Aug. 10, 1965 P. M. CURTAY ETAL 3,200,037

TOPIC ANGIOTONIC COMPOSITIONS

Filed Jan. 22, 1962

Fig. 1

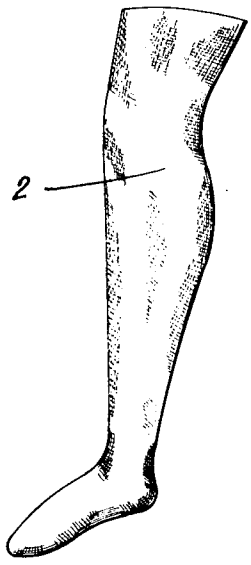


Fig. 2

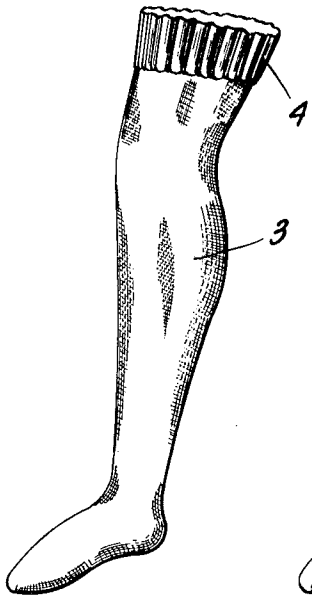


Fig. 3

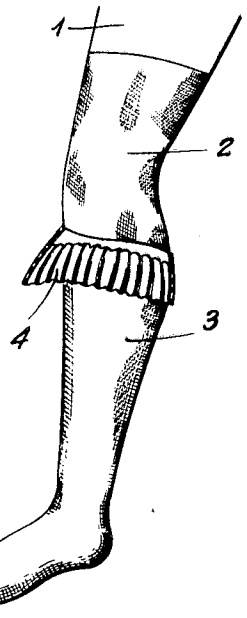
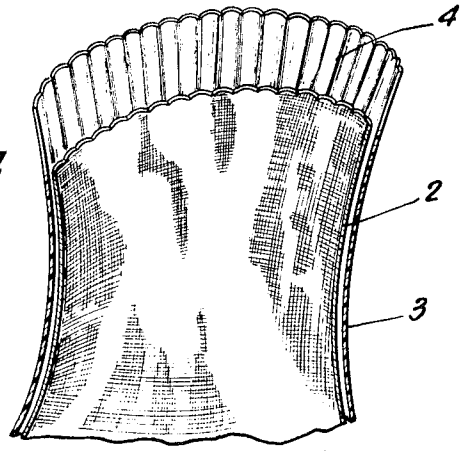


Fig. 4



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3,200,037

TOPIC ANGIOTONIC COMPOSITIONS

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2 Claims. (Cl. 167—62)

It is an object of this invention to provide pharmaceutical compositions to be applied locally on skin for the treatment of circulatory disorders, more particularly pharmaceutical compositions to be maintained locally on the skin of an upper or lower limb with a view to improving in depth circulatory insufficiency, more especially predominantly venous or venolymphatic circulatory insufficiency.

Another object is to provide compositions as aforesaid useful for prophylactic, therapeutic or cosmetic purposes.

Up to this time, from a prophylactic standpoint uneasily applicable or little efficient precepts had been given. Creams to be applied by rubbing have the inconvenience of congesting tissues which on the contrary should be decongested. Special "Nylon" stockings as proposed often produce an unpleasant heat feeling. True varix stockings provide a desirable aid, but few women accept to wear the same at an age at which protection is still possible. Cures in watering places are often too costly, considering the sojourn expenses and the loss of salary for three weeks.

From a therapeutic standpoint sclerose and surgery do away with the bad parts, they improve circulatory hydraulics, but there is no improvement in depth of tissues and vessels. Furthermore there are numerous cases in which both methods cannot be resorted to either by reason of a lack of visible veins to be removed, or because people are scared of injections or surgery, or because any one of those methods previously applied failed to produce the expected result.

Our method and compositions have been devised more particularly for the following curative, prophylactic and esthetic purposes:

(1) Curative purposes: treatment of disorders arising from the presence of more or less important varices, ulcers, recent or old phlebitis sclerous, hypodermites (lymphlegs); associated troubles such as edemas, varicose eczema and stiffness in joints, and lymphedemas in upper and lower limbs (in the latter case as a complementary treatment associated with intermittent compression treatment).

(2) Prophylactic purposes: patients about to be operated or as a pre-, per- or post-operatory treatment in the case of admittedly thrombogenous operations, for pregnant women or after delivery, for patients having familial varicose records, for standing workers (e.g. shopmen and women, dental surgeons, mothers of family), for preventing lymphangitis rashes, for persons having varicosities.

