

Generalized Muscular Stiffness, Fasciculations, and Myokymia of Peripheral Nerve Origin

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THE PERIPHERAL nerve disorders, unlike central nervous system and muscle diseases, have not been widely recognized as causes of generalized muscular stiffness. Isaacs,^{1,2} in 1961 and 1967, reported three patients with an entity of generalized muscular stiffness, fasciculations, continual electromyographic (EMG) activity at rest and depressed deep tendon reflexes. The muscular stiffness and continual EMG activity were abolished by curare but persisted during spinal anesthesia and after peripheral nerve blocks, suggesting that the syndrome was due to isolated, spontaneous, peripheral nerve hyperactivity. Isaacs also discovered that diphenylhydantoin (DPH) induced a substantial and sustained decrease in the muscular stiffness. Similar cases were reported by Mertens and Zschocke³ and by Levy et al,⁴ both groups confirming the effects of spinal anesthesia and curare. Mertens and Zschocke³ also found carbamazepine as effective as DPH in treatment. Sig-

wald et al,⁵ Gardner-Medwin and Walton,⁶ and Hughes and Mathews⁷ have reported apparently identical patients; however, these cases did not undergo investigation to determine the peripheral nerve origin of the condition. Despite the convincing pharmacological evidence that localized the source of the stiffness to the peripheral nervous system, no abnormality was found in the motor conduction velocities in the one patient where this was studied,² and none of the reported patients has undergone nerve biopsy. The etiology is unknown.

This paper reports two patients similar to those described by Isaacs^{1,2} and offers new neurophysiological and histological evidence relating the disease to the peripheral nerves. The etiology is discussed in view of similar animal experimental models which can be produced with exposure to certain chemicals⁸⁻¹¹ including a herbicide dichlorophenoxyacetic acid (2,4-D), a compound to which one of our patients was exposed. A preliminary report has been made.¹²

Report of Cases

CASE 1.—A 21-year-old Puerto Rican man presented to the New York Hospital complaining of difficulty walking. He had been well until two years earlier when over two days he de-

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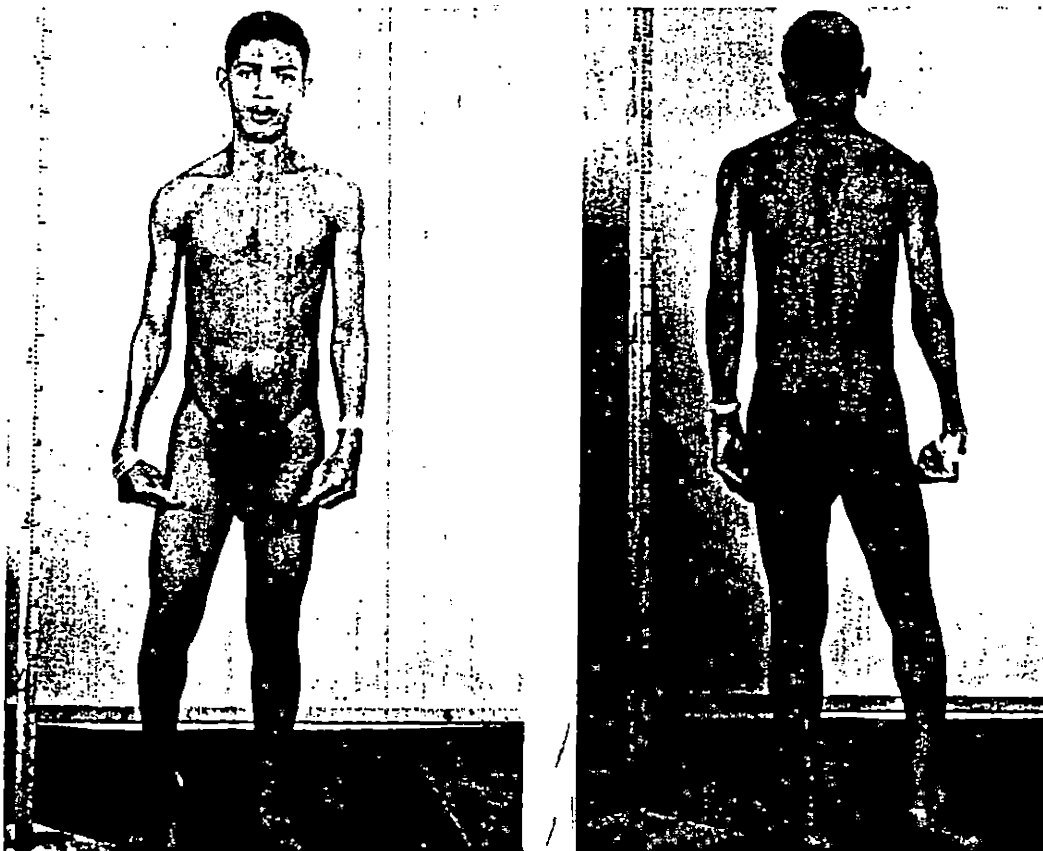
veloped painful paresthesias in his feet and hands. At the time he had been employed for one year spraying sugar cane fields with chemical herbicides containing 2,4-D. He utilized no protective mask or clothing and handled the herbicide freely. Three days after the paresthesias began, he developed painful muscular stiffness in all four limbs and was forced to stop work. The pain disappeared over the next week, but the muscular stiffness gradually progressed over the next two years, severely impairing his gait and manual dexterity. During this time he noted diffuse muscular twitching, increased sweating, and fatigue. One month before entering the New York Hospital he experienced mild dysphagia and exertional dyspnea. His symptoms were not affected by changes in temperature. There was no family history of neurological disease. His past medical history was unremarkable except for mild bronchial asthma. Despite many previous lacerations he did not recall receiving tetanus immunization.

