROUNDS

May 29, 1975

IDIOPATHIC ACUTE POLYRADICULONEURITIS

(The Landry-Guillain-Barre-Strohl Syndrome)



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INTRODUCTION:

The syndrome of idiopathic acute polyradiculoneuritis was initially described in France in 1859 by John Batiste Octave Landry (Gaz. Hebd. Med., 6:472, 1859) who described an ascending form of paralysis. Guillain, Barre and Strohl redescribed the syndrome of ascending paralysis again in 1916 in the French literature (Bull. Soc.Med.Hop. Paris, 40:1462, 1916) and in 1936 (Arch. Neurol. Psych. 36:975-990, 1936) in the American literature and emphasized the ascending flaccid quadriparesis characteristic of this syndrome and added the important observation of an elevated cerebrospinal fluid protein without a significant cerebrospinal fluid pleocytosis.

Since the decline in the incidence of poliomyelitis in the past 15 years, idiopathic acute polyneuritis of Guillain-Barre-Strohl (GBS) type has become in the United States the most common cause of acute paralytic disease in man. Unlike poliomyelitis, acute idiopathic polyneuritis is a self-limited disease in which the paralysis is potentially completely reversible thus, proper identification, understanding of the pathogenesis of this disease and appropriate supportive therapy are appropriately emphasized to reduce morbidity and mortality. Recently, there has been considerable progress in understanding the pathogenesis of the disease, and an experimental animal model of the human condition has been achieved and has provided additional important insights to the human disorder.

CLINICAL MANIFESTATIONS:

An analysis of 100 patients (51 female, 49 male) in 1966 by McFarland and Heller (Arch. Neurol. 14:196-201, 1966) demonstrated (Table I) that the disorder occurs throughout the year with a lower incidence in summer months. A preceding infectious illness occurred

TABLE 1.—*Month of Onset*

Month	No. of Cases	Season	Total
December	8		
January	9	Winter =	25
February	8		
March	11		
April	9	Spring =	31
May	11		
June	8		
July	4	Summer =	16
August	4		
September	9		
October	6	Fall =	28
November	13		
			100

(McFarland and Heller, 1966)

in 58 patients [39 viral, 8 bacterial and 11 unknown-type]. The time interval between the onset of infection and the occurrence of neurologic deficits varied between 3 and 84 days with a mean of 20 days. Paresthesias or pain were the first symptoms of paralytic illness for 55 patients, whereas motor weakness was the initial finding for 45 patients. Sensory symptoms were usually mild and transient and invariably followed by motor deficits. An ascending sequence of motor deficit was usual although a descending sequence was not uncommon. In several patients the occurrence of facial diplegia has been noted as the first sign leading to a generalized quadriparesis or quadriplegia. Patients having quadriparesis developed profound involvement of trunk and <u>proximal</u> musculature leading to their usually being unable to sit or lift arms or legs. A minority of patients had profound distal distribution of weakness or an equal proximal distal distribution. It should be emphasized that the predominance

of proximal weakness is an unusual manifestation of a polyneuropathy and therefore is of diagnostic significance to differentiate acute polyneuritis of GBS type from other types of acute neuropathy. The usual rate of onset of sensory-motor symptoms to the height of the paralytic disease is in a range of 3-21 days. The occurrence of neurological findings at the time of hospital admission is recorded in Table IV. Twenty-three patients had marked personality change

TABLE 4.—*Analysis of Neurological Signs at Admission*

	No. of Cases
Mental disturbance	
Irrational	5
Anxious	5
Lethargic	5
Depressed	4
Irritable	4
Cranial nerves	
Normal	25
Oculomotor	6
Trigeminal	15
Abducens	7
Facial	55
Glossopharyngeal and vagus	48
Spinal accessory	8
Hypoglossal	10
Respiratory paralysis	22
Weakness	
Legs and arms	74
Legs	24
Arms	1
Face	1
Sensation	
Normal	30
Relative anesthesia,* legs	52
Relative anesthesia, arms	29
Vibration or position loss or both, legs	9
Hypesthesia, legs	5
Sensory level	6
Generalized myalgia	7
Leg pains (cramps)	8
Meningeal irritation	11

(McFarland and Heller, 1966)

with their illness. Cranial nerves were affected in 75% of patients. Oculomotor and abducens deficits appeared in 13 patients, all presenting with diplopia. 15 patients developed trigeminal deficits which included weakness of mastication, decreased corneal reflex or facial sensation. Facial diplegia resulted in 55 patients and was

usually symmetrical. Cranial nerves IX and X were commonly affected as well, producing dysphagia, dysarthria, impaired speech and nasal regurgitation. Weakness of the sternocleidomastoids was reported in 8 cases. Pupillary reactions were impaired in several patients but the occurrence of this due to third nerve or sympathetic involvement could not be precisely determined. One patient clearly developed a Horner's syndrome. Papilledema has been reported on occasions and usually in those patients with marked elevation in CSF protein. There were 7 patients with nystagmus.

Weakness was present in both arms and legs in the vast majority of patients but usually more profound in the legs. 24% of patients had weakness only in their legs and one only in the upper extremities. One patient was seen with a facial diplegia without other cranial nerve involvement and without other extremity involvement. The deep tendon reflexes were characteristically depressed with preservation of superficial reflexes. An occasional transient extensor plantar response has been documented. Sensory examination demonstrated a mild to moderate impairment of pain, light touch, position sense and vibration in about 50% of the patients in their legs and about 1/3 of patients in their upper extremities. There is often a hyperpathic, hypersensitivity of the feet and sensory levels have been demonstrated. Dysfunction of bowel and bladder are unusual and are usually encountered only with patients with dense sensory involvement. It is common for patients to complain of leg pains or cramps, usually in the gastrocnemius and soleus muscles.

The cerebrospinal fluid as emphasized by Guillain, Barre and Strohl has an elevated total protein, a normal sugar and less than 10 lymphocytes/mm^3. As seen in Table 5, protein can be increased to several hundred mgs% with a small number of lymphocytes and a normal CSF serology and glucose. It may take several days to a week

TABLE 5.—*Cells and Protein in Cerebrospinal Fluid at Different Time Intervals of the Disease*

	Days From Onset of Paralytic Disease				
	0-6	7-15	16-30	30-60	Over 60
No. of determinations	31	33	39	39	13
Prevalent cell type	Lymph	Lymph	Lymph	Lymph	Lymph
Mean no. of cells	2.8	3.6	3.0	3.7	2.7
Mean protein mg/100 cc	140	189	213	209	159

(McFarland and Heller, 1966)

for the CSF protein to become elevated.

Respiratory paralysis and resultant inadequate respiratory ventilation occur in about 25% of hospitalized patients with this disorder. Patients may develop respiratory embarrassment quickly and therefore great care should be given to frequent monitoring of forced vital capacity and tidal volume. In general, a vital capacity of less than 2000 cc's may be grounds for intubation and maintenance on a positive pressure ventilator.

It should be emphasized that this disease is usually completely reversible even in those patients with respiratory embarrassment and quadriplegia and thus careful attention to respiratory status during the initial phases of the disease is essential. The average number of days from hospital admission to dismissal is on the order of 75 days. About 75% of patients are completely cleared of any neurological deficit. About 20% will have some minor residual deficit and

about 5% will have significant neurological impairment. The most significant early predictor of incomplete recovery is the time interval between the greatest weakness and beginning improvement; a period longer than 18 days of plateau before gains are evident is indicative of incomplete recovery (J. Peds. 86:356-359, 1975).

Mortality rates in several large series are between 2 and 5%. The lower recent mortality figures compared with a 20% mortality 30 years ago is due largely to early tracheostomy, meticulous respiratory care, prompt identification of pneumonia and use of antibiotics and careful follow-up of those patients with recurrent polyneuropathy (McFarland and Heller, Arch. Neurol. 14:196-201, 1966).

Osler and Sidel in 1960 (New Eng. J. Med. 262:964-969, 1960) emphasized the need for precise criteria for the GBS syndrome from the larger number of entities producing acute polyneuritis. They state that the Guillain-Barre type of acute polyneuritis is a specific entity with characteristic clinical features, course and prognosis which should be separated out from other types. They emphasize several important distinguishing criteria:

a) The syndrome occurs, frequently, 1-3 weeks after an infection, most often an upper respiratory infection;

b) Sensory complaints such as dysesthesias occurring in hands and feet precede the occurrence of paralysis;

c) There is a rapid occurrence of a symmetrical loss of strength, usually in proximal muscles of the legs and later arms;

d) Objective sensory impairment is minimal and transient;

e) Bladder and bowel dysfunction are rare;

f) Cranial nerve dysfunction most frequently involves the seventh nerve symmetrically;

g) Improvement begins about the third week and continues without relapse;

h) The cerebrospinal fluid shows an elevated protein without a cell count of over 10 lymphocytes/mm^3.

Features which they regard as atypical of the syndrome would be patients demonstrating profound and constant sensory loss, a prolonged clinical course, and persistent disability. The occurrence of significant sphincter and bowel and bladder involvement, optic nerve involvement or CSF pleocytosis would not be compatible with this precise form of acute polyneuritis.

