PRISCOL IN CIRCULATORY DEFICIENCY.

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THE purpose of this article is to illustrate the value, especially over the five colder months, of the peripheral vasodilator, benzyl imidazoline (Priscol, Ciba) in the care of the circulatory disorders of the aged.

The drug has been advertised in the British medical press since January, 1949; but the literature refers to some 10 years. It has consisted mainly of pharmacological studies in animals and man; or has described clinical effects in man over a short period, e.g. as a test prior to surgical measures. An exception is the work of Grimson *et al.* (May, 1948), where periods of trial vary, but in one case extend over five years.

The present article differs from others in describing clinically a group of ten females suffering from circulatory disorders of the feet or legs, and whose previous relevant history was known; and who, during the period of the test, were continuously under survey in an environment whose temperature was known. These conditions were imposed by the fact that the group consisted mainly of typhoid contacts in a mental hospital, but no actual cases or carriers are included. One case, "C," was found accidentally to be excreting for a few days *S. typhi murium*, but she was not showing any signs of dysentery.

It is a well known feature of most chronic conditions that when a patient who was formerly ambulant is compelled by intercurrent conditions to become bedfast even for a few weeks, he loses some of his remaining capacity for co-ordinated and purposeful activity; and this capacity must be laboriously regained in the early days of convalescence. This is a serious enough complication of such illnesses as, for instance, disseminated sclerosis, where the patient may be young and adaptive enough to make the necessary effort. In geriatric and some psychotic cases, however, the situation is aggravated by a tendency to passivity, to give up hobbies, interests, social contacts, and by withdrawing from the environment, to earn the label "demented" or doted. Under these circumstances a combined attack by nurse, physio- and occupational therapist, and social worker, guided by physician or orthopaedic surgeon may be necessary to achieve even limited results. One need not labour the point that considerable effort and vigilance is justified if it will permit such a patient to pursue, unhindered, his few remaining interests without having to take to his bed periodically.

Of increasing importance in this field, owing to an ageing population is a seasonal incidence of circulatory disorders of the feet and legs which is found in a proportion of the patients in the chronic wards of a mental hospital. Among physical conditions, those associated with the names of Raynaud, Buerger and

https://doi.org/10.1192/bjp.97.407.278 Published online by Cambridge University Press

Bazin spring to mind, but in the present series it was found that arteriosclerosis with myocardial degeneration, and diabetes were numerically more important, among the elderly, especially when associated with depression or inactivity. In the psychotic field are found especially deteriorated or catatonic schizophrenics, usually women.

Whatever the cause, it is common to find cases where the feet in cold weather become cold, swollen, congested and blue, with obviously diminished blood flow, and developing cutaneous sensory loss. These conditions are made worse by tight garters, shrunken stockings and hard leather shoes. When the earlier of these signs appear it is customary to confine the patient to bed with the object of preventing more serious lesions, but in spite of this one may find—

(1) Indolent ulcers of the lower part of the leg or of the pressure points of ankle and heel.

(2) Gangrene of the tips of the toes, which may heal with loss of a little tissue, e.g. nails; or may progress proximally, involving deeper structures.

(3) Several patchy shallow areas of skin death or superficial gangrene on the dorsum of foot or toes. These may be caused by injudicious use of hot water bottles, etc., and take the form of irregular spots of ½ to 3 cm. diameter, where the skin is dry, hard or tough, purplish at first and turning brown. If treated and kept free from infection they show a tendency to heal without breaking down.

(4) Injuries, e.g. falling, due to numbness or muscular inco-ordination.

These, with or without superadded sepsis, were the conditions typical of the group of ten females to be described. Seven of them were over 60 years old, but three other females under 60 were successfully treated with Priscol for similar conditions. They will not be described because their previous histories were not adequately known, and because they were under treatment for a shorter period. On the male side of the hospital was found only one among the over 60's who had an obstinate septic ulcer of the foot with circulatory inadequacy. He responded slowly to Priscol. The total population over 60 was 178 females and 119 males, a ratio of 3 to 2. Since the death rate and the discharge rate of the two sexes were exactly proportional to this ratio; and since the average age at death was the same, 72 years, one might claim that the male and female populations of the hospital over 50 are comparable both physically and mentally. Without suggesting that circulatory disorders of the over 60's attack 6 per cent. of women, but only 1 per cent. of men, there is reasonable evidence of a disparity in their incidence in mental hospital populations. Possible causes of this difference are:

(1) Men dress their bodies and limbs warmer than women, who may be seen with cotton or silk stockings and elbow length dresses even in cold weather.

