Lymphology 16 (1983) 150–156

The Effect of "Unguentum Lymphaticum" on Acute Experimental Lymphedema and other High-protein Edemas

J.R. Casley-Smith, M.A. and J.R. Casley-Smith, D.Sc., M.B.

Electron Microscope Unit, University of Adelaide, South Australia

Summary

A cream, *Unguentum lymphaticum,* which has been shown to be effective (clinically and experimentally) in lymphedema, was tested in dextran and burn edemas and acute lymphedema in rats. It was very effective indeed in lymphedema, completely preventing the 36% increase in the volumes of the legs found with in those treated with its drug-free base. This protection was much less if the macrophages were selectively poisoned with silica, and the edema reached maximum volume much more rapidly. This shows that most of the cream's activity against lymphedema is via an increase of the normal proteolysis by macrophages, and also confirms that these are of considerable importance in limiting lymphedema (and other high-protein edemas). Curiously, the cream slightly increased the edema of the feet in acute lymphedema, and also in dextran and burn edema, although other workers did not find this with histamine and egg albumin. This, and other evidence, suggests that another part of its action is vaso-dilatory – at least to rat-feet. Obviously it has many actions. While they should be investigated, the most important thing is that this cream offers a relatively cheap therapy (perhaps in combination with others: perhaps alone) for the nearly 300,000,000 people who suffer from lymphedema.

Introduction

High-protein edemas are very common. *Casley-Smith* (1983a) estimates that one person in three, in a developed "Western" country, seeks medical attention every year for a disease involving high-protein edema, e.g., inflammation of all kinds – trauma (accidental and surgical), dental extractions, fractures, burns, infections – chronic venous insufficiency, and lymphedema. Although many of these were relatively trivial and short-lasting, they were still painful. If, however, high-protein edemas last for two months, it has been shown (in rats) that the simple excess of protein in the tissues produces all the changes of chronic inflammation (*Casley-Smith* and *Gaffney* 1981). Indeed it appears that chronic lymphedema is one form of chronic inflammation, and that the alterations to the tissues which occur in this condition are caused just by this simple excess of normal protein (*Casley-Smith* 1983a; *Casley-Smith* and *Gaffney* 1981; *Casley-Smith* et al. 1980; *Földi* and *Casley-Smith* 1978; *Gaffney* and *Casley-Smith* 1981). Chronic lymphedema, just as caused by filariasis alone, affects 250,000,000 people (WHO 1980); post-mastectomy lymphedema affects about 30,000,000 (*Casley-Smith* 1983a). Thus it can be seen that high-protein edemas, including lymphedema, are far more common than is usually appreciated.

Unfortunately the treatment of high-protein edema in general, and of lymphedema in particular, is often very unsatisfactory (*Casley-Smith* 1983a; *Clodius* and *Gibson* 1983). For lymphedema, surgery in selected cases produces good results, but often it does not (*Clodius* and *Gibson* 1983); a complex physical method is usually excellent, but is expensive in terms of a trained masseur's time (*Földi* 1983); drug therapy (the benzo-pyrones – *Casley-Smith* 1976, 1983a, b) is effective, but takes months to years to produce its full effect. Thus it seemed worthwhile to investigate a cream (*"Unguentum lymphaticum"*, Pharmazeutische Gesellschaft mbH & Co., München), which was empirically formulated by *Sichert* specifically to aid in the treatment of lymphedema (*Veith* and *Sichert,* 1971).

Early clinical studies (*Reincke* 1975; *Weiß* 1981; *Veith* and *Sichert* 1971) found that it was effective in this condition. Recently an open, randomized trial of 26 patients with post-mastectomy lymphedema showed that it very significantly reduced the amount of pain (*Földi* and *Földi* 1983). Both the controls and the experimental group also had a complex physical decongesting therapy (*Földi* 1983). There was no significant difference, clinically, in the reduction of edema between these two groups (*Földi* 1982, pers. com.), but the reduction in pain implied that this occurred – at a subclinical level.

