DRUGS IN PREVENTION AND TREATMENT OF FROSTBITE

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Pathophysiology of frostbite as yet is not clearly understood, its pharmacotherapeutics empirical, the specific drugs are lacking and treatment most of the time is palliative and symptomatic. There are mainly two schools of thoughts regarding the mechanism of cold injury. One school believes that cold directly acts on the tissue and causes traumatic lesion to the tissue which is like any of the other physical agents.

The other group propounds that tissue damage is secondary to the injury to the blood vessels with vasoconstriction, stasis of blood and sludging of R.B.C.'s in the vessels causing occlusion, resulting in ischaemic necrosis of the part.

The work of H. T. Meryman supports this contention. He has shown that in experimentally induced cold injury the blood entering into the tissue is markedly slowed in its passage by vasoconstriction and increased viscosity. There is a marked discrepancy between the oxygen consumption and oxygen supply to the tissue, thus the slight but significant oxygen demand of the tissue at that cold temperature is sufficient to deplete all available oxygen and results in ischaemic necrosis (Naval Project, 1953).

Keeping these observations in view, it is presumed that one of the ways to prevent frostbite would be to develop a drug or drug combination which would maintain patency of blood vessels and adequacy of blood flow. With this object in view work was undertaken on various vasodilators with blood flow as a parameter.

MATERIAL AND METHODS

A large number of drugs, sympatholytics, ganglionic blocking agents and the vasodilators, have been used in frostbite but are far from ideal.

The well known vasodilatory properties of nicotinic acid with an assumption that vasodilation is accompanied with increase in blood flow induced us to take up work on nicotinic acid and some of its congeners. As is well known that long term administration of nicotinic acid is not devoid of side-effects and causes gastrointestinal disturbances, hepatotoxicity and pooling of blood in the vascular bed. To obviate these side-effects and to get an enhanced activity of the drug the following congeners were synthesised and tried.

1. Nicotinic acid (Sodium salt-water soluble)
2. Ethyl nicotinate (Water soluble)

3. Methyl nicotinate (Water soluble)
4. Calcium nicotinate (Suspension in Gum acacia)
5. Aluminium nicotinate (Suspension in Gum acacia)

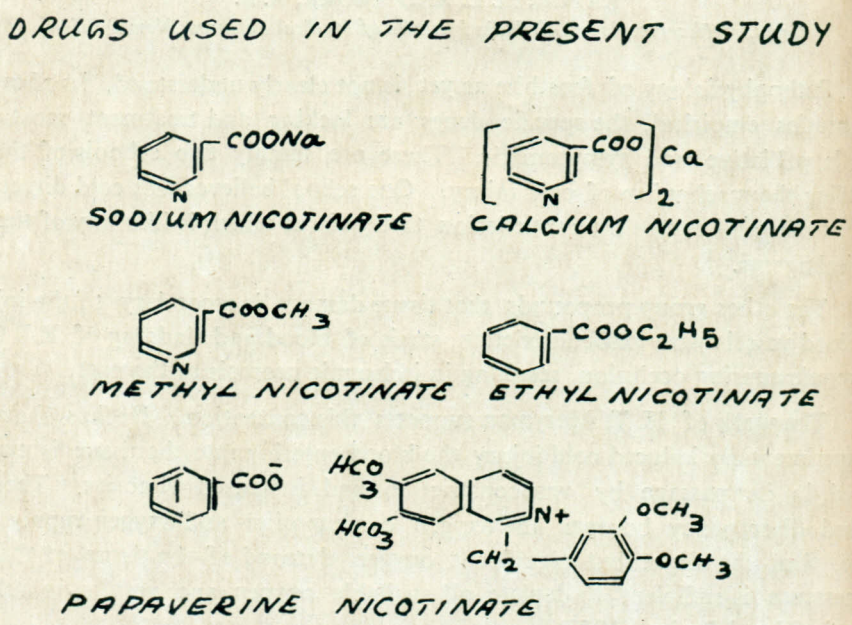

Fig. 1. Showing chemical structure of some of the compounds.

Some of the other known vasolidators which were tried are:

1. Tolbutamide (as aqueous solution)
2. B. Pyridyl carbinol (as aqueous solution)

Drugs were given in graded doses by various routes in permutation and combination, keeping the final volume of the drug to be injected as constant.