(2) Men wear boots or shoes which tend to be dearer, and to last longer than women's. They therefore are a better fit for a longer period than women's shoes.

The males in this hospital lived in less overcrowded wards than females, and their opportunities for stimulating outdoor and indoor activities have not been so curtailed by staff shortage.

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Survey of Population at Risk, January to April, 1950.

Age-group.	Males.	Females.
60–65	39	48
65–70	35	31
70–	45	99
Total	119	178
Discharges	6	9
Died	8	11
Treated	1	10
Percentage	1	6

Pharmacology of Related Compounds.

Improvement of the peripheral circulation by interruption of the sympathetic outflow is the aim of various procedures. The pharmacology of this field has advanced during the past 15 years and comprises to some extent the pharmacology of the pentavalent nitrogen atom. One may note, however, that as long ago as 1867 Crum Brown drew attention to the curarizing effects of quaternary ammonium compounds. Generally speaking these compounds owe the intensity of their activity to the number of such ammonium groups in the molecule, e.g. tetraethyl ammonium bromide, with one, curare with presumably two, and Flaxedil (M. & B.) with three; and owe their specificity to the nature of the substituting groups or their position in a homologous series, e.g. in the series of Methonium compounds the pentamethylene produces autonomic block and antagonizes the decamethylene (Davison). The hexamethylene has been used to produce parasympathetic block of gastric secretion and motility (Kay and Smith) and higher members produce skeletal muscular block more marked in the deca- than the octomethylene member (Paton and Zaimis). To digress here for the sake of completeness, it may be mentioned that the simplest of such effective compounds is tetraethyl ammonium bromide (TEAB Boots), which in doses of 0·2 to 0·5 gm. intravenously produces an immediate vasodilation of the foot, with concomitant fall of blood pressure. The patient is usually supine when it is used, to avoid subjective or other symptoms due to this fall in B.P., and the effect on the circulation passes off in a few hours.

A recent addition to the group is the drug Flaxedil (M. & B.), which has three quaternary nitrogen atoms: $C_6 H_3 (O.CH_2.CH_2.NEt_3.I)_3$. It has a marked curare-like action, no sympathicolytic action, and little parasympathicolytic, in animals; but in man it produces skin flushing and usually a slight rise in blood pressure. For instance, in a patient drowsy with Pentothal who showed relatively little curarising effect, the B.P. before and at 1, 3, 7 mins. after a small dose of 40 mgm. were 134/96, 148/90, 150–142/90, 136/90 mm.

A related substance mentioned here for the sake of its universal interest is nicotine, pyridyl-N-methyl pyrrolidine. It is not a quaternary nitrogen compound, but a di-tertiary one, which is oxidized in the cold by atmospheric

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oxygen; and readily forms additive quaternary nitrogen compounds. It is tempting to suppose that a reaction of this nature is a normal stage in its metabolism, for this would account for its well known effect on autonomic ganglia.

The substance mephenesin (Myanesin, B.D.H.) produces a relaxing effect on skeletal muscle; but as an α-substituted glycerol ether it is unrelated chemically or pharmacologically to the nitrogen compounds under consideration.

The pharmacology of Priscol is described as "very complex" by Alquist *et al.*, and consequently side actions are known and even forecast in their paper. They will be described later.

(1) There is, in effective doses, a peripheral arterial dilatation which can be seen; measured by blood-flow meters; and detected by pulse pressure contour studies. This is considered to be partly adrenolytic and partly histamine-like (Hendrix, Grimson), and by Alquist *et al.* to be sympathomimetic-antipressor, similar to certain adrenaline derivatives.

(2) Stimulant action on the heart muscle, with coronary dilatation, a sympathomimetic effect, capable in some dogs and some humans of causing at least a temporary pressor effect in spite of the previous result. Increase in rate of blood flow seems to be invariable.

3. A cholinergic effect on the intestinal musculature and on the cardiovascular system of rabbits.

(4) A histamine effect on the intestine and uterus.

Priscol (tablets of 25 mgm.) was chosen for this investigation, because it has a well marked vasodilator action particularly on the lower limb; because, unlike the other drugs mentioned, it is available in tablet form, convenient for oral administration over a long period, and because it is cheap, costing only about 3d. daily in the small dosage here used, i.e. 3 tablets daily. This small dose was chosen initially with a view to avoiding unforeseeable side-effects, which might occur during a prolonged course of treatment; and as the clinical effects seemed adequate on the whole, there seemed to me no indication for an increase of dose.

