ml min^{-1} kg^{-1} (n = 10) and that from the left femoral artery was 6.55 ± 1.15 ml min^{-1} kg^{-1} (n = 6). No deterioration in flow was seen over the 2–4-h-periods of the experiments.

Results and discussion. In several preliminary experiments, dose-response curves were compiled for the dilator effects of intra-arterial injections of DA, isoprenaline (ISO) and acetylcholine (ACh) on renal flow and for ISO and ACh on femoral flow. Both ISO and ACh produced increases of renal and femoral blood flows, together with falls in systemic blood pressure. DA increased renal blood flow and caused a slight fall in systemic blood pressure. In the femoral bed the net effect of DA was vasoconstriction, due to activation of α-adrenoceptors marking the weak dilator effect of DA-receptor activation[8]. For each agonist 2 doses were chosen from the concentration range corresponding to the steepest portion of the dose-response curve. The doses chosen were: ISO 0.05 and 0.5 μg, DA 5 and 20 μg, ACh 0.1 and 0.5 μg.

Propranolol is regarded as a selective antagonist at β-adrenoceptors[9], while ergometrine has been demonstrated recently to behave as a selective antagonist at canine vascular DA-receptors[5,8]. In the present experiments propranolol (0.1 mg/kg i.v.) profoundly reduced femoral dilator responses to ISO, but did not affect renal responses to DA. Ergometrine, in the dose previously reported to be effective in blocking DA receptors (0.5 mg i.a.)[5,8], reduced renal dilator responses to DA but did not affect femoral responses to ISO. Neither antagonist reduced either femoral or renal dilator responses to ACh (tables 1 and 2). These results indicated lack of non-specific depressant activity of propranolol and ergometrine on vascular reactivity and confirmed the absence of cross-antagonism of propranolol on DA-receptors or of ergometrine on β-adrenoceptors. In addition, the absence of any effect of propranolol on renal DA responses indicated that over the dose range used DA did not activate renal β-adrenoceptors. Lack of appreciable β-adrenoceptor stimulant activity has been reported previously for DA in the canine vascular system[6,7,10].

By contrast, both propranolol and ergometrine caused reduction of renal dilator responses to ISO (table 2). In view of their lack of cross-antagonism, this result suggests that the dilator effect of ISO in the canine kidney is mediated partly through activation of DA-receptors. Such non-specificity of action must therefore be considered when assessing the role of β-adrenoceptors in renal function.

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Hormonal manipulation of carrageenin-induced pyresis in rats[1]

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Summary. The intensity of the hyperthermic response in rats promoted by subplantar injection of 1 mg of carrageenin is directly related to the irritant properties of the type of carrageenin. The overall pyretic response is more dramatic in female rats than in male rats. Subtle changes in the time-course hyperthermic profiles are seen after hormonal modifications.

Since the introduction by Winter et al.[2] of the use of carrageenin as an experimental inflammatory agent, much research has been devoted to the characteristics and mechanisms underlying the acute inflammatory insult and testing pharmacologic agents which act to prevent the typical phlogistic reaction promoted by carrageenin. Well-defined studies on the biological properties of carrageenin may be found in a review by DiRosa[3]. In a recent study, Sobanski et al.[4] reported that subplantar injections of carrageenin in the rat produced not only the expected local phlogistic insult but also promoted a dramatic hyperthermic response which was monitored by rectal temperature. Our initial study was designed to determine a possible correlation between the phlogistic efficacy of various types of carrageenin as reported by Moore and Trottier[5] and the hyperthermic profile. A remarkable difference was noted in the hyperthermic response between male and female rats. Hormonal modulation of this response is reported here.

Materials and methods. Male Sprague-Dawley and female Wistar rats, 150–185 g, groups of 10 each, were used in these studies in an environment maintained at 25 ± 1 °C ambient temperature. Rectal temperature was determined using a Yellow Springs Instrument Company thermistor. Carrageenin samples were supplied by Marine Colloids, Rockland, Maine. Carrageenin suspensions (1%) were prepared in 0.9% saline and 0.1 ml volumes were injected s.c. in the plantar surface of the left hind paw. Control groups received 0.1 ml injections of 0.9% saline. Hormonal treatments consisted of: injections of testosterone propionate 2.5 mg per day s.c. × 2 days; estradiol valerate 2.5 mg s.c. × 2 injections on alternate days; and tests accomplished in ovariectomized groups of rats.

