A NEW TREATMENT FOR ANTHROPOPHILIC TINEA TONUSURANS
(MICROSPORON AUDOUINI)

A PRELIMINARY REPORT

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PREFACE

It is generally agreed that scalp ringworm caused by microsporon of animal origin (zoophilic) is cured with relative ease by manual epilation of fluorescent hairs plus topical fungicides, and that it tends toward spontaneous recovery. It is also the consensus that tinea capitis caused by human microsporon is much less prone to disappear spontaneously even at puberty, that it does not respond favorably to topical treatment, that it is usually necessary to depend upon x-rays or thallium acetate, and that it may occur as a wide-spread epidemic.

Most recent authors are in accord with the foregoing statements (Lewis and Hopper (1), Wise and Sulzberger (2), MacKee (3), Spiller, Sharp and John (4), and others). Contrarily, Livingood and Pillsbury (5) state that cure following "little or no treatment" occurred in 36.6 per cent of all their cases of microsporon Audouini infections. This has not been our experience except beyond puberty.

Thallium acetate is not used in this country because of its high toxicity. It has been customary to depend entirely upon x-ray epilation, plus adequate post radiation treatment.

The present epidemic of scalp ringworm, the first in the United States, began in some of the Eastern ports including New York City more than three years ago, and is spreading over the entire country. In the vast majority of cases the causal organism is the microsporon Audouini. While x-ray epilation is the best treatment, only a small proportion of the large number of patients can receive such treatment for the following reasons: 1. There are comparatively few dermatologists, roentgenologists and technicians capable of the exacting technic and after care. 2. The method is used in only some of the larger urban centers. 3. It is difficult to apply the method to restless children, especially under the age of two years. 4. X-ray treatment is not always successful and it is not entirely free of danger; many parents refuse the treatment.

Five years ago MacKee, Sulzberger, Herrmann and Baer (6-10) began research with penetrating liquid vehicles one of which is now called "Intraderm". Three years ago we began to use "Intraderm" in which was incorporated a fungicide for the treatment of Audouini scalp ringworm. The research is still in progress and will be continued. The encouraging results have prompted

1 From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

2 This research was made possible by a grant from the Wallace Laboratories, Inc., New Brunswick, New Jersey.

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3 Trade name of Wallace Laboratories, Inc., New Brunswick, New Jersey.
this preliminary report in the hope that the method will help reduce the present epidemic.

RATIONALE

As demonstrated in previous publications (6, 7, 8), as a result of chemical histologic and histochemical studies, the carrier "Intraderm", impregnated with a testing chemical, therapeutic agent, or a dye incorporated as an indicator, enters the skin by the following route: it penetrates the entire hair follicle and stains the hair including the pulp. It then enters the cutis through the sebaceous glands and the sides of the follicle, and finally upward into the epidermis. When applied to the unbroken skin it impregnates the upper horny layers, but it does not penetrate the epidermis directly.

This saturation of the follicle and hair is essential for our purpose. We failed to obtain such penetration with other liquids, emulsions and ointments. Hairs on slides were exposed, under comparable conditions, to many carriers containing a dye (0.4% Alphazurin 2G), then washed with water and alcohol and examined in damar resin-xylene under cover slips. Our vehicle was the only one that stained the hair intensely and completely. When inspected hairs were treated in this manner and examined microscopically, spores and mycelium appeared stained inside the hair sheaths as well as at the edges. When other carriers were used, only the organisms along the outer edges were stained.

It is admitted that an extracted hair may not be anatomically complete, also that it is difficult to prove, microscopically, that the interior of the hair is stained, not just the outer layer. However, the staining was more intense, more persistent and more extensive with "Intraderm" than with any of the other carriers investigated.

Marchionini and cow (11), Peck and Rosenfeld (12), both these authors with Leifer and Bierman (13), Keeney (14), the latter and Broyles (14), have shown that the growth of fungi (trichophyton gypseum, epidermophyton inguinale, and monilia albicans) is impaired by certain fatty acids, to a much lesser degree by their salts, but quite distinctly by the presence of these acids in the form of acid buffer mixtures. Keeney obtained a similar result with cultures of microsporon Audouini, and we have recently verified these findings in our experiments in vitro. Most of these acids are normal constituents of the natural sweat, and after free evaporation of sweat a protection against moulds results on the skin through formation of an acid coat (Marchionini and cow. (11), F. Herrmann and K. Fuerst (15, 17). A number of fatty acids are considered of particular value in the treatment of dermatophytooses, when present or liberated in sufficient quantity. Clinical application of this principle was made by Herrmann and Fuerst (16), Marchionini (17), Peck, Rosenfeld, Leifer and Bierman (13), Livin-good and Pillsbury (5), Keeney and Broyles (15) a.o. We decided to add this factor to "Intraderm" containing a fungicide.

