Neurologic Munchausen's redux

To the Editor: We too had the opportunity to care for the patient described by Folger et al.¹ In February 1980, a 30-year-old man arrived in the Saint Paul-Ramsey Hospital emergency room, purportedly from Twin Cities Metropolitan Airport. He stated he had lost consciousness just after landing an experimental high-altitude NASA jet airplane. He claimed there had been several mysterious deaths under similar circumstances among test pilots and that the problem was "top secret."

Though he complained of a left hemisensory loss, neurologic exam revealed no objective signs and EEG, CT, and blood studies were normal. In the course of 3 days his tale became more elaborate and grandiose and an alert chief resident discovered he was mispronouncing the name of a city near Stanford, California where he had studied "aerospace physics." Further investigation revealed almost complete confabulation. The patient then signed out of the hospital after refusing psychiatric referral. Minneapolis and Saint Paul hospitals were notified and the pilot moved on to Chicago.

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Reply from the Authors: The experience of Drs. Steier and Reder above, plus an additional experience by a physician in Maine, reaffirmed the widespread impact this young gentleman is having on the neurologic community. It is our hope that with proper recognition he may fall into the proper hands.

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Pacemaker palsy

To the Editor: The radial nerve in the upper arm is often the site of compression. I have treated two patients with radial nerve palsy due to compression from an indwelling cardiac pacemaker inserted over the anterior chest, a complication not previously described.

Case 1. For several weeks, this 84-year-old woman had

progressive weakness of the right hand, with intermittent pain radiating down the posterior aspect of the arm into the dorsum of the hand. Because of cardiac dysrhythmia, an indwelling pacemaker had been inserted beneath the skin of the right anterior chest wall 2 years earlier. On examination, there was severe weakness of the finger extensors of the right hand and moderate weakness of the right wrist extensors and brachioradialis. The triceps was unaffected. There was mild sensory loss for pinprick over the dorsum of the right hand. The pacemaker was laterally situated, and the upper outer edge was seen to compress the humeral aspect of the right axilla when she lay on her right side. She said she always slept on her right side.

Because the radial nerve was probably compressed in the axilla by the pacemaker tip, we suggested repositioning it, but the patient declined. Three years later, there was complete paralysis of the muscles previously affected.

Case 2. This 71-year-old woman had a pacemaker inserted in the left anterior chest. From that time, she awoke about once a month with her left arm "asleep," always related to sleeping on her left side. She used pillows to prevent this. At age 74, the left hand became increasingly clumsy. Three months later there was mild weakness of the left triceps, wrist extensors, and finger extensors, and impaired pinprick sensation over the radial surface of the left forearm and dorsum of the hand. The left triceps and brachioradialis reflexes were depressed. The upper outer tip of the pacemaker unit compressed the humeral aspect of the left axilla when she lay on her left side.

Nerve conduction velocities of the left peripheral radial motor and sensory nerve were normal. The radial F-wave was absent. The radial sensory action potential at the wrist was reduced (1- μ V amplitude at 14 cm proximal to the metacarpophalangeal joint; normal, more than 4 μ V.) EMG demonstrated increased insertional activity and a reduced interference pattern in the left extensor pollicis brevis and extensor indicis.

The patient declined to move the pacemaker; the weakness progressed and she had pain in the radial distribution. The radial sensory action potential at the wrist was now absent. EMG signs were unchanged. The pacemaker was repositioned more medially under local anesthesia. Postoperatively, the aching pain did not recur and the weakness improved in 6 weeks.

Discussion. The radial nerve is susceptible to compression at the axillary outlet and in the upper arm where it lies against the humerus.¹ Compressive agents include axillary crutches, tourniquets,² and rifle slings around the upper arm.³ Sleeping on the arm, particularly in inebriated patients, may result in "Saturday night palsy." In these two patients, the hard outer corner of the cardiac pacemaker compressed the axilla in a way that could compromise the radial nerve; the progressive difficulty was more compatible with recurring trauma than an isolated episode of damage. In the first patient, triceps function and forearm sensory functions were preserved. The branches to the triceps and the posterior cutaneous

nerve of the forearm may leave the radial nerve high in the axilla, and were presumably spared. These branches, which usually run with the radial nerve in the upper arm, were involved in the second case.

These cases indicate the danger of leaving the pacemaker where it can continue to impinge on the nerve. Improvement followed repositioning of the instrument in one case. "Pacemaker palsy" should be considered when the pacemaker is initially implanted. The outer edge of the pack should be medial enough to avoid impinging on the axilla.

