Myasthenia gravis in the dog

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SUMMARY An account is given of four cases of myasthenia gravis in the dog. All animals showed fatigue, and considerably reduced tolerance to exercise. Recovery followed rest or treatment with neostigmine. Three animals, two of which are still alive, had dilatation of the oesophagus. The fourth eventually died from an aortic body tumour. The occurrence of myasthenia in the dog may be of value in elucidating the cause of the disease in man.

Recent case reports suggest that myasthenia occurs in the dog as well as man (Ormrod, 1961; Hall and Walker, 1962; Zacks, Shields and Steinberg, 1966). This paper describes four further cases in the dog which appear to fulfil the necessary criteria for such a diagnosis. The occurrence of myasthenia in the dog as well as in man is important in relation to possible common causative factors.

CASE 1

This 6-year-old alsatian bitch collapsed after a half mile walk on 20 October 1965 and had to be carried home. Thereafter it developed a progressively reduced exercise tolerance. Heart tonic tablets (Astra-Hewlett) containing glyceryl trinitrate, digitalis, strophanthin, and atropine were given, although no abnormality of heart sound was heard; vitamin E was also prescribed. The owner kept a 60-acre orchard and the dog was reported to be in the habit of eating unripe pears. The animal was sent to the School of Veterinary Medicine in Cambridge, with the possibility that the illness arose from the ingestion of toxic orchard spray.

The dog was admitted on 10 November 1965 (day 1) and was found to be in good general condition; its heart was normal. Stance was normal, but exercise tolerance considerably reduced. The animal would walk about 20 yards (18.3 m), and then drag back on its lead, refusing to walk. It took shorter and shorter strides with its forelegs, falling forwards on to its nose if forced to go on. Seconds before collapsing there appeared to be normal strength in the hind-legs and the gluteal muscles felt hard. Recovery followed a few minutes' rest, the dog picking itself up. There was no visible muscle wasting in the limbs, and resistance to passive movement felt normal. Triceps and patellar reflexes were equal and brisk. There was no sign of sensory or motor deficit ascribable to a lesion of the spinal cord. Ptosis was not present, and no abnormality of the cranial nerves was seen.

Haematological examination, blood glucose, serum calcium, sodium, and potassium were all within normal limits. An electrocardiograph was normal.

The animal's exercise tolerance remained limited to 20 yards (18 m) for the subsequent five days. On day 6, 0.65 mg atropine sulphate and 2.5 mg neostigmine methylsulphate were injected intramuscularly. Twenty minutes later, the animal walked and trotted 900 yards (823 m).

On day 16, at a time of clinical improvement, electro-myographic studies were carried out under general anaesthesia before and after edrophonium chloride (Tension: Roche). No convincing evidence of abnormal skeletal muscle 'fatigue' was seen. A muscle biopsy from the rectus abdominis was taken. The histological appearances were normal in sections stained with haematoxylin and eosin.

The alsatian was discharged on day 23 without it having been necessary to give further neostigmine. The owner kept a diary of the animal's progress, and found it necessary to give a total of four 15 mg tablets neostigmine bromide between days 29 and 33. Increased salivation for several days accompanied neostigmine medication. On day 68 the owner reported that there had been no weakness or distress for five weeks and that exercise had included two mile runs. A year later the animal had shown no relapse.

Nineteen months after the original illness, the animal went off its food, showing signs of respiratory distress. Anticholinesterase injections had no effect on the condition. There was pyrexia, abdominal breathing, and increased pulse rate, and pleural effusions were seen on radiographs of the chest. Transient improvement accompanied antibiotic treatment but a relapse occurred one week later and the animal was readmitted. Under general anaesthesia, 3 l. of fluid were removed from the chest,
with immediate relief of respiratory distress. However, two days later the owner decided to have the animal put down.

**POST-MORTEM EXAMINATION** The animal appeared well nourished with no enlargement of the superficial lymph glands or obvious neoplasm of mammary glands or tonsils. The thyroid was macroscopically normal; no abnormalities were seen in the abdominal cavity. Kidney, pancreas, and liver tissue samples were taken. A blood stained watery fluid was present in the pleural cavity and masses of hard grape-like substance were felt in the mediastinum, both anterior and posterior to the heart. A small similar lesion was present in a diaphragmatic lobe of the lung.