EXPERIMENTAL PROCEDURE

126 successful experiments have been done in all. Mongrel dogs of either sex weighing between 12-15 kg. were taken for the experiments. After a prior inhalation of ether they were given chloralose 120 mg/kg at 41°C as one per cent solution intravenously. Blood was rendered incoagulable by intravenous administration of heparin 340 international units/kg as initial dose and repeating half the initial dose after every one hour.

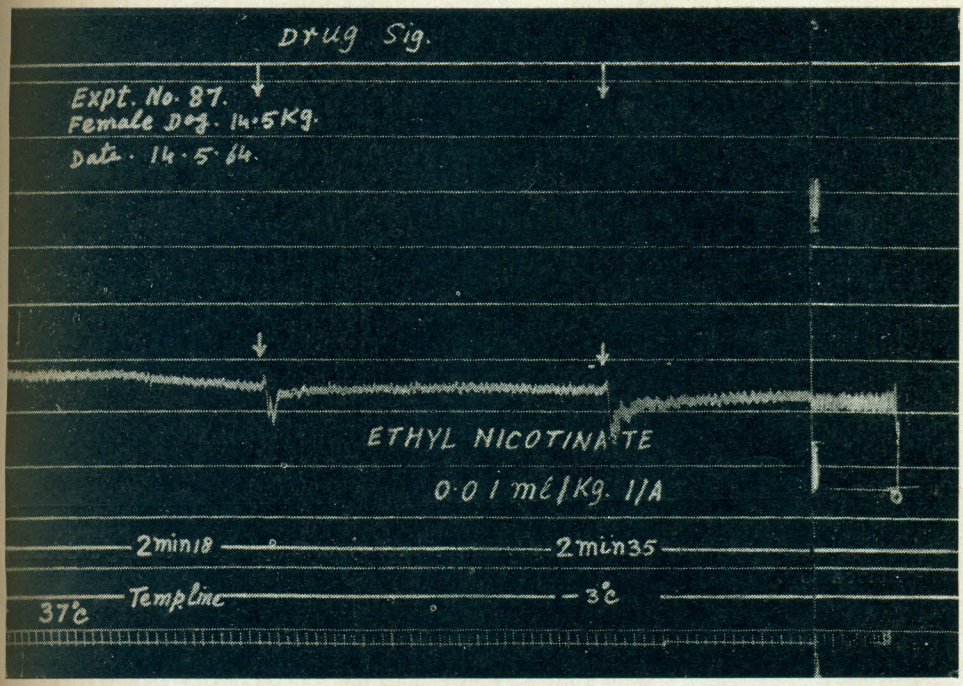

Fig. 2. Showing effect of ethyl nicotinate on dog's carotid blood pressure tracing and femoral blood flow.

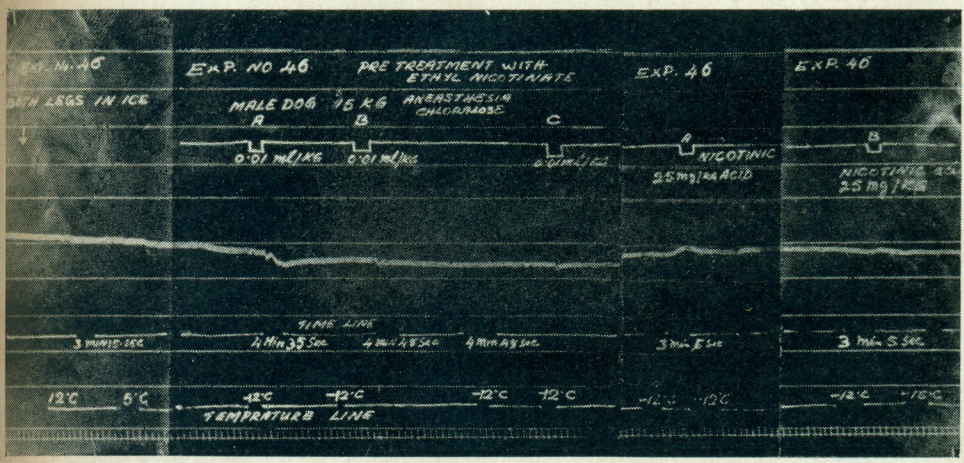

Fig. 3. Showing effect of nicotinic acid after pretreatment with ethyl nicotinate.

