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VASODILATORS IN PERIPHERAL VASCULAR DISEASE

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Brilliant achievements in the field of therapeutics have deprived the aged of peaceful death from pneumonia. We shall necessarily be faced with an increase in the number of sufferers from obstructive disorders of the peripheral arteries and arterioles. Their treatment is still disappointing, though sympathectomy marks a therapeutic advance. It is a major operation fraught with hazards for the elderly, and in any case is disappointing in the long run because of the frequency of relapse.

The common vasodilators—for example, nitrites, thiocyanates, and nicotinic acid—though producing intense flushing of the head and neck, seldom, in tolerable doses, influence the circulation in the hands or feet. Throbbing, headache, giddiness, palpitation, and transience of action render the volatile nitrites useless. Glyceryl trinitrate, though persistent, is more likely to cause headache than flushing of the extremities. The thiocyanates in therapeutic doses seem to have no influence on the peripheral limb vessels. Nicotinic acid was hailed as a drug likely to relieve Raynaud's disease and intermittent claudication (inflammatory or arteriosclerotic). It is true that it may cause an appreciable rise in the skin temperature of the feet and hands and its action is more prolonged than that of the nitrites, but the intense burning, pricking, and flushing of the face which must be caused if the extremities are to be influenced renders its use insupportable to the majority.

In the local treatment of vasospastic conditions carbachol or "amechol" (acetyl- β -methylcholine) ionization is of proved value.

Benzyl-imidazoline

The quest for more satisfactory vasodilators led to the discovery of benzyl-imidazoline. The hydrochloride of 2-benzyl-4:5-imidazoline, known by the trade name of "prisol," consists of colourless water-soluble crystals. The structural formula is:

Reports on its efficacy as a vasodilator began to appear in 1939, but interest in the drug lapsed during the war years. Braun (1942) claimed that it dilated arteries, arterioles, and arteriovenous anastomoses but had no effect on

capillaries. It differed, therefore, from histamine, and was stated to have in general a sympathicolytic action which would not be exerted in the absence of an intact sympathetic system. Experimentally it has been shown to block the pressor action of adrenaline. Furthermore, subsequent to prisol administration adrenaline exerts a vasodilator effect, thus resembling its action after ergotoxine. It was at first denied that it had a cholinergic action, but accumulated evidence suggests that this does exist, though the vascular effects mentioned above are not antagonized by atropine.

On the other hand, it increases the gastric HCl and stimulates the gut to contract; both actions can be prevented or overcome by atropine. It is probable that it does have some direct action on the vessel walls which is independent of the sympathetic supply.

Effects on Normal Subjects.—Winsor and Ottoman (1949) studied the influence of benzyl-imidazoline on the peripheral circulation of 70 males with no cardiovascular disease. In these experiments 50 mg. of the drug was injected intravenously. Changes in the volume and temperature of the digits were recorded. The temperature variations in muscle were also noted by means of a special needle inserted into the muscle and connected with the thermo-electric couple. The usual precautions in respect of preliminary rest and constant room temperatures were taken. In normal subjects 30 minutes after injection the temperatures increased over the resting readings as follows: forehead, $1^{\circ}\text{C}.$; index finger, $1^{\circ}\text{C}.$; calf muscle, $0.5^{\circ}\text{C}.$; subcutaneous tissue of calf, $0.25^{\circ}\text{C}.$; skin of calf, $0.5^{\circ}\text{C}.$; skin of toe, $3.75^{\circ}\text{C}.$ There was no measurable alteration of rectal temperature. An increase of volume in fingers and toes was found, it being greater in the toes. The first effect on skin temperature of the digits was noted in about eight minutes after injection and the beginning of subsidence in 50 minutes. The two most noteworthy points emphasized by their experiments were that the lower limbs were affected more than the upper extremities, and that the action of the drug was exerted for much longer than that of the older vasodilators. The first fact is no doubt to be explained by the greater sympathetic control of the leg vessels.

Pallor, sweating, weakness, palpitation, and giddiness occasionally arose in these experiments and in similar ones by others. This effect is known as "prisol shock." It is advisable to test the sensitivity of the subject by administering 25 mg. by mouth. If such a dose has no unpleasant effect, 50 mg. intravenously may be given. If the oral dose causes appreciable flushing of the face, giddiness, or faintness, it is inadvisable to inject the drug into the blood stream.