The components of *Unguentum lymphaticum* are: extracts of Conium maculatum e herb., Colchicum autumnale e sem., Digitalis purpurea e fol., Podophyllum e rhiz., Hyoscyamus niger e fol., calendulae spiss. e flor. The amounts of these in 100 g of cream are, respectively: 4.2, 3.0, 2.1, 2.1, 2.1, 0.21 g, plus ol. petrae rect. 8.8 g, and p-Hydroxybenzoic acid methyl ester 0.2 g, in an inert base. It would be preferable, academically, to identify and investigate each of the pure components of each of the extracts individually. However, such is the need of about 10% of the World's population for any drug which will help to treat lymphedema, that we felt it best to work first with the whole formulation – since this has been shown to be effective in clinical practice. Later it may be possible to isolate the specific effects of its various parts and to combine them as required.

In the past it has been found that a battery of tests often provides much more information than just one (*Casley-Smith* 1983a; *Koh* et al. 1978; *Willoughby* et al. 1978). Thus we used dextran and burn edemas, acute lymphedema, and this last combined with the destruction of the macrophages by silica.

Materials and Methods

Unless otherwise indicated, after each injury the animals were immediately treated with *Unguentum lymphaticum* on one foot, using about 0.75 g gently spread over the food and massaged in, again very gently. The other foot was treated identically with the inert base of the cream, which contained no drugs. Most of the creams passed into the skin, although a minor amount remained as a residue; however, repeated observations showed that the rats did not lick the feet with the *Unguentum lymphaticum* cream (which also tastes very disagreeable to humans), although they did lick the drug-free base. This treatment was repeated twice every day for the duration of the experiments. Because of the adherence of saw-dust to the residues of the creams, the rats were placed in cages with plain plastic floors (without saw-dust); these were changed at each treatment. The animals were kept in air-conditioned surroundings (20 °C ± 0.5) and fed on standard rat-nuts.

Dextran Edema

Ten hooded rats (S.P.F.; 500 ± 25 g) were given an intraperitoneal injection of 12 g/dl dextran (m.w. 70,000) in physiological saline – 1 ml/kg. Fifteen hours later they were killed, the hind-feet disarticulated at the ankle joint and weighed.

Thermal Edema

Hooded rats (S.P.F.; 350 ± 25 g) were divided into two groups of ten. Each animal was anesthetized with Sagital, and each hind foot was burnt, up to the Achilles tendon, by immersing it in water (continually changed) at 57 °C for 60 seconds. One group was treated immediately after the burn with *Unguentum lymphaticum* and the inert base; the other was treated after a delay of 90 minutes (to see if the influence of either the cream or its base, just on the delayed-phase of burn, differed from its effect on both phases). The volumes of the burnt and the control legs, up to the Achilles tendon, were estimated, by plethysmography, before burning, and at 1 and 2 days after this. Final weights, after 3 days, were obtained by disarticulating the feet at the ankle joint.

Acute Lymphedema

Twenty hooded rats (S.P.F.; 450 g ± 25) were anesthetized with Sagital. Both legs were given lymphostasis by a modification of the method of *Piller* and *Casley-Smith* (1975). The skin

was transversely incised on the medial aspect of the thigh, 1 cm distal to the linguinal ligament. The fascia overlying the femoral vessels was removed and the vessels undercut with a scalpel until they were free of the muscle for a distance of 0.5 cm. Care was taken to dissect along, but to avoid cutting, any major vascular tributaries. All collateral lymphatics were obstructed by a pair of ligatures, which were pulled as tight as possible; these were passed, beneath the femoral vessels, through the musculature of the thigh, and around the skin in both medial and lateral directions. Thus the femoral vessels and nerves were not occluded, but every other vessel was.

This form of acute lymphedema is maximal at 90–100 hours (*Gaffney,* 1982, unpublished). Hence the animals were killed, with chloroform, at 96 hours after operation. Then their legs were cut off at the ligatures and weighed. A second weighing was also performed: the tibio-calcaneal joint was disarticulated and the foot was weighed.