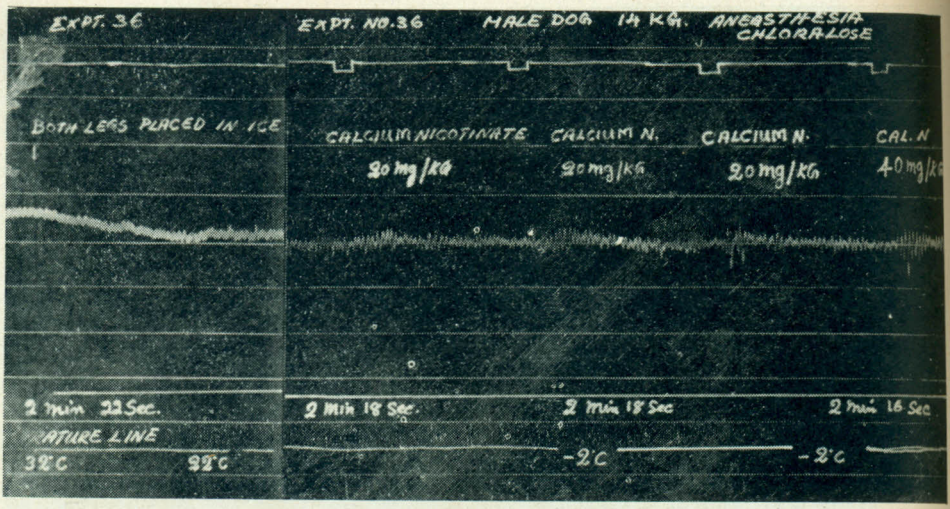

Fig. 4. Showing effect of calcium nicotinate on carotid artery blood pressure tracing and femoral blood flow.

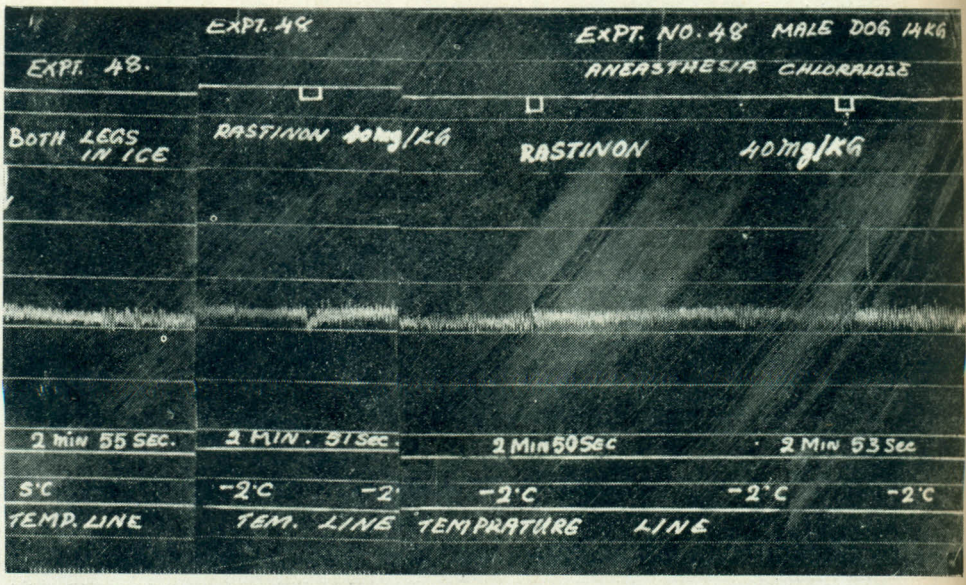

Fig. 5. Showing effect of intravenous injection of rastinon on blood pressure and blood flow.

