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The History of Onychomycosis

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1.1 Introduction

The modern history of medical mycology is relatively short (Table 1.1). It was Agostino Bassi (1773–1856) who in 1836 described the muscardine disease of silkworms which was caused by a fungus that would be named eventually *Beauveria bassiana* in his honor [1]. The clinical aspects of dermatomycoses have been known for a much longer time. Aulus Cornelius Celsus (c. 25 BC to c. 50 AD) recognized inflammatory tinea and described the first kerion celsi, a name still used today [2]. At that time, no microscopic knowledge existed and therefore the study of diseases was purely based on clinical findings. *Favus* and *sycosis* were already known in ancient times (the word means tinea in Egyptian).

Johannes Schönlein was the first to understand the fungal nature of dermatomycoses [4]. Sabouraud began his scientific studies of the dermatophytes around 1890, culminating in the publication of his classic volume, *Les Teignes*, in 1910 [11]. No specific antifungal drugs existed until after World War II.

1.2 The History and Discovery of Onychomycosis

A German medical student, Georg Meissner (19 November 1829 to 30 March, 1905) was the first to describe the fungal nature of onychomycosis in 1853 (Figure 1.1) [9]. It was Meissner later who became famous for discovering the tactile instrument of the skin (Meissner's corpuscle). Meissner described accurately both the clinical and mycological form of onychomycosis [9]. He also included drawings of the clinical appearance of the disease (Figure 1.2). He described how he softened the nail by using sodium hydroxide, and it is important that to remember that at that time microscopes were still very simple and dyes were not used. Meissner also described and drew filamentous fungi and spores (Figure 1.3).

Most scholars give Meissner the honor of having discovered onychomycosis [12], although the fungal nature of onychomycosis had been suspected earlier. In a letter to the editor of *The Boston Medical and Surgical Journal*

Table 1.1 Early development of medical mycology and onychomycosis.

Year	Author	Comment	References
1835	Bassi	Discovers that muscardine disease of silkworms is caused by a fungus	[1]
1837	Remak	Observes microscopic structures appearing as rods and buds in crusts from favic lesions. Does not publish his observations, but allows his findings to be cited in a doctoral thesis of Xavier Hube	Not published [3]
1839	Schönlein	Communicates the fungal nature of dermatomycoses	[4]
1841–1844	Gruby	Unware of Remak's and Schönlein's findings, he describes clinical and microscopic characteristics of the causative agent of favus	[5–8]
1853	Meissner	Discovers that onychomycosis is caused by fungi	[9]
1854	Virchow	First to use the name onychomycosis for this new disease	[10]

IX.

Pilzbildung in den Nägeln.

Von

G. MEISSNER,
 Stud. med. in Göttingen.
 (Hierzu Tafel I.)

Die zahlreichen Beobachtungen, welche über das Wuchern von Pilzen in und auf dem menschlichen Körper, wie auf der Verdauungs- und Respirationsschleimhaut, auf der äusseren Haut, gemacht worden sind, zerfallen nach der Bedeutung, welche in jedem einzelnen Falle die Pilzbildung für die pathologischen Prozesse hat, mit denen verbunden sie beobachtet wird, in zwei ganz verschiedene Classen. — Während in den einen Fällen die Erzeugung jener niedersten pflanzlichen Organismen nur etwas rein Zufälliges ist und der Zusammenhang mit den gleichzeitigen pathologischen Vorgängen eben kein anderer ist, als dass dieselben durch ihre Ausgänge oder durch die Producte, welche sie setzen, die Bedingungen liefern, den Boden bilden für die Vegetation; sind in den bei Weitem spärlicheren Fällen, welche der anderen Classe angehören, diese krankhaften Veränderungen der Organe weit inniger mit der Pilzbildung verbunden, stehen beide in dem engsten Causalnexus zu einander, so zwar, dass der Pilz gewissermassen die Krankheit selbst ist. — Das Gebiet der hieher gehörigen Fälle ist sehr klein, indem mit Sicherheit wohl nur der Pilz der *Porrigio lupinosa* und der von *Pityriasis versicolor* dahin zu zählen sind und es von den *Aphthenpilzen* zweifelhaft und unwahrscheinlich bleiben muss. —

Figure 1.1 The first page from Meissner's paper where he describes his discovery of the fungal nature of onychomycosis.

