

## MEDICAL PRACTICE

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*Side Effects of Drugs*

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**Drug-induced peripheral neuropathies**

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Review of the various drugs in current clinical use showed that over 50 of them may cause a purely sensory or mixed sensorimotor neuropathy. These include antimicrobials, such as isoniazid, ethambutol, ethionamide, nitrofurantoin, and metronidazole; anti-neoplastic agents, particularly vinca alkaloids; cardiovascular drugs, such as perhexiline and hydrallazine; hypnotics and psychotropics, notably methaqualone; antirheumatics, such as gold, indomethacin, and chloroquine; anticonvulsants, particularly phenytoin; and other drugs, including disulfiram, calcium carbimide, and dapsone.

Patients receiving drug treatment who complain of paraesthesiae, pain, muscle cramps, or other abnormal sensations and those without symptoms who are receiving drugs that are known or suspected to be neurotoxic should undergo neurological examination and studies of motor and sensory nerve conduction. This will allow the incidence of drug-induced peripheral neuropathy to be determined more precisely.

**Introduction**

Various drugs may cause peripheral nerve damage when used therapeutically.<sup>1, 2</sup> Some, such as thalidomide and cloquinoxil,

have been withdrawn from clinical use, while others are still freely prescribed. In this review we deal only with the second group of drugs, particularly those that have recently been recognised or suspected to be neurotoxic. We consider only those forms of neuropathy resulting from the therapeutic use of such drugs, and do not discuss the complications of drug addiction.<sup>3</sup>

Awareness of the possibility of drug-induced peripheral nerve damage is important because of the ever-increasing number of therapeutic agents being introduced into clinical practice, and prompt recognition of this complication is imperative if severe neurological deficits are to be avoided. The incidence of drug-induced peripheral neuropathy is difficult to establish, since the association with drug treatment is not always recognised, mild forms are easily overlooked, and subclinical disorders are probably more frequent than is generally appreciated.<sup>4, 5</sup>

**Pathogenesis**

Experimental studies have clarified the pathogenesis of certain drug-induced neuropathies,<sup>6, 7</sup> but the basic mechanisms are generally still poorly understood. Because these disorders are potentially reversible the opportunities for histological and other studies of peripheral nerve in man are limited. Nevertheless, with some exceptions, such as perhexiline neuropathy, in which segmental demyelination is prominent,<sup>8</sup> axonal degeneration is the major pathological process in most drug-induced neuropathies.

The mechanism of action of some drugs is relatively well understood. Vincristine and colchicine have a specific effect on neurotubules.<sup>9, 10</sup> Isoniazid interferes with pyridoxine metabolism,<sup>11</sup> thalidomide inhibits riboflavin,<sup>12</sup> prolonged administration of chloramphenicol may lead to vitamin B<sub>12</sub> deficiency,<sup>13</sup> and the nitrofurans interfere with pyruvate oxidation by competing with thiamine pyrophosphate.<sup>14</sup> Perhexiline may interfere with lipid metabolism.<sup>15</sup> Other drugs may cause ischaemic nerve damage by inducing arteritis<sup>16</sup> or severe vasospasm, as in chronic ergotism.<sup>17</sup>

Several factors may predispose to the neurotoxic effects of drugs. The best-known genetic predisposition is the striking susceptibility of the Japanese to develop subacute myelo-optic neuropathy as a complication of cloquinoxil treatment.<sup>1</sup> Variations in drug pharmaco-

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kinetics are also important. Slow acetylators of isoniazid are more likely to develop peripheral neuropathy,<sup>18</sup> as are patients with impaired renal function, who may develop toxic blood concentrations of drugs such as nitrofurantoin.<sup>19</sup> Strenuous exercise was thought to predispose to the development of neuropathy in patients treated with the older sulphonamides.<sup>20</sup> The underlying disease may itself modify the susceptibility to neuropathy—for example, patients with lymphoma develop vincristine neuropathy more often than those with other malignancies.<sup>21</sup> Others who may be predisposed include patients with cancer, diabetes, alcoholism, or vitamin deficiency, conditions in which the peripheral nerves may already be affected.

### Clinical presentations

Most of the drugs we considered cause either a purely sensory neuropathy or a mixed sensorimotor neuropathy. Sensory manifestations usually precede motor disorders, and neurological deficits usually develop first and are most severe distally in the legs. Paraesthesiae alone are difficult to evaluate,<sup>22</sup> but suggest that sensory nerve function may be disturbed. Some drugs, such as dapsone,<sup>23</sup> cause an almost exclusively motor neuropathy. Symptoms of autonomic dysfunction may be prominent, particularly in patients with vincristine neuropathy.<sup>24</sup> Localised damage to peripheral nerves or a nerve plexus may result from intramuscular injections, intra-arterial infusions of cytotoxic agents,<sup>25 26</sup> or haemorrhage in patients in whom anticoagulant treatment is poorly controlled.<sup>27</sup> Brachial plexus neuropathy may occasionally develop after intramuscular injections of penicillin, presumably on an "allergic" basis.<sup>28</sup> Certain cranial nerves may also be affected, either selectively or as part of a more generalised neuropathy, the optic,<sup>29</sup> trigeminal,<sup>2</sup> and eighth cranial<sup>30</sup> nerves being most often affected.

