THE EFFECTS OF PRISCOL (2-BENZYL-4, 5-IMIDAZOLINE HCl) ON PERIPHERAL VASCULAR DISEASES, HYPERTENSION AND CIRCULATION IN PATIENTS*†‡

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ADRENOLYTIC AND SYMPATHOLYTIC DRUGS have been known and investigated for many years. By blocking action of adrenalin or blocking effector sympathetic pathways these drugs might aid study, diagnosis, or treatment of paraganglioma, pheochromocytoma, peripheral vascular diseases or hypertension. Currently, three drugs are receiving clinical trial. Etamon (tetraethylammonium chloride or bromide) is essentially a ganglionic blocking agent but is not adrenolytic (Acheson and Moe[1]). By blocking ganglia other than those of the sympathetic nervous system, it may produce abnormal function of the eye, bladder, and gastro-intestinal tract. Dibenamine (dibenzyl beta-chlorethyl amine hydrochloride), Nickerson and Goodman,[2] and Priscol (2-benzyl-4, 5-imidazoline HCl) more specifically block sympathetic motor pathways acting apparently at their termination in smooth muscle. These drugs are adrenolytic. Dibenamine has a more prolonged action than Priscol but must be administered intravenously. Effects of Priscol last three to eight hours and the drug may be given orally, intramuscularly, or intravenously.

Hartman and Isler[3] first reported Priscol in 1939, stating that of a group of phenyl-substituted alkyl imidazolines examined, it produced greatest depression of blood pressure. The same year Meier and Mueller[4] reported that Priscol dilates vessels of mucosa and skin but that vasodilatation is more pronounced in extremities. Also, they demonstrated that Priscol and adrenalin together produced lowering of blood pressure. Meyer[5] later clarified and proved adrenolytic properties of Priscol. Chess and Yonkman[6] demonstrated that although Priscol was adrenolytic as judged by reduction of blood pressure, it was not adrenolytic or sympatholytic with respect to all cervical sympathetic functions studied. Yonkman et al[7] also demonstrated stimulation of ileum of dogs, a cholinergic response blocked by atropine. Ahlquist and Woodbury[8] observed that Priscol inhibits pressor and constrictor effects of several sympathomimetic drugs but has little action on their depressor or dilator effects. Ahlquist, Huggins, and Woodbury[9] subsequently report that Priscol acts primarily as a sympathomimetic agent producing peripheral vasodilatation, cardiac stimulation, coronary vasodilatation, increased cardiac out-

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put and some inhibition of the gastro-intestinal musculature. They describe occasional elevations of blood pressure and believe that changes of pressure depend upon a balance between peripheral vasodilatation and increased cardiac output. In animals they describe histamine-like properties and also acetylcholine-like effects. They conclude that Priscol is an effective sympathomimetic anti-pressor and adrenolytic agent. Further experimental studies will not be reviewed except to state that Hatt[10] using the Starling heart-lung preparation found that damaging doses of Priscol were one hundred times greater than those used to reduce blood pressure. Our own experiments[11-14] confirm adrenolytic and sympatholytic properties in dogs and man. Current experiments also show that neurogenic hypertension in dogs is occasionally reduced but rarely brought to normal even by large doses. Pituitrin will increase blood pressure after reduction with Priscol.

There are many reports of clinical use of Priscol in the European and South American literature. Only a few will be quoted. Zothe[15] demonstrated decrease of circulation time to the toe. Siedek[16] calculated cardiac output in 14 patients and usually found moderate increase. Lipross[17] reported increase of finger and toe temperatures in patients after Priscol[18] and abolition of skin temperature gradient of arms and legs. De Gennaro and Bertazzi[19] demonstrated increase of gastric motility and hastening of gastric evacuation. Luft[20] compared effects of several drugs upon skin temperature of healthy individuals, with effects in two patients with thromboangiitis obliterans and one with arteriosclerosis. He found that Priscol caused greatest increase of temperature. Other observers have reported using Priscol for frostbite, Shroder;[21] Raynaud's disease, Kohlmayer;[22] diabetic arteriosclerosis, Schietz;[23] and hyptertension, Singer.[24] More than 40 additional authors have reported varying degrees of success using Priscol for a wide variety of circulatory disorders. Frequently relief from pain associated with vascular disease has been described.

This report deals with results of clinical investigation during the last two years. No patient has been treated longer than nine months, but many are continuing treatment.[25, 26] Material will be presented in three sections: (1) clinical observations during testing or treatment of peripheral vascular disease; (2) testing or treatment of hypertension; and (3) general effects of Priscol on circulation.

Experimental and early clinical evidence indicated advisability of using larger dosage schedules than previously reported. Except for time of onset and maximum response little difference in total effect has been observed between administration by oral, intramuscular, or intravenous routes. Amounts of Priscol administeerd to some patients with peripheral vascular disease described in section 2 now seem excessive and amounts administered in hypertension, section 3, may be too low. To facilitate interpretation schedules now believed approximately correct will be presented. Twenty-five to 75 mg. intravenously or intramuscularly apparently adequately tests patients with peripheral vascular disease and 25 to 50 mg. orally every three or four hours

apparently maintains maximum therapeutic effects. Tests for patients with hypertension have been based upon intravenous injection of 50 mg. followed an hour later by another 50 mg. and usually followed after another hour by injection of 100 mg. Dose schedule for treatment of hypertension varies but is usually gradually increased to a maximum of 75 mg. every two hours. Since lowering of blood pressure has not constantly followed test or treatment, effective dose range or potential value for treatment of hypertension has not been established.

Complications or side effects will be presented in advance of clinical reports. Twenty-five to 75 mg. as an initial dose produces a sensation of crawling in the skin, a feeling of warmth of face and ears, a sensation as if hair were rising, a chilly sensation with development of "goose flesh," and occasionally apprehension. Patients may also describe increase of heart rate. Occasionally nausea occurs and, rarely, vomiting. Continued treatment, using 25 to 75 mg. every two to four hours is usually associated with fewer or milder symptoms. Test doses as high as 200 mg. per patient, accentuate the above symptoms and also produce disability from postural hypotension. Occasionally such doses cause audible peristalsis, dizziness or a far-away feeling, sweating, congestion of the nose, or headache.

EFFECT OF PRISCOL IN PERIPHERAL VASCULAR DISEASE AND RELATED CIRCULATORY DISORDERS

Forty-three patients with vascular disease or related disorders of extremities received Priscol. Six had Raynaud's disease; 15, arteriosclerotic obstructive vascular disease; six, thromboangiitis obliterans; three, popliteal aneurysms; seven, extremity pain loosely grouped as causalgia; four, phlebitis; and two, acute ischemia. Observations varied from simple testing of the effects of single doses to study of results of prolonged treatment.

Results of administration of similar doses of Priscol orally, intramuscularly, or intravenously were compared in ten of these patients with peripheral vascular disease. Intravenous injection produced generalized vasodilatation within two minutes. Intramuscular administration produced vasodilatation within ten minutes and oral within half an hour. Although delayed flushing after oral administration was less intense than that produced by intravenous or intramuscular administration, its lasting or total effect was usually equivalent.