(today *N Engl J Med*) “On Fungus Ulcer of the Toe, or That Disease Usually Styled Inverted Toe Nail”, J.P. Leonard describes various methods for treating onychomycosis [13].

Onychomycosis and tinea pedis usually go hand in hand. It is hard to imagine that the first case of tinea pedis was described only 129 years ago by an Italian dermatologist, Celso Pellizzari [14]. Most of the early reports on onychomycosis and tinea pedis are from Europe [15]. The first reported case of tinea pedis in the United States was noted in Birmingham, Alabama, in the 1920s [16].

World War I troops returning from battle may have transported *Trichophyton rubrum* to the United States [16]. The first case of toenail onychomycosis presented in the United States is from 1937, when Montgomery presented a 28-year-old woman with onychomycosis before the Manhattan Dermatologic Society on 14 December 1937 [17]. However “mycotic conditions of the nails” were described much earlier in the United States and Guy and Jacob in 1923 recognized hyperhidrosis as a risk factor for onychomycosis and tinea pedis. They also understood that “injury is a definite factor; mycotic conditions of the nails, especially, often date from injury” [18]. In a personal case series from 1927, White reported on 1013 patients diagnosed with “fungus diseases of the skin” between 1910 and 1925 [19]. Only three patients were diagnosed in 1910 and 147 in 1925. Out of these 1013 patients, 23 (2.3%) had onychomycosis and 341 (33.7%) had tinea pedis [19].

Figure 1.2 Meissner's original clinical drawings of infected nails.

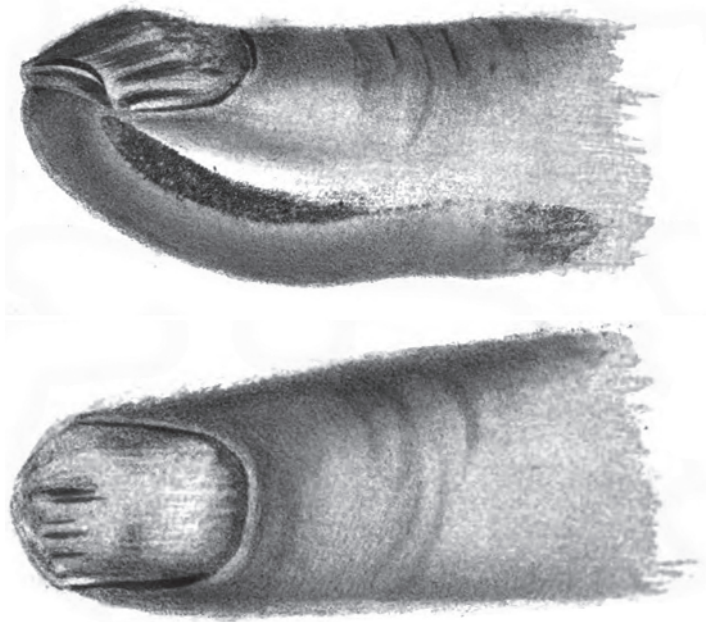


Figure 1.3 Meissner's original drawings of the microscopic appearance of onychomycosis.



The history of onychomycosis is short and parallels that of tinea pedis and the invasion of dermatophyte *T. rubrum* into the Western world [20]. *T. rubrum* is today the major cause of onychomycosis worldwide [21].

T. rubrum originated from West Africa and the Eastern world. The native populations of these areas did not develop tinea pedis or onychomycosis, probably because they mainly walked barefoot [22]. When the colonialists and soldiers arrived, wearing boots, which caused hyperhidrosis and maceration of the feet, it was easy for *T. rubrum* to find a new home. During the late eighteenth and early nineteenth centuries, there was increased urbanization and traveling. The great wars (World War I and II and the Vietnam War) may have contributed further to the spread of *T. rubrum*. Modern lifestyle with leisure travel and the “health boom” with frequent use of gyms and shared bathing facilities may have helped further with the dramatic increase of onychomycosis that we have seen during the past 100 years.

1.3 The Early Epidemiology of Onychomycosis

Onychomycosis is so common today that every dermatologist examines several cases a week or even several a day. On the other hand, during the nineteenth and early twentieth centuries onychomycosis was a very rare disease.