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Polyneuropathy and exposure to parathion

To the Editor: We read with interest the paper by de Jager et al¹ on polyneuropathy after massive exposure to parathion. This topic is of great importance to neurologists, toxicologists, and occupational health physicians because of the growing use of organophosphate pesticides and laboratory animal models in attempting to predict delayed neurotoxicity.

Organophosphate (OP) delayed neurotoxicity is not related to acetylcholinesterase (AChE) inhibition, is not necessary to the pesticide action, and could be primarily prevented by using the appropriate compound. Therefore, case reports of delayed neurotoxicity by OPs have not only a theoretical but also a practical relevance.

This case report does not give evidence of any chemical analysis of the incriminated bottle of parathion, nor was there any toxicologic evaluation of the basic chemicals or metabolites in blood or urine. The description of the clinical symptoms does not support evidence of inhibition of RBC AChE, and there is no information concerning physical findings or laboratory tests of severe methanol poisoning such as metabolic acidosis, osmolar gaps, or evidence of blindness.

The authors' estimated doses of parathion and methanol are so large as to raise the question of an instantaneous death. The estimated dose of methanol ingested is many times the estimated lethal dose in humans, and the dose reported for parathion is some 500 times the lethal dose estimated for humans.²

The molecular target in nervous tissue for the delayed neurotoxicity of organophosphate esters is known as neurotoxic esterase (NTE).³ NTE is an esterase in nervous

tissue that is insensitive to paraoxon both in vivo and in vitro in experimental animals. Studies in vitro with human enzymes and in postmortem human brain of poisoned patients have shown a close correlation to experimental animal enzyme systems.⁴⁻⁶ Experiments in vivo are usually performed with animals protected and treated against cholinergic symptoms. By those means, it is possible to increase the lethal doses 10 to 20 times. One can predict whether organophosphate compounds are neurotoxic or not if the chemical fails to produce delayed neurotoxicity at the maximal tolerable doses in these experimental conditions.

All this is in sharp contrast to the presentation of the authors, which suggests that there is great difficulty in predicting these toxicities.

In summary, the authors fail to present toxicologic analysis of the offending toxins. They do not present a patient with symptoms and laboratory tests that are consistent with the reported ingestion of a mixture of methanol and parathion. They also report estimated levels that would likely have caused instantaneous death. The authors also fail to appreciate a large body of in vivo and in vitro studies showing a relative predictability of the neurotoxicity of organophosphate esters. Based on all of these factors, it is unlikely that the case reported is an example of true delayed neurotoxicity due to organophosphates. Unfortunately, the authors have presented such limited clinical data that it would be difficult to explain the entire case only with clinical findings. Parathion is able to produce a dose-dependent necrosis of rat skeletal muscle within 24 hours after dosing. This myopathy seems to begin at the motor endplate and requires a critical loss of AChE activity over a short period of time. However, if a motor nerve is transected, the lesion does not occur, suggesting a neurally mediated process.⁷⁻⁹ We wonder if the described pathology and EMG alterations could be compatible with an involvement of muscles by the etiologic agent.

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Reply from the Authors: Very high plasma levels of parathion were found in this patient. On the first day the RBC AChE was less than 100 E (normal 1900 to 3700 E). This value slowly increased to normal during the following months, as we published elsewhere.¹ These findings point clearly to a severe parathion intoxication. The poison could not be analyzed by us, but according to the manufacturer it contained a 25% solution of parathion in 70% methanol (manufactural purity 99%).

A single dose of methanol does not cause polyneuropathy.² Late signs of methanol intoxication (for instance, blindness) were not found. In the acute phase the patient had combined respiratory and metabolic acidosis; in addition to the methanol, this was probably also caused by hypoxia, hypercapnia, and the parathion itself.^{3,4}

Recovery after a "supralethal" dose of parathion is possible.³ Our patient was treated by the general practitioner within a few minutes after he took the poison. Treatment included atropine, cardiac massage, and artificial respiration. Within 30 minutes, he arrived at the outpatient clinic, was given atropine and obidoxime, and then admitted to the Respiratory Care Unit. Charcoal hemoperfusion was carried out the same day for four hours.

As far as we know from experimental tests of the neurotoxicity of parathion and paraoxon in laboratory animals, none used doses as high as our patient took. Also, protection against direct cholinergic effects in these animals was carried out only with atropine and obidoxime but not with more extensive measures such as artificial respiration and charcoal perfusion.^{5,6}

The EMG findings were not consistent with myopathy. Distal limb muscles were more affected than the proximal ones and muscles with chiefly fast muscle fibers were severely affected. These findings made it improbable that the clinical picture was due to an organophosphor myopathy.⁷⁻⁹

Summarily, the amnesic data, laboratory findings, and the acute clinical picture all point to severe parathion intoxication. That the patient did survive can be explained by the early, extensive treatment. The clinical picture and course, EMG findings, and sural nerve biopsy findings were in full concurrence with the delayed-onset organophosphorus polyneuropathy described.