Major interference of pH changes as such with the growth of fungi could be expected only under very acid condition (pH 3), or drastic alkalinity (pH 10). Just as trichophyton gypseum changes the original pH of media to a more suit-
able environment (Peck and Rosenfeld (12), so does microsporon Audouini, in culture, change the pH to one more favorable for its needs. As soon as a growth started in a buffered Sabouraud's agar, we observed an increase of the original pH of 5.6 to 7.5. These changes occurred at first in the vicinity of the fresh culture and appeared in more distant parts several days later.

Comparative pH examinations on both diseased and normal scalp areas of children with tinea capitis, and on the scalps of normal children and adults, are still in progress and will be reported elsewhere. It was found that the ringworm patches gave a distinctly higher pH than the normal areas. This was not considered a specific finding, since similar figures were obtained in other inflammatory eruptions by Bernstein and Herrmann (17). It did suggest, however, the therapeutic use of the fact that the diseased areas developed a pH more favorable for the growth of the causative organisms than the pH of normal skin. Thus, an attempt was made to alter the pH in the lesions toward conditions less favorable for the mold. Our effort was concentrated on the application of acid solutions as the pH of the diseased areas can be altered in this direction with less irritation than to a sufficient degree of alkalinity.

IN VITRO EVALUATION OF FUNGICIDAL ACTION

The fungicidal action of many chemicals in combination with our and other vehicles, was demonstrated in vitro by experiments on hairs from children infected with microsporon Audouini. Plain cultures were less suitable, because they showed too high susceptibility, i.e., inhibition of growth by almost any preparation. The use of infected hair, on the other hand, is more comparable with the important and difficult problem in vivo, i.e., to procure access of the agent to the molds inside the hair. Our experimental procedure was similar to the technic used by v. Berde (18). Since different strains of microsporon Audouini may show different susceptibility to the same fungicide, one strain (infected hair from one child) was used for one complete test. This applied not only to all tests of a single series in which an equal number of hairs was exposed to a given product for different periods of time, but also to a larger number of test series in each of which a single individual preparation was under investigation. As many infected hairs as possible, therefore, were collected from one scalp by manual epilation under filtered ultraviolet radiation, before treatment was started in the child. The presence of spores was confirmed under the microscope, before a hair was used in the test. The same number of hairs (4–8) was exposed on a slide to 0.25 cc. of the fungicide solution for 1, 3, 5, 10, 15, 20, 25, and 30 minutes. The fungicide solution was removed by capillary absorption with filter paper. The hairs were then rinsed with 0.25 cc. distilled water, and placed in Sabouraud's media.

A large number of chemicals were tested. Their incorporation in our carrier

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4 When after the pH increase a fraction of culture medium was taken from an area distant to the culture and kept in an open vessel, the pH dropped to 5.6. This may indicate that the alkali formed by the fungi is volatile, perhaps ammonia originating from protein components.
required the addition of other ingredients in many instances in order to effect solubility, since “Intraderm”—as was discussed in previous publications (6, 8, 9)—is not a vehicle to which may be added any therapeutic chemical. The concentration of the various drugs was based on clinical practicability rather than on an attempt to compare the effect of equimolar concentrations. When the results with one of the active ingredients appeared promising, this test series was repeated two or three times with the same strain (stored hairs of the same scalp), and then with hair from other scalps.

While we have examined the fungicidal action of many substances in our carrier, modified as far as necessary for accommodation of the active ingredient, and in other carriers, only a few have shown promise. The best results thus far have been obtained with trimethyl cetyl ammonium pentachlorphenate (TCAP) in rather high concentrations in “Intraderm”. The copper compounds with organic radicals followed in efficacy and next salicylic acid plus benzoic acid in the various combinations tested.