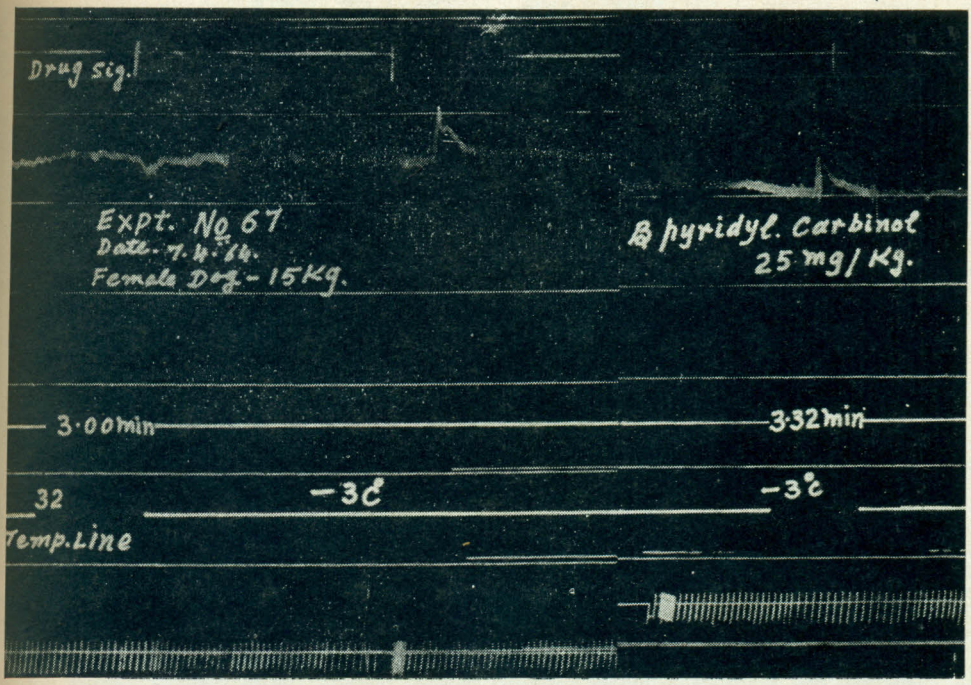

Fig. 6. Showing effect of intravenous injection of beta pyridyl carbinol (Ronicol) on blood pressure and blood flow.

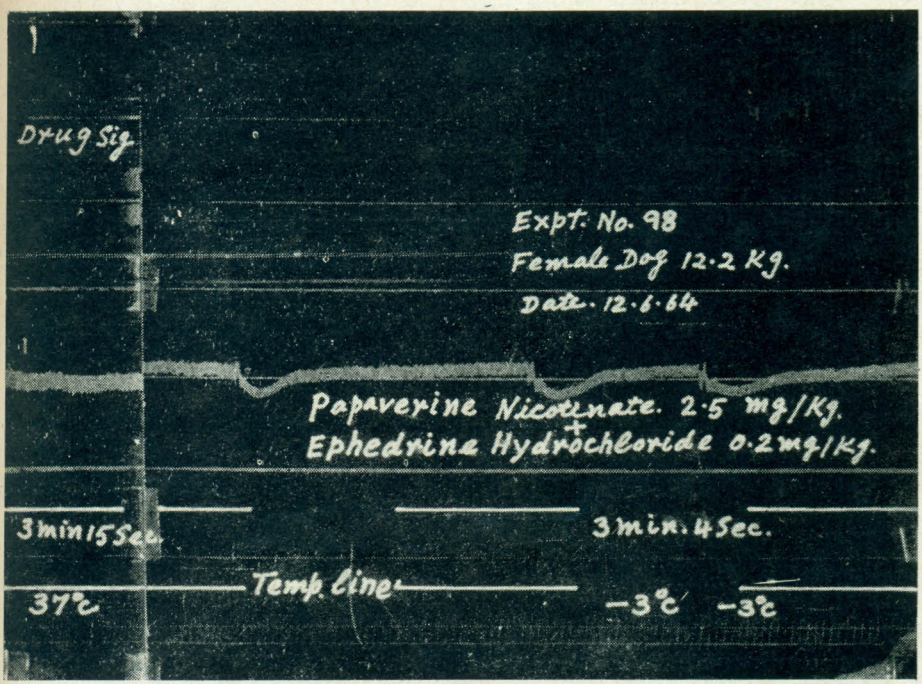

Fig. 7. Showing effect of papaverine nicotinate and ephedrine hydrochloride on blood flow and blood pressure.