Julius Heller, a German dermatologist (1864–1931), published a book on nail diseases which he simply named *Diseases of the Nails (Die Krankheiten der Nägel)*. It was first published in 1900 [23], and a second edition came out in 1927 [24]. This book can be considered the bible of nail diseases at that time.

In his book, Dr. Heller writes: “I myself pay close attention to the nail diseases and have, despite large nail medical material, at most seen 7–8 cases between 1896 and 1923” (one case every 4–5 years). What a contrast to the modern dermatologist, who can see several cases in a single day. Despite this, Heller’s clinical description is impeccable and also includes photographs (Figure 1.4).



Abb. 72. Onychomycosis trichophytina.
(mittelstarker fall.)



Abb. 71. Onychomycosis trichophytina.
(fall von Prof. BLASCHKO.) vorgeschrittener fall.

Figure 1.4 Clinical photographs of patients with onychomycosis. *Source:* [24]. Reproduced with permission of Springer.

The famous dermatologist Jean Darier collected material from 3000 cases of dermatomycoses. In this material there were only three patients with onychomycosis [25].

Dr. Sabouraud, considered by many to be the father of modern mycology, noted in 1910 in his classic monograph that out of 500 patients with superficial fungal infections only one (0.2%) had onychomycosis [11]. This is in great contrast to recent laboratory series, where more than 50% of the subjects have onychomycosis [26].

In the United States, Dr. Milton Foster looked at immigrants in 1915 on Ellis Island and found 101 cases out of 521 366 (0.02%) immigrants examined with onychomycosis (cited in Heller [24]). White, in 1902, examined 485 patients with nail disease and found eight with onychomycosis, or 1.6%, [27]. This is far from the figures seen today where at least 50% of patients with nail diseases have onychomycosis.

Onychomycosis was rare at the start of the 20th century but has increased dramatically during the last century. Krönke comments in his thesis that onychomycosis rose sharply in Germany after World War I [28]. This is

understandable and likely, because of poor hygienic conditions during the war and close-quarter living [29].

Data on the changes in prevalence of onychomycosis do not exist. However, by examining the ratio between onychomycosis and all other mycoses, one can predict the changes in prevalence of onychomycosis. Also, in hospital series that exist, there is information about all cases seen at these hospitals and how many of these had onychomycosis. In Figure 1.5 the ratio over time of onychomycosis compared to all other superficial mycoses is shown. In this figure it is interesting to see that the increase in prevalence of onychomycosis goes hand in hand with the increase of *T. rubrum* (data from [21] and a personal database from the literature). Single-center data over long periods, on the prevalence of onychomycosis, are rare. One of the best series is from Mexico [30]. It is obvious that this single-center data shows the same trend (Figure 1.6) as the accumulated data (Figure 1.5) and further supports dramatic increase of onychomycosis, mostly due to an increase in *T. rubrum*, during the last 100 years.

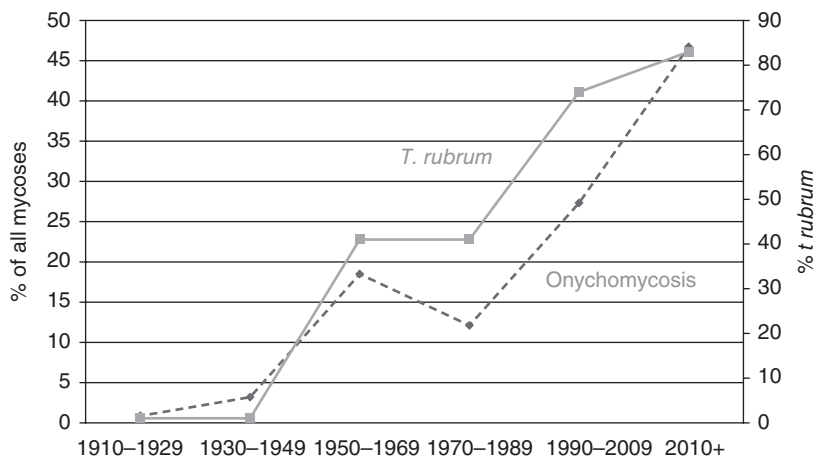


Figure 1.5 The percentage of patients with onychomycosis out of all other mycoses (dashed line, % on left y-axis). The percentage of *T. rubrum* out of all other fungi (solid line, % on right y-axis).

