3. Urinary volume decreased in 3, increased in one and remained unchanged in one. Proteinuria averaging 0.61 mg/min. appeared during erect lordosis in these subjects.

Discussion. These results indicate that significant reduction in glomerular filtration rate and renal plasma flow, usually with an increased filtration fraction occurs in the erect lordotic posture in both normal individuals and those with orthostatic proteinuria. The changes in these two groups appear to be in the same range in the 10 subjects studied here. In the patients with orthostatic proteinuria the rate of protein excretion is not related to the degree of concurrent renal hemodynamic change on erect lordosis. These observations do not confirm any direct or causal relationship between alterations of renal hemodynamics in erect lordosis and the excretion of protein as suggested by others(1-4).

Despite a moderate hydropenic state with control urinary volumes averaging 1.20 cc/min, the anticipated antidiuresis of the erect posture was obtained in 7 of the 10 subjects.

Errors in clearance determinations inherent in studies by others(4,6), due to transition from induced water diuresis during recumbency to oliguria on standing were avoided in the present study. The hydropenic state assured initial low urine flow, preventing extreme change in urine volume on assumption of erect lordosis. Precise urine collections were obtained by urethral catheterization.

Conclusions. 1. Decreased glomerular filtration rate, renal plasma flow and urine volume of a comparable degree occur in erect lordosis in both normal man and subjects with orthostatic proteinuria. 2. The rate of protein excretion in orthostatic proteinuria is not related to the magnitude of hemodynamic change occurring with erect lordosis.

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Inhibition of Egg-White Edema by Proteolytic Enzymes. (21187)

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Trypsin has a marked anti-inflammatory action(1,2) and a thrombolytic effect(2), and catalyzes the conversion of profibrinolysin to fibrinolysin(3). The action of trypsin on inflammation occurs before its effect on thrombi (2). The mechanism of the anti-inflammatory effect is not clear but its rapidity appears to rule out activation of another enzyme. The following results indicate that the profibrinolysin-fibrinolysin reaction is not of primary importance in this action.

Methods. A number of proteolytic enzymes were tested to determine their effect on the inflammatory reaction. The egg-white edema reaction of Selye(4), as previously reported (1), was used throughout. This has been used as a standard testing method in our laboratory, although trypsin has been shown to reduce edemas(5) produced by other agents, such as yeast(6). The egg-white edema test was carried out on rats 60-90 g in weight. The enzymes tested were injected

TABLE I. Inhibition of Egg-White Edema by Proteolytic Enzymes.

Enzyme	Dose (mg/kg)	Wt difference, rt. leg-left leg (g)	Stand. dev.	Inhibition (%)
C*	—	1.50	.06	—
Trypsin	10	.80	.18	45
C	—	1.38	.08	—
Trypsin	2	.90	.05	35
C	—	1.48	.07	—
Trypsin	1	1.40	.18	0
C	—	1.68	.13	—
Streptokinase†	20	1.30	.12	20
C	—	1.68	.13	—
Streptokinase	10	1.40	.12	15
C	—	1.63	.23	—
Streptokinase	2	1.50	.27	0
C	—	1.90	.09	—
Chymotrypsin	2	.93	.20	50
C	—	1.90	.09	—
Chymotrypsin	1	1.83	.20	0
C	—	1.68	.13	—
Prolase B	10	1.13	.15	30
C	—	1.90	.09	—
Prolase B	2	1.51	.19	20
C	—	1.90	.09	—
Prolase B	1	1.75	.21	0
C	—	1.97	.17	—
Fibrinolysin‡	400	1.70	.12	15
C	—	1.93	.08	—
Fibrinolysin	200	1.93	.11	0

* Control.

† The commercial preparation "Varidase" was used.

‡ Obtained by courtesy of Dr. E. C. Loomis, Parke, Davis & Co.

subcutaneously on the ventral surface in 0.3 ml of aqueous solution and again 30 minutes later. Immediately after the second injection 0.1 ml of egg-white was injected subcutaneously into the dorsal side of the right hind paw and 0.1 ml of saline into the left. After 90 minutes the animals were killed with ether. Both hind legs were removed at the knee joint and weighed. The difference in weight between the saline-injected and egg-white injected legs was taken as an index of the extent of edema. A decrease in weight gain in the edematous leg over that of controls indicates inhibition of edema formation.

Results are presented in Table I. Doses of the various enzymes used are expressed by weight, since unitages are not interconvertible. Figures refer to total dose, given in 2 portions as noted above. The differences in weight between the right (egg-white injected) and left (saline-injected) legs are averages for 5 animals. Since the extent of edema obtained varied to some extent with the particular group of animals and with the source of egg-white each experimental group is compared to its own control run simultaneously.