It is also available for injection, and is said to be effective when applied topically.

In a group of five specially selected because of the uniformity of their environment over the test period, an attempt was made to determine whether, after three months' treatment, there were any signs of habituation, or whether withdrawal symptoms would be evident. In particular one wanted to know whether the clinical effects were as marked in February as at the beginning of the course, and so the drug was withheld on that date, while observation continued. The Priscol tablets were then given again five days later, and the effect compared with the initial effects.

Ward Temperatures.

The temperature of the ward was noted night and morning, but all the readings need not be given here. Instead, each month has been divided into four "weeks" of seven or eight days, and their morning and night readings averaged separately. The minimum reading for each month is given in degrees F.

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Weekly average temperature of ward in month of:

Oct.		Nov.		Dec.		Jan.		Feb.		Mar.	
M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.
61	67	51	53	50	54	54	60	54	58	50	58
59	61	50	54	49	53	54	55	52	59	52	59
56	57	50	53	48	55	51	54	55	58	56	60
49	54	52	58	53	58	49	52	52	57	54	59
Minimum:											
48	52	46	48	42	48	44	48	42	48	44	46

It is, of course, regrettable that no information is available about humidity, rate of air-flow, or katathermometer readings, but enough has been shown to indicate that healing processes were not indebted to the environmental temperature.

Results of Treatment.

The effects of treatment are described in notes made from time to time under the headings.

Temperature.
Colour.
Degree of oedema.
Presence or absence of dorsalis pedis pulse.
Duration in seconds of the white mark made by finger pressure.
Blood pressure.
Pulse rate and rate of blood flow to the foot in c.c. per minute.
Progress of lesions.
Side effects.

To describe these in all cases would be tedious, so only three—cases C, I and K—have been given in full. The others have been given in the condensed statement, or under the headings of Signs and Symptoms.

More briefly still it may be said that ten patients who had spent part of the winter '48–'49 in bed on account of poor circulation of the feet, as well as a few of the previous winters, were treated with Priscol. Eight were ambulant, usually wearing slippers throughout the winter '49–'50, and while ambulant their existing lesions healed. One who had a diabetic gangrene was not ambulant, developed wet gangrene and recovered from the consequent mid-thigh amputation. She died in coma. The tenth, case I, was found inadequately clad on two occasions, and was subsequently treated in bed—successfully.

Signs and Symptoms.

Individual signs or symptoms showed the following changes during or after treatment:

Colour.

Ten cases showed cyanosis of feet or toes. One (case C) remained cyanotic; four became pale; three became dusky at times, pale at others.

Two cases, D, K, were pale before and during treatment.

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Temperature.

Skin temperature was estimated by two methods:

(*a*) Touch, the examining hand being "warm," i.e. between 27° and 29° C.

(*b*) By an ordinary thermometer attached to the skin. The bulb and adjacent skin were covered with a small blob of lubricating jelly which was in turn covered with a layer of fine gutta percha to prevent evaporation.

The latter method was found unsatisfactory as it could not integrate the temperature of a skin area of a whole foot at a time. Consequently, the less accurate but more useful method of touch was relied upon.

It was found that a skin temperature predominantly below 20° C. was judged to be "cold," and one above 27° was considered to be "warm." Between these two temperatures the skin was described "cool." Using these standards, eight out of the ten cases, before treatment, had "cold" feet while in bed; and they all became "warm" under treatment, though two of them, B and H, were occasionally found to be "cool."

The other two, D and K, were "warm" both before and during treatment.

Oedema.

All cases except E showed oedema before treatment, and none showed any material improvement so long as they remained up. Two cases showed slight increase of oedema, amounting to an increase in circumference of ½ to 1 in. approximately. No attempt was made to control the oedema, by limitation of salt or water intake.

Pulse.

The dorsalis pedis pulse was sought before the patient had got up in the morning, and the feet were usually warm at the time. It was absent bilaterally in all cases before treatment; during treatment it returned in eight cases. In cases B and E it remained absent in one foot and doubtful in the other.

Blood Pressure.