Miller Fischer in 1956 (New Eng. J. Med., 255:57-65, 1956) described three patients with an unusual variant of acute idiopathic polyneuritis which included 1) ophthalmoplegia, 2) ataxia and 3) areflexia. This variant was thought to be related to acute polyneuritis of Guillain-Barre type due to the similarity of the syndrome and the occurrence on occasion of a markedly elevated CSF protein. Acute bilateral ophthalmoplegia had previously been reported in association with severe wide-spread paralysis, first by Pinkney in 1936 in two patients (Brit. Med. J. 2:333-335, 1936) and later by Garvey and Slavin in 1938 (Internat. Clin. 48:38-45, 1938), by Baker (Lancet, 63:384-398, 1943) and in the series of Haymaker and Kernohan in 1949 (Medicine, 28:59-141, 1949). The ophthalmoplegia was of an acute external type with preservation of pupillary and ciliary muscles. Recovery was rapid and complete in all series. Wernicke's encephalopathy bears a a great similarity to this syndrome with those patients exhibiting

ataxia, ophthalmoplegia but also alteration in consciousness, an important feature of Wernicke's syndrome, thus differentiating it from acute polyneuritis. It is assumed by Fischer that the occurrence of the symmetrical ophthalmoparesis with ptosis indicated a peripheral involvement of the ocular motor and abducens nerves. The ataxia was a striking feature and typical of a cerebellar form of ataxia. Ataxia of peripheral nerve disease in patients with sensory involvement is well known, but in these patients of Fischer there were no objective sensory deficits at a time when they had severe appendicular and gait ataxia. It is important to note that these patients did not have a cerebellar type of scanning dysarthria. These patients, as expected, with a variant of the Guillain-Barre type of acute polyneuritis were also areflexic. In summary, Fischer interprets this triad of findings to be a variant of acute polyneuritis of Guillain-Barre type with involvement of motor and sensory cranial pheripheral nerves.

DIFFERENTIAL DIAGNOSIS:

The differential diagnosis includes poliomyelitis, diphtheritic polyneuritis, acute botulism, acute myasthenia gravis, transverse myelitis, nuclear or cytoplasmic neuronopathy (of Ramos-Alvarez-Bessudo and Sabin) and possibly Buckthorn polyneuropathy and tick paralysis. The occurrence of paralysis with poliomyelitis usually occurs with fever and with idiopathic polyneuritis the occurrence of paralysis is afebrile, a helpful but not absolute differential finding. Polio tends to produce asymmetric paralysis and poly-

neuritis is more symmetrical. Poliomyelitis more often produces an impressive pleocytosis in the CSF. Acute generalized myasthenia gravis is unlikely in the absence of significant cranial nerve palsies especially of musculature intervated by cranial nerves III, IV and VI. It is unusual for acute polyneuritis to involve these cranial nerves to any significant degree. Areflexia is most atypical also in myasthenia. Acute botulism produces pupillary abnormalities, impairment of visual acuity as well as clear involvement of extraocular muscle function, findings unusual for acute neuritis. Acute transverse myelitis can be difficult to distinguish from acute symmetrical polyneuritis. One would hope to find a definite sensory level with evidence of spinal cord involvement including hyperreflexia, extensor plantar responses and an increase in extremity tone.

Ramos-Alvarez and co-workers (JAMA, 207:1481-1492,1969) have described a neuropathological entity resembling acute polyneuritis which they refer to as non-inflammatory disease of the cord producing nuclear or cytoplasmic neuronopathy. The interval between the onset of paralysis and death in cytoplasmic and nuclear neuronopathies is less indicating a more fulminant course compared to idiopathic acute polyneuritis (Table 2). This may be the only

Table 2.—Distinctive Neuropathologic Findings and Other Pertinent Data in 25 Cases of Fatal, Acute Lower Motor Neuron Paralytic Disease Without CNS Inflammatory Changes

Neuropathologic Category	Case No.	Case Year	Month of Onset	Residence, State	Age, yr	Sex	Interval Between Onset of Paralysis and Death, Days
Landry-Guillain-Barré	1-74*	1962	July	Queretaro	3	F	10
	2-2	1964	Dec	Mexico	7	F	10
	3-112	1966	Aug	Michoacan	4	F	13
	4-114	1966	Aug	Mexico, DF	1	M	7
	5-123	1966	Sept	Michoacan	5	F	13
	6-149	1966	Nov	Mexico, DF	1	M	30
	7-152	1967	Oct	Veracruz	3	M	28
	8-159	1967	Nov	Queretaro	3	M	5
	9-49	1968	March	Guerrero	2	F	4
	10-229	1968	Sept	Mexico, DF	3	M	12
Cytoplasmic neuronopathy†	1-77	1963	July	Mexico, DF	5	M	6
	2-178	1964	Nov	Veracruz	5	M	6
	3-5	1965	Jan	Veracruz	7	F	6
	4-15	1965	Feb	Veracruz	5	F	7
	5-100	1965	Nov	Mexico, DF	10	M	3
	6-65	1967	May	Mexico	7	M	7
	7-6	1967	Dec	Mexico	13	M	10
	8-71	1968	March	Veracruz	9	M	15
Nuclear neuronopathy‡	1-33	1965	April	Mexico, DF	3	M	1
	2-48	1966	March	Tamaulipas	3	M	16
	3-116	1966	Aug	Mexico, DF	4	M	6
	4-126	1966	Sept	Mexico	2	M	3
	5-136	1966	Nov	Mexico, DF	3	F	1
	6-46	1967	April	Puebla	1	M	1
	7-100	1967	Aug	Mexico, DF	10	M	3

*The second set of numbers in this column represents the hospital and study record number.
†Extensive chromatolysis in majority of anterior horn cells.
‡Nuclear argyrophil lesion in majority of anterior horn cells (no chromatolysis).

No 8 (Paralytic Syndromes—Ramos-Alvarez et al JAMA, 1969)

distinguishing feature in nuclear and cytoplasmic neuronopathy. It is primarily the anterior horn cell which undergoes either pyknotic or chromatolytic changes. Thus the severe type of acute polyneuritis syndrome may be in actuality an attack upon the anterior horn cell directly, rather than on its peripheral nerve axon.

Buckthorn polyneuropathy (New Eng. J. Med., 277:69-71, 1967) is due to Karwinskia humblotiana, a poisonous shrub of the Buckthorn family, that grows in Mexico, Texas and New Mexico. The clinical picture is that of a progressive and symmetrical polyneuropathy beginning in the lower extremities and ascending, producing a quad-

oily seeds - leaves & roots for fever.

riparesis with eventual respiratory and bulbar impairment. The peripheral nerve biopsy is similar to that encountered in the acute polyneuritis of the Guillain-Barre type.

Acute toxic neuropathy with predominantly motor manifestations specifically induced by drugs and heavy metals would include thalidomide, dilantin, vincristine, INH, furadantin, acrylamide, thallium and lead. All of these agents primarily involve the axon primarily and produce an axonal dystrophy. Acute motor neruopathies primarily involving the Schwann cell include GBS syndrome, chronic lead exposure and diphtheritic polyneuropathy. I.V. Heroin use may result in the G-B syndrome in 4-12 hours after injection (JAMA, March 31, 1975; 231:1367, 1975).

RECURRENT POLYNEUROPATHY

There is a variant of acute polyneuritis which has a slower, insidious, progressive onset and development with a persistent elevation in the spinal fluid protein (Hinman and Magee, Annals of Int. Med., 67:1007-1012, 1967). This report describes four patients in whom over a six year period maintained strikingly elevated CSF protein, usually greater than 100 mg% and who have a remitting and relapsing course of polyneuropathy and who while symptom free and with a normal neurological examination between episodes even continue to maintain an elevated CSF protein (Figure 2). The authors indicate that about 2% of patients overall with acute polyneuritis behave in this manner.

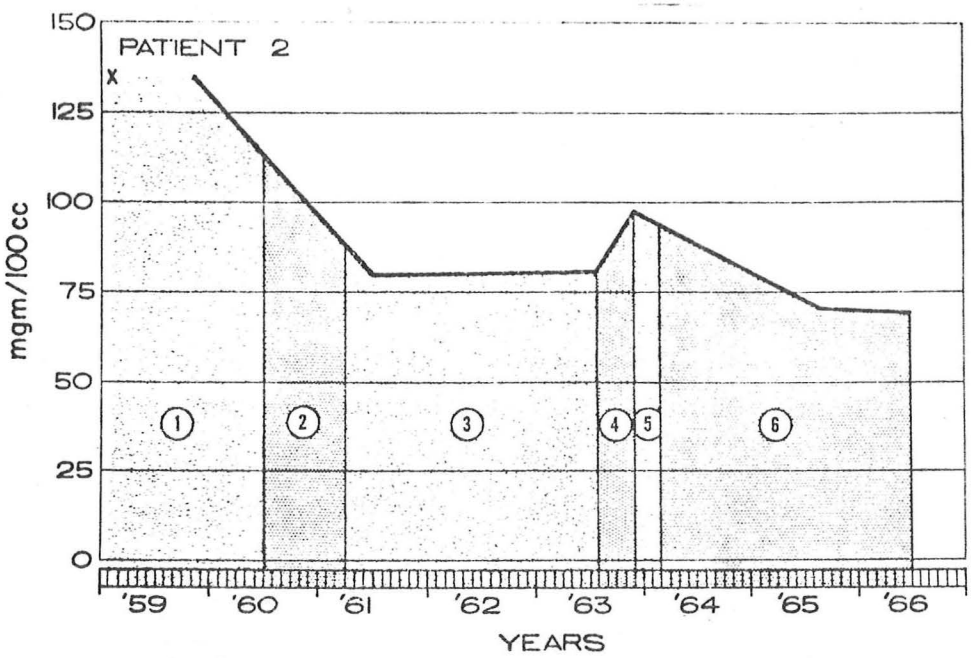


FIGURE 2. Relation between cerebrospinal fluid protein and clinical course in *Case 2*. 1. Progressive neurologic dysfunction during initial illness. 2. Improving neurologic function during initial illness. 3. No symptoms and normal on examination. 4. Progressive neurologic dysfunction during relapse. 5. Improving neurologic function after relapse. 6. No neurologic symptoms and normal examination.

