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Dermatophyte lesions in the hedgehog as a reservoir of penicillin-resistant staphylococci

By JOHN M. B. SMITH* and MARY J. MARPLES
Department of Microbiology, Medical School, University of Otago, Dunedin, New Zealand

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The investigations described in this paper were undertaken in an attempt to explain why such a high proportion (86 %) of the strains of *Staphylococcus aureus* carried by hedgehogs were resistant to penicillin (Smith & Marples, 1964). Since the discovery and classification of this antibiotic, several penicillin-like substances have been derived from organisms other than *Penicillium notatum*. These organisms include a number of *Penicillium* and *Aspergillus* species (Peck & Hewitt, 1945). The occurrence of antibiotic substances has been demonstrated in only a limited number of pathogenic fungi. Waksman, Horning & Spencer (1942) noted the production of antibiotics by *Aspergillus fumigatus*. Peck & Hewitt (1945) recorded the production of a penicillin-G-like substance during the *in vitro* growth of a number of dermatophytes, and in particular *Trichophyton mentagrophytes*. Uri, Szathmary & Herpay (1957) succeeded in demonstrating the *in vivo* production in ringworm lesions of an antibiotic biologically resembling penicillin G. The possible ecological implications of this antibiotic production on the microbial flora of a chronic ringworm lesion were not investigated. It is rare that antibiotic production can be shown to have ecological significance in a natural environment (Brian, 1957), although the story of the increasing incidence of antibiotic-resistant staphylococci in such man-made selective environments as the hospital ward has been well documented. Smith & Marples (1964) suggested that chronic mycotic infection of hedgehog skin (*Erinaceus europaeus*) provided an environment in which penicillin-resistant staphylococci had a selective advantage over sensitive strains, and that hedgehog skin is one in which the natural production of an antibiotic is affecting the structure of the biocenose.

This paper embodies the full report of these findings and demonstrates that ringworm lesions may be an important reservoir of penicillin-resistant strains of *Staphylococcus aureus*.

* Present address: Department of Animal Health, Faculty of Veterinary Science, Massey University of Manawatu, Palmerston North, New Zealand.

MATERIALS AND METHODS

In vitro *antibiotic production by dermatophytes*

The ability of the following strains of dermatophytes to produce antibiotic-like substances *in vitro* was determined.

Serial no.	Species	Source
FM 10 (IMI 101, 051)	*Trichophyton mentagrophytes* var. *erinacei*	Hedgehog
FM 16		Hedgehog
FM 22		Hedgehog
Tt	*T. terrestre* (pigmented)	Hedgehog
M. 11	*T. mentagrophytes* var. *granulare*	Mouse
OAM	*T. mentagrophytes* var. *interdigitale*	Human foot
Fi/10	*Epidermophyton floccosum*	Human foot
Fi/140	*Trichophyton rubrum*	Human foot
Fi/146	*Microsporum canis*	Human scalp
TC 11	*Trichophyton concentricum*	Tokelau Is. (human)
TC 17	*T. concentricum*	Tokelau Is. (human)

A small portion (pin head) of a 7-day Sabouraud's dextrose agar culture of each of these eleven dermatophytes was inoculated into 25 ml. Sabouraud's dextrose broth contained in a 50 ml. Erlenmeyer flask. All flasks were shaken in a 30° C. water-bath for 15 days. Each day 0·2 ml. of fluid was removed aseptically from the flasks and examined for antibiotic activity against the Oxford strain of *Staph. aureus*. The method used was that described by Peck & Hewitt (1945).

Any inhibitory substance active against the staphylococcal test strain was examined for inactivation by penicillinase. Sterile Sabouraud's dextrose broth (pH 8·0) was found to have no antagonistic effect on the test strain.

Strains FM 10 and FM 16 were also grown in 25 ml. of 5-strength Sabouraud's dextrose broth and the 'antibiotic' concentrations reached after 5 days agitation at 30° C. recorded. A flask with 25 ml. of Sabouraud's dextrose broth containing 2·5 units/ml. of penicillin G was also shaken in the 30° C. water-bath and the penicillin concentration recorded each day. Any changes in the pH of the fungal filtrates were recorded.

The antibiotic produced by *T. mentagrophytes* var. *erinacei* (FM 10), which gave a zone of inhibition equal to that of 1·1 units of penicillin G per ml. against the Oxford staphylococcus, was also examined for inhibition of the organisms listed in Table 1. In all experiments a control solution of Sabouraud's dextrose broth containing 1·1 units/ml. of penicillin G was run in parallel.

