

experimental SE [1, 6, 8], the patient also had severe transient hypoglycemia and hepatic dysfunction. Both the biochemical and histological features of the hepatic damage, as well as its course, were characteristic of "ischemic hepatitis" [3]. It is suggested that this condition was induced by the severe hypoxemia resulting from the prolonged SE. Liver damage is probably uncommon in epilepsy, as we were able to trace only a single documented case of centrilobular necrosis after prolonged seizures (Case 1 of Fowler [4]). Hypoglycemia was occasionally observed in primates sustaining prolonged seizures and was attributed to increased whole-body glucose consumption [8]. It has also been stated that hypoglycemia may occur in human SE [5, 11]. We were unable, however, to find any recorded case with hypoglycemia of the magnitude observed in our patient. It is possible that the fulminant liver damage contributed to the hypoglycemia.

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# The Pathophysiology of Penicillamine-Induced Myasthenia Gravis

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The temporal course and pathophysiology of penicillamine-induced myasthenia gravis were studied in detail in a typical case. Our results suggest that this disorder and idiopathic autoimmune myasthenia gravis share the same essential pathophysiological features, including the presence of anti-acetylcholine receptor (AChR) antibody, serum-induced blockade of AChRs, antibody-mediated accelerated degradation of AChRs, and a resultant quantitative reduction in available junctional AChRs. An initial severe reduction in junctional AChRs was reversed and the patient recovered, both within 8 months of stopping penicillamine. Our data suggest that penicillamine probably produced myasthenia gravis by initiating a new autoimmune response rather than by enhancing ongoing autoimmunity.

Kuncel RW, Pestronk A, Drachman DB, Rechthand E: The pathophysiology of penicillamine-induced myasthenia gravis. *Ann Neurol* 20:740-744, 1986

Although penicillamine-induced myasthenia gravis (PMG) occurs in less than 1% of patients with rheumatoid arthritis who are treated with the drug, it has attracted attention because of the opportunity it provides to study the pathogenesis of myasthenia [1, 3, 5, 11, 15, 18]. PMG and idiopathic autoimmune myasthenia gravis (MG) are similar clinically and on electrodiagnostic study, differing chiefly in the lesser severity and brief temporal course of the former [1, 3, 4, 6]. Yet very little is known about the immunopathophysiology of PMG, except that penicillamine pretreatment augments the autoantibody response to an acetylcholine receptor (AChR) challenge in certain species of mice [3] and that PMG is sometimes associated with low titers of anti-AChR antibody in humans [18]. It is generally accepted that the basic defect in MG is an antibody-mediated reduction of available AChRs at the neuromuscular junction [9]. We asked whether similar pathogenetic mechanisms underlie PMG. If so, then patients with PMG also

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Received Dec 2, 1985, and in revised form May 2, 1986. Accepted for publication May 10, 1986.

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ought to express anti-AChR antibodies with functional activities that reduce available AChRs at neuromuscular junctions. A second question also arises: Does PMG occur because an ongoing immune dysregulatory state (with subclinical myasthenia) becomes enhanced by penicillamine, or does the drug initiate an autoimmune response *de novo*? If PMG is initiated by producing a new autoimmune state, then when penicillamine is stopped the reduction in junctional AChRs should recover to normal. This might not be the case if penicillamine merely enhanced an ongoing autoimmune disease. To answer these questions, we performed serial studies in a patient with typical PMG, including measurement of junctional AChRs, assays of antibody titer, and tests of antibody functions clinically relevant to the pathogenesis and severity of MG [7].

### Case Report

A 57-year-old steel worker had retired because of disabling rheumatoid arthritis that had not responded well to prednisone or hydroxychloroquine therapy. Twenty months before admission, treatment with D-penicillamine was begun. Three weeks before admission he noticed variable left-sided ptosis that was absent upon awakening but became apparent in the afternoon hours. He next developed intermittent diplopia and hoarseness. He noted discomfort on swallowing. At admission, medications included D-penicillamine (500 mg twice daily; this dose had been sustained for more than a year), prednisone (12.5 mg daily), digoxin, cimetidine, and metolazone.