1. *Raynaud's disease.* Six patients gave histories and presented clinical criteria compatible with diagnosis of Raynaud's disease. Phasic color changes of digits of hands and feet occurred spontaneously and were produced by exposure to cold or by emotional stress. Blanching, rubor, and cyanosis occurred in each patient, often simultaneously in separate areas of fingers or toes. Rubor or cyanosis was produced by placing hand or foot in ice water and blanching by exposing the patient to refrigerator temperatures. Not included are any patients complaining solely of reddening or pallor of the hands on exposure.

Two patients had undergone sympathectomy of the upper extremities.

One had symptoms seven years. Two years after onset of symptoms, a preganglionic sympathectomy was performed on the left and a ganglionectomy on the right. Some scleroderma had developed before sympathectomy and ulcers had appeared. Improvement of either hand lasted less than a year and trophic changes were progressing. Because of persistent pain and ulceration this patient was tested and treated with Priscol. Two hundred milligrams intramuscularly increased temperature of the fingers and toes four degrees centigrade. The patient could not tolerate immersion of the hands in ice water before Priscol. Afterward he kept his hands submerged five minutes without pain or blanching. Pain was relieved for eight hours. He was sent home taking 25 mg. every four hours. During seven months symptoms have been relieved, although not completely, and treatment is continuing.

The second patient had bilateral upper dorsal ganglionectomy one year after onset of symptoms. A year after operation discoloration and pain recurred. When treated, trophic changes of skin or ulcer had not developed. Three intramuscular injections of 75 mg. of Priscol were given at half hour intervals. The first dose effected warming of hands and relief of pain. Second and third injections effected no further change. Oral administration of 25 mg. at six hour intervals in the hospital and at home maintained improvement. After five weeks the patient reported that his hands were better in color and more comfortable but that the drug made him nervous.

A third patient had treatment by Priscol before and after sympathectomy. Symptoms had been present two years. All four extremities were involved but the feet troubled most. Periods of ischemia and pain lasting several days recurred. When first seen an episode had persisted two weeks and produced sharp burning pain and paresthesia of the right foot. This foot was cold and pale but developed rubor when dependent. Dorsal pedis and posterior tibial arteries were fully palpable and oscillometric pulsations in the mid-calf were normal. There was an area of anasthesia about the toe. The left leg and both hands evidence phasic color changes characteristic of Raynaud's disease. On admission the temperature of the right toe was 22.4° C. and of the left, 28.8° C. After hospitalization for two hours without treatment temperatures were respectively 23 and 32. Temperature of skin near the umbilicus varied between 36.3 and 37. Forty milligrams of Priscol were given intramuscularly. Twenty-five minutes later temperature of the right toe was 30.3 and of the left, 36. Fifteen minutes later temperatures were respectively 34.1 and 36. Three hours after Priscol temperatures were right toe, 36.5; left, 36.4, and umbilicus, 37. Twenty-five to 50 mg. were then given intramuscularly every two hours for five days. Toe temperatures were maintained always over 33. Finger temperatures were similarly increased and maintained. Placing of hands or feet in ice water was well tolerated. Treatment was omitted for one day and relapse occurred. Since chronic treatment by Priscol was not being employed when this patient was tested, bilateral lumbar sympathetic ganglionectomies were performed and three months later bilateral upper dorsal

sympathetic ganglionectomies. Increase of temperature of digits similar to that effected by Priscol followed operation. During the next nine months symptoms were relieved but as cold weather returned moderately severe phasic color changes reappeared. Priscol, 50 mg. four times a day, was then given orally at home with definite benefit.

Because of these encouraging results the next three patients encountered were treated by Priscol and have not since required sympathectomy. Their clinical course, tests and treatment were similar and will be described together. All were women. Duration of symptoms was respectively eighteen months, thirty months, and two years. One patient had undergone a right upper dorsal ganglionectomy followed by recurrence. After a year symptoms were again equal in the two hands even though the right remained warmer. In all three patients symptoms were progressive but advanced trophic changes of skin or ulceration had not developed. Fifty mg. of Priscol orally, intravenously, or intramuscularly increased temperature of the digits in each limb of each patient with the exception of one right arm previously sympathectomized. The increase was to within three degrees of abdominal skin temperature in the extremities of two patients and within one degree in the third. The temperature of the sympathectomized limb, however, did not increase. Before Priscol patients would hold their hands in ice water 36 to 89 seconds with sever pain. This was followed by intense rubor and cyanosis and rarely areas of ischemia. Within 15 to 30 minutes after administration of Priscol these patients held their hands in ice water three to five minutes comfortably and stated they could continue indefinitely. Following removal of the hands from ice water after Priscol some redness developed but little, if any, cyanosis and no ischemia. The single oral dose required to effect this protection was 25 mg. in one patient, 50 in another, and 75 mg. in the third. Exposure of two patients in a large refrigerator at temperatures of 40° C. induced phasic color changes, predominantly pallor, before Priscol. After the drug, exposure for fifteen minutes produced no change. Protection against pain and discoloration of the one sympathectomized arm equaled that of the opposite arm.

These three patients have been taking Priscol at home six to nine months. Dose schedules have been varied to determine amount necessary to afford protection from attacks. Each patient has required a minimum of 50 mg. morning, before lunch, mid-afternoon, and evening in cool weather, decreasing dosage on warm days and only occasionally increasing it above this amount. Although slight discoloration of fingers occurs once in a while, particularly before the morning dose, the patients are enthusiastic about results. There has as yet been no evidence of development of toxicity or tolerance and side effects have been considered of minor importance.

2. *Arteriosclerotic obstructive disease of legs.* Fifteen patients varying in age from 47 to 77 had gradually progressive symptoms of incompetent arterial circulation through the legs and feet and clinical critera warranting a diagnosis of arteriosclerosis. Results will be described in three groups: patients tested

and treated by Priscol, tested and treated by sympathectomy, or tested only.

Five patients were tested and then treated by Priscol. Two men, aged 71 and 77, had ulcers about both ankles and feet. They also had angina on exertion. Fifty milligram test doses produced moderate increase of temperature of the feet, and during treatment in the hospital and at home ulcers healed. Since conservative and other medical treatments were also employed, evaluation is difficult but Priscol seemed to assist management.

A third patient, male, age 55, had had one leg amputated. Circulation in the remaning leg was minimum and resting pain had developed. Fifty milligrams of Priscol intramuscularly increased great toe temperature 2 degrees. After an hour another 50 mg. increased it an additional 2 degrees, or to within three degrees of temperature of the skin near the umbilicus. Treatment at home using Priscol and no other medication effected moderate relief of symptoms.

A fourth patient, male, age 55, gave a history of exertional and substernal discomfort and mild episodes of nocturnal dyspnea, during five years. Intermittent claudication developed during the last eleven months. Fifty milligrams intravenously warmed both feet and markedly improved circulation as judged by postural tests. Fifty milligrams were then prescribed for use at home orally four times a day. Although Priscol made this patent nervous, he now states that the feet no longer ache and no longer are fatigued or cramped within two blocks. He can now walk seven or eight blocks before claudication. On two occasions after evening drinking, he has been awakened at night by transient shortness of breath and cough. This patient also states that mental faculties are much clearer when taking the drug.