In vivo *antibiotic production by* T. mentagrophytes *var.* erinacei

An attempt was made to determine if the hedgehog strain of *T. mentagrophytes* produced an antibiotic-like substance when growing *in vivo*. Two lines of investigation were adopted.

(i) An attempt to demonstrate, by a plate assay method, antibiotic production by fungus-infected rabbit skin.

(ii) An examination of the organisms, especially *Staph. aureus*, recoverable from

fungus-infected guinea-pig skin to determine if any selection of those showing penicillin resistance had occurred. From previous experiments conducted *in vitro* it had been found that *T. mentagrophytes* var. *erinacei* produced appreciable amounts of an antibiotic substance biologically resembling penicillin G.

Assay of fungus-infected skin

A young male rabbit (600 g.) was experimentally infected with *T. mentagrophytes* var. *erinacei*. A 7-day Sabouraud's dextrose agar culture of the fungus (FM 10) was rubbed into a shaved scarified area of skin on the right hind quarter. When the ringworm had developed for 11 days, fungus-infected skin was removed and placed directly on plates seeded with a lawn of the Oxford strain of *Staphylococcus*. After overnight incubation at 37° C., any zones of inhibition were recorded. Normal skin from the same animal served as a control. Infected skin was also placed on a lawn of the staphylococci to which 6 drops of penicillinase had previously been added.

Investigation of organisms

Four young male guinea-pigs (less than 250 g.) were shaved on the right hind quarter, and the exposed skin scarified with a blunt scalpel. Replica plates were then taken of this shaved area using the method described by Gorill & Penikett (1957).

Swabs were also taken from the shaved area, inoculated into salt broths and incubated at 37° C. for 12–18 hr. Samples from each broth were then streaked on blood agar. After suitable incubation these plates were examined for coagulase-positive staphylococci. Subcultures of representative staphylococcal types from each plate were tested for coagulase production using the tube method.

All *Staph. aureus* strains were phage typed and their penicillin sensitivity was determined in tubes of broth containing penicillin concentrations of 0·037, 0·075, 0·15, 0·312, 0·625, 1·25, 2·5, 5·0, 10·0, 15·0, 20·0, 25·0, and 50·0 μg./ml., incubated overnight at 37° C. With each series of experiments, a control consisting of the Oxford strain of *Staph. aureus* was included.

After the replica plates and swabs had been taken, two of the four guinea-pigs were inoculated with *T. mentagrophytes* var. *erinacei* as described above. At weekly intervals, replica plates and swabs were taken from the two ringworm and two control animals, and examined as just described.

One of the fungus-infected guinea-pigs (and one of the non-infected control pigs) received regular doses of triamcinolone acetonide beginning 4 days after infection, in an attempt to produce a chronic fungal infection as described by Gross, Actor, Jambor & Pagano (1963).

RESULTS

In vitro *antibiotic production*

Of the eleven dermatophyte strains examined, only six showed any sign of antibiotic production during the 15 days of the experiment. These were *T. mentagrophytes* var. *erinacei*, FM 10, FM 16, FM 22; *T. mentagrophytes* var. *granulare*, M 11;

T. mentagrophytes var. *interdigitale*, OAM; and *E. floccosum*, Fi/10. Of these, *T. mentagrophytes* var. *erinacei* strains produced the highest antibiotic yield. The three hedgehog strains (FM 10, FM 16, FM 22) gave uniform results as regards antibiotic production. This reached a maximum after 5 days and was equivalent to 1·1 units/ml. of penicillin G. *T. mentagrophytes* var. *interdigitale* had a maximum yield after 5 days and was equal to 0·2 units/ml. of penicillin G. The maximum reached by *T. mentagrophytes* var. *granulare* occurred after 11 days and was equivalent to 0·3 units/ml. of penicillin. *E. floccosum* appeared to produce two anti-