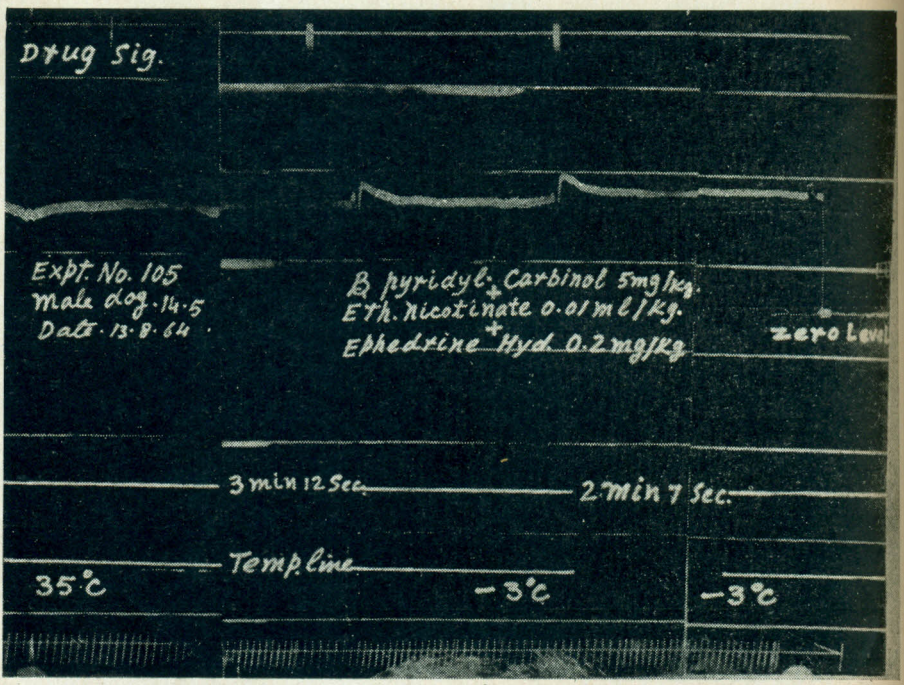

Fig. 8. Showing effect of combination of beta pyridyl carbinol, ethyl nicotinate and ephedrine hydrochloride.

Dogs were put under positive pressure respiration and carotid artery blood pressure tracings were recorded on a kymograph. Temperature of the leg was recorded after implanting an ordinary mercury thermometer in the leg by giving a sub-cutaneous nick in the thigh. Bubbleflowmeters (Green 1948) were interpolated in both the femoral arteries and continuous flow time readings were taken after every five minutes, before and after keeping the legs in ice and salt mixture and before and after administration of the drugs.

RESULTS

The results of 126 successful experiments have been given in the form of four tables.

CONCLUSIONS OF RESULTS

Nicotinic acid 25 mg/kg. ethyl nicotinate 0.01 mg/kg. papaverine nicotinate 2.5 mg/kg. methyl nicotinate 2 mg/kg. when given separately by intravenous route cause a fall in blood pressure and decrease in the blood flow to the limbs, however, calcium nicotinate 50 mg/kg. aluminium nicotinate 25 mg/kg. and tolbutamide

TABLE IA

GROUP	NO. OF EXP.	MINI. TEM	DRUG	AVERAGE CHANGE ± IN B.P	AVERAGE CHANGE ± IN FLOW TIME Rt. LIMb.	AVERAGG CHANGE ± IN FLOW TIME LC. LIMB.
A	9	-2°c	NICOTI-NIC ACID (SODIUM SALT)	-153 % FALL	+ 41 % INCREASE IN FLOW TIME	+29 % INCREASE IN FLOW TIME
B	10	-2°C	ETHYL NICOTI NATE	- 41% FALL	+28% INCREASE IN FLOW TIME	+ 29 INCREASS IN FLOW TIME
C	10	-2°C	NICOTI-NIC ACID AFTER ETHYL NICOTI-NATE	-16 % FALL	-13% DECREASE IN FLOW TIME	-24 % DECREASE IN FLOW TIME

TABLE I

Group	No. of Exp.	Minimum Temp.	Drug	Average% Change ± In B.P.	Average % Change ± in flow time Rt. limb.	Average % Change ± in flow time Lt. limb.
1	4	-3°C	Papaverine nicotinate 2.5 mg/kg	-21.4% fall	+ 10.2% increase	+11.7% increase
2	5	-3°C	Methyl nicotinate 2mg/kg	-27.3% fall	+4.4% increase	+6.3% increase
3	4	-3°C	Calcium nicotinate 50 mg/kg.	+1.9% rise	No change	No change
4	4	-3°C	Aluminium nicotinate 28 mg/kg.	No change	No change	No change
5	4	-3°C	Tolbutamide 25 mg/kg	No change	No change	No change
6	7	-3°C	Beta pyridyl carbinol 25 mg/kg.	+9.5% increase	-14.5% decrease	-16.3% decrease

Showing results of intravenous injection of various congeners acid and other vasodilators.