Of the copper preparations studied, copper oleate as part of an acid buffer (together with oleic acid), dissolved in our carrier by the addition of benzyl benzoate and sulfonated castor oil, was the most effective. The effect of salicylic and benzoic acids was increased by an acid buffer mixture, and the action still further enhanced by combination with brilliant green or thymol.

All the chemicals and combinations in the subjoined list were tested:

The carrier, “Intraderm”, as a control; various accepted acid and alkaline buffer mixtures; these mixtures with detergents and various sulfonated oils (shampoos); mercury succinimide; mercury bichloride; mercury thioglycolate; sodium thiosulphate; potassium permanganate; zinc thioglycolate; copper sulphate with acid buffer mixture; copper napthenate; copper oleate; copper oleate with acid buffer mixture; copper oleate with benzyl benzoate; same with acid buffer mixture; salicylic acid; benzoic acid; salicylic and benzoic acids; iodine; iodocholeate®; thymol; thymol iodine; salicylic acid with thymol; salicylic and benzoic acids with thymol; salicylic acid with acid buffer mixture; benzoic acid with acid buffer mixture; thymol with acid buffer mixture; salicylic and benzoic acids with acid buffer mixture; cinnamic acid; cinnamic acid with acid buffer mixture; thyrothricin; penicillin, compound G-11® with acid buffer mixture; β-naphthol; hydrophen, acriflavine; acriflavine with acid buffer mixture; gentian violet; gentian violet with acid buffer mixture; malachite green with acid buffer mixture; brilliant green with acid buffer mixture; malachite green plus salicylic and benzoic acids with acid buffer mixture; brilliant green plus salicylic and benzoic acids with acid buffer mixture; desenex (undecylenic acid—undecylenate buffer); sopronol solution (propionic acid—sodium propionate buffer with n-propyl alcohol 12.5%); sopronol ointment (sodium propionate—propionic acid, propyl alcohol, zinc stearate in water soluble base); human sebum in our carrier; phemerol (p-tertiary-acetyl-phenoxy-ethoxyethyl-dimethyl-benzyl-ammonium chloride monohydrate); two other quarternary ammonium salts; dithane A-10; various concentrations of TCAP in “Intraderm”; this combination plus different concentrations of acid buffer mixture; this fungicide solution varied by omitting one by one the individual “Intraderm” ingredients; different concentrations of TCAP in a vanishing stearate base.

* We are indebted to Dr. P. Goedrich, N. J. College of Pharmacy, Rutgers University, for placing this compound at our disposal.

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The fungicides listed above were tested, also, on infected hairs, after the hairs were exposed to the acid shampoo (to be defined below) for 10 minutes, and then rinsed with water.

The experimental results were considered favorable when no growth occurred in Sabouraud's media after exposure of hair to the fungicide for more than three minutes. The most efficient preparations prevented growth after only one minute's exposure. When no growth occurred in six weeks, the hairs were replanted in order to be certain that there was a fungicidal, and not a fungistatic action. Controls in plain Sabouraud's media served as the standard for establishing oppression, retardation, etc., of growth in each test series.

"INTRADERM TCAP"

Several different preparations with any one of the fungicides found to be promising in vitro (TCAP, copper oleate, salicylic and benzoic acids) were given extensive clinical trials. However, in this first part of our report we confine ourselves to the description of the formulas as well as the mode of treatment relating to TCAP only, for this compound (the final one we have studied) affords an active ingredient which thus far has served our purpose best.

The following material has been found after much study to be best suited for our present therapeutic method.

Solution A. An acid shampoo containing 70 grams of a wetting agent, preferably of the alkyl benzene sulfonate type, 140 ml. propylene glycol, 140 ml. sulfonated castor oil and 700 ml. distilled water, brought to pH 3.0 with citric and propionic acids. This solution produces a good lather and removes crusts and scales. It acidifies the scalp (pH 3.5) for at least four hours.

Solution B. A fungicidal solution containing 425 grams TCAP, a wetting agent of the alkyl benzene sulfonate type 700 grams, antipyrine 1700 grams, propylene glycol 1400 ml., sulfonated castor oil 1400 ml., distilled water 7600 ml., brought to a pH of ca. 4 with citric acid and propionic acid.

