TABLE III.
Antipyridoxine Activity of Desoxypyridoxine as Measured in 9-day Curative Assays with Chicks Receiving a Pyridoxine-Deficient Diet.

Oral supplement*		Survival of chicks, alive/total	Wt gain per chick, g	Loss in pyridoxine activity, μg	Ratio of inhibition, analog : vit.
Pyridoxine hydrochloride, μg	Desoxypyridoxine hydrochloride μg				
16	32	2/7	15.5	11	3:1
16	16	6/7	20.5	7	2:1
16	8	7/7	18.8	8	1:1
4	—	6/7	14.5		
8	—	6/7	19.5		
16	—	7/7	28.0		
16	16	5/7	23.4	3	5:1
24	16	7/7	30.2	8	2:1
35	50	6/7	21.4	23	2:1
—	—	3/7	7.2		
8	—	6/7	16.1		
12	—	7/7	19.6		
16	—	6/6	32.0		

* Amt given per chick on each of 4 successive alternate days.

activity of one part of pyridoxine (Table III).

Previously reported B vitamin antagonists are relatively much weaker antivitamins. For example, only one molecule of thiamine was required to overcome the antithiamine activity of 40 molecules of pyrithiamine in mice,[4] and a similar ratio was found between riboflavin and isoriboflavin rats.[5] It therefore appears that desoxypyridoxine is the most potent of the B vitamin inhibitors as yet discovered.

Summary. Bioassays with chicks have shown that 2,4-dimethyl-3-hydroxy-5-hydroxymethylpyridine is a very potent inhibitor of pyridoxine. Under the conditions of these experiments, two molecules of the inhibitor were sufficient to offset the vitamin activity of one molecule of pyridoxine. This ratio was found to hold for suboptimal and optimal amounts of pyridoxine given to pyridoxine-deficient chicks.

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Adrenolytic and Sympatholytic Actions of Priscol (benzyl-imidazoline)

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Experimentally employed adrenolytic agents include ergotoxine, ergotamine tartrate, yohimbine hydrochloride, various esters of yohimbic acid and the Fourneau Compounds, F933 and F899. In some respects these agents seem to be sympatholytic as well as adrenolytic. It has been reported[1] that Priscol exerts this dual effect.

The adrenolytic properties of priscol have

[1] Meier, R., and Meyer, R. Th., *Schweiz. Med. Wschr.*, 1941, **71**, 1266.

been corroborated[2] in respect to alterations in blood pressure in urethanized cats and it seemed desirable to test the drug's sympatholytic properties. This was done not only in relation to general circulatory responses but also in reference to other functions under control of the sympathetic nervous system.

Methods. Adult cats of both sexes were prepared under urethane or DIAL-With-Urethane for carotid cannulation to record arterial pressure by the Anderson[3] manometer. The vagi were severed. The drugs employed, injected intravenously on a basis of milligrams per kilogram, included: epinephrine HCl, priscol HCl, atropine SO_4, ephedrine SO_4 and pituitrin.

In some of our experiments shielded electrodes were attached to either or both sets of splanchnic nerves and the adrenal glands were extirpated or ligated.

The secretory function of the submaxillary gland, as influenced by injection of drugs or faradization of the ipsilateral chorda tympani and cervical sympathetic nerves, was determined after cannulation of Wharton's duct by measuring the salivary flow on a horizontally placed manometer. Pupillary responses were observed and measured directly.

Results. Twenty-four experiments were performed and the most significant findings were:

1. Priscol, 5 mg, without exception, produced a drop in blood pressure of 50% or more; pressure gradually returned to normal within an hour or two. Adrenolysis invariably prevailed for vasoconstrictor neural components since an "epinephrine reversal" was consistently obtained during the hypotension caused by priscol. Sympatholysis of vasoconstrictor components, however, did not prevail with this dose of priscol, although it could be produced readily with a 10 to 15 mg dosage (Fig. 1).

