Vitiligo through the Ages

ajanta

In Vitiligo & Atopic Dermatitis

℞ PACROMA 10g / 30g

Pimecrolimus 1% w/w Cream

PURE PROVEN & SAFE

ajanta pharma limited

For the use of Registered Medical Practitioner or Hospital or Laboratory Use Only.

PREFACE

The enigma of vitiligo has challenged mankind since time immemorial. From its first description in Vedic and Egyptian texts, circa 3,000 years ago, archives of vitiligo have been fraught with fear, confusion, stigma and resentment.

Vitiligo has been tried for as long as it has been recognized. From an herbalist's extracts of leaves, seeds, and roots to the use of psoralens and ultraviolet phototherapy, treatment of vitiligo has witnessed an evolution like no other.

This compilation attempts to reflect on the history of vitiligo up until the end of the 20th century. Spanning from ancient descriptions to the advent of novel therapeutics, this book captures moments of human disarray, grit, and achievements in the face of an unpardoning disease.

Dedicated to the indomitable spirit of people with vitiligo and their practitioners.

Vitiligo remains the most intriguing dermatosis. With scarce symptoms, while the disease may not life threatening, its psychological impact has deep ramifications on one's quality of life. Indisputably, the emotional and social repercussion of vitiligo might be unforgiving for patients, had it not been for the care, compassion, and ingenuity of doctors.

We at Ajanta Pharma, acknowledge your untiring resolve to reach out to patients with the best in therapeutic and coping strategies in vitiligo. We believe that your experience and support, will continue to imbibe in patients, a sense of fulfilment and value for the world around them.

We remain indebted!

Our Heartfelt gratitude for your untiring efforts to make life better each day, in your vitiligo patients

INSIDE

Ancient nomenclature of white spots

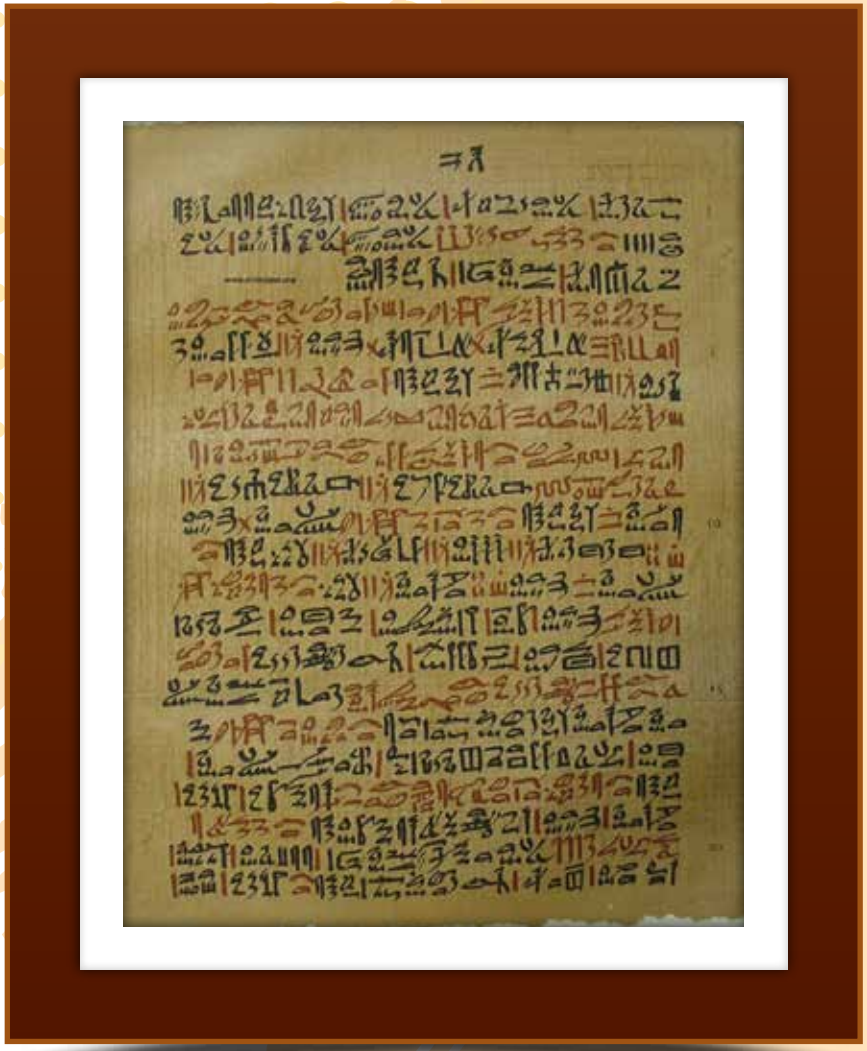
Epic (classic)/language	Era (period)	Nomenclature
Buddhist sacred book	Vinaya Pitaka - 624-544 BC	Kilas (white spotted deer)
Manusmriti	200 BC	Suitra
Amarkosha	600 AD	Suitra - A) Padasphota B) Twakpushpi
Atharvaveda	1400 BC	Sweta - Kustha
Arabic medicine		Bohak, bahak, baras
Bible		Zoraat
Makatomino harai	Japanese - 1200 AD	Shirabito

White spots: Historical reminiscence

Over 4,000 years of known history has elapsed from the time man became aware of disturbing white spots on the skin.

The Egyptian ‘Ebers Papyrus’ (1550 BC), the Indian scriptures of ‘Atharvaveda’ (1500-3000 BC) and ‘Vinaya Pitaka’ (500 BC) of Buddhism recognized white spots on the skin under different names.

Sehgal VN, Srivastava G. Vitiligo: Compendium of clinico-epidemiological features. Indian J Dermatol Venereol Leprol 2007;73:149-56.



Early records

Ebers Papyrus, also known as Papyrus Ebers, is the Egyptian medical record of herbal knowledge dating to circa 1550 BC. It describes 700 magical formulas and folk remedies.

Ebers Papyrus descriptions

Egyptian medical text, Ebers Papyrus (circa 1500 BC), a 110-page scroll, and about 20 meters long, is among the oldest preserved medical documents thats contains many incantations meant to turn away disease-causing demons.

Ebers Papyrus describes two types of diseases affecting the color of the skin. One, associated with swellings and recommended to be left alone and the other, manifesting with only color changes.

Ebers Papyrus, the oldest preserved collection of medical writings, described diseases affecting the color of the skin

Ebbel B. The papyrus Ebers. Copenhagen: Levin and Munksgaard; 1963.

Vedic texts give a clear record of skin depigmention. Vedic myth described anthropomorphic deification of the Sun, Bhagavatam, who developed white spots after being gazed upon by his illegitimate son.

White spots in ancient India

In the Atharvaveda, Switra or white patch, appeared for the first time in the commentary of Darila on Kau Sutra 26.22. References to Kilasa (like spotted deer) was also found in Atharvaveda in two hymns (Verse1.23 and 1.24).

Rigveda reference to Kilasa (Verse 53.1) appeared in Vajaseneji Samhita, Kathaka Samhita; Taittiriya Brahmana and Tandya Mahabrahmana.

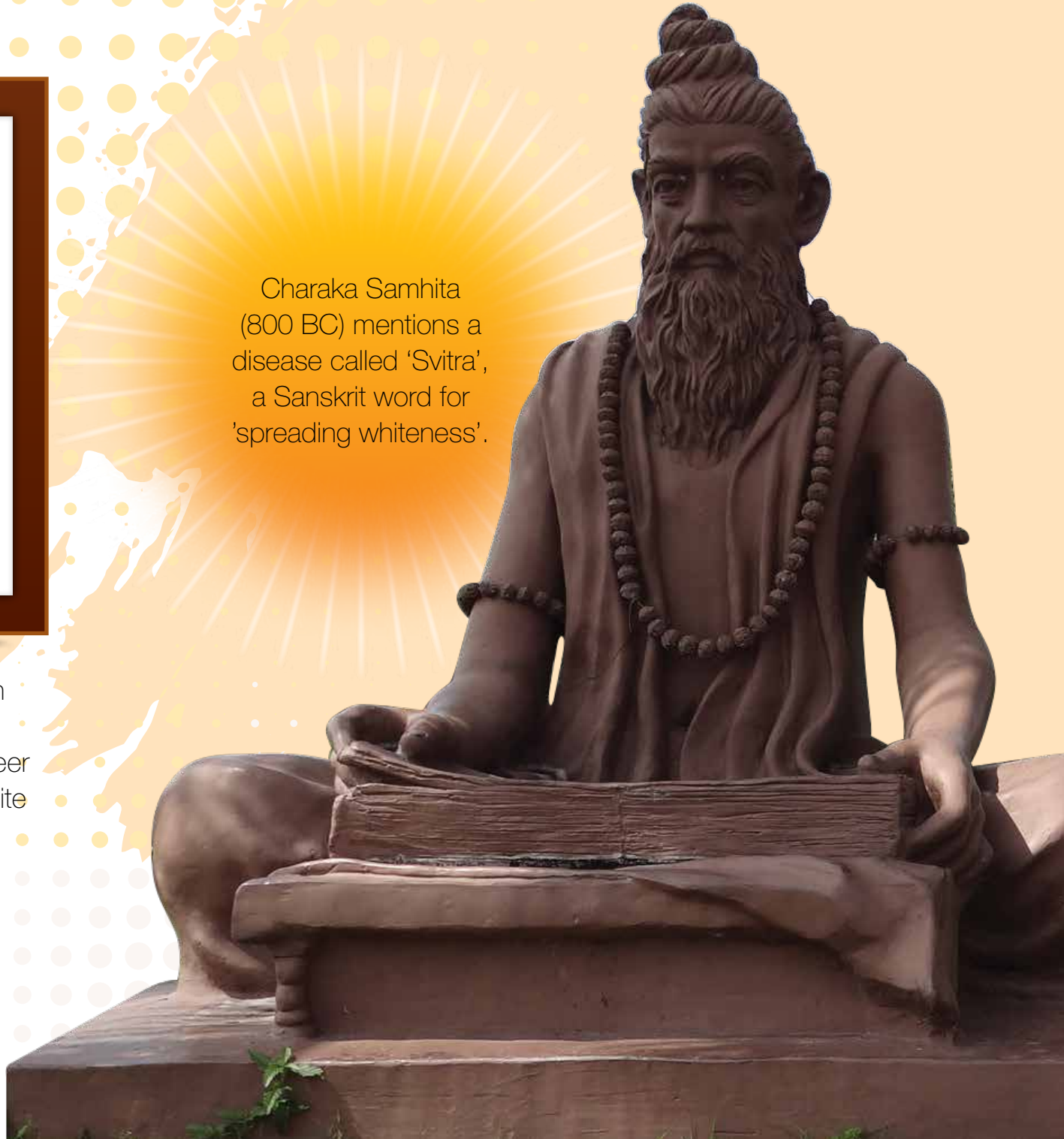
Switra is also described in Panini Vyakarana and Samhita Kala. Manu abhors marriage to the son or daughter of a Switra Kushtha patient.

'Kilasa' derives from Sanskrit word 'kil' meaning 'white' or 'casting away'.

Barman S. Ancient Science of Life, 1995;15(1):71-74, Pandey YK et al, Int. J. Res. Ayurveda Pharm. 9 (4), 2018.