(Hinman and Magee, Annals Int. Med., 1967)

Further recurrent polyneuropathy, which becomes dependent upon corticosteroid treatment has been described (Austin, Brain 81:157-192, 1958; Matthews, Howell, Hughes, J. Neurol. Neurosurg. and Psych. 33:330-337, 1970). 30 Patients (Austin, Brain, 1958) with a symmetrical acute polyneuritis with recurrences were collected from the literature and additional cases provided. An example representative of the clinical picture would be a young adult who slowly developed over weeks or months the progressive occurrence of symptoms and signs of a symmetrical, chiefly distal motor, polyradiculopolyneuropathy involving all extremities and cranial nerves 3,4,6,7,9 and 10. There is no obvious cause such as infection or systemic illness in the prodromal period. CSF protein is elevated

in the range of 200 mg%. The course is one of eventual plateauing and then gradually improving. The typical episode would be the development of quadriparesis over two months which plateaus for three months and then improves for the next seven months to a normal state, approximately one year after the onset. Thus this is a slowly evolving form similar to that reported by Hinman and Magee. It is important to point out that about 1/3 of these patients have findings of enlarged and firm peripheral nerves. Several patients have abnormally enlarged nerves before recurrent bouts of neuropathy begin but many have developed the hypertrophic nerve changes with recurrent episodes. Several of these patients have been studied with ATCH and cortisone, as in Figure 2, demonstrating the very

RECURRENT POLYNEUROPATHIES

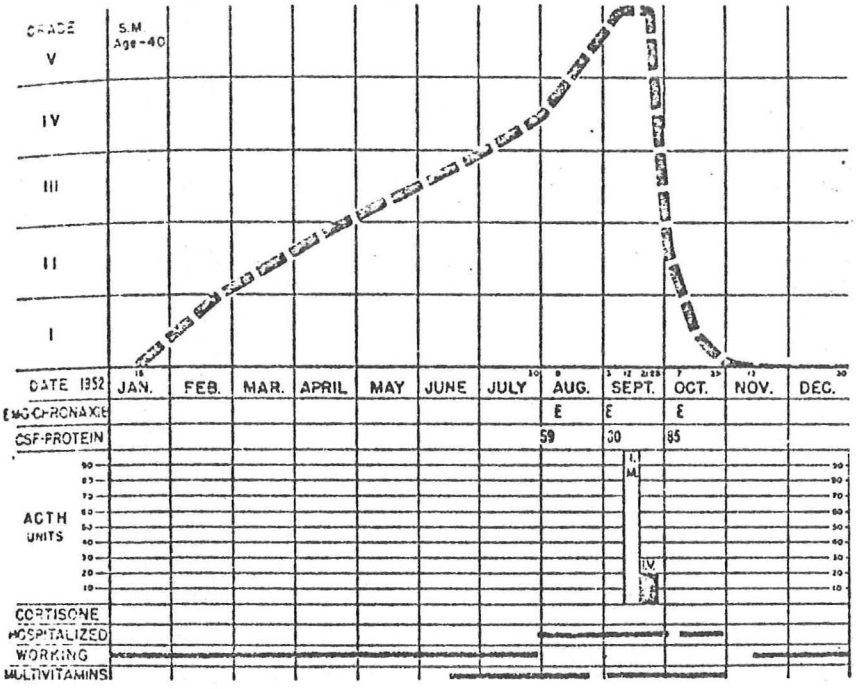


FIG. 2.—First bout in 1952. Note the very slow onset and relatively rapid recovery after maximal dosage ACTH.

(Austin, Brain, 1958)

slow rate of onset of the neuropathy to virtual total paralysis and a rapid recovery after 90 units of ATCH IM for a ten day period q.d. Figure 3 shows the patient again developing another episode

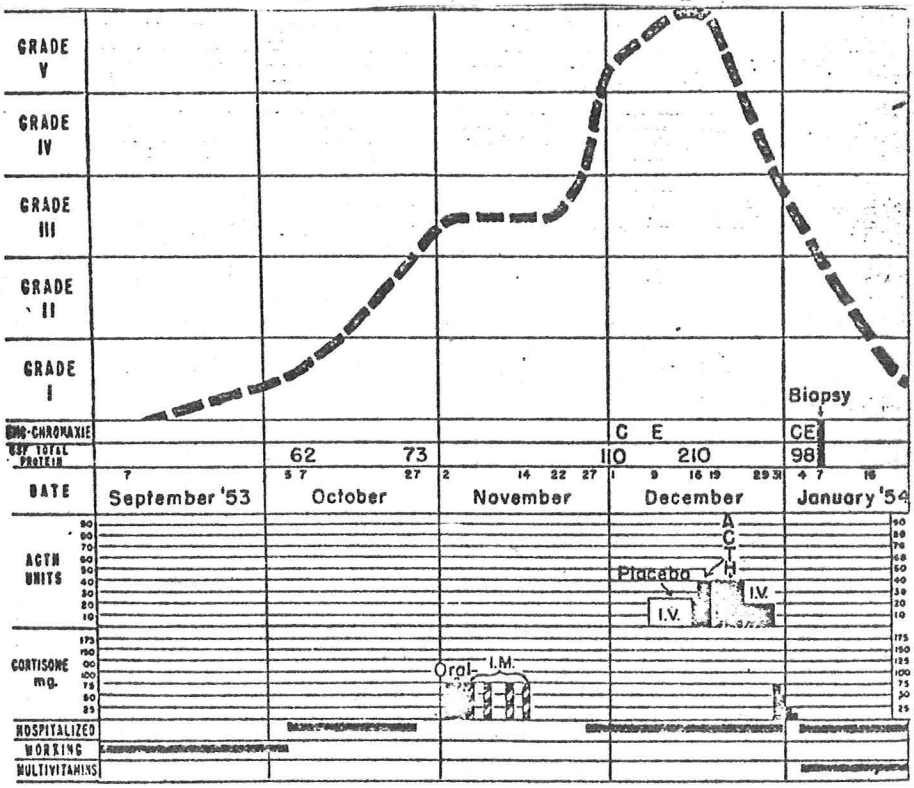


FIG. 3.—Second bout in 1953. Note the checking of progression during cortisone and the relatively rapid response to ACTH.

(Austin, Brain, 1958)

of neuropathy which plateaus with oral and IM cortisone 90 mgs on alternate days. The patient again deteriorated when steroid therapy had ceased, did not improve with placebo but dramatically improved in a four week period of time with intervenous ACTH followed by cortisone. The same patient while maintained on low dosage of ACTH, 25 units intermuscularly, daily, raised to 40 mgs. maintained virtually intact neurologic functions from March to August, 1954, at which time a brief episode of polyneuropathy occurred. The next figure (Austin, Brain, 1958), Figure 9, points out that less severe recurrent episodes

occurred on maintenance cortisone. A severe attack resulted when cortisone was tapered.

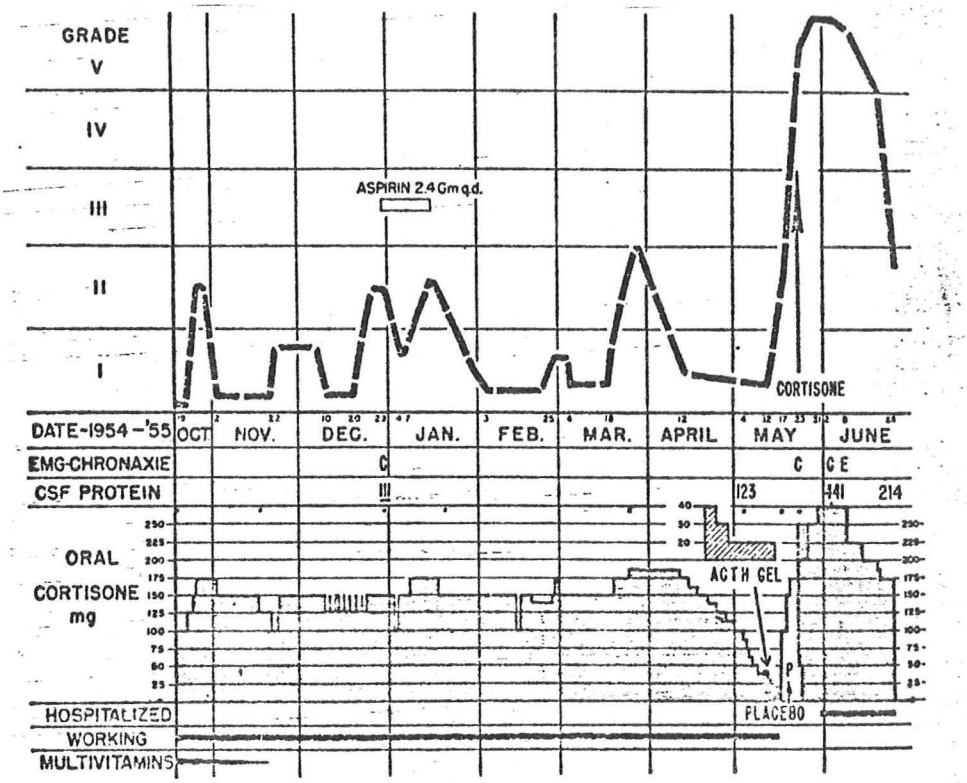


FIG. 9.—Bouts 7–14. Less severe bouts occur on maintenance cortisone. Note the severe episode after cortisone withdrawal, lack of response to placebos, and clinical and CSF protein response when cortisone was restarted.

(Austin, Brain, 1958)

Although steroid therapy in general is controversial and potentially harmful in the treatment of acute polyneuropathy, here is an example representing a variant of the syndrome where clearly it is of value. Heller and DeJong (Arch. Neurol. 8:179-193, 1963) reported on the use of ACTH and prednisone with acute polyneuritis of Guillain-Barre type. Their review of the literature and their own experience with 100 patients indicate that there is no significant therapeutic response due to these agents in patients with typical disease.

