Matters arising

although the latter is more potent and has a longer plasma half-life.³

Given their mild D2 blocking effect in addition to their calcium entry channel antagonist activity, it has been speculated that either or both of these properties could account for their unwanted extrapyramidal effects. To date we have studied over 100 patients showing that these complications are not uncommon and may lead to permanent disabilities as in patients with tardive dyskinesias.

To provide a deeper insight into their mechanisms of action we studied the effects of cinnarizine, flunarizine and nifedipine on the release of ³H dopamine from the rat caudate nucleus.

Male Wistar rats (150–200 g body weight) were decapitated and 1.0 mm coronal brain slices prepared. Slices corresponding to 1.5–2.5 mm rostrally to the anterior commissure were selected and a prism of caudate nucleus removed. Krebs solution⁴ equilibrated with 95% O₂ at 37°C was employed. Endogenous stores of dopamine were labelled in vitro by incubating the tissue for 30 min with 10 µCi of (2,5,6-³H) dopamine. Following incubation, tissue samples were transferred to an open cylinder with a piece of nylon mesh of 100 filaments per cm² placed at the bottom and forming a small basket. The whole device was placed in tube containing 3 ml of Krebs solution. Tissue slices were then exposed to eight 1 min, then to ten 5 min and again to ten 1 min washing periods. The tissue was stimulated by 1 min exposure to medium containing 20 mM K⁺. Stimulation was immediately followed by several 1 minute washings until the basal level of tritium overflow had been reached.

Radioactivity released by the tissue into the medium was monitored by counting aliquots of the bathing solution. Total radioactive overflow elicited by the stimuli was expressed as a percentage of the radioactivity contained in the tissue at the onset of stimulation.⁵ Statistical calculations were performed according to conventional procedures. Differences were considered significant if $p < 0.05$.

As shown in the table, the stimulation of

isolated caudate slices by one minute exposure to 20 mM K⁺ induced a tritium overflow of 3.9% of tissue content. Cinnarizine, flunarizine and nifedipine at doses able to block calcium channels lowered the total tritium overflow elicited by potassium.

Since dopamine release by potassium stimulation depends on a calcium mechanism, our findings suggest that Parkinsonism induced by these drugs is caused by their calcium antagonism.

Further research is needed to evaluate any possible effect on dopamine presynaptic receptors.

Clinical and experimental evidence indicates that patients on calcium antagonist drugs should be closely monitored to disclose early extrapyramidal side-effects.

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Chronic relapsing inflammatory polyneuropathy complicating sicca syndrome

Sir: Dr Gross has described a patient known to have the sicca syndrome, who subsequently developed chronic relapsing inflammatory polyneuropathy.¹ His report has prompted us to describe a patient with the same association but in whom the sicca syndrome was only diagnosed after the development of her inflammatory polyneuropathy.

In April 1987, a 38 year old West Indian housewife was admitted to another hospital with a two week history of progressive weakness in her arms and legs. There was no previous history of weakness or sensory disturbance. On examination she had mild right facial weakness, slight weakness of finger extension and abduction bilaterally, and moderate (grade 4) weakness distally in her legs. Her ankle reflexes were absent, and her plantar responses downgoing. Sensation was normal. Examination of the cerebrospinal fluid revealed an increase in protein concentration (0.8 g/l), but no cells. On the basis of these findings, a diagnosis of Guillain-Barré syndrome was made.

Following transfer to our hospital her weakness progressed until, eight weeks after the onset, she was areflexic and her limbs were paralysed. Ventilatory function, however, remained normal, and sensation was only mildly impaired. Bilateral thickening of the ulnar nerves was noted. Median nerve conduction velocity in the forearm was 7 m/s, and sural nerve biopsy showed loss of myelinated fibres and extensive subperineurial oedema, consistent with a diagnosis of chronic inflammatory polyneuropathy. The patient was started on prednisolone 60 mg daily, and there was a dramatic clinical response. She was able to stand without support within four weeks, and had minimal residual distal muscle weakness after 10 weeks of treatment. Median nerve motor conduction velocity increased to 12 m/s after 2 weeks of prednisolone, and was 21 m/s 4 weeks later. Further investigation revealed a strongly positive antinuclear factor without DNA-binding antibody. Anti-Ro and Anti-La

Table Fractional release of ³H. Dopamine from slices of caudate nucleus by exposure to 20 mM K⁺

	M	N	Tritium overflow as a percentage of tissue content
Control	—	15	3.9 ± 0.25
Flunarizine	1 × 10 ⁻⁶	10	2.7 ± 0.30*
Cinnarizine	2 × 10 ⁻⁷	6	2.4 ± 0.30*
Nifedipine	2 × 10 ⁻⁷	6	2.78 ± 0.30*

Means ± SEM; * $p < 0.05$.

antibodies were, however, present and a labial salivary gland biopsy showed numerous lymphoid aggregates consistent with a diagnosis of the sicca syndrome. The patient subsequently admitted to rather dry eyes, and had moderate caries. A Schirmer's test confirmed poor tear production.