TABLE II

Group	No. of Expt.	Minimum Temp.	Drug	Average % Change ± in B.P.	Average % Change ± in flow time limb Rt.	Average % Change ± Flow time Lt. limb
7	4	-3°C	Nicotinic acid 25 mg/kg.	- 14.3% increase	+9.3% increase	+12.7% increase in flow time
8	5	-3°C	Papaverine nicotinate 2.5 mg/kg.	-20% fall	+17.6% increase	+15.3% increase in flow time.
9	3	-3°C	Aliminium nicotinate 25 mg/kg.	No change	Flow gets blocked	Flow gets blocked
10	3	-3°C	Calcium nicotinate 50 mg/kg.	No change	Flow gets blocked	Flow gets blocked.
11	6	-3°C	Ethyl nicotinate 0.01 ml/kg	-18.1% fall	+11.1% increase in flow time.	+13.3% increase in flow time.
12	5	-3°C	Beta pyridyl carbinol 5 mg/kg.	+2.6% rise	-12.5% decrease in flow time.	-11.2% decrease in flow time.

Effect of Intra arterial injection of various vasodilators.

TABLE III

Group	No of Expt.	Minimum Temp.	Drug	Average % Change ± in B.P.	Average % Change ± in flow time Rt. limb.	Average % Change ± in flow time Lt. limb.
13	8	-3°C	Nicotinate acid 25 mg/kg +Ephedrine	+33.3% rise	-12.4% decrease	-10.7% decrease in flow time
14	5	-3°C	Papaverine nicotinate 2.5 mg/kg +Ephedrine	+9% rise	4.8% decrease	-6.2% decrease
15	7	-3°C	Methyl nicotinate 2 mg/kg +Ephedrine	+16.6% rise	-11.4% decrease in flow time	-9.6% decrease in flow time
16	7	-3°C	Ethyl nicotinate 0.01 ml/kg +Ephedrine	+28.5% rise in B.P.	-17.1% decrease in flow time.	-13.8% decrease in flow time.
17	7	-3°C	Beta Pyridyl cabinol 5 mg/kg +Ephedrine	+56% rise	-23% decrease in flow time.	-21% decrease in flow time
18	9	-3°C	Beta Pyridyl carbinol 5 mg/kg + Ethyl nicotinate 0.01 ml/kg +Ephedrine	+18.9% rise in B.P.	-24.8% decrease in flow time	-33.2% decrease in flow time.

Combination of Ephedrine with various vasodilators on intravenous administration.

Note:- Ephedrine hydrochloride was given in the doses of 0.2 mg/kg.

25 mg/kg. do not produce any change in either B. P. or blood flow, beta pyridyl carbinol increases both the blood pressure and blood flow to the limbs.

Intra-arterial injections of nicotinic acid 25 mg/kg. ethyl nicotinate 0.01 mg/kg. or papaverine nicotinate 2.5 mg/kg. are accompanied with fall in blood pressure and decrease in blood flow to the limbs, calcium nicotinate 50 mg/kg. and aluminium nicotinate 25 mg/kg. block the femoral arteries and injection of beta pyridyl carbinol (Ronical) is accompanied with increase in blood flow.

When nicotinic acid is given after pretreatment with 0.01 mg/kg. of ethyl nicotinate there is beneficial effect on the limb blood flow by showing a substantial increase.