There is generally a fall in systolic B.P. of 10–50 mm. In three cases the pulse pressure increased by 5 to 10 mm. and in five was unchanged. In one there was a fall in pulse pressure of 15 mm. and in the case A above mentioned the fall was, of course, 27 mm. This is the case which relapsed and needed special attention as described below.

Pulse Rate.

Simultaneous with the fall in B.P. there was a rise in pulse rate which, in round figures, was 65 per minute, rising to 75.

Withdrawal Signs.

In five patients where it was considered safe to do so, the Priscol was stopped for five or more days on February 17, when the ward temperature averaged 54° F. in the mornings and 58° F. in the evenings. All of them showed, during

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five days, a progressive return to their original state. The feet became cooler, cyanosis reappeared, and the dorsalis pedis pulse gradually disappeared. All of them showed a rise in blood pressure above its original level. In one case, K, the rise was alarming, and continued for about a month. (See case note.) These withdrawal effects have not been adequately described in the literature. The timing of these withdrawal signs is in line with the findings of Grimson, who, in a few cases, found that treatment need not be continuous, but could be interrupted for a week or more at a time.

In all cases the Priscol was withdrawn finally about the beginning of April, except where stated specifically, when the rising temperature made further treatment unnecessary. The dose was diminished over a week or ten days to zero.

There was in most cases, some deterioration in blood supply; but no case developed any lesion.

Side Effects.

Habituation.

At the end of four months' treatment the drug seemed to be exerting its original effect both on those who had received it continuously; and also where it was withdrawn for five or more days, and then restarted, the original effects were exactly reproduced as in the first few days of treatment.

Minor Subjective Complaints.

There were no complaints under this heading among the ten cases studied. The reason for this can probably be deduced from their mental notes. None of the three elderly control patients over 60 made any complaint either, but three younger cases who were receiving benefit for Raynaud's disease and chilblains (two cases) each made complaints. One, whose chilblains stopped itching within a few days of treatment, stopped taking the drug because of headaches.

One complained of tingling of legs and chilliness of back and shoulders after the first few doses only.

One (Raynaud's) complained of abdominal discomfort.

Diarrhoea.

Diarrhoea is a recognized side effect, but it was not noticed in the above series. Among the ten were four incontinent patients whose bowel movements were noted at night, as a routine. They showed no increase whatever in frequency of bowel activity during the period of test, compared with the month preceding it.

Leucopenia.

The possibility of leucopenia as a complication of treatment is raised by the mention of a case who, while receiving Priscol (dose ?) received also two daily doses of sod. pentobarbital, 0·1 gm. His W.C.C. fell from 9,000 per c.mm. before Priscol to 3,110 ten days after starting the Priscol and two days after the

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Pentobarbital. Two days later it was 5,550 and a month after stopping Priscol had regained its initial value (Grimson *et al.*, 1948).

In this series white cell counts were not done before treatment. In any case they would have been vitiated by the presence of sores or sepsis. White cell counts were, however, carried out on all patients early in April, while still on Priscol. A control group, from the age of 60 to 75, and free from disease, was chosen. In the columns below they are compared, the cases being lettered, and controls numbered. In averaging the case column two figures were omitted: Case C, who was only 35 years, and case I who was known to have pernicious anaemia. This does not actually affect the conclusion, which is that Priscol does not normally diminish the white cell count in doses of 75 mgm. daily.

Cases.		*Controls.*	
A	7,187	1	5,000
B	6,875	2	5,625
C	10,927	3	5,937
D	5,000	4	5,937
E	8,150	5	3,593
F	3,125	6	5,000
G	3,125	7	7,343
H	6,562	8	6,875
I	3,437	9	5,781
K	6,200	10	5,700
Mean:	5,778		5,679

All counts were carried out by one technician under strictly comparable conditions.

It was still thought possible that a few individuals might exist whose bone marrow activity was already depressed, or were otherwise sensitive to the drug, and who would show a leucopenia after months of treatment, as in cases F, G and I. Hence these cases were counted at 7, 9 and 15 weeks after the Priscol was withdrawn.

In addition, the three controls, 1, 5 and 6, whose W.C.C. were lowest, were given Priscol, 75 mgm. daily for 10 weeks, and their progress noted.

