ministration of cortisone may first result in a decrease of adrenocorticotropin secretion and a consequent removal of the inhibiting effect of this hypophyseal fraction on thyrotropin secretion. Subsequently the direct inhibiting effect of cortisone on thyrotropin secretion comes into play.

The results of the studies reported from this laboratory would suggest that the phenomenon of stress is characterized by a discharge of adrenocorticotropin and thyrotropin from the adenohypophysis, and that the subsequent secretion of thyrotropin is inhibited both by adrenocorticotropin and by certain fractions of the adrenal cortex.

Summary. The administration of adrenocorticotropin results in a decreased collection of I_{131} by the thyroid gland of both the intact and adrenalectomized rat, suggesting that adrenocorticotropin inhibits the adenohypophyseal secretion of thyrotropin.

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Pathological Changes in Rabbits from Repeated Intravenous Injections of Periston (Polyvinyl Pyrrolidone) or Dextran. (18626)

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The paucity of information in the American literature on the histopathological changes resulting from intravenous injections of periston (polyvinyl pyrrolidone), a blood plasma substitute, prompts the presentation of this report. In addition to clinical experience with periston, the histological changes in animals and in a few infants have been reported(1). Dextran, another plasma substitute, has been stated to cause no morphological changes in animals injected repeatedly(2).

We have administered to rabbits, over a 2 month period, 16 intravenous injections of 10 cc/kg of 6% dextran* in distilled water, or 3½% peristont in distilled water, or 10% dextrose in physiological saline solution (Table I). The ear veins were used, and each injection took about 10 minutes. No systemic effects, even of a minor nature, were observed during the experimental period. One male rabbit on dextrose died from dysentery 2 weeks after the start of the experiment; this death could not be attributed to dextrose. No blood counts or blood chemical studies were done on these animals.

1. Schoen, H., *Klin. Woch.*, 1949, v27, 463.
2. Thorsén, G., *Lancet*, 1949, v256, 132.

* Pharmacia "Macrodex", lot 153.

† General Aniline and Film Corp., lot 1687-202.

Gross pathology. In the animals given dextran there were no gross abnormalities that could be attributed to that agent. In the group given periston, the spleen showed definite slight enlargement (Table I). Except for the increase in size, there was no difference in the appearance of the spleen. The periston animals had an average of 0.70 g of spleen per kg animal, while the values for dextran and dextrose were 0.40 and 0.41 respectively. In the dextrose group, there was possibly slight renal enlargement (Table I). With respect to "spontaneous" lesions and parasitism, the rabbits on the whole were very free from these conditions.

Microscopic pathology. The one outstanding lesion of the entire experiment was a foam cell storage phenomenon in the periston animals; this was seen best in the spleen, and in lesser degree but sometimes prominently in several other structures. In the *spleen* the foam cells made up an estimated ⅓ to ½ of the volume of the organ. The foam cells had reticular type nuclei, basophilic and markedly vacuolated cytoplasm, and were from 15 to 100 (usually 20-25) μ in diameter, the larger ones generally being multinucleated. The foam cells and especially their vacuoles contained periston or some near derivative, the

TABLE I. Weights of Rabbits and of Various Organs.

Rabbit No.	Sex	Substance injected	Wt of rabbit, kg		Wt in g		
			Start	Finish	Liver	Kidneys	Spleen
1	M	6% Dextran	2.52	3.32	101	16.0	1.27
2	M		2.50	3.50	114	14.3	1.60
3	M		2.92	3.22	130	19.1	1.32
4	M		2.63	3.08	114	14.5	0.90
5	F		2.52	3.12	100	16.0	1.48
6	F		2.75	3.50	101	16.5	1.43
		Avg	2.64	3.29	110	16.1	1.33
7	M	3½% Periston	2.38	2.88	96	16.5	2.70
8	M		2.80	3.32	95	18.5	2.45
9	M		2.58	3.40	125	21.0	1.50
10	M		2.36	3.10	110	16.0	1.60
11	F		2.63	3.08	111	15.5	2.55
12	F		2.26	3.02	97	20.0	2.47
		Avg	2.50	3.13	106	17.9	2.21
14	M	10% Dextrose	3.25	3.72	128	23.0	1.05
15	M		2.83	3.02	73	16.3	0.97
16	F		2.83	3.47	129	24.3	1.35
17	M		3.44	3.60	118	23.5	1.80
18	F		2.62	3.15	93	16.5	1.75
		Avg	2.99	3.39	108	20.7	1.38

identification of which will be discussed further on. Some of the larger foam cells also contained a few leucocyte fragments. Among other organs than the spleen, the foam cell storage phenomenon in the periston animals was seen in moderate degree in the *lymph nodes, bone marrow,* and *adrenal medulla,* and in lesser degree in the *liver, lungs,* and *thymus.* These structures were otherwise unaffected in all groups of animals. It will be observed that the distribution of the foam cells is essentially that of the reticulo-endothelial system, or that involved in intravital staining. *Periston,* apart from the foam cell storage phenomenon, caused slight testicular atrophy, slight epithelial swelling and rarefaction in the distal portions of the proximal convoluted renal tubules and in the choroid plexus of the brain, and (by inspection) a slight "shift to the left" of leucocytes in the bone marrow, with a possible slight reduction in the myeloid/erythroid ratio. *Dextran* caused very slight testicular atrophy, the same leucocyte shift, and a slight reduction in the M/E ratio. *Dextrose* caused no changes. In *all groups,* heart, gall bladder, pancreas, small intestine, thyroid, prostate, seminal vesicle, uterus, ovary, urinary bladder, and voluntary muscle showed no effect of treatment.