His blood pressure was 120/70 mm Hg, heart rate 80 beats per minute and regular, tempera-

ture 98.6 F (37 C), and respirations 26 breaths per minute and slightly labored. He was well developed and nourished, and his skin was warm with marked engorgement of the superficial veins. He perspired heavily at rest. No cataracts or frontal baldness were present. Auscultation of the chest revealed a few scattered inspiratory wheezes, but results of the general physical examination were otherwise normal.

He was intellectually intact. The remainder of his neurological examination disclosed abnormalities limited to changes in motility, skeletal muscle function, and the deep tendon reflexes. The man was bent forward and visibly stiff in all his skeletal muscle groups. He was muscularly well developed but thin, and the forearms tapered towards the wrist, appearing moderately atrophied (Fig 1). His hands were held in fixed, flexed positions, and his feet were plantar flexed in the equinovarus position. When he tried to walk he moved with deliberate slowness but much effort, as if in a slow motion film, or trying to pull himself through some great external resistance. The facial, masseter, trunk,

Fig 1.—Note posture of hands and right foot. Musculature is tense and well developed (case 1).



and extremity muscles all contracted visibly with fine and coarse twitching and rippling adventitious movements when he placed himself completely at rest. Passive flexion of the limbs met with a steady uniform resistance which gradually increased as the arc of movement increased. The speed and range of voluntary movement were limited in the jaw, extremity, and respiratory muscles, and what muscular contraction was accomplished cost great effort so that he fatigued quickly and perspired even more. After prolonged muscular contraction, muscular relaxation was slow and incomplete. This phenomenon was particularly prominent in relaxing the grip; however, percussion myotonia was not present. During sleep, the muscular stiffness persisted. No tendon jerks could be obtained, but the cutaneous abdominal and cremasteric reflexes were brisk. No Babinski signs or other pathological reflexes were present. Sphincter function and results of the sensory examination were normal.

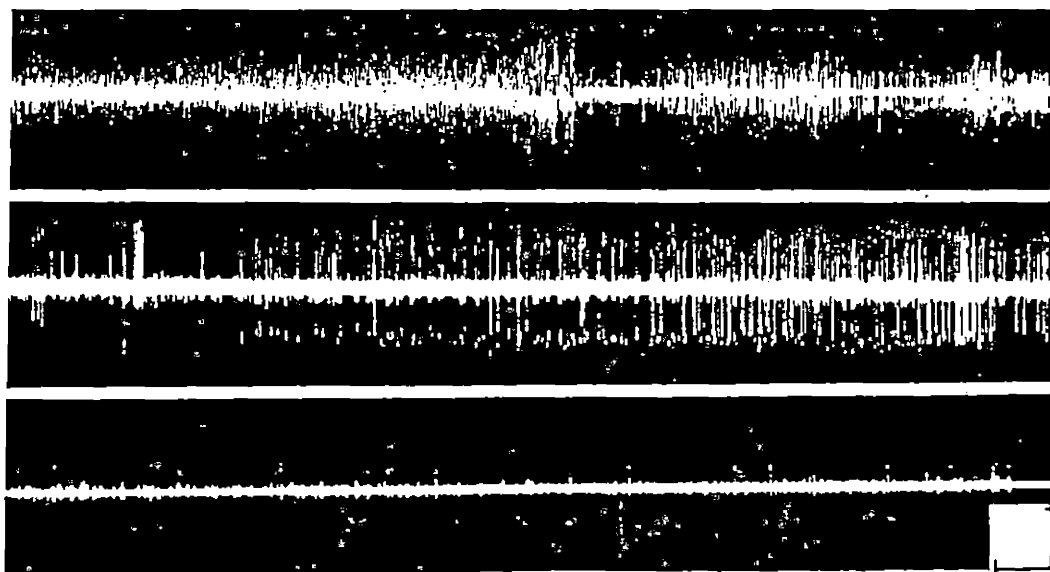
The complete blood count, urinalysis, serum electrolyte analyses, serum calcium/phosphorous, magnesium, blood urea nitrogen, two-hour postprandial blood glucose, fasting blood glucose, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, serum lactic dehydrogenase, serum creatine phosphokinase, chest and skull roentgenograms, stool guaiac, stool for parasites and ova, electroencephalogram, electrocardiogram, and lumbar puncture findings were all within normal limits.

Fig 2.—EMG recordings from first dorsal interosseous muscle. Top tracing, Resting record demonstrating continuous skeletal muscle discharge; middle trace, recorded after ulnar and median nerve block; spon-

Electrophysiological and Neuropharmacological Investigations.—*Electromyography*.—All major muscle groups were sampled with a concentric needle electrode and standard amplifying equipment and disclosed similar findings. No myotonic response was present on insertion or movement of the needle or on percussion of muscle. At rest, continual waxing and waning electrical discharges were present with only occasional widely separated periods of electrical silence (Fig 2) lasting three to five seconds. The activity consisted of both normal-appearing motor units and periodic bursts of repetitive short duration (2 msec or less) action potentials of variable amplitude and usually a diphasic and stereotyped configuration (Fig 3). Many of the normal-appearing motor units corresponded to visible fasciculations in the vicinity of the needle. The interference pattern was full and the motor units under voluntary control appeared normal.