TECHNIC

Instructions for Home Treatment

The scalp of the infected child is examined under filtered ultraviolet radiation. The fluorescent areas are shown to the person in charge of the child, and are marked with a skin pencil. The hair is removed by clipping as closely as possible, and instructions are given to repeat the clipping twice weekly. Persons with the child are advised to purchase clippers and to disinfect them by boiling for ten minutes after use. We prefer clipping to other methods of hair removal, such as shaving and depilatories. General prophylactic instructions are given. After removal of the hair, liberal quantities of Solution A are rubbed thoroughly into the scalp. This is then partially rinsed off, using not more than a cup full of luke warm water. It is preferable to leave some of the acid shampoo (Solution A) on the scalp every time. The scalp is dried well with a towel and immediately treated with Solution B. If there are circumscribed diseased patches, they are inuncted first. The smooth end of a thick glass rod is used for the rub-
bing of the solution into these areas. Each patch is rubbed with the liquid for 6—10 minutes.

This is followed by a liberal application of the solution with the hands, over the whole scalp for 15 or 20 minutes. It is advisable for the person giving the treatment to wear rubber gloves. The moderate lather that forms is allowed to dry spontaneously.

Where there are diffusely scattered fluorescent hairs instead of patches, the solution is applied to the entire scalp with the hands, the application beginning in normal areas if there are any. The diseased part is then rubbed with particular effort. One such treatment requires 30—45 minutes.

Glabrous skin around the scalp is protected by zinc oxide paste. Four rubbing treatments are given during the day. Only in greatly improved cases is treatment reduced to three or even to two daily applications. The first induction is given not later than 9 A.M.; the last one so, that the child can go to bed one hour after the application.

The scalp is kept uncovered for 45 minutes to one hour after each treatment. It is then covered with a white cap of smooth, linen-like material. Several (6—8) caps are kept on hand. After 24 hours of use the cap is sterilized by boiling in water. An ointment containing 2% TCAP is used, when the scalp becomes irritated or too scaly. In such cases, the ointment is spread freely all over the scalp, as long as possible before the morning treatment. It is not necessary to remove the ointment, because the latter and Solution A mix well and form a creamy lather.

Control and Criteria of Cure

As is obvious, the treatment is time consuming, and difficult to carry out and to control under ambulatory conditions. Parents are given written and verbal instruction at the time of the first visit. Patients revisit once weekly for inspection under filtered ultraviolet radiation, and for instruction. We hope later to evolve a more potent remedy and a simplified technic. The percentage of cures is much higher with hospitalized than with ambulatory patients. Thus far we have been able to hospitalize only twenty patients.7

Before the admission of a case to the group under study, the causative organism is identified by culture. A diagram of the initial findings on the scalp as seen under filtered ultraviolet radiation is made, and progress is followed by a physician at least once weekly. In addition to the regular weekly observation by fluorescence, suspected hairs are examined microscopically, and cultures made. Treatment is continued until these examinations remain negative for at least 6 weeks. Patients remaining negative for one month after cessation of treatment are considered cured.

SIDE EFFECTS

Scaliness of varying degree appeared on most scalps treated. Moderate forms of inflammation were encountered in half of the children. One form

7 These were not treated with TCAP, but with some of the other fungicides in "Intra-derm."
consisted of erythema, slight infiltration, and moderate tenderness, mostly noticeable behind the ear and near the posterior hair border. This kind of irritation may occur early or late after the beginning of treatment. It usually subsided after 2 to 6 weeks, without modification of the treatment. The other form of inflammatory reaction was characterized by follicular papules on the forehead, sometimes extending downward over the face. This eruption appeared as a late complication in 19% of all the cases, preponderantly in those who neglected the protective application of zinc paste around the scalp before each treatment. The lesions resembled the well known picture of industrial chloracne.\(^8\) Similarly to the other types of inflammatory reaction, these eruptions disappeared spontaneously in the majority of cases; in others a mild treatment with sulfur preparations, or a bland lotion was helpful. In all, there was much less irritation with “Intraderm TCAP” than with any of the other effective fungicidal combinations we had tried. Some of these will be dealt with in a subsequent report. The side reactions due to solution B never caused interruption or a major modification of treatment.

