PRESENTATION OF THE HYPOTHESIS THAT TRICHOPHYTON INTERDIGITALE IS A DEGENERATED TRICHOPHYTON GYPSEUM

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It has been suggested for many years that fungi which have been described as different species may be only different stages of the same organism (Sabouraud (1)). This theory has been advanced by several authors. Grigoraki's classification "is based in part on a premise that some of the species of Sabouraud are degeneration stages in the life cycle of other species" (quoted from Dodge (2)). Experimental evidence (Catanei (3), Emmons (3a), Langeron and Talice (quoted by Dodge)) for this hypothesis is relatively scanty and has been reviewed by Dodge (2) and Emmons (3a). Dodge himself seems to acknowledge this theory to a certain extent in regard to the genus ectotrichophyton, as he writes: "this genus is here conceived as the primitive group from which all the other dermophytes were derived by degeneration."

Emmons experimenting on Achorion gypseum and Trichophyton gypseum lacticolor, is lead to the belief "that many of the dermatophytes now known as species are only varieties of a single unstable species." As shall be pointed out in the following, one cannot differentiate Trichophyton interdigitale² from Trichophyton

¹ The experiments presented were carried out in the University Dermatological Clinic, Breslau; Director, Prof. J. Jadassohn.

² The classification of this fungus is still disputed. Many authors, MacCarthy (9), Dodge (2) and the majority of European workers classify it as Epidermophyton; others, Ota and Langeron (47) and Weidman (4) as Trichophyton. Sabouraud (1936) concurred in the latter viewpoint and grouped the fungus among the microides. Hopkins (American Academy of Dermatology and Syphilology, Jan. 15, 1938, Detroit) identified Tr. interdigitale with Tr. gypseum.
by botanical criteria, although I have not been successful in transferring *Trichophyton interdigitale* to a cultural form identical with primary *Trichophyton gypseum*.

All experiments to restore a pleomorphic fungus to its primary appearance have been unsuccessful; and only such a demonstration could serve to settle the problem definitely on botanical grounds.

In this paper I shall first present the most important known facts which tend to support the theory that *Trichophyton interdigitale* and *Trichophyton gypseum* seem to be so closely related that the best explanation of this relationship is based upon the assumption that the former is a degenerated form of the latter; and second I shall present new evidence in support of such a theory as demonstrated by my own experiments on animals and in man.

**BOTANICAL RESEMBLANCE BETWEEN TRICHOPHYTON INTERDIGITALE AND TRICHOPHYTON GYPSEUM**

Weidman (4, 13) has questioned "whether, botanically speaking, *Trichophyton asteroides*, *radiolatum* and *interdigitale* were different species" and Miescher (5) has stated that differentiation from a botanical point of view seems unnatural. According to the older concepts the differentiation of *Trichophyton interdigitale* from *Trichophyton gypseum* was made on the following basis: *Trichophyton interdigitale* is a fungus which cannot be differentiated botanically from *Trichophyton gypseum*; its only distinguishing characteristic is that it does not invade the hair. Therefore if a fungus resembling *Trichophyton interdigitale* is cultured from follicular lesions in which the hair has been invaded it must be classified—from an orthodox standpoint—as *Trichophyton gypseum* or *Trichophyton niveum*. Among many cultures of *Trichophyton interdigitale* I have found strains resembling *Trichophyton gypseum* asteroides, others resembling *Trichophyton gypseum radiolatum* and still others, which did not show outspoken similarity to any gypseum group.

During the war the clinic at Breslau was forced to use a medium containing Maltose (Merck) and Peptone (Witte). The use of
this medium was afterwards continued in parallel series with Sabouraud’s maltose, glucose and peptone media. The Breslau “substitute medium” was decidedly inferior in general, but it showed the difference between *Trichophyton radiolatum* and *asteroides* much better, the former cultures exhibiting a full yellowish color in the center. Pleomorphic subcultures could be differentiated on this medium longer than on Sabouraud’s.

On the “substitute medium” some of the cultures of *Trichophyton interdigitale* exhibited the same or nearly the same variations in color as the *gypseum* strains and this may have enabled me to differentiate varieties among the group of *Trichophyton interdigitale* more easily than those investigators who have been using Sabouraud’s medium only. It is interesting to note that many of my strains of *Trichophyton interdigitale* resembled *Trichophyton gypseum radiolatum*, which was also the most frequent *gypseum* variety in Breslau. Sabouraud himself mentions the resemblance of *Trichophyton interdigitale* to *Trichophyton gypseum lacticolor*.

**CULTURAL VARIABILITIES OF BOTH TRICHOPHYTON INTERDIGITALE AND TRICHOPHYTON GYPSEUM**

*Trichophyton interdigitale* was first described by M. Kaufman-Wolf (1914) (6) and by Priestley (7). Their reports have been confirmed by many authors; a number of similar or only slightly different fungi have been described by others (Hodges (8), MacCarthy (9), Ota (10) etc.). The term “*Epidermophyton interdigitale*” was suggested by Lee MacCarthy.

Even today there is no unanimity about what is included under this name. This is easily understood as *Trichophyton interdigitale* is outstanding in its variability, whence Karrenberg’s (11) suggestion: “*Epidermophyton variabile*.” Formerly chiefly four types have been described: (a) a whitish downy type, (b) a more or less powdery type, (c) a cerebriforme-like type, (d) a pink type. Some authors have tried to establish different species, but have been opposed by those who have seen transitions between different types. This is true for the gypseum-like type. Cremer (12) states that he has never seen a transformation of the
cerebriforme-like type into the gypseum-like type and this corresponds to my own observations. Dodge now distinguishes *Epidermophyton cerebriforme* as well as the pink varieties from "*Epidermophyton interdigitale*" (as he classifies the fungus); and I shall follow him in this report, by excluding the cerebriforme and pink types from the group designated as *Trichophyton interdigitale* in this paper.