On examination, the left lid was ptotic; during sustained upgaze it further fatigued to cover the pupil; the right lid developed 1 mm of ptosis. Cogan's lid twitch sign was present. Pupils were normal, and eye movements were full with no nystagmus. The voice was mildly hoarse and nasal. The tongue was normal. Vital lung capacity was 3.8 liters. The flexors and extensors of the neck and the proximal and distal limb muscles were normal in strength. He could sustain forward arm abduction for more than 5 minutes. Muscle bulk and deep tendon reflexes were normal. General examination showed manifestations of rheumatoid arthritis.

An esophagogram showed hypoactivity of the oropharynx and hypopharynx, with poor clearing of the valleculae and pyriform sinuses. Rheumatoid factor was positive (titer, 1:320). Other investigations, including computed tomographic scan of the mediastinum, antinuclear antibodies, erythrocyte sedimentation rate, serum thyroxine, serum creatine kinase, and routine laboratory chemistries and blood counts, yielded normal results.

An edrophonium test was positive. The left-lid ptosis resolved within 30 seconds after injection of the test drug.

Electrodiagnostic studies showed a very mild distal sensorimotor polyneuropathy, but concentric needle electromyography of distal and proximal muscles was normal. Repetitive stimulation of the left abductor pollicis brevis, biceps brachii, and deltoid at 3 and 10 Hz failed to show any decremental responses, either before or during the 5 minutes following 1 minute of intense isometric exercise.

On the day of admission, penicillamine was discontinued

and serum was obtained for antibody assay and functional *in vitro* tests. The patient's condition improved on pyridostigmine treatment alone. From the fourth to the sixth months after discontinuation of penicillamine, he rarely noticed any symptoms, and after 6 months he was asymptomatic, requiring no pyridostigmine. At 8 months, serum was obtained with findings that confirmed recovery.

### Methods

Anti-AChR antibody was assayed by standard radioimmunoassay (using AChR from human skeletal muscle) [10] modified to increase the sensitivity.

For assays of AChR blockade or degradation activity, cultures of rat skeletal muscle were prepared conventionally [7] and used at 7 days. Large numbers of 35-mm dishes were prepared simultaneously to obtain matched sets of cultures with closely comparable numbers of AChRs.

Serum-induced blockade of  $^{125}\text{I}$ - $\alpha$ -bungarotoxin binding sites on AChRs was measured in rat muscle cultures under conditions that maximize the blocking effect of the patient's immunoglobulin and eliminate degradation of AChRs, using a previously described technique [7]. Sets of five replicate cultures were incubated with medium containing 20% serum from the patient or each of four controls (normal laboratory personnel). The number of sites blocked by each serum was calculated by subtracting the number of remaining sites in cultures from the mean number of sites in all 20 control cultures from the same experimental run.

Degradation of AChRs *in vitro* was measured by counting radioactive material derived from degraded  $^{125}\text{I}$ - $\alpha$ -bungarotoxin-AChR complexes released into the culture medium over time under established conditions previously described [7]. Replicate sets of five cultures were incubated with 20% serum from the patient or the four normal controls. The rate of degradation was calculated as the percentage of total radioactivity released per hour per dish. As a positive control, in assays of AChR blockade and degradation, serum from a patient with high anti-AChR antibody titer and moderate generalized MG was simultaneously assayed.

Motor point biopsies were obtained after the procedure and the research intent were fully explained and appropriate informed consent was obtained. The number of AChRs per neuromuscular junction was determined by an  $^{125}\text{I}$ - $\alpha$ -bungarotoxin-binding technique [14].

Data are presented as mean  $\pm$  standard error. With respect to degradation or blockade, each set of cultures treated with an individual patient or control serum was compared with all control cultures done on the same day. The significance of the difference between the patient and controls was calculated with Student's *t* test (two-tailed), unless otherwise noted.