2. Priscol was both adrenolytic and sympatholytic in respect to sympathetic control of salivary secretion. The response to epinephrine was usually diminished or lost before the response to faradization of the cervical sympathetic nerve had been completely abolished. The required dose of priscol varied from 1 to 20 mg for adrenolysis and from 5 to 20 mg for sympatholysis. No consistent correlation could be established between the sympathetic inhibition of salivation and the loss of vasoconstrictor control of blood pressure effected with equal doses of priscol. These dose ranges were greater than those suggested in our preliminary report.[2]

3. Atropine, 0.2 mg, did not interfere with the antisympathetic actions of priscol and neither did pituitrin (Fig. 1).

4. Priscol also inhibited the salivary response that normally is invoked by ephedrine.

5. Priscol initiated salivation, but in only 2 cases and only after high dosage, 12 to 30 mg.

6. The pupil responded well after priscol by dilating in response to administration of epinephrine or to faradization of the cervical sympathetic nerve. In some of our experiments, priscol caused constriction of the pupil; this occurred with a dose of 3 to 5 mg.

Discussion. With these experiments it has been confirmed that priscol possesses the dual antisympathetic action of other known sympathetic-blocking agents, namely, the adrenolytic and sympatholytic actions which characterize such substances. This is most obvious in the responses of the vascular system after priscol: epinephrine reversal precedes nullification of splanchnic vasoconstriction to faradization.

In order to rule out the severe hypotension induced by priscol as the cause of splanchnic nerve paralysis, the pressure was raised by pituitrin (Fig. 1); during this elevation of tension adrenolysis and sympatholysis still prevailed.

Atropine was employed for two reasons: (1) to determine the effect of the loss of cholinergic control of salivation in relation to priscol's antisympathetic actions and, (2) to rule out vagal stimulation of the gut by faradization since vagal components may run through splanchnic nerves, in which case con-

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[3] Anderson, F. F., *J. Lab. and Clin. Med.*, 1941, **26**, 1520.

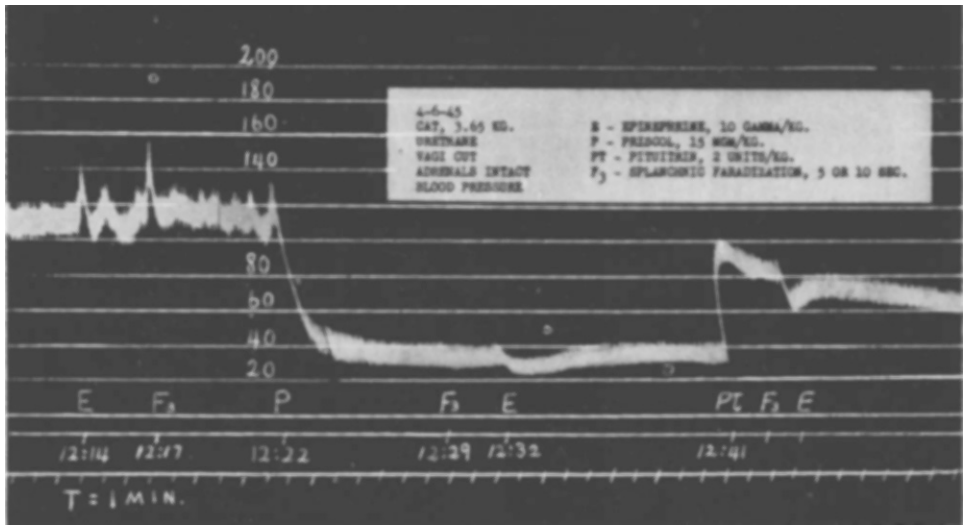

FIG. 1.

traction of the intestinal musculature under vagal influence might account in part for elevating blood pressure; this could be erroneously interpreted as resulting from splanchnic vasoconstriction. The blood pressure, however, was elevated during splanchnic faradization in the atropinized animal and, therefore, such pressure elevation must have been due only to vasoconstrictor stimulation.