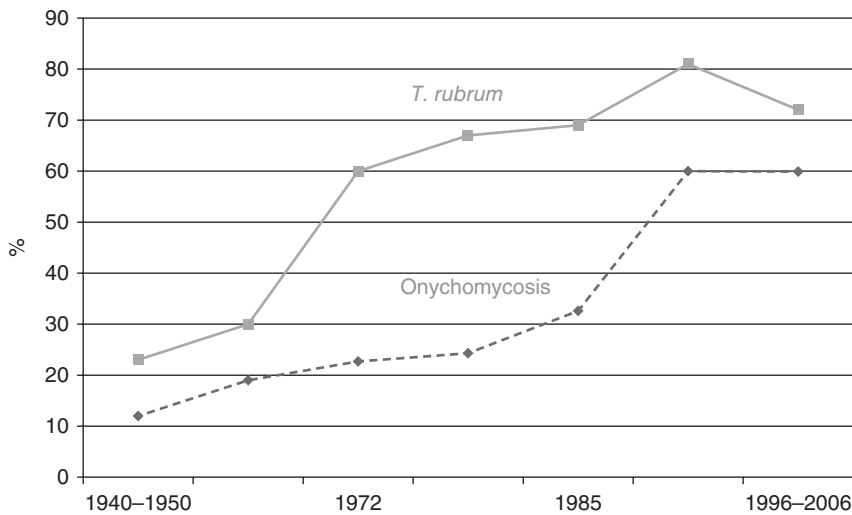


Figure 1.6 The percentage of patients with onychomycosis out of all other mycoses from Mexico [30] (dashed line). The percentage of *T. rubrum* out of all other fungi (solid line). *Source:* Reproduced with permission of Oxford University Press.

1.4 History of Treatment of Onychomycosis

The medical treatment of onychomycosis has changed considerably over the past 150 years from the crude topical treatments (Table 1.2) to the current use of active and specific antifungal agents. When the fungal nature of onychomycosis was discovered, there were not many treatment options (Table 1.3). Treatment was almost exclusively topical. The mechanism of action was nonspecific. Historically, several topical antifungal agents have been used in the treatment of onychomycosis; however, the evidence for their effectiveness is based on very limited data or anecdotal reports. The following treatment was presented by Wigglesworth in the *Boston Medical and Surgical Journal* (later *N. Engl. J. Med*), based on a case he saw at the St. Louis Hospital in Paris:

To treat true onychomycosis the nail should be thinned by scraping with a bit of glass, and then wet frequently with corrosive sublimate

(mercuric chloride) one gramme in two hundred of water, which is about three times as strong as one would use it upon the skin or hair [31].

This treatment is representative for what was available during the late 19th century and the beginning of last century.

In 1907 Whitfield's ointment was discovered. It contains benzoic acid, with a keratolytic, salicylic acid and showed some antifungal effect. Not very much happened until the time of World War II, when developments in treatment started to focus on drugs with more specific antifungal activity. The first of these were derivatives of undecylenic acid such as tolnaftate, which was one of the first inhibitors of squalene epoxidase, which plays a key role in the biosynthesis of ergosterol in the fungal cell membrane [46].

In 1958, griseofulvin was discovered. This is a metabolic product derived from several species of *Penicillium*, which was first isolated from *Penicillium griseofulvum*. Its activity, which is fungistatic, is largely restricted to

Table 1.2 Change prevalence of onychomycosis over time. Myc = Mycological series. Shows the ratio of onychomycosis patients to other patients with superficial mycoses. Pat = Patient series. Pat nail = Series of patients with nail disease. Shows the ratio of patients with onychomycosis to patients visiting a clinic or hospital. Pop = Population series. Shows the ratio of patients with onychomycosis to the general or otherwise defined population.