### Results

#### Antibody Titers

The patient's initial serum had a mild but definite elevation of anti-AChR antibody level, 0.49 pmole/ml. Five normal control sera, assayed simultaneously, had a mean level of  $0.02 \pm 0.002$  pmole/ml (range, 0.0 to

Table 1. Serum-Induced Blockade of Acetylcholine Receptors

Serum Source	Moles AChR Blocked ( $\times 10^{-13}$ ) <sup>a</sup>	<i>p</i> vs Control
Present patient during symptoms	0.429 <sup>b</sup> $\pm$ 0.119	0.03
Present patient at recovery	-0.223 $\pm$ 0.178	NSD
Normal controls ( <i>n</i> = 4)	0.000 $\pm$ 0.076	...

<sup>a</sup>Per 35-mm dish, rat skeletal muscle culture. Control plates had  $6.670 \pm 0.077 \times 10^{-13}$  moles of  $\alpha$ -bungarotoxin binding sites per dish.

<sup>b</sup>Significantly different from recovery, *p* < 0.03.

AChR = acetylcholine receptor; NSD = no significant difference.

0.06). The "recovery" serum, assayed at the same time, had no detectable anti-AChR antibody.

### Blockade of AChRs

The patient's initial serum produced significant blockade of AChR binding sites in vitro (Table 1). Blocking activity was comparable to that of mildly impaired patients with MG [7]. By contrast, in the same assay, blocking activity in a patient with high anti-AChR antibody titer and moderate generalized MG was  $1.38 \pm 0.098 \times 10^{13}$  moles AChR. No blocking activity could be detected in the serum of the patient with PMG following recovery.

### AChR Degradation

Compared to control sera, the initial serum of the patient with PMG significantly increased the rate of degradation of AChRs in vitro (Table 2). The ability of serum to accelerate degradation was comparable to that of mildly impaired patients with MG [7]. By contrast, serum from a patient with high anti-AChR antibody titer and moderate generalized MG, tested simultaneously, increased the AChR degradation rate three-fold. The "recovery" serum of the patient with PMG had no effect on AChR degradation.

### Motor Point Biopsy

Two weeks after penicillamine was stopped, when the patient's symptoms remained unchanged, the left deltoid (with normal strength) was biopsied. Sections of frozen muscle stained histochemically and with hematoxylin-eosin showed no abnormality. The number of AChRs per neuromuscular junction was determined in a motor point specimen (serial biopsy data, norms, and associated probabilities are given in Table 3). The junctional AChR count in the patient's muscle was significantly reduced to levels seen in MG. In the absence of clinical or biopsy evidence of myositis, this finding is diagnostic of MG [13, 14].

The second motor point biopsy (right deltoid), done

Table 2. Serum-Induced Degradation of Acetylcholine Receptors

Serum Source	Degradation Rate (% increase over control)	<i>p</i> vs Control
Present patient during symptoms	8.6 $\pm$ 4.6	0.04
Present patient at recovery	0.1 $\pm$ 1.1	NSD
Normal controls ( <i>n</i> = 4)	0.00 $\pm$ 1.3	...

NSD = no significant difference.

Table 3. Junctional Acetylcholine Receptors in Penicillamine-Induced Myasthenia Gravis

Biopsy Source	AChR/NMJ ( $\times 10^7$ )	Range ( $\times 10^7$ )
Present patient during symptoms	0.8 <sup>a</sup>	...
Present patient at recovery, 8 months after onset	1.7 <sup>b</sup>	...
Normal controls ( <i>n</i> = 18) <sup>c</sup>	2.1 $\pm$ 0.2	0.9-3.4
Myasthenia gravis ( <i>n</i> = 40) <sup>c</sup>	0.7 $\pm$ 0.1	0.2-1.8
Mean variation within muscle sample ( <i>n</i> = 18) <sup>c</sup>	0.1	0.0-0.3

<sup>a</sup>Probability of a control deltoid having fewer than  $0.9 \times 10^9$  AChRs/NMJ is 1.2%, Bootstrap nonparametric method [8].

<sup>b</sup>Probability of a myasthenic patient's deltoid having greater than  $1.5 \times 10^7$  AChRs/NMJ is 5.3%, Bootstrap nonparametric method [8].