### Table 1

<table>
<thead>
<tr>
<th>NUMBER OF CASES</th>
<th>AGE</th>
<th>NEGATIVE FINDINGS</th>
<th>DISTINCTLY IMPROVED</th>
<th>LITTLE OR NOT IMPROVED</th>
<th>AVERAGE TIME OF TREATMENT UP TO PERSISTENTLY NEGATIVE</th>
</tr>
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<tbody>
<tr>
<td>59</td>
<td>2-15 years (7 above 11 years)</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
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<td>32</td>
<td>54</td>
<td>4</td>
<td>7</td>
<td>20</td>
<td>34</td>
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<td>36</td>
<td>61</td>
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### RESULTS

The accompanying table gives a summary of the clinical results\(^9\) attained with the treatment herein described.

Our criteria of cure necessitates the addition of roughly 10 weeks to the average time\(^10\) of treatment “up to persistently negative findings,” in order to define the average length of treatment until cure was finally established. The shortest period after which negative findings were obtained was one week, the longest ten months. These figures indicate the great individual variation.

\(^8\) We are in agreement with a suggestion of Dr. S. Peck, that these lesions may be caused by the chlorine in TCAP.

\(^9\) In addition, one baby of 9 months with a microsporon lanosum infection (scalp) was cured with this treatment; after 6 weeks all findings were and stayed negative.

The results of the use of “Intraderm TCAP” in other dermatophytoses will be dealt with in a forthcoming report.

\(^10\) Recently, removal of solitary infected hairs by electrolysis under filtered ultra-violet radiation was of value for abbreviating the treatment time in some of the cases.
The 59 cases listed include all the children who were treated with TCAP in “Intraderm” for a minimum of three months. While many other children were treated, these are excluded, because of inadequate cooperation or because the duration of treatment was too short for final evaluation. The series herein presented comprises the children treated during the past 15 months. A much greater number was treated with some of our other preparations during the preceding 2 years. Fourteen of these cases appear among those listed above, since the application of the other solutions had been unsuccessful, and was followed by our present procedure. The series includes also other cases in which previous methods had failed—x-ray epilation, in some instances, even repeatedly applied.

The series cannot be considered an average group of microsporon Audouini infections. They present a comparatively unfavorable series for treatment. It has been our experience that untreated cases are much more susceptible to the application of fungicides than are those which had had previous lengthy treatment.

As shown by the chart, some of our children were approaching, or had even reached, puberty. Many had failed to be cured by other methods, including x-ray epilation. These patients showed great resistance to the treatment. The longest time spent in treatment was with some of these older children.

The distinctly improved cases (34%) include only those who were found by several successive examinations to approach the stage of cure. The duration of treatment will be very long in a number of these children, before they are definitely cured.

Because of the experience recorded by Livingood and Pillsbury (5), the question may arise as to whether our cures were spontaneous, or caused by the inflammatory reaction. Our experience is to the contrary. We have observed a large number of young children with microsporon Audouini scalp infection who had the affection for from a few months to a year or two, and who had received little or no treatment. There were no spontaneous cures among these children. They all showed continued spread of the affection.

The inflammatory response in some of our cases was different in character from the more violent and more deep seated changes described as favorable by Livingood and Pillsbury (5). Even the severe inflammation caused by our more early preparations did not speed recovery. To the contrary, as will be discussed in a subsequent report, severe reactions have been a handicap.

DISCUSSION

Results justify encouraging others to make trials with TCAP in “Intraderm”. Considering the difficulties of x-ray epilation, the percentage of cure may outweigh the disadvantages of our technic.

There is a possibility that the new treatment may be usefully combined with x-ray epilation. We have in mind the use of solutions A and B following x-ray epilation, and x-ray epilation, after our treatment has failed. We have a considerable number of patients who, after “Intraderm treatment” over a period
of three months, still have one or a few small, isolated resistant patches. Fo-
calized irradiation by the method advocated by Lewis (19) might be successful
in such cases.

In view of the continued spreading of the present epidemic, it appears logical
to try this new treatment as a prophylactic. This applies particularly to families,
institutions, and districts where children are known to be infected. Frequent,
if possible daily, use of Solution A is suggested for this purpose, in combination
with about three inunctions a week of Solution B.

The new form of therapy is far from being perfect. The cases of failure may
be attributed to:

1. Difficulties in carrying out the proper technic.
2. A few living spores not reached by the fungicide.
4. Immunobiologic peculiarities.
5. Anatomical peculiarities (great length of hair roots; ingrown hairs).