In reference to pressure variations, it seemed to make little difference whether the adrenal glands were intact. In almost every instance faradization of the splanchnic nerves resulted in vasoconstriction, as evidenced by hypertension. Rarely, after priscol paralysis of vasoconstrictors did faradization of the splanchnic nerves produce a slight, transient drop in pressure. This may have been due to splanchnic stimulation of the adrenal gland, resulting in the production of epinephrine, which, in the presence of adequate amounts of priscol, would produce a typical "epinephrine reversal." Such a drop in pressure could also have attended the added relaxation of the intestines resulting from faradization of splanchnic inhibitory fibers to the musculature of the intestine. Since this slight pressure drop occurred also in the absence of the adrenals, it was undoubtedly due chiefly to intestinal relaxation attending stimulation of sympathetic inhibitory fibers in the splanchnic nerves.

The fact that adrenergic salivation, as produced by epinephrine, ephedrine, or cervical sympathetic faradization is depressed by priscol indicates that this drug is a general sympathetic depressant, more potent in respect to some functions than to others. Militating against this generalization, however, is the persistence of mydriatic responses to epinephrine and faradization after priscol in the doses employed. Whether higher doses would nullify pupillary responses is problematic; in any event, sufficient evidence is presented to indicate that priscol varies in its adrenolytic and sympatholytic potencies in the cat in respect to different sympathetic functions. Such variance might prevail in other species, including man.

The antisympathetic properties of priscol suggest the use of this drug in Raynaud's disease as recently reported by Lindquist[4] and in other conditions of sympathetic predominance, for instance in hypertension of neurogenic origin as postulated by Heymans[5] where it should act not symptomatically as a depressor but etiologically as an antagonist to excessive adrenergic stimuli.

[4] Lindquist, T., *Acta Med. Scand.*, 1943, **113**, 83, abstracted in *J. A. M. A.*, 1945, **127**, 618.

[5] Heymans, C., and Bouckaert, J. J., *C. R. Soc. Biol.*, 1931, **106**, 471.

Summary and Conclusions. Priscol (benzyl-imidazoline) is sympatholytic as well as adrenolytic in reference to the sympathetic neural control of blood pressure and salivation. Adrenolysis invariably precedes sympatholysis with any dose that is adequate to produce both effects. These pharmacodynamic actions persist during priscol hypotension, pituitrin hypertension and in the presence of atropine.

Although sympathetic depression of salivation and vasoconstriction can be produced with variable doses of priscol, up to 15 mg, they are without sympatholytic or adrenolytic effect upon the cervical sympathetic neural components controlling mydriasis, indicating that a differential sympathetic depression characterizes this antisympathetic agent.

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Observations on Cobalt Polycythemia. I. Studies on the Peripheral Blood of Rats.*

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The experimental production of polycythemia by the administration of cobalt has been demonstrated by a number of investigators since its discovery by the Waltners.[1-9] This effect of cobalt has also received application in the treatment of various anemias in both animals and human beings.[10,11]

The mechanism of action of cobalt remains obscure. Several theories have been advanced, however none has been fully agreed upon as a satisfactory explanation by those who have investigated the problem. During the course of some experiments relating to factors influencing various types of anemia, certain new observations concerning the action of cobalt came to our attention.

Male rats of the Sprague-Dawley strain, 4 to 5 months of age, weighing approximately 200 g were given cobaltous chloride, $CoCl_2 \cdot 6(H_2O)$, 0.4% solution, by subcutaneous injection in the back and shoulder region 6 times weekly throughout a period of 8 months. Nine animals, divided into 3 groups of 3 each, received 2.5 mg, 5.0 mg and 10.0 mg per kg of body weight respectively. Other animals of the same age, weight, and sex served as controls. The rats were fed dog chow only (Friskies, Albers Milling Co.)

Erythrocyte, reticulocyte, leucocyte and differential counts as well as hemoglobin determinations were made every 2 weeks. Care was taken to draw only the amount of blood necessary for the determinations, the puncture wound in the tail vein being promptly closed after each bleeding. A Haden-Hausser hemoglobinometer (Improved Clinical Model) was used for the hemoglobin determinations.

At the end of 32 weeks, blood volumes

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