The fifth patient was a 73-year-old woman, who gave a history suggesting a myocardial infarction seventeen years ago. She since has had recurring attacks of angina. Electrocardiograms were consistent with coronary insufficiency. Slightest exertion produced substernal pain. One year before admission an ulcer of the left big toe developed. It was treated conservatively without healing. During the month before admission pain of the left toe and foot steadily increased. The patient was then hospitalized and treated by intermittent venous occlusion and papaverine hydrochloride for four days with no relief from pain. During the next four days two lumbar sympathetic blocks were employed, each effecting partial relief from pain. In spite of the bad cardiac status, Priscol was tested. Fifty milligrams given intramuscularly and repeated after 45 minutes effected moderate relief of pain but there was no increase of temperature of the involved toe. Two days later lumbar paravertebral block was repeated with a similar result. During the next two weeks 50 mg. of Priscol were given intramuscularly or by mouth every two hours. Intermittent venous occlusion was continued. Pain gradually ceased with the ulcer slowly decreasing in size. The patient was then discharged with instructions to take 25 or 50 mg. at home every three hours when awake. Acute substernal pain, which had been occurring every few weeks before

treatment, recurred once, one month later. Two months after leaving the hospital a fatal myocardial infarction occurred. Comfort in the foot had persisted and at the time of death the ulcer had healed.

Five additional patients with arteriosclerotic vascular obstructive disease were tested using Priscol but not treated by the drug. Three developed increase of temperature of all extremities except the most seriously involved. Because of severe pain, or local gangrene, amputation was advised in each. The fourth had less advanced arterial obstruction. One hundred milligrams of Priscol increased temperature of the left toe 1.7 degrees, and temperature of the right toe, 6.2 degrees. Sympathectomy was advised on the left, to be followed by sympathectomy on the right. The fifth patient, age 41, was tested on two occasions. His right great toe had been amputated a year previously and the wound had healed. When first seen the right little toe was gangrenous. Fifty milligrams of Priscol orally increased temperature of the left great toe until it equaled that at the umbilicus but increased warmth of the right middle toe only to a temperature 3.2 degrees below that of abdominal skin. A right lumbar sympathectomy was then performed, and the remaining toes were amputated. Pain was not relieved and gangrene developed about the amputation site. Twenty-one days after operation pain had increased and the patient was obviously deteriorating. Priscol was again employed as a test. Temperature of the gangrenous foot did not increase after 50 mg. orally. Two and one-half hours later 75 mg. orally again did not increase temperature or relieve pain. An hour later necrotic tissue about the wound was dissected free and removed. Following this the patient screamed with pain even though morphine was given. During the next six hours pre-cordial pain developed and radiated to the left arm. Electrocardiogram the next day revealed abnormal tracings consistent with a posterior infarct. Nine days later the right leg was amputated. Two and six days after amputation electrocardiograms revealed left axis deviation only. Ten days after amputation a cerebral vascular accident occurred with right hemaplegia. Death occurred eight days later. At no time was this patient treated chronically with Priscol.

The remaining five patients of the arteriosclerotic group had tests before or after lumbar sympathetic ganglionectomy. Three were tested before and a week or more after operation. Fifty to 75 mg. of Priscol warmed the most involved foot and toe of two of the patients to a temperature equivalent to that effected by sympathectomy. A week after operation 50 to 75 mg. warmed the other extremities of each patient but did not increase temperature of the sympathectomized limb. The least involved normally innervated limb of the third patient behaved differently. Preoperatively 50 mg. intramuscularly increased temperature of both feet to that at the umbilicus. The day after left lumbar ganglionectomy the temperature of the left foot equaled that at the umbilicus but the right toe temperature was 4 degrees colder than before operation. Temperature of this cool right foot increased only one degree after 100 mg. of Priscol intravenously. Temperature of the sympathectomized leg did not

increase. Two days later the right foot was warmer and responded to 50 mg. of Priscol intravenously by equaling abdominal temperature. Repetition of the same test five days later again similarly increased temperature of the right foot without increasing that of the sympathectomized limb.

Two patients were tested at longer intervals after sympathectomy. One was examined five years after left leg amputation and right lumbar sympathetic ganglionectomy. The temperature of the right foot and toe equaled abdominal skin temperature and did not increase after 50 mg. of Priscol intramuscularly. The other patient was tested eight months after right lumbar ganglionectomy and four months after left lumbar ganglionectomy. Foot and toe temperatures on both sides equaled or slightly exceeded umbilicus temperature. Fifty milligrams of Priscol intramuscularly did not further increase temperature of foot and toe.

3. *Thromboangiitis obliterans (Buerger's disease).* History and clinical observations led to a probable diagnosis of thromboangiitis obliterans in six patients. As nearly as could be determined each had discontinued smoking. The first, a 33-year-old veteran, had involvement of hands and feet during six years and had had episodes of migratory phlebitis. He had been hospitalized elsewhere repeatedly, receiving various treatments including lumbar sympathetic blocks. Sympathectomy had been refused. Priscol, 50 mg. warmed the digits of the extremities less than 2 degrees. Fifty to 75 mg. was then given every three or four hours intramuscularly or orally during three weeks in the hospital. Symptomatic relief was described and an ulcer on the right middle finger healed. A small area of phlebitis developed in the right leg and healed. Treatment was continued orally at home ten days and then discontinued for two weeks. During the holiday another finger developed an ulcer, and the patient stated that his hands were stiffer and more painful. For seven months he has taken 50 mg. of Priscol orally every three hours while awake and has reported satisfaction with treatment.

The next two patients were likewise treated in the hospital before home treatment by Priscol was instituted. One, age 46, had involvement of all four extremities with pain and discoloration of the tip of the right index finger. He was treated in the hospital for nine days, using Priscol and conservative treatment. Relief of pain occurred and the discolored finger improved with demarcation of a small patch of dry gangrene. The other patient, age 58, had had symptoms of thromboangiitis obliterans for fifteen years. His left leg had been amputated and diagnosis had been confirmed by pathological examination. An ulcer of the index finger of the right hand developed and caused pain. An excessively large dose of Priscol, 175 mg., was given intramuscularly. This effected relief of pain and increase in temperature of right thumb and toe. It also produced reduction of blood pressure from 140/95 to 68/60, a chilly sensation and vomiting and diarrhea.