On histological examination abnormalities were confined to the tumour mass in the mediastinum, and to that in the lung. Both consisted of an aggregation of cells, separated by connective tissue trabeculae. Cell nuclei were of two types; small round nuclei with a moderate amount of chromatin, and larger vesicular oval nuclei (Fig. 1). The latter cells showed considerable palisading around the trabeculae which contained blood vessels whereas the dark nuclei were more widely scattered. In some areas both types were mixed at random; mitoses were not seen. The position of this tumour and its morphology indicated a heart base or carotid body tumour, described by Jubb and Kennedy (1963) as a cardio-aortic tumour. Further tissue samples and skeletal muscle sections showed no histological abnormality.

**CASE 2**

This male golden retriever was purchased as an 8-week-old puppy. It was vaccinated against distemper and appeared quite normal until 8 months of age. It then had periodic bouts of diarrhoea and vomiting sometimes with a slight temperature rise. When the dog was first seen at the age of 10 months, it showed symptoms of ocular congestion and was vomiting frothy mucus. Temperature was normal. Two days later it had difficulty in rising as though it had hind-leg cramp, and showed weakness after minimal exercise. The dog was treated with the same proprietary heart tablets as the previous case. However, these were stopped four days later because of the onset of haemorrhagic gastroenteritis, and antibiotics were given. During the next three weeks the animal collapsed for a brief period when excited or after walking 20 to 30 yards (18 to 24 m).

On first examination at the School of Veterinary Medicine, the animal was in good condition, but had difficulty in rising to its feet. The favoured posture was prone with limbs widely abducted (Fig. 2). When helped to its feet it could walk with unduly short steps, but collapsed after about 20 yards. Strides became shorter and shorter, the animal then refusing to move its forelegs. After a rest, the dog would get up and resume walking for a short distance only to collapse again. No muscle wasting was seen, muscle tone felt normal, and deep tendon reflexes were unremarkable. There was no ptosis or deviation of the eyes, but a passive blowing in and out of the nose was observed. The animal was comfortable on lying down. Fever was absent.

**FIG. 1.** Case 1. Photomicrograph of mediastinal tumour, showing the differentiation into two primary cell types. H and E × 1,000 (approx.).
of the cheeks accompanied respiration. Hip radiographs were normal. After a barium meal, the oesophagus was seen to be widely dilated, being 4 cm in diameter. The barium bolus took over 10 minutes to reach the stomach (Fig. 3).

Blood samples on the second day after admission showed a normal haematological picture. On several subsequent samplings, blood glucose and urea, serum sodium, potassium, calcium, magnesium, and phosphorus were found to be normal.

The day after admission, the dog was led from its kennel but soon collapsed. Neostigmine, 1 mg, with 1-3 mg atropine were injected intramuscularly. Four minutes later, the dog rose to its feet and after a further three minutes walked round wagging its tail. Improvement continued; it looked alert, the gait becoming springy. Three hours later it was still standing normally. The next day the dog had reverted to its collapsed condition, but recovery again followed neostigmine injection. During the subsequent 10 days, intermittent muscle 'fatigue' was seen, which was again relieved by either oral or intramuscular neostigmine. Even during drug-induced improvement, however, a barium swallow still showed the oesophagus to be dilated. On the eighth day after admission 15 mg neostigmine orally led to improvement, so that five hours later it walked half a mile. The oral treatment was repeated two days later with beneficial results lasting 24 hours. Satisfactory control of muscle fatigue was gained from the twelfth day after admission with oral neostigmine. However in the subsequent 10 days, the animal had repeated bouts of diarrhoea and vomiting, and excessive salivation only poorly controlled by atropine. The treatment was complicated by a purulent nasal discharge, probably caused by infection from vomitus lodged in the nasal cavities. The infection was controlled by tetracycline.