Peripheral Nerve Block.—Electromyography of the first dorsal interosseous muscle showed a substantial but by no means complete reduction in the abundant electrical activity at rest after blocking of the ulnar and median nerves with 1% procaine (Fig 2). The effectiveness of the block was tested by stimulating both nerves at the elbow without producing an evoked electrical response in the muscle. All distal sensory and motor function of ulnar and median nerves was absent clinically after the block. Spinal and general anesthesia were induced after first fully

taneous muscle activity is moderately reduced; bottom trace, recorded on separate occasion after giving patient 1 gm DPH, spontaneous activity greatly reduced. Calibrated: horizontal, 1 second; vertical, 100 μ v.



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Curare.—Administ intravenously produ laxation and electrica

Repetitive Nerve : to 30 cps supramaxi delivered to the m while the evoked re: the abductor pollicis electrodes. No signifi the amplitude of evoke

Motor Conduction performed using sur over muscle while sti supramaximally. All ties were either slight range of normal (Tabl

Histological Studi light microscopic exan sy taken from the r stained with hematoxy

Nerve Biopsy.—Th nerve was biopsied a cally. A small number undergone severe de; the majority of the re sheaths appearing intic ular abnormalities we

Other Investigation rate was +95 but tl (PBI) value was nor tests revealed restricti (Table 2). Fluoroscopy motility studies of the mal. A urine sample serum contained no tetanus.

Treatment.—Diazep: 10 mg, three times da infusion of magnesium duced no improvement ministration previously DPH were administe six-hour period while serial DPH blood levels No EMG or clinical ch: DPH dose of 750 mg

and Neuropharmacology.—Electromyography.—All were sampled with a constant and standard amplified and recorded similar findings. was present on insertion needle or on percussion of equal waxing and waning were present with only short periods of electrical activity lasting three to five seconds. of both normal-appearing periodic bursts of repetitive (2 msec or less) action amplitude and usually a normal configuration (Fig 3). Disappearing motor units and fasciculations in the The interference pattern or units under voluntary contraction.

Block.—Electromyography of peroneous muscle showed a complete reduction of electrical activity at rest after ulnar and median nerves with . The effectiveness of the stimulating both nerves at producing an evoked electromyogram. All distal sensory of ulnar and median nerves after the block. Spinal and are induced after first fully

is moderately reduced; bottom rate occasion after giving peroneous activity greatly reduced. second; vertical, 100 μ v.

explaining the investigational nature of the procedure to the patient and obtaining his consent. Muscle and nerve biopsy were performed under anesthesia. Ten cubic centimeters of 1% lidocaine (Xylocaine) were injected into the subarachnoid space at the L-3 interspace producing complete voluntary paralysis of the legs and anesthesia to the T-10 level; no change was detected in either the clinical stiffness or the EMG activity. Deep anesthesia was induced with 500 mg of intravenously administered thiopental sodium without any change in the muscular stiffness or the EMG.

Curare.—Administration of 10 mg of curare intravenously produced complete muscular relaxation and electrical silence on the EMG.

Repetitive Nerve Stimulation.—Trains of 10 to 30 cps supramaximal electrical stimuli were delivered to the median nerve at the wrist while the evoked response was recorded from the abductor pollicis brevis muscle with surface electrodes. No significant change occurred in the amplitude of evoked potentials.

Motor Conduction Velocities.—Studies were performed using surface recording electrodes over muscle while stimulating the nerve trunk supramaximally. All motor conduction velocities were either slightly below or in the lower range of normal (Table 1).

Histological Studies.—Muscle Biopsy.—A light microscopic examination of a muscle biopsy taken from the right vastus lateralis and stained with hematoxylin-eosin was normal.

Nerve Biopsy.—The right sural (sensory) nerve was biopsied and examined microscopically. A small number of individual fibers had undergone severe degenerative changes with the majority of the remaining fibers and myelin sheaths appearing intact. Inflammatory or vascular abnormalities were lacking.

Other Investigations.—The basal metabolic rate was +95 but the protein-bound iodine (PBI) value was normal. Pulmonary function tests revealed restrictive chest wall dysfunction (Table 2). Fluoroscopy of the diaphragm and motility studies of the small bowel were normal. A urine sample contained no 2,4-D. The serum contained no detectable antibodies to tetanus.