Lymphedema without Macrophages

In order to test whether the cream were effective in lymphedema primarily because it increased the proteolysis by macrophages (as occurs with the benzo-pyrones – *Casley-Smith* 1976, 1983a, b), acute lymphedema and its treatment with the cream and its base, was repeated – but with the macrophages destroyed by silica. This is a standard method of selectively poisoning the macrophages (e.g. *Casley-Smith* et al. 1977, 1978; *Piller* 1976). The tridymite form of silica was intraperitoneally injected each day (100 mg/kg in a 10 g/dl solution, in physiological saline), from 8 days before lymphedema was produced (in twenty S.P.F., 190 g ± 25, hooded rats) until they were killed.

Results

Acute Lymphedema

Macroscopically, the legs treated with *Unguentum lymphaticum* were most remarkably smaller than those treated with the cream's base. This is reflected in the very significant differences between them (Table). The lymphedema produced a 36% increase in the volume of the leg when it was only treated with the base; those treated with *Unguentum lymphaticum* had no increase at all. Curiously, this only occurred in the legs; in the feet there was a 36% increase in the volumes of those treated with the placebo and a 46% increase in those treated with the drugs. Possible reasons for this divergence are discussed later. In this experiment, and the next, it was noted that the feet treated with *Unguentum lymphaticum* were considerably more red than those treated with its drug-free base.

Lymphedema in the Absence of Macrophages

When lymphedema was produced in macrophage-free animals it was found that the protection afforded by the cream was greatly reduced. There was a 41% increase in the volume of the legs; The increase was 49% in the legs treated with the drug-free placebo, and this difference was significant – showing that the drugs still had some effect. Whether this was due to some other action of the drugs cannot be decided at this stage. It was also obvious that the legs (treated with either cream) reached their maximum volumes very much more rapidly than in the previous experiment.

Dextran and Burn Edema

For the dextran and both burn experiments, the amounts of edema and redness of the feet appeared approximately equal at 15 hours, and in the burnt animals at 36 hours. There were no visible differences between the feet treated with *Unguentum lymphaticum* and those with the placebo (drug-free base). By 72 hours, however, 14 out of the 20 burnt feet which had been treated with the placebo had turned gangrenous; none of those treated with *Unguentum lymphaticum* became gangrenous. This difference is very highly significant (at much less than the 0.1% level). Neither in this, nor in any of the other measurements were there any significant differences between the burnt animals treated immediately and those treated after 90 minutes delay. As shown in the Table, while there were no significant differences between the treated and untreated volumes of the dextran-injured, or of the burnt feet, up to 36 hours, the volumes of

Table Volumes (ml) of legs and feet after treating various edemas; standard errors fo the means are given in [ ]

Site	Number	Normal	Treated	Placebo	Treated – Placebo (using individual differences)		Significance of difference of previous column from zero
Acute lymphedema							
Upper legs only	20	5.99 [0.163]	5.94 [0.390]	8.12 [0.424]	−2.18 [0.345]	***	***
" no macrophages	20	5.53 [0.206]	7.77 [0.198]	8.25 [0.203]	−0.483 [0.200]		
Feet	20	1.89 [0.0141]	2.76 [0.0892]	2.58 [0.0807]	0.177 [0.0843]	NS	*
" no macrophages	20	1.69 [0.0170]	2.61 [0.0940]	2.37 [0.0794]	0.235 [0.112]		*
Dextran							
Feet; at 15 hours	10	1.93 [0.0411]	2.11 [0.0736]	2.07 [0.0633]	0.0417[0.0650]		NS
Burn – Treated immediately							
Feet; at 15 hours	10	1.66 [0.020]	2.20 [0.150]	2.19 [0.191]	0.0125 [0.0970]		NS
" at 36 hours	10	"	1.99 [0.161]	2.08 [0.170]	−0.088 [0.0640]		NS
" at 72 hours	10	"	3.30 [0.286]	2.77 [0.328]	0.526 [0.171]		*
Burn – Treated after 90 minute delay							
Feet; at 15 hours	10	1.83 [0.0158]	2.64 [0.124]	2.52 [0.0995]	0.122 [0.0967]		NS
" at 36 hours	10	"	2.50 [0.128]	2.26 [0.105]	0.244 [0.111]		NS
" at 72 hours	10	"	3.47 [0.105]	2.99 [0.150]	0.476 [0.204]		*
All burns; Number of gangrenous feet							
Feet, at 72 hours	20 (in each groups		0	14			***