(3) Esthetic purposes: cases of cellulitis, thinning of legs and ankles, heaviness feeling, tiredness in the evening or during hot periods, swelling without apparent medical reason in the evening or during hot periods, red or purplish colour, feeling of burning or cold in feet.

We have found that for preventively or curatively treating circulatory disorders, particularly in legs, both for therapeutic and esthetic purposes, it is desirable to provide

compositions to be laid without rubbing and maintained on skin, and which are so compounded as to comprise along with an angiotonic agent or agents capable of being absorbed transcutaneously, one or more volatile agents effective to cause a mild cooling of skin and underlying tissues, i.e. a mild hypothermia (hibernotherapy).

The maintenance of such a composition on a more or less wide area of human body skin, for example a leg or portion of a leg, may be visualized as a local bathing, the effects of which may be compared to those of a cure in a health resort but are more quickly and intensively developed.

Angiotonic agents of vegetable origin of the class of benzoin tincture and preparations containing vitamin P were found particularly effective for association with a volatile cooling agent or agents; for practical purposes we found by research and experiment that liquid extracts of hamamelis and benzoin extracts should be preferred although other preparations containing vitamin P such as horse-chestnut extracts and alcoholatures, and compositions containing rutoside may also be employed.

Suitable volatile cooling agents which may be employed singly or jointly are acetone, camphor, menthol, ethyl ether and chloroform. Preferable cooling agents are camphor and menthol which appear to produce a favorable angiotonic effect in addition to produce a mild hypothermia. It is well-known that applied on skin camphor and menthol determine a feeling of coolness. For example camphor which volatilizes at 15° C. causes a mild hypothermia if it is contacted with leg epidermis at a temperature of 28° C.

A further desirable ingredient of our compositions is ethyl alcohol which plays the roles of a carrier, of a penetrating agent, assisting the ingress of the angiotonic agent or agents into and through the epidermis and derm, and also of a cooling agent. Alcohol is capable of dissolving fats and also produces a vasodilation facilitating penetration before cold has produced a vasoconstriction, the sequence of which is believed favorable as vasomotricity gymnastics.

A still further desirable ingredient of our compositions is glycerol which is useful as a carrier for the angiotonic and cooling agents. It is our feeling as a result of numerous experiments that glycerol has a favorable effect which is not simply that of a carrier, in the treatment of the disorders above referred to, but so far we are not in position to bring a scientifically satisfactory proof of that effect. An alternative carrier for liquid compositions is propylene glycol.

Our pharmaceutical compositions preferably contain from 1 to 20 parts by weight of an angiotonic agent or agents intimately mixed with from 2 to 10 parts by weight of a volatile cooling agent or agents, and 97 to 70 parts by weight of a carrier selected from the class consisting of glycerol, aqueous glycerols, hydroalcoholic glycerols, propylene glycol and ointment excipients.

Preferred compositions are compounded as follows, the percentages being by weight:

Menthol	2.5 to 6%
Camphor	2 to 4%
Ethyl alcohol (90 percent by volume)	20 to 30%
Chloroform	2 to 6%
Benzoin tincture	2 to 5%
Hamamelis liquid extract	10 to 15%
Glycerol (30° Bé.)	61.5 to 34%

The hamamelis liquid extract referred to (Extractum Hamamelidis liquidum) is produced by percolating moderately coarse hamamelis leaf with 45 percent ethyl alcohol, and the benzoin tincture (Tinctura benzoinis) by causing crushed benzoin (200 g.) to macerate for 10 days in 75 percent ethyl alcohol then filtering.

A particularly effective composition (A) contains the above ingredients in the following proportions by weight:

(A)

	Percent
Menthol	4
Camphor	2.5
Ethyl alcohol (90% by volume)	23.5
Chloroform	4
Benzoin tincture	3
Hamamelis liquid extract	13
Glycerol (30° Bé.)	50

In making composition (A), it is preferred to add crystalline camphor to menthol, to leave the mixture standing for say 24–48 hours, to add chloroform, then alcohol and afterwards benzoin tincture and hamamelis liquid extract while stirring, and to leave the mother mixture or master batch thus prepared standing for say 24 hours or more. Glycerol may be added at the time or later, the composition being stirred at the time of use.

In the above compositions when used for cosmetic purposes, chloroform may be omitted, the ethyl alcohol and/or glycerol being increased correspondingly. To the angiotonic agents shown as being hamamelis liquid extract and benzoin tincture may further be added azulene, alantoin or histamin by as small an amount as about 0.001 to about 0.1%; azulene and/or histamin are desirable for patients liable to eczema. Also a perfume may be added.