Author	Year	Country	Comment	Type	%	References
Anderson	1873	UK	11 000 consecutive patients with skin diseases Of these, 178 had superficial fungal infections but no cases of onychomycosis were discovered	Pat	0	[32]
Bulkley	1875	US	Analyzed 1000 patients with skin disease 300 had superficial fungal infection but no cases of onychomycosis were found	Pat	0	[33]
Block	1888	Germany	3000 patients with skin disease 300 with superficial fungal infections 2 with onychomycosis	Myc	0.7	[34]
Arnozan	1889	France	3700 patients with skin diseases 11 cases of onychomycosis	Pat	0.3	[35]
Heller	1900	Germany	Dr. Heller writes: "I myself pay close attention to the nail diseases and have, despite large nail medical material, at most seen 7–8 cases between 1896 and 1923" (case every 4–5 years)	Pat	?	[23]
White	1902	US	Examined 485 patients with nail disease and found 8 with onychomycosis	Pat nail		[27]
Crocker	1905	US	Out of 1000 patients with skin diseases, 2 had onychomycosis	Pat	0.2	Cited in Heller [24]
Sabouraud	1910	France	Only 1 case of onychomycosis amongst 500 patients with superficial fungal infections	Myc	0.2	[11]
Foster	1915	US	Looked at immigrants on Ellis Island and found 101 onychomycosis cases out of 521 366 (0.02%) immigrants	Pop	0.02	Cited in [24]
Wirz	1923	Germany	2898 patients with superficial mycoses	Myc	0.14	[36]
Darier	1928	France	Only 3 cases of onychomycosis amongst 3000 patients with a superficial fungal infection	Myc	0.1	[37]
Krönke	1935	Germany	Single-center epidemiological study between 1919 and 1934 Total of 273 258 patients with skin disease 91 cases of onychomycosis were found Male/female ratio was 1.5	Myc	2.2	[28]

(Continued)

Table 1.2 (Continued)

Author	Year	Country	Comment	Type	%	References
Boedyn	1938	US	Single-center mycological study during the year 1935 106 cases diagnosed with a superficial mycosis 5 with onychomycosis	Myc	4.7	[38]
Zündel	1939	Germany	133 cases of superficial mycoses 13 with onychomycosis	Myc	10	[39]
Mu	1939	China	Between 1925 and 1938, 36 847 patients were seen 6006 cases of superficial mycoses were diagnosed 113 patients had onychomycosis	Myc	1.9	[40]
Perpignano	1939	Italy	Superficial mycoses in the province of Cagliari 2107 superficial mycoses were diagnosed	Myc	0.6	[41]
Grimmer	1954	Germany	134 cases of superficial mycoses between 1952 to 1954 60 with onychomycosis	Myc	44	[42]
Langer	1957	Germany	1705 cases of superficial mycoses between 1955 to 1956 441 with onychomycosis	Myc	26	[43]
Kriester	1967	Germany	Between 1956 and 1965, 188 590 patients were seen 6,113 cases of superficial mycoses were diagnosed	Myc	56	[44]
Götz	1938 (pub 1952)	Germany	Single-center mycological study during the year 1935 106 cases diagnosed with a superficial mycosis one with onychomycosis	Myc	0.1	[45]
Grimmer	1939 (published 1954)	Germany	128 cases of superficial mycoses 13 with onychomycosis	Myc	10	[42]
Götz	1949 (published 1952)	Germany	Single center mycological study during the year 1949 537 cases diagnosed with a superficial mycosis 58 with onychomycosis	Myc	1	[45]

Table 1.3 The history of onychomycosis treatment.

Year	Author	Treatment	Reference
1853	Meissner	Discovers that onychomycosis is caused by fungi, but does not offer any treatment options	[9]
1870	Neumann	Remove the lamellae of nail substance, which are readily detached by applying solutions of caustic potash (potassium hydroxide), corrosive sublimate (mercuric chloride), Ol. Terebinth (oil made from the turpentine tree)	English translation [47]
1880	Wigglesworth	To treat true onychomycosis the nail should be thinned by scraping with a bit of glass, and then wet frequently with corrosive sublimate (mercuric chloride) one gramme in two hundred of water, which is about three times as strong as one would use it upon the skin or hair	[31]
1907	Whitfield	Whitfield's ointment, which combined a weak antifungal, benzoic acid, with a keratolytic, salicylic acid shows some effect	[48]
1944	Woolley	First azole discovered	[49]
1951	Hazen and Brown	Nystatin discovered	[50]
1958	Gentles	Griseofulvin discovered. It is synthesized of the mold fungus <i>Penicillium griseofulvum</i> and was found to be active orally in the treatment of dermatophyte infections	[51–53]
1977	Heeres	Ketoconazole, the first oral azole becomes available	[54]
1978	Richardson	Development of fluconazole starts	[55]
1983	Polak	Topical amorolfine discovered	[56, 57]
1984	Hay	Itraconazole discovered Has broader spectrum compared to fluconazole	[58]
1991	Ryder	Discovered in 1983, it is closely related to naftifine Terbinafine was licensed in Europe in 1991	[59, 60]
1991	Abrams	Topical ciclopirox discovered	[61, 62]
2014	Del Rosso	Topical efinaconazole becomes available	[63]
2014	Ciaravino	Topical tavaborole becomes available	[64]
2017	Sigurgeirsson	Several new antifungals in development	[65, 66]

