

## OBSERVATIONS ON THE TREATMENT OF SCABIES

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The old saying that "a disease with many remedies has no cure" is sometimes rather unjustly applied to scabies, for sulphur has for many centuries been regarded, with good reason, as a specific in its treatment. Nevertheless, the search for a better remedy has continued, and to-day the increased incidence of scabies in this country, particularly among the armed Forces, has once again centred attention on the treatment of this troublesome and time-wasting disease, with the result that numerous remedies have been advocated to supplant the traditional sulphur therapy. This search for a better remedy seems to be due partly to the liability of sulphur to provoke dermatitis, and partly to the fact that it is commonly prescribed in the inelegant form of an ointment, which is uncomfortable for the patient and damaging to his clothes.

At the present time the three principal rivals to treatment by sulphur or its inorganic compounds are preparations containing one of the following three drugs: benzyl benzoate ("proscabin"); rotenone, a constituent of derris root ("sarevan"); and dimethylthianthrene ("mitigal," "sudermo"), which is an organic sulphur compound. Although these three drugs are all known to be efficacious, there unfortunately exists considerable difference of opinion regarding their respective merits. Other important points upon which agreement has not been reached are the preparation of the patient for treatment and the necessity or otherwise for disinfecting the patient's clothes after treatment.

It is our object to discuss these points in the light of our own investigations, and to give a brief account of some experiments in which the therapeutic action of benzyl benzoate and dimethylthianthrene has been compared with that of a new substance—tetraethylthiuram monosulphide—supplied to us by Imperial Chemical Industries Ltd.

### Choice of Vehicle for applying Sarcocidal Drugs

As Mumford (1938) points out, there has been a tendency to overlook the importance of the vehicle in which drugs are applied to the skin. For example, benzyl benzoate is usually given in a mixture of soft soap and rectified spirit, which is irritating to the skin and painful when applied to scratched areas; and sulphur is commonly applied in a mixture consisting largely of hard and soft paraffin—substances that have small penetrating power. Eller and Wolff (1939) have shown that, in general, animal and vegetable oils penetrate the skin, via the hair follicles and sebaceous glands, more readily than do mineral oils, and this has been confirmed by Harry (1941). We have shown (Gordon and Seaton, 1941) that tetraethylthiuram monosulphide, dimethylthianthrene, and benzyl benzoate, when mixed with an equal quantity of a vegetable oil (the methyl ester of the fatty acids of coco-nut oil), all penetrate the skin within 15 minutes of their application, and that they do so at an equal rate and to a similar depth.

Several proprietary preparations for application in scabies make use of surface active agents, with a view to increasing their power of penetrating the burrows. The effect of adding such an agent to an oil is to allow it to form a stable emulsion in water without impairing its miscibility with other oils. Con-

sequently, such a mixture is able to blend with both the oily and the watery secretions of the skin and thus to come into more intimate contact with the tissues. On theoretical grounds, therefore, a sarcocidal drug should be prescribed in solution in an animal or vegetable oil to which a small amount of a surface active agent has been added. We have, however, examined the effect of adding a small percentage of a surface active agent (the condensation product of a mixture of higher fatty alcohols, mainly cetyl alcohol, with ethylene oxide) to tetraethylthiuram monosulphide, and have found that the sarcocidal action of this drug was apparently diminished by such an addition (Gordon and Seaton, 1941). A possible explanation is that the surface active agent produced too high a degree of diffusion of the drug into the deeper layers of the skin, where the mites do not occur.

### Preparation of the Patient for Treatment

Most dermatologists consider that, whatever the drug used, its application should be preceded by a hot bath, during which the body is soaped and scrubbed in order to lay open the burrows, thus rendering the mites and eggs more accessible. We have shown (Gordon and Seaton, 1941) that in rat scabies preliminary washing and scrubbing not only open most of the burrows but mechanically remove numerous superficial mites and eggs. Although it is reasonable to suppose that this preliminary bathing is a valuable adjunct to the treatment of human scabies it is possibly not essential, for Saunders (1941), using a suspension of derris root, was able to dispense with it. None the less, bathing should not be omitted if facilities are available.

Furthermore, scabies is not a disease which should be left to the patient to treat. To give a person suffering from scabies a prescription for sulphur ointment and instructions for its use is unlikely to prove satisfactory, since in many homes facilities for adequate treatment do not exist. It is noteworthy that the most satisfactory results, irrespective of the drug used, come from clinics, where the treatment is carried out under skilled supervision, or from the Services, where the patients are under discipline. It should also be recognized that it is often useless to treat a patient unless his contacts are treated simultaneously—a point which was emphasized by Kissmeyer (1937), who was accustomed to treat contacts whether or not they showed signs of infection. From this it follows that the adequate provision of centres where the treatment of scabies can be carried out is an important measure in the control of the present epidemic.