The remaining three patients with thromboangiitis obliterans had sympathectomies before or after Priscol. One gave a history of involvement of

TABLE I.—*Range of Blood Pressure Before .6 Gm. of Sodium Amytal and During Night, Before Priscol and During First Hour Afterward, and After Second Stage of Paravertebral Sympathectomy**

Patient	Age	Sodium Amytal Test		Priscol "Acute Test"		One to two weeks After Sympathectomy
		Before Test	During Night	Before Drug	After Drug	
A. Good reduction after sympathectomy:						
ML	43	250/150→210/130	205/140→154/100	254/170→232/140	189/110→124/70	170/100→100/70
EE	31	200/124 160/110	140/100 130/90	182/122 168/118	148/92 124/74	152/96 104/70
MH	26	290/170 230/150	200/150 160/122	234/162 220/154	210/160 178/132	165/130 140/88
NL	43	240/118 170/98	172/110 130/70	174/92 164/94	186/94 162/86	140/100 100/66
B. Moderate reduction after sympathectomy:						
IS	44	230/140→180/120	178/132→150/100	208/144→190/132	160/102→116/66	164/104→130/70
RR	31	230/130 170/100	180/120 150/100	182/128 160/120	144/96 124/72	170/147 110/88
HF	37	220/170 180/124	190/140 170/120	202/148 182/144	210/132 142/96	180/120 110/82
FP	45	232/130 180/100	180/110 170/96	236/134 212/118	142/112 108/80	198/100 140/70
C. Insignificant reduction after sympathectomy:						
SO	45	210/130→186/106	180/100→150/90	220/136→188/130	110/70 → 86/50	210/132→170/100
MC	44	240/130 200/122	220/140 190/100	230/126 210/188	280/160 240/124	240/130 180/90

* All readings obtained with patient resting in supine position.
Interpretation is difficult but it would appear that reduction after Priscol agrees with that after sympathectomy in patients ML and RR, amytal in FP and SO, both in EE, IS, and MC and neither in MH, NL, and HF.

toes and fingers, beginning ten years ago at the age of 25. Five years before receiving Priscol a bilateral lumbar sympathectomy had been performed and two years ago a bilateral upper dorsal sympathectomy. During the month before treatment an ulcer had developed on the tip of the left middle finger and the entire distal phalanx had discolored. Eight days of treatment using 50 mg. every four hours produced moderate relief from pain. Amputation of the distal phalanx was then performed and the wound healed. Since discharge from the hospital this patient has taken four to six, 50 mg. doses of Priscol each day for five months with the exception of occasional intervals of a week or two without drug for control observation. He states that while taking Priscol the hands and feet feel better, with less stiffness and no pain. His hands and feet feel colder and stiffer and are "tired and more easily fatigued" during periods without treatment. Another patient, age 42, was tested two years and seven months after left lumbar sympathetic ganglionectomy and just preceding right ganglionectomy. One hundred milligrams of Priscol intramuscularly effected moderate increase of temperature of the toes of the non-sympathectomized limb but did not increase temperature of the sympathectomized leg. Increase of temperature of the right toes after the right lumbar sympathectomy was moderate, equaling that effected by Priscol. The last patient, age 32, received 200 mg. intravenously with little increase of temperature of the involved foot. There was also little increase of temperature after sympathectomy.

4. *Popliteal aneurysm.* Three patients with popliteal aneurysm were tested. One had a left popliteal aneurysm at the age of 19. It had been noticed as a small lump for three years and had ruptured six days before admission, producing pain and swelling. Left lumbar sympathectomy and ligation and excision of the defective area of the popliteal artery were performed. The day after operation 50 mg. of Priscol were given intramuscularly. This effected increase of temperature of the right foot and toe, equaling the temperature of the sympathectomized side but did not increase temperature of this operated side. Fourteen days later 50 mg. were given twice intramuscularly, an hour apart, again with warming of the right foot to equal the temperature of the skin near the umbilicus and without increase of temperature of the left leg. The remaining two patients, aged 70 and 77, had popliteal aneurysms associated with thrombosis. Each was treated by Priscol with little effect and both developed gangrene and had amputation.

5. *Causalgia-type of pain and circulatory disorder.* Seven patients with limb pain have been grouped together under the heading *causalgia,* using the term as it is conventionally broadly defined. Each has been treated by Priscol. No patient had peripheral nerve injury with neuroma and pain required for a diagnosis of causalgia according to the limited definition of the term.

The first patient had burning of both feet associated with increased warmth and blood flow, persisting seven months. Pain began after fracture of several foot bones during a fall. Tenderness and pain prevented walking. Sympathetic

blocks were compared with intramuscular injection of 100 mg. of Priscol. Subjective relief of pain was described as lasting 15 to 20 minutes after both procedures. Similar relief was also described after placebo tablets or injections of saline into the lumbar muscles. Treatment since has been psychiatric.

The second patient, five weeks before testing, had had a right great toenail removed for "ingrowing toenail" and had subsequently developed intense pain in the right foot, with increased warmth, dependent rubor, and evidence of increased blood flow. Fifty milligrams of Priscol intramuscularly partially relieved pain and another 50 mg. an hour later completely relieved pain for seven hours. The test was repeated two days later, again with relief, this time persisting six weeks. She returned two weeks after recurrence. Circulation at this time was essentially normal as judged by postural tests. Priscol taken at home for two weeks again relieved pain.

A third patient developed pain in the left great toe after wearing a tight shoe three months before treatment. All arteries were fully palpable but there was dependent rubor of the left foot. Two intramuscular injections of 65 mg. of Priscol increased the temperature of both feet and relieved pain. Priscol was continued at home for one month. All symptoms were relieved, and when the patient returned after a two-week holiday, there had been no recurrence. Postural tests of circulation were normal.

The three remaining patients in this group had upper arm pain associated with some injury of the brachial plexus or the cervical nerve roots. One had an avulsion injury followed by paralysis of the left arm one year before treatment. Motor function had partially returned. When first examined the arm and hand were cold. Atrophy and persistent pain had developed. Upper dorsal sympathetic blocks relieved pain temporarily and a sympathectomy was performed. Warmth and motor functon of the hand increased and muscular development improved but pain recurred within two months. One year after sympathectomy he was hospitalized one week and treated by progressively increasing doses of Priscol. The maximum was 75 mg. every two hours. Pain was relieved but recurred within three weeks. Three months later he was sent Priscol for use at home and took 50 mg. every four hours. Again he reported relief but during continued treatment pain returned. He finally stated that the medicine did not help and discontinued treatment.

A second patient injured his right shoulder two months before admission and gradually developed pain in the right middle and index fingers with ulceration of the index finger. A sympathetic block partially relieved pain for thirty minutes. Fifty milligrams of Priscol orally also temporarily relieved pain. Increase of finger temperature equaled that produced by the block.

The third patient complained of pain in the ring finger and palm of the right hand. This had been present for seven weeks and began after the patient had awakened one night with intense pain between the shoulders. A diagnosis of rupture of the cervical disc between C-7 and T-1 was established and the neurosurgeons removed the protruding portion of the disc. Pain recurred

three weeks later. Three upper dorsal lumbar sympathetic blocks each relieved this pain. One hundred ten milligrams of Priscol intramuscularly and 100 mg. orally similarly relieved pain for an hour and a half. Sympathectomy was subsequently performed but pain again recurred.

The last patient in this group had both legs amputated because of arteriosclerotic vascular obstructive disease with gangrene and intense pain. Pain had persisted one year following the last amputation. Twenty-five milligrams of Priscol were given orally every two hours for two days. This did not relieve pain but did produce nausea and apprehension.