dermatophyte infections. Treatment duration for onychomycosis is very long.

In the early 1970s, the first azole antifungals were introduced, whose mode of action was targeted on the formation of the fungal cell membrane at the step of inhibition of 14- α demethylase [65]. Ketoconazole, the first oral azole, became available in 1977. It was the first broad-spectrum oral antifungal drug.

The discovery of ketoconazole succeeded by fluconazole and itraconazole. Both had far fewer side effects. Terbinafine was discovered in 1991 and is today considered the gold standard of treatment for onychomycosis [66]. Topical efinaconazole was licensed in 2014 and seems more promising compared to previously marketed topical antifungals. At the present time, several antifungal drugs are in development.

References

- 1 Bassi A. Del mal del segno, calcinaccio o moscardino, malattia che affligge i bachi da seta e sul modo di liberarne le bigattaje anche le più infestate, 2 pts. Lodi; 1835–1836.
- 2 Proudfoot LE, Morris-Jones R. Kerion Celsi. *New England Journal of Medicine* 2012; 366(12): 1142.
- 3 Weitzman I, Summerbell RC. The dermatophytes. *Clin Microbiol Rev* 1995; 8(2): 240–259.
- 4 Seeliger HPR. The Discovery of *Achorion schoenleinii*: Facts and “Stories”: Die Entdeckung des *Achorion schoenleinii* Tatsachen und “Geschichten.” *Mycoses* 1985; 28(4): 161–82.
- 5 Gruby D. Recherches sur les cryptogames qui constituent la maladie contagieuse du cuir chevelu décrite sous le nom de Teigne tondante (Mahon), Herpes tonsurans (Cazenave). *Herpes tonsurans (Cazenave) CR Acad Sci* 1844; 18: 583–585.
- 6 Gruby D. Recherches sur la nature, le siège et le développement du porrigo decalvans ou phytoalopécie. *CR Acad Sci* 1843; 17: 301–302.
- 7 Gruby D. Sur les mycodermes qui constituent la teigne favéuse. *CR Acad Sci* 1841; 13: 309–312.
- 8 Gruby D. Mémoire sur une végétation qui constitue la vraie teigne. *CR Acad Sci* 1841; 13: 72–75.
- 9 Meissner G. Pilzbildung in den Nägeln. *Arch Physiol Heilkd* 1853; 12: 193–196.
- 10 Virchow R. Zur normalen und pathologischen Anatomie der Nägel und der Oberhaut. *Verhandl Physikal Med Gesellsch Würzburg* 1854; 5: 83–105.
- 11 Sabouraud RJA. *Les Teignes*. Paris: Masson; 1910.
- 12 Haas N, Sperl H. A medical student discovers onychomycosis. *Hautarzt* 2001; 52(1): 64–67.
- 13 Leonard J. On fungous ulcer of the toe, or that disease usually styled inverted toe nail. *Boston Medical and Surgical Journal* 1846; 34(4): 76–77.
- 14 Pellizzari C. Ricerche sul Trichophyton tonsurans. *Giornale Italiano delle Malattie Veneree e della Pelle* 1888; 29(März): 8–40.
- 15 Fabry J. Ueber Onychomycosis favosa. *Archives of Dermatological Research* 1890; 22(1): 21–30.
- 16 Weidman FD. Laboratory aspects of epidermophytosis. *Archives of Dermatology and Syphilology* 1927; 15(4): 415–450.
- 17 Montgomery RM, Hopper ME, Lewis GM. Favus involving a toe nail: Report of a case. *Archives of Dermatology* 1938; 38(6): 856.
- 18 Guy WH, Jacob FM. Differential diagnosis of parasitic infections of hands and feet. *Penn Med Journ* 1923; 26(March): 384.
- 19 White CJ. Fungus diseases of the skin clinical aspects and treatment. *Archives of Dermatology* 1927; 15(4): 387.