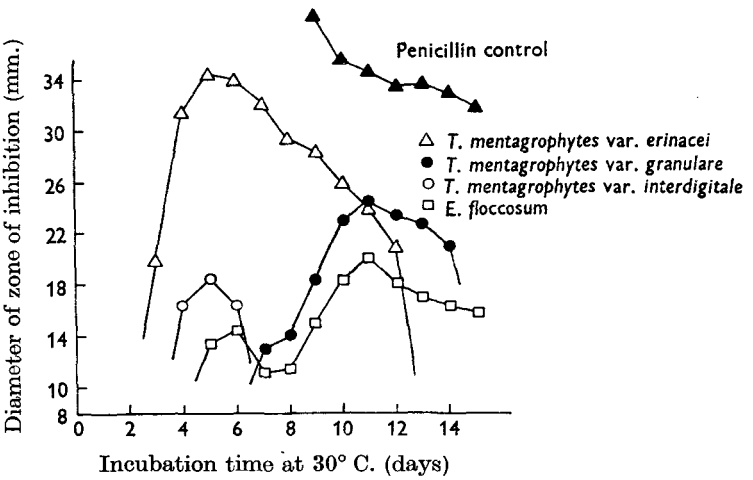

Fig. 1. Production of antibiotics by certain dermatophytes.

biotics, the first reaching a maximum after 6 days and the second after 11 days. Whereas the antibiotic produced by *T. mentagrophytes* strains was inactivated by penicillinase, that produced by *E. floccosum* was not completely neutralized. It appeared that more than one substance inhibitory to the Oxford staphylococcus was being produced by *E. floccosum*. These results are shown in Fig. 1.

If the flasks were not shaken during growth the fungus grew as a surface pellicle, and very little antibiotic was produced as compared with that from shaken flasks. If the flasks were shaken, the growth was microscopically very like that produced *in vivo* by dermatophytes, and it has been termed pseudo-parasitic.

As this paper is concerned with the effect of *T. mentagrophytes* var. *erinacei* on the skin microflora, no attempt was made to investigate fully the antibiotics produced by var. *interdigitale*, var. *granulare* or *E. floccosum*. The following results apply only to var. *erinacei*. The antibiotic factor first appeared in the fungal filtrate after 2 days, the concentration rising sharply to reach a maximum after 5 days. As already stated, this was equivalent to 1·1 units/ml. of penicillin G. This concentration then slowly declined at the same rate as the penicillin G control (see Fig. 1). The antibiotic production was accompanied by a sharp increase in the pH of the filtrate. This rose from the initial 5·6 to 8·3 during the first 4 days, and remained at this level for the remainder of the experiment. Sterile Sabouraud's

dextrose broth, pH 8·0, did not inhibit the staphylococcal test organism. When the fungus was grown in 5-strength broth, the concentration of antibiotic reached after 5 days was equivalent to 7·0 units/ml. of penicillin G.

The antibiotic produced by *T. mentagrophytes* var. *erinacei* was inactivated by penicillinase. The fungal filtrate appeared to have the same effect on the various test organisms as an equal concentration of penicillin G in Sabouraud's dextrose broth pH 8·0. Sensitive and resistant organisms are shown in Table 1.

Biologically therefore, the 'antibiotic substance' produced *in vitro* by *T. mentagrophytes* var. *erinacei* closely resembled penicillin G.

Table 1. *The reaction of various organisms to the antibiotic produced* in vitro *by* T. mentagrophytes *var.* erinacei

Sensitive organisms	Resistant organisms
α-Haemolytic streptococci	*Candida albicans*
Oxford strain of *Staphylococcus aureus*	*Proteus mirabilis*
Pneumococci	*Aerobacter aerogenes*
Sarcina lutea	*Escherichia coli*
	Salmonella typhimurium
	Enterococci
	Penicillin-resistant strain *Staphylococcus aureus*

In vivo *antibiotic production by* T. mentagrophytes *var.* erinacei

Assay of ringworm skin

Skin removed from the var. *erinacei* rabbit lesion inhibited the growth of staphylococci close to the skin. This effect was not shown by normal skin or in the presence of penicillinase. This is shown in Pl. 1.

Examination of organisms

The bacterial counts obtained from the four guinea-pigs by the replica plating technique are shown in Tables 2 and 3. An indication of the species present is also given. Unfortunately the hair had regrown into the uninfected skin after 2 weeks, which made further replica plating from these two animals unreliable. Replicas of the skin and hair were taken and any coagulase-positive staphylococci isolated counted. These isolations are shown in brackets in Table 3. The outstanding feature of the results was the increase of coagulase-positive staphylococci in fungal-infected skin as compared with the non-increase on normal skin. If the number of colonies of *Staph. aureus* is taken as a percentage of the total count both ringworm-infected guinea-pigs present a similar picture. Normal skin is relatively resistant to colonization by pathogenic staphylococci (Williams, 1963). It is probable that isolations obtained from the skin and hair of non-infected guinea-pigs represented transient 'visitors' from the air, and not organisms which were multiplying on the skin.