Treatment.—Diazepam in oral doses of up to 10 mg, three times daily, and an intravenous infusion of magnesium sulfate 0.32 mg/kg produced no improvement. Using methods of administration previously described,¹³ 1,500 mg of DPH were administered intravenously over a six-hour period while a continual EMG and serial DPH blood levels were obtained (Fig 4). No EMG or clinical changes were noted until a DPH dose of 750 mg was reached, and the

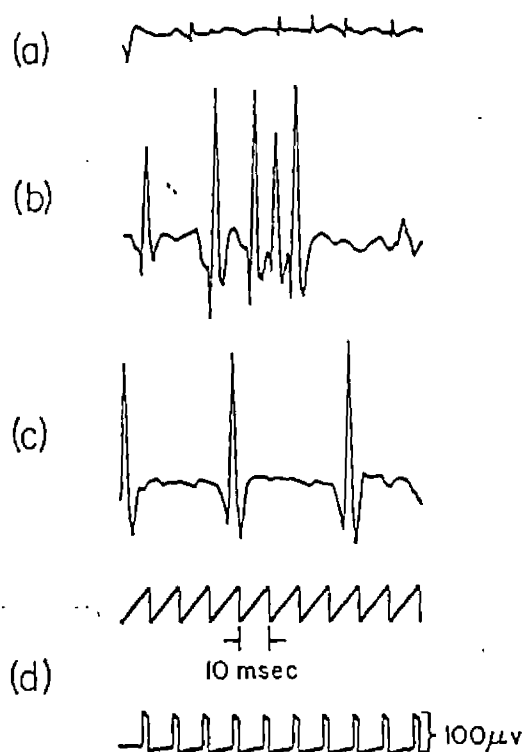


Fig 3.—Tracing from resting EMG records (case 1). (a) Short duration units resembling fibrillations which, however, disappeared after curarization; (b) normal-appearing action potentials; (c) repetitive normal-appearing stereotyped action potentials; (d) calibrations. Various combinations of a, b, and c were present in resting EMG.

blood level was 13 μ g/ml. (A DPH blood level of 10 to 15 μ g per milliliter usually provides effective anticonvulsant action.) Following this, the muscular stiffness and associated EMG activity progressively decreased until maximal improvement was achieved at a dose of 1 gm of DPH (blood level 17 μ g/ml). No further change occurred as the dose was increased to 1.5 gm and the blood level to 25 μ g/ml. Occasional fasciculations and scant spontaneous electric activity persisted after treatment (Fig 2).

Coinciding with the subsidence of spontaneous EMG activity, the patient improved markedly in his gait, breathing, and ability to move (Table 2). The previously absent stretch reflexes reappeared. The excess sweating, venous engorgement, and hypermetabolism disappeared. The entire improvement persisted after initiating 0.3 gm DPH therapy daily. After one month of treatment, the DPH was discontinued and three days later all of his pretreatment symptoms and findings returned. Restitution of DPH at 0.3 gm daily produced a remission which has now lasted eight months. The de-

Table 1.—Motor Conduction Velocities in Case 1

Nerve	Meters/Second		
	Left	Right	Normal (35)
Median	42	39	40-58
Ulnar	44	39	40-60
Common peroneal	33	36	43-57
Tibial	37	34	40-55

Table 2.—Comparison Before and After Treatment in Case 1

	Before DPH Treatment	After DPH Treatment
Basal Metabolic Rate	+95	+20
Diaphoresis	Intense	Normal
Superficial venous engorgement	Marked	Normal
Pulmonary functions (% predicted values)		
Forced expiratory volume (1 sec)	33%	68%
Vital capacity	43%	67%
Maximum breathing capacity	26%	81%

formities of the hands and feet gradually disappeared with physical therapy.

CASE 2.—A 30-year-old farmer's wife was healthy and free from neurological symptoms until the age of 26 years when painful paresthesias began in her hands followed by a progressive stiffness of all four extremities. These symptoms progressed during the next year, but her only limitations were in fine movements of the hands and in rapid walking. At the age of 28, at the Auckland Hospital of New Zealand, a muscle biopsy was normal and an EMG contained continuous motor unit discharges at rest. The results of a lumbar puncture and studies of muscle enzymes in serum were normal. Her physicians noted difficulty in muscular relaxation, generalized muscle stiffness, fasciculations, and depressed muscle stretch reflexes. She was discharged without treatment but her muscle stiffness improved moderately over the next two years. She denied exposure to herbicides or industrial toxins. There was no family history of neurological disease. Cold weather did not affect the muscular stiffness, but she did note improvement with repeated exercise.

She was examined by one of us (W.W.) in October 1968. Her blood pressure was 120/75