- 20 Charif MA, Elewski BE. A historical perspective on onychomycosis. *Dermatol Ther* 1997; 3: 43–45.
- 21 Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: A literature study. *J Eur Acad Dermatol Venereol* 2013.
- 22 Vanbreuseghem R. Prevalence of onychomycoses in Zaire, especially in sugar cane cutters. *Ann Soc Belg Med Trop* 1977; 57(1): 7–15.
- 23 Heller J. *Die Krankheiten der Nägel*: A. Hirschwald; 1900.
- 24 Heller J. (9ed.), *Die Krankheiten der Nägel*. Berlin: Springer; 1927.
- 25 Darier J. *Précis de Dermatologie*, 2nd ed., Masson et Cie; 1918.
- 26 Drakensjö IT, Chryssanthou E. Epidemiology of dermatophyte infections in Stockholm, Sweden: A retrospective study from 2005–2009. *Med Mycol* 2011; 49(5): 484–488.
- 27 White CJ. The clinical study of four hundred and eighty-five cases of nail disease. *Boston Medical and Surgical Journal* 1902; 147(20): 537–542.
- 28 Krönke A. Epidemiologische Betrachtungen bezüglich der in den Jahren 1919 bis 1934 an der Universitäts-Hautklinik in Berlin beobachteten Pilzkrankungen der Haut. Berlin; 1935.
- 29 Gazes MI, Zeichner J. Onychomycosis in close quarter living review of the literature. *Mycoses* 2013.
- 30 López-Martínez R, Manzano-Gayosso P, Hernández-Hernández F, et al. Dynamics of dermatophytosis frequency in Mexico: An analysis of 2084 cases. *Med Mycol* 2010; 48(3): 476–479.
- 31 Wigglesworth E. Recent Progress in Dermatology. *Boston Medical and Surgical Journal* 1880; 103(17): 393–396.
- 32 Anderson M. *On the Treatment of Diseases of the Skin with an Analysis of Eleven Thousand Consecutive Cases*; Henry C. Lea, 1873.
- 33 Bulkley D. *Analysis of One Thousand Cases of Skin-Diseases*. Louisville, KY; 1875.
- 34 Block. *3000 Fälle von Hautkrankheiten aus Köbners Klinik*. Berlin; 1888.
- 35 Arnozan, D. De la tricophytie des mains et des ongles. *Arch clin de Bordeaux* 1889.
- 36 Wirz F. Feature of nail mycosis. *Dermatologische Wochenschrift* 1923; 76(1/26): 380–386.
- 37 Darier J. *Précis de Dermatologie*, 4th ed., Paris: Masson; 1928.
- 38 Boedyn KB, Verbunt JA. Annotations about dermatomycoses in Batavia. *Mycopathologia* 1938; 1(3): 185–198.
- 39 Zündel W. Die europäischen Epidermophytonpilze. *Archives of Dermatological Research* 1939; 179(1): 1–57.
- 40 Mu JW, Kurotchkin TJ. Statistical and mycological studies of dermatomycoses observed in Peiping. *Chinese MJ* 1939; 55: 201–219.
- 41 Perpignano G. Experimental ringworm studied in relation to tinea in Province of Cagliari. *Gior ital di dermat e sif* 1939; 80: 489.
- 42 Grimmer H. Die Berliner Epidermophytien in den Jahren 1952–1954. *Archiv für Dermatologie und Syphilis* 1954; 198(4): 363–374.
- 43 Langer H. Epidemiology & clinical studies on onychomycosis: Observations on Berlin's fungus flora, 1954–1956. *Arch Klin Exp Dermatol* 1957; 204(6): 624–636.
- 44 Kriester C, Kaden R. Epidemiologische Untersuchungen der Dermatomykosen im Berliner Raum. *Mycoses* 1967; 10(11): 509–522.
- 45 Götz H. Klinische und experimentelle Untersuchungen Über die Hautpilzkrankheiten im Gebiet von Hamburg 1948–1950. *Archiv für Dermatologie und Syphilis* 1952; 195(1): 1–76.
- 46 Robinson HM, Raskin J. Tolnaftate: A potent topical antifungal agent. *Arch Dermatol* 1965; 91(4): 372–376.