Further compositions also found to be effective particularly for cosmetic purposes are given below to illustrate possible modifications in the nature and proportions of the ingredients.

(B)

	Percent
Camphor	4.7
Ethyl alcohol (90 percent by volume)	17
Benzoin tincture	1.7
Azulene	0.3
Perfume	0.3
Glycerol	26
Distilled water	50
	100

(C)

	Percent
Ethyl alcohol (90% by volume)	12
Menthol	2.25
Hamamelis liquid extract	6.75
Propylene glycol or glycerol	79
	100

For maintaining on skin our pharmaceutical compositions which are of liquid character, several means may be employed, particularly according as the case is severe or not.

With severe cases, it is desirable to employ gauze bands for example having a width of about 4 inches and a length of about 12 feet, moisten the same with water, drain to remove excess water, and dip the same in the pharmaceutical composition. A first band thus impregnated with pharmaceutical composition is then wound loosely for example around a leg from the toes up to below the knee, then one to three like bands may be wound similarly, and the combination is covered with a dry band for example a cotton band. Such a bandage will be renewed as frequently as required, generally twice or three times a week. In average cases, twelve bandage applications are enough; more are required in the case of a severe ulcer, phlebitis

or post-phlebitis disorders. The treatment is an "ambulatory" treatment, no rest being required.

With less severe cases, a thicker, slightly elastic band, preserving its resiliency after impregnation with the pharmaceutical composition may be applied, such a band being wound preferably from the toes to the top of the thigh with a view to compensating for the shorter period of application one hour for example, by means of a wider application area.

With still milder cases or for esthetic purposes where the patient wishes to be treated at home or by himself or herself, it is desirable to employ a sheath or hose which will now be described (reference will also be made to copending U.S. patent application Serial No. 109,522 filed May 12, 1961 in the name of Adrienne M. Curtay).

The sheath is made of an absorbing, resilient material adapted to be impregnated with the pharmaceutical composition; said sheath may have the shape of a complete hose, a sock, with or without toe end, or a thigh piece, to be placed on the leg or corresponding part of leg and retained thereon by its own elasticity; it may be made of woven or knitted fabric with or without ribs, resiliency being provided by the texture and/or the nature of the material, and/or by incorporating resilient, for example rubber threads in the fabric.

Although cotton is preferred as a constituting material for the sheath, other materials, whether textile or not, may be employed.

Such a sheath after it has been impregnated with the pharmaceutical composition and put on the leg is adapted to maintain a considerable amount of the active components of the composition in contact with the leg skin providing a kind of permanent bathing in the pharmaceutical composition.

The absorbing sheath may be combined with an impervious sheath having the same shape which may be made of any impervious, flexible material to be placed over the absorbing sheath. The impervious sheath is made preferably of a plastic material, in particular from a polyvinyl chloride or other thermoplastic material sheet which is cut to the suitable shape and welded, or of impervious textile material suitably sewn or welded. The impervious sheath is effective to prevent the garments from being moistened or stained by the pharmaceutical composition.

The impervious sheath is preferably made with suitable resiliency to be maintained in position on the absorbing sheath or as the case may be to maintain the absorbing sheath in position on the limb. For that purpose, the impervious sheath may have ribbed edges or may be provided with separate resilient edgings, or arranged to be held with garters.

Alternatively the absorbing sheath and the impervious sheath may be combined into a piece of garment, the absorbing sheath providing an inner lining for the impervious sheath. For practical purposes, the piece of garment is turned inside out to expose the absorbing face thereof which is impregnated with the pharmaceutical composition then the whole is turned again and the leg introduced into the same.

In the herewith drawings, illustrating our invention:

FIG. 1 shows an absorbing sheath,

FIG. 2 shows an impervious sheath,

FIG. 3 shows the absorbing sheath only partly covered with the impervious sheath.

FIG. 4 is an exploded view of the top portion of an absorbing sheath and an impervious sheath placed over the same.

For the treatment of a leg 1, an absorbing sheath 2 (FIG. 1), preferably made of cotton and adapted to be impregnated with a pharmaceutical composition is shaped as a hose to be placed as shown on FIG. 3.

An impervious sheath 3 (FIG. 2) made of plastic material or rubbered textile fabric for example, is adapted to be placed over the absorbing sheath 2 and has the

same hose shape; the impervious sheath 3 may be formed with a top, resilient, ribbed squeezing section 4 as shown or alternatively may be employed with garter. The impervious sheath 3 is shown on FIG. 3 before it has been completely drawn over the absorbing sheath 2.

It will be readily apparent that like sheaths may be made to be placed on an arm.