Electromyographic studies were performed under general anaesthesia. After acepromazine and atropine premedication, anaesthesia was induced with thiopentone sodium (Pentothal: Abbot) and after intubation, was maintained on nitrous oxide, oxygen, and methoxyflurane (Penthrane: Abbot). Induced action potentials were recorded from the right tibialis anterior muscle with a concentric needle electrode, the peroneal nerve in the region of the fibular head being stimulated via surface electrodes at a frequency of 17 c/s, with supramaximal pulses. This repetition rate was kept constant for one minute, and the cycle repeated after injection of edrophonium chloride 10 mg (Tensilon: Roche). Results are shown in Fig. 4. Induced action potentials in the tibialis anterior declined five-fold in voltage during the initial 30 seconds of nerve stimulation. After Tensilon, this decline was twofold. Motor conduction velocity in the right peroneal nerve was within normal limits at 52 m/sec.

The owner was supplied with tablets of neostigmine and atropine, but had difficulty in dose regulation. However, the animal appeared to make a spontaneous recovery, so that at the end of two months it was able to walk a mile.

Twenty-seven months after the original episode, the animal was reported in the best of health, with no evidence of relapse.

**CASE 3**

This animal was an 8½-month-old male labrador, referred to us from the same veterinary practice as case 2. The dog had been vaccinated against distemper and had been boarded out temporarily in kennels. Three days after its return, the owners noticed the animal had a hoarse-sounding bark and on the fifth day it started to vomit and had diarrhoea. Symptomatic treatment was given. A week after coming out of kennels the dog was seen to fall down, and over a period of time it became unable to walk at all. Treatment with neostigmine tablets ½ to 1 tablet twice daily and atropine was reported to result in improvement, but later this improvement was not maintained. Radiography showed a dilated oesophagus.

Seventeen days after the onset of the condition the
animal was admitted to the School of Veterinary Medicine. On examination, there was drooling of saliva, persistent bouts of vomiting (mostly of mucus), and minimal tolerance to exercise. When attempting to walk the pattern of behaviour was similar to that in cases 1 and 2: it would begin to take progressively shorter and shorter strides with the forelegs and eventually would lie down, refusing to move. The cheeks puffed in and out with each respiration and the animal looked dejected. During the onset of such an episode, the head was held stiffly, straight forward. After a period of rest, the dog tended to regain its strength, and this happened especially overnight. Levels of serum calcium, sodium, and potassium were within the normal range. Dilatation of the oesophagus was visible on radiographs, a contrast medium not being required.

Treatment consisted of intramuscular injections of 1.8 mg neostigmine and 0.65 mg atropine. Within five minutes the animal looked alert, wagged its tail, and four minutes later got up and walked about \( \frac{1}{2} \) mile, pulling strongly on the lead. The next day the animal was again in a collapsed state with slight respiratory distress and pyrexia (treated with penicillin). Subsequently the doses of neostigmine were reduced to 1.25 mg which controlled the muscle weakness, occasionally for up to two days. However, sometimes a second dose was required within 24 hours. Despite a good appetite, salivation and vomiting persisted. A total of nine doses of neostigmine was given, eight of which resulted in dramatic improvement of strength and ability to walk. Unfortunately, pneumonia developed which could not be controlled with antibiotic treatment and the animal became dehydrated. An intravenous drip of 1/5 N saline dextrose had little effect and in view of the animal's distress it was decided to put it down.

**POST-MORTEM EXAMINATION** The only macroscopic abnormalities observed were severe pneumonia and dilatation of the oesophagus throughout its length (Fig. 5). There was no evidence of neoplasia or of myopathy. A total of 36 tissues was subjected to histological examination. There was severe inflation type pneumonia, but the morphological appearance of the oesophageal muscle was normal in sections stained with haematoxylin and eosin. There were no significant abnormalities of the myocardium, skeletal muscle, central nervous system or sciatic nerve. The thymus was showing normal regressive changes. Thoracic lymph nodes showed some hyperplasia. All other organs appeared normal.

**CASE 4**

This 16-months-old male alsatian showed clinical signs similar to the previous cases. The presenting manifestations were those of obstruction of the oesophagus—namely, retching and gagging. A probang was passed into the stomach, with the animal under general anaesthesia, but the symptoms returned within three days. The dog was referred to the Cambridge Veterinary School on 21 March 1969, 11 days after the operation.