- 47 Neumann I. *Textbook of Skin Diseases*, R. Hardwicke; 1871.
- 48 Gooskens V, Pönnighaus JM, Clayton Y, *et al.* Treatment of superficial mycoses in the tropics: Whitfield's ointment versus clotrimazole. *International Journal of Dermatology* 1994; 33(10): 738–742.
- 49 Woolley D. Some biological effects produced by benzimidazole and their reversal by purines. *Journal of Biological Chemistry* 1944; 152(2): 225–232.
- 50 Hazen EL, Brown R. Two antifungal agents produced by a soil actinomycete. *Science (New York, NY)* 1950; 112(2911): 423.
- 51 Gentles J. Experimental ringworm in guinea pigs: Oral treatment with griseofulvin. *Nature* 1958; 182(4633): 476–477.
- 52 Williams D, Marten R, Sarkany I. Oral treatment of ringworm with griseofulvin. *Lancet* 1958; 272(7058): 1212–1213.
- 53 Russell B, Frain-bell W, Stevenson C, *et al.* Chronic ringworm infection of the skin and nails treated with griseofulvin: Report of a therapeutic trial. *Lancet (London, England)* 1960; 1(7135): 1141.
- 54 Heeres, J.; Backx, L.J.J.; Van Cutsem, J. Antimycotic imidazoles: 3: Synthesis and antimycotic properties of 1-[2-(aryloxyalkyl)-2-phenylethyl]-1H imidazoles. *J. Med. Chem.* 1977; 20: 1516–1521.
- 55 Richardson K, Cooper K, Marriott M, *et al.* Discovery of fluconazole: A novel antifungal agent. *Reviews of Infectious Diseases* 1990; 12(Suppl. 3): S267–S271.
- 56 Polak A. Antifungal activity *in vitro* of Ro 14-4767/002: A phenylpropyl-morpholine. *Sabouraudia* 1983; 21(3): 205–213.
- 57 Lauharanta J. Comparative efficacy and safety of amorolfine nail lacquer 2% versus 5% once weekly. *Clin Exp Dermatol* 1992; 17(Suppl. 1): 41–43.
- 58 Heyl T. Treatment of chromomycosis with itraconazole. *British Journal of Dermatology* 1985; 112(6): 728–729.
- 59 Ryder NS. Specific inhibition of fungal sterol biosynthesis by SF 86-327: A new allylamine antimycotic agent. *Antimicrob Agents Chemother* 1985; 27(2): 252–256.
- 60 Goodfield MJ. Short-duration therapy with terbinafine for dermatophyte onychomycosis: A multicentre trial. *Br J Dermatol* 1992; 126(Suppl. 39): 33–35.
- 61 Abrams BB, Hänel H, Hoehler T. Ciclopirox olamine: A hydroxypyridone antifungal agent. *Clin Dermatol* 1991; 9(4): 471–477.
- 62 Yu B, Zhou G, Wang B, *et al.* A clinical and laboratory study of ciclopirox olamine (8% Batrafen) in the treatment of onychomycosis. *Chin Med Sci J* 1991; 6(3): 166–168.
- 63 Del Rosso JQ, Reece B, Smith K, Miller T. Efinaconazole 10% solution: A new topical treatment for onychomycosis: Contact sensitization and skin irritation potential. *J Clin Aesthet Dermatol* 2013; 6(3): 20–24.
- 64 Ciaravino V, Coronado D, Lanphear C, *et al.* Tavaborole, a novel boron-containing small molecule for the topical treatment of onychomycosis, is noncarcinogenic in 2-year carcinogenicity studies. *Int J Toxicol* 2014; 33(5): 419–427.
- 65 Sigurgeirsson B, Hay RJ. The antifungal drugs used in skin disease. In: Ólafsson J, Hay R (eds), *Antibiotic and Antifungal Therapies in Dermatology*. Springer, Cham; 2016; 141–156.
- 66 Sigurgeirsson B. Onychomycosis. In: Ólafsson J, Hay R (eds), *Antibiotic and Antifungal Therapies in Dermatology*. Springer International Publishing, Cham, Switzerland; 2016; 203–209.