Studies on all these problems are in progress. The greatest handicap is the
complicated and time-consuming technic. Lack of cooperation of the responsible
persons is very common, and for many reasons. The much higher percentage
of cures in the hospital (details of which will be reported later) suggests the
advisability of public facilities such as hospitalization, ringworm clinics and
nurses in public schools. In this connection we have been authorized to men-
tion the results obtained by Dr. J. J. Russo in a group of children with micro-
sporia Audouini infection in Albany, New York. These patients were under
ambulatory care of school nurses, who applied this new treatment while the
heads were exposed to filtered ultraviolet radiation. Of 16 cases, 13 have been
declared cured thus far.

SUMMARY AND CONCLUSIONS

1. Based on the results of histologic, mycologic, and biochemical experiments,
studies were made on the therapeutic effect of trimethyl cetyl ammonium
pentachlorphenate in a combination of solvents on microsporon Audouini in-
fec tions of the scalp, without x-ray epilation.

2. This fungicide solution was used in combination with an acid buffered
detergent.

3. As a result of this treatment, 54% of the infected children were cured. The
average duration of treatment needed to bring about persistently negative find-
ings was approximately 14 weeks.

4. Whereas the new form of treatment herein presented still has major handi-
caps, especially concerning the technic of application, it offers a help for those
cases in which x-ray epilation is not possible.

5. In view of the expansion of the present epidemic, further use of the treat-
ment by others is suggested.

6. Prophylactic studies, and the combination of this treatment with x-ray
epilation seem worthy of trial.
BIBLIOGRAPHY

A New Treatment for Anthropophilic Tinea Tonsurans (Microsporon Audouini): A Preliminary Report. G. M. Mackee, F. Hermann, F. L. Karp. Biology. A PRELIMINARY report on a method of treatment for plantar warts by electrosurgical removal was published in 1942. 1 It covered observations for only 21 patients. Since that time I have treated 106 patients. Trichophyton tonsurans, Microsporum canis, and Microsporum audouinii are most common. The condition presents with hair loss (alopecia), usually with scale. Patchy areas of broken hairs covered by white scales can resemble seborrheic dermatitis. When tinea capitis invades the hair shaft the scalp shows a characteristic black-dot pattern, in which hairs broken off at scalp level resemble comedones within patches of alopecia. Inflammatory tinea capitis occurs in the setting of tinea infection coupled with a brisk host inflammatory response. A boggy inflamed plaque (kerion) may form, which is associated with systemic symptoms, including fever, pain, and regional lymphadenopathy. Permanent hair loss may occur. Microsporum audouinii is an anthropophilic fungus in the genus Microsporum. [1] It is a type of dermatophyte that colonizes keratinized tissues (primarily hair) causing infection. [2] The fungus is characterized by its spindle-shaped macroconidia (7–30 μm), clavate microconidia (2.5–3.5 μm), and its pitted or spiny external walls. [3] Microsporum audouinii causes the infections Tinea capitis (scalp ringworm) and Tinea corporis. [2] These superficial dermal diseases are generally found in prepubescent children (starting at 6 months) and rarely affect adults. [3] There are several reasons why children are more susceptible to M. audouinii. "Germination and initial growth of Microsporon audouinii from infected hairs". Mycopathologia et Mycologia Applicata. Abstract Tinea pedis, which is a dermatophytic infection of the feet, can involve the interdigital web spaces or the sides of the feet and may be a chronic or recurring condition. The most common etiological agents are anthropophiles, including Trichophyton rubrum sensu stricto, which is the most common, followed by Trichophyton interdigitale and Epidermophyton floccosum. There has been a change in this research arena, necessitating a re-evaluation of our knowledge on the topic from a multidisciplinary perspective. Thus, this review aimed to provide a solid overview of the current status and c Trichophyton tonsurans is an anthropophilic dermatophyte with a worldwide distribution and is responsible for superficial mycosis with a wide range of clinical manifestations. We report two atypical cases of tinea due to T. tonsurans in two children: a case of extensive tinea corporis. We report two atypical cases of tinea due to T. tonsurans in two children: a case of extensive tinea corporis and a case of inflammatory tinea capitis. Publication types. Case Reports.