### Necessity for Disinfecting Clothes at the Conclusion of Treatment

It is the usual practice, at the end of a course of treatment, to order the patient's underclothes and bedding to be disinfested, although from time to time the necessity for this procedure has been doubted. Hebra as long ago as 1868 stated that of 1,500 cases treated annually at his hospital less than 1% relapsed, although disinfestation of clothes was not practised; and recently Mellanby (1941) succeeded in infecting volunteers with the underclothes or blankets of scabietic patients in only 2 out of 63 trials, and stated his belief that scabies is normally spread by personal contact. On the other hand, MacCormac and Small (1917) concluded that blankets were the chief means

of disseminating infection among groups of men quartered together, and Munro (1919) infected 2 out of 6 volunteers who slept in beds previously occupied by scabies patients. Munro was also able to transfer the infection by the gloves and underclothing of infected persons, and showed that such underclothing might remain infective under ordinary atmospheric conditions for at least 11 days. We have been able to transfer scabies from one rat to another by means of a piece of artificial silk, which was loosely wrapped round the tail of an infected rat for 12 hours and then transferred to a healthy rat for 24 hours. One such piece of artificial silk which had been applied overnight to the tail of a heavily infected rat was dissolved in acetone and the solution centrifuged. In the deposit were found one egg and 156 mites, of which over 90% were larvae. It is therefore certain that scabies may be acquired from infected clothing, although it is not yet known whether in human scabies this method of transmission is common enough to warrant the disinfection of clothing in every case.

### Choice of Sarcopticide

Apart from sulphur ointment, the objections to which have been mentioned, the substances in general use, as already stated, usually contain benzyl benzoate, rotenone, or dimethylthianthrene.

The use of benzyl benzoate in the treatment of scabies was first reported by Kissmeyer (1937), who treated some 8,000 cases. He found that the relapse rate was about 5%, and claimed that serious dermatitis did not occur. The benzyl benzoate was applied mixed with equal parts of soft soap and isopropyl alcohol, a prescription which is at present widely used, with the substitution of rectified spirit for the more costly isopropyl alcohol. Kissmeyer's treatment, which had the advantage of rapidity (it took less than an hour to complete), was carried out as follows:

The patient anoints the whole body with soft soap, which is rubbed with special care into the affected parts. He then rubs himself for 10 minutes in a bath at 100° F., and while still wet applies the lotion to the whole body for 10 minutes. He allows himself to dry, and then applies the lotion for a further 5 minutes, after which he gently dries himself with a towel and resumes his clothes. Twenty-four hours later a second bath is taken and clean clothes are put on, the dirty ones being sterilized.

Dimethylthianthrene, under the name of mitigal, was introduced in Germany by Bayer after the end of the war of 1914-18. It is an oily liquid containing about 25% of combined sulphur. The earliest reports of its use were uniformly enthusiastic (Tiefenbrunner, 1921; Sauerbrey, 1921; Kromayer, 1921), and emphasized the non-irritant nature of the drug; but Kiess (1922), who developed a "rapid cure" in which mitigal was applied twice, with an interval of one hour, found that dermatitis was apt to occur, particularly if the drug was not washed off after 24 hours. In this country it is the usual practice to apply dimethylthianthrene on each of three successive days, after the preliminary bath.

Rotenone, a complex organic substance which is present in derris root in amounts up to 10%, was first used in the treatment of scabies by Japanese workers, who afterwards abandoned it, considering it to be too irritant. Later, in the same country, Ra (1936) successfully tried a bromine derivative of rotenone in a small series of cases. Thomas and Miller (1940) used 1% or 2% rotenone for the treatment of 24 cases, and claimed that it was safe, effective, and non-irritant. Other writers, however, have stressed the liability of rotenone to provoke dermatitis, particularly of the scrotum, in which site it is apt to be severe and intractable (Mumford, 1941; Carslaw, 1941). Because of the relative scarcity and expense of rotenone Saunders (1941) treated 90 military cases with a suspension of derris in soapy water, in the proportion of 4 oz. to 1 gallon, 3 applications being made on each of 2 successive days. Eighty-three out of 84 of these patients were said to be cured when examined 4 weeks after treatment. Scrotal dermatitis was observed in a number of cases, but it was so mild as seldom to require treatment. Saunders found that this dermatitis occurred in an even milder form in 3 out of 50 cases treated with half-strength suspension. It should be noted that Saunders's suspension contained at most 0.25% of rotenone, and probably less. An important feature of his treatment was

that baths and disinfection of clothing were found unnecessary. This observation was confirmed by Buchan (1941), working with naval cases, but Forman (1942) failed to cure 6 out of 15 out-patients treated by this method. Thus a treatment which was highly successful for Service personnel, subject to discipline, failed in a civilian out-patient department, a fact which emphasizes the necessity for the proper supervision of treatment.