Therefore *Trichophyton interdigitale* as referred to in this paper includes only the gypseum-like varieties and the white fungus. However, as the pleomorphic endstages of many fungi look alike, I cannot be certain that all the white fungi which I have here included really belong to this group.

Even with this restricted definition *Trichophyton interdigitale* still exhibits a great variability. Although many strains keep their special characteristics for quite a time, one not infrequently finds changes from the gypseum-like picture to the white fungus and vice versa, under both natural and artificial conditions. Moreover, cultures of the same fungus may vary in appearance, when taken at different times. I shall later mention the interesting report of Weidman (13) concerning changes in the cultural appearance of a fungus observed over a period of years.

Furthermore, one may culture different types of colonies from the same or different lesions of one and the same patient (illustrated in fig. 1).

Similar observations are reported by others. Sometimes these changes are noticeable only in the subcultures. As a whole the variation is always within the limits of a gypseum-like and downy pleomorphic fungus and it resembles various stages of *Trichophyton gypseum*.

One has to admit that the opposite does not seem to be true. The picture of a fresh, powdery culture of *Trichophyton gypseum asteroides* or *radiolatum* is a very distinct one and no one could confuse it with *Trichophyton interdigitale*; but even the primary culture of *Trichophyton gypseum* is not always so characteristic.

I know of only one report of primary pleomorphic culture of *Trichophyton gypseum* as such. Sabouraud (14) reports that Rivalier has been able to culture primarily pleomorphic colonies
among powdery ones from a trichophytosis caused by *Trichophyton gypseum* and that the pleomorphism persisted in subcultures. I, myself have obtained primarily pleomorphic cultures several times. My records show four instances (two cases of deep trichophytosis of the scalp and beard and two cases of superficial trichophytosis of the knee and back of the hand) of primary cultures which I would have called *Trichophyton interdigitale* if they had been obtained from characteristic interdigital lesions.

Moreover, I recall several instances in which *Trichophyton gypseum* showed slight pleomorphic degeneration immediately
in the first culture, a degree of pleomorphism which persisted after subculture and guinea-pig passages.

Of course if one obtained a completely pleomorphic *Trichophyton gypseum*, one would call it a *Trichophyton niveum*. Sabouraud suggested in 1910 that *Trichophyton niveum* may be nothing but a natural pleomorphic stage of *Trichophyton gypseum*, an opinion which today seems well established (Dmitriev (15)) and which is concurred in by others. Recently (1936) however, Sabouraud (14) has revoked his original hypothesis.

Cultural changes in aging cultures of *Trichophyton gypseum* have frequently been described. It is a fact that under equal conditions different strains of *Trichophyton gypseum* do not become pleomorphic with the same speed; and that some become completely pleomorphic whereas others persist for a long time in a partly pleomorphic state. Catanei (16) described three different types developing from an aging culture of *Trichophyton gypseum radiolatum*. In two instances the morphologic characteristics were preserved during passage through guinea pigs.

I shall not discuss the microscopic appearance of *Trichophyton interdigitale* and *Trichophyton gypseum*. To my knowledge there are no special characteristics which permit the differentiation of these two forms.

**OBSERVATIONS ON CLINICAL MATERIAL**

*a. Findings in culture*

While there is a consensus that one finds *Epidermophyton inguinale* as the causative fungus (Karrenberg (11)) in practically all cases of epidermophytosis of the groin (eczema marginatum) in northern countries there is no such uniformity as regards the fungi recovered in cases of epidermophytosis of the feet and hands. It is of great importance here to stress that there are a number of reports of cases in which fungi of the *Trichophyton gypseum* group have been found in “epidermophytosis” of the feet and hands because this tends to show that fungi of this type can become purely “epidermophytic.” Alexander (Berlin) (17), Miescher (Zuerich) (5) and Matras (Vienna) (18) found *Trichophyton interdigitale* exclusively in such cases, while other fungi such as *Trichophyton*,

Microsporon and Achorion may be the cause of epidermophytosis according to several other observers. Table 1 shows the detailed statistics of several such observers. This viewpoint that different species of fungi can cause epidermophytosis is also clearly taken in Weidman’s work. Miescher lists the following fungi in this connection: Trichophyton acuminatum, Trichophyton crateriforme, Trichophyton rotundum, Trichophyton violaceum, Trichophyton gypseum and Trichophyton gypseum-like fungi, Trichophyton equinum-like fungi, Microsporon Audouini, Microsporon lanosum, Achorion Quinckeanum. On the other hand Miescher doubts whether all of these seven cultures were true Ep. inguinale. I have described them previously (45) as Ep. inguinale-like fungi as they showed slight differences which I do not consider important, except for two strains.