Effects in Vascular Disorders.—The influence of prisol on obstructive vascular diseases has been widely studied. An excellent summary, with references, is provided by Grimson *et al.* (1948). It seems to be generally agreed that the best therapeutic results are to be seen in diseases in which vascular spasm plays the most important part. Raynaud's disease, erythema pernio, frostbite, and venous spasm resulting from faulty injection of irritants—for example, neosphenamine—are stated to respond dramatically well.

The results in intermittent claudication due to arteriosclerosis are, according to Grimson, less encouraging, and those in Buerger's disease frankly disappointing. He reiterates that prisol has no effect after sympathectomy.

Investigation of Prisol Action

For the purpose of this investigation 10 patients with no vascular disease, 4 with rheumatoid arthritis, 9 with Raynaud's disease, 24 with intermittent claudication of

arteriosclerotic origin, 2 with claudication of thromboangiitis obliterans, and 6 with arterial hypertension without claudication were observed. A miscellaneous group of 6 is also mentioned.

Method.—In every case a test dose of 25 mg. was given orally. In only two was there evidence of prisol shock. They have been excluded from this series. The patients on whom temperature observations were made spent 24 hours in bed before the investigations. The room or ward temperatures were kept as constant as possible, and no experiment was carried out if a variation of more than $1^{\circ}\text{C}.$ was recorded for 30 minutes before the test. Both index fingers and big toes were connected with the thermo-electric coupling skin leads, and 50 mg. of the drug was injected intravenously when a constant skin temperature was recorded from the digits.

Effects in Patients with no Symptoms of Vascular Disorder

Within one to five minutes of the injection a deep flush appeared over the face and neck and there was suffusion of the conjunctivae. A sensation of fullness in the head was complained of, but there was no severe headache. Consciousness of the heart's action or palpitation was not mentioned spontaneously, but was admitted on questioning. The pulse rate never rose more than 10 beats to the minute, and it dropped to normal as soon as the facial symptoms subsided. The rise was probably due to apprehension. Although some flushing of the face might have persisted for 10 to 15 minutes, the sensation and appearance of intense flushing usually disappeared within three to four minutes. About this time a noticeable change in colour of the fingers and hands was observed. A pink flush was soon seen in the feet, usually 10 minutes after the injection but sometimes later. The flushing of the feet and hands and the associated rise of temperature lasted from 50 to 90 minutes.

The readings before the injection showed that the finger-tip temperature was usually 5 to $6^{\circ}\text{C}.$ higher than that of the toes. Coincident with the flushing there was a rise of skin temperature in the fingers from 2 to $3^{\circ}\text{C}.$; and in the toes from 6 to $7^{\circ}\text{C}.$ (Fig. 1). During the height of the drug's action the two temperatures closely approached each

FIG. 1.—Man aged 32. No vascular disease. Record of finger and toe temperatures after intravenous injection of 50 mg. of prisol.

FIG. 2.—Man aged 67. Vessels normal for age. Note poor response owing to age. Compare with Fig. 1.

other, but the skin temperature of the toe never exceeded that of the finger.

It was found that individuals who were 60 years of age or more showed a slighter reaction both in the form of flushing and in the rise of temperature (Fig. 2). The latter might be only 0.5 to 1° C. in the finger and toe. Six such patients who were investigated were entirely free from symptoms of vascular disease: it must be assumed that senile rigidity of the vessel walls was already appreciable.

Effects in Patients with Vascular Disease

(a) Rheumatoid Arthritis

It is known that in active rheumatoid arthritis there is a grossly deficient circulation in the arterioles and capillaries of the fingers and of the toes if these are involved in the disease. Four such cases were given priscol, and in

FIG. 3.—Woman with rheumatoid arthritis chiefly affecting the fingers.

two of them temperature recordings were made. In three the general reaction was very much that already described in the normal, but in one whose temperature record is shown (Fig. 3) and whose fingers were chiefly involved it is seen that the finger temperature was much lower than that of the toe and that it rose rapidly some 5 or 6° C. after injection of priscol. During the priscol action there was some relief of stiffness in the affected joints in all four cases, but it was not enough to encourage further treatment, and in fact the subsequent administration of the drug by mouth produced no noticeable benefit.