We are still convinced that this patient had a polyneuropathy caused by a massive exposure to parathion.

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Neuroleptic malignant syndrome caused by dopamine depleting drugs

To the Editor: One major point in the interesting paper by Burke et al,¹ was that the drugs which provoked the neuroleptic malignant syndrome acted by depletion of catecholamines rather than by dopamine receptor blockade. Both alpha-methyl-para-tyrosine and tetrabenazine have, indeed, clearly been proven to deplete catecholamine storage pools. The issue we raise here is that tetrabenazine does have properties of a dopaminergic antagonist. Four communications lend support to the impression that tetrabenazine itself behaves as a dopamine receptor antagonist independent of its reserpine-like ability to block uptake and deplete amine pools.

1. A closely related structural analog of tetrabenazine, Rol-9564, greatly increased dopamine turnover with minimal amine depletion.²

2. Tetrabenazine itself caused both increased dopamine turnover and amine depletion, yet reserpine, which greatly lowered amine stores, did not enhance turnover.³

3. Tetrabenazine treatment of patients with Huntington chorea increased the cerebrospinal fluid concentration of homovanillic acid suggesting increased dopamine turnover.⁴

4. Tetrabenazine is reported to have blocked the effects of the directly acting dopamine agonist, apomorphine.⁵ Increased dopamine turnover is considered to be strong pharmacologic evidence of blockade of pre- and/or post-synaptic receptors.

From our own preliminary biologic and pharmacologic observations we conclude that tetrabenazine does have important and relevant properties as a dopamine receptor antagonist. We found that tetrabenazine blocked the

inhibitory effect of dopamine on prolactin secretion from rat anterior pituitary glands and displaced ^3H -spiperone binding from specific dopamine receptors.

The paper by Burke et al is important, but it may be that many of the beneficial (and toxic) tetrabenazine effects previously attributed solely to a reserpine-like action need to be reexamined for the likely presence of a dopamine receptor antagonist component as well.

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Reply from the Authors: Dr. Login and associates make the very good point that the effect of tetrabenazine on dopaminergic systems may not be limited to depletion of dopamine stores, which is documented.¹ They cite several lines of evidence to suggest that tetrabenazine may have a dopamine receptor blocking effect as well. They will probably agree, however, that the cited evidence is indirect and not compelling at this time.

Reference to an analog of tetrabenazine is not convincing, because there are many examples of structural analogs having dissimilar pharmacologic properties. That tetrabenazine elevates CSF homovanillic acid (HVA) levels² is consistent with, but does not necessarily imply, a dopamine receptor blocking effect, because the latter is only one of several possible explanations.³ For example, reserpine, as well as tetrabenazine, can elevate rat striatal HVA levels, and, in the case of tetrabenazine, this effect has been thought to be due to saturation of HVA removal mechanisms.⁴ We do not agree that Kuczenski⁵ showed that tetrabenazine increased dopamine turnover, or that his study can be taken as evidence of a dopamine blocking effect of tetrabenazine. He showed that when tetrabenazine, unlike reserpine, was given in vivo there was increased dopamine synthesis (not turnover), in rat striatal synaptosome preparations. He attributed this difference to a differential effect on

endogenous dopamine pools which regulate tyrosine hydroxylase activity. The only cerebral effect of apomorphine which Pletscher states is blocked by tetrabenazine is emesis in dogs.¹ Again, although this is consistent with a dopamine blocking effect, there may be other explanations.

One type of evidence for a dopamine blocking property of tetrabenazine that would be more direct is displacement of radioligands which presumably bind to the dopamine receptor, and Logins' findings with ^3H -spiperone are of interest. In the past, tetrabenazine has been thought to probably compete for the reserpine binding site,⁶ and reserpine does not displace ^3H -haloperidol binding.⁷

We believe that the question of dopamine receptor blocking properties of tetrabenazine is still very much an open one, but we agree with Login and associates that it is an important question which needs to be studied. Tetrabenazine is finding increased use in the treatment of movement disorders, and a better understanding of its properties will be essential.

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Correction

"Prevalence of monoclonal protein in peripheral neuropathy" by John J. Kelly, Jr., Robert A. Kyle, Peter C. O'Brien, and Peter J. Dyck, November 1981, p. 1481, right column, first paragraph, line 5, should read, "In the remaining 334 (group 2), either no associated systemic condition was apparent, or a specific plasma cell disorder was found only after discovery of a monoclonal protein or hematologic abnormalities."

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Prevalence of monoclonal protein in peripheral neuropathy

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