Special stains. Periston is highly soluble in water and alcohol, so that paraffin or even frozen sections contained little of the stored material in the foam cells. The stored material was well demonstrated, however, in the foam cells in unfixed imprints. About 2 minutes after a few drops of Gram's iodine solution and a coverglass were applied, the foam cells showed numerous deep brown small and large globular masses, while other structures (bone marrow) were relatively unstained. Glycogen as the material taking up iodine was ruled out by the total lack of staining of any material within the vacuoles in alcohol-fixed tissue to which a periodic acid-Schiff stain was applied, and with which liver glycogen was deeply stained. Other negative tests on the foam cells in addition to that for glycogen were those for doubly refractive material, for fat, and for metachromasia, using appropriately fixed material and standard technics. In frozen sections of formalin fixed material, the foam cells (at least if fixation had been fairly recent) still contained a fair amount of iodophilic material, but paraffin sections of similar material gave almost no reaction, as was also true with alcohol fixed material. However, in paraffin sections of Zenker fixed material the foam cells took iodine somewhat selectively.

Discussion. Our results are presented be-

cause of current interest in these substances, and because little if any report of animal studies has appeared in the American literature. A report of results with an older type of dextran has appeared(3). The Swedish dextran has been stated to cause no lesions in animals(2), and we found very little effect. The lesions observed by us following periston injections are of the type and order of magnitude already reported. The foam cell accumulations caused by periston are said to disappear after several weeks(4). Periston in our material did not cause the arterial alterations, in addition to foam cell storage, noted with some previously tried plasma substitutes(5).

Summary. Seventeen rabbits were each given 16 intravenous injections of 10 cc/kg of one or another plasma substitute over a 2-month period. The solutions used were 6% dextran in distilled water, 3½% periston (polyvinylpyrrolidone) in distilled water, and 10% dextrose in physiological saline solution. No effects of treatment on behavior or body weight were noted. At autopsy, there was slight enlargement of the spleen, on the average about 70%, in the periston animals. Kidney and liver weights were not affected except for a possible slight increase in kidney weight with dextrose. On detailed microscopic examination, the one outstanding lesion was a foam cell storage of periston or some near derivative. Certain other and minor lesions were caused by periston and dextran, and none by dextrose.

3. Goldenberg, M., Crane, R. D., and Popper, H., *Am. J. Clin. Path.*, 1947, v17, 939.

4. Barfuss, F., and Eichler, O., *Arch. f. exp. Path. u. Pharm.*, 1949, v206, 346.

5. Hueper, W., *Arch. Path.*, 1942, v33, 267.

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Chronic Toxicity of a Purified Extract of *Veratrum viride*.* (18627)

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Examination of available literature failed to reveal long term chronic toxicity studies on *Veratrum viride* or its extracts. Perdue *et al.* (1) reported a short term (8 week) paired feeding study using powdered root of *Veratrum viride* in Long-Evans rats. They concluded severe toxicity was not encountered until about 3% was included in the diet, and that the toxicity could be related to inanition.

Since clinical use of veratrum preparations in the treatment of hypertension requires the ingestion of the drug over a period of years it seemed desirable to observe the effects of feeding this drug over 12 months to rats and dogs. The use of the purified extract of *Veratrum viride* (Veriloid†) for the present study offered the first opportunity to feed mixtures of hypotensive potency known to be uniform(2).

Method. Rats: Albino rats (Wistar Strain), 30 days of age, weighing 64.6 ± 12.9 g were divided into 5 groups of 30 (15 females and 15 males) animals. The rats were fed a modified Steenbock's diet(3) and water *ad libitum*. The drug was incorporated in the diet of the first 4 groups while the fifth group served as the control. In 3 of the experimental groups (low, medium and high dose) the drug concentration was gradually increased over a 4- to 10-week period until 7.3, 11 and 19 mg % had been attained in the respective diets. The fourth group (intensive group) were, from the beginning, given diet

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1. Perdue, Adaline S., Bell, Francis, Stearnes, W. R., Hitchcock, Philip and Teague, R. S., *J. Am. Pharm. A.* (Scient. Ed.) 1950, v39, 91.

† Trademark of Riker Laboratories, Los Angeles, Calif. A purified reproducible hypotensive extract of *Veratrum viride* assayed in the dog.

2. Maison, G. L. and Stutzman, J. W., *Arch. internat. de pharmacodyn. et de therap.*, 1951, v85, 357.

3. Steenbock, H., *Science*, 1923, v58, 449.