Atharvaveda describes vitiligo, with reference to “Kilasa” and “Palita”. Kilas indicated white patches or deer spots on the skin. Palita meant white spots with a yellowish tinge.

Charaka Samhita (800 BC) mentions a disease called ‘Svitra’, a Sanskrit word for ’spreading whiteness’.



Descriptions in the Vedas

According to Atharvaveda (1500 BC), white spots on skin was due to deficiency of Pitta dosha in skin and vitiation of Maamsa, Meda and Asthi dhatu.

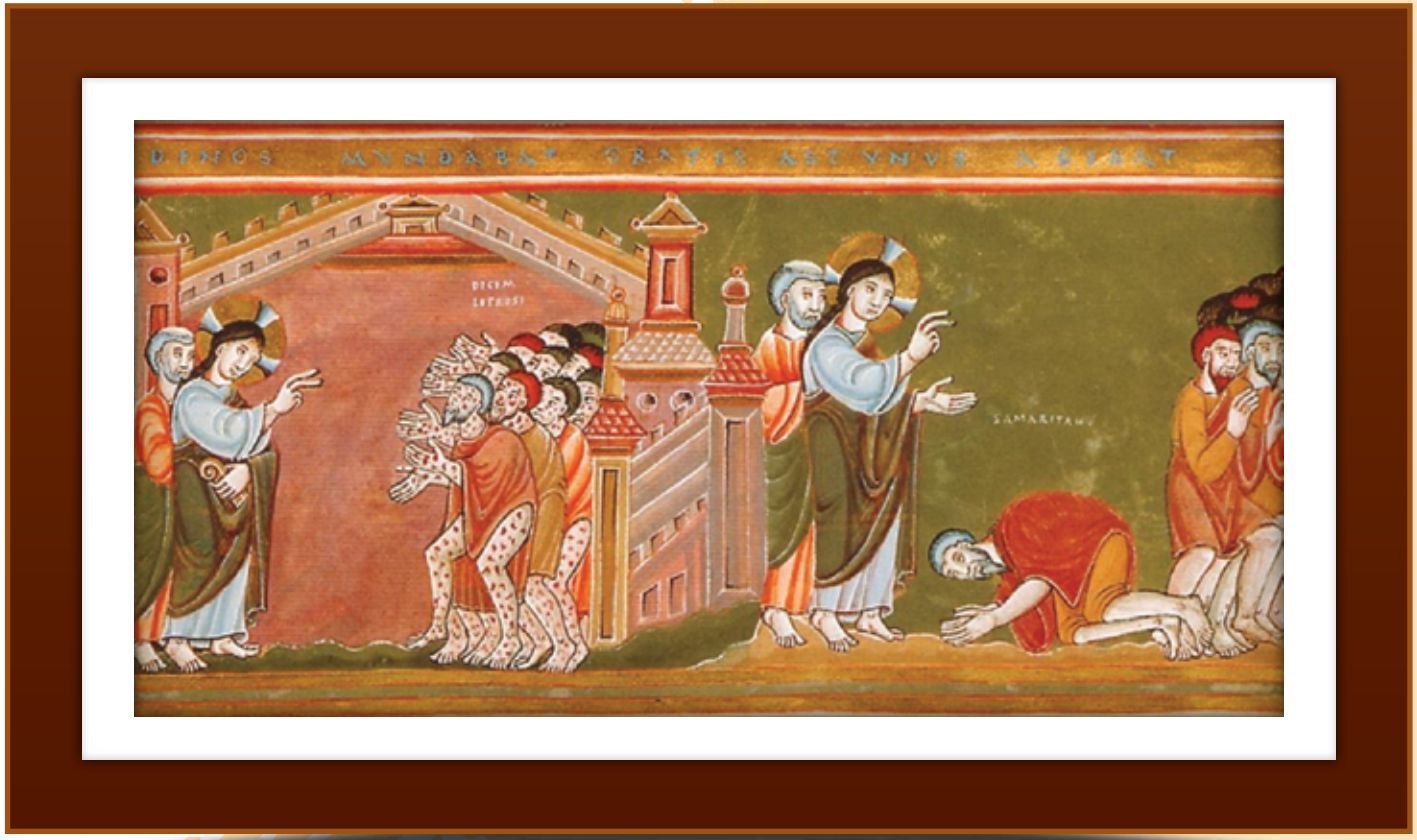
In the first kaanda of Atharvaveda, two types of Shveta kushtha described were Kilasa and Palita. Dry red patches on skin were Kilasa and white patches characterized Palita.

In the Vivaha Vidhana chapter of Manusmruti (1000 BCE), marriage was prohibited from 10 wrongdoing girls. In these 10, marriage was prohibited to the Shvitri girl.

According to Kashyapa Samhita (6th century BC), Shvitra was 'Shweta bhava Micchanti switra' or reflection of white colour. Kilasa was known to be Rakta, Maamsa and Medadhatugat, Tridoshaja skin disease by Charaka Samhita. Kilasa occured in the fourth layer (Tamra) of twacha (skin).

Earliest reference to Kilasa was in 2200 B.C. Atharvaveda describes Kilasa along with several herbal prescriptions.

Koranne, R.V. & Sachdeva, K.G. (1988) Vitiligo. International Journal of Dermatology 27, 676-81.
Nair, B.K.H. (1978) Vitiligo -A retrospect. International Journal of Dermatology 17,755-757.



Christ cleanses the Leper: White spots were confused as leprosy

Biblical Mention of White Spots

Leviticus XIII, 34: Anyone with white skin spots must wear torn clothes, have his hair dishevelled and must conceal his upper lip, and call out “unclean, unclean”.

The book of Leviticus

Levit. I3:I2:

"And the priest shall look on the plague in the skin of the flesh, and when the hair in the plague is turned white, and the plague in sight be deeper than the skin of his flesh, it is a plague of leprosy; and the priest shall look on him and pronounce him unclean. **Then the priest shall consider and behold, if the leprosy have covered all his flesh pronounce him clean, that hath the plague: it is clean**"

Reference to white spots in the Bible

OLD TESTAMENT

Exodus: 4:6, Leviticus 13 and 14;21:17-22:4, Numbers 5:2, 12:10 Deuteronomy 24:8, II Samuel 3:29, II Kings 5:27, II Chronicles 26-19:23

NEW TESTAMENT

Matthew 8:2-3, Matthew 10:8, Matthew 11:5, Mark 1:40, Mark 14:3, Luke 4:27, Luke 17:12-19

Goldman, L., Moraites, R.S. & Kitzmiller, K.W. (1966) White spots in biblical times. Lee, S. (1982) Vitiligo auf einem historischen Portrait. Hautarzt 33,335-336.

Impressions from the middle & far east

"Bohak", "baras" and "alabras" are Arabic names used to describe vitiligo.

Portrait of Chang-Myeong Song (1689-1767), a high ranking official of the Yi dynasty of Korea (1392-1910), showing vitiligo.

In the Far East prayers, known as Makatominoharai, recognized white skin as vitiligo.

Practices in early middle and far east

Ancient Iranian literature (2200 BC), in the period of Aushooryan, refers white skin spots as “Tarkh-e-Tibble”

Arabic literature mentiones “Bohak,” “Bahak,” and “Baras”, terms used for vitiligo. “Baras” or “white skin” was also mentioned in the Koran.

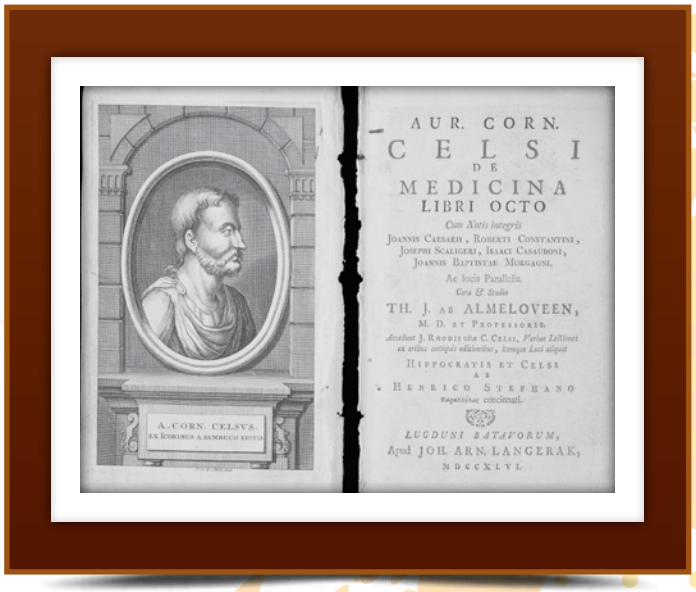
In the Koran (Surah the family of Imran chapter 3, verse 48, and Surah the table spread chapter 5 verse 109) reads “In accord with God’s will Jesus was able to cure patients with Baras.

“Makataminoharai”, a collection of Shinto prayers, mentions “Shirabito” or disease of the white man.

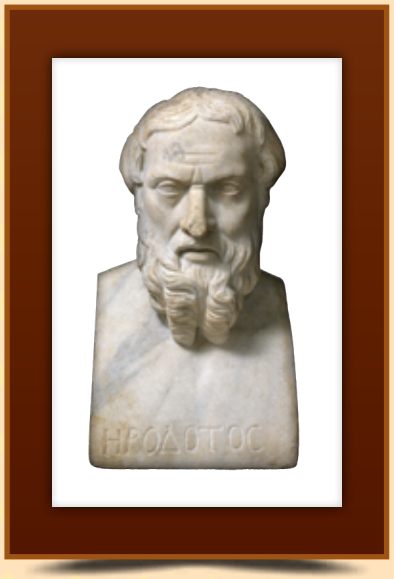
While the Koran described white spots as inherited but not contagious, accurate description also exists in Japanese Shinto prayers, Amarakosa, dating from 1200 BC.

Hann SK, Chung HS. Historic view of vitiligo in Korea. Int J Dermatol. 36: 313-315, 1997. Hann S-K, Nordlund J, editors. Vitiligo: a monograph on the basic and clinical science. Oxford (England): Blackwell Scientific Publishers; 2000. p. 13–7.

“White spots” in ancient Greece



Aulus Cornelius Celsus wrote De Medicina, the first medical textbook in Latin. He was also the first to use the word vitiligo.



Herodotus (484-425 BC) associated “white spots“ as sins against the Sun.

There is in Samicum […] the Cave of the Anigrid Nymphs. Whoever enters it suffering from alphos or leuke first has to pray to the nymphs and to promise some sacrifice or other, after which he wipes the unhealthy parts of his body. Then, swimming through the river, he leaves his old uncleanness in its water, coming up sound and of one color.

Pausanias, Description on Greece, 5.5

From Celsus to the modern period

Hippocrates (460–355 BC) was the first to report that white spots were easier to treat at the onset of the illness rather than after many years had elapsed.

Much emphasis on 'white spots' can be found in the Greek literature. Herodotus (484-425~c), Greek historian, wrote in his book Clio that foreigners who suffered from such lesions, must have 'sinned against the Sun'.

Vitiligo was coined and first used by the Roman physician Aulus Cornelius Celsus, in second century AC, in his medical classic De Medicina. The word vitiligo has often been said to have derived from "vitium" (defect or blemish) rather than "vitellus" meaning calf.