Instead of impregnating a porous support with the pharmaceutical composition and placing the support on skin as described, it is possible to spray the composition, provided the composition is fluid enough, by means of an inert gaseous propellant such as nitrogen or a Freon either directly on the skin or on and through a porous support previously laid on skin. The composition may be compounded to contain a propellant as employed for aerosols which is liquid under the pressure prevailing in the container provided with a spray nozzle.

In the development of our invention, the first step in our research was the local application of CO_2 snow. We were impressed in finding that a thickened face skin (trophic disorders) with dilated vessels (circulatory disorders) gave a very favorable response to slight, simply weekly applications of carbonic snow.

We then attempted to act similarly on trophic and circulatory disorders in lower limbs. As physical agents such as carbonic snow did not prove to be satisfactory enough, we substituted therefor one then several of the above mentioned volatile cooling agents. We then conceived to add angiotonic agents as above set forth. The best results were obtained with a temperature drop of from about 2° to about 5° C. The desired drop in the various cases was induced with a single or several volatile cooling agents according to the rate of volatilization. It was found that a mild hypothermia causes the local metabolism to be lowered, inhibiting catabolism more than anabolism. In spite of the oxygen scarcity due to stasis, diseased tissues were eventually regenerated and showed transformations which characterize young tissues.

With the addition of angiotonic medicines to said cooling agents, we found a therapeutic and prophylactic effect showing a synergetic cooperation, which is by far more potent than the effects of the components considered singly. There is a surprising therapeutic effect which is proved clinically and corresponds to a restored-to-normal, functional condition with almost complete disappearance of some lesions. Although our invention should not be considered as limited by any theoretical tentative explanation, the effect obtained is likely to be ascribable to hypothermia placing tissues in a relative rest condition by lowering the metabolism thereof and rendering said tissues more receptive to the action of angiotonic agents by a potentializating effect.

Ulcers quickly heal and the tissues which are rebuilt do not have the "cigarette paper" thinness found after application of usual medical methods, nor a pigmented or blackish color, but have the color of healthy tissues and an absolutely normal consistence. Any admittedly irreversible lesions such as pigmentations of old ulcers or dark pigmentary dermititis of varicose patients, with or without sclerosis are more clear and flexible in most cases. Pain is alleviated then disappears very quickly *pari passu* with a recovery of normal functional condition in about 90 percent of cases, whether benign or severe. Recent phlebitis can be healed by means of our pharmaceutical compositions without anticoagulating agents and without requirement for rest: post-phlebitic disorders such as edemas, pains, joint stiffness, indurated hypodermitis and various troubles with chronic varicose patents are improved to a wide extent. Our pharmaceutical compositions cause disappearance of the feeling of heaviness, tiredness and pains of standing workers and pregnant women; they also provide a useful assistance in the treatment of upper limb circulatory disorders, in particular lymphedemas following mastectomy, painful or painless lymphedemas of lower limbs, lymphangitis and cellulitis (in the latter case the improvement in blood circulation renders the tissues receptive to action of conventional treatments which have been so far ineffective), pre-, per- and post-operation prevention in admittedly thrombogenous surgical operations or with predisposed varicose patients. The compositions of this invention enable of preparing patients for sclerosis or surgery or varicose veins because they improve blood circulation in depth and impart increased vitality to tissues and vessels.

Our pharmaceutical compositions are also of prophylactic interests for those who have familial varicose records or are predisposed by reason of their calling or a pregnancy condition, or for those who have small lesions such as varicosities, slight edema in the evening or like signs indicating a latent venous or venolymphatic insufficiency. The compositions according to this invention produce a quick lightening of legs, a removal of the permanent feeling of burn or cold, a steady thinning and a more natural color, which should be appreciated by women who take care of the esthetic appearance of their legs.

What we claim is:

1. A composition for improving in depth predominantly venous or venoylmphatic circulatory troubles in limbs, which comprises from 2.5 to 6 percent by weight of menthol, 2 to 4 percent by weight of camphor, 20 to 30 percent by weight of 90 percent by volume ethyl alcohol, 2 to 6 percent by weight of chloroform, 2 to 5 percent by weight of benzoin tincture, 10 to 15 percent by weight of hamamelis liquid extract and 61.5 to 34 percent by weight of glycerol.

2. A composition for improving in depth predominantly venous or venolymphatic circulatory troubles in limbs, which comprises 4 percent by weight of menthol, 2.5 percent by weight of camphor, 23.5 percent by weight of 90 percent by volume ethyl alcohol, 4 percent by weight of chloroform, 3 percent by weight of benzoin tincture, 13 percent by weight of hamamelis liquid extract, and 50 percent by weight of glycerol.

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