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Author} & \text{Place} & \text{Total of Cultures} & \text{Tr. interdigitale} & \text{Trichophyton and Achorion} \\
\hline
\text{Maschkilleison (20)} & \text{Voronieje (Russia)} & 80 & 7 & 93 \\
\text{Lomholt (20a)} & \text{Kopenhagen (Denmark)} & 25 & 12 & 84 \\
\text{Cremer (8)} & \text{Amsterdam (Netherlands)} & 57 & 2 & 98 \\
\text{Schmidt (19)} & \text{Munster (Germany) Feet} & 180 & 20 & 77 \\
& \text{(Germany) Hands} & 110 & 11 & 60 \\
\text{Epstein (not published previously)} & \text{Breslau (Germany)} & 157* & 4† & 91 \\
\hline
\end{array}
\]

* Including three cases where a cerebriforme fungus (Ep. cerebriforme) and two cases where Ep. lanoroseum were found (= 3 per cent).
† I am not sure whether all of these seven cultures were true Ep. inguinale. I have described them previously (45) as Ep. inguinale-like fungi as they showed slight differences which I do not consider important, except for two strains.

whether all the fungi described as Trichophyton gypseum or niveum have been correctly classified. However, several observations by Schmidt (19) and others and my experiment in a human volunteer (see below) prove that Trichophyton gypseum is capable of producing pure epidermophytosis.

\[b. \text{Comparison of clinical pictures}\]

Clinically it seems rather difficult to compare the lesions caused by Trichophyton interdigitale, Trichophyton gypseum, and Epidermophyton inguinale because at least two of these fungi
produce a single uniform and rather typical clinical picture. For my present purpose it seems important to present only those instances in which a deviation from these typical findings has been reported. It may be said that *Trichophyton gypseum* produces nearly all possible clinical pictures of ringworm infection from acute deep trichophytosis of the hairy parts to superficial chronic infections of the glabrous skin and intertriginous and eczematous lesions (as reported by Sabouraud (14) and Maschkilleison (20) (the latter author in addition to a report of his own cases reviewed the pertinent literature).

Miescher stated that "neither *Trichophyton interdigitale* nor *Epidermophyton inguinale* have been found to cause a kerion or any other picture of a follicular trichophytosis. This is very remarkable when one considers the extraordinary extent of dyshidrotic mycosis. It can hardly be explained except by assuming a special fungus with special affinities demonstrated by its location." I believe that such a statement holds true for *Epidermophyton inguinale*. There are records of cases of eczema marginatum showing involvement of the scalp (Weiss (21), Arzt and Fuss (22), Takeya (quoted by Miescher)) where the fungus did not affect the hair. A similar case has recently been reported by Gjessing and Mossige (23).

However, I do not think that Miescher's statement can be considered valid in the case of *Trichophyton interdigitale* because there are no cases on record in which this fungus was found on the scalp. Yet it would appear rather surprising that a fungus—which in regard to its localization has much more in common with *Trichophyton gypseum* than has *Epidermophyton inguinale*—should never be found in the main localization site of *Trichophyton gypseum*. And it seems to be much more plausible to suspect that *Trichophyton interdigitale* may have invaded the scalp in some cases and produced the lesions characteristic of a real "trichophytosis" of the hairy parts; but that, because this fungus cannot be differentiated botanically from *Trichophyton gypseum* when it was recovered from such a scalp lesion it was classified as a *Trichophyton gypseum* or *niveum* and not as an *interdigitale*. 
What may be a typical example of such an occurrence is the one cited by P. W. Schmidt, who cultured identical fungi from an interdigital space of the foot and from a deep trichophytosis of the beard in one and the same patient and who classified both fungi as *Trichophyton gypseum*.

**c. Biological behavior**

Consideration of the biological behavior of *Trichophyton interdigitale, Trichophyton gypseum* and *Epidermophyton inguinale* shows a further parallelism between *Trichophyton interdigitale* and *Trichophyton gypseum*. For neither Miescher (5) nor Bloch (24) record a single case of an epidermophytid due to *Epidermophyton inguinale*; and I myself have never seen an epidermophytid produced by this fungus. However, there is a report by Burgess (25) of an epidermophytid in a case from which he cultured the “pleomorphic variety of *Epidermophyton inguinale*” and another report by C. M. Williams (26) of a secondary eruption following the local irritation of the lesions of a tinea cruris (eczema marginatum) by the application of iodine. Unfortunately no cultures of the original fungus were made in Williams’ case.

In contrast to this, epidermophytids are frequently found in cases of mycotic infections of the hands and feet as discussed by Williams (27), Bloch (24), Sulzberger (28), Weidman (4), Peck (29), W. Jadassohn and Peck (30).

This marked tendency to produce epidermophytids brings “epidermophytosis” due to *Trichophyton interdigitale* (in contradistinction to epidermophytosis due to *Epidermophyton inguinale*) biologically close to the *Trichophyton* group of fungi, especially to the *Gypseum* group, which is most frequently found in lesions causing trichophytids (Bloch). The analogy is further stressed both in the severe nature of generalized epidermophytids and in the youth of patients suffering from this type of eruption (Matras: three cases six to twenty years of age; Epstein: six cases five to eighteen years of age). Moreover, both *Trichophyton interdigitale* and *Trichophyton gypseum* have been recovered from lymph glands (Cleveland White (31), Sutter (32), H. Hoffmann (33)) and from the blood-stream (Peck (29), M. Jessner (34)).
It might be advanced as an argument against the identity of *Trichophyton interdigitale* and *Trichophyton gypseum* that in 1934 U. Scholz (35) and Ruete and Scholz (36) reported experiments and observations which demonstrated that hypersensitivity in guinea pigs produced by inoculation with *Trichophyton interdigitale* and *Trichophyton gypseum* is absolutely species-specific, i.e., a primary inoculation with the former fungus does not affect the course of a reinoculation with the latter and vice versa. Also, reactions to "trichophytin (Hoechst)" and "epidermophytin (Ruete-Scholz)" are reported to be absolutely species-specific in both patients and guinea pigs.