<sup>c</sup>Data for deltoid from [14].

AChR = acetylcholine receptor; NMJ = neuromuscular junction.

8 months after drug discontinuation, showed more than a doubling of the number of AChRs during that interval, with recovery into the normal range. A change in the AChR number of this magnitude would not be caused by error of measurement, nor by variation of samples between deltoid muscles (see Table 3), nor is it seen with the passage of time in serial biopsy specimens from patients with MG [14; Pestronk, unpublished observations].

### Discussion

The diagnosis of myasthenia in this patient was based on typical clinical signs, response to anticholinesterase drugs, and elevated anti-AChR antibody titer. That his correct diagnosis was PMG was supported by the short temporal course of the disease, with recovery from symptoms in 6 months and recovery from AChR deficit within 8 months. It seems unlikely that the patient had idiopathic autoimmune MG coincidental with rheumatoid arthritis. Less than 3% of patients with

MG have complete remission in the first 6 months [12], whereas disease in more than 70% of patients with PMG remits within the first 8 months [1].

It is not immediately predictable how penicillamine might produce a myasthenia-like disorder, as the drug has both immunosuppressive and immunostimulatory properties [5]. Further differences between PMG and MG have at times prompted speculation that they differ in pathophysiology. For example, in the guinea pig model of PMG, penicillamine administration produces a necrotizing inflammatory myopathy [5, 11], weight loss [5], pulmonary infections, and decremental responses only at high rates of repetitive stimulation [3, 6, 11], quite unlike MG. In humans, the age of onset in women is later for PMG than it is for MG [1]. Further, a decrement on repetitive stimulation has been reported in fewer than 20% of patients with PMG, and serum anti-AChR antibodies have been lower and less frequently elevated than in the general population of patients with MG [1, 2, 4, 16]; of course, such differences could merely reflect mild or local symptoms in PMG [18]. Our patient clearly shows that PMG, which shares the essential clinical features of MG, also shares its basic pathophysiological defect—a reduction in the number of available AChRs at the neuromuscular junction.

The reduced availability of AChRs caused by penicillamine could be caused by several possible mechanisms, among them: (1) a direct toxic effect of the drug; (2) enhancement of ongoing subclinical MG; and (3) initiation of a new drug-induced autoimmune state. The timing of the motor point findings in the present patient provides circumstantial evidence against a direct toxic effect of penicillamine. It is reasonable to assume that the reduced junctional AChRs at the first motor point biopsy reflected the patient's state during his symptomatic months. However, the first biopsy was done 2 weeks after discontinuation of penicillamine, not during drug administration, and the level of available junctional AChRs was still greatly reduced. A direct toxic effect of penicillamine on the AChR would probably have largely recovered during this time, given that penicillamine is rapidly metabolized and that mammalian AChRs turn over with a half-time of approximately 5 to 13 days [17]. Our patient's symptoms lasted even longer, persisting several months after penicillamine was stopped, making a direct toxic effect on AChR turnover even more unlikely. Rather, the temporal course correlated with the presence of anti-AChR antibodies and with their measurable ability to block AChRs and to accelerate their degradation, recapitulating the pathophysiology of ordinary MG.

The remaining question is whether PMG is a newly initiated response or an enhancement of ongoing subclinical MG in a patient with a generalized immune

dysregulatory state. PMG nearly always occurs in patients with rheumatoid arthritis, an immune disorder having some association with MG. However, the early remission of myasthenic symptoms in this patient was accompanied by recovery of a normal complement of AChRs per neuromuscular junction. In idiopathic MG, recovery to an asymptomatic state is usually still associated with a reduced number of AChRs [14]. The finding of an AChR level as high as  $1.7 \times 10^7$  AChRs per neuromuscular junction rules out MG with a high probability (greater than 98%) [14]. It is reasonable to assume that the patient's normal number of AChRs reflected not only his state at recovery but was also similar to his premorbid state. This makes prior ongoing autoimmune MG unlikely. In summary, the serial studies in this case, showing the early full recovery of neuromuscular junctions to a normal number of AChRs, suggest that penicillamine probably produces MG by initiating a new autoimmune response rather than by enhancing ongoing autoimmunity.