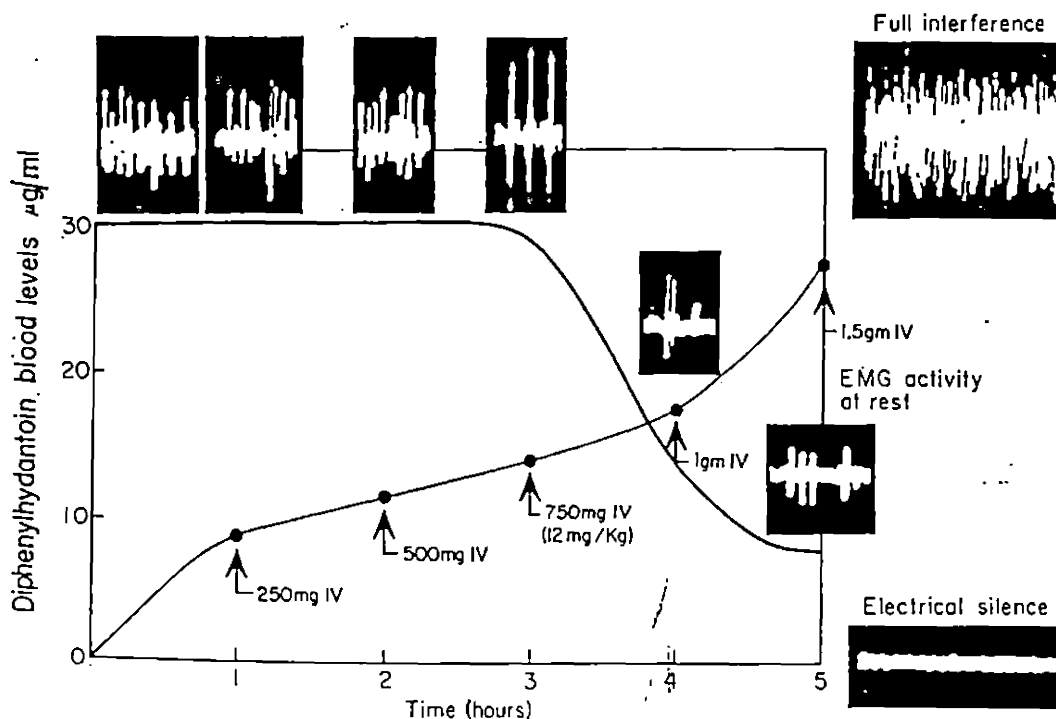
mm Hg, heart rate 80 b regular, and her temper The general physical ex: markable except for obesi tually normal. The only n ities were in the motor : findings similar to, but mil patient in case 1. She wal and could knit and perfo ments with difficulty. Non tender, but the calves a were mildly hypertrophie in slight plantar flexion, flexed and claw-like. Th uniformly resistant to pas ably contracted at rest. M lations were visible and major muscle groups in t movements as well as the muscles persisted durir myotonia was absent, bu ness improved after act ment. She initially had muscles after a vigorous don jerks were 1+ and : the ankles where they c despite reinforcement.

The following laborato complete blood count, u genogram, serum electro phorus, and PBI.

EMG.—The right ab and both tibialis anterior using a concentric needle EMG was almost continu long runs and intermit This activity was interrup riods of electrical silence onds. The motor units amplitude and duration short duration (2 msec or peering units. The interfe and those motor units u appeared normal.

Treatment was initiate of 1,000 mg of orally ad in divided doses over 48 orally four times daily. N stiffness of fasciculations dose was increased to 6 without improvement. S signs of DPH toxicity d therefore, an abnormality or absorption was susp was begun on carbama times daily, and improv Following treatment, m cluding the posture in h normal except for the p

Fig 4.—Resting EMG activity at various DPH blood levels. Note that depression of EMG activity begins with a DPH dose of 750 mg and a blood level of 13 μ g/ml. Maximal improvement occurred with a dose of 1,000 mg and a blood level of 17 μ g/ml.



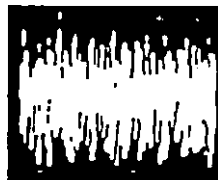
feet gradually disappeared.

The farmer's wife was neurologically normal when painful paresthesias followed by a paresthesia of the extremities. These occurred the next year, but with fine movements of walking. At the age of 30, she moved to New Zealand, and an EMG of the lower extremities at rest, after a 24-hour fast, and studies of the muscle were normal. Her clinical picture and studies of the muscle were normal. Her clinical picture in muscular relaxation, stiffness, fasciculations, and reflexes. She was not aware of any muscle stiffness, but her muscle stiffness completely over the next year. Exposure to herbicides or other chemicals, as no family history of similar illness, but she did note stiffness.

One of us (W.W.) in 1975, blood pressure was 120/75

Pressure of 120/75 mm Hg. Maximal 17 µg/ml.

Full interference



0.5 gm IV

EMG activity at rest



Electrical silence



mm Hg, heart rate 80 beats per minute and regular, and her temperature 98.6 F (37 C). The general physical examination was unremarkable except for obesity. She was intellectually normal. The only neurological abnormalities were in the motor system which showed findings similar to, but milder than, those of the patient in case 1. She walked slowly and stiffly and could knit and perform other fine movements with difficulty. None of her muscles were tender, but the calves and thenar eminences were mildly hypertrophied. The feet were held in slight plantar flexion, and the hands were flexed and claw-like. The muscles were stiff, uniformly resistant to passive stretch, and palpably contracted at rest. Myokymia and fasciculations were visible and palpable in all the major muscle groups in the extremities. These movements as well as the stiff resistance of the muscles persisted during sleep. Percussion myotonia was absent, but her muscular stiffness improved after active or passive movement. She initially had difficulty relaxing the muscles after a vigorous contraction. The tendon jerks were 1+ and symmetrical except in the ankles where they could not be obtained despite reinforcement.

The following laboratory data were normal: complete blood count, urinalysis, chest roentgenogram, serum electrolytes, calcium, phosphorus, and PBI.

EMG.—The right abductor pollicis brevis and both tibialis anterior muscles were sampled using a concentric needle electrode. At rest, the EMG was almost continuously active with both long runs and intermittent bursts of activity. This activity was interrupted by occasional periods of electrical silence lasting 10 to 15 seconds. The motor units themselves varied in amplitude and duration and included both short duration (2 msec or less) and normal-appearing units. The interference pattern was full and those motor units under voluntary control appeared normal.

Treatment was initiated with a loading dose of 1,000 mg of orally administered DPH given in divided doses over 48 hours and then 100 mg orally four times daily. No change in either the stiffness of fasciculations occurred and the daily dose was increased to 600 mg for three days without improvement. She failed to develop signs of DPH toxicity despite this high dose; therefore, an abnormality of DPH metabolism or absorption was suspected. Accordingly, she was begun on carbamazepine, 250 mg four times daily, and improved within 24 hours. Following treatment, muscle examination including the posture in her hands and feet was normal except for the persistence of moderate

numbers of fasciculations. The ankle tendon jerks could now be obtained easily.