	Leucocyte count.			
Case.	On Priscol.	Weeks after Priscol withdrawn.		
		7.	10.	15.
F	3,125	6,406	5,935	8,437
G	3,125	3,593	3,125	4,843
I	3,437	3,125	3,125	7,187

		Weeks on Priscol.		Weeks after Priscol withdrawn.
Controls.	Before Priscol.	7.	9.	6.
1	5,000	4,531	6,562	3,906
5	3,593	5,156	6,562	6,250
6	5,000	3,906	5,156	7,500

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These figures show that three controls whose normal W.C.C. was fairly low, showed no significant increase or decrease during nine weeks while receiving Priscol 75 mgm. daily.

On the other hand, three of the cases who had been treated with the drug in doses of 75, 75 and 100 mgm. daily for four months showed a low W.C.C., and a definite tendency to increase towards normal two to four months after withdrawal. Even if one excepts the case I, who was known to need treatment from time to time for pernicious anaemia, the conclusion seems to be that a few cases show, after prolonged dosage, a tendency to a lowering of the white cell count, which, so far as one can tell, is not dangerous or alarming; and which makes a spontaneous recovery, and should not indicate an immediate withdrawal of the drug.

Every white cell count mentioned above was completed with a differential leucocyte count. Nothing of interest was seen, and so they have not been reproduced. For example, the cases F, G and I, at the end of their course of Priscol had the following differential white cell counts, and venous blood leucocyte counts:

Case.	W.C.C.	Venous W.C.C.	Poly-morph.	Lympho-cyte.	Large monos.	Eosin.	Mast.
F	3,125	3,300	71%	28%	0	1%	0
G	3,125	3,467	66%	20%	8%	6%	0
I	3,437	4,375	73%	25%	0	2%	0

These three cases were edentulous and free from oral sepsis; there was no question of agranulocytosis. The high eosinophil count was unexplained.

Notes on Case C, aged 35.

Admitted 17.xii.38 on certificate, as a schizophrenic with paranoid features, lacrymose and violent at times.

Her heart was normal, P.R. 86 p.m., and the general condition was fair. There was no history of tuberculosis.

28.vi.42: She remained apathetic and dull; mute, asocial and suspicious. A small abscess appeared in the right breast, and an ulcer on the left external malleolus. Later, the right ankle ulcerated, and these ulcers did not clear up for several months.

10.xii.43: Dry sores on the ankles. She had a course of E.C.T. and went to work in the laundry.

18.xii.45: Peripheral circulation poor; feet cold and blue.

3.xii.46: Marked cyanosis and oedema of the feet; confined to bed.

11.xii.47: Stands motionless for long periods; ankles very hard and oedematous.

24.xi.48: In bed, and picking at her skin.

12.iv.49: Catatonic, depressed and suspicious; unemployable and reacting badly to treatment with E.C.T. Cyanosis and oedema of the feet, with long-standing ulceration of lower third of the legs, posteriorly. Leucotomy performed.

17.xi.49: In bed, apathetic and idle. The left calf showed an irregular ulcer of about 4 sq. in., while the right ankle showed two smaller areas of about 2 and 1 sq. in. The floors of these ulcers were dry, dark in colour and showed no signs of healing. (Pulseless.) B.P. 160/110 mm. Received Priscol, 25 mgm. *t.i.d.*

17.xii.50: In bed; feet cool, pale, free from oedema, but still pulseless. Ulcers were scabbed over, and diminished to half the above measurements. Priscol was increased to 100 mgm. daily, and she was allowed up, wearing long woollen stockings, without garters.

12.iv.50: Ambulant; ulcers soundly healed, but with the skin thin and glossy over their sites. There was brawny oedema of both legs, and B.P. 144/100 mm. Cyanotic.

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Condensed Statement of Results.

Case.	Age.	Former lesions; and condition in November, 1949.	Duration (years).	Result of treatment, 31.iii.50.	Mental state.
A	68	Varicose ulceration, with scarring and much loss of tissue	10	Remained well; ambulant	Paraphrenia.
B	48	Healed phthisis; scarring and oedema *Ulcer right calf, ? Bazin*	20 ½	Healed ambulant	Ad. 1930; cert. schizophrenia
C	35	Bazin; *bedfast with spreading ulcers of both legs*	7	Ditto	Leucotomized; catatonic schizophrenia; apathetic
D	52	Extensive scarring; obese *with four large septic ulcers*	5	Healed; ambulant later	Depressed; toxic confusion; ad. 1949
E	78	Unstable diabetic *Gangrene of fourth left toe partly healed*	? 1	Moist; amputated; healed	Organic dement; died in coma three months later
F	75	Scars of sores and shallow ulcers. *Blood blisters*	4 ¼	Healed; ambulant	Feeble-minded deaf mute
G	64	Lymphangitis, sepsis and oedema *Cellulitis*	9 ½	Ditto	Ad. 1930; cert. epileptic
H	73	Oedema both feet *Ulceration both feet*	2 1	,,	Ad. 1908; chronic mania
I	61	Loss, by gangrene, of tips and nail of 6 toes; brown stains of skin-gangrene, healed *Recent spots of skin death*	6	,,	Pernicious anaemia; dementia
K	75	Gangrene toes and ulcerating sores Fracture femur *Incipient gangrene*	30 3 ¼	,,	"Religious mania"; dement