This patient provides another example of an association between the sicca syndrome and inflammatory polyneuropathy, and lends further support to the hypothesis that, like the sicca syndrome and systemic lupus erythematosus with which they are also associated,² the inflammatory polyneuropathies have an auto-immune basis. Our patient developed a clinical neuropathy at a time when symptoms of the sicca syndrome were minimal. This finding illustrates the value of maintaining a high index of clinical suspicion, and of performing a serological auto-antibody screen in patients suspected of having an inflammatory polyneuropathy, but in whom there are no overt features of an associated disease. By this means, associated auto-immune disorders may be uncovered prior to the development of serious manifestations.

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to present with a focal painful epilepsy affecting one half of his scrotal sac.

We told him at the time he should have published it.

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Thymoma without myasthenia gravis: electrophysiological study after thymectomy

Sir: Martinez and Jimenez¹ reported a patient with thymoma without clinical evidence of myasthenia gravis, in whom single-fibre EMG (SF-EMG) studies demonstrated abnormal neuromuscular transmission. We had previously reported increased jitter on SF-EMG studies in three patients with thymoma, none of whom had clinical myasthenia gravis.² One patient had a malignant thymoma with red cell aplasia (table, Pt 1) but there was no weakness on examination. Acetylcholine receptor antibody (AChR-Ab) levels were normal and jitter was increased in the extensor digitorum communis (EDC) muscle. After receiving prednisone for treatment of anemia, he developed mild weakness of ocular and shoulder muscles which improved after edrophonium. SF-EMG studies performed on four occasions over a 6 week period demonstrated persistently abnormal neuromuscular transmission (table). He died of infection 2 months after his initial SF-EMG study.

In the second patient (table, Pt 2), a mediastinal mass was discovered on routine chest radiography and a benign, encapsulated thymoma was removed. The patient had no weakness on examination before surgery or six months later. He had had no symptoms of myasthenia gravis 10 years after surgery. AChR-Ab was normal. Jitter was increased in the EDC before surgery and miniature end-plate potential amplitude was decreased in an intercostal muscle biopsy obtained at thymectomy. Jitter was still increased in the EDC three weeks after surgery. Six months after surgery there was a decremental response to stapedial reflex fatigue testing, and this was partially reversed after the administration of edrophonium.³

The third patient (table, Pt 3) was a man who was found to have an anterior mediastinal mass on routine radiography at age 78 years. Retrospective review of previous radiographs revealed that the mass had been present for at least three years, with slowly progressive enlargement. There was no evidence of myasthenia gravis by history or on examination and serum AChR-Ab levels were normal. Jitter was increased in the EDC and there was a decremental response to stapedial reflex testing which did not change after administration of edrophonium.

The clinical manifestations of myasthenia gravis may be subtle and may not be detected unless carefully sought. These patients demonstrate that neuromuscular transmission may be abnormal in patients with thymoma even when clinical examination is normal. We feel that all patients with thymoma should be suspected of having myasthenia gravis and should be evaluated for this possibility before surgery. Since the history, physical examination, AChR-Ab level and repetitive nerve stimulation may all be normal in such patients, increased jitter may be the only evidence of abnormal

Serotal pain with testicular jerking: an unusual manifestation of epilepsy

Sir: I was interested in Dr Bhaskar's description of a man presenting with focal epilepsy in his scrotum.¹ I am afraid it has been described before, but only to the students and junior staff of Dr Michael Kremer. Dr Kremer is at present unable to relate the story himself, but he described a man whom he saw during the 1939-45 war who had a bullet wound to the brain. Bullets in those days created damage only between entry and exit wounds, and he survived the experience

Table Details of patients

		SF-EMG in EDC			AChR-Ab (nMoles) (< 0.1)	
Patient	Diagnosis (Normal value)	Date	Mean MCD (μ Sec) (< 34)	% Fibre pairs with		
				Blocking		Normal jitter (> 90%)
1.	Malignant thymoma, red cell aplasia	10/ 7/76	43	11%	83%	0.016
		10/28/76	41	5%	64%	
		11/ 1/76	38	0	95%	
		11/23/76	64	24%	68%	
2.	Benign thymoma	7/13/77	49	12%	76%	0
		7/21/77	46	9%	70%	
		8/ 8/77	44	0	77%	
3.	Probable thymoma	5/13/78	43	0	91%	0