ASSOCIATED FINDINGS:

Vasomotor disturbances in acute polyneuritis may be responsible for sudden death. Many reports implicating vasomotor and cardiac dysfunction with a fatal outcome are however, difficult to evaluate because of the frequent accompanying respiratory failure that have influenced the terminal picture. Therefore, extremity coldness, cyanosis, sweating, hypotension and cardiac arrhythmias might be the result of peripheral nerve disease primarily but equally well could be due to hypoxia and hypercapnia (Appenzeller and Marshall, Arch. Neurol. 9:56-60, 1963).

Acute nephritis and neuritis have been noted in the same patient. Bradford in 1918, two years after the original description of Guillain, Barre and Strohl noted the occurrence of nephritis in each of six autopsied cases of acute neuritis (Bradford et al., Quart. J. Med. 78:391-395, 1973) collected nine patients with acute neuritis of Guillain-Barre type between February, 1969 and March, 1972, in which there was evidence of acute glomerulonephritis with histological confirmation during the development of acute polyneuritis. Clinical manifestions of renal disease were hypertension, microscopic hematuria, or both, which was obtained only after repeated examinations. One patient who showed histological changes of nephritis did not have clinical or laboratory findings of nephritis. In general, these patients were young adults with moderate to severe quadriparesis with some subsequent atrophy of extremity musculature and all of whom had elevated CSF protein with minimal CSF cell response. Their

creatinine clearances in mls/min ranged between 26 to 70. Behand et al. (Lancet, April 21, 1973, 850-854) described a patient with acute polyneuritis and nephrotic syndrome occurring simultaneously after a presumed viral illness. Immunofluorescent studies of his kidneys showed immunoglobulin IgM and IgG in a fine granular pattern and electron microscopy showed electron dense deposits in the sub-epithelial areas. They demonstrated using both kidney and nerve antigens that there was a cell mediated hypersensitivity as well as serum antibody to the same antigens in low titer in this patient. Thus, the nephrotic syndrome in this patient may be the result of antigen antibody complex formation with deposition of the complex in the renal glomerulae.

ASSOCIATED VIRSUSES:

This syndrome has been associated with well defined viral diseases as chicken pox, measles and mumps (Miller, Stanton and Gibbons, Quart. J. Med. 25:427, 1956). It has also been associated with enterovirus infections and following various immunizations. More recently Grose and Feorino (Lancet, December 16, 1972, pages 1285-1287) report the occurrence of acute polyneuritis with infection with the Epstein-Barr virsus. Two of the five reported patients had clinical infectious mononucleosis and three had neither clinical nor laboratory evidence of the disease. It has also been associated with mycoplasma pneumoniae infection. The clinical presentation is identical in all respects (Hodges and Perkins, JAMA, 210:2088-2090, 1969).

ASSOCIATION WITH IMMUNOSUPPRESSION:

G-B polyneuritis also occurs in association with disorders in which some degree of suppression of cell-mediated immunity may be present, such as Hodgkin disease, viral infections, SLE, pregnancy, and in immunosuppressed patients following renal transplantation. These observations suggest that suppression of normal immune surveillance might allow the triggering of an autoimmune disease of the peripheral nervous system (Lisak, R., et al., Archives of Neurol. 32:355, 1975).

TREATMENT:

The treatment of this disease is basically supportive. Patients should be monitored carefully for acute respiratory failure by frequent determinations of forced vital capacity. Continual physical therapy is crucial to prevent atelectasis and subsequent pneumonia. If the patient has a deteriorating respiratory state an endotracheal tube or tracheostomy tube must be placed and the patient placed on a ventilator. Antibiotics are to be avoided except when there is a clear indication of bacterial pneumonia. Except for the chronic relapsing form of polyneuritis steroids are contraindicated. As previously mentioned, there is no clear indication in the literature of any direct benefit of steroid therapy, and indeed, there may be harm as the result of their use. Azathioprine has been reported by Yuill et al. (Lancet, October 24, 1970, 854-856) in patients who are stated to have failed to respond to ACTH or corticosteriods. The authors are enthusiastic about this form of therapy with immunosuppressive drug but there is no convincing evidence in this paper that they were not treating at a time during the natural remitting phase of the disease.

NEUROPATHOLOGICAL FINDINGS:

The description of the sequential neuropathological findings in this disorder have best been presented by Haymaker and Kernohan in their classic paper entitled "Landry-Guillain-Barre-Strohl Syndrome-50 Fatal Cases and a Critique of the Literature" (Medicine 28:59, 1940) and the paper by Asbury, Arnason and Adams entitled the "Inflammatory Lesion in Idiopathic Polyneuritis" (Medicine 48:173-215, 1969). These papers point out that the characteristic lesion occurring from the very early phase throughout the entire course of the illness is one of an acute inflammatory polyneuritis with the occurrence of lyphocytes present in the spinal nerve roots and peripheral nerves in every case examined. The early significant and diffuse occurrence of this lymphocytic infiltration lead the authors logically to the consideration of an allergic, viral or autoimmune mechanism for this disease. The compelling neuropathological similarities between idiopathic polyneuritis and experimental allergic neuritis as described by Waxman and Adams (J. Exp. Med., 102:213-236, 1955) suggest that acute polyneuritis is the result of an autoimmune mechanism perhaps secondary to a primary infectious agent.

The common denominator in all the patients of Asbury et al. was an impressive diffuse lymphocytic inflammatory infiltration of the peripheral nervous system. There was an admixture of polymorphonuclear leukocytes in the early intensely destructive lesions and occasional plasma cells were present in lesions of long-standing duration. This inflammatory process persisted in some patients in a low grade fashion for months or years after clinical recovery and

is an important finding to explain recurrent cases of neuropathy. The inflammatory infiltrate had a predilection for endoneural and epinerual vessels usually veins with a random multifocal distribution. It is important to indicate that the peripheral nervous system was vulnerable to lymphocytic attack including both the anterior and posterior roots, dorsal root ganglia, and proximal and distal nerve trunks as well as terminal twigs, cranial nerves, sympathetic chains and sympathetic chain ganglia. In general, patients who had exclusive motor signs showed extensive anterior root disease with sparing of the posterior roots and conversely, patients with significant sensory disease showed more involvement of the posterior root nerve segments.

Associated with the round cell infiltration of perivenular regions of the peripheral nerve there was segmental demyelination as a predominant form of the nerve damage. Segmental demyelination refers to the involvement of a segment of the peripheral nerve supplied by one Schwann cell. Many regions were completely devoid of myelin, others demonstrated a reduction in content of myelin, edemia of myelin and phagocytosis by macrophages of involved myelin.

POLYRADICULONEURITIS

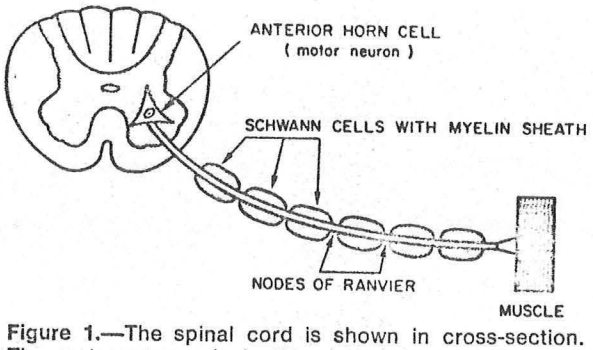


Figure 1.—The spinal cord is shown in cross-section. The motor neuron is in the ventral horn of the cord and its axon innervates a muscle fiber. The axon is normally myelinated by Schwann cells which are interspersed with gap-regions referred to as nodes of Ranvier.

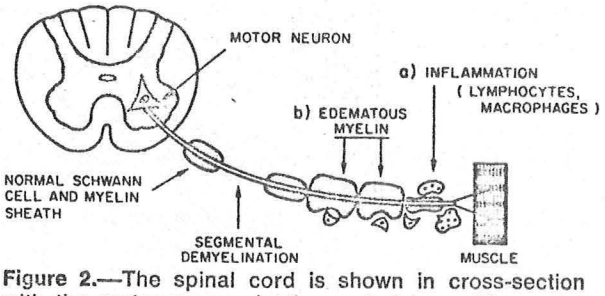


Figure 2.—The spinal cord is shown in cross-section with the motor neuron in the ventral horn. The motor nerve axon illustrates the pathologic changes in the myelin sheath seen in acute idiopathic polyneuritis: (a) the early inflammatory response; and (b) edema and phagocytosis of myelin by macrophages. Segmental demyelination is a later stage in the process showing loss of Schwann cell and its myelin leaving a widened node of Ranvier.

(Figure 1 and 2, Rosenberg and Mendoza, West. J. Med. 120:124-130, 1974). In addition, axonal interruption and Wallerian degeneration was observed frequently. There was evidence of Schwann cell proliferation seen by 8 days after the onset of neurologic deficits and was abundantly evident by 14 days and thereafter.

The findings in the central nervous system could be interpreted as being entirely secondary to the changes of the peripheral nervous system. Central chromatolysis was seen in the motor nerve cell bodies of the anterior horns and motor nuclei of cranial nerves. The central chromatolytic changes were in general proportional to the amount of Wallerian degeneration present distally. There was evidence of secondary posterior column degeneration due to involvement of the dorsal roots and ganglia. Anoxic encephalopathic changes were encountered in patients who had been on a respirator for extended periods of time and had become comatose prior to death. Muscle demonstrated denervation atrophy.