(b) Raynaud's Disease

The nine female patients with Raynaud's disease had suffered from this for periods varying from 4 to 15 years. The three worst cases showed either small ulcers or scarring from previously healed ulcers on one or more finger-tips, extensive trophic changes of the skin and subcutaneous tissue of the fingers, and persistent patchy pallor with areas of cyanosis extending the whole length of the fingers and present even in the summer. The remaining six frequently had typical and severe attacks in the winter months and again when the hands became chilled, especially from immersion in cool water.

The immediate effect of priscol injection was dramatic, and was well shown in three cases of extreme severity. The usual changes, already described under "Effects on Normal Subjects," were seen, but in Raynaud's disease the feet flushed before the hands. We observed an early flushing of the proximal portion of the palms of the hands, and then some 10 to 15 minutes after the injection we could observe a steady advance of the edge of the pink area, spreading over the back and palm of the hands and up the fingers from the roots until finally even the tips were pink and warm. In the milder cases not actually presenting Raynaud's changes at the time, these were induced in one hand

by immersion in cool water. Flushing from the drug then spread in the normal manner in the opposite hand and feet, and after a delay of about five to ten minutes the hand showing the Raynaud phenomenon gradually partook of the general vasodilatation. The most remarkable effect of priscol on patients with Raynaud's disease is that benefit seems to be much more lasting than it does in other vascular diseases (Fig. 4).

FIG. 4.—Unmarried woman with Raynaud's disease had had 25 mg. of priscol by mouth two days previously; this had caused her hands to flush, and they remained warm. The toes of one foot remained blue and cold until 30 minutes after injection of priscol, when they slowly flushed. Feet and hands remained warm and of normal colour for seven days, though no further treatment was given.

In one patient whose life had been made a misery by pain and coldness of the fingers without intermission for the previous six months a single injection of 50 mg. of the drug caused warmth of the fingers and loss of pain for seven days. In every case it was noted that in Raynaud's disease the effect never passed off completely in less than eight hours, and benefit lasted from one to two days after single injection in five other patients.

The treatment was then continued by giving 25 mg. of priscol by mouth four times a day with the aim of raising the dose to double this amount if it could be tolerated. The late results were not so encouraging as those which followed injection. The drug produced warmth of the extremities, but the patients seem to be peculiarly susceptible to the side-effects of priscol when it is taken regularly, although this is not shown on the single injection. Of the nine sufferers five declared themselves completely comfortable on a dose of 25 mg. four times a day; the other four have elected to take the drug from time to time, for it seems that if it is taken by mouth for a day or two it will give relief extending up to two weeks. During the days they are taking it they do, however, experience unpleasant palpitation, flushing, and giddiness which is more noticeable now that they are ambulant. If the dose is reduced to a level which will not cause these side-effects it also seems to fail to relieve the Raynaud symptoms.

With the exception of the results of ionization with carbachol or amechol the effects of priscol are far and away superior to those of any of the other vasodilators. It has been noticed, in local treatment with the carbachol group of drugs, that after 10 to 12 daily applications there is a tendency for the disease to remain quiescent for two or three months. It therefore seems that anything which will break the vasospasm is likely to give quite prolonged relief

in Raynaud's disease, whereas this does not occur in other forms of vascular obstruction.

(c) Intermittent Claudication

There were 24 male patients suffering from intermittent claudication due to arteriosclerosis. The youngest was 55, the oldest 70. Temperature recordings were made in six of these, and it was noticeable that the rise of temperature in feet and hands was at a much lower level than that of the normal. It corresponded, however, closely to the group of elderly persons without symptoms and signs of arteriosclerosis. These patients were later tested with priscol by mouth, again aiming at a dose of 50 mg. four times a day. This dosage was tolerated by them quite well except in five instances where only half could be taken. The effect of treatment was judged by the distance which could be walked without bringing on pain: this had been noted carefully before treatment was undertaken. Results were not recorded as good unless this distance was at least double the pre-treatment exercise. In 12 the results were good, the best being in a man of 56, whose walking capacity increased from 100 yards (91.5 metres) to half a mile (804 metres). In the older patients who improved, the range of increased activity without pain was usually an extension from 100 yards up to 500 yards (457 metres). It was noticeable, however, that the night pain of which so many of these patients complained was abolished in all the successful cases. There seemed to be no close relation between the age of the patient and the result, apart from the exceptionally good result already mentioned in the man of 56. In two there were trophic ulcers on the toes, which were blue and cold; the ulcers healed completely after three weeks' treatment.