### Specific drugs

The drugs that have been implicated and the clinical syndromes they produce are listed in the table.

#### ANTIMICROBIAL AGENTS

Some of the antituberculosis agents in use may cause peripheral or optic neuropathy. Isoniazid produces a mixed sensorimotor peripheral neuropathy that may be prevented by giving vitamin B<sub>6</sub> supplements.<sup>31</sup> The condition has been reviewed in detail by Le Quesne.<sup>1</sup> Ethambutol is less neurotoxic but may cause optic neuropathy,<sup>32</sup> a mixed sensorimotor neuropathy, or a predominantly sensory neuropathy.<sup>33</sup> Ethionamide, which is structurally related to isoniazid, may rarely cause peripheral neuropathy,<sup>34</sup> as may streptomycin after prolonged administration,<sup>35</sup> although this is less frequent than the ototoxic effects of the drug.

Sensorimotor neuropathy of variable severity in patients treated with nitrofurantoin is well recognised.<sup>36</sup> Symptoms may develop during or

after a course of treatment, particularly in patients with renal insufficiency. Electrophysiological studies have shown a high incidence of subclinical neuropathy, even in non-uraemic patients,<sup>37</sup> and in healthy volunteers taking therapeutic doses of the drug.<sup>4</sup> Histological studies have shown axonal degeneration in peripheral nerves and associated spinal cord damage in a postmortem study.<sup>1</sup> Long-term experimental studies have shown evidence of a "dying-back" neuropathy.

There are several reports of sensory neuropathy developing in patients treated with conventional doses of metronidazole for 6-24 weeks.<sup>38-40</sup> Electrophysiological studies have shown that both sensory and motor nerve fibres may be affected.<sup>40</sup> A sural-nerve biopsy specimen from one patient showed axonal degeneration affecting both small- and large-diameter fibres.<sup>40</sup> The neuropathy is reversible after withdrawal of the drug but recovery may be protracted. The incidence of this complication is not known, and further clinical and electrophysiological studies of patients receiving short- and long-term treatment are required.

#### ANTINEOPLASTIC AGENTS

The vinca alkaloids, which have been used in treating various forms of malignancy, are particularly neurotoxic. Most patients receiving long-term vincristine treatment develop a peripheral neuropathy that may be associated with a painful proximal myopathy.<sup>41</sup> The clinical features of vincristine neuropathy are well documented.<sup>41 42</sup> Both sensory and motor nerves may be severely affected, and the tendon reflexes are lost at an early stage. Postural hypotension and constipation due to autonomic disorders may be early symptoms.<sup>24</sup> Electrophysiological studies have shown evidence of severe axonal damage affecting motor and sensory fibres,<sup>41</sup> the reflex loss probably being due to damage to afferent fibres from the muscle spindles.<sup>43</sup> Histological studies have shown severe axonal degeneration with only minor segmental demyelination.<sup>41</sup> Several other cytotoxic drugs may cause peripheral nerve damage but are less neurotoxic than vincristine (table).

#### CARDIOVASCULAR DRUGS

Peripheral neuropathy has been recognised only relatively recently in patients treated with the coronary vasodilator perhexiline, but is now well documented.<sup>8 44-46</sup> Symptomatic neuropathy occurs in about 0.1% of treated patients, but subclinical disorders have been found in as many as two-thirds of patients studied electrophysiologically.<sup>5</sup> Sensory symptoms, including muscle pain and tenderness, are usually prominent, appearing as early as three weeks after treatment begins, and may be followed by severe weakness of distal and even of proximal muscle groups. In most cases symptoms have occurred only after several months of treatment with daily doses of 200-300 mg of the drug. Papilloedema, dysgeusia, deafness, cerebellar signs, autonomic disorders, and raised concentrations of protein in cerebrospinal fluid have been reported.<sup>46 47</sup> Histological studies of peripheral-nerve biopsy specimens have shown prominent segmental demyelination