These reports, which might represent a strong argument against the identity of *Trichophyton interdigitale* and *Trichophyton gypseum*, are, however, in contradiction to all observations hitherto reported by other authors and to my own observations. All investigators in this field have found that the allergy acquired by the first inoculation of a hyphomycete is not specific for this particular species but only for the particular group of fungi involved (Bloch, Peck, Sulzberger). My own experimental results with cross-inoculations of *asteroides* and *radiolatum*, *asteroides* and *rosaceum*, *radiolatum* and *cerebriforme*, *gypseum* and *Achorion Quinckeanum* are in agreement with Bloch's statement. Further results have shown that this holds true also for *Trichophyton gypseum* and *Trichophyton interdigitale* (table 2). Moreover, Matras (18), numerous observers at the clinic in Breslau as well as the majority of American observers (Van Dyck, Kingsbury, Throne, Myers (37), Sulzberger and Wise (38) Sulzberger (39)) have found that "trichophytin (Hoechst)" (the identical trichophytin which was used by Ruete and Scholz) as well as trichophytins from various other strains of trichophyton fungi regularly produced reactions in cases of "epidermophytosis."

The findings of the last-named workers although demonstrating a certain degree of cross-reactions between *Trichophyton interdigitale* and *Trichophyton gypseum*, nevertheless do not exclude the presence of species-specific allergens. Furthermore occasional species-specific reactions with "favin," "microsporin" and "epidermophytin" are on record. The question under discussion has
been approached by means of the Schultz-Dale test by Werner Jadassohn and his co-workers (40). They found a common antigen for all the four examined species (*Achorion Quickeanum, Achorion Schoenleinii, Trichophyton gypseum, Trichophyton interdigitale*) and in addition to the common antigen found specific antigens for the single species (with the exception of *Trichophyton interdigitale*).

These interesting experiments cannot be completely evaluated at the present time and the rôle they will play in the future in the classification of fungi will depend upon the fundamental question whether these antigenic properties are a constant characteristic of a species. I am inclined to the opinion that this may not be the case but that the allergen content of the various strains may be variable. Sabouraud thinks that the products produced by fungi are not constant, an idea which is well supported by many clinical observations.

**TABLE 2**

<table>
<thead>
<tr>
<th>FIRST INFECTION</th>
<th>SECOND INFECTION</th>
<th>RESULT OF SECOND INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tr. gypseum</em> (2705)</td>
<td><em>Tr. interdigitale</em> (307)</td>
<td>Abortive, slightly inflammatory reaction of 7 days duration. No fungi found</td>
</tr>
<tr>
<td><em>Tr. interdigitale</em> (835)</td>
<td><em>Tr. interdigitale</em> (307)</td>
<td>Same result, 7 days duration, even less inflammation</td>
</tr>
<tr>
<td><em>Tr. gypseum</em> (2705)</td>
<td><em>Tr. interdigitale</em> (210)</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Tr. interdigitale</em> (835)</td>
<td><em>Tr. interdigitale</em> (210)</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Tr. interdigitale</em> (433)</td>
<td><em>Tr. interdigitale</em> (433)</td>
<td>Superficial infection with shortened incubation and course. Fungi found in some of the experiments</td>
</tr>
<tr>
<td>Several animals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EPIDEMIOLOGIC CONSIDERATIONS**

It is well known that *Trichophyton gypseum* and *Trichophyton interdigitale* have been found all over the world; and it is equally well known that the frequency of "epidermophytosis" has been
rapidly increasing during recent years, especially since the world war. This is the general impression among older dermatologists (cf. Dodge) such as Bruhns and Alexander (40a), Gilchrist (41) and Ch. J. White (42). Brunsting (according to Goldsmith (43)) states that at the New York Skin and Cancer Hospital epidermophytosis ranked as the seventh or eighth most frequent disease between 1913 and 1927, whereas it took second place in 1928 and 1929. While there are no exact statistics on the incidence of trichophytosis during the world war (1914–1918) figures from the clinics in Munich and Breslau (O. Muensterer (44), Epstein (45)) show the following interesting data:

From 1911 to 1913 and from 1923 to 1925 trichophytosis was diagnosed in 1 to 2 per cent (Munich) and 2.6 to 3.6 per cent (Breslau) of all dermatoses. But in 1919 the corresponding figure was 20 and 23 per cent; in 1920, 11 and 13.7 per cent; and in 1922, 4 and 5.2 per cent respectively.

These figures demonstrate excellently the extent of the trichophytosis epidemic and its fairly rapid disappearance. Though it may just be a coincidence it is extremely interesting to note that the “epidermophytosis-wave” began at about the period when the “trichophytosis-wave” receded. It seems permissible to consider the possibility that the “trichophytosis-wave” may have left behind degenerating fungi, which—possibly in combination with other factors—caused the enormous increase of interdigital, plantar and palmar epidermophytosis.

These epidemiologic considerations again suggest very strongly that Trichophyton interdigitale is a degenerated Trichophyton gypseum because of the striking time-relationship of the “trichophytosis-” and the “epidermophytosis-wave.”