The low total counts on the fungus-infected animal which received triamcinolone acetonide can probably be attributed to the inhibition of the inflammatory response

in the ringworm lesion by this substance. This lesion was not nearly so scabby and raw as that in the other fungus-infected animal.

The *Staph. aureus* strains isolated from the four guinea-pigs via the salt broth enrichment were all of similar phage type. This strain was lysed by many or all of

Table 2. *Organisms recovered by replica plating from fungal-infected guinea-pig skin*

	Total	Micro-cocci	Gram + rods	α-Haem. streps.	Coag. + staphs
Guinea-pig 1. Ringworm + triamcinolone acetonide					
Original	90	83	7	—	—
Week 1	430	410	20	—	—
Week 2	270	69	17	180	4
Week 3	156	62	2	90	2
Week 4	151	32	1	100	18
Guinea-pig 2. Ringworm only					
Original	110	102	8	—	—
Week 1	420	370	50	—	—
Week 2	500	449	10	20	21
Week 3	500	463	7	10	20
Week 4	500	429	5	—	66

Table 3. *Organisms recovered by replica plating from normal guinea-pig skin*

	Total	Micro-cocci	Gram + rods	α-Haem. streps.	Coag. + staphs
Guinea-pig 3. Control. Triamcinolone acetonide					
Original	126	120	6	—	—
Week 1	30	15	15	—	—
Week 2	—	—	—	—	—
Week 3	—	—	—	—	(1)
Week 4	—	—	—	—	—
Guinea-pig 4. Control					
Original	101	94	7	—	—
Week 1	38	18	20	—	—
Week 2	—	—	—	—	(1)
Week 3	—	—	—	—	(2)
Week 4	—	—	—	—	(1)

the following phages, 6/7/42E/47/53/54/75/77/83A/81. Slight variations were found each week, as shown in Table 4. Also shown in this table is the inhibitory concentration of penicillin for each strain. As shown, the penicillin inhibitory concentration of the staphylococcal strains recovered from the ringworm lesions increased from the initial 5·0 μg./ml. to approximately 20 μg./ml. after 3 weeks. No such increase was apparent with the staphylococci recovered from the normal control animals. Organisms with high penicillin resistance appear to be selected for propagation in *T. mentagrophytes* var. *erinacei* infected guinea-pig skin.

Table 4. *Phage type and inhibitory concentration of penicillin of* Staphylococcus aureus *strains recovered from* Trichophyton mentagrophytes *var.* erinacei *infected and non-infected guinea-pig skin*

The inhibitory concentration of penicillin, in μg./ml., is shown below each phage type.

	Guinea-pig 1. Ringworm +ve. Triamcinolone acetonide	Guinea-pig 2. Ringworm +ve.	Guinea-pig 3. Control. Triamcinolone acetonide	Guinea-pig 4. Control.
Originally	6/7/42E/47/53/54/75/77/83A/81 5·0	—	—	6/7/42E/47/53/54/75/77/83A/81 5·0
Week 1	6/7/42E/47/53/54/75/77/83A/81 5·0	6/7/42E/47/53/54/75/77/83A/81 5·0	6/7/42E/47/53/54/75/83A+ 5·0	6/7/42E/47/53/54/75/77/83A+ 5·0
Week 2	6/7/42E/47/53/54/75/83A/81 20·0	6/7/42E/47/53/54/75/83A+ > 20·0	6/7/42E/47/53/54/75/83A/81 2·5	6/7/42E/47/53/54/75/77/83A+ 5·0
Week 3	6/7/42E/47/53/54/75/77/83A+ 15·0	6/7/42E/47/53/54/75/77/83A+ > 20·0	6/7/42E/47/53/54/75/77/83A+ 5·0	6/7/42E/47/53/54/75/77/83A+ 5·0
Week 4	6/7/42E/47/53/54/75/83A/+ 20·0	6/7/42E/47/53/54/75/77/83A+ > 25·0	6/7/42E/47/53/54/75/83A+ 5·0	6/7/42E/47/53/54/75/83A+ 2·5
Week 5	6/7/42E/47/53/54/75+ 15·0	6/7/42E/47/53/54/75+ 25·0	6/7/42E/47/53/54/75+ 1·25	6/7/42E/47/53/54/75+ 5·0