#### Clinical syndromes of drug-induced neuropathy and drugs implicated\*

Clinical presentation	Antimicrobial drugs	Antineoplastic drugs	Cardiovascular drugs	Hypnotics and psychotropics	Antirheumatic drugs	Other drugs
Sensory neuropathy	ethionamide chloramphenicol <sup>34</sup> thiamphenicol <sup>35</sup> diamines <sup>36</sup>	procarbazine <sup>33</sup> nitrofurantoin <sup>1</sup>				calcium carbimide sulfoxone ergotamine propylthiouracil <sup>105</sup>
Paraesthesiae only	colistin <sup>22</sup> streptomycin nalidixic acid <sup>22</sup>	cytarabine <sup>33</sup>	propranolol <sup>22</sup>	phenelzine		sulthiame <sup>22</sup> chlorpropamide <sup>22</sup> methysergide <sup>22</sup>
Sensorimotor neuropathy	isoniazid ethambutol streptomycin nitrofurantoin cloquinol <sup>1</sup> metronidazole	vincristine podophyllum <sup>100</sup> chlorambucil <sup>101</sup>	perhexiline hydrallazine amiodarone disopyramide clofibrate	thalidomide <sup>1</sup> methaqualone glutethimide amitriptyline	gold indomethacin colchicine <sup>102</sup> chloroquine phenylbutazone	phenytoin disulfiram carbutamide <sup>2</sup> tolbutamide <sup>103</sup> chlorpropamide <sup>104</sup> methimazole <sup>106</sup>
Predominantly motor	sulphonamides <sup>20 97</sup> amphotericin			imipramine		dapsone
Localised neuropathies	amphotericin <sup>2</sup> penicillin	mustine <sup>25</sup> ethoglucid <sup>26</sup>				anticoagulants

\*References are given only for drugs not discussed in the text.

with associated axonal degeneration, and membranous and paracrystalline inclusions in Schwann cells and endothelial cells.<sup>8-48</sup> Biochemical studies have shown an increased ganglioside content in peripheral nerve.<sup>15</sup> Complete recovery usually occurs within several months of stopping treatment.

A predominantly sensory neuropathy may occur in patients treated with hydralazine.<sup>49-50</sup> Mild or subclinical neuropathy may occur in as many as 15% of patients taking the drug.<sup>51</sup> This seems to be unrelated to the systemic lupus erythematosus-like syndrome induced by the drug, and may be due to a disturbance of pyridoxine metabolism, since hydralazine is structurally related to isoniazid.<sup>52</sup> Peripheral neuropathy may occasionally develop in patients receiving amiodarone<sup>53</sup> or disopyramide.<sup>54</sup> The evidence suggests that amiodarone causes a demyelinating neuropathy. Rarely peripheral nerves may be affected in patients with the typical painful myopathy caused by clofibrate.<sup>55-56</sup>

#### HYPNOTIC AND PSYCHOTROPIC DRUGS

Several reports have raised suspicion that methaqualone may be neurotoxic. Some patients have transient acroparaesthesiae or numbness shortly after taking the drug before the onset of sleep.<sup>57</sup> At least 11 cases of a sensorimotor neuropathy have been reported in patients taking 200-600 mg of methaqualone nightly for a few days to two years, either alone or with diphenhydramine, diazepam, meprobamate, or promazine.<sup>58-60</sup> Symptoms improved in most patients after methaqualone was withdrawn, improvement being rapid and complete in those whose symptoms were of recent onset. In a German study of 232 patients taking the drug, 44 of whom had undergone electromyographic studies, only a single case of peripheral neuropathy was found.<sup>61</sup> Few cases of neuropathy have been reported in Great Britain, and further clinical and electromyographic studies of regular consumers of the drug are required to determine the incidence of this complication.

A predominantly motor neuropathy may occasionally develop in patients treated with imipramine<sup>62-63</sup> and amitriptyline,<sup>64</sup> but such cases have not been studied fully. Reports of "neuritis" developing in patients receiving chlorprothixene and of acroparaesthesiae in those receiving phenelzine are difficult to evaluate.<sup>2-22</sup> Sensory neuropathy has been described in patients addicted to glutethimide but is not a complication of conventional use of the drug.<sup>65-66</sup>

#### ANTIRHEUMATIC DRUGS

Peripheral neuropathy occurs in 0.5-1% of patients with rheumatoid arthritis who have gold treatment.<sup>67-68</sup> Motor disorders are prominent and sensory symptoms may be inconspicuous. An abrupt onset and rapid progression in some cases, and associated facial diplegia and raised protein concentration in cerebrospinal fluid may mimic acute postinfective polyneuropathy. Few cases have been studied electrophysiologically or pathologically but axonal degeneration appears to be the main process.<sup>69</sup> Indomethacin has also been implicated in causing a neuropathy. A report on four patients with a sensorimotor neuropathy and two with sensory symptoms only suggested that the drug was responsible.<sup>70</sup> Electromyographic studies showed considerable slowing of motor conduction velocities in one case. Further studies are needed to determine the incidence of this complication.