6. *Miscellaneous Vascular and Pain Problems.*

A. VENOUS THROMBOSIS OR PHLEBITIS. Three patients with intravascular clotting in deep veins of the leg were tested but not treated by Priscol. Two had had pulmonary emboli, and one had recurring phlebitis with edema. In each patient Priscol warmed the involved leg and foot and relieved discomfort.

A fourth patient had had recurring episodes of left lower leg superficial thrombophlebitis. After removing the saphenous veins and tributaries by stripping and evulsion, episodes of lower leg cellulitis occurred on both sides and edema developed. After the last episode 50 mg. of Priscol intramuscularly brought toe temperatures up to temperature at the umbilicus. A left lumbar sympathectomy was then performed and subcutaneous tissue and veins of the areas of recurrence in both lower legs were radically excised. Two days after operation and again eight days later Priscol brought the temperature of the right foot up to that of the left and equal to that at the umbilicus.

B. ISCHEMIA. Three patients with acute obstruction of blood flow to a limb were tested and treated with Priscol. The first, a 24-year-old athlete, fractured the right tibia. After reduction the right leg and foot were placed in a cast. Two days later pallor of the toes was observed and it was found that motor function and sensation were diminished. The cast was removed. Two hours later the foot remained colorless and neither dorsal pedis or posterior tibial arteries could be palpated. Fifty milligrams of Priscol intravenously effected restoration of a pink color and return of warmth within five minutes. Fifty milligrams were then given intramuscularly every four hours. Twenty-four hours later the dorsal pedis and posterior tibial arteries were fully palpable.

A second patient developed a colorless lower leg after fracture and dislocation of the right knee. Emergency surgery was performed elsewhere. The popliteal artery was thickened and contained a thrombus. The thrombus was removed but blood did not flow through the injured artery. Three days later the foot was discolored. Priscol was then tried without improvement. The third patient, a 65-year-old hypertensive patient with coronary disease, developed an embolus presumably located in the right popliteal artery. Fifty mill-

grams of Priscol were given every four hours for three days, and the patient was heparinized. The foot remained viable, but after recovery the patient complained of claudication and fatigue on exercise.

C. PAIN. As a control for relief of pain described in the above reports six patients with pain or other varieties were tested with Priscol. Four had abdominal pain, one from intussusception, one from common duct obstruction, and two from peptic ulcer. Each was given 50 mg. of Priscol intramuscularly or intravenously without relief from pain. The fifth patient had a painful stasis dermatitis of the left leg. Twenty-five milligrams orally produced warming of the legs but no relief of pain. Another patient with arthritis in the hands was tested both by sympathetic block and by 50 mg. of Priscol intravenously without relief of pain.

THE EFFECT OF PRISCOL ON BLOOD PRESSURE OF PATIENTS WITH HYPERTENSION

Thirty-nine hypertensive patients have been treated or tested with Priscol. In general each had advanced essential hypertension or hypertensive cardiovascular renal disease. Only one had definite coronary disease demonstrated by electrocardiogram. Many had hypertensive retinitis and a few papilledema. The oldest patient was 53. Treatment in the hospital consisted of 25 to 75 mg. of Priscol usually by hypodermic administration every two to four hours. Treatment at home employed 25 to 75 mg. orally every three or four hours. Many patients had tests using Priscol. These were performed by injecting 50 mg. intravenously, followed one hour later by another 50 mg. and then with three exceptions completing the test at the third hour by injection of 100 mg. Blood pressure during the hour after the last injection will be described and transient changes omitted. Occasionally sympathectomy was performed after a week or more of treatment or after a Priscol test. All blood pressures reported below were taken with the patient resting in a supine position. Six types of observations will be presented separately.

1. *Hypertension treated by Priscol during a week or more of hospitalization and then by sympathectomy.* (Five patients.) The first patient had tachycardia and fluctuating blood pressure and was suspected of having an adrenal tumor. After receiving Priscol in the hospital for nine days pressure decreased from around 190/110 to around 134/96. Treatment was continued one month at home. Fluctuations of pressure with frequent high readings recurred and tachycardia persisted. A splanchnicectomy of the posterior Smithwick-type was then performed. Both adrenal glands were explored and neither contained a tumor. The complaint of tachycardia persists but blood pressure remains reduced.

The remaining four patients failed to have significant lowering of pressure during 5- to 10-day periods of treatment even though dosage was increased to 75 mg. every two hours. Each was then treated by total thoracic and partial

to total lumbar paravertebral sympathectomy, splanchnicectomy, and caliac ganglionectomy[27].* Blood pressure following operation was reduced toward normal in two and only moderately lowered in two.

2. *Hypertension tested by Priscol and subsequently treated by sympathectomy.* (Eleven patients.) One patient had no significant lowering of pressure after 200 mg. of Priscol and also no reduction during the second week after splanchnicectomy. Ten patients had Priscol tests, standard sodium amytal tests, and then subtotal to total paravertebral sympathectomy. Results are presented in Table I.

3. *Priscol tests in patients with hypertension persisting after sympathectomy.* Tests were performed in six patients with hypertension persisting 8 to 36 months after treatment by sympathectomy. One had had a splanchnic ectomy. Blood pressure which ranged around 176/114 did not change after 200 mg. Another after splanchnicectomy had a pressure around 230/120. It reduced to 122/68 after 200 mg. of Priscol. The remaining four patients had subtotal to total paravertebral sympathectomies. In three Priscol did not produce significant reduction of pressure. In the fourth the test lowered the reading from around 204/122 to 140/94. This patient was then treated at home and had moderate lowering of pressure.

4. *Hospital treatment of patients with hypertension persisting after sympathectomy.* Four additional patients with hypertension persisting 6 to 26 months after sympathectomy were treated five days or longer in the hospital without using the Priscol test. Three had thoracolumbar splanchnicectomy. Treatment did not produce significant change of blood pressure. The fourth patient had paravertebral sympathectomy. She was treated in the hospital with slight reduction and subsequently at home for two months without significant reduction of pressure.

5. *Hypertension tested and treated by Priscol.* Six patients had 200 mg. tests and then treatment by Priscol. The tests effected reduction of pressure to normal in three and little, if any, reduction in three. During treatment in the hospital for a week or more, a moderate and probably insignificant reduction of pressure occurred. Each was then sent home instructed to take the drug three weeks, discontinue it two weeks, and then, if desired, resume treatment. One patient discontinued treatment after three weeks, stating she felt better and no longer needed it. Of five that resumed treatment for a second three week period only two definitely report relief from headaches or other symptoms. All five continue with hypertension at levels slightly if at all lower than before treatment or than during the two-week holiday.

Three additional patients were tested and then discharged without Priscol but with conventional treatment. In one after the second 50 mg. of the test had reduced blood pressure from 220/140 to around 156/102 weakness

* For convenience this operation will be referred to below as subtotal to total paravertebral sympathectomy. It includes in its denervation sympathetic nerves to the heart and to the adrenal glands.

of the right leg and paralysis of the right arm developed. This subsided after two hours as blood pressure again rose. There was no residual difficulty. The remaining two refused treatment, one did not have lowering of blood pressure with the test but the other had reduction of pressure to normal.

