centration of diltiazem injected into cockroaches deprived of water for 5 days resulted in significant (55%, $P < 0.05$; $N = 11$) mortality at 48 h post-treatment.

Discussion. Our observations that diltiazem inhibits spontaneous myogenicity in cockroach hindgut muscle and has inhibitory effects on glutamate responses extend the findings[4] on the crayfish neuromuscular preparation. In addition, diltiazem had varied effects against proctolin responses in this cockroach system. When tested on nerve preparations, diltiazem was found to have a biphasic effect on spontaneous neural activity, producing an initial excitation followed by inhibition of on-going activity. This inhibition or nerve block which was demonstrated to occur in the proctodeal nerve innervating the hindgut may account for the inhibition of neurally-evoked contractions seen with diltiazem perfusion of the hindgut preparation. The similarity between the effects of diltiazem and those of insecticides such as bioresmethrin (fig. 2B) on the nervous system led to an investigation of diltiazem toxicity in vivo. We found that diltiazem produced intoxication symptoms similar to those reported[11] by Van Asperen and Van Esch (paralysis, slow movements, animals lying on their backs) for injections of ethylenediamine tetraacetate (EDTA) solutions into cockroaches that reduced hemolymph free calcium to below detectable limits. Unlike EDTA, the calcium antagonist diltiazem produced longerlasting behavioral changes and significant mortality. Miller[9] reported that perfusion with low calcium concentrations duplicated the effect of pyrethroid poisoning on flight motor units in the housefly, and Clements and May[12] found that pyrethroids were able to inhibit glutamate- and neurally-induced contractions in locust muscle. The toxicity of injected diltiazem to cockroaches may be due to its effects on the nervous or neuroendocrine systems, with induced release of hormones perhaps contributing to toxicity[13]. The observed decrease of hemolymph levels in diltiazem poisoned cockroaches would be consistent with this idea since diuretic hormone is know to be released upon insecticide poisoning[14]. Interestingly, water-stressed cockroaches were more susceptible than unstressed controls to diltiazem poisoning.

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Examination of the fundus of the eye of renal hypertensive dogs

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Summary. Only 1 of 7 dogs with long-standing renovascular hypertension showed clear changes in the fundus. No distinct retinopathy was seen in the others. Ophthalmoscopy alone is thus of limited value in assessing the progress of benign hypertension in the dog.

In man, the following fundoscopic signs are of diagnostic and prognostic value in the management of hypertension: a) Sclerosis of the arterioles with segmental constrictions; b) Constriction of the venules at the intersections with the arterioles (Gunn's crossing sign); c) Oedema and exudation; d) Hemorrhages into the retinal tissue; e) Oedema of the optic disc.

As the dog is a frequently used experimental animal in cardiovascular research, the present investigation was made to see whether ophthalmoscopy shows comparable changes of the fundus in hypertensive dogs, and whether the severity of hypertension in the dog can be assessed in this way.

Methods. In a group of 14 mongrel dogs, comprising 7 with hypertension of 1–10 years' duration following bilateral constriction of the renal arteries[1] and 7 normotensive dogs of approximately the same age range (about 1 to over 10 years), the fundus was examined for evidence of vascular damage. Blood pressure was measured in a percutaneously punctured femoral artery at intervals of approximately 1 week. The fundus was photographed with a Kowa RC2 camera on Kodachrome film after administration of a mydriatic (tropicamide).

Results. a) Normotensive dogs. In 7 normotensive dogs between 1 and 13 years of age, the retina was found to differ from that of normotensive man in the following respects. The upper half of the retina appears in a luminous colour that varies from bright metallic blue to a golden yellow. This is due to a light-reflecting layer within the retina (tapetum lucidum) that improves night vision. The lower half of the retina has a dark pigmentation which, makes the vessels unrecognizable. The border-line of this pigmentation passes through or slightly below the optic disc. The myelination of the optic nerve fibers

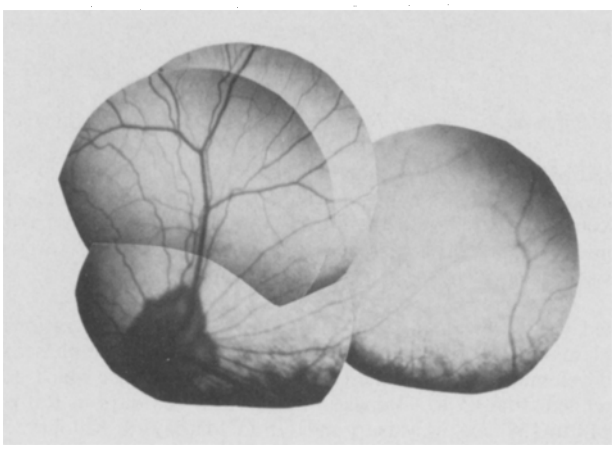

Figure 1. Normal fundus with optic disc below. The many thin arterioles leading away from the optic disc and 2 thick venules from above and from the right returning to it are visible. (Normotensive dog, age 5 years, blood pressure 160/85).