From the observations of Ratcliffe (1949) it seems probable that large doses of vitamin E are likely to be more effective for this group. It might be well to combine it with benzyl-imidazoline in the first two months of treatment.

Only two patients with thromboangiitis obliterans were available for testing. In one, a man aged 41 (Fig. 5), the

FIG. 5.—Man with thromboangiitis obliterans with severe claudication. No arterial pulsation below femoral level.

temperature reaction to intravenous injection was extremely good, being pronounced in the legs. He, as might be expected, benefited considerably from taking the drug, although he was unable to manage more than 25 mg. five times a day. If any individual dose was larger than this he suffered from unpleasant side-effects. His walking capacity has been increased from 250 yards (228 metres) to a mile (1.6 km.). The other patient, aged 48, showed only a very slight flush after an intravenous injection of 50 mg., and oral administration was of no benefit.

(d) Hypertension

Six patients with hyperpiesia and no signs of arterial obstruction were tested for the effect of priscol, symptomatically and on the height of blood pressure. It has long been recognized that the blood pressure is not affected by the drug in doses below 100 mg. This dose was given to all six by mouth and caused intense flushing, palpitation, headache, and giddiness, and in two a sensation of dying. The pulse rate rose from 15 to 30 beats a minute. The systolic blood pressure fell 30 to 55 mm. Hg and the diastolic 10 to 15 mm. Hg. It was observed that smaller doses might produce almost equally unpleasant side-effects in hyperpietics without any fall of blood pressure.

(e) Miscellaneous

Five patients with chronic fibrositis and much general stiffness and one with sclerodactyly were treated with priscol intravenously and subsequently by mouth. In the rheumatic cases the flushing followed the usual pattern, but there was no appreciable loss of stiffness or pain. The woman with sclerodactyly showed a slow but satisfactory response in the fingers, which had already undergone trophic changes closely resembling those of Raynaud's disease. Improved movement followed, but she has not been under observation long enough to justify any further report.

Discussion

From the above observations it is clear that benzyl-imidazoline is a powerful vasodilator which seems to exert its main effect on the arteries and arterioles of the extremities; only in larger doses does it give rise to widespread dilatation and fall of blood pressure. It is singular in that, in contrast to other vasodilators, it has only transient effect on the blush area but has striking and prolonged influence on the vessels of the fingers and toes. Although the study of the pharmacology is not yet complete, it seems that the main effect of the drug is that of a sympatholytic substance, but, in spite of earlier statements to the contrary, it is probable that there is also some direct effect on the vessel wall independent of the sympathetic supply. In one of the three very severe cases of Raynaud's disease mentioned above, the patient had been subjected to sympathectomy, both lumbar and cervical, with relapse of symptoms within one year. Her reaction to priscol was prompt and highly satisfactory.

From what we have observed of the effect on the temperature of the skin of the limbs in elderly persons as compared with the young, and in the purely vasospastic diseases as compared with the organic obstructive affections, it must be obvious that the best results are to be looked for where the element of spasm is maximal and organic blockage of the lumen is minimal. The complaint which stands out as suitable for priscol treatment is Raynaud's disease, but the proportion of cases of arteriosclerotic intermittent claudication which benefit from the drug is surprisingly high. It would seem rational to give the substance in cases of arterial spasm following trauma or embolism, and again in those disastrous instances of vasospasm arising from the introduction of thiopentone into an artery.

Summary and Conclusions

The effects of benzyl-imidazoline have been investigated in 10 normal subjects, 45 persons suffering from vascular disorder, one with sclerodactyly, and five with fibrositis.

Its pharmacology and literature have been briefly described.

Its value as a vasodilator in certain diseases has been discussed.

Benzyl-imidazoline has been found to have a more lasting vasodilator effect than other drugs commonly employed for this purpose. It has an elective affinity for the smaller arteries and arterioles of the fingers and hands and toes.

It is relatively non-toxic, but may produce certain unpleasant side-effects, which can usually be avoided by suitable gradation of dose.

It is outstandingly successful in the treatment of Raynaud's disease and of appreciable value in that of intermittent claudication of arteriosclerotic origin.

It should not be used for the treatment of arterial hypertension.

The weight of evidence is that it is of little value in thromboangiitis obliterans, but even here it is worthy of trial.

We express our thanks to Messrs. Ciba Laboratories Limited for the generous supply of priscol for these tests.