DISCUSSION

Skin carrying a pathogenic fungus appears to provide a favourable habitat for coagulase-positive staphylococci (Marples & Bailey, 1957). Guinea-pig skin experimentally infected with *T. mentagrophytes* var. *erinacei* was readily colonized by *Staph. aureus* strains, which appeared to thrive in the ringworm tissue. In wild hedgehogs the skin is the primary site of staphylococcal multiplication (Smith, 1965). The presence of *T. mentagrophytes* var. *erinacei* in the skin of a high proportion of the animals (Smith & Marples, 1963) may be partly responsible for the growth of *Staph. aureus* strains in such an environment. Experiments have been conducted on possible symbiotic relationships between dermatophytes and staphylococci. When they are grown together on solid media, the results depend on which organism is favoured by the cultural conditions (Elek, 1959). Patiala (1947) found fluid cultures of some dermatophytes to exert an inhibitory effect on staphylococci. Elek (1959) considered the clinical significance of such observations to be doubtful. The reverse effect has also received attention. Catanei (1929) and Fabiani (1932) found *T. schoenleini* to be stimulated by staphylococci, while Vanbreuseghem (1948) found that certain staphylococcal strains inhibited this fungus *in vitro*. The present investigations indicate that, in hedgehogs, *T. mentagrophytes* var. *erinacei* and penicillin-resistant strains of staphylococci do live symbiotically on the skin.

In vitro, *T. mentagrophytes* appeared capable of producing an antibiotic biologically resembling penicillin G. Of the three varieties of *T. mentagrophytes* examined, var. *erinacei* was most proficient in producing the antibiotic. This *in vitro* production of penicillin by *T. mentagrophytes* had previously been demonstrated by Peck & Hewitt (1945). These workers found granular strains to be proficient in producing penicillin (var. *erinacei* not being discovered at this time). Whether or not *T. mentagrophytes* var. *erinacei* will prove of value as a commercial source of penicillin is outside the scope of this paper. By simply increasing the concentration of the medium fivefold, 7·0 units of penicillin/ml. could be produced in 5 days. Glaxo Laboratories in England have been able to produce up to 3·0 units/ml. of penicillin from *Trichophyton* strains (other than var. *erinacei*) (Richmond, personal communication).

The penicillin production by var. *erinacei* was accompanied by a sharp increase in the pH of the medium from 5·6 to 8·3. Peck & Hewitt (1945) noted a similar pH rise in the filtrates of their dermatophyte strains. Whereas var. *erinacei* reached its maximum concentration of penicillin and highest pH value after only 5 days growth, Peck & Hewitt found their strains of *T. mentagrophytes* to take nearly 12 days to reach maximum production and pH level. This is similar to the findings with var. *granulare* in the present investigations (see Fig. 1).

Peck & Hewitt (1945) were able to demonstrate antibiotic production in *T. violaceum*, *T. tonsurans* and *E. floccosum* but not in *Microsporum canis*, *M. audouini* or *T. rubrum*. In the present investigations, *M. canis*, *T. rubrum*, *T. concentricum* and *T. terrestre* did not appear capable of producing antibiotics *in vitro*.

T. mentagrophytes and *E. floccosum* have been shown to produce a substance resembling penicillin G when growing *in vivo* (Uri *et al.* 1957). These workers found that skin from ringworm lesions inhibited the growth of penicillin-sensitive organisms (*Bacillus subtilis*), the inhibition being neutralized by penicillinase. Rabbit skin infected with *T. mentagrophytes* var. *erinacei* appeared to have the same effect. A substance active against penicillin-sensitive organisms and neutralized by penicillinase could be demonstrated in fungus-infected skin. Normal skin did not show this effect.

The production of penicillin by var. *erinacei* in guinea-pig skin was well demonstrated by the increase in penicillin resistance of the *Staph. aureus* strain residing in the ringworm. The staphylococci, which were initially inhibited by 5·0 μg./ml. of penicillin G, were found to increase in resistance as the ringworm progressed. After 3 weeks, the inhibition level had risen to above 20 μg./ml. The *in vivo* production of penicillin by var. *erinacei* would not have to be great to account for this increase. Leitner, Sweeney, Martin & Cohen (1963) demonstrated that between 0·6 and 2·0 units/ml. of penicillin had the same effect as 20 units/ml. in triggering off the enzymic action of penicillinase production. Even 0·01–0·02 units/ml. of penicillin were sufficient to induce penicillinase production. It is easy to imagine this concentration being produced in chronic ringworm lesions.