"NS", "*", "**" and "***" signify that a difference is not significant, or is significant at the 5%, 1% or 0.1% levels, respectively

the ones treated with *Unguentum lymphaticum* were somewhat greater than those treated just with the placebo – its base. This difference was significant at 72 hours. Possible reasons for this are discussed later.

Discussion

Lymphedema

It is evident from these results that the cream has a remarkable activity in reducing acute lymphedema. This is similar to what was observed in the rabbit ear by *Kovach* and *Koller* (1983). The complete protection it offered shows that *Unguentum lymphaticum* is singularly efficacious. Why should this be so?

The electron microscopy of the legs of these animals (*Casley-Smith* 1983d) shows that in the animals treated with the drugs, compared with those treated with the placebo, not only is the amount of edema much reduced, but the concentration and amount of protein in the tissues and lymphatics is also much less. Thus it is obvious that the drugs act in some way to remove the excess protein which is the result of the lymphostasis and the cause of the lymphedema. The results of lymphostasis in macrophage-free animals implies that most of the effect of the drugs is by their actions on these cells. While this cream does not contain benzo-pyrones (*Wagner* et al. 1983), a similar effect is observed with the benzo-pyrone group of drugs. These greatly reduce lymphedema by increasing the normal proteolysis by the macrophages in the tissues (*Casley-Smith* 1976, 1983a, b). These cells are normally quite numerous; their numbers are increased in lymphedema, and still more by the benzo-pyrones (*Casley-Smith* 1983a). This effect on lymphedema is abolished if the macrophages are destroyed by silica (*Casley-Smith* et al. 1978). The benzo-pyrones, in fact, reduce all high-protein edemas (*Casley-Smith* 1976, 1983a, b); in both contusion and thermal edema it has been shown that destruction of the macrophages abolishes this effect (*Casley-Smith* et al. 1977; *Piller* 1976). It is impossible to say, at present, which of the cream's components are responsible for that part of its effect on lymphedema which is abolished by poisoning the macrophages.

It is evident that in acute lymphedema in animals (as shown by these results, and those of *Kovach* and *Koller*, 1983), as well as in clinical studies (*Földi* and *Földi* 1983; *Reincke* 1975; *Weiß* 1981; *Veith* and *Sichert* 1971), *Unguentum lymphaticum* is extremely effective in reducing the amount of edema, and hence of pain. *Földi* and *Földi* (1983) found it a very useful adjunct to complex physical decongestive therapy, especially in the early stages. It even seemed to have remarkable effects on a traumatic lymphedema from which one of us recently suffered (*Casley-Smith* 1983c), but multiple methods of treatment were used in this case. Whether the cream can be used, alone, to treat lymphedema is something which must be investigated in the future.

We are left, however, with the need for explaining why the drugs, while they greatly reduced the edema of the leg, actually increased that of the foot, in experimental lymphostasis. Perhaps they have a vaso-dilating effect on the blood exchange vessels (capillaries and post-capillary venules) of the skin which, in the leg, is masked by their effects on the tissues in general? (The amount of skin in the foot is relatively very much greater than in the leg). Also, the tissues of the foot of the rat have different reactions (e.g. to dextran) to those of the rest of the animal, and indeed to those of many other animals; hence dextran edema occurs only in rats and largely only in their feet. There is other evidence pointing towards a vaso-dilatory effect of *Unguentum lymphaticum* (see below).