The word vitiligo, implying a defect, is thought to be derived from Latin '*vitium*'. Vitiligo has been mentioned in the book, *De Mediccina*, by the Roman physician Celsus.

Nair BK. Vitiligo-a retrospect. Int J Dermatol 1978;17:755-7. Köckerling F. Langenbecks Arch Surg (2013) 398:609–616.

Disability in the middle ages

Disability in the middle ages was thought to result from punishment for sin or from being born under the hostile influence of the planet Saturn. “There was no state provision for people with disabilities. Most were cared for by monks and nuns who sheltered pilgrims and strangers as their Christian duty.

“Vitiligo (baras) or leprosy (judham) can be simulated by boiling up and then applying to the body a compound of indigo-leaf, basil, cubeb and green vitriol or copperas ....”

Ibn Butlan quoted in Lewis, Islam from the Prophet Muhammad, 2: 273.

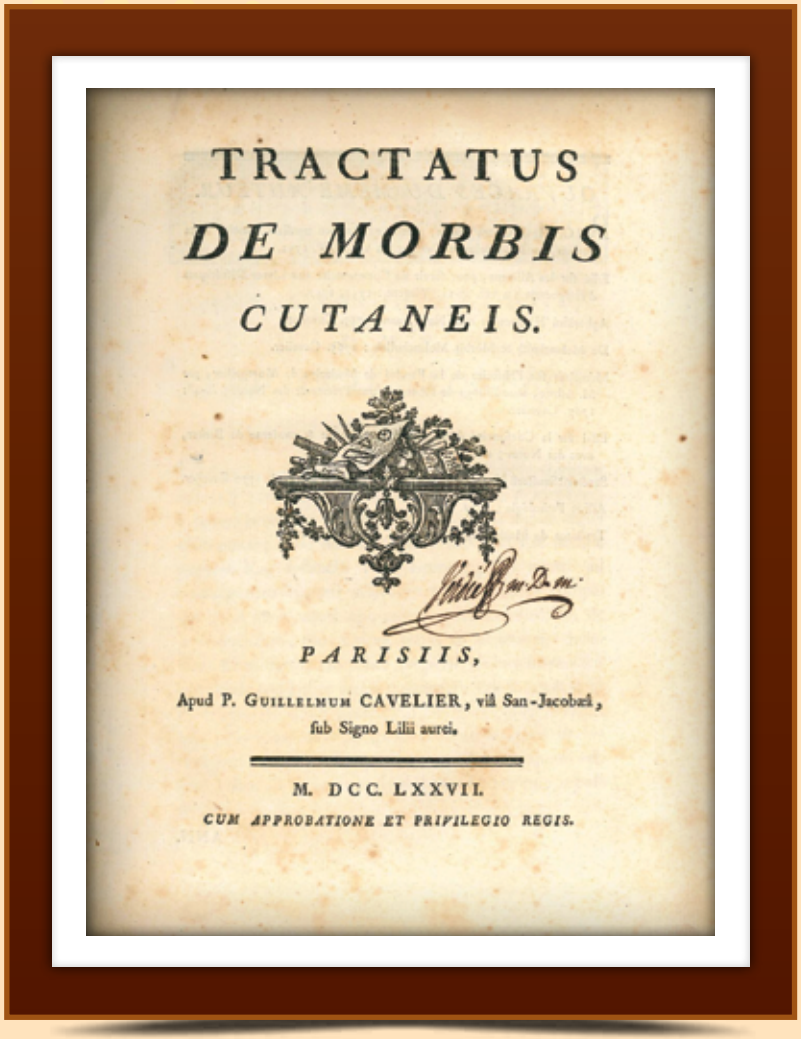
Europe and the Levant in the middle ages (1050-1348)

Vitiligo was not known to Europeans in the Middle Ages and was confused with leprosy and other disorders manifesting with hypopigmentation.

As incidence of “leprosy” in Europe increased markedly during the crusades (1095–1291), consequences were dire, once the diagnosis was made. Lepers and those inflicted with vitiligo were forbidden to earn a living, except by begging. The stigma may have been less in the Levant, as both Christians and Muslims, under Islamic rule, were known to feigning the illness for “charitable” purposes.

People with vitiligo, misdiagnosed as “Lepers”, were forbidden to earn a living, except by begging. They were often persecuted, driven out of town and forced to live in isolation.

Dols MW. The leper in medieval Islamic society. Speculum 1983; 58: 891–916. Ell SR. Leprosy and social class in the Middle Ages. Int J Lepr Other Mycobact Dis 1986;54:300–305. Millington GWM. Vitiligo: the historical curse of depigmentation. International Journal of Dermatology 2007;46:990–995.



TRACTATUS
DE MORBIS
CUTANEIS.

PARISIIS,

Apud P. Guillelmum CAVELIER, viâ San-Jacobæâ,
sub Signo Lilii aurei.

M. DCC. LXXVII.
CUM APPROBATIONE ET PRIVILEGIO REGIS.

Mercurialis (1530–1606)

Vitiligo, the “small blemish” (from the latin vitulum; Mercurialis, 1572) was first described more than 1500 years BC. It is probable that ancient descriptions represent other diseases, such as leprosy.

Mercurialis & his etymological contribution to vitiligo

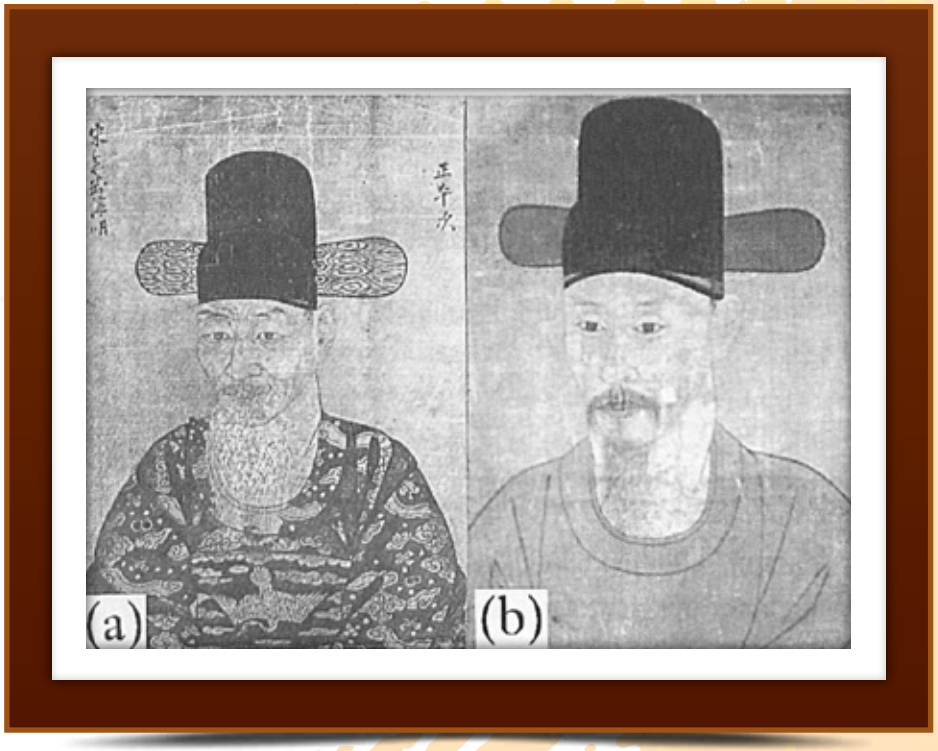
The 16th century Italian philologist and physician, Mercurialis, attempted to define the pathogenesis of vitiligo in his book De Morbus Cutaneis (on diseases of the skin).

Written in Latin, De Morbus Cutaneis described white patches to be the result of phlegm or "mucous blood" nourishing the vitiliginous skin, rather than blood.

Mercurialis considered morphea to be hyperpigmented and thus distinguished it from vitiligo. He also described several subtypes of depigmentation and noted that vitiligo might be associated with altered sensation. He was the first European to try to separate the disorders of hypopigmentation.

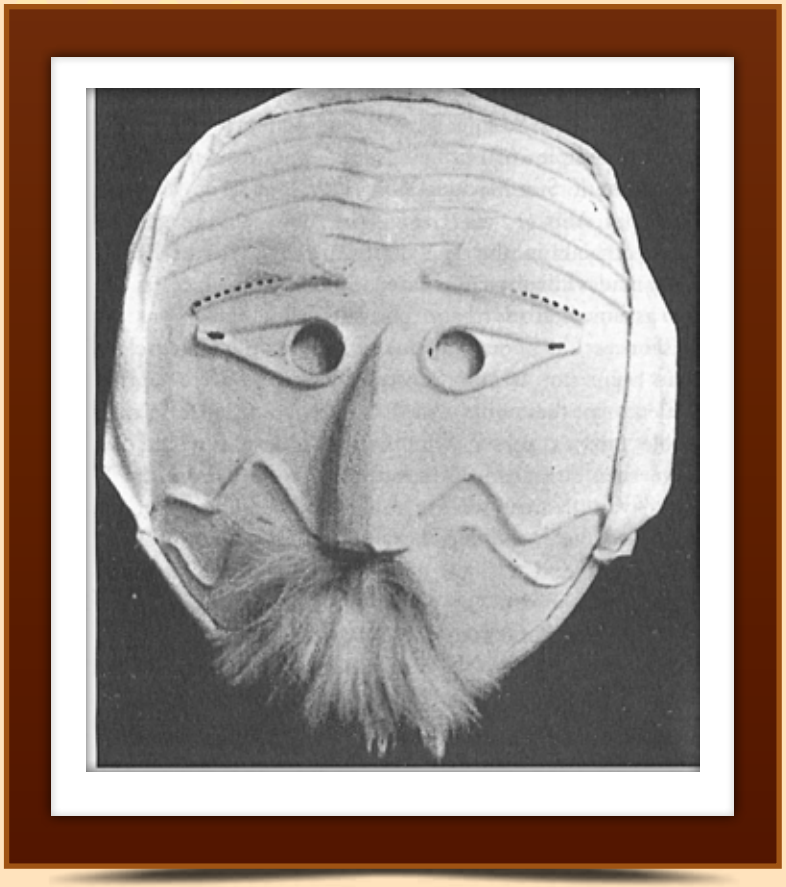
Mercurialis defined the pathogenesis of vitiligo in his book *De Morbus Cutaneis*. He described several subtypes of depigmentation and was first to separate disorders of hypopigmentation.

http://art.thewalters.org/detail/19054/portrait-of-gerolamo-mercuriale/ Singh G, Ansari Z, Dwivedi RN. Letter: vitiligo in ancient Indian medicine. Arch Dermatol. 109: 913, 1974.



Historic view of vitiligo in Korea

Vitiligo spots was drawn on the portraits of Sun-Myoung Song (1708-?) (Fig. a) and Sung-Bin Ahn (1732-?) (Fig. b), high-ranking government officials in the Yi dynasty (1492-1910) of Korea. They had vitiliginous spots on the neck and face. It can be assumed from these portraits that there was no misconception about vitiligo patients in the noble class.



Dancers of the old traditional Korean dance called “Mask Dance,” which was popular to the common people, wore funny looking masks with faces of albinism or vitiligo which showed that vitiligo was a well-known disease to the general public.