When either nicotinic acid 25 mg/kg. ethyl nicotinate 0.01 mg/kg. methyl nicotinate 2 mg/kg. papaverine nicotinate 2.5 mg/kg. or beta pyridyl carbinol 5 mg/kg. is given along with 0.2 mg/kg. of ephedrine hydrochloride, there is a significant increase in blood flow to the limbs, but the best results available so far are with a combination of beta pyridyl carbinol 5 mg/kg. + ethyl nicotinate 0.01 mg/kg. and ephedrine hydrochloride 0.2 mg/kg. With this preparation there is 34.2 per cent increase in the blood flow to the limbs which is sustained for about 40 to 50 minutes.

DISCUSSION

A variety of drugs have been used in frostbite which include sympatholytics, ganglionic blocking agents, vasodilators and anticoagulants like heparin, drugs effecting the capillary permeability and integrity like ascorbic acid and rutins and antioxidants like Vit. E—the alpha tocopherol. But none of these are ideal. New congeners of nicotinic acid were synthesised with an object to minimise the side-effects such as gastrointestinal disturbances, hepatotoxicity etc. and to have an enhanced vasodilatory activity, increased peripheral blood flow and to avoid pooling of blood into the vascular bed. For this purpose calcium nicotinate was synthesised as calcium is known to diminish capillary permeability. Aluminium salts have very poor solubility and active ingredient is very slowly released, so to get a long lasting sustained action, aluminium nicotinate was synthesised but results of our experiments with this salt are not encouraging enough to warrant any further studies on this compound.

It is interesting to note that studies conducted on some of the analogues of nicotinic acid such as amides and hydrazides show that their prior administration causes moderate to marked inhibition of nicotinic acid's activity, so in the present studies these compounds have been excluded (Cheverland and Claud, 1960).

DRUGS WHICH INHIBIT THE ACTION OF SODIUM NICOTINATE

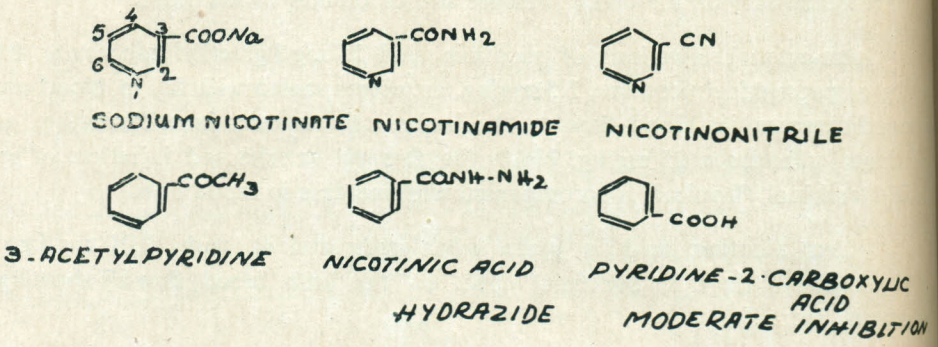

Fig. 9. Showing structure of few compounds which inhibit the action of nicotinic acid.

As intra-arterial route of injection of drugs is a well established technique, so we thought it worthwhile to try this route of administration also. But this did not show any superiority over the usual intravenous route. A look at the structure of the present compounds (Chevesland and Giano, 1960) will show that ethyl and methyl nicotinate were synthesised with an idea that esters not only retain vasodilatory properties but enhance the spasmolytic activity which is a good property in relieving spasm induced due to exposure to cold and also esters have a longer duration of action than the free acids or corresponding salt of the parent compound. Papaverine nicotinate was selected because papaverine is a known vasodilator. So its addition with nicotinic acid was expected to have additive effect.

In first series of experiments it became evident to us that most of the drugs when given alone are not beneficial at all, because the concomitant fall in blood pressure decreases the effective blood flow to the limbs.

It was also observed that pretreatment of animal with ethyl nicotinate prior to nicotinic acid administration results in increase of blood flow. What exactly is the mechanism of this potentiation is not clearly worked out. The main drawback of the drugs used in present series of experiments was a fall in blood pressure. To combat this untoward effect ephedrine hydrochloride was incorporated in the combination and a final combination of ethyl nicotinate and beta pyridyl carbinol with ephedrine gave the best results so far.

Therapeutic acceptability of this combination will depend upon the results of complete pharmacodynamic study of this drug and after its long-term chronic toxicity studies in experimental animals which are at present in progress in our department.

REFERENCES

Cheverland, L. and Claude, M. (1960). *Chem. Abs.*, 21456 h.

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