is often seen beyond the optic disc. In most of these cases the optic disc loses its round appearance. The ratio of the thickness of the arterioles to that of the venules is 1:3–4, as compared to 2:3 in man. The greater number of arterioles leading away from the optic disc compared to the number of venules returning to it might compensate for their smaller diameter. In man arterioles and venules form pairs with each other. Within the optic disc the venules often describe a circle. None of the dogs in this group showed changes that could be classified as pathological. The fundus of 1 of the normotensive dogs is illustrated (fig. 1).

b) Dogs with hypertension of less than 5 years' duration. The 4 animals in this group showed no gross changes in the fundus as compared to the group of normotensive dogs, although the average blood pressure (248/132) was distinctly elevated.

c) Dogs with hypertension of more than 5 years' duration. Of the 3 dogs in this group, only 1 (fig. 2) showed clearly pathological changes, consisting of relatively widespread fresh hemorrhages in the retina. In the same dog the caliber of a few arterioles appeared irregular. In another dog in this group, small, light spots were noted, spread over the pigmented area of the retina, the significance of these is unclear. No vascular damage to the retina was observed in the third animal in this group.

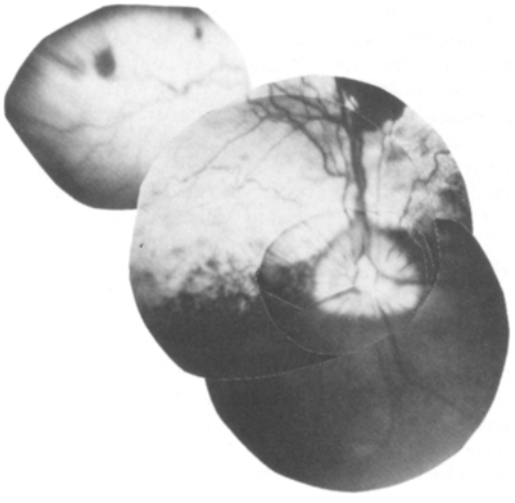

Figure 2. Fundus with wide-spread and fresh hemorrhages in the retina. (Hypertension of ca. 10 year's duration, blood pressure 245/135).

Arterial blood pressure in normotensive and renal hypertensive mongrel dogs

	Number	Systolic mm Hg	Diastolic mm Hg	Mean mm Hg
Normotensive	7	181 ± 6	95 ± 6	116 ± 4
Renal hypertensive	7	248 ± 3	132 ± 1	169 ± 3
				$\bar{x} \pm SE$

Discussion. In contrast to the ophthalmological changes seen in hypertensive patients, no signs of slow, progressive damage to the blood vessels of the retina were observed in dogs with marked and sustained hypertension. The only pathological finding consisted in acute bleeding. This low frequency of distinct changes is in contrast with previous reports. Ferrario et al.[2] describe retinal hemorrhages, papilloedema and even blindness in their dogs. These authors however, were dealing with malignant hypertension associated with impaired renal function, developing within a relatively short time after renal-artery constriction. Usually, such dogs do not survive for long. In 2 early publications (Keyes and Goldblatt, Ferrario et al.), retinal damage is described. Keyes and Goldblatt explored the retina of dogs with long-standing hypertension by ophthalmoscopy and histological methods[3]. They reported on a multitude of abnormal changes of the retina such as hemorrhages, oedema, detachment of the retina, tortuous and occluded blood vessels and papilloedema. There is a great discrepancy between these observations and our findings, hemorrhages in 1 dog with hypertension of 10 years' standing being the only distinct symptom we could detect. It is possible that the divergent results may be attributable to the higher blood pressures in the dogs examined by Keyes and Goldblatt. The possible role of other factors, such as the breed of the dogs, diet and environment, cannot be assessed, as no information on these aspects was given in their publication.

J.C. Fasciolo[4] explored the effect of arterial hypertension on the eyes of dogs within the first 15 days after partial occlusion of the renal arteries. He found ocular lesions in 8 out of 15 dogs, consisting of bleeding into the vitreous body or the anterior chamber and detachment of the retina. 3 dogs were further observed over a period of 12 months. These symptoms disappeared in time, but were replaced by chronic changes such as tortuosed arteries in 1 case and 'silver-wire arteries' and whitish-yellow spots. Even judging from the changes noted in this small lastmentioned group of dogs, it can be assumed that retinal injuries appear more frequently and earlier in long-standing hypertension than our results might suggest. One important difference is the average of the mean arterial blood pressures of Fasciolos' hypertensive dogs (over 200 mmHg compared to 169 mmHg in our animals).

Conclusion. The paucity of distinct changes and the absence of slow, progressive damage in our dogs, combined with the results of previous reports, suggest that ophthalmoscopical findings need to be supplemented by additional examinations in order to assess the progression and prognosis of hypertension in dogs, particularly when the blood pressure elevation is moderate and the malignant stage has not yet been reached.

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