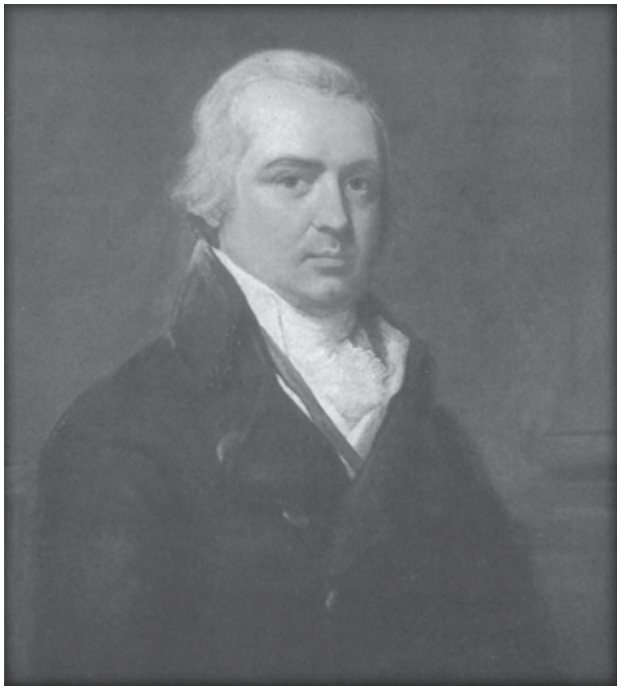
Vitiligo in 17th century Korea

Historically, not all societies discriminated against the depigmented. In the 17th century Yi Dynasty in Korea, the medical text book, the Doney Bogam, describes the skin disorders of vitiligo, tinea versicolor, nevus depigmentosus, nevus anemicus, and albinism as a single hypopigmentary disorders.

Socially, the 17th century Koreans were tolerant of depigmentation cosmetically, as evident by portraits of high-ranking government official in the Yi Dynasty, showing "vitiliginous" depigmentation of the face and neck.

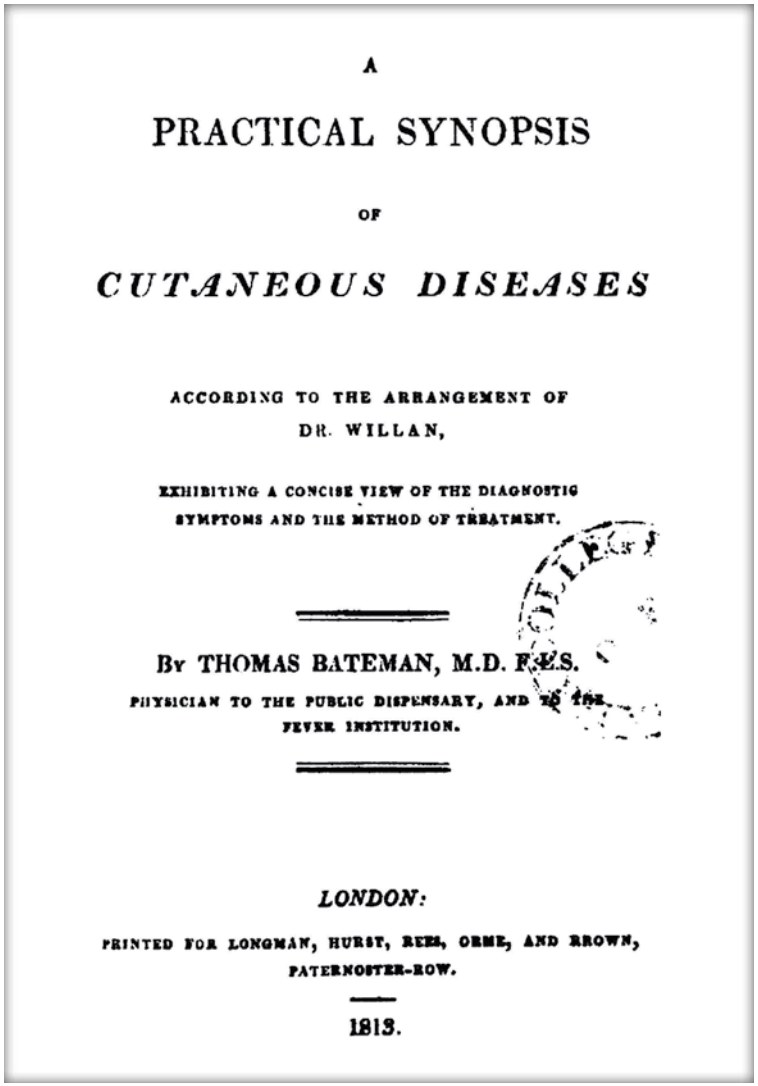
As no distinction was made between vitiligo and other hypopigmentary disorders in ancient Korea, they were regarded as one disease entity.

Hann SK. Traditional Korean medicine in dermatology. International Journal of Dermatology 1997, 36, 313-315.



Robert Willan, MD FRS (1757–18)

Robert Willan proposed the first classification system of cutaneous diseases which earned him the nomination of “Dermatologist of the Millennium”.



A

PRACTICAL SYNOPSIS

OF

CUTANEOUS DISEASES

ACCORDING TO THE ARRANGEMENT OF
DR. WILLAN,

EXHIBITING A CONCISE VIEW OF THE DIAGNOSTIC
SYMPTOMS AND THE METHOD OF TREATMENT.

BY THOMAS BATEMAN, M.D. F.L.S.
PHYSICIAN TO THE PUBLIC DISPENSARY, AND TO THE
FEVER INSTITUTION.

LONDON:

PRINTED FOR LONGMAN, HURST, REES, ORME, AND BROWN,
PATERNOSTER-ROW.

1813.

Vitiligo in 18th and early 19th century Europe

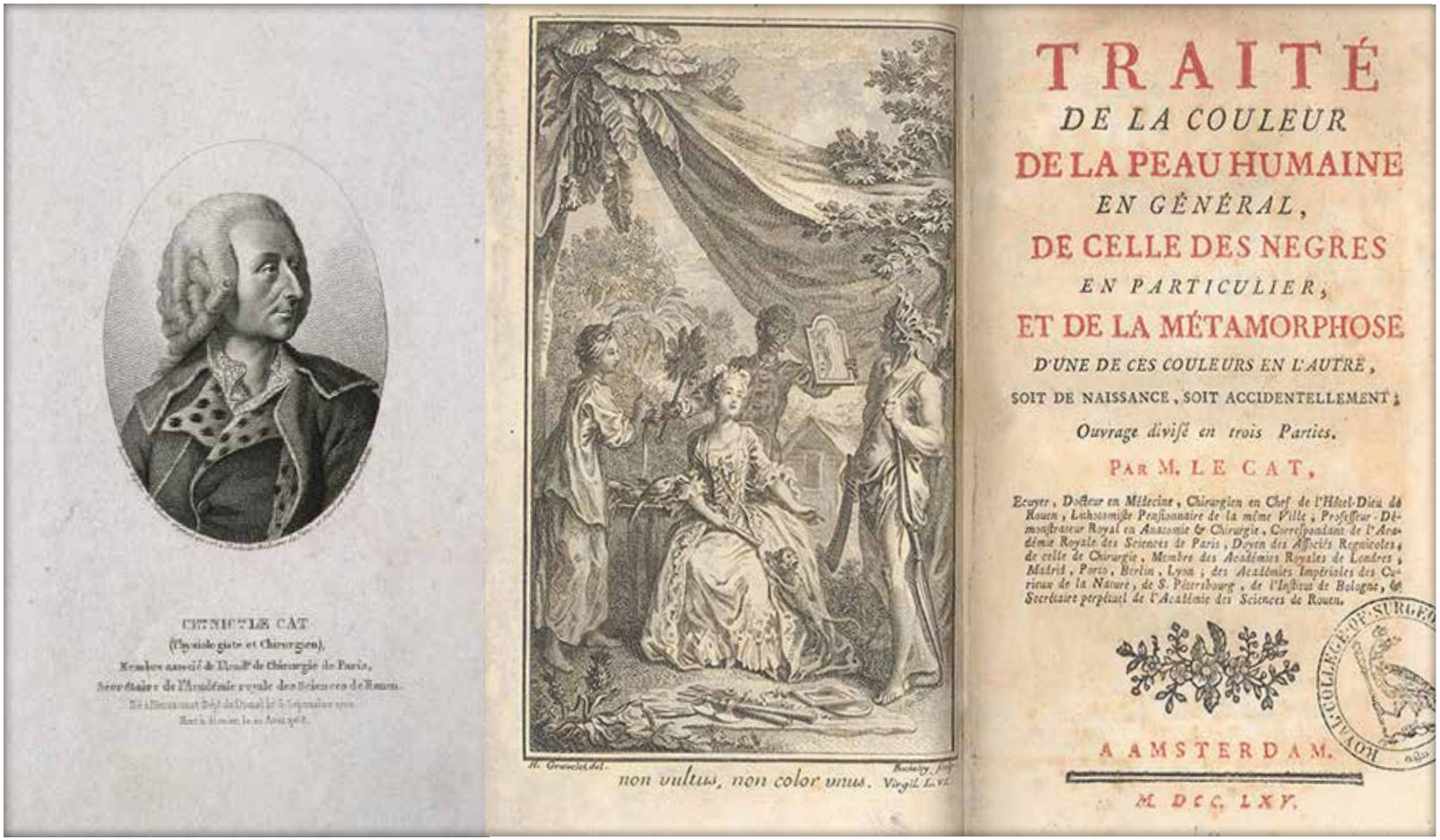
Robert Willan was an English physician whose major contributions to dermatology was to introduce a classification system for skin diseases and to give detailed clinical descriptions of many diseases.

Willan's comprehensive classification of skin diseases went beyond ancient descriptions of vitiligo to represent other diseases. His classification system was composed of eight orders: Papulae, squamae, exanthemata, bullae, pustulae, vesiculae, tubercula, and maculae. He was also the author of the first atlas of skin diseases, containing colored pictures.

Willan was the first person to give the correct and detailed clinical descriptions of many diseases such as prurigo, impetigo, and psoriasis.

With the first classification system of cutaneous diseases, Robert Wilan brought order to a clinical subject riddled with extraordinary confusion and uncertainty.

Rathish S, Criton S. Robert Willan – A true pioneer. J Skin Sex Transm Dis 2019;1:30-1. Booth CC. J R Soc Med. 1999 Jun;92(6):313-8.



Le Cat's book on skin color and its disorders, 1765

French physician Claude Nicolas le Cat published an exhaustive tome on ethnic differences in skin pigmentation where he accurately detailed several cases of vitiligo.

