Ergothioneine is known to occur in some mammalian tissues, although earlier workers have reported its absence from brain[3], and Melville *et al.* have developed a highly specific and relatively sensitive method for its quantitative determination in tissue extracts[4]. We have applied the method to brain with the results, for the rabbit, given in Table 1.

Table 1. ERGOTHIONEINE CONTENT (IN μg/g) OF PARTS OF THE RABBIT CENTRAL NERVOUS SYSTEM

		Mean
Cerebellum	4·3, 4·6, 5·0, 5·5	4·9
Cerebral hemispheres	0·9, 1·2, 1·2, 1·3, 1·5	1·2
Optic nerves	21·0, 36·0, 29·0	28·7
Dorsal columns	< 1·0, < 1·0	< 1·0

A similar distribution has been found in other mammalian species: it corresponds to that found for the cerebellar factor. We have also found that ergothioneine has an action on the electrical activity of the cerebellum similar to that produced by the cerebellar factor. In sensitive preparations, 0·1 μg is sufficient to cause a marked increase in cerebellar activity. In their original experiments, Crossland and Mitchell were able to produce cerebellar excitation by the injection of an extract of 20 mg of rabbit cerebellum and this amount of tissue would have contained approximately 0·1 μg of ergothioneine (Table 1). Thus, the excitatory action of cerebellar extracts can be completely accounted for by their contained ergothioneine.

The actions of ergothioneine are probably not confined to the cerebellum. Preliminary experiments, in which ergothioneine has been applied to small groups of cells in the parietal cortex, using the technique developed by Mitchell[5], have indicated that it also excites some cortical cells. Outside the central nervous system it appears to be without detectable action.

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Guanethidine as an Anti-fibrillatory Agent

CATECHOLAMINES have for many years been known to produce cardiac arrhythmias[1]. The influence of acetylcholine or vagal stimulation on arrhythmias, especially of the atria, has overshadowed the influence of the sympathetic mediators[2]. Sharma[3] has reported that administration of epinephrine or norepinephrine simultaneously with acetylcholine enhanced the fibrillatory activity of the latter. Thus, it would seem appropriate to examine further the relationship between acetylcholine and catecholamines in their effect on heart rhythm.

The introduction of guanethidine, a drug which acts at adrenergic nerve terminals by preventing release of norepinephrine on nerve stimulation, suggested the possibility of studying the susceptibility to experimental atrial fibrillation in animals with deficient adrenergic mechanisms.

Healthy male dogs weighing about 10 kg were premedicated with morphine sulphate (2 mg/kg subcutaneously). In 30 min, the dogs were anæsthetized with sodium pentobarbital (35 mg/kg intraperitoneally). An endotracheal tube was inserted and the dogs immobilized in the prone position. They were given guanethidine at various doses and intervals before and during the experiment (Table 1). The method of Leveque was used for the production of atrial fibrillation[4]. With this procedure during control tests, all the experimental dogs demonstrated susceptibility to acetylcholine-induced atrial fibrillation at doses of 0·3 mg/kg or less. A total of 26 experiments were performed on 14 dogs.

Table 1. DOSE AND DURATION OF ACTION OF GUANETHIDINE AS AN ANTI-FIBRILLATORY AGENT

Experiment No.	Dose of guanethidine (mg/kg)	and route	Time delay before challenge (h)	Percentage protection versus acetylcholine-atrial fibrillation (0·5 mg/kg intravenous)	
121	1·0	Intravenous	1	0	(2)
125	1·0	,,	1	100	(3)
127	1·0	,,	1	100	(2)
141	1·0	,,	1	100	(3)
147	1·0	,,	1	100	(3)
73	1·0	Subcutaneous	4	0	(3)
65	2·5	,,	4	100	(2)
69	2·5	,,	4	100	(3)
77	2·5	,,	4	50	(4)
95	2·5	,,	18	0	(1)
109	2·5	,,	18	66	(3)
113	2·5	,,	18	0	(2)
129	2·5	,,	18	0	(2)
135	4·0	,,	18	0	(2)
39	10·0	,,	24	100	(2)
41	5·0	,,	24	100	(2)
43	5·0	,,	24	100	(2)
45	5·0	,,	24	100	(2)
137	4·0	,,	24	100	(3)
139	4·0	,,	24	100	(3)
79	2·5	,,	24	100	(2)
81	2·5	,,	24	0	(3)
97	2·5	,,	24	0	(2)
115	2·5	,,	24	0	(2)
117	2·5	,,	24	0	(2)
131	2·5	,,	24	0	(2)

The usual protective dose of guanethidine within 20 min appeared to be about 1·0 mg/kg although 0·5 was sometimes adequate. These low doses were protective for at least 1–2 h, but the effect did not usually last as long as 4 h. With increasing doses of guanethidine (up to 10·0 mg/kg), the anti-arrhythmic effect of this drug was prolonged up to 24 h.

Anti-fibrillatory drugs are in general related in structure to local anæsthetics and antihistaminic agents. The chemical structure of guanethidine shows similarities to this general structure, and Green has reported that guanethidine possesses a highly persistent local anæsthetic action[5].

Using the method described here for testing the anti-fibrillatory action of guanethidine, other drugs such as procaine, diphenhydramine, chlorpheniramine, tripellenamine and quinidine have been found previously to be protective[4].

It is interesting to note that the anti-arrhythmic action of guanethidine is apparent with doses that are smaller than those generally used for adrenergic blockade[6]. This might suggest that the anti-arrhythmic effect of this drug does not depend on changes in catecholamine stores. Investigations to elucidate the mechanism of action of guanethidine in preventing cardiac arrhythmias are now in progress.

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