Chloroquine may cause a mild sensorimotor neuropathy as well as a severe vacuolar myopathy.<sup>71-73</sup> Histological studies have shown both axonal degeneration and damage to Schwann cells.<sup>74</sup> Peripheral neuropathy has been reported in patients treated with penicillamine,<sup>75</sup> but less often than the myasthenic syndrome that develops in some patients treated with the drug. The mechanism of the neuropathy may be related to that caused by isoniazid, since penicillamine has an antipyridoxine effect.<sup>76</sup> Paraesthesiae and muscle weakness have been reported in some patients treated with phenylbutazone but are difficult to evaluate.<sup>77</sup>

#### ANTICONVULSANTS

Patients receiving long-term phenytoin treatment may develop a predominantly sensory polyneuropathy that is usually mild and rarely causes symptoms.<sup>78-79</sup> The incidence of this complication is uncertain, but signs of peripheral nerve disorders, such as depression of tendon reflexes, are found increasingly often in patients receiving prolonged

treatment.<sup>80</sup> Electrophysiological studies have shown that subclinical lesions are common and that the neuropathy is of the "dying-back" axonal degeneration type.<sup>80</sup> The drug also has acute, reversible effects, particularly on slow-conducting motor nerve fibres.<sup>81-82</sup> There is no convincing evidence to show that any of the other commonly used anticonvulsants cause peripheral nerve damage.

#### OTHER DRUGS

Disulfiram and citrated calcium carbimide,<sup>83</sup> which are used in treating alcoholism, may both cause peripheral neuropathy. Disulfiram causes a sensorimotor neuropathy with axonal degeneration and may also cause optic-nerve damage.<sup>84-87</sup> These effects may be due to its neurotoxic metabolite carbon disulphide.<sup>1</sup> A number of the sulphones may also cause neuropathy. Dapsone, which has been used in treating leprosy and several dermatological conditions, may cause a subacute, almost purely motor neuropathy, particularly after prolonged high-dose treatment.<sup>23-88-92</sup> Sulfoxone sodium, on the other hand, may cause a purely sensory neuropathy.<sup>93</sup>

#### Conclusions

Drugs used in treating various conditions may cause peripheral nerve damage. This may be clinically manifest, but in many instances is asymptomatic. We suggest that a careful neurological examination and studies of motor and sensory nerve conduction should be performed in patients who complain of paraesthesiae, pain, muscle cramps, weakness, or other abnormal sensations during drug treatment. Investigation of such patients and of patients without symptoms who are being treated with drugs that are known or suspected to be neurotoxic will allow the incidence of drug-induced peripheral nerve damage to be determined more precisely.

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*Is there now a method by which people on continuous corticosteroids—for instance, for Addison's disease—can be vaccinated against smallpox. Also, may they have injections against yellow fever?*

Apart from the recent Birmingham outbreak, no cases of smallpox have occurred anywhere in the world for nearly one year. It would therefore seem an unwarrantable risk to vaccinate any person taking continuous corticosteroids who has not been in actual contact with a smallpox case. In such circumstances vaccination could be carried out under cover of vaccinal globulin, which is distributed by the Public Health Laboratory Service and is administered by intramuscular injection in a dose that is dependent on body weight. For an average adult this is 0.5 g.

As yellow fever vaccine is also made up of live virus, theoretically it would seem prudent to avoid this vaccination in patients taking steroids.

*Will there be any harmful effect in the recipient if the blood from a donor who takes diuretic or iron tablets is used for transfusion?*

This is unlikely since patients requiring either iron or diuretic treatment should not at the same time be donating blood for trans-

fusion. Iron entering blood after oral treatment or even if given parenterally is unlikely to produce symptoms in a recipient. Only free iron is toxic. Iron absorbed by mouth would be bound to transferrin in plasma, and parenteral iron would remain as part of a larger organic complex. Similarly, the dose of diuretic in, say, 200 ml of plasma in a unit of blood will be too small to produce an effect in most recipients. An extensive review of untoward effects of transfusion does not record any reported examples of recipients affected by such preparations.<sup>1</sup>

<sup>1</sup> Mollison, P L, *Blood Transfusion in Clinical Medicine*, 5th edn, p 571. London, Blackwell, 1972.

*Is dried yeast of value in the treatment of multiple sclerosis?*

I have not only never used dried yeast to treat multiple sclerosis but I have never seen any results from a controlled study. I would doubt very much whether it had any useful part to play in treating the disease. One could only presume by its contents that it might be a form of immunotherapy such as giving *Corynebacterium parvum*. Until we know more about the aetiology of the disease I do not think I would recommend it.