The owner remarked that during the previous few days the dog's exercise tolerance had become reduced and that after walking 20 yards (18 m), it sat down for a rest. Dilatation of the oesophagus was confirmed by radiography after a barium meal (although, in radiographs
The cardinal clinical features of human myasthenia are abnormal skeletal muscle fatigue after exertion and recovery with rest together with response to anticholinesterase drugs. The four animals described showed these features. Human myasthenia gravis is commonly punctuated by remissions and relapses; remissions were not seen in three of these four dogs. In man, the muscles of the upper limbs are slightly more frequently affected than those of the lower (Simpson, 1960); the forelimbs of the dogs seem to have been primarily affected. The dog's oesophagus contains a large proportion of striated muscle fibres (Trautmann and Fiebiger, 1952; Mann and Shorter, 1964) and this is probably significant in relation to the mega-oesophagus described. This dilatation, a prominent feature in three of our cases, and in that reported by Zacks *et al.* (1966) may thus well be a feature of myasthenia in this species. Hereditary dilatation of the oesophagus, with or without achalasia, has frequently been recorded in the dog (Clifford and Gyorkey, 1967), but concomitant signs of myasthenia apparently have not been observed.

A myasthenic syndrome in man has been described in association with carcinoma, polymyositis, and several other conditions. There was no histological evidence of primary muscle disease in any of the animals described. Prolonged good health, in the second, makes a carcinoma unlikely and, in the third, no signs of neoplasia were found at necropsy. The excellent response to neostigmine favours myasthenia gravis rather than a myasthenic syndrome. However, individual species show marked differences in response to anticholinesterases. The electromyographic features described, closely resemble those in the dog described by Zacks *et al.*, and mimic those seen in human myasthenia gravis rather than those in the myasthenic syndrome accompanying carcinoma. Evidence has been given to show that there was no concomitant hypoglycaemia or electrolyte imbalance which might have been responsible for similar clinical features.

The previously reported cases in the dog have several features in common. The cocker spaniel reported by Ormrod (1961) responded to neostigmine. Through the kindness of the late Mr. Ormrod, a ciné film of this animal was made available to us, and shows clearly the animal's reluctance to walk, taking the characteristic short strides, with improvement after anticholinesterase. The case in a chow bitch reported by Hall and Walker was somewhat

**FIG. 5.** Case 3. Post-mortem specimen showing severe dilatation of the oesophagus.

taken at a later date, this dilatation could be seen without contrast medium. When exercised the animal could run for about 50 to 60 yards (45 to 54 m), and then began to take short strides with the forelegs and gradually sank into a sitting position, refusing to go further. After a 30 second period of rest it was able to resume walking, only to collapse again after a much shorter period of exercise.

The animal was taken into the hospital and observed for the next three weeks. During this time the reduced tolerance to exercise was demonstrated many times, but rest overnight was usually followed by marked improvement. Haematological results showed no abnormality and blood glucose was within normal limits. When fatigued by exercise, there appeared to be a tremor of the forelegs and increased tone. The animal salivated and panted excessively and frequently vomited, especially overnight. A biopsy was taken from the intercostal muscles under general anaesthesia.

Injection of 1.75 mg neostigmine and 0.6 mg atropine intramuscularly effectively controlled the muscular weakness but the treatment had to be repeated every three to four days. The dog was discharged, but within four days the owner reported collapse after exercise. Neostigmine was given intramuscularly, but this treatment was replaced by 15 mg pyridostigmine bromide (Mestinon: Roche) given daily in tablet form. However, the animal 

could not be maintained satisfactorily on this preparation and so neostigmine therapy was reinstated, in tablet form, dosage being related to the severity of signs.

**DISCUSSION**

In man, myasthenia gravis has been observed in association with carcinoma, polymyositis, and several other conditions. There was no histological evidence of primary muscle disease in any of the animals described. Prolonged good health, in the second, makes a carcinoma unlikely and, in the third, no signs of neoplasia were found at necropsy. The excellent response to neostigmine favours myasthenia gravis rather than a myasthenic syndrome. However, individual species show marked differences in response to anticholinesterases. The electromyographic features described, closely resemble those in the dog described by Zacks *et al.*, and mimic those seen in human myasthenia gravis rather than those in the myasthenic syndrome accompanying carcinoma. Evidence has been given to show that there was no concomitant hypoglycaemia or electrolyte imbalance which might have been responsible for similar clinical features.