Comment

Pathophysiology.—The pharmacologic and physiologic evidence indicates that this disorder results from isolated, spontaneous hyperactivity in various segments of the peripheral motor unit. A central cause is unlikely since the muscular stiffness was unchanged by sleep, spinal anesthesia, and deep barbiturate anesthesia. An origin in the muscle or postsynaptic neuromuscular junction is ruled out, since curare eliminated the muscle contraction and all EMG activity. The decrease in EMG activity after peripheral nerve block indicates that the spontaneous activity arose from sites both distal and proximal to the nerve block. In addition, many of the action potentials were abnormally brief (2 msec or less), reflecting fractional activation of a motor unit. This suggests that some of the activity also arose in the nerve at sites beyond the major axon branching. This combination of normal and fractionated motor unit potentials is similar to the fasciculatory EMG activity evoked by neostigmine and other facilitatory drugs that act on the motor nerve terminals.⁸

The remarkable effect of DPH in the patient in case 1 (and in Isaacs' patients) also supports the idea of a peripheral motor nerve disorder. DPH in standard therapeutic doses has little effect on peripheral nerve conduction or synaptic transmission, but does act specifically on motor nerve terminals to block posttetanic potentiation (PTP)¹⁴ in tonic muscles. In this phenomenon a conditioning tetanic volley establishes a hyperexcitability of motor nerve terminals, such that repetitive discharges arise when the terminals are invaded by subsequent single impulses. Thus, both physiological and pharmacological evidence favors the motor terminals as the site of part of the peripheral nerve hyperexcitability in these patients. In this regard it is of interest that the unmyelinated terminal region is particularly sensitive to dysfunction and this region develops early degenerative changes following experimental injury to the peripheral motor axon.¹⁵

The results of the motor conduction veloc-

ities and nerve biopsy in case 1 also suggest peripheral nerve disorder. The sural nerve biopsy is to our knowledge the only available anatomic study of nerve in this syndrome. Since motor nerve biopsy was not considered warranted, we can only speculate that the minimal degenerative changes found in the sensory nerve reflects a similar process involving motor nerve fibers.

Clinical Features.—Generalized muscular stiffness, fasciculations, and myokymia of peripheral nerve origin present three essential clinical features which were consistently present in our cases and those previously reported: (1) generalized muscle stiffness; (2) fasciculations; (3) myokymia. Other features such as depressed muscle stretch reflexes, joint deformities, sweating, venous engorgement, and elevated basal metabolic rate were not uniformly present and are probably epiphenomena, ie, manifestations only of the severity of the muscle contraction.

The muscle stiffness was widely distributed and confined to the skeletal musculature. Smooth and cardiac muscle as well as the eye muscles were spared. The muscle stiffness was continually present and in severe cases, such as the patient in case 1, persisted during sleep. Difficulty in muscular relaxation has been noted in many instances and has resembled the myotonia of muscle disease except for the absence of percussion myotonia and repetitive discharges on moving the EMG needle. The myotonia of muscle disease as noted in myotonia dystrophica and the myotonia of goats is thought to be a primary muscle phenomenon since it persists after curarization.^{10,17} Landau¹⁶ believed that the difficulty in relaxation following prolonged muscular contraction observed in patients with myotonia dystrophica represented a normal lengthening reaction in muscles stretched by persistent myotonic contraction in antagonist muscles. Such a normal physiological mechanism may be responsible for the difficulty in muscle relaxation noted in patients with spontaneous peripheral motor-axon hyperactivity.

Fasciculations are a prominent part of the illness and important in distinguishing it from other disorders producing muscular hypertonus. The presence of muscle fasciculations at rest has most often been linked to

diseases of the anterior horn cells,¹⁸ but they can accompany a variety of conditions including generalized metabolic disorders¹⁹ and peripheral nerve lesions.²⁰ Fasciculations are thought to represent the spontaneous isolated discharge of individual motor units,¹⁸ but it is far from clear that they necessarily originate in the motor neuron soma; indeed much evidence indicates a peripheral source. Thus, the fasciculations that follow the administration of neostigmine are initiated in the distal unmyelinated terminals of the motor nerve, and even in motor neuron disease itself some fasciculations persist following procaine block or anatomic section of the nerve supplying the muscle in question.²¹ The unchanged EMG findings after spinal anesthesia indicate that the fasciculations in the present cases originated entirely in peripheral motor axons.

The fasciculation is manifested clinically as a single muscle twitch and on the EMG as a single spontaneous motor unit. When fasciculations are multiple, closely grouped, and follow one another continuously in different muscle bundles, they give the appearance of muscle undulation rather than a single twitch. These undulations were called myokymia by Schultze²² who coined the term to describe benign spontaneous undulating contractions of the calves and thighs. Electromyographically, one cannot distinguish the individual fasciculations accompanying anterior horn cell disease from those accompanying more peripheral dysfunction although the combination of a slow rate of discharge and accompanying giant potentials helps electrically to localize the proximal lesions while the combination of a high rate of discharge and the presence of small subunit potentials identifies peripheral hyperexcitability. Thus, peripheral hyperexcitation in these patients leads to fasciculations which, when frequent and widespread, cause the undulations of myokymia; the latter is the clinical result of the rapid and widespread repetition of the first, not a disease itself any more than fasciculation is a disease itself.