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Supported by a Teacher Investigator Development Award 5K07NS00734 (R. W. K.), by an MDA Clinical Fellowship (E. R.), and by NIH Grant No. 5R01 HD04817 (A. P.).

We are grateful to R. N. Adams, P. Shih, and M. J. Peper for technical assistance, to C. F. Salemi for manuscript preparation, and to Drs Howard Moses and Harry L. Klinefelter for referring the patient.

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## Magnetic Resonance Imaging of the Midbrain in Parkinson's Disease

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We have analyzed magnetic resonance images of the midbrain in patients with Parkinson's disease, and have found that there is a narrowing of the signal from the pars compacta of the substantia nigra relative to controls. The nature of the histological changes that may be responsible for this effect is discussed. Magnetic resonance imaging has the potential of becoming a useful diagnostic tool in the management of parkinsonism.

Duguid JR, De La Paz R, DeGroot J:  
Magnetic resonance imaging of the midbrain in  
Parkinson's disease. *Ann Neurol* 20:744–747, 1986

Magnetic resonance (MR) imaging has emerged as a powerful diagnostic tool in neurology. The wealth of anatomical detail in MR images of the midbrain has

been correlated with normal structures [1, 6]. We have examined the midbrain MR image in patients with Parkinson's disease and have found significant changes compared to a control population.

### Methods and Materials

Parkinsonian patients were recruited from the neurology clinics of the affiliated University of California, San Francisco, hospitals. Informed consent was obtained from all experimental subjects. All had cogwheel rigidity and resting tremor in the absence of a history of stroke, encephalitis, or toxic exposure, corroborating the diagnosis of idiopathic Parkinson's disease. All but one of the patients had been treated chronically with Sinemet (carbidopa-levodopa). Control subjects comprised 10 consecutive cases, aged 50 years or more, scanned for complaints not related to a disorder of the midbrain or basal ganglia.

Patients were scanned with a General Electric Signa MR system (Milwaukee, WI) operating at 1.5 Tesla. T<sub>2</sub>-weighted images were obtained using a spin-echo sequence with a repetition time of 2,000 msec and an echo time of 40 msec. All scans represent 5-mm-thick sampling volumes. Axial scans were obtained with maintenance of scan plane orientation between 0 and 20 degrees positive to the inferior orbitomeatal line. Studies with a cadaver brain have shown that there is no significant change in the breadth of the pars compacta signal within this range of head position. Using the algorithm described below, breadths of the pars compacta were determined for the following scan plane orientations: –2 degrees, 5.5 mm; +8 degrees, 5.6 mm; and +17 degrees, 5.5 mm.

Determinations of the breadth of the pars compacta signal in these patients were made using optical density profiles of the scans photographed on x-ray film, obtained with an LKB densitometer (Broma, Sweden). The path of the densitometer beam was perpendicular to the band of high intensity representing the pars compacta, through the center of the red nucleus and 1 mm to either side (see Fig 1), yielding three parallel profiles for each hemi-midbrain. The width of the valley at half-height between the peaks of optical density representing the red nucleus and the crus cerebri–pars reticulata complex was taken as an index of the breadth of the signal from the pars compacta. The three values for each hemi-midbrain were averaged to reduce the contribution of signal noise.

### Results and Discussion

Two scans of control patients (Fig 1) are provided in which the major anatomical structures are identified. The location of the low-intensity (dark) signal from the substantia nigra pars reticulata, separating the pars compacta from the crus cerebri, is indicated. The pars reticulata is more prominent anteromedially where it extends into the substance of the crus. The low-intensity signal of the red nucleus and pars reticulata on T<sub>2</sub>-weighted MR images has been ascribed by Drayer and associates [1] to the paramagnetic effect of ferric iron in these structures. While the pars reticulata

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Received Jan 27, 1986, and in revised form Apr 22. Accepted for publication Apr 26, 1986.

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