6. *Hypertension treated by Priscol without test or sympathectomy.* Four patients received progressively increasing doses of Priscol during a week in the hospital. In three significant lowering of the blood pressure did not occur. The fourth had moderate reduction but Priscol subsequently taken orally at home failed to maintain lowering.

MISCELLANEOUS OBSERVATIONS AND TESTS OF EFFECTS OF PRISCOL ON CIRCULATION

The first two sections of this paper have described clinical aspects of use of Priscol omitting reference to special observations. Effects of Priscol upon circulation determined by observations made during tests or treatment will be presented below. Material will be grouped under method of observation rather than disease.

1. *Oscillometric studies.* Oscillometric readings obtained at mid-calf level in five patients with severe arterial obstructive vascular disease varied from four-tenths of a point to 3 points. After effective doses of Priscol, readings were unchanged. Similarly, oscillometric readings in three other patients previously treated by lumbar sympathectomy had not been changed by sympathectomy and were not changed after Priscol. Oscillometric readings in six patients with more normal circulation increased a half point or more after the drug.

2. *Peripheral skin temperature gradient.* Skin temperatures were obtained at 10 and 15 minute intervals an hour or more before Priscol and three to twenty-four hours afterward using a McKesson Dermalor. Room temperature could not be kept cool or constant. The gradient of each leg was determined by comparing temperatures just below the umbilicus, over the trochanter, on the medial aspect of the knee, below the medial malleolus, over the dorsum of the foot, and on the tip of the great toe. The gradient of each arm was determined by comparing temperatures over the sternum, over the deltoid, on the lateral aspect of the elbow, over the thenar muscles, and at the tip of the middle finger. Usually, the toes were four to ten degrees centigrade cooler than skin by the umbilicus and the finger zero to four degrees cooler than skin over the sternum.

In general after Priscol this gradient decreased, usually within five minutes after intravenous administration, within twenty minutes after intramuscular injection, and within forty-five minutes after oral administration.

Before Priscol the gradient of five hypertensive and twelve peripheral vascular disease patients was within normal range, and of six peripheral vascular disease patients exaggerated. After 50 mg. or more of Priscol skin temperature gradients of the hypertensive patients were abolished, toe tem-

perature equaling temperature by the umbilicus. The gradient of eight of the peripheral vascular disease patients was similarly abolished after Priscol. Another eight had decrease of gradient. Gradient was unchanged after Priscol in only two patients.

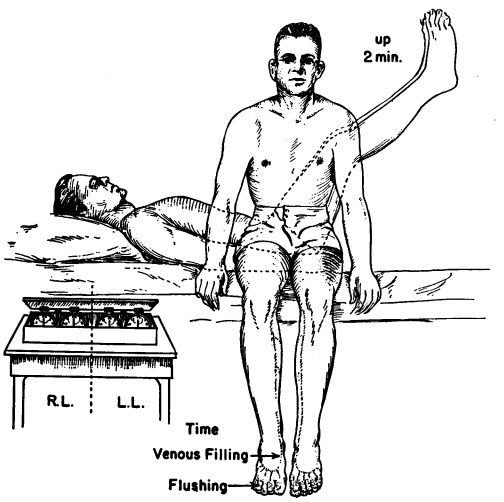
Six patients were tested after lumbar sympathectomy. Gradient of the sympathectomized limb had been abolished by the sympathectomy. After Priscol, gradient of the opposite limb without sympathectomy was similarly abolished but temperature of the sympathectomized limb remaind unchanged or increased slightly, less than 1°. Similar observations and similar results were obtained by testing upper extremities of three patients with upper dorsal sympathetic ganglionectomy. Five of the above nine patients also had Priscol tests before sympathectomy. In each the loss of gradient by test equaled that produced by sympathectomy.

Patients who were treated continuously, receiving 50 or 75 mg. of Priscol every few hours, had moderate increase of foot and toe temperature but did not maintain the marked warming of the foot or abolition of skin temperature gradient accomplished by initial single test doses.

POSTURE TEST-OBSTRUCTIVE VASCULAR DISEASE.

MILD ARTERIOSCLEROTIC

Right		Left	
Flushing	Venous Filling	Flushing	Venous Filling
4.0	25.5	5.8	30.0
6.0	21.0	6.0	30.0
5.5	24.0	5.5	25.0
4.0	28.2	5.5	24.5
5.7	24.6	5.5	30.0
4.6	25.0	4.4	26.3
--	--	--	--
Priscol 50 mg. i.v.			
--	--	--	--
3.6	16.9	3.1	14.3
3.4	18.9	2.3	13.3
0	23.7	0	13.3
0	15.1	0	12.6
0	15.3	0	12.0
0	15.8	0	11.4
0	14.3	0	9.3
0	10.0	0	9.5



SEVERE ARTERIOSCLEROTIC

Right		Left	
Flushing	Venous Filling	Flushing	Venous Filling
4.7	7.6	72.2	26.0
3.8	6.0	69.1	25.9
3.3	8.6	84.2	27.2
3.9	10.4	97.0	37.2
--	--	--	--
Priscol 50 mg. i.v.			
--	--	--	--
4.9	15.7	126.6	36.3
3.3	10.4	124.7	55.7
3.1	10.0	96.0	33.8
3.7	7.9	85.0	20.3
2.7	7.7	95.2	24.6
2.9	6.5	96.1	21.0
2.7	5.5	86.2	17.9
2.1	5.2	91.0	21.5

FIG. 1.

3. *Dependent flushing and venous fillng.* These observations were made after a patient had been lying in bed two minutes with feet elevated at a 45-degree angle. (Figue 1). The patient then sat up and dropped his feet over the side of the bed. Time of appearance of pink color, "flushing" of toes, and time of onset of filling of veins of the foot were observed. Approximate observation and timing in 14 patients without serious arterial obstruction indicated that after Priscol flushing and filling of superficial veins occurred more promptly. Color photographs taken in five patients after 15- and 30-second intervals of dependency before and after Priscol confirmed this observation. Accurate timing in 12 patients using four stop-watches also

confirmed the observaton. The record presented at the left of Figure 1 and the change after Priscol is typical of most studies. The record at the right of Figure 1 illustrates a typical response to Priscol of the right leg. Flushing time in the left leg is, however, further delayed after the drug. This patient had been admitted for amputation of the left leg. Sympathectomy was probably contraindicated.

4. *Cold pressor test.* A "cold pressor test" was performed before and after Priscol in 23 patients with hypertension. Blood pressure was first observed at minute intervals six times or until constant. One hand was then placed in ice water for one minute obtaining pressure readings at 30 seconds and at one minute. Subsequently six additional readings were obtained at minute intervals. Twenty hypertensive patients without sympathectomy were tested. A definite increase of pressure occurred in eighteen. After two 50 mg. doses of Priscol an hour apart, the cold pressor test was repeated in nine patients. Pressor response was abolished in five and reduced in four. After a third injection of 100 mg. an hour later, 17 patients were tested. The pressor response was abolished in 12, reversed in 3, and reduced in 2. Three patients previously treated by subtotal paravertebral sympathectomy were also tested. A pressor response occurred in each before the drug. After 200 mg. it was reduced in 2 and abolished in one.

