ment produced in mice. These substances were investigated because it has been reported that they possess therapeutic activity against some types of microorganisms. The sulfones, promin, and promizole have been reported to be active against some of the acid-fast bacilli.[19-21] P-aminosalicylic acid has also been used to treat experimental tuberculosis.[22] P-aminobenzoic acid has been shown by Snyder *et al.*[23] to be effective in protecting mice infected with a type of epidemic typhus. Methylene blue was shown to be of value in increasing the survival time of mice infected with the etiological agent of Tsutsugamushi disease.[24] None of the above-mentioned agents cured any of the mice of the joint involvement produced by infection with *Streptobacillus moniliformis*.

Summary. A study of the chemotherapy of the arthritis produced in mice by inoculation with a virulent strain of *Streptobacillus moniliformis* was made. Three days after the animals developed joint involvement, therapy was initiated. Under the conditions studied streptomycin was the most effective agent in curing the joint involvement. Penicillin was also effective but to a lesser degree. No cures were obtained with promin, promizole, sulfathiazole, p-aminobenzoic acid, p-aminosalicylic acid, methylene blue, and two gold compounds (Myochrysine and Solgonal-B).

The authors wish to thank Dr. Carl E. Duffy for his advice and assistance during the course of this study.

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Influence of Diet, Sex, and Testosterone Propionate on the Toxicity of Monocrotaline in Rats.*

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Robertson[1] described the production of hepatic damage in horses fed *senecio*, an observation confirmed in other species.[2-4] Adams and Rogers[5] demonstrated that monocrotaline, an alkaloid derived from *crotalaria*, contained the same active retronecine alkanolamine present in *senecio* alkaloids. Harris, Anderson and Chen[6] observed that mice injected intravenously with monocrotaline died with pulmonary edema, ascites, hydrothorax, and thymic necrosis. There was central hepatic necrosis, hemorrhage and sinusoidal congestion, with little leukocytic reaction. Repeated administration of sublethal doses produced unimpressive hepatic lesions. In

* This work was supported by a grant from the U. S. Navy Department Office of Naval Research.

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TABLE I.
Survival Time of Rats Injected with Monocrotaline.

Diet	Strain	No.	Sex	Wt, g*	Survival time, days*
A	MacCollum	10	♂	264 (182-327)	18.4 (14-22)
		3	♀	180 (165-196)	22.0 (18-28)
	Total Group A	13			19.2
B	Harvard	7	♂	234 (221-249)	9.0 (6-16)
		4	♀	186 (168-203)	18.7 (8-28)
	MacCollum	11	♂	209 (193-237)	9.3 (6-24)
		7	♀	169 (158-192)	19.3 (8-31)
	Total Group B	29			12.9
C	MacCollum	4	♂	156 (139-179)	18.8 (15-22)
		6	♀	151 (133-167)	20.7 (19-25)
	Total Group C	10			19.9

* Avg; range in parentheses.

rats, monocrotaline prolonged the prothrombin time.[7]

In the course of studies on dietetic hepatic pathology in rats, the toxicity of monocrotaline was investigated.

Methods. Hooded rats of 2 strains were individually housed after weaning, allowed water as desired, and fed one of the following diets: Diet A: Purina Dog Chow as desired for 5 to 13 weeks. Diet B:[8] Casein, 4%; dried brewer's yeast, 16%; corn starch, 71%; cod liver oil, 1%; peanut oil, 5%; salt mixture,[9] 3%; plus thiamine chloride, 20 μg, riboflavin, 25 μg, pyridoxine, 20 μg, and calcium pantothenate, 120 μg per rat daily. Each rat received 11 g daily for 8 to 24 weeks, and then 8 g daily for 2 to 6 weeks. Diet C: Diet B, 8 g daily for 7 to 11 weeks. Each rat was then injected intraperitoneally every second day with 46 mg of 1% buffered monocrotaline† per kilo (half the intravenous LD_{50} dose). During this period, rats on Diet A were fed as desired and those on Diets B and C received 8 g daily.

Results. (1) *Pathologic Effects of Monocrotaline.* In brief, the injection of monocrotaline resulted in apathy, anorexia, weight loss, dark urine, epistaxes, purpuric paws and occasional terminal paraplegia. The gross pathologic findings included bloody peritoneal and pleural fluid, splenic enlargement, hemorrhagic livers, thymus and mesentery and, with longer survival, yellow stained tissues, firm red lungs, and right auricular dilatation. The histopathology included disruption of lymphoid follicles in the spleen, thymus and lymph nodes; in the liver, early, severe central hemorrhage was followed by central and midzonal necrosis without leucocytic reactions.

(2) *Effect of Diet and Sex on Survival Time of Rats Injected with Monocrotaline.* The effect of repeated injections of monocrotaline in rats is demonstrated in Table I and Fig. 1.

The data suggest that male rats of 2 strains fed a moderately low protein diet (Diet B) were more susceptible to monocrotaline than pair-fed females, or males and females fed a balanced diet (Diet A). The males were more susceptible only if they were fed sufficient diet so that they weighed more than pair-fed females. When the low protein diet was limited so that the sexes were of equal weight (Diet C) both sexes were equally resistant to monocrotaline. The rats, 10 to 14 weeks old at the time of the first injection, never showed gross evidence of sexual maturity. Half of them received injections of mixed methionine 60 mg and menadione, 5 mg daily without effect on survival time.

(3) *Effect of Testosterone Propionate on Survival Time of Rats Injected with Mono-*

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† Monocrotaline was obtained through the courtesy of Dr. Roger Adams and Dr. K. K. Chen.