Burn and Dextran Edema

In these experiments the cream tended to increase the edema in the feet, after burning or dextran. However, it should be pointed out that other workers, using rat feet, have found that the cream reduced the edema caused by histamine and egg albumin (*Sterner* and *Grahwit* 1973). Why there should be this discrepancy is uncertain. Perhaps it is because they measured the edema over the first four hours after injury, while we measured the delayed-phase, from 15 to 72 hours. It has been shown, clinically, to reduce inflammatory edema caused

by infection or trauma (*Veith* and *Sichert* 1971). Our own electron microscopical results showed that the amount of damage in the tissues, neglecting the edema, was rather less than with the inert base (*Casley-Smith* 1983d). Perhaps the cream causes a vaso-dilatation, with extra fluid reaching the tissues (and hence extra edema), but this washes out some of the protein and prevents some of the damage the tissues would otherwise undergo.

The highly significant reduction in the amount of gangrene in the burnt feet also implies that *Unguentum lymphaticum* has a vaso-dilatory effect on the blood microcirculatory vessels of the skin. One wonders, indeed, if this very spectacular result might not be used in clinical medicine in conditions where local vasoconstriction is a problem (e.g. frost-bite); possibly it might even be effective in conditions with a more generalized tendency towards this (e.g. Raynaud's phenomenon etc.). One of us, using it to treat his own lymphedema, noticed that it produced redness of the skin (*Casley-Smith* 1983c). The results of *Kovach and Koller* (1983) showed that it also prevented discoloration in lymphedematous ears of rabbits. In the present experiments, on the animals with lymphostasis, it was noted that the feet treated with the cream were much redder than those treated just with its base.

General

The presence and amount of edema depends on the varied functioning of all parts of the microcirculation: exchange blood vessels, interstitial tissue channels, proteolysis by the cells, and the lymphatic system (*Casley-Smith* 1983a). Each of these parts has a number of aspects which may be affected by drugs. The benzo-pyrones, alone, have many different actions, affecting many of these aspects of all four parts of the microcirculation (*Casley-Smith* 1976, 1983a), although it appears that their actions in reducing high-protein edemas are largely restricted to increasing proteolysis in the tissues. Since *Unguentum lymphaticum* contains many components (although no benzo-pyrones, as such, *Wagner* et al. 1983), one can see that it may well have many actions.

It is evident that the cream is very effective in lymphedema. As pointed out at the beginning, there is an enormous, and immediate, need for preparations with activity against high-protein edemas in general, and lymphedema in particular. Therefore, when confronted with a preparation which has been shown in animal (*Kovach* and *Koller* 1983; *Sterner* and *Grahwit* 1973; and the present series) and clinical (*Földi* and *Földi* 1983; *Reincke* 1975; *Weiß* 1981; *Veith* and *Sichert* 1971) trials to have such an effect, the logical course is to make use of it. Future research will show how it may be simplified, made cheaper and, perhaps, improved. However, until we are convinced that we can usefully discard (or improve) part of it, we would be well advised to use it as it is.

References

Casley-Smith, J.R.: The actions of the benzo-pyrones on the blood-tissue-lymph system. Folia Angiologica 24 (1976) 2–22

Casley-Smith, J.R.: High-Protein Oedema and the Benzo-pyrones. Lippincott, Phil., 1983a, in press

Casley-Smith, J.R.: Human trials of the benzo-pyrones. Folia Angiologica, 1983b, in press

Casley-Smith, J.R.: A case of localised traumatic lymph oedema: observations concerning the obstruction of initial lymphatics and tissue channels by fibrin, and Menkin's Hypothesis. Lymphology 16 (1983) 143–149

Casley-Smith, J.R.: Electron microscopy of the effects of *Unguentum lymphaticum* on lymphoedema and various high-protein oedemas. Lymphoedema, 1983d, in press