The phenomenon of koebnerization

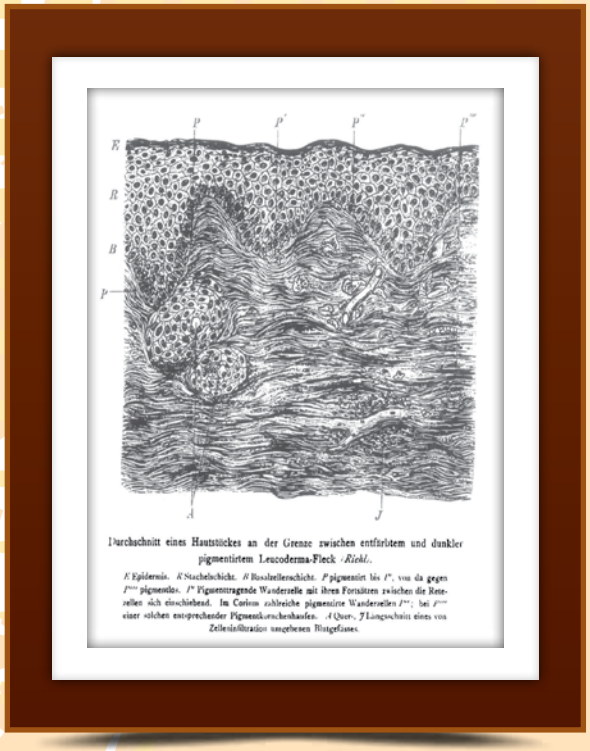
Claude Nicolas le Cat published an exhaustive tome on ethnic differences in skin pigmentation. In this book, he accurately detailed several cases of vitiligo that started in small areas and then progressed symmetrically over the hands and face.

He also described depigmentation following burns from boiling water in such subjects thus illustrating the phenomenon of koebnerization.

Claude Nicolas le Cat accurately detailed vitiligo starting in small areas and progressing symmetrically over the hands and face. He also illustrated the phenomenon of koebnerization.

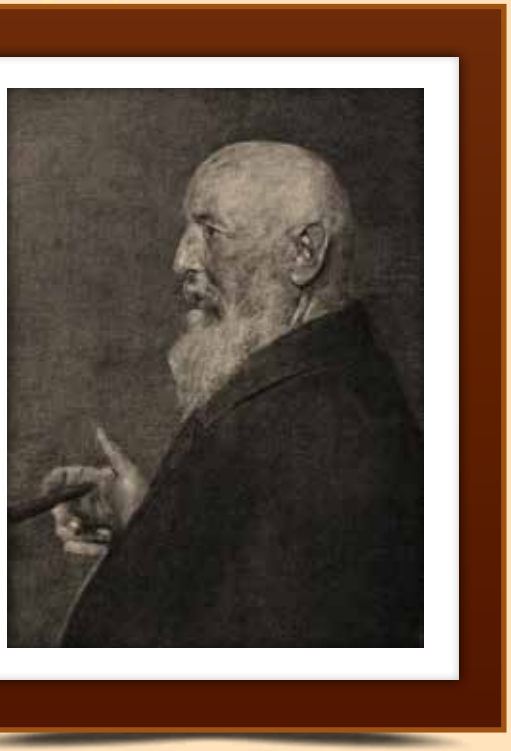
Claude Nicolas Le Cat. Stipple engraving by A. Tardieu after himself after Thomiers. Wellcome Collection. Public Domain Mark. Reference 5475i.

Vitiligo in the late 19th century



Durchschnitt eines Hautstückes an der Grenze zwischen entfärbtem und dunkler pigmentirtem Leucoderma-Fleck (Riehl).

E Epidermis. R Stachelschicht. B Basalzellenschicht. P pigmentirt bis P', von da gegen P'' pigmentlos. P'' Pigmenttragende Wanderzelle mit ihren Fortsätzen zwischen die Reihezellen sich einschiebend. Im Corium zahlreiche pigmentirte Wanderzellen P'''; bei P'''' einer solchen entsprechender Pigmentkörnchenhaufen. A Quer-, J Längsschnitt eines von Zelleninfiltration umgebenen Blutgefässes.



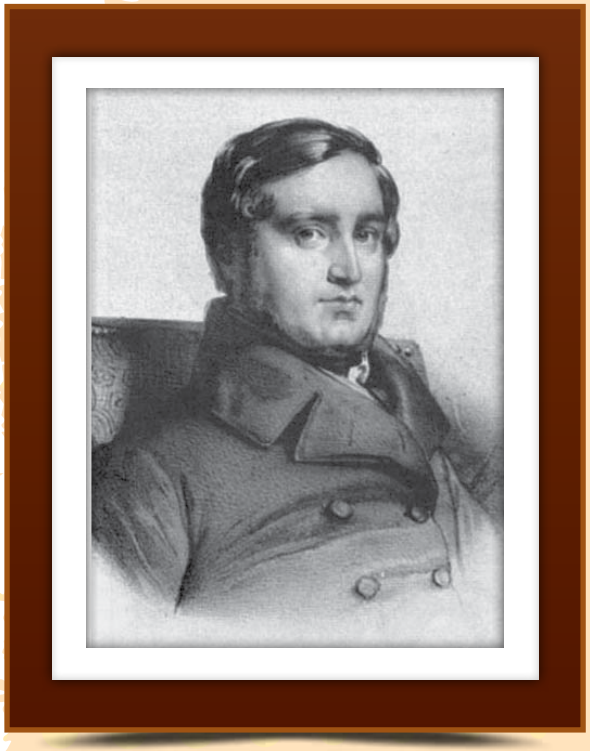
Moriz Kaposi (1837-1902) was the first to observe lack of pigment granules in vitiligo

Moriz Kaposi in Vienna was one of the first to describe the histopathology, observing only a lack of pigment granules in the deep rete cells

Vitiligo/leucoderma illustration from Kaposi textbook: Pathologie und Therapie der Hautkrankheiten (1st Edition 1879)

Gerhard Henrik Armauer Hansen (1841-1912)

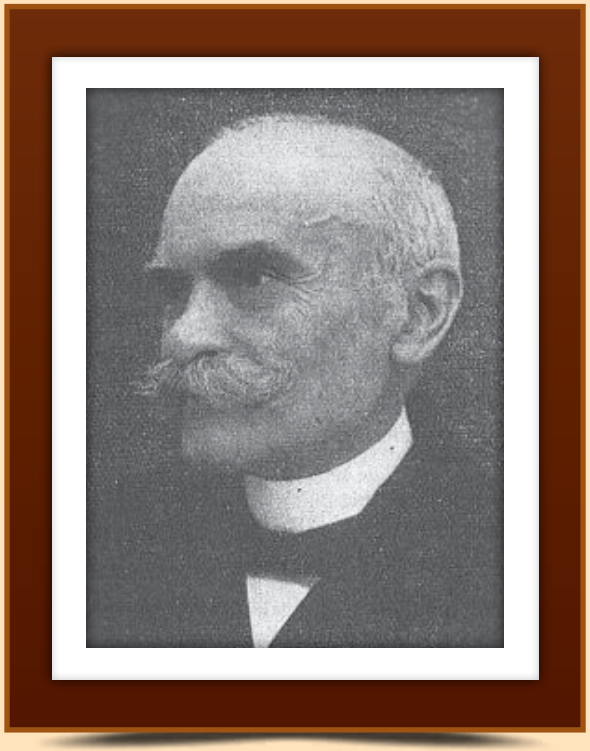
Hansen observed the presence of small rods within “lepra cells” and thus established a clear pathogenesis for leprosy.



Pierre-Luis-Alphée Cazenave (1795–1877)

Working in France, Cazenave made the link between vitiligo and alopecia areata.

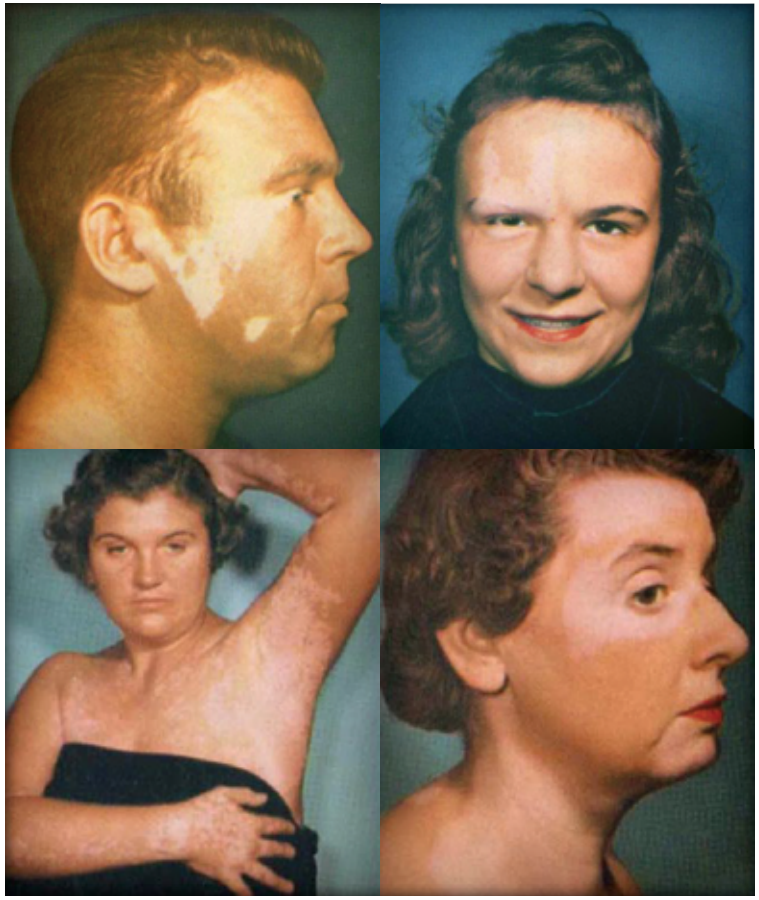
Isidor Neumann 1832-1906



Louis-Anne-Jean Brocq 1856-1928

Both Neumann in Vienna and Brocq in Paris observed that episodes of emotional stress could lead to flare-ups of vitiligo. They also noticed that none of the then available treatments made much impact on the disease!

Kopera D. Clin Dermatol. Nov-Dec 1997;15(6):841-3. Grzybowski A. Clin Dermatol. Sep-Oct 2013;31(5):653-55. Millington GWM. International Journal of Dermatology 2007, 46, 990–995. Fritz Luckhardt - Österreichische Nationalbibliothek, Bildarchiv Austria, Inventarnr. Pf 104075:B (2). Images from the History of Medicine (NLM), http://www.biusante.parisdescartes.fr/histmed/medica/page?100000x1929xartorig&p=217,



AARON B. LERNER (1921-2007)

Vitiligo results from increased output at peripheral nerve endings in the skin of an agent like melatonin that lightens the color of pigment cells and decreases new melanin formation.

Vitiligo in the 20th century

In the early 20th century, the cause of vitiligo was first attributed to damage to peripheral nerves.

Lerner in 1959, reported a patient with transverse myelitis whose vitiligo was limited to the skin above the cord lesion.

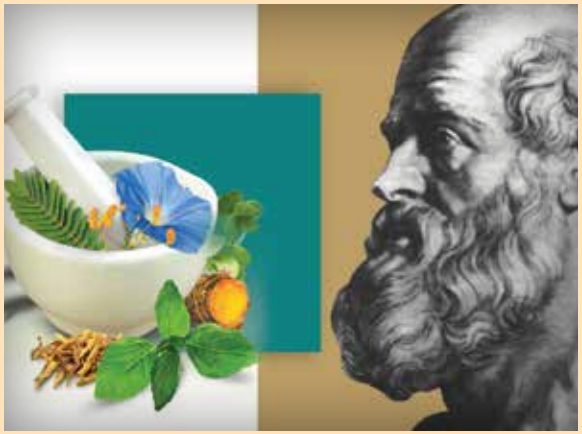
"One patient had transverse myelitis with paralysis from the waist down. She developed vitiligo on the face and upper portion of her body—neck, axillas, arms, hands. No hypopigmentation occurred below the level of cord damage. This was noteworthy since in a patient with typical vitiligo, depigmentation would have been expected over most of the body" .... Aaron B. Lerner.