Peripheral nerve conduction studies. It is a characteristic finding that there is slowing of peripheral nerve conduction velocities to a significant degree in this disease. It is common to find a 50% reduction of conduction velocities to the order of 30 meters/second in the ulnar or median nerves and less than 20 meters/second in the peroneal nerve. (Figure 3, Rosenberg and Mendoza, West. J. Med., 120:124-130, 1974). It may be difficult to record a compound muscle

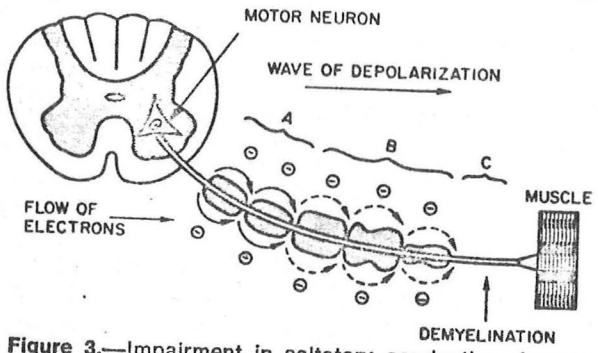
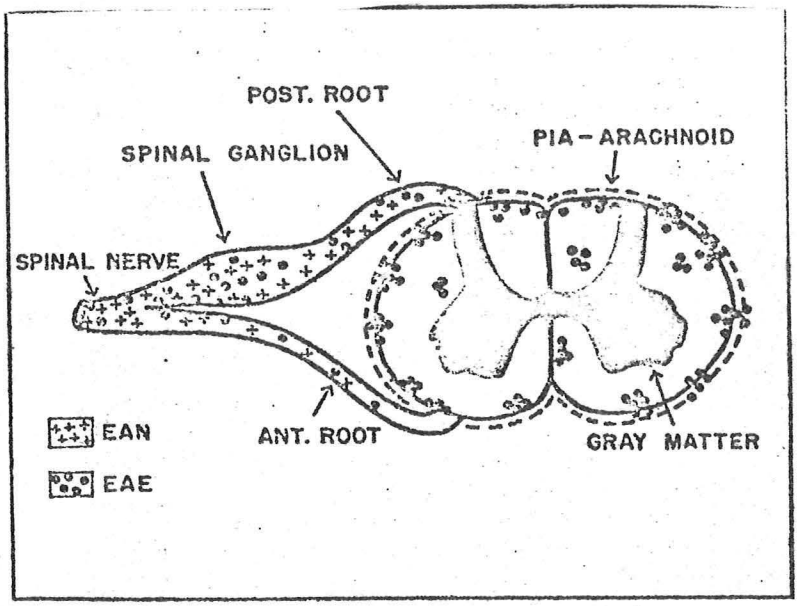


Figure 3.—Impairment in saltatory conduction down a motor nerve fiber. Region A shows a normal conduction velocity due to the normal rate of the flow of electrons in a region of the motor nerve that is myelinated and has intact nodes of Ranvier. Region B has slowed conduction velocities due to myelin edema and hypomyelination. A total blockade of electrical conduction is seen in region C where the motor nerve axon is entirely demylinated.

action potential by supramaximal stimulation of peripheral nerve. There may be improvement in conduction velocity before one can determine clinical improvement. With clinical improvement back to a normal level there may not be an absolute return of conduction velocities to a normal rate. With remyelination of peripheral nerve, the internodal distance is reduced thus requiring an increased number of saltatory jumps per unit length required for conduction to continue. The increased numbers of internodes per unit distance of nerve requires more time for saltatory conduction to be achieved between the anterior horn cell and the neuromuscular junction and it is common to find a permanently slowed conduction velocity in the order of 20% reduced in an otherwise intact patient (Lambert, E.H., Electroencephalography and Clinical Neurophysiology, Supplement 22, page 2, 1962).

Pathogenesis of Disease. In 1955, Waksman and Adams published a classical paper entitled "Allergic Neuritis in Experimental Disease

of Rabbits Induced by the Injection of Peripheral Nervous Tissue and Antigens" (Waksman, B. and Adams, R.D., J. of Exp. Med. 102: 213-235, 1955) and in so doing provided an experimental model for acute polyneuritis of man. They described the disease in rabbits produced by the innoculation of homologous or heterologous sciatic nerve. They referred to the rabbit disease as experimental allergic neuritis (EAN). The lesions were confined in nerve roots, spinal ganglia and peripheral nerves. There was a characteristic change in the cerebrospinal fluid with an elevation of protein without pleocytosis. The average day of onset of the EAN was about 14 days after innoculation. Figure 1 points out the predominant involvement



TEXT-FIG. 1. Diagram illustrating anatomical relationships in the central and peripheral nervous systems, with approximate distribution of the lesions of EAN and EAE.

(Waksman and Adams, J. of Exper. Med., 1955)

of the peripheral nervous system in EAN without involvement of the central nervous system parenchyma. Experimental allergic encephalomyelitis (EAE) produced by the injection of central nervous system

produced lesions in the central nervous system and some minor involvement of the peripheral nerve structures. The lesions consisted of infiltration of histiocytes and lymphocytes with a small number of polymorphonuclear leukocytes. In the region of the inflammation there was disruption of the myelin sheath and demyelination. Intraneural veins were surrounded by a variable number of lymphocytes and mononuclear cells. The extent of the demyelination could be best appreciated with myelin, axis cylinder and sudan fat preparations of the nerve roots. Table 1 points that in EAN there is a consistent involvement of meninges, root entry zones,

TABLE I

Relative Involvement of Different Regions of the Nervous System in EAN and EAE

Region of nervous system	EAN					EAE				
	No. of rabbits*	Per cent with severity				No. of rabbits*	Per cent with severity			
		0	+	++	+++		0	+	++	+++
Cord, brain, and optic nerve	52	100	0	0	0	94	11	38	35	16
Meninges	52	85	11	4	0	94	8	43	32	17
Root entry zones	51	35	63	2	0	92	26	42	28	4
Spinal nerve roots	52	12	54	32	2	89	45	47	6	2
Spinal ganglia	52	8	48	36	8	67	22	45	21	12
Peripheral nerves	51	20	54	24	2	56	63	26	9	2

* In certain rabbits, particular parts of the peripheral nervous system were missing, largely in groups with EAE autopsied before the present study was begun.

(Waksman and Adams, 1955)

spinal nerve roots, ganglia and peripheral nerve, all structures which contain myelin synthesized by Schwann cells. At no time was central nervous system tissue involved, that is, tissue associated with myelin synthesized by the oligodendrocyte. However, animals in whom EAE was produced by central nervous system tissue injection had prominent involvement of an inflammatory demyelinating lesion in the central nervous system and also extension of this process into the peripheral nervous system. Table 2 points out the relationship

TABLE II

Relation of Symptomatology of EAN to Severity of Histologically Observed Lesions

Severity of EAN symptoms	Average day of onset	Severity of histological EAN*			
		0	+	++	+++
0	—	4	2	2	0
± or +	17	0	11	7	1
++	13	0	4	13	2
+++	12	0	0	3	3

* Severity in this table is the grade assigned to the most severely affected region of the nervous system.

(Waksman and Adams, 1955)

of the symptomatology of EAN to the severity of the lesions seen histologically. As one goes from a minimal to the most severely involved experimental animal, there is an increase in the severity of the lesion both for round cell infiltration, edema and demyelination. Table III points out the similarity of CSF findings in EAN

TABLE III

Spinal Fluid Findings in Normal and Diseased Rabbits

Disease category*	Fluids examined	Fluids forming clot	Total protein			White cells		
			Range	Mean	Median	Range	Mean	Median
Normals	23	0	17–53	24	25	1–38	7	5
No disease following inoculation with adjuvants‡	94	0	14–65	31	29	2–40	10	8
EAE								
Mild	19	0	24–88	46	39	3–154	26	10
Moderate-severe	15	3	54–575	251	222	13–2650	348	96
EAN								
Mild	18	1	33–175	58	47	2–144	15	6
Moderate-severe	25	5	36–650	139	98	3–80	23	14

* Disease considered mild when symptoms and histological grade were + or less.

‡ Omitting 3 clearly positive fluids, in which disease (EAE) had apparently been missed both ante mortem and histologically. Includes cases with questionable symptoms and no histological findings.

(Waksman and Adams, 1955)

to what has been discussed previously in polyneuritis of man, that is, there is an elevated CSF protein which tends to be higher in the more moderately to severely affected animals and the white cell count is

minimal with a mean of 23 cells in the severely affected animals.

Table 4 (Waksman and Adams) points out that a variety of

TABLE IV

Comparison of the Effectiveness of Peripheral Nerve Antigens from Different Species in Producing EAN

Antigen	No. of Rabbits	Per cent with involvement of:					Average day of onset*
		CNS	Menin-ges	Roots	Ganglia	Nerve	
Rabbit sciatic	12	0	17	83	83	75	17
Autoclaved rabbit sciatic	4	0	25	100	100	50	18
Rabbit ganglia	6	0	17	83	83	67	14
Bovine sciatic	7	0	14	100	86	100	13
Human sciatic	4	0	0	75	100	75	14
Dog sciatic	7	0	29	100	86	100	13
Guinea pig sciatic	12	0	17	92	100	92	12
Total.....	52	0	18	90	91	83	14

* Excluding rabbits with minimal signs of disease.

different animals serving as source of peripheral nerve antigen could be used to produce EAN and again, without central nervous system involvement. The use of central nervous system as antigenic source consistently did produce central nervous system inflammatory demyelinating lesions and also was responsible for peripheral nervous system inflammatory demyelinating lesions. Thus, peripheral nerve antigen from a variety of species is restricted in producing only lesions of the peripheral nervous system whereas central nervous system is capable of evoking both central and peripheral acute inflammatory demyelination. Table 6 (Waksman and Adams) points out

TABLE VI

Antibody Production in EAN

Rabbit No.	EAN		Complement fixation titre against:			
	Day of onset	Histologic severity	Rabbit sciatic		Rabbit cord	
			Day 10	Day 16	Day 10	Day 16
1	17	++	30	240	60	>480
2	—	0	60	240	120	480
3	9	+++	120	—	60	—
4	17	++	30	120	60	480
5	18	++	60	120	120	240
6	0	+	0	120	0	240
7	16	++	60	240	60	>480

that complement fixation antibody titers against either rabbit sciatic nerve or rabbit cord significantly increases between 10 and 16 days after injection and at a time when there are significant histologic lesions of EAN already present.