The results show that all the enzymes tested were effective in inhibiting edema formation. However, the effects appear to bear no relationship to ability to catalyze the reaction profibrinolysin-fibrinolysin. Thus chymotrypsin, which does not catalyze this reaction (3), is of the same order of activity as trypsin; the effect of fibrinolysin even at the very high doses used is of doubtful significance. The fact that an effect was shown by several different enzymes suggested that it might be a function of simple proteolytic activity. In order to investigate this partially and completely inactivated samples of trypsin were tested for their effect on egg-white edema. Proteolytic activity was determined by the method of Anson (7).

For standard crystalline trypsin, at 100% activity, the minimum effective dose was 2 mg/kg (see Table I). For trypsin at 50% activity, the MED was 4 mg/kg; completely inactivated trypsin showed no anti-inflammatory effect in doses up to 10 mg/kg. This shows definitely that the anti-inflammatory effect of trypsin is a function of its proteolytic activity. Although the profibrinolysin-fibrinolysin system is not precluded, these results show that anti-inflammatory effects are manifested by enzymes which do not catalyze this reaction. Moreover fibrinolysin itself has a comparatively weak action. The anti-inflammatory effect of proteolytic enzymes may bear some relation to the work of Spector (8) which indicates that polypeptides are involved in the production of inflammation.

Summary. In an attempt to elucidate the mechanism of the anti-inflammatory action of trypsin a number of proteolytic enzymes were tested against edema produced in rats by local injection of egg-white. Enzymes tested included chymotrypsin, streptokinase, prolase B and fibrinolysin. All were active in suppressing the experimental edema and all showed the same order of activity as trypsin except fibrinolysin, which was appreciably weaker.

In the case of trypsin the anti-inflammatory action was found to be a function of proteolytic activity; it varied with the activity of partially and completely inactivated samples of this enzyme.

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Use of Artificial Kidney for Removal of Barbiturates in Dogs.* (21188)

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Barbiturates are responsible for one-third of all fatalities resulting from exposure to toxic substances and for 30 to 40% of all hospital admissions due to ingestion of poisons(1,2). Prompt recognition of barbiturate intoxication coupled with effective therapy can be life saving. With the advent of ultraviolet spectrophotometric methods(3-7), much of the difficulty previously involved in the laboratory determination of barbiturates in biological fluids has been eliminated. In 1 to 2 hours, one can not only determine the barbiturate level in biological material but also, in many cases, the specific barbiturate that was ingested. Thus, prompt chemical confirmation of barbiturate intoxication is now possible.

The removal of toxic substances, such as salicylates and bromides, by the use of hemodialysis has already been demonstrated(8, 9). There are relatively few available data to indicate the feasibility of this technic for the removal of barbiturates, although treatment of several patients has been reported (10). In a preliminary report from this laboratory hemodialysis was shown to be of limited value in pentobarbital intoxication in dogs(11).

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Methods. A series of dogs was given a known dose of a specific barbiturate intravenously or intraperitoneally. Using Goldbaum's technic(3) blood or plasma barbiturate levels were determined at 2-hour intervals, until 12 hours elapsed, then at 6-hour intervals until the animal recovered or died. Interspersed with the "control" dogs, another group of dogs, referred to hereafter as "dialyzed" dogs, were given the same dose of barbiturate and treated by hemodialysis 1 to 3 hours later. A Skeggs-Leonards(12) artificial kidney with a

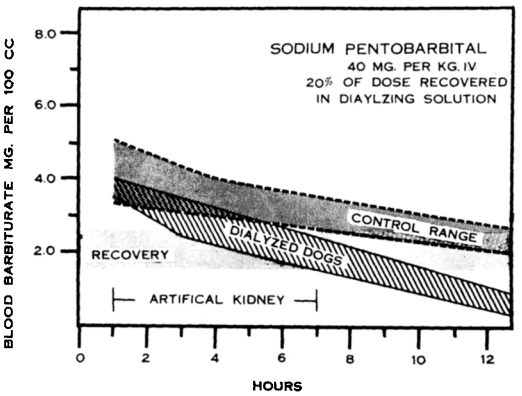

FIG. 1. Blood pentobarbital levels as a function of time. Control and dialyzed ranges represent all the values between maximum and minimum blood pentobarbital levels for all dogs in the respective groups. Recovery range represents spread of blood pentobarbital levels obtained when animals first began to move.