Lerner proposed that vitiligo resulted from increased output at peripheral nerve endings in the skin of an agent like melatonin that lightened the color of pigment cells and decreased new melanin formation.

Lerner AB. Vitiligo. J Invest Dermatol. 1959 Feb;32:285-310.

Medical treatment of vitiligo

Early records






Born by night art thou, O plant Dark, black, sable, do thou That art rich in colour, stain This leprosy and white grey spots. Even colour is the name of thy mother, Even colour is the name of thy father. Thou, O plant produced even colour, Render this spot to even color.

Atharva Veda (2000–1400 BC)

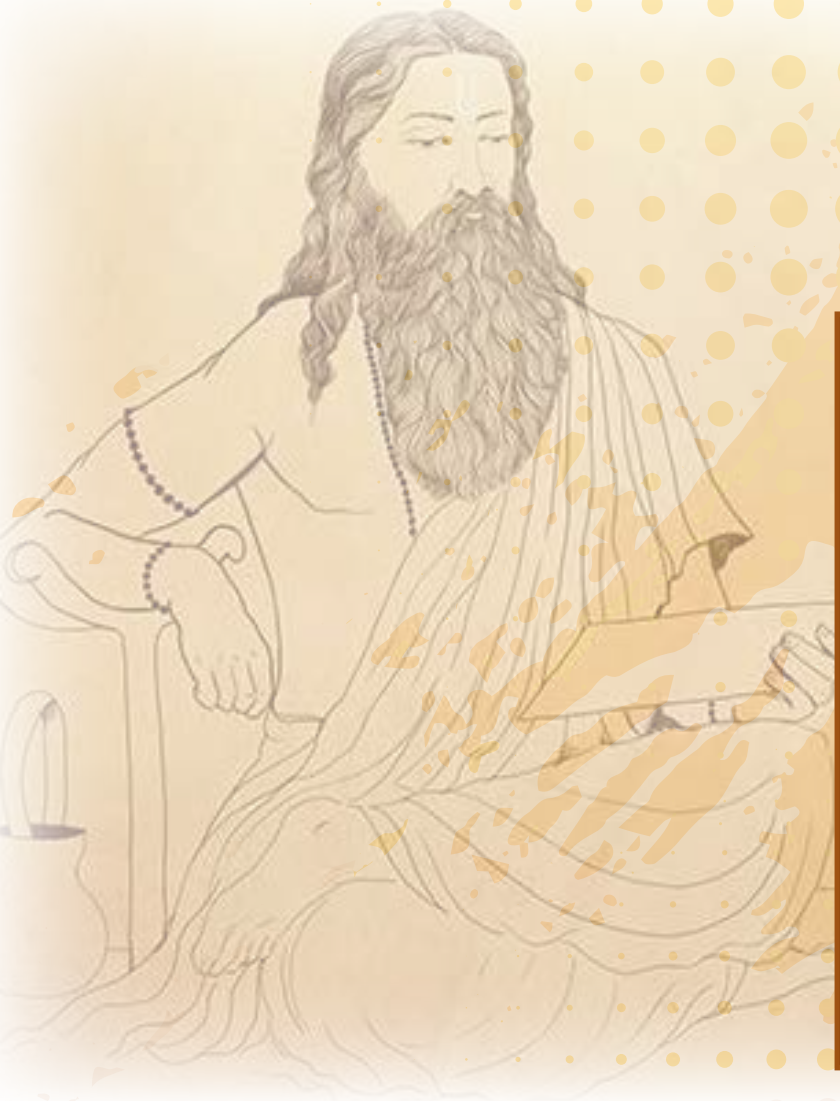
Psoralea corylifolia grows in India. It is a small, erect, annual herb growing up to 60–120 cm in height throughout sandy, loamy plains of Central and East India. Treatment of vitiligo were made from seeds of this plant.

Medical treatment of vitiligo: Early history

The Ebers Papyrus (circa 1500 BC), Atharva Veda (circa 1400 BC), the Buddhist medical literature (circa 200 AC) and the Chinese manuscript from the Sung period (circa 700 AC) made reference to the treatment of vitiligo with black seeds from the plant Bawachee or Vasuchika, which is now called *Psoralea corylifolia*.

In Ayurveda, use of Psoralea corylifolia (Leguminosae family) for inducing the repigmentation of vitiligo has been carefully recorded.

Donata SR. Ancient Sci Life. 1990;4:202–6. Khushboo P. S., Pharmacogn Rev. 2010 Jan;4(7):69-76.



Charaka Samhita (450 BCE - 400 CE)

Charaka Samhita, using Switra and Kilasa as synonyms for vitiligo, clearly mentioned its treatment, classification and prognosis.

Panacea to vitiligo: Psoralea corylifolia

- In Charaka Samhita both topical and systemic uses of figs were used before sun exposure. In Atharvaveda, treatment of vitiligo with “Bawachee” was described to be associated with exposure to solar radiation and worshipping prayer.

- In Ayurveda, dried ginger, black pepper, pippali and leadwort root fermented in cow’s urine, and local ointment with a paste made of several medicinal herbs, including Psoralea corylifolia, was used to induce repigmentation of vitiligo.

Black seeds like Vakuchi (Psoralea corylifoli) together with Bhringaraja (Eclipta psostrata), Indravaruni (Citrullus colocynthis) and Rajan (Curcuma longa) was recommended for Switra Roga.

Pharmacogn Rev. 2010 Jan;4(7):69-76. Chakravarthy S.K. 1988 “Evaluation of some Ayurvedic Compound drugs in the management of Switra (Vitiligo)’ M.D. Thesis (BHU).

Psoralea corylifolia seeds and plant

Nearly all parts of the plant, roots, stems, leaves and seeds, were used in the treatment of vitiligo.

Psoralea corylifolia

- Psoralea corylifolia, a very ancient remedy for vitiligo, has been tried extensively not only by the practitioners of the Indian medicine, but also by the followers of the Western system.

- Fruits of Psoralea corylifolia consist of a sticky oily pericarp (12% of the seed), a hard seed coat and kernel. Seeds of Psoralea corylifolia contain essential oil, coumarins, alkaloids, flavonoids, and terpenoids. In vitiligo, powder form of Psoralea corylifolia was ingested while paste and ointment was used for external application.

Most amazing aspect of Psoralea corylifolia plant is that every part of it is useful. Roots, stems, leaves, seeds, all have been used to treat vitiligo.

Krishnamurthi AK. Raw Materials. Vol. 7. New Delhi: CSIR; 1969. p. 295-98. Khushboo PS. Pharmacogn Rev. 2010 Jan;4(7):69-76.

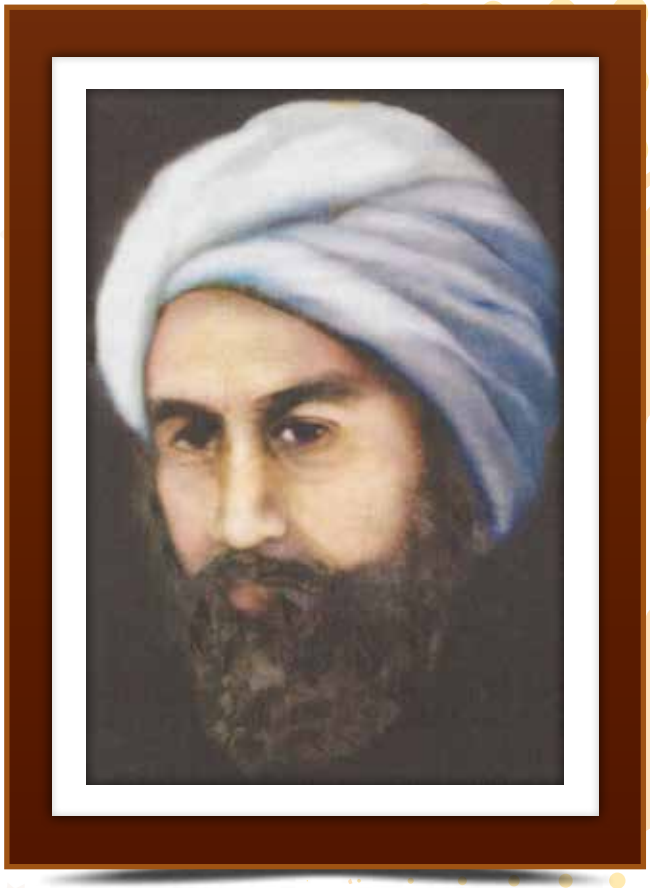
Ammi majus Linnaeus (Aatrilal), is a weed which grows throughout the Nile Valley. In ancient Egypt, seeds of Aatrilal were used in the treatment of vitiligo.

Ammi majus Linnaeus: Multifunctional properties

- Ammi majus Linnaeus., a member of the family Apiaceae, is native to Egypt and widely distributed in Europe, the Mediterranean, and West Asia.
- Ammi majus is a rich source of furanocoumarins with other compounds viz. flavonoids, terpenoids, proteins, essential oil constituents, etc.
- Photosensitizing activity of furanocoumarins, naturally occurring in Ammi majus fruits, has been utilized to treat vitiligo.
- Ammi majus is known for its anti-inflammatory, analgesic, antibacterial, antiviral, cytotoxic, and many other activities.

Ammi majus Linnaeus has diverse pharmacological actions and efficacy in treating dermatological disorders. It figures as first-line treatment option of vitiligo in alternative medicine.

Botany, Herbals and Healing In Islamic Science and Medicine FSTC Research Team. http://muslimheritage.com/article/botany-herbals-and-healing.



Ibn al-Baytar (1197-1248 AD)

Mafradat Al Adwiya

In Mafradat Al Adwiya, Ibn el Bitar described the treatment of vitiligo with Aatrilal and sunlight.