On the other hand the specific localization (feet and hands) and the outspoken contagiosity (epidemics) of Trichophyton interdigitale are facts which are in contrast with the ordinary behavior of Trichophyton gypseum in the orthodox or older

* The lack of knowledge of the mycotic origin of hand and foot “epidermophytosis” in former years as well as the lack of accurate differentiation between this condition and true epidermophytosis make comparative statistical studies rather difficult if not impossible.
concept. The gypseum fungus is found in almost every part of the world and its tendency to transmission from man to man is certainly not very great, although a few epidemics are on record (Fischer (quoted by Bruhns and Alexander), Pautrier (46)). One cannot deny that these are distinct differences in behavior. Yet these differences do not prove that one is dealing with different species; on the contrary one has reason to believe that a degenerating microorganism may not only lose certain morphologic and cultural characteristics, but that it may also exhibit a different biologic behavior, including a different degree of infectivity.

EXPERIMENTS IN ANIMALS

a. On the question of invasion of the hair by Trichophyton interdigitale

Hodges (8), Ota (10), and Takakashi (48) were the first to demonstrate that *Trichophyton interdigitale* can invade the hair; but their observations have been doubted by several authors because they were based only upon extemporaneous microscopic examination of fresh preparations.

Furthermore Catanei (3) reported that an aging culture of *Trichophyton gypseum radiolatum* became less virulent for guinea pigs and showed less affinity for the hair until it finally failed to involve the hair at all.

In order to study the question of the growth of *Trichophyton interdigitale* within the hair, I have inoculated into guinea pigs six strains grown from typical cases of epidermophytosis of the hands and feet and two strains of "*Epidermophyton* gypseum" and "*Epidermophyton* niveum" (MacCarthy (9)) respectively. In the majority of these experiments the following technique was employed:

From one to six animals were infected with each strain tested.

A large area of one side of the guinea pig was slightly traumatized with sandpaper; the fungus-culture was carefully rubbed into this traumatized area and kept in place for 3 to 5 days by means of a dressing.

This method appeared to be superior to the ordinary technique previously employed in animal experiments. The developing lesions were observed clin-
Fig. 2. *Trichophyton interdigitale*. Fungi around hair of guinea pig 645 (biopsy 6502) (17th day). Typical "Ectothrix" (Microide type)
See table 3

Fig. 3. Sheath of spores around hair in guinea-pig infection by *Tr. interdigitale*
(Culture 433, guinea pig 622. See table 3)
### TABLE 3

**Inoculation of Tr. interdigitale in guinea pigs**

<table>
<thead>
<tr>
<th>NUMBER OF EXPERIMENT</th>
<th>CULTURE NUMBER</th>
<th>GUINEA PIG NUMBER</th>
<th>RESULT</th>
<th>COURSE OF INFECTION IN THE ANIMALS</th>
<th>PENETRATION OF FUNGI INTO HAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>307</td>
<td>654</td>
<td>Pos.</td>
<td>14th day: Ring-shaped, scaly lesion, about size of a bean. Superficial until 17th day. 19th-29th day: Larger, 2 cm. in diameter, infiltrated, crusted. 37th day healed</td>
<td>14th day (Biopsy 6496): Fungi surrounding the hair as sheath of spores, and within the hair: some hairs are filled with fungi with subsequent destruction of the hair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>657</td>
<td>Neg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>313</td>
<td>645</td>
<td>Pos.</td>
<td>13th day: Ring-shaped lesions, slightly scaly. No inflammation. 14th day: 2 lesions about the size of a pea, round, scaly edge, smooth center. Superficial. 17th day: Lesions larger, no inflammation. 21st-26th day: Lesions confluent, infiltrated. 32nd-36th day: Healing. 41st day: Healed</td>
<td>13th day. Fungi only in scales</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17th day (Biopsy 6502): (see fig. 2) Fungi surrounding hair and within hair</td>
</tr>
<tr>
<td>3</td>
<td>410A</td>
<td>2 animals</td>
<td>Pos.</td>
<td>Deep trichophytosis. (Superficial lesions after passage from one animal to another, see table 4)</td>
<td>Fungi within the hair (no biopsy)</td>
</tr>
<tr>
<td>4</td>
<td>433</td>
<td>2 animals</td>
<td>Pos.</td>
<td>Superficial trichophytosis</td>
<td>Fungi around and within the hair (in subsequent animal passages). See fig. 3</td>
</tr>
<tr>
<td>5</td>
<td>462</td>
<td>649</td>
<td>Pos.</td>
<td>Superficial infection. 9th day: Lentil-sized lesion. 11th day: Very small, crusted lesions (see fig. 4). 14th-20th day: 2 more lesions. 22nd-25th day: Healing</td>
<td>11th day (Biopsy 6498): Fungi in crust. 21st day (Biopsy 6506): Typical &quot;ectothrix&quot; picture. Not certain whether fungi within the hair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>648</td>
<td>Pos.</td>
<td>Superficial infection 9th day: Redness over 1 cm. in diameter. 13th and 14th day: Polycyclic lesion about 2 cm. in diameter. 19th-24th day: Healing</td>
<td>14th day (Biopsy 6569): No fungi in hair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>647</td>
<td>Neg.</td>
<td>Superficial infection. Similar to guinea pig 648</td>
<td></td>
</tr>
</tbody>
</table>
ically, microscopic examinations of the hair were done and in all except one instance biopsies were taken in order to confirm the invasion of the hair by the fungi. In all cases in which retro-cultures could be obtained they corresponded to the primary cultures. Utmost care was taken in handling the cultures and in keeping the animals isolated.