5. *Breath holding.* Breath holding tests were performed in the same group of patients described under the cold pressor test. Blood pressure was recorded six times at minute intervals. Patients then held their breath in expiration as long as possible. Time of breath holding varied from fifteen to thirty-five seconds, average twenty-five. At the moment the patient again took a breath blood pressure readings were obtained. Subsequently pressures were recorded at minute intervals for six minutes. Of twenty hypertensive non-sympathectomized patients tested, eighteen had a definite increase of pressure before Priscol. Ten were tested after two 50 mg. intravenous injections of Priscol an hour apart. The pressor response was not changed in one, reduced in five, and abolished in four. After a third intravenous injection of 100 mg., seventeen patients were tested. The pressor response was reduced in three, abolished in thirteen, and reversed in one. Three patients previously treated by paravertebral sympathectomy were also tested. Two had a positive response which was reduced but not abolished after 200 mg.

6. *Blood pressure—supine position.* The effect of intravenous administration of varying doses of Priscol upon blood pressure of patients with hypertension and of patients with peripheral vascular disease but with relatively normal pressure was determined. Twenty-two patients with hypertension were tested. During one hour after injection of 50 mg., fifteen had no change of pressure, three moderate reduction, and four moderate increase. A second injection of 50 mg. was then given. During one hour afterward fourteen had no change, seven moderate reduction and one reduction to normal values. Seventeen patients received a third injection of 100 mg. or

altogether 200 mg. of Priscol. Blood pressure remained unchanged in five, moderately reduced in four, and reduced to normal in seven. One patient had temporary reduction below normal to shock levels but recovery was spontaneous. Temporary pressor responses not exceeding 20 mm. systolic were observed in four of the above 22 patients during the first five minutes after injection.

Three patients with hypertension persisting after paravertebral sympathectomy were similarly tested. After 50 mg., pressure was unchanged in two and increased in one. After 100 mg., it was slightly reduced in two and increased in one. After 200 mg., it was reduced in two and reached normal values in one.

Thirteen patients with peripheral vascular disease and essentially normal blood pressure were tested. During one hour after 50 mg. nine had no change, one slight reduction, and three moderate increase. Nine were tested after 100 mg. Six had no change, one moderate reduction, and two moderate increase. Three were tested after 150 mg. Pressure remained unchanged in six and was moderately reduced in three. Temporary pressor responses not exceeding 18 mm. systolic were observed in three of these thirteen patients during the first five minutes after injection.

7. *Blood pressure—standing.* Blood pressures were obtained in sixteen patients with hypertension an hour or more after the third injection, or a total of 200 mg. of Priscol. After standing several seconds to a minute, twelve had reduction of pressure to the point of syncope. Four had marked postural hypotension although not to syncope. Blood pressures while standing were also obtained twice daily in ten hypertensive patients during a week or more of treatment in the hospital. Each persisted with moderate postural hypotension but not to syncope. A moderate postural hypotension also usually persisted in patients treated at home a month or more. Patients with normal blood pressure and with peripheral vascular disease also developed marked postural hypotension after injection of 100 to 200 mg.

8. *Pulse rate.* Pulse rates were determined frequently during tests of twenty of the group of patients with hypertension. Transient increase of rate during the first two or three minutes after each injection occurred in sixteen patients. Persisting rate during the hour following each injection varied from patient to patient. In ten after 50 mg. there was no change, in eight, an increase up to ten beats per minute, and in two an increase of ten to twenty. After the second injection, altogether a total of 100 mg., pulse rate remained unchange in five, increased up to ten per minute in six, increased ten to twenty in six, and increased by twenty to thirty in three. In 19 patients after a third injection or altogether 200 mg., pulse rate remained unchanged in five, increased up to ten per minute in nine, increased ten to 20 in three, and increased 20 to 30 in two.

Three patients were tested after heart and adrenal denervation by paravertebral sympathectomy. Pulse rate did not change after 50 to 100 mg. After

200 mg. the rate of two patients remained unchanged and of one increased four beats per minute.

Patients receiving continuous treatment ordinarily have a normal pulse rate. A few describe occasional sensation of rapid beating of the heart lasting a few minutes.

9. *Pupil.* Temporary dilatation of the pupil was observed after injection of 50 mg. in four of 20 patients with hypertension, and after 100 mg. in two. Dilatation did not occur in three patients with paravertebral sympathectomy which includes sympathetic denervation of the head. In all patients after all doses, pupils appeared normal, dilated in darkness, and constricted in light. Patients read easily throughout test periods even after a total of 200 mg. of Priscol.

10. *Respiration.* After intravenous injection of small or large doses of Priscol a few patients described momentary "shortness of breath" and took several deep breaths. Persisting respiratory rate of twenty-four patients accurately timed did not change in nineteen and was increased from two to four per minute in five.

11. *Response to adrenalin.* Response to adrenalin was tested in one patient with hypertension. Control blood pressure was around 206/108. After 10 drops intravenously of a mixture of 200 cc. of saline and 1 cc. to 1000 adrenalin pressure increased to 234/92. After twenty drops it increased to 248/100 and again after 8 drops to 240/100. This patient was then treated for three days by hypodermic injection of 50 mg. of Priscol every 4 hours. During the second day of treatment adrenalin was again administered using a similar and freshly prepared solution. Sixty drops were injected within two minutes. Blood pressure decreased from around 218/116 to 200/78. Twelve hours after Priscol was discontinued 10 to 23 drops of a similar solution again produced marked pressor responses.*

12. *Response to anesthesia.* A 58-year-old-man patient suspected of having a pheochromocytoma or a paraganglioma was given three successive intramuscular injections of 50 mg. of Priscol during two hours preceding exploratory laparotomy. Ethylene, ether and curare were used for anesthesia. During two and one half hours under anesthesia and during the administration of 750 cc. of whole blood, 500 cc. of plasma, and 800 cc. of 5% dextrose in saline, blood pressure varied from around 110/160 to 170/110. There was no evidence of reflex change of pressure from manipulation or traction of abdominal viscera or of increased pressure when adrenal glands were inspected and palpated. No tumor was found.

13. *Temperature gradient of pedicle skin tubes.* Three patients with skin tubes in various states of preparation or transplant were given Priscol intramuscularly. One tube had been raised from the lower leg but had both ends attached. After 69 mg. of Priscol temperature in the center of this graft rose 1.6° C. A second tube had been raised from the chest to the ear, but was

* A preliminary report (25) has described additional experiments in man demonstrating adrenolytic action of Priscol. Results will be amplified in another paper.

still attached to its site of origin. Temperature in the center of the graft rose 1.4° C. after 65 mg. of Priscol. The third tube had been transplanted to the right hand and then moved from the site of origin to a defect of the lower lip, thus eliminating its original nerve supply. Temperature rose 1.9° C. after 53 mg. of Priscol. Color photographs of each tube clearly demonstrated increased redness.