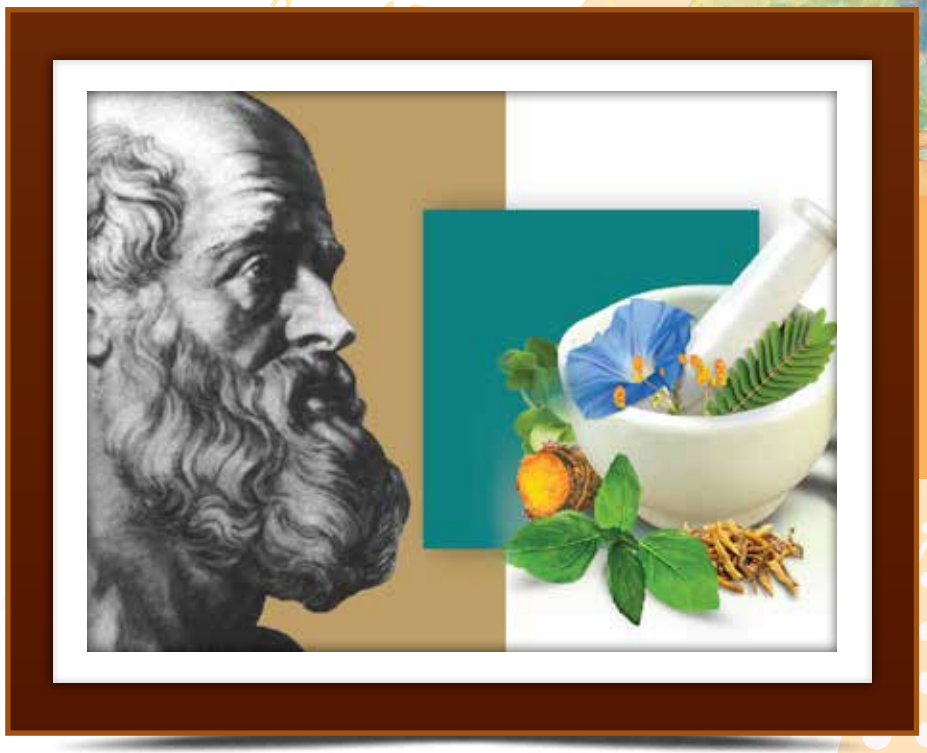
Ammi majus Linnaeus: Virtuous in vitiligo

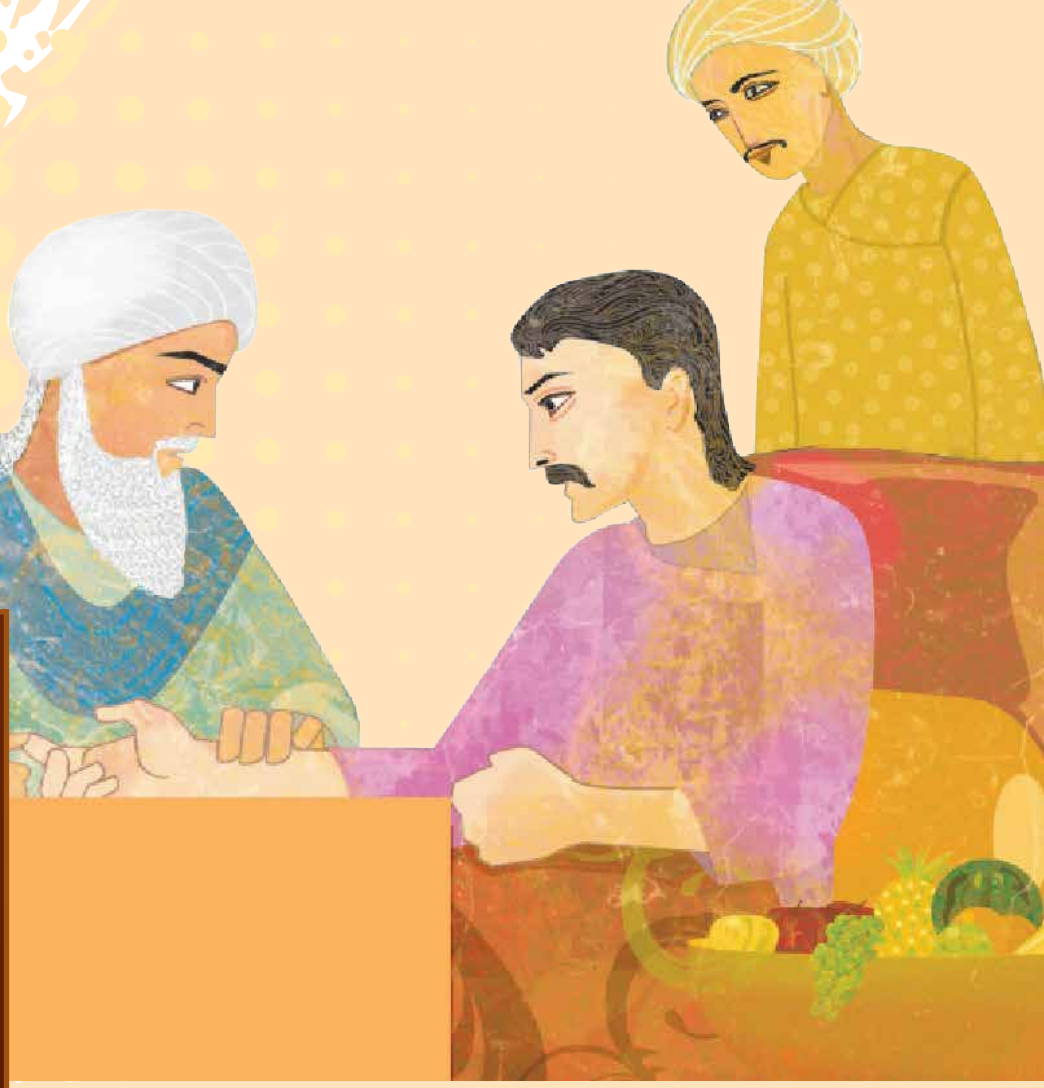
- Ammi majus Linnaeus efficacy was first known to a tribe of Berbers (Bani Abi Shoaib) in the Middle West African desert. They kept this drug hidden from others and used it to treat vitiligo. In his thirteenth-century book Mafradat Al Adwiya, *Ibn al Baitar*, a Spain Arab physician, described Ammi majus Linnaeus under the heading of its Berberian name "*Aatrilal*".

- Dawud al-Antaki (1541-1599 AD) mentioned that Aatrilal to be very effective prescription for chronic vitiligo. Powder of Aatrilal fruits 3 g, Zanjabeel (Zingiber officinale) and Turbud (Ipomoea turpethum) 3.5 g each were mixed with honey and ingested orally with hot water. This was followed by exposure of hypopigmented areas to sunlight.

Extract of Ammi majus Linnaeus, applied as powder or paste, followed by sunlight exposure, was the mainstay treatment of vitiligo.

Botany, Herbals and Healing In Islamic Science and Medicine FSTC Research Team. http://muslimheritage.com/article/botany-herbals-and-healing.





Unani is based on the Hippocratic doctrine of four humours viz. blood, phlegm, yellow bile, and black bile with their four temperamental qualities viz. hot and moist, cold and moist, hot and dry and cold and dry, respectively.

Vitiligo in Unani medicine

- The Unani system of medicine owes its immediate origin to ancient Greece and has been subsequently developed by Roman, Arabic, Spanish, Iranian and Indian physicians.

- In Unani medicine, Ammi majus Linnaeus (Aatrilal) has been the mainstay treatment of vitiligo and other hypopigmentation disorders for centuries.

- According to Hakeem Akbar Arzani (1722 AD), powder of Aatrilal, Aqerqerha (Anacyclus pyrethrum DC.), Post Bekh Kibr (Capparis spinosa L.), Sheetraj (Plumbago zeylanica L.), each 7 gm is taken and mixed with vinegar or honey, from which 5 gm is taken orally daily along with exposure of affected area under sunlight.

As per Unani doctrine, Bars or vitiligo was a chronic disease caused by Sue Mizaj Barid or altered cold temperament. Ammi majus Linnaeus (Aatrilal), had been the mainstay treatment of vitiligo and other hypopigmentation disorders, for centuries.

Usmani QI. Journal of Ethnopharmacology 276 (2021) 114144.

The Healing Sun

As far as 2000 BC, vitiligo patients were encouraged to lie in the sun after picking Ammi majus from the Nile River valley and rubbing the juice on their skin. Boiled extracts of Psoralea corylifolia (scurf-pea), from which the term “psoralen” has been derived, has been used in Ayurveda since 1500 BC.

History of phototherapy

- Belief in the healing properties of sunlight was associated with the ancient cult of the Sun. Heliotherapy has remained the longest used form of phototherapy until the mid-nineteenth century.

- The Ebers Papyrus (1550 BC) recorded the treatment of hypopigmented skin lesions that were covered with Psoralen corylifolia and Ammi majus extracts and subjected to sunlight.

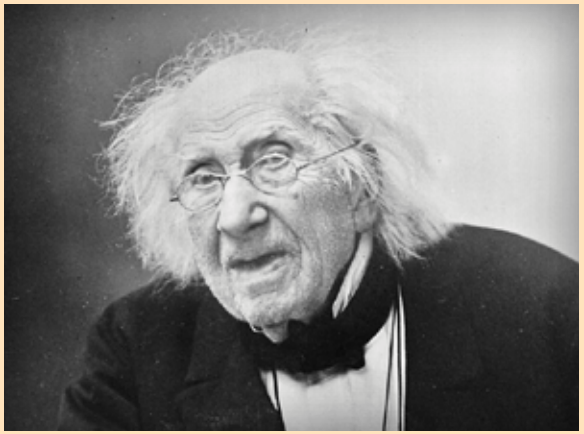
- Ancient Chinese were known to use colored sheets of paper to direct sunlight on skin lesions.

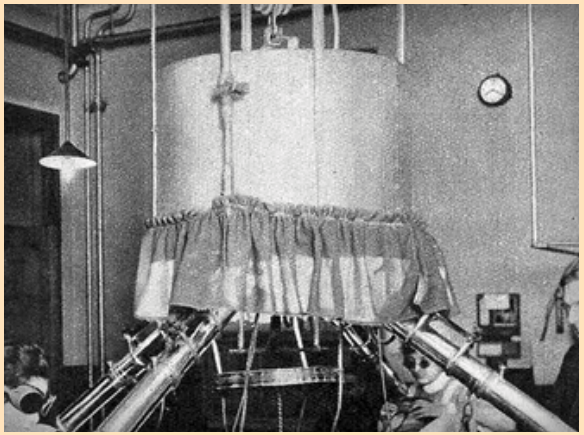
Phototherapy, dating back to more than 3500 years, had been successfully used in the treatment of dermatoses, including vitiligo.

Barros NM, Sbroglio LL, Buffara MO, BakaJLCS, Pessoa AS, Azulay-Abulafia L. Phototherapy. An Bras Dermatol.2021, https://doi.org/10.1016/j.abd.2021.03.001. Grzybowski Andrzej. A brief report on the history of phototherapy, Clinics in Dermatology (2016).