Table 3 demonstrates the results obtained in these experiments: Three out of six strains of *Trichophyton interdigitale* employed produced lesions in all inoculated guinea pigs; the other three strains produced lesions in some but not in all of the inoculated animals. The lesions were generally superficial or abortive in character and corresponded to those reported by previous observers. However, strain 410A produced primarily deep gypseum-like lesions. Several lesions which were superficial in the beginning later on became more or less infiltrated. Microscopic extemporaneous examination of unstained scrapings demonstrated involvement of the hair follicle in all six instances. The fungi were "ectothrix" (Sabouraud's microide type) but seemed to invade the hair. Some hairs were covered with sheaths of spores.

**Histological studies of biopsies taken from lesions produced by the strains used in experiments 1, 2, 4, 5 and 6, in three instances proved the fungi within the hair and the pictures observed in these biopsies were absolutely identical with those found after inoculation with *Trichophyton gypseum*.**

These histological studies did not confirm my microscopic findings in all instances, for in two instances I have not been able to demonstrate fungi within
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the hair in the histologic section, although on microscopic extemporaneous examination I had the impression that there was invasion of the hair. The experiments with inoculations of MacCarthy's strains of "Epidermophyton" gypseum and "Epidermophyton" niveum confirmed MacCarthy's findings that these two strains do not invade the hair.

b. Change of virulence of Trichophyton interdigitale and Trichophyton gypseum by means of passage from animal to animal

Before describing my own experiments demonstrating the change in virulence of Trichophyton interdigitale and Trichophyton gypseum during passage through guinea pigs it seems justified to mention that M. Jessner and H. Hoffmann (49) reported the attenuated virulence of a Trichophyton gypseum cultured from the blood-stream of a patient suffering from trichophytosis, thus showing the reduction in virulence of Trichophyton gypseum through the influence of the human body.

H. Hoffmann (33) later on published an analogous instance in which he was able to compare the virulence of Trichophyton gypseum cultured from the primary "kerion"- lesion with that of a fungus of the same species recovered from a lymph-gland, both fungi coming from the same patient, a boy suffering from "kerion" with accompanying lymphadenopathy. The fungi were identical in morphologic appearance but different in virulence. Guinea-pig inoculation of the "kerion"-fungus and the "gland"-fungus gave the following results:

1. The "kerion"-fungus produced a deep trichophytosis as usually seen after Trichophyton-gypseum inoculation, but the "gland"-fungus gave rise to an abortive lesion with small nodules and crusts and hardly any infiltration. (Hoffmann's pictures illustrating this difference, correspond well to my figs. 6 and 4 respectively.)

2. The change in virulence showed a great degree of stability. Repetition of the experiment after culture on artificial media

4 In a series of inoculations (which were carried out for another purpose) 23 more strains of Trichophyton interdigitale were inoculated with the ordinary technique (small areas, no dressings). Nine out of twenty-three strains were found to be virulent for guinea pigs. (The possibility of the growth of fungi within the hair was not studied in this series.)
over a period of nine months gave a nearly identical result for each fungus.

3. In passages through animals by means of retro-cultures the attenuation of the virulence of the “gland”-fungus was demonstrated up to the fourth passage, but was lost in the fifth passage. At this stage the virulence of the “gland”-fungus became equal to that of the “kerion”-fungus.

The following experiments were done in order to study the effect of carrying Trichophyton interdigitale and Trichophyton gypseum through a series of guinea-pig passages.

Two to four animals were inoculated in each passage. The first inoculation was made with culture material except in experiment 8, where scales directly from the human lesion were used. The subsequent inoculations were carried on directly from animal to animal. In order to be able to carry the strains through several passages and over a long period of time, the material which was used for passage from one guinea pig to another was regularly taken from the more severely infected animals. This may account for the delayed appearance of decrease in virulence and for the small number of negative inoculations.

From these experiments it may be concluded that both fungi undergo marked changes in their virulence, when subjected to the procedure of guinea-pig passage. The results, as shown in table 4, may be summarized as follows:

*Trichophyton gypseum* can be attenuated by repeated passages from animal to animal. Subsequent inoculations produce superficial and abortive lesions or even fail to infect the animal (experiments 8 and 9). The superficial and abortive lesions then resemble those produced by *Trichophyton interdigitale*. This decrease in virulence was observed with a strain of *Trichophyton gypseum*, which was transferred directly from man to animal (experiment 8); as well as with a strain of *Trichophyton gypseum*, which had been proved pleomorphic on cultures for many years and which had never lost its virulence during all these years of in vitro culture (experiment 9). The change in virulence in experiment 8 did not take place until after the tenth passage through guinea pigs.

On the other hand the virulence of *Trichophyton interdigitale* can be increased by passage through guinea pigs, as demonstrated in two instances (experiments 10 and 12), the first inoculation
### TABLE 4