In 1962, Astrom and Waksman (J. Pathol. and Bact., 83:89-106, 1962) reported on the passive transfer of EAE and EAN with lymphoid cells. Table I summarizes rabbits injected with either bovine spinal cord or bovine sciatic nerve. Donor sensitized animals were killed

TABLE I

Detailed findings in selected recipients showing lesions after intravenous injection of living sensitised cells

Cells used for intravenous injection derived from lymph-glands of rabbits injected with	Recipient no.	Dose of cells ($\times 10^6$)	Symptoms		Day of necropsy	Cerebrospinal fluid		Cerebrospinal lesions* in							
			Time of onset (days)	Degree		Total protein (mg. per 100 ml.)	Cells per c.mm.	cerebrum	cerebellum	brain-stem	spinal cord	meninges	nerve roots	spinal ganglia	sciatic nerve
Bovine spinal cord plus adjuvant	2-1	5·6	—	—	7	48	3	—	—	—	++	±	+	+	...
	9-1	2·9	—	—	6	39	107	—	+	+	+	+	—	+‡	—
	20-1	1·9	—	—	4	24	20	—	—	—	+	+	—	+	—
	25-2	8·8	4	+	7	...	...	+	—	+†	++‡	+	+	++	+
	27-2	6·0	—	—	3	39	35	—	—	—	—	+	+	+	+
Bovine sciatic nerve plus adjuvant	10-1	5·3	—	—	5	30	5	—	—	—	—	—	—	+	—
	30-1	6·9	—	—	7	30	11	—	—	—	—	—	—	++‡	+
	41-1	8·5	6	+	6	30	23	—	—	—	—	—	—	+	—

Lesions due to encephalitozoon infection were absent throughout.

* Lesions graded + when fewer than 5 distinct lesions observed, ++ when more than 5.
† Invasion of parenchyma by hæmatogenous cells, or microglial activation, or both.
‡ Invasion with demyelination, or fat, or both.

(Astrom and Waksman, 1962)

and cells from lymph glands injected intravenously or intracisternally into recipient animals who had received 400 R of total body irradiation 1-8 days before transfer. Animals injected with EAE cells developed lesions throughout the central nervous system, meninges, and sciatic nerve. Animals injected with EAN cells did not develop

lesions in the central nervous system nor meninges but as noted developed impressive lesions in the spinal ganglia and sciatic nerve. Similar findings were obtained with the injection of sensitized lymphocytes into the intracisternal compartment. Animals receiving sensitized EAE cells developed inflammation of the subarachnoid space adjacent to the brain stem, spinal cord, and dorsal root ganglia and peripheral nerves. Control animals injected with kidney tissue and subsequent passive transference of their lymphocytes produced no PNS nor CNS lesions. Thus only animals injected with EAN sensitized lymphocytes produced both a meningitis and an acute polyneuritis without brain lesions. Astrom and Waksman point out that the intravenous injection of sensitized EAE or EAN lymphocytes produced symptoms and lesions proportional to the dose of injected cells. Killed lymphocytes and control material did not produce lesions. A similar quantification occurred with intracisternal injection of sensitized lymphocytes and control, killed lymphocytes had no affect.

Winkler in 1965 extended the passive transfer phenomenon to an in vitro system (Annals of the N.Y. Acad. of Sci., 122:287-295, 1965). Lymph node cells from rats with latent or symptomatic EAN produced demyelination of cultures of fetal rat trigeminal ganglia after an exposure of 24-72 hours with the maintenance of intact axis cylinders. Winkler and Arnason (Science 153:75-76, 1966) extended their earlier observation by demonstrating that lymph node cells from rats immunized with sciatic nerve demyelinate trigeminal ganglia cultures

but that rabbit antiserum to rat immunoglobulin A blocks this cytodestructive event. They speculate that antiserum may act by combining with IgA on the lymphoid cell surface and thus preventing the interaction of cell bound antibody and tissue antigen. Figure 1 (Winkler and Arnason) shows a normal trigeminal ganglion culture with intact myelin (a) and (b) demonstrates impressive demyelination after 96 hours exposed to sensitized lymphocytes. Table 1 shows the protective effect of antisera to rat IgA with the control sensitized lymphocyte population demyelinating cultures. Further lymph node cells that had been treated with high frequency sound do not demyelinate cultures suggesting that intact cells are necessary for this effect.

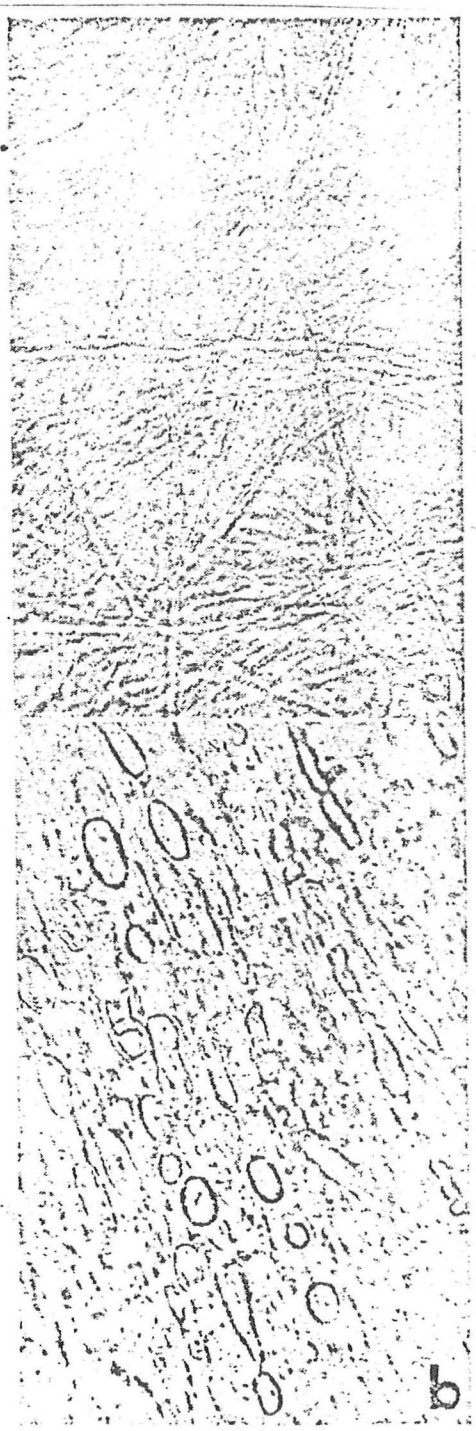


Fig. 1. (*a*) Representative myelinated trigeminal ganglion culture. There is an abundance of myelin (× 270). (*b*) Culture 96 hours after addition of sensitized lymphocytes. The myelin is breaking down (× 400).

(Winkler and Arnason, 1966)

Table 1. Inhibition of demyelination by antiserum to IgA. The proportion of cultures undergoing demyelination when exposed to sensitized lymph node cells is compared to the proportion undergoing demyelination when exposed to cells plus rabbit antiserum to IgA.

Day node cells taken after immunization	Cultures demyelinated	
	Node cells plus rabbit antiserum to rat IgA	Node cells only
7	*0/2	3/3
8	1/2	2/2
9	0/3	3/3
10	2/2	1/1
11	0/2	3/6
12	0/2	2/2
12	1/3	3/6
12	1/3	1/3

* One culture showed incipient degeneration i two fibers.

(Winkler and Arnason, 1966)

Asbury and Arnason pointed out that the lymphocytes in peripheral nerve of animals having EAN are stimulated or transformed cells (J. of Neuropath. and Exp. Neurol., 27:581-590, 1968). Figure 1 (Asbury and Arnason) obtained from a rat sciatic nerve 20 days

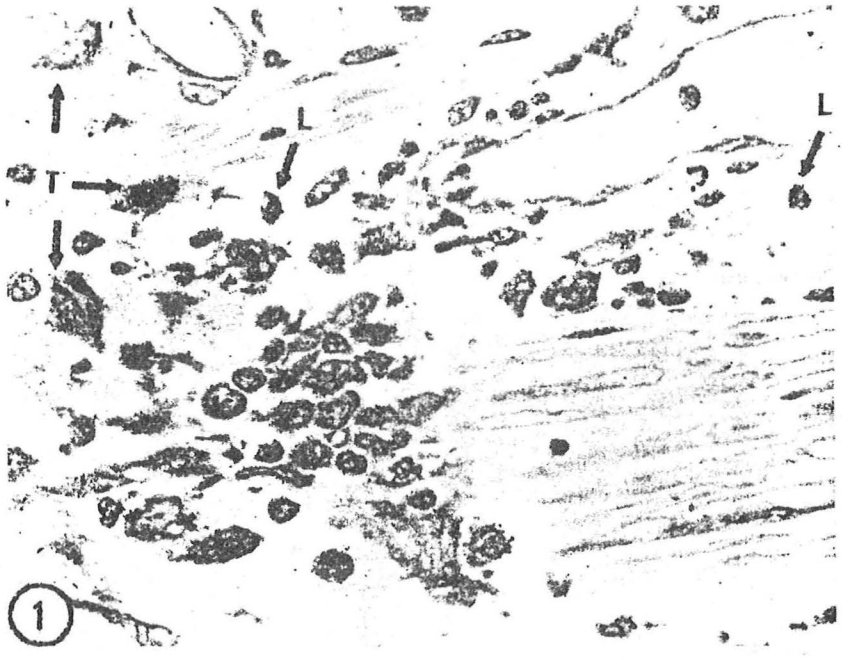


FIG. 1. EAN in rat sciatic nerve 20 days after inoculation. Lymphocytes (L) and transforming cells (T) clustered in the spaces around an endoneurial vessel. Several lymphocytes and transforming cells are labeled. The amount of labeling indicates active DNA synthesis. Toluidine blue stain; 530×.