Treatment.—With DPH or carbamazepine treatment, all the previously reported patients and both of our own demonstrated an immediate and remarkable decrease in muscular stiffness and improvement of hand

and foot deformities. The improvement was evident in the turned almost incapacitated manual movements of the feet without any very likely therapeutic effect on the motor nerve itself to improve the condition. It is involved pathophysiology different from that although not DPH blood levels is possible the absorption or responsible.²³

The therapeutic effect of DPH, carbamazepine, treatment of the disease. It protects induced convulsive effect the spinal trigeminal ganglion shares the at lower equivalent carbamazepine peripheral nerve.

Etiology.—unknown, but sure of the pathogenesis. 2,4-D. In laboratory induces a rigidity resembles the skeletal stiffness, fasciculations. Curare will not stiffness or the respect 2,4-D myotonia and this paper. None of isolated myotonia Stein et al²⁴ also reported that neuropathy in patients, a generalized disease revealed no evidence of closed normal fasciculations of—similar to drugs such as patients also require

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anifested clinically and on the EMG motor unit. When le, closely grouped, continuously in dif- ey give the appear- ion rather than a lations were called who coined the term aneuous undulating s and thighs. Elec- cannot distinguish ions accompanying from those accom- al dysfunction al- of a slow rate of ying giant poten- localize the proxi- bination of a high e presence of small lies peripheral hy- ripheral hyperexci- leads to fascicula- nt and widespread, myokymia; the lat- of the rapid and the first, not a dis- a fasciculation is a

H or carbamaze- previously reported own demonstrated rkable decrease in provement of hand

and foot deformities. This was particularly evident in the patient in case 1 who returned almost to normal from being severely incapacitated and unable to perform fine manual movements or walk more than 100 feet without exhaustion. As noted, DPH very likely induces this remarkable therapeutic effect by depressant effects upon the motor nerve terminals. The failure of DPH to improve the patient in case 2 is unexplained. It is possible that her disorder involved pathophysiological mechanisms different from those in the patient in case 1, although nothing else suggested it. Since DPH blood levels were not obtained, it also is possible that an abnormality of DPH absorption or metabolism may have been responsible.²³

The therapeutic mechanism of carbamazepine is less clear than that of DPH. Like DPH, carbamazepine is effective in the treatment of epilepsy and trigeminal neuralgia. It protects animals against strychnine-induced convulsions²⁴ and has a specific suppressive effect upon synaptic transmission in the spinal trigeminal nucleus.²⁵ Carbamazepine shares this latter effect with DPH but at lower equivalent dose levels. The effect of carbamazepine upon PTP in isolated peripheral nerves is not known.

Etiology.—The cause of this syndrome is unknown, but it is worth noting the exposure of the patient in case 1 to the herbicide, 2,4-D. In laboratory animals 2,4-D exposure induces a rigid state which superficially resembles the syndrome of generalized muscular stiffness, fasciculations, and myokymia.¹¹ Curare will not abolish either the muscular stiffness or the electrical activity, and in this respect 2,4-D poisoning resembles myogenic myotonia and not the syndrome described in this paper. Nevertheless, spontaneous firing of isolated motor nerves also occurs.¹¹ Goldstein et al²⁶ and Monarca and Di Vito²⁷ have reported that 2,4-D can induce a peripheral neuropathy in man, and one of Goldstein's patients, a 65-year-old farmer, developed generalized fasciculations. The EMG revealed no evidence of denervation but disclosed normal motor unit potentials and fasciculations of "the grouped discharge type"—similar to those that can be caused by drugs such as neostigmine." Goldstein's patients also reported distal paresthesias simi-

lar to those of our cases, and a colleague has reported to us similar muscular stiffness, muscle twitching, and paresthesias documented by his physician and lasting four months after using 2,4-D. Despite these suggestive observations, 2,4-D is widely used and generally thought to be nontoxic in workers spraying it.²⁷

Many pharmacological agents and chemicals can induce spontaneous repetitive action potentials in muscle.⁸⁻¹⁰ These include anticholinesterases, the veratrine alkaloids, and other facilitatory drugs and poisons. Many of these chemicals induce repetitive firing in the motor nerve terminals and muscle and thus produce states which share the characteristics of myotonia and this syndrome. An example is the recently reported drug, 2-azaridiny ethanol (2 A-E).¹⁰ This drug induces continuous fasciculations; nerve section abolishes these when they are induced by small doses, but the fasciculations return if the dose is raised. The fasciculations are abolished by curare. No significant effects are exerted by 2 A-E upon the central or autonomic nervous system, and DPH in therapeutic doses effectively suppresses the isolated peripheral nerve hyperactivity.¹⁰ That the human disease can be simulated so closely in experimental animals suggests that in some patients it may be a nonspecific response to peripheral nerves damaged by any of a variety of toxic agents which might include 2,4-D or still-unidentified chemicals such as 2 A-E.