**Change of virulence of Tr. gypseum and Tr. interdigitale by means of passages from animal to animal**

<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>FUNGUS</th>
<th>NUMBER OF PASSAGES CARRIED OUT DURING MONTHS</th>
<th>RESULT</th>
<th>TYPE OF LESIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><em>Tr. gypseum radiatum</em>, slightly pleomorphic. Originated from acute follicular trichophytosis</td>
<td>28, 19</td>
<td>Decrease and loss of virulence</td>
<td>Deep trichophytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superficial or abortive lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In all animals up to the 10th passage, and part of later passages</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1 or 2 animals of the 11th, 14th, 15th, 17th, 19th, 21st-27th passage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative inoculations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1 animal of the 23rd and 24th passage</td>
</tr>
<tr>
<td>9</td>
<td><em>Tr. gypseum</em>. Pleomorphic for over 8 years without loss of virulence. Originated from deep trichophytosis of the beard</td>
<td>10, 8</td>
<td>Decrease and loss of virulence</td>
<td>Deep trichophytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superficial or abortive lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In all animals of the 1st and 2nd passages and some of the 3rd, 4th and 5th passages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1 animal of the 3rd, 4th and 5th passages and in all animals of the 6th-10th passage (except negatives)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1 or more of the 8th, 9th and 10th passages</td>
</tr>
<tr>
<td>10</td>
<td><em>Tr. interdigitale</em>, No. 261. Originated from &quot;epidermophytosis&quot; of feet</td>
<td>7, 5</td>
<td>Increase and variability of virulence</td>
<td>Deep trichophytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superficial or abortive lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In all animals of 3rd-7th passage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 2 animals of the 1st and one of the 5th passage. The lesions produced in the 2nd passage were between the superficial and deep type</td>
</tr>
<tr>
<td>11</td>
<td><em>Tr. interdigitale</em>, No. 410A. Originated from &quot;epidermophytosis&quot; of feet (with &quot;epidermophytid&quot;)</td>
<td>3, 2</td>
<td>Decrease and variability of virulence</td>
<td>Deep trichophytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superficial or abortive lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In all animals of 1st, and one of the 3rd passage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 2 animals of the 3rd passage</td>
</tr>
<tr>
<td>12</td>
<td><em>Tr. interdigitale</em>, No. 433. Originated from &quot;epidermophytosis&quot; of foot</td>
<td>16, 10</td>
<td>Increase of virulence</td>
<td>Deep trichophytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superficial or abortive lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1 animal of the second and all of the 3rd passage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In all animals of the first and 1 of the second passage</td>
</tr>
</tbody>
</table>
Fig. 4. Primary infection of guinea pig (1st passage) with Trichophyton interdigitale. Small crusted lesions, 11th day after inoculation (Strain 462, guinea pig 649. See table 3)

Fig. 5. Deep infection produced by 3rd passage of Tr. interdigitale from animal to animal (Strain 433, guinea pig 652. See table 4)
producing superficial lesions, while in subsequent passages the character of the lesions varied between abortive infections and deep trichophytosis. Another strain of this fungus (experiment 11) showed definite attenuation in the third passage in which only one out of three animals developed deep trichophytosis, the infection being abortive and superficial in the other animals.

Retro-cultures invariably have been identical with the primary cultures and the change in virulence had no influence on the cultural appearance in any of these experiments.

**Fig. 6. Typical Picture of Guinea-Pig Infection (1st Passage) with **

*Tr. gypseum*

Acute inflammatory, strongly infiltrated crusted lesion. (Strain 2705, guinea pig 658, 12th day after inoculation.)

**Experiments in Man**

The ability of *Trichophyton interdigitale* experimentally to produce typical interdigital lesions has been demonstrated by several authors (see Weidman). Peck (29) has since reproduced the typical picture of an intertriginous “epidermophytosis” in a classical experiment with primary and secondary infection and “epidermophytid.”
Reports of experimental infection of the glabrous skin are scanty (Taniguchi (50)). Selma Gruenmandel (unpublished experiment) inoculated the normal skin of two normal volunteers with *Trichophyton interdigitale* and in one of these produced a superficial trichophytosis of the inoculated site on one shoulder. The question of involvement of the hair was not studied in this case nor in Taniguchi’s. As long as inoculations of the human skin in a large series of volunteers, as suggested by Weidman, have not been performed, the question whether some strains of *Trichophyton interdigitale* can produce a follicular trichophytosis and infect the human hair, cannot be decided. But I have been able to do the opposite. For I succeeded in experimentally producing in a normal non-infected volunteer a typical “epidermophytosis” of the toes by inoculating a *Trichophyton gypseum*, which had been cultured from a deep trichophytosis of the beard. The following is the abridged record of this experiment:

Mrs. E. E. has never had a skin disease of feet or hands. Her reaction to trichophytin was negative. The first interdigital space of the right foot was inoculated with *Trichophyton gypseum*. No changes were seen for about three weeks. After that time itching, redness and vesiculation developed in and around the inoculated area. Eleven days later the patient had a typical interdigital “epidermophytosis.” The first interdigital space showed a slightly eroded lesion, the size of the small fingernail, surrounded by a somewhat macerated, scaly edge, partly covered with small vesicles. Itching was severe. The lesion increased slightly in size and three weeks after the first appearance of symptoms, a dry, red lesion with a distinct and scaly edge was found. Microscopic examination of the scales for fungi was positive and cultures were identical with the primary inoculated culture. Treatment was instituted and the lesion cleared up within two weeks.

**DISCUSSION OF EXPERIMENTS**

Whereas the invasion of the hair of experimental animals by *Trichophyton interdigitale* has been previously reported by several authors, these reports have always been based upon microscopic extemporaneous examination only. In the experiments here submitted, all the strains of *Trichophyton interdigitale* which were used invaded the hair follicles in most, if not all, inoculated animals, while they were found within the hair in three out of six instances.
These findings were confirmed by biopsies and are not based merely upon extemporaneous examination. It seems to me that this is conclusive proof that *Trichophyton interdigitale* is a fungus which is capable of invading the hair of the guinea pig.