Lesions indicated in italics actually existed and demanded treatment during the month of November, 1949.

Extract from Notes on Case I.

14.xi.49: Bedfast, her feet cold, cyanosed and pulseless; slightly oedematous, with numerous small areas of skin death scattered over the dorsum of feet and toes, some recent, others healing, but all dry and hard.

The finger-nails were normal, but all the toe-nails were absent or atrophic, and the tips of seven toes lost as a result of attacks of gangrene during the last six years.

She was put to bed and given Priscol, 25 mgm twice daily. By the next day her feet were warm and pale, both dorsalis pedis pulses being palpable. B.P. 150/80 mm. P.R. 60 p.m.

24.xi.49: Her feet were found to be cool, so the dose was increased to 25 mgm. *t.i.d.*

29.xi.49: Feet were warm, pink, and all the skin lesions were healing. There was no apparent oedema, the circumferences of ankle and forefoot* being 15½ in. and 15¼ in. on both limbs. Both pulses were palpable.

30.xi.49: Allowed up.

* The sum of the circumferences of the forefoot behind the first metatarso-phalangeal joint, and of the ankle above the malleoli, on each foot.

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11.i.50: Her feet were cold, dusky, pulseless and oedematous, the circumferences being now 16½ in. on both legs. The blood pressure had fallen to 106/70 mm., but the Priscol was now given 6-hourly and she remained ambulant.

12.i.50: Found seated motionless and idle as usual, but quite inadequately clad, with elbow-length frock, cotton stockings, garters, when the ward temperature was 52° F. All the peripheral skin areas, face, neck, arms, hands and thighs were cool or cold. There were several fresh areas of skin death, brownish and papery, with some blister formation, on the dorsum of the feet and most of the toes.

14.i.50: Ambulant, with particular attention to dress, e.g. woollen stockings to mid-thigh, held up without garters, and warmer dress—cardigan. General condition no worse.

15.i.50: The skin was found broken on dorsum of 3rd right toe and behind both heels, probably due to new leather shoes worn inadvertently instead of her own slippers of felt. Her feet were cool, cyanosed and oedematous, 16½ in., 16½ in., and fingermarking for five seconds. B.P. 130/85 mm. P.R. 72 p.m. She was kept in bed, where her feet became warm and dusky, fingermarking for three seconds, but still pulseless.

19.ii.50: Her feet were healing satisfactorily, warm and dusky, both pulses having returned faintly. They were slightly oedematous, measuring 15 in., 15½ in., fingermarking for five seconds. The B.P. had risen to 148/78 mm. P.R. 64 p.m.

20.iii.50: The feet were satisfactory, warm, pink, without oedema and healed. The B.P. showed a continued tendency to rise, 160/80 mm. P.R. 78 p.m.

3.iv.50: Blood examination showed a slight symptomless leucopenia, R.B.C. 3,768,000 per c.mm. Hb. 90 per cent., C.I. 1·2, with slight anisocytosis. (Progress of W.B.C. elsewhere.)

Notes on Case K, aged 75.

Admitted to this hospital in 1895 as a case of "dementia" resulting from "religious mania" she is now amnesic, confused, idle, unable to care for her daily needs and unable to converse. She has a long history of peripheral circulatory disorders, chiefly affecting the feet.

25.iv.10: Vasomotor paresis; cyanosed extremities with small ulcerating sores of the feet.

10.i.11: Confined to bed; small sores on the feet.

11.i.12: Confined to bed; small sores on the feet.

31.iii.13: Tips of second left and third right toes gangrenous. Healed slowly with some loss of tissue. In bed part of every winter.

1.ix.33: Feet blue and oedematous.

14.ii.46: Fracture of neck of left femur, with ultimate recovery.