(Asbury and Arnason, 1968)

after innoculation of peripheral nerve antigen shows an accumulation of lymphocytes and that these are cells which have taken up tritiated (H^3) thymidine indicating active DNA synthesis during the acute lesion period. Forty days after innoculation as seen in Figure 9 (Asbury and Arnason) there is a proliferation of Schwann

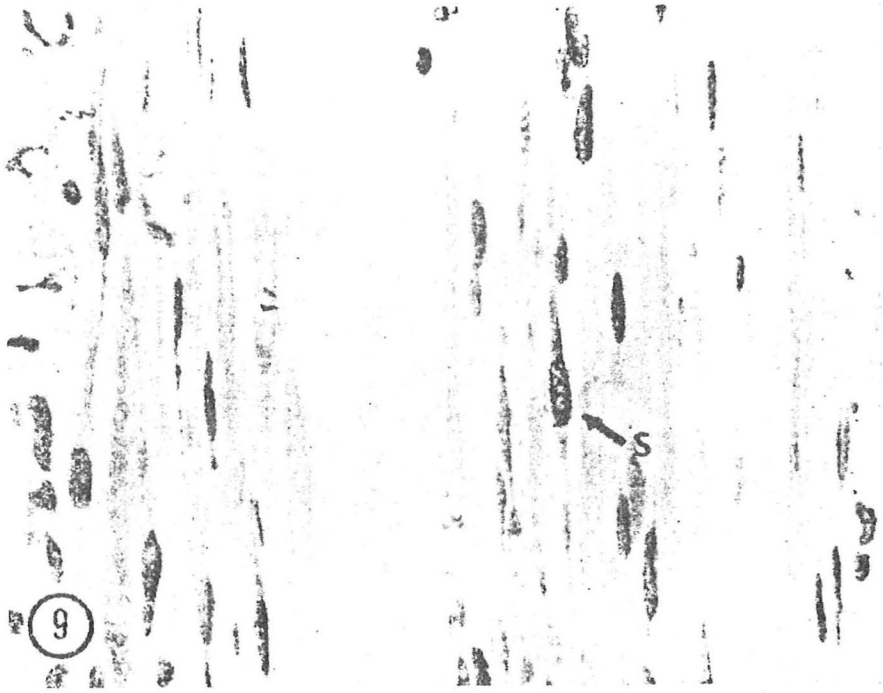


FIG. 9. EAN in rat sciatic nerve 40 days after inoculation. Cellular proliferation has subsided to a large degree, however, an occasional labeled Schwann cell (S) may be identified. These were also found at 3 and 4 months after inoculation indicating that the reparative process persists long after the inflammatory process has disappeared. Toluidine blue stain; 560×.

cells as a repairative process and that there is a marked reduction in the degree of inflammation and lymphocyte thymidine incorporation. They conclude that there are two distinct waves of cellular proliferation in EAN with the initial population being stimulated lymphocytes invading perivenular tissue at about 20 days after innoculation and a second wave of proliferation being Schwann cells which lasts for several months long after the inflammatory process has ceased.

Rocklin et al. (N.E.J.M., 284:803-808, 1971) reported that blood lymphocytes from some 83 subjects were examined for the presence of cellular hypersensitivity to peripheral and central nervous system antigen by means of in vitro production of the macrophage migration inhibitory factor (MIF). In a group of 25 patients with peripheral neuropathies, only lymphocytes from patients with the syndrome of acute idiopathic polyneuritis of Guillain-Barre type produced MIF in response to peripheral nerve antigen. Lymphocytes from 5 to 15 patients with multiple sclerosis produced MIF when incubated with central nervous system antigen. This is seen in Figure 2 (Rocklin et al) in which only patients with Guillain-Barre

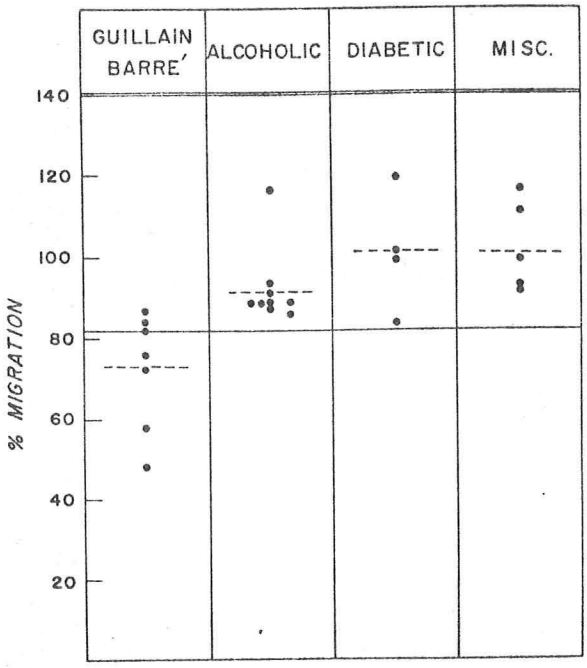


Figure 2. Distribution of MIF Production to Peripheral-Nervous-Tissue Antigen by Lymphocytes from Patients with Peripheral Neuropathies.

(Rocklin et al., 1971)

showed this factor compared to alcoholic, diabetic, or patients with miscellaneous neuropathies. There does not appear to be any correlation between the severity of clinical symptoms and the presence or absence of MIF production. It was of note that the patients whose lymphocytes had the greatest affect on macrophages were the ones with persistent symptoms for greater than a year. The findings of lymphocytes sensitive to peripheral nerve antigen but not to central nervous system antigen in patients with acute polyneuritis of Guillain-Barre type is consistent with investigators who sought to implicate sensitized lymphocytes in tissue damage seen in this disease.

Thus, there is a correlation between EAN and idiopathic neuritis of Guillain-Barre type by virtue of the fact that in both conditions a cell mediated response has been identified. Histotypic lesions have been produced by the passive transfer of lymphocytes: lymphocytes from animals with EAN and lymphocytes from patients with idiopathic neuritis similarly demyelinated trigeminal ganglion cultures as reported by Arnason et al. in Laboratory Investigation (21:1-10, 1969). CSF or serum from patients with idiopathic neuritis had no effect on these cultures, but the buffycoat cells from these patients produced impressive demyelination.

Germane to this discussion is the paper of Gonatas and Howard (Science, 186:839-841, 1974) in which they demonstrate the necessity of T-lymphocytes for the generation of experimental allergic encephalomyelitis. Using Lewis rats which were depleted of thymus derived

cells the authors could not produce either EAE or antibody against myelin based protein. The same rats reconstituted with 690 million thymocytes developed EAE and levels of antibodies against myelin basic protein comparable to those of controls. This is seen in Table 2 (Gonatas and Howard), Series 1, in which intact Lewis B

Table 2. Protection from EAE in Lewis B rats. In series 1, half of each group received 110 mg of GPSC and half received 500 μg of GPBP; in series 2, half of each group received 110 mg of GPSC and half received 100 μg of GPBP. The intensity of histological EAE was measured on a modified scale of Alvord and Kies (*6, 18*). The antigen-binding capacity (ABC) of serum was determined by the method of Lisak *et al.* (*8, 16*).

Immunized Lewis rats	No. immunized	No. surviving to assay	Day of killing	Histologic EAE (No.)	Intensity of EAE	Serum ABC (%)
			Series 1			
Normal	10	10	14, 35	10	++ to +++	45 to 95
B rats	24	16*	14, 21	0	0	1.0 to 3.6
			Series 2			
Normal	8	8	16, 25	8	++ to +++	58 to 63
B rats	18	17†	16, 25	1	0(16) ± (1)	9 to 12; 20 for one animal
B rats reconstituted with thymocytes	18	18	16, 25	17	0(1) ++ to +++(17)	30 to 73

* Of eight rats dying before assay, six were examined histologically postmortem and found free of EAE. † One B rat immunized with GPSC died 4 days after immunization; necropsy showed focal hemorrhages in the white matter of the spinal cord.

rats immunized with guinea pig spinal cord or guinea pig basic protein developed severe EAE whereas animals totally devoid of T lymphocytes were unable to generate lesions. Similar experiments have not yet been carried out to see if EAN or acute polyneuritis of man are also T lymphocyte dependent phenomenon. The Arnason passive lymphocyte transfer experiments however would suggest that EAN and acute polyneuritis of man are T lymphocyte, cell mediated responses.

A similar explanation might be forth coming to explain the remote effect of oat cell carcinoma of the lung producing carcinomatous neuromyopathy. Paty et al. (J. of Neurol., Neurosurg. and

Psych., 37:142-151, 1974) report that 36% of patients with proven lung cancer have sensitized lymphocytes against peripheral nerve antigen as demonstrated again by the macrophage inhibition factor test. Whether the factor is expressing a primary antigen-antibody reaction productive of the disease or whether the disease process primarily exposes previously protected antigens and that there is as a result a secondary antibody response is at present not clear.