Penicillin-resistant strains of *Staph. aureus* were present before the therapeutic use of penicillin. Until now no satisfactory theory has been advanced to account for this. It appears as if the presence of *T. mentagrophytes* var. *erinacei* in hedgehog skin does provide an environment selective for penicillin-resistant strains of staphylococci. The presence of the fungus is considered the main reason why so high a proportion (86 %) of the strains of *Staph. aureus* carried by hedgehogs are penicillin resistant.

As 90 % of the hedgehog *Staph. aureus* strains were typable with human staphylophages (Smith, 1965) it would appear that these animals provide a reservoir of penicillin-resistant pathogenic staphylococci. We consider that chronic ringworm lesions of other animals and man may also be of importance as reservoirs of penicillin-resistant *Staph. aureus*.

SUMMARY

An antibiotic substance biologically resembling penicillin G was produced by the growth of *Trichophyton mentagrophytes* var. *erinacei*, *T. mentagrophytes* var. *granulare* and *T. mentagrophytes* var. *interdigitale* in Sabouraud's dextrose broth. An antibiotic concentration equivalent to 7 units/ml. penicillin G could be produced by var. *erinacei* when grown in a suitable nutrient medium. *Epidermophyton floccosum* also produced a substance which inhibited the growth of the Oxford staphylococcus. However, this substance was not completely inactivated by penicillinase. No *in vitro* antibiotic production could be demonstrated with *T. rubrum*, *T. concentricum*, *T. terrestre* or *Microsporum canis*.

Penicillin production could be demonstrated in rabbit skin infected with *T. mentagrophytes* var. *erinacei*. Pathogenic staphylococci falling on a var. *erinacei* guinea-

pig lesion increased rapidly in the ringworm tissue. The inhibiting concentration of penicillin G for such staphylococci was shown to increase from 5·0 μg./ml. to above 20·0 μg./ml. as the ringworm progressed.

The presence of *T. mentagrophytes* var. *erinacei* in a high percentage of hedgehogs is considered the main reason why the skin is the primary site of staphylococcal multiplication in hedgehogs and why most of the *Staphylococcus aureus* strains recoverable from these animals are penicillin resistant.

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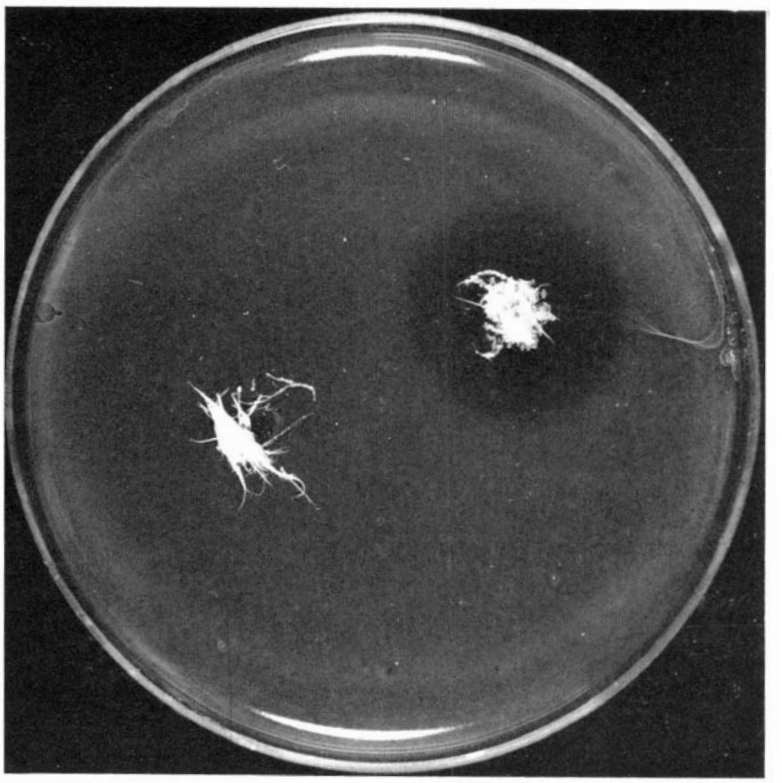

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EXPLANATION OF PLATE

Effect of *T. mentagrophytes* var. *erinacei* infected rabbit skin (right) and normal rabbit skin (left) on the growth of the Oxford strain of *Staphylococcus aureus*.

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