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FACTORS ASSOCIATED WITH PERFORATION IN PEPTIC ULCER

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This article records the results of a study designed to determine the factors associated with the development of perforation of peptic ulcers, and in particular to see if it is possible to predict the imminence of this complication.

The material consists of all cases of perforated peptic ulcer admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, during the one-year period February 1, 1948, to January 31, 1949. In this time 189 patients were admitted. All, except two who came to necropsy, were treated surgically, consequently the diagnosis was confirmed in every case. Each patient was seen by one of us within a few days of admission and a detailed history was taken by following a set questionnaire. Thus, in addition to the patients' own statements, each was asked the same leading questions, and the moment of perforation was such a dramatic event that, almost without exception, they retained a vivid memory of what they were doing at the time and immediately before it. A full history was not obtained, however, in three critically ill patients.

Sex Incidence.—Of the 189 cases, 177 were males and 12 were females. Thus the male-to-female ratio is 14.8:1, which is much greater than the same ratio for peptic ulcer as a whole, which Tidy (1945) has given as 3.6:1. We have collected figures from the literature showing that of 1,349 cases of perforated peptic ulcer only 51 occurred in women, giving a ratio of 26.4:1. Therefore it would appear that not only is peptic ulcer less common in women but that, when present, the liability to perforation is considerably less than in men. Table I shows the age distribution in decades, the mean age, and the standard deviation for both sexes. It indicates that perforation is rare under the age of 20, but has a fairly even distribution in other decades.

TABLE I.—Age Incidence

Age in Years	No. of Male Cases	No. of Female Cases
Under 20	0	0
20-29	36	0
30-39	40	2
40-49	40	5
50-59	38	3
60-69	15	2
70-79	7	0
80 and over	1	0
Total	177	12
Mean age	44.5 ± 1.1	49.3 ± 2.9
Standard deviation ..	14.3	10.0

Occupation.—Thirty-five patients (18.5%) had jobs entailing a degree of responsibility which in our opinion was at least equivalent to that usually held by a foreman. This figure may be significant, for only 5% of the population served by this hospital have employment with a similar amount of responsibility.

Personal Factors.—An inquiry was made into some of the personal habits of the patients during the month which preceded perforation. The results of this are listed as follows:

Unusual cause of worry (e.g., employment, housing, or domestic difficulties)	33 cases
Unusually long hours of work	47 "
Irregular and hurried meals	58 "
Moderate smokers	116 "
Heavy smokers (over 20 cigarettes a day) ..	55 "
Heavy drinkers (over 4 pints (2.3 litres) of beer each night or 15 pints (8.5 litres) at the week-end)	20 "

History

Previous Perforation.—A history of previous perforation was obtained in 22 cases (20 men, 2 women), and three of these had perforated twice before their present admission. Therefore 11.6%, or 1 in 8.6 cases in this series, had had a recurrent perforation. Pearce (1932) analysed the reports of 4,813 cases of perforated ulcer and found only 33 instances of recurrent perforation—an incidence of 0.69%, or 1 in 145 cases. The information in our series was deliberately sought by direct questioning, and it may be that recurrent perforation is more common than hitherto supposed.

Previous Haemorrhage.—A history of previous gastrointestinal haemorrhage was obtained in 13 cases (6.9%).

Length of History.—Table II shows the duration of preceding gastric symptoms. It was once thought that most ulcers which perforated were acute or of recent origin. It will be seen from Table II that 129 cases (68%) had

TABLE II.—Duration of Symptoms

No. of Cases	No. of Cases
No previous symptoms	13
Less than 1 week	4
1 week to 1 month	18
1 month to 1 year	22
1 to 5 years	46
5 to 20 "	61
20 to 30 years	15
30 to 40 "	6
Over 40 "	1
No information	3
Total	189

suffered from gastric symptoms for a year or more. This suggests that a long history has a definite bearing on the likelihood of an ulcer to perforate, and these figures support the view put forward by Gilmour and Saint (1932) that the older an ulcer becomes the more chance it has of perforating.

Type of History.—Those patients who gave a history of previous indigestion were divided into two groups (Table III), one comprising those with a typical ulcer history

TABLE III.—Type of History

Typical ulcer history	121 cases, 64.0%
Vague dyspepsia	52 " 27.5%
No previous indigestion	13 " 7.0%
No information	3 " 1.5%
Total	189 " 100%