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Results. Table 1 illustrates the difference between groups of male and female rats which received subplantar injections of 1 mg of carrageenin. The time-course temperature profiles of untreated male and female rats repeatedly demonstrated an early-phase drop in body temperature in male groups which was not seen in female groups. The typical carrageenin-induced pyretic trends in male and female groups may be reversed by pretreatment with estradiol in males and testosterone or ovariectomy in females. It was also found that pretreatment of male rats with testosterone and female rats with estradiol resulted in a slightly depressed pyretic pattern as compared to the respective non-pretreated groups. Pyretic studies in the estradiol-pretreated females were carried out at the state of full estrus as determined by microscopic examination of vaginal washings according to the Doisy method[6]. Non-pretreated females were found to be in random stages of the estrus cycle on the day of carrageenin testing while vaginal smears from females pretreated with testosterone resembled a typical castrate or modified diestrus stage. Table 2 summarizes the over-all peak in temperature increase seen in the various experimental designs used in this study.

Table 1. Average increase per group in rectal temperature of rats promoted by subplantar injection of 1 mg carrageenin

Type of carrageenin	Peak rise in temperature (°C) from pre-injection value	
	Male	Female
Lambda	0.63	1.37
Viscarin	0.42	1.59
Gelcarin	0.23	0.57
Kappa	0.20	0.26
Iota	0.24	(–) 0.28

Peak temperature rise invariably occurred at 5–7 h post injection.

Table 2. Changes seen in the average peak temperature increase in groups of male and female rats under different experimental pretreatments

Experimental Design/pretreatment	Peak rise in temperature (°C) from pre-injection value
Females/(no pretreatment)	1.59
Males/(no pretreatment)	0.42
Females/testosterone	1.00
Males/estradiol	1.43
Ovariectomized	0.55
Males/testosterone	0.22
Females/estradiol	1.17

These values summarize the hormonally-modulated 'reversal' trend.

Discussion. This study demonstrates that subplantar injections of 1 mg carrageenin causes an increase in core body temperature which closely correlates with the inflammatory efficacy of the type of carrageenin used. The generalized pyretic response which reaches a maximum at 5–7 h after subplantar injection is more pronounced in intact females than it is in males. The time-course pattern of this hyperthermic response is in some manner dependent upon sex hormones. Select pretreatment schedules resulting in male/female hormonal modulation can alter the typical pyretic profiles such that the male and female pyretic patterns tend to 'reverse'. The relationship between the local inflammatory insult and the pyretic response is not entirely clear as it has been found by Sobanski et al.[4] that pretreatment with hydrocortisone reduces the local edematous response but does not prevent the onset or development of the hyperthermia. The biologic mechanisms whereby the female hyperthermic response surpasses that of the male remain to be elucidated. According to our data it is an interesting observation, however, that the endogenously regulated stage of estrus in the intact female does not seem to play a major role in that carrageen pyresis is a most dramatic and reliable event in random-cycle animals.

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Modification of clonazepam anticonvulsive activity by its association with other anti-epileptic drugs

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Summary. The modification of the anti-epileptic activity of clonazepam by other anticonvulsivants is studied. The results vary according to the drug and technique used. The usefulness of the 2 techniques employed is discussed.

Although the first derivatives of dibenzoazepines and dibenzodiazepines were not developed as anti-epileptic drugs but only as tranquilizers and hypnotics[1], they showed that chlorodiazepoxide, diazepam and nitrazepam reduce the thalamic epileptogenic excitability of the cat without reducing it in the cortex, while phenobarbital reduces both.Recently a new benzodiazepine, clonazepam, has been introduced. The difference with nitrozepam is an atom of chloride in position 2 of the benzenic ring. Swinyard and Castellion[2] have studied the experimental pharmacology and more recently Vuillon-Cacciuttolo and Issautier[3] have studied the electroencephalographic effects and found that it has barbiturate-like properties, with the exception of the hypnotic activity. Gastaut et al.[4], as well as Poire et al.[5], have undertaken trials in humans with clonazepam and have seen that the product is useful in all types of epilepsy in adults.

The various types of convulsive syndromes, especially major epilepsy, are generally treated with combinations of different anti-epileptic drugs[6]. This is the reason why we undertook the present experiment. Our aim has been to study the modification of clonazepam anticonvulsivant activity by other anti-epileptic drugs such as dipropylacetic acid, phenobarbital, mephobarbital, diphenyl-