14. *Cardiac output.* Observations have been made on three patients by J. B. Hickam, who will report details and further studies. All readings were taken in the horizontal position. Two patients had mild hypertension and one thromboangiitis obliterans involving four extremities. No patient had clinical evidence of impairment of cardiac function. Cardiac outputs were determined by the Fick principle using the technic of cardiac catheterization. Patients were tested under basal conditions and again 30 minutes after 50 mg. of Priscol intravenously. In two, cardiac output did not change. In the third, an apprehensive patient with a high control value, the output decreased to a normal level after Priscol. One patient received a second injection of 150 mg. of Priscol one-half hour after the first. His output one-half hour later was unchanged. Response to five minutes of leg exercises was also tested before and one-half hour after 50 mg. of Priscol. For equal amounts of exercise the cardiac outputs were identical.

15. *Urinalyses and blood counts.* Urinalyses were obtained in seventeen patients before, during, and at the end of continuous treatment with Priscol for a week or more in the hospital. The longest period of treatment was nineteen days. Changes or abnormalities did not occur. Hemoglobin, red and white blood counts were similarly obtained in fifteen patients, in four instances supplemented by differential counts. With one possible exception changes or abnormalities did not occur. In one patient the white blood count dropped from 9,000 before Priscol to 3,110 after ten days on the drug. Two days later while receiving the drug the count was 5,550 and one month after discontinuing treatment it was 9,000. The only other drug administered with the Priscol in this patient was sodium pentobarbital, .1 Gm. the two evenings before the low count. Eleven patients checked while receiving Priscol at home for periods up to seven months have had no significant change in urinalysis or red and white blood count.

DISCUSSION

Favorable reports of use of Priscol for a variety of peripheral vascular diseases have appeared in European and South American literature. Our clinical experiences with this drug during periods of treatment not exceeding nine months have confirmed these reports. Single doses of 25 to 75 mg. evidently with few exceptions produce changes in circulation of limbs equivalent to those produced by sympathetic block or sympathectomy. Continuing treatment by this dose schedule maintains benefit but does not entirely equal the effect of sympathectomy. Results in treatment of Raynaud's disease have been encouraging and unless evidence of toxicity or tolerance develops, sympathectomy is no longer recommended by us. Results in treatment of vasospastic

ischemic extremity problems and causalgia states have been encouraging. Results in treatment of thromboangiitis obliterans and arteriosclerotic peripheral vascular disease are less easily evaluated. At present treatment is limited to patients refusing sympathectomy or those with complications contraindicating sympathectomy. Treatment has been and is currently being offered to patients with peripheral vascular disease complicated by coronary heart disease. Nevertheless, theoretically at least, harm may develop from drug action on the heart. Of 9 patients with known progressive generalized arteriosclerotic vascular disease and coronary involvement, tested or treated by Priscol, two developed myocardial infarction. Our clinical impression that this would have occurred had Priscol not been used cannot be established without further experience. Patients without known coronary heart disease have not as yet developed cardiac complications. Doses of Priscol over 75 mg. should, however, be avoided in patients with known obstructive disease of coronary or other arteries since reduction of blood pressure might occur with adverse effects.

A test intravenous injection of 50 or 75 mg. of Priscol may aid prediction of immediate results of sympathectomy in patients with peripheral vascular disease.

Attempted treatment of hypertension by Priscol in dose ranges up to 75 mg. every two hours has yielded encouraging results in only a few instances. Similarly, use of a Priscol test for hypertension or of Priscol treatment a week or more in the hospital has not aided prediction of results of sympathectomy.

Oscillometric readings at calf level in patients with marked organic arterial disease were not changed by Priscol. It is our experience that low readings are seldom altered during the first week after surgical sympathectomy. Increase of readings occurred after Priscol in patients with less arterial obstruction. Skin temperature gradient of arms and legs was usually decreased or abolished after Priscol test doses. Warming of hands and feet was less marked during continuous treatment. Evidence of more rapid dependent flushing and venous filling of toes and feet after Priscol adds to evidence that blood flow through extremities may be increased, arterial supply permitting.

It is of interest that goose flesh frequently would be observed over the body after Priscol; also, it appeared on the skin of sympathectomized limbs. This would indicate a peripheral effect. Sweating, frequently produced by doses of Priscol of more than 75 mg., never appeared in sympathectomized areas. This would indicate dependency on innervation.

Doses between 100 and 200 mg. blocked pressor responses to placing a hand in ice water or to breath holding. Cold pressor block is conventionally believed an indication of complete sympatholysis. We have, however, observed definite pressor responses in patients evidently totally sympathectomized. Block of pressor response to breath holding is possibly an indication of sympatholysis. Postural hypotension develops after sympathectomy for hypertension. Postural hypotension observed after large doses of Priscol equals or exceeds that after subtotal to total paravertebral sympathectomy.

Ordinarily, injection of Priscol did not dilate pupils. Dilatation did occur in a few patients but never occurred if the pupil had been sympathectomized. It would seem that dilatation when observed was caused by apprehension or an alarm-type of reaction. Rate of respiration was not significantly altered even by large doses, and there is no indication except for block of pressor responses of the breath holding tests that respiratory mechanism is effected.

Occasional observations in the absence of sympathetic innervation have indicated that Priscol may have a peripheral and perhaps histamine-like effect. Patients who have had sympathectomy, for such diseases as Raynaud's, state that the drug makes their hands feel warmer and more comfortable. One completely transplanted skin tube increased in temperature after Priscol. It is possible that a peripheral effect might be related to block of action of circulating adrenalin. Presumably, all of the hypertensive patients treated by paravertebral sympathectomy had denervation of both adrenal and cardiac areas. Nevertheless, blood pressure lowering was occasionally produced by Priscol. It could also be assumed that block of circulating sympathin might permit dilatation of denervated vessels. From experimental evidence in animals, however, it would appear that Priscol may have histamine-like action in addition to its potent andrenolytic and sympatholytic properties.

CONCLUSIONS

1. Priscol in doses of 25 to 75 mg. is a useful adjunct to treatment of many peripheral vascular diseases or circulatory disorders and in this dose range usually is tolerated with few side effects.
2. Priscol in test doses of 100 to 200 mg. has lowered blood pressure of many patients with hypertension but sustained treatment by smaller doses has aided only a few.
3. Priscol has adrenolytic and sympatholytic properties in patients and may also have some histamine-like effect.

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DISCUSSION.—DR. GEORGE D. LILLY, Miami, Florida: I should like to compliment Doctor Yeager upon his presentation of this most timely subject. I agree with him that we must stress the importance of thorough sympathectomy.

Due to the fact that I live in a semi-tropical climate, I probably see more failures than most people, because so many of these patients come south in the winter to avoid some of the misery which cold weather produces in persons suffering with peripheral vascular disease. It has been most discouraging to me to examine many people who have had little or no improvement following sympathectomy, only to find that they are sweating profusely down to the knee, or lower. I feel that inadequate sympathectomies are giving the procedure a bad name. Too many of these procedures have been turned over to house officers with inadequate experience, and too many of them have been attempted by persons who have not familiarized themselves with the bizarre anatomy of