The objection of orthodox mycologists may be that the fungi, I have experimented with are *Trichophyton gypseum* and not *Trichophyton interdigitale*—just as Sabouraud recently classified the fungus of Ota which invaded the hair and which looked like *Trichophyton interdigitale* as a degenerated *Trichophyton gypseum*. My hypothesis agrees fully with Sabouraud’s objection. However, it must be stated that the fungi used in my experiments were cultured from lesions, which appeared to be clinically typical “epidermophytosis” of the hands and feet; and that the cultures of these fungi showed the typical picture of the whitish or gypseum-like variety of *Trichophyton interdigitale*, which surely does not infect the animals in all instances and which does not always behave as an “ectothrix.”

Moreover, in some of my experiments fungi of identical type which were cultured from identical lesions did not infect guinea pigs at all.

Therefore according to orthodox mycology some of these fungi would have to be considered as a degenerated *Trichophyton gypseum* as the result of one guinea-pig inoculation and as a *Trichophyton interdigitale* as the result of another.

One could assume the existence of a third species of fungi which in animal inoculations sometimes acts like *Trichophyton gypseum* and sometimes like *Trichophyton interdigitale*. However, this seems to me an unsatisfactory and unnecessary assumption. For in addition to all the work that has been previously done in this field and in addition to clinical, biological and epidemiological evidence—which I have outlined above and which lends strong support to my hypothesis—my experiments have shown that both *Trichophyton gypseum* and *Trichophyton interdigitale* can undergo such marked changes in virulence that they cannot be differentiated biologically.

Moreover, the deliberate inoculation of a human volunteer as reported above has brought experimental confirmation of the
clinical observation that *Trichophyton gypseum* can cause typical "epidermophytosis."

Naturally one may question in how far the results of animal experiments can be applied to the behavior of these fungi in man. This doubt appears justified, although those who consider *Trichophyton interdigitale* an Epidermophyton have not hesitated in accepting the involvement or lack of involvement of the hair in guinea pigs as a decisive factor in differentiating "Trichophyton" from "Epidermophyton." Because experiments in man are (for obvious reasons) relatively scanty, we are forced to rely chiefly on animal experiments, cultural findings and clinical evidence.

There are certainly more aspects of this problem which might be discussed. Many more writers could be cited among those who have either contributed experimentally or who have set forth their ideas on the different problems. But it seems beyond the scope of this paper to give a complete review of the many authors who have contributed experimentally to this subject. However, it should be pointed out that I do not consider the ideas expressed here as original or completely new; nevertheless I thought it might be worthwhile to correlate the existing material and to add my own experiments in order to again present and to strengthen the theory that *Trichophyton interdigitale* is not an Epidermophyton, but a Trichophyton. When one considers the former evidence plus the evidence of my own experiments it seems to me that it is now justified to make the statement that *Trichophyton interdigitale* is in all probability a degenerated *Trichophyton gypseum*; and I believe that further experimental studies will confirm this viewpoint.

**SUMMARY**

1. *Trichophyton interdigitale* (synonyms: *Epidermophyton interdigitale*; Kaufmann-Wolf-fungus) and *Trichophyton gypseum* cannot be differentiated botanically or microscopically.

2. Experiments are reported showing that these two fungi cannot be differentiated by means of guinea-pig inoculations; for several strains of *Trichophyton interdigitale* were shown to be
capable of producing both deep and superficial lesions and of invading the hair as typical "ectothrix" (Sabouraud's "microides"). This involvement of the hair was demonstrated both by extemporaneous microscopic and histological examination. (Inoculation with MacCarthy's strains of *Epidermophyton gypseum* and *Epidermophyton niveum* did not produce invasion of the hair.)

3. Serial animal passages caused marked changes in virulence of *Trichophyton gypseum*, some strains of which became attenuated. Animal passage also produced changes in virulence in *Trichophyton interdigitale*, some strains undergoing a marked increase in virulence.

4. Epidermophytosis of the feet and hands is a very distinct entity in which the causal fungi show no relationship either botanically, epidemiologically or biologically to *Epidermophyton inguinale*, the fungus causing true epidermophytosis (eczema marginatum). However, there is a very close analogy between "epidermophytosis" of the hands and feet and true Trichophyton (Gypseum) infections of the hairy areas.

5. The conclusion is drawn that *Trichophyton interdigitale* is a Trichophyton and not an Epidermophyton.

6. The hypothesis is presented that *Trichophyton interdigitale* is a degenerated *Trichophyton gypseum*. This hypothesis is based upon the following observations:

a. The variability of fungi in general and the cultural similarity of *Trichophyton interdigitale* and *Trichophyton gypseum*.

b. The similar behavior of both fungi in guinea-pig inoculations.

c. The biological parallelism between the two fungi (production of skin hypersensitivity to trichophytin and production of epidermophytids and trichophytids; invasion of the lymph-apparatus and blood-stream).

d. The epidemiological evidence showing that a severe epidemic of deep trichophytosis produced by *Trichophyton gypseum*, when it subsided was shortly followed by an even more severe epidemic of "epidermophytosis" caused by *Trichophyton interdigitale*.

e. The fact that inoculation of *Trichophyton gypseum* into the interdigital space of a previously non-infected human volunteer...
resulted clinically in a typical interdigital "epidermophytosis"; and that the *Trichophyton gypseum* fungus exhibited no cultural change when retrocultured after having undergone this experimental human passage, and after having produced a typical human interdigital "epidermophytosis."

**BIBLIOGRAPHY**

A complete bibliography (up to 1933) will be found in Dodge's book. I refer also to the bibliographies of the articles by Weidman, Bruhns and Alexander, and Miescher.

TRICHOPHYTON INTERDIGITALE


(41) GILCHRIST, T. CASPAR: Discussion of Karrenberg's paper (11).