Thus, immunological mechanisms may be involved in the occurrence of acute idiopathic neuritis of man similar to the development of EAN in experimental animals. The fact that lymphocytes from patients or animals with EAN will demyelinate in vitro myelinated cultures suggest such a pathogenetic event. To date, however, lymphocytes from patients with polyneuritis have not yet produced lesions of EAN in experimental animals nor do antibody levels against peripheral nerve antigen nor MIF production directly correlate with the severity of disease.

IDIOPATHIC POLYNEUROPATHY ASSOCIATED WITH ANTI-NEURONAL IgM AND IgG:

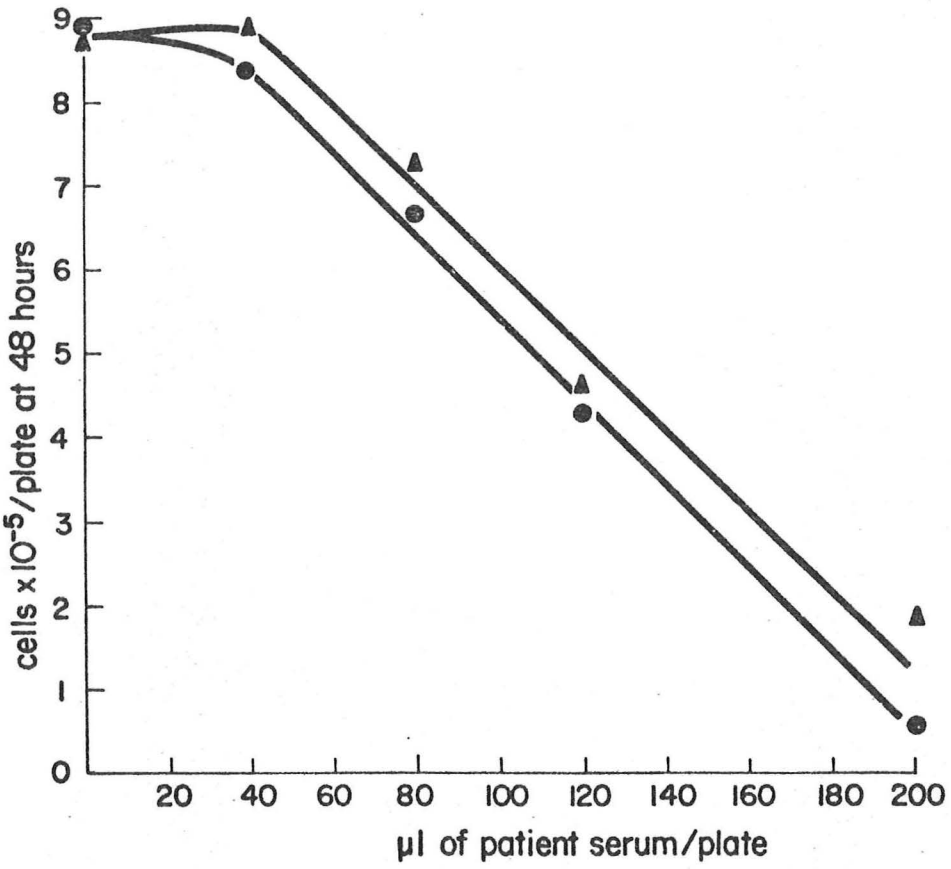
Additional new information from our laboratory suggest that serum factors may be involved in the occurrence of idiopathic acute and chronic polyneuritis of Guillain-Barre type in man.

The determination of a precise cause for an acute or chronic progressive polyneuropathy is limited using current clinical and pathological procedures. We recently had the opportunity to evaluate six patients with progressive acute or chronic polyneuropathy with mainly motor manifestations and in the course of these evaluations

incubated their sera with cholingeric and noncholingeric mouse neuroblastoma cells and with rat astrocytoma cells in cell culture. The rationale for this approach was to examine whether there might be a serum factor which might alter the viability for cell growth of these transformed neuroblasts and astrocytes which would provide immunological or molecular insight as to the generation of the patients motor neuropathy. Sera from patients with other motor systems disorders such as diabetic, alcoholic, traumatic and familial polyneuropathies and amyotrophic lateral sclerosis, myasthenia gravis and Werdnig-Hoffman disease were also incubated with neuroblastoma and astrocytoma cells for similar reasons. All patients with progressive polyneuropathy had a factor which was cytolytic to neuroblastoma cells and not to astrocytoma cells and the other normal and experimental controls did not affect the growth and viability of either neuroblastoma or astrocytoma cells to the same degree.

A summary of our findings in these six patients with progressive neuropathy, other patients serving as controls who have a variety of neurological motor system disorders, and normal controls are seen in Table I. Patients with progressive motor neuropathy had a factor in their sera which had a cytolytic effect of between 78 and 93 per cent of growing neuroblastoma cells with no effect on astrocytoma cells. As seen in this table, the factor can be adsorbed from serum by neuroblastoma membrane fractions, is heat labile and partially inactivated by freezing. Starch gel electrophoresis and subsequent

Sephadex and ion-exchange column chromatography of one patient's serum indicated that the activity was present in two peaks off the Sephadex column with molecular weights of 9×10^5 and 1.5×10^5 which corresponds to IgM and IgG. Further, the data indicate that the IgM and IgG anti-neuroblast factor (factors) can be quantitated and standardized by using neuroblastoma cells as a bio-assay as seen in the adjacent figure.



The fact that the anti-neuroblastoma factor is present in the sera of patients with chronic polyneuropathy (2 patients) and in idiopathic polyneuritis of Guillain-Barre type (4 patients) suggests they may be causally related and represent a continuum of disease. Thus, our data indicate that the sera from patients with idiopathic polyneuritis possess an additional serum anti-body which may be responsible in part for the occurrence of disease. (Rosenberg, Aung, Tindall, Molenich, Baskin and Capra, Neurology (April) 25:352, 1975).

TABLE I

PERCENT GROWTH INHIBITION OF NEUROBLASTOMA AND ASTROCYTOMA CELLS BY PATIENT SERA[a]

Patient	Clinical Diagnosis	PERCENT INHIBITION OF NEUROBLASTOMA CELL GROWTH			PERCENT INHIBITION OF ASTROCYTOMA CELL GROWTH
		Untreated Sera	Heated[b] Sera	Adsorbed[c] Sera	
1.	Chronic, progressive idiopathic polyneuropathy (49 yr. female)	85	0	0	0
2.	Chronic, progressive idiopathic polyneuropathy (68 yr. male)	93	0	19	0
3.	Acute idiopathic polyneuritis (6 yr. female)	92	52	23	0
4.	Acute idiopathic polyneuritis (17 yr. male)[e]	78	0	0	0
5.	Acute idiopathic polyneuritis (2 yr female)	70	40	0	0
6.	Acute idiopathic polyneuritis (4 yr. male)	80	60	40	0
7.	Arrested motor polyneuropathy (65 yr. male)	0	0	0	0
8.	Diabetic polyneuropathy (27 yr. female)	0	0	0	0
9.	Traumatic sciatic neuropathy (19 mo. female)	0	0	0	0
10.	Alcoholic polyneuropathy (60 yr. male)	0	0	0	0
11.	Cervical spondylosis (54 yr. male)	0	0	0	0
12.	Pseudotumor cerebri (34 yr. male)	0	0	0	0
13.	Herpes zoster geniculate ganglionitis (46 yr. female)	0	0	0	0
14.	Generalized major motor seizure (40 yr. female)	0	0	0	0
15.	Amyotrophic lateral sclerosis (50 yr. female)	0	0	0	0
16.	Amyotrophic lateral sclerosis (55 yr. male)	0	0[d]	0[d]	0

17.	Myasthenia gravis (50 yr. male)	0	0	0	0
18.	Werdnig-Hoffman (11 mo. female)	0	0	0	0
19.	Familial neuropathy (28 yr. female)	0	0	0	--
20.	Familial neuropathy (27 yr. male)	0	0	0	--
21.	Multiple sclerosis (35 yr. female)	0	0	0	--
22.	Multiple sclerosis (50 yr. male)	0	0	0	--
23.	Normal (42 yr. female)	0	0	0	0
24.	Normal (26 yr. female)	0	0	0	0
25.	Normal (25 yr. female)	0	0	0	0
26.	Normal (29 yr. female)	84	71	41	0
27.	Normal (32 yr. male)	0	0	0	0
28.	Normal (30 yr. male)	0	0	0	0

[a] 0.5×10^6 S-20 cholinergic mouse neuroblastoma cells or 0.2×10^6 astrocytoma cells were plated per 60 mm tissue culture dish in 2.5 ml 10% fetal calf serum - 90% DMEM, and 0.2 ml of human serum was added immediately. The cultures were grown at 37°C in 90% air - 10%CO_2 100 % humidity for 48 hours. Cells were then trypsinized and counted in a Coulter Z_{BI} counter. Growth inhibition is expressed as the cells in control plates minus cells in experimental plates divided by cells in control plates x 100. All values represent the average of duplicate plates, all data pairs agreeeing ± 10%.

[b] Serum was heated at 50° C for 30 minutes

[c] Membrane fraction from 25×10^6 S-20 neuroblastoma cells was added/ml human serum and the suspension shaken 5 minutes at 4° C and then spun at 12,000g for 10 minutes at 4°C. Supernatant was removed and tested for inhibitor.

[d] 0.5×10^6 C-46 clone noncholinergic neuroblastoma cells were used here.

[e] Patient of Dr. L.P. Rowland, College of Physicians and Surgeons, Neurological Institute, Columbia University, New York, with idiopathic polyneuritis of Guillain-Barre type.