It will be seen that, from a survey of the literature, it is impossible to decide which drug is the most suitable sarcopticide. All are more or less apt to cause dermatitis, and all are more or less effective when properly used. We therefore selected two drugs of established value, benzyl benzoate and dimethylthianthrene, for purposes of comparison with tetraethylthiuram monosulphide. We did not use rotenone, partly because of its reputation for provoking dermatitis in the strength ordinarily employed, and partly because it is unsuitable for administration in the oily vehicle which was used for the other preparations.

Tetraethylthiuram monosulphide is a crystalline solid of a tawny-yellow colour, melting at about body temperature and soluble in the usual organic solvents. Its chemical constitution is  $(C_2H_5)_2NCS.SNC.(C_2H_5)_2$ , and it thus contains about 37% of combined sulphur. It is not yet on the market, but is likely to be so in the near future.

### Effects of Benzyl Benzoate, Dimethylthianthrene, and Tetraethylthiuram Monosulphide Compared

The animals used in our experiments were, for the most part, albino rats naturally infected with mites of the genus *Notoedres*, which commonly cause scabies in rodents and other small mammals and occasionally infect man (Buxton, 1941). Though differing from *Sarcoptes* in certain anatomical points, *Notoedres* is essentially similar to it in its life-history and in its response to treatment. Its tendency is to produce heavy infestation approximating, in the amount of scabbing and the number of mites present, more to the so-called "Norwegian scabies" than to the ordinary human infection. This form of scabies is well adapted for the comparison of different remedies, since it permits the effects of the drugs on the mites and their eggs to be examined histologically at varying intervals after application. The three drugs were applied in 50% dilution in the methyl ester of the fatty acids of coco-nut oil,\* and before use they were saturated with Sudan IV (Scharlach R), so that their subsequent distribution in the tissues might be determined microscopically. Before application of the mixtures of drug, vehicle, and dye the areas of skin to be treated (usually the tails) were subjected to a standardized form of washing, after which the preparations were massaged into the skin for 3 minutes. Portions of the skin were removed 24 hours and 3 days later, fixed in formol saline, and sectioned by the freezing microtome. The sections were examined microscopically, and the distribution of the dye and the presence or absence of degeneration in the mites and eggs were noted.

### Results

The results with regard to staining and degeneracy of the mites and eggs 24 hours and 3 days after application of the drugs are shown in Tables I and II.

TABLE I.—Comparative Effects on Mites after Rubbing in the Drugs for 3 Minutes

Drug	24 Hours Afterwards			3 Days Afterwards		
	No. of Mites	Degenerate	Stained	No. of Mites	Degenerate	Stained
Dimethylthianthrene..	45	49%	91%	68	94%	98%
Benzyl benzoate ..	72	67%	96%	60	100%	100%
Tetraethylthiuram monosulphide	62	76%	98%	68	100%	100%

From the tables it can be seen that all or almost all the mites were killed 3 days after a single application of any of the drugs. That tetraethylthiuram monosulphide had the most rapid action is shown by the observations made 24 hours after the application. The eggs were evidently more resistant than

\* This diluent is not altogether suitable for tetraethylthiuram monosulphide, as at low temperatures crystallization takes place in the mixture.

the mites, a considerable number being apparently unaffected by the treatment, although almost all of them contained stain, and therefore presumably drug. There was no significant difference between the actions of benzyl benzoate and dimethylthianthrene on the eggs, both being inferior to tetraethylthiuram

TABLE II.—Comparative Effects on Eggs after Rubbing in the Drugs for 3 Minutes

Drug	24 Hours Afterwards			3 Days Afterwards		
	No. of Eggs	Degenerate	Stained	No. of Eggs	Degenerate	Stained
Dimethylthianthrene	36	25%	69%	10	50%	90%
Benzyl benzoate	76	34%	99%	58	47%	100%
Tetraethylthiuram monosulphide	65	50%	98%	45	78%	98%

monosulphide, which was more lethal and more rapid in its action. The results show that a single application of any of the drugs was probably insufficient to produce a cure, and we suggest that in human scabies it would be a sound policy to make a second application of the drug after a week, by which time any viable eggs would have hatched.