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different. The disease was unmasked by suxamethonium chloride before hysterectomy, the animal becoming quadriplegic for three days after operation. The only movement possible was a reflex closure of the eyelids when the eyes were threatened; the limbs flaccid, and deep reflexes depressed. Restoration of muscle power followed the giving of neostigmine. There was suggestive evidence of respiratory infection before the onset of myasthenia in Ormrod's case and this is a noteworthy feature commonly described before onset in man. Respiratory infection may precipitate the onset or exacerbation of the disease in man.

The third case (Zacks et al., 1966) was a male 8-month-old mongrel. This puppy was from a litter of seven, six of which died between 3 and 4 weeks of age from unknown causes. At 5 weeks of age the puppy was vomiting every other day about one hour after feeding. At 3 months the bark was abnormally high pitched, and the dog limped, and the hind-legs occasionally collapsed. There was difficulty in rising from the lying position and the animal fell down after taking a few steps. A mega-oesophagus was shown. Eventually the animal could stand only for micturition and defaecation. Good recovery followed the administration of anticholinesterases. Electron microscopy showed end-plate changes comparable to those in human myasthenia gravis. The dog recovered well following a Heller-Ranstedt operation to relieve the mega-oesophagus, and one year later, showed no recurrence of signs.

During the last 11 years, three other animals have been seen at the Cambridge Veterinary School showing signs suggestive of myasthenia. All were labradors (two being litter mates) but the diagnosis was not confirmed by neostigmine. One other condition in the dog is worthy of mention because of the similarity of clinical presentation. A 2-year-old Jack Russell terrier ate between 70 to 80 g thyroid. A fortnight later all limbs became progressively weak; sensation was unaffected. There was some atrophy of masseters and limb musculature, with no significant response to 0.5 mg neostigmine intramuscularly. This perhaps represented a thyrotoxic myopathy.

In the animals described here, anticholinesterases had a more prolonged action than is seen in man. After the first neostigmine injection, the first alsatian never relapsed to its previous state. In the golden retriever, relapses became less marked after successive treatment. This may indicate a natural recovery or, alternatively, a cumulative drug effect. The dog, as compared with man, shows a different sensitivity to neuromuscular blocking agents. Thus a basically similar pharmacological defect at end-plate level in dog and man shows slight differences in behaviour in the two species.

The first alsatian's habit of eating unripe pears has been reported, and the possibility arises of the dog's condition being provoked by ingestion of toxic insecticide. Insecticides of the organophosphorus group are potent cholinesterase inhibitors provoking acetylcholine accumulation. Neostigmine could only precipitate further deterioration. The owner had several other dogs that ate unripe pears, none of which showed signs of muscle weakness. Myasthenia has been reported three times in association with trimethadione (Booker, Chun, and Sanguino, 1968) and carbamates, sometimes used as insecticides, have a very similar chemical structure. However, other insecticides, those of natural origin such as pyrethrum, chlorinated hydrocarbons, and organophosphorus compounds do not show any chemical relation to the oxazolidine nucleus or side chains of trimethadione (3,5,5,—trimethyloxazolidine—2-4-dione).

The occurrence of the aortic body tumour in the first alsatian suggests some possible relationship to the muscle fatigue. However, symptoms provoked directly by the tumour were not seen for over one year after the onset of myasthenia, and review of other cases of aortic body tumour in the dog does not give any evidence of similar clinical signs. On the other hand, it is perhaps noteworthy that the aortic body in man develops from a mesodermal in-pouching of the third pharyngeal cleft, the thymus developing from the third and fourth clefts. The small round cell of the aortic body tumour bears a superficial resemblance to the thymocyte. If relevant to the cause of human myasthenia, reports of myoid fibres within the thymus (Strauss, Kemp, and Douglas 1966) may be paralleled by such inclusions within aortic body tissues.

While our cases do not mimic exactly all the clinical features of human myasthenia gravis, there seems to be sufficient evidence suggestive that a similar disease, and not solely a myasthenic syndrome, occurs in the dog. Identification of further cases and study of possible precipitating causes will be of considerable value in the search for a prime cause of this disease.

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Myasthenia gravis in the dog