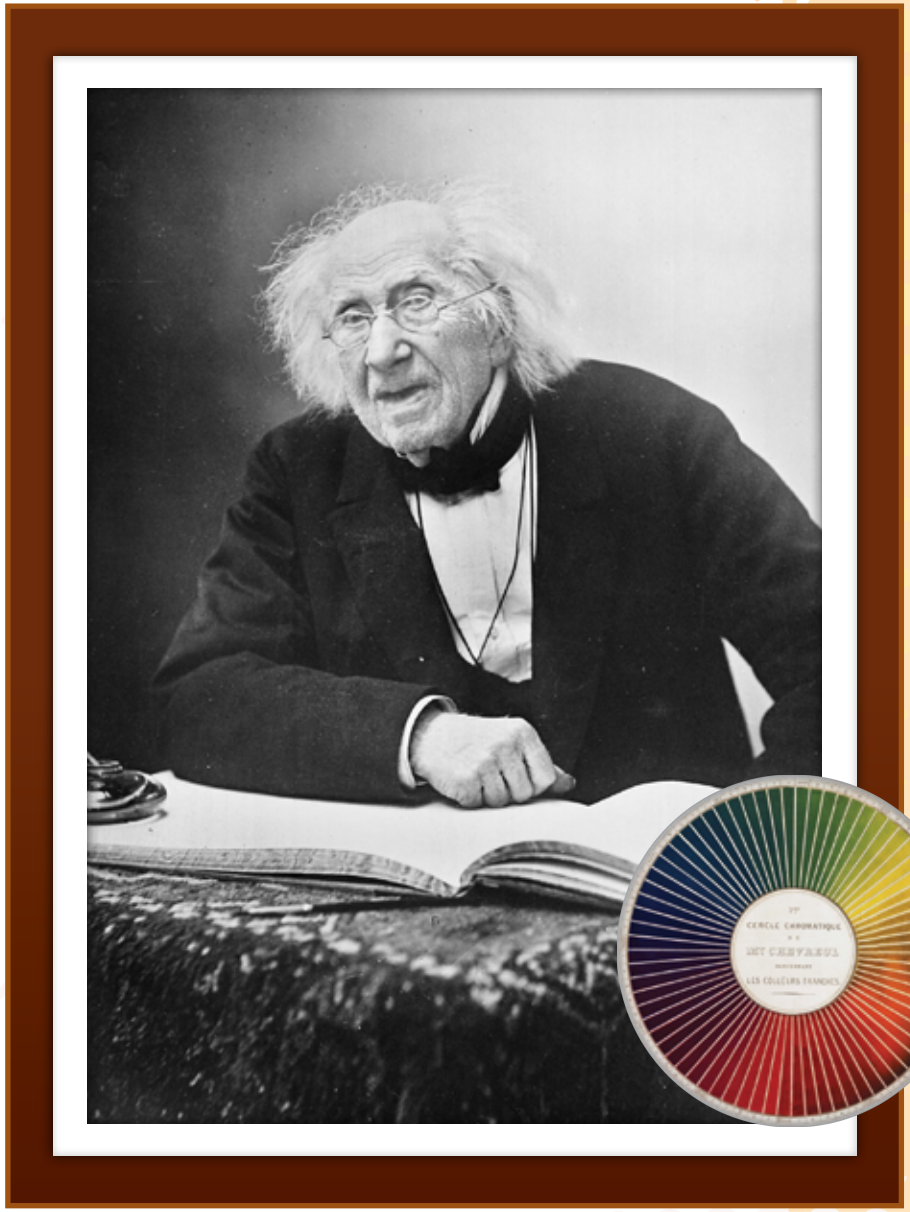
Medical treatment of vitiligo

Modern records



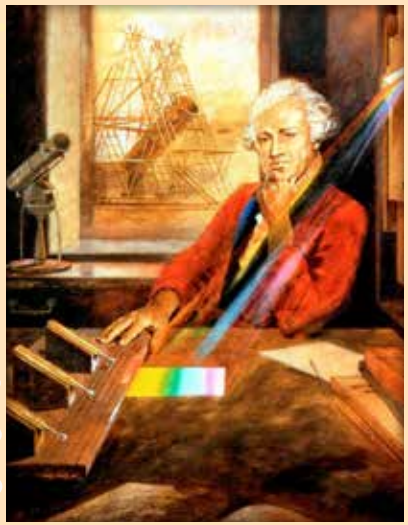


Pioneers of Modern Phototherapy



Michel-Eugène Chevreul (1861)and his Chromatic circle.

Isaac Newton dispersing sunlight through a prism for a study of optics.



Herschel pioneered the use of astronomical spectrophotometry. He discovered infrared radiation.

Beginnings of modern phototherapy

Something new under the Sun

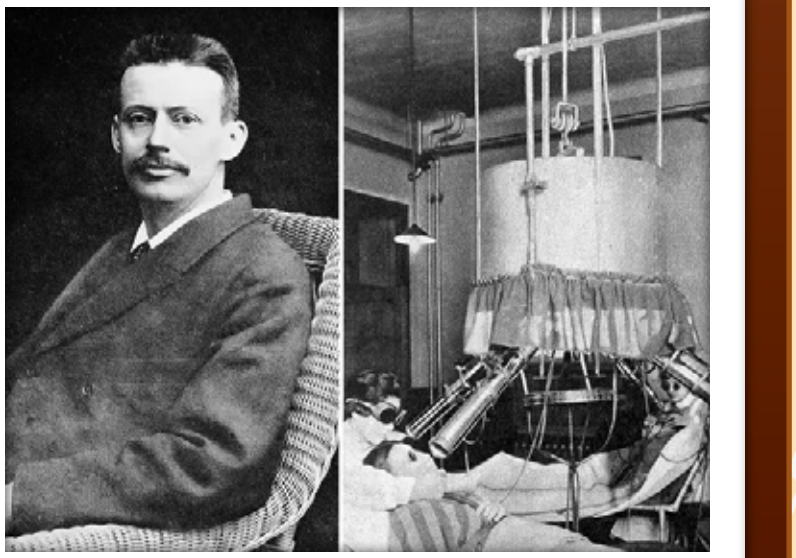
- Isaac Newton's (1642-1727) discovered splitting of a light beam into seven basic colors, using a prism and his so called color wheel.

- Friedrich Wilhelm Herschel's (1738-1822) discovered infrared spectrum of the sun in 1800, and ultraviolet radiation in 1801.

- Michel Eugène Chevreul (1786-1889) expanded upon Newton's theory of seven colors by formulating the concept of simultaneous contrast in 1830. He described the phenomenon of an interaction of two colors, side by side, changing human perception.

Michel-Eugène Chevreul [Public domain] via Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Michel_Eug%C3%A8ne_Chevreul_2.jpg.
Roelandts R. Bicentenary of the discovery of the ultraviolet rays. Photodermatol Photoimmunol Photomed 2002;18:208. Chevreul ME. De la loi du contraste simultané des couleurs. Paris: Pitois-Levrault [Internet]. 1839 [cited 2015 Aug 10].

Artificial phototherapy unravels the greatest therapeutic possibilities in dermatology



Medical use of filtered sunlight, and later UV radiation from the arc lamp by Finsen in 1893, created an opportunity for an effective treatment of not only lupus vulgaris but also other forms of skin infections prior to the antimicrobial era.

Phototherapy in dermatology

- Niels Finsen studied the effect of a “chemical rays” lamp on patients with lupus vulgaris. Finsen then assembled a focusable carbon-arc torch with which he treated over 800 patients with lupus vulgaris in his Phototherapy Institute in Copenhagen.

- In 1903, Finsen was awarded the Nobel Prize, so far, the only Nobel Prize ever awarded for photomedicine.

- Another important stage in the transition from heliotherapy to artificial light phototherapy was the invention of the ultraviolet quartz lamp by Richard Küch in 1906.

Finsen NR, Forchhammer H. Resultate der Lichtbehandlung bei unseren ersten 800 Fallen von Lupus vulgaris. [Results of light therapy in our first 800 cases of lupus vulgaris]. Mitt Fins Med Lichtinst 1904;5-6:1–48.

New ultraviolet and light techniques ushered in the era of Photodermatology

William H. Goeckerman (1884–1954)

Lupus vulgaris treatment at the Finsen Institute in Copenhagen

- Real modern phototherapy began with Niels Ryberg Finsen, the father of ultraviolet therapy. In 1896, Finsen developed a “chemical rays” lamp with which he treated a friend who had lupus vulgaris; within a few months the lesions were completely resolved.

- In 1923, Goeckerman used a high-pressure mercury lamp to produce artificial broadband UV-B plus coal tar to treat dermatosis. In 1947, the active ingredients from the extract of Ammi majus were discovered, eventually leading to the discovery of PUVA therapy for psoriasis.

- Targeted phototherapy, such as excimer laser, introduced for the treatment of psoriasis in 1997, is now being used to treat vitiligo.

Over many centuries, “heliotherapy” was used in the treatment of skin diseases. More than 3500 years ago, ancient Egyptian and Indian healers used the ingestion of plant extracts or seeds, in addition to sunlight, for treating vitiligo.

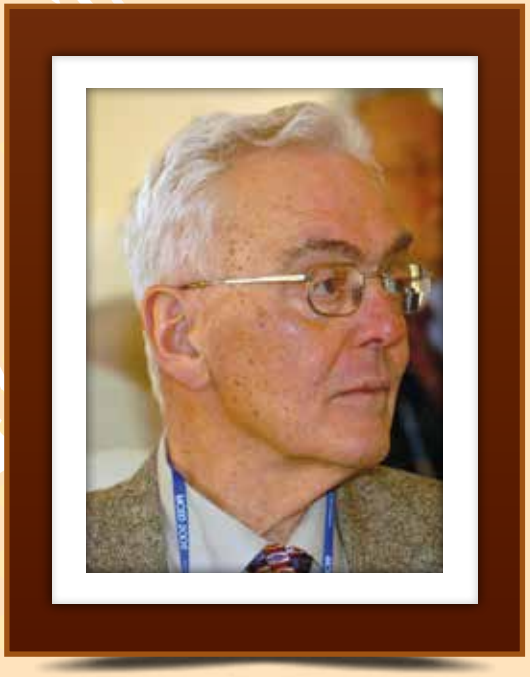
Roelandts R. The history of phototherapy: something new under the sun? J AmAcad Dermatol. 2002;46(6):926-930.

Novel phototherapeutic modalities in dermatosis

John A. Parrish,
Professor of Dermatology emeritus

John Parrish defined the action spectrum for psoriasis with a peak at 313 nm. However, it took almost a decade for commercially produced artificial lamps at this wavelength to be available as narrowband UVB.

First PUVA unit in Vienna, 1975.



Jan C. van der Leun in 1984 demonstrated the clinical efficacy of narrowband UVB.

Evolution of Narrow-Band Ultraviolet-B Therapy

1974	Use of PUVA by Parrish in psoriasis.
1977	Fischer found that 313 nm UV light cleared psoriatic plaques.
1978	Diffey and Farr found UVB to be most effective and viable at 311 nm
1990	313 nm was established as the most reduced, effective wavelength and least erythemogenic-ideal “phototherapy index” for psoriasis.

Hönigsmann H. History of phototherapy in dermatology. Photochem Photobiol Sci. 2013 Jan;12(1):16-21. Roelandts R. The history of phototherapy: something new under the sun? J AmAcad Dermatol. 2002;46(6):926-930. Kumar U. Indian Dermatol Online J 2019;10:234-43.

Narrowband UVB cabin

1977: NB–UVB phototherapy becomes a valuable therapeutic armamentarium vitiligo

Therapeutic use of Narrowband UVB (NB-UVB) phototherapy first came to prominence in 1977 when Fischer discovered that ultraviolet light at a wavelength of 313 nm achieved effective clearance of plaque psoriasis and had the advantage of being less erythemogenic at higher doses compared to BB-UVB. This heralded the development of the TL-01 fluorescent lamp, which is still a widely used light source for NB-UVB.

NB-UVB phototherapy has established itself as a relatively safe and cost-effective therapeutic modality for a wide range of UVB-responsive dermatoses

Fischer T. et al, Comparative treatment of psoriasis with UV-light, trioxsalen plus UV-light, and coal tar plus UV-light Acta Derm Venereol. 1977;57(4):345-50.

British Journal of Dermatology (1987) 117, 49-56

Review

An appraisal of ultraviolet lamps used for the phototherapy of psoriasis

B.L. DIFFEY AND P.M.FARR*

Regional Medical Physics Department, Dryburn Hospital, Durham and * Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.

Accepted for publication 19 January 1987