We would emphasize that these results have been obtained in animal scabies caused by mites of the genus *Notoedres*; but we consider it is probable that they are applicable to human scabies caused by *Sarcoptes scabiei*. We are unable to say to what extent tetraethylthiuram monosulphide may produce dermatitis, but its superiority over benzyl benzoate and dimethylthianthrene suggests that it should be given a clinical trial.

**Summary and Conclusions**

The conclusions we have reached as a result of the experiments may be summarized as follows:

Preliminary washing and scrubbing of the skin facilitated the sarcopticidal action of the drugs tested.

The vegetable oil used as a vehicle for the drugs allowed these to penetrate the skin to a satisfactory depth within 15 minutes of their application. Such a vehicle should prove more satisfactory than the semi-solid mineral substances commonly used as ointment bases.

A single application of any of the drugs tested produced degenerative changes in almost all the mites within 3 days, but a proportion of the eggs still remained apparently unaffected. It is suggested, therefore, that a second application of the drug should be made after an interval of a week, by which time any eggs which survived the first application would have hatched.

The results of our investigations of animal scabies supported the generally accepted view that the larval mites leave their burrows, wander on the surface of the skin and clothing, and can be transmitted by the garments. Until the frequency with which this occurs in human scabies has been determined it would be unwise to dispense with the disinfection of undergarments and bedclothes.

No significant difference was detected between the actions of benzyl benzoate and dimethylthianthrene (mitigal). Tetraethylthiuram monosulphide was more rapid and more lethal in its action than either of those drugs; its superiority was such that it is worthy of a trial in human scabies.

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**PENETRATION AND DISTRIBUTION OF SODIUM SULPHACETAMIDE IN OCULAR TISSUES OF RABBITS**

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Recent work has shown that the local application of sulphonamides may be of value in the prevention and treatment of septic conditions. Thus various investigators have used sulphonamides in the form of powders and pastes (Colebrook, 1941; Fraser, 1941; Buxton, 1940; Robson and Wallace, 1941; Hrad, 1941) for the local treatment of wounds and burns. A great advantage of such a method of administration is that much higher concentrations can be attained locally than can safely be produced by the oral or parenteral routes; moreover, the whole organism is not flooded with the drug, and toxic symptoms are thus avoided.

A number of sulphonamides have been used for this method of treatment. It is important that the substances should penetrate readily into the tissues without producing any injury. It appears likely that penetration will be favoured by a reasonable degree of solubility in water, and that injury will be kept to a minimum if the solution does not appreciably deviate from neutrality. The number of sulphonamides possessing these properties is limited. Among these, sodium sulphacetamide (albuclid soluble) has proved of value when applied locally in the treatment of eye infections and burns, and there is, moreover, evidence that its application produces a beneficial effect on experimental infections of the cornea with *B. pyocyaneus* in rabbits (Robson and Scott, 1942). It seemed of interest, therefore, to determine how readily this substance penetrates into the tissues and how rapidly it diffuses through them and reaches the general circulation; this was the object of the present investigation.

**Methods of Investigation**

Experiments were performed on 75 mature rabbits of both sexes and various breeds. For the prolonged application of the solutions celluloid funnels were made (see Fig. 1). These

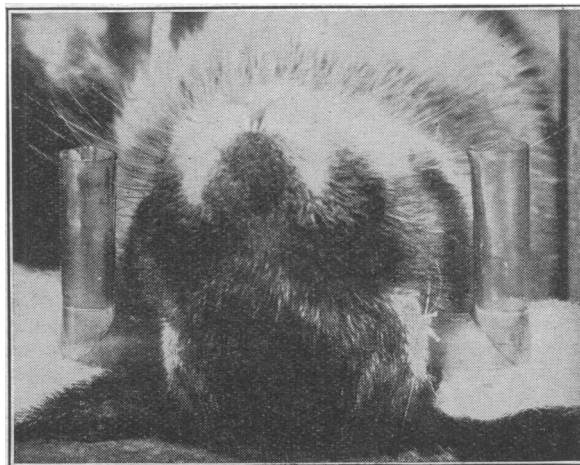


FIG. 1.—Showing the celluloid funnels in position in the eyes of a rabbit, in the method used for the prolonged application of solutions.

were placed into the conjunctival sac under ether anaesthesia and kept in position by means of purse-string sutures through the lids. The funnels were so designed that their apertures