21.i.49: Confined to bed (till April, 1949).

5.ix.49: Sore on right shin. B.P. 140/93 mm.

27.xi.49: Third left toe shows early gangrene. The feet are warm and pink, but swollen to 9 in. round the instep and pulseless. She was given Priscol, 25 mgm. *t.i.d.*, and her progress was as follows:

27.xii.49: The feet were warm and pink, but oedematous, the sums of the circumferences of the forefoot and ankle being 17 in. and 17½ in. Fingermarks lasted for four seconds. The pulses were palpable, B.P. 132/100 mm. and P.R. 65 p.m.

3.i.50: Third left toe healed; allowed up.

1.ii.50: Feet were warm and pink, fingermarks lasting two and 4 seconds, but the oedema had slightly increased to 17½ in. and 18 in. The pulses were present, the B.P. 130/90 mm., P.R. 60 p.m.

5.ii.50: Volume of blood flow through foot (left) was 15 c.c. per minute. (See below.)

17.ii.50: Priscol was stopped till 20.iii.50. Confined to bed.

18.ii.50: Feet were cool, dusky, fingermarking for five and eight seconds, but otherwise unchanged. The blood pressure was 140/90 mm. and P.R. was 70 p.m.

19.ii.50: Feet unchanged, but B.P. now 150/105 mm. and P.R. 48 p.m.

23.ii.50: The oedema diminished to 17 in., 17 in., and fingermarks lasted only two seconds. The feet were pulseless. The systolic pressure varied between 190 and 212 mm., diastolic remained at 105 mm. P.R. 60 p.m. The morning urine contained 1·95 per cent. urea, and a faint trace of albumen. The blood urea was

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45 mgm. per cent. Rate of blood flow through the left foot was now estimated at 2 c.c. per minute.

27.ii.50: Feet remained as before, the oedema diminishing to 16½ in. and 16½ in., and the systolic pressure varying between 185 and 170 mm., while the diastolic was 80 mm. P.R. was 52 p.m.

20.iii.50: Feet as before and blood pressure was 142/75 mm. P.R. 58 p.m. Priscol restarted and patient allowed up.

31.iii.50: Feet warm, pink, fingermarking for three seconds. Both pulses were present and B.P. 132/95 mm. P.R. 65 p.m. Rate of blood flow estimated at 12 c.c. per minute.

Rate of blood flow was estimated by a plethysmograph method. A bivalve transparent plastic case, made gastight with adhesive plastic strapping was applied to the foot and ankle. It fitted fairly snugly round the ankle and was lightly packed with cotton wool and vaseline at the ankle to minimize accidental movement. Air displaced from it drove a small plug of water along a horizontal glass tube for measured distances. The venous return was occluded at zero seconds as usual by suddenly inflating a sphygmomanometer to 30 mm. below diastolic pressure (Lovatt Evans, 1947, and Barcroft and Walker, 1949). The estimated rate of blood flow is probably less than the actual rate, but the following figures have a comparative value.

Rate of Blood Flow.

Date.			Lapse of time, secs. after occlusion. 5.	10.	20.	30.	Estimated rate of flow c.c. per min.)
5.ii.50	Priscol 75 mgm. daily	Vol. displ. (c.c.)	1·10	2·50	4·80	—	—
		Rate of flow (c.c.)	13·2	15·0	14·4	—	15
26.iii.50	Off Priscol 9 days	Vol. displ. (c.c.)	—	·25	·70	1·0	—
		Rate of flow (c.c.)	—	1·5	2·1	2·0	2
31.iii.50	Priscol 75 mgm. for 5 days	Vol. displ. (c.c.)	·90	1·9	3·7	—	—
		Rate of flow (c.c.)	10·8	11·6	11·1	—	12

Conclusions.

Priscol is a valuable and safe drug in the care of the circulatory disorders of the elderly. It may enable them to remain symptom-free during cold weather without becoming bedfast.

In ambulant cases it does not help oedema caused by stasis. In one elderly diabetic it may have precipitated wet gangrene, where dry gangrene existed.

Side effects in elderly people are negligible where the dose is 100 mgm. daily or less. The drug should be withdrawn gradually.

I should like to thank Dr. Lorriman, of Ciba Laboratories, for his helpful advice and criticism; and Dr. McGregor, of Saxondale Hospital, for his interest in the work. I am very grateful to Mr. Hubbard for the blood counts.

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