Differential Diagnosis.—This syndrome is easily differentiated from other causes of muscular stiffness. It only superficially resembles the so-called "stiff-man syndrome," for which the diagnostic criteria²⁸ include (1) generalized muscular stiffness which disappears during sleep, (2) a normal neurological examination aside from the muscle stiffness, (3) continual EMG activity at rest, (4) depression of EMG activity and muscle stiffness with general anesthesia, spinal anesthesia, and peripheral nerve blocks. On the basis of No. 4, the stiff-man syndrome is thought to have a central origin, although of all the patients reported only one has undergone all the tests. These patients are said to improve with diazepam treatment which was without effect in the patient in case 1.

This syndrome is also readily differentiated from the myotonia of muscle disease which available evidence suggests arises in the muscle membrane itself.^{16,17} Although some patients with generalized muscular stiffness and fasciculations of peripheral nerve origin find it difficult to relax their muscles and show a decreased stiffness with repeated motions, they demonstrate neither percussion myotonia, increased stiffness with exposure to cold, nor other stigmata of a myopathy. Unlike the myotonia of muscle disease, generalized fasciculations are present while they are not in a myopathy. In muscle myotonia the EMG is generally silent at rest, responding with the repetitive potentials only after percussion of the muscle or movement of the recording needle, while in the syndrome described here, the EMG shows continual activity at rest. Finally, the EMG activity is fully blocked by curare, which it is not in the myotonia of muscle disease.^{16,17}

The basal ganglia disorders, pyramidal tract spasticity, muscle spasm resulting from spinal interneuron damage,²⁹ and tetanus are not associated with fasciculations, myokymia, and depressed stretch reflexes. In tetanus and muscle spasm from spinal interneuron damage, the EMG may contain continual activity at rest which corresponds to the visible muscle spasm^{20,30}; however, both tetanus and spinal interneuron disease are associated with hyperactive deep tendon reflexes and other signs of spinal cord dysfunction. Tetanus is usually an acute illness and does not last for periods of two to six years such as in our cases.

Nomenclature.—A number of patients have been described with various combinations of muscle stiffness, myokymia, fasciculations, myotonia, "pseudomyotonia," and muscle atrophy.³¹⁻³⁴ Most of these patients have not undergone the pharmacological dissection necessary to establish firmly that their disorder originated in peripheral nerve and not spinal cord or muscle, but their disease so closely resembled the present cases clinically that they were probably the same. However, the rarity of the disorder, and the different views of its pathogenesis have led to the following names, most of which either overlook the unusual pathophysiology or utilize confusing or hybrid terms:

Continuous muscle fiber activity^{1,2}

Neuromyotonia³

Pseudomyotonia⁵

Myokymia with impaired muscular relaxation⁶

Pseudomyotonia and myokymia⁷

The term "generalized muscular stiffness, fasciculations, and myokymia of peripheral nerve origin" is admittedly cumbersome, but does convey the essential clinical and pathological features.

Recently, the patient in case 1 returned from his native Puerto Rico, and we were able to reexamine him. Clinically, he was unchanged from his initial examination two years previously, and he still required full therapeutic levels of DPH to prevent incapacitating muscle contraction. Dr. Thomas R. Swift recorded the EMG from the abductor digiti quinti muscle after the patient had been removed from DPH for two weeks. He electronically counted the number of spontaneous muscle potentials with the muscle at rest and following successive ulnar nerve blocks at the elbow and wrist, respectively. Dr. Swift will publish the details subsequently, but block at the elbow reduced the potentials 53% from a resting mean and SE of $5,300 \pm 281$ per minute to $3,500 \pm 610$ per minute. Block at the wrist further reduced the number of potentials to 300 ± 19 per minute. The results provide clear evidence that a significant amount of the spontaneous activity arose from the peripheral nerve between the two blocks.

Summary

Two patients with a syndrome of generalized muscular stiffness, fasciculations, and myokymia of peripheral motor nerve origin are reported. The muscular stiffness was unchanged by sleep, general anesthesia, or spinal anesthesia, but was reduced by distal peripheral nerve block and abolished by curare, thus confirming Isaacs' view that isolated spontaneous firing of the peripheral motor nerves is responsible. The configuration of many of the electromyographic (EMG) action potentials and the effect of peripheral nerve block suggest that the action potentials originate in various portions of the peripheral motor axons including the nerve terminals. Further evidence of a peripheral nerve disorder was found in abnormal motor nerve conduction velocities and an abnormal sural nerve biopsy in one patient. The disorder is readily differentiated from other conditions producing muscular stiffness such as

pyramidal tract disease, myogenic "man" syndrome and carbamazepide decrease the rest move the clinical toxin probably ex depressing the ex unmyelinated mo The cause of th damage to peripl to certain chemi oxyacetic acid (2

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pyramidal tract disease, parkinsonism, tetanus, myogenic myotonia, and the "stiff-man" syndrome. Both diphenylhydantoin and carbamazepine ameliorate the stiffness, decrease the resting EMG activity, and remove the clinical disability. Diphenylhydantoin probably exerts its therapeutic effect by depressing the excitability of the peripheral unmyelinated motor nerve terminals.

The cause of the disorder is unknown, but damage to peripheral nerves from exposure to certain chemicals such as dichlorophenoxyacetic acid (2,4-D) may play a role. An

identical experimental model can be produced in animals with 2-aziridiny ethanol (2 A-E).

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The patient in case 2 was referred to us by Gavin Glasgow, FRCP, and Dr. W. F. Riker made helpful suggestions.

Nonproprietary and Trade Names of Drug

Diazepam—Valium.

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