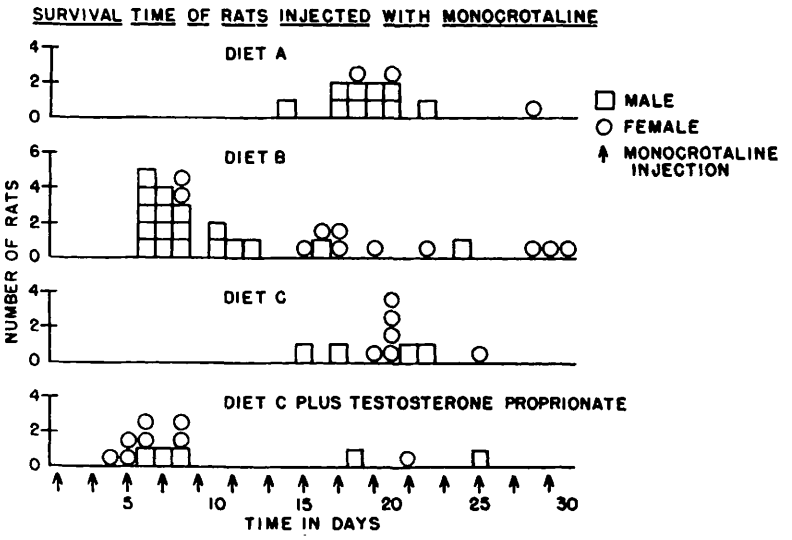

FIG. 1.
The survival time of rats injected intraperitoneally every second day with 46 mg per kilo of monocrotaline. The diets are described in the text.

TABLE II.
Influence of Testosterone Propionate upon Survival Time of Rats Injected with Monocrotaline.

Regime	No. of rats	Sex	Wt † g*	Survival time, days*
Control	4	♂	139 (128-146)	19.2 (14-25)
	9	♀	137 (115-161)	17.3 (13-20)
Testosterone propionate	5	♂	147 (128-167)	12.8 (6-25)
	8	♀	149 (133-160)	7.9 (4-21)

* Avg; range in parentheses.
† At time of first monocrotaline injection.

crotaline. Thirteen rats which had been fed Diet C for 6 to 8 weeks were injected subcutaneously with 2.5 mg of testosterone propionate in sesame oil (Rare Chemicals, Inc.) daily for 2 weeks, and then with monocrotaline as described, while the testosterone propionate was continued. At the same time 13 control rats of the same litters and on the same diets were injected with monocrotaline alone. Injection of testosterone propionate increased the susceptibility to monocrotaline of male and female rats fed low protein diets so that there was no difference in weight between the sexes. (Table II).

Discussion. The extensive hepatic destruction observed leaves little doubt of the importance of hepatic failure in the death of rats injected with monocrotaline. György and Shipley[10] observed that female rats fed low protein diets were more resistant than males to carbon tetrachloride, and that estrogenic substances, particularly in combination with methionine, were lipotropic.[11] The present study suggests that the presence of male hormones may accentuate the toxicity of monocrotaline. It is noteworthy that Blackman, Thomas, and Howard[12] have observed histologic changes in the livers of testosterone-treated dogs.

Summary. Male rats fed a moderately low protein diet were more susceptible than females, or than both sexes on a normal diet, to monocrotaline, an alkaloid causing hemor-

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rhagic hepatic damage and other lesions. Rats of both sexes on still more deficient diets were as resistant as normal rats. Testosterone propionate increased the toxicity of monocrotaline for both sexes on the more deficient diet. These experiments suggest that the greater susceptibility of male rats to monocrotaline may be due to the metabolic effects of male sex hormones.

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Total 17-Ketosteroid Excretion in Normal and Ovariectomized Rabbits.*

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The excretion levels of the 17-ketosteroids in urine have been studied extensively in humans. Comparisons of the levels of normal and castrate females vary; some workers have reported no significant difference after ovariectomy,[1,2] while others reported below normal levels, but with some overlapping.[3] Friedgood[4] observed a drop following castration, then a rise to normal. In a study on 2 Rhesus monkeys, Dorfman[5] reported a marked rise immediately after gonadectomy, returning to normal by the 22nd day in 1 animal while the other showed only a slight decrease during the first 5 days.

Because the environmental conditions of experimental animals are more easily controlled than those of human subjects, it was considered that the animal affords better opportunity for study of excretion levels under experimental conditions. This report deals with the normal and castrate levels of the total 17-ketosteroids in female rabbit urine.

Materials and Method. All animals were of the New Zealand strain, varying in age between 5 months and 2½ years. They were fed complete rabbit pellets with the exception of one change which is discussed later. The animals were housed in separate cages over screened trays which connected collecting flasks. When bilaterally ovariectomized, the animals were allowed at least a 17- to 21-day recovery period before collections were begun. Two animals had been ovariectomized one year previously.

The urine samples were collected for 48-hour periods over 5 ml hydrochloric acid, and were stored at 5°C until used. They were extracted according to the method of Pincus,[6] using a volume of 250 or 300 ml of urine. The crude neutral fractions were treated with Girard "T" in the cold.[6] Colorimetric assay was carried out in absolute alcohol[7] using a Beckman spectrophotometer, with a dehydroisoandrosterone standard.‡ The reaction color obtained with rabbit urine extracts is similar

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‡ Crystalline dehydroisoandrosterone was generously supplied by Ciba Pharmaceutical Products, Inc., and by Schering Corporation.