Casley-Smith, J.R., R.M. Gaffney: Excess plasma proteins as a cause of chronic inflammation and lymphoedema. Quantitative electron microscopy. J. Path. 133 (1981) 243–277

Casley-Smith, J.R., P. Eckert, E. Földi-Börcsök, M. Földi: The effect of macrophage poisoning by silica on experimental pulmonary contusion and its benzo-pyrone treatment. Brit. J. Exp. Path. 58 (1977) 386–390

Casley-Smith, J.R., E. Földi-Börcsök, M. Földi: A fine structural study of the removal of the effectiveness of benzo-pyrone treatment of lymphoedema by the destruction of the macrophages by silica. Brit. J. Exp. Path. 59 (1978) 116–127

Casley-Smith, J.R., L. Clodius, N.B. Piller: Tissue changes in chronic experimental lymphoedema in dogs. Lymphology 13 (1980) 130–141

Clodius, L., T. Gibson: Surgical therapy for lymphoedema. In "Textbook of Lymphangiology", ed. M. Földi and J.R. Casley-Smith. Schattauer, Stuttgart – New York 1983, 683–706

Földi, M.: Lymphoedema. In: Textbook of Lymphangiology, ed. by M. Földi and J.R. Casley-Smith, Schattauer, Stuttgart – New York 1983, 667–682

Földi, E., M. Földi: Prevention and treatment of postmastectomy lymphoedema. Lymphology, 1983, in press

Földi, M., J.R. Casley-Smith: The roles of the lymphatics and the cells in high-protein oedema. Molecular Aspects Medicine, 2 (1978) 77–146

Gaffney, R.M., J.R. Casley-Smith: Excess protein as a cause of chronic inflammation and lymphoedema. Biochemical estimations. J. Path. 133 (1981) 229–242

Koh, M.S., L. Parente, D.A. Willoughby: Immunological and non-immunological plural inflammation: the effects of anti-inflammatory and anti-rheumatic drugs. Europ. J. Rheumatol. Inflam. 1 (1978) 283–295

Kovách, G.B., A. Koller: The effect of Unguentum lymphaticum on the experimental lymphoedema of the rabbit ear. In preparation (1983)

Piller, N.B.: The ineffectiveness of coumarin treatment of thermal oedema of macrophages-free rats. Brit. J. Exp. Path. 57 (1976) 266–273

Piller, N.B., J.R. Casley-Smith: The effect of coumarin on protein and PVP clearance from rat legs with various high-protein oedemas. Brit. J. Exp. Path. 56 (1975) 439–443

Reincke, A.: Behandlung vom Lymphödemen – Salben-Behandlung. Ärztl. Praxis 27 (1975) 1751–1754

Sterner, W., G. Grahwit: Prüfung von „Unguentum lymphaticum" auf lymphaktivierende Wirksamkeit am Rattenpfotenödem nach lokaler Applikation. Intern. Bio-Research Inc., Dallas, U.S.A., unpubl. report to Pharmazeutische Gesellschaft München, 1973

Veith, H., R. Sichert: Neue lymphwirksame Salbenzubereitung. Ärztl. Praxis 23 (1971) 633–635

Wagner, H. et al.: personal communication, 1983

WHO: Sixth Report on the World Health Situation, 1973–1977, I: Global Analysis", WHO, Geneva, 1980, p. 87

Weiß, R.-F.: Phytotherapeutische Möglichkeiten bei der Tumorbehandlung (Phyto-Onkologie). Die Heilkunst 94 (1981) 1–4

Willoughby, D.A., W.C. Spector, G.C. Huskisson, M. Földi, J.R. Casley-Smith, C.J. Dunn: New types of therapy for the arthropathies and inflammatory disease. Agents and Actions 8 (1978) 166–168

J.R. Casley-Smith, M.A. and J.R. Casley-Smith, D.Sc., M.D., Electron Microscope Unit, University of Adelaide, Box 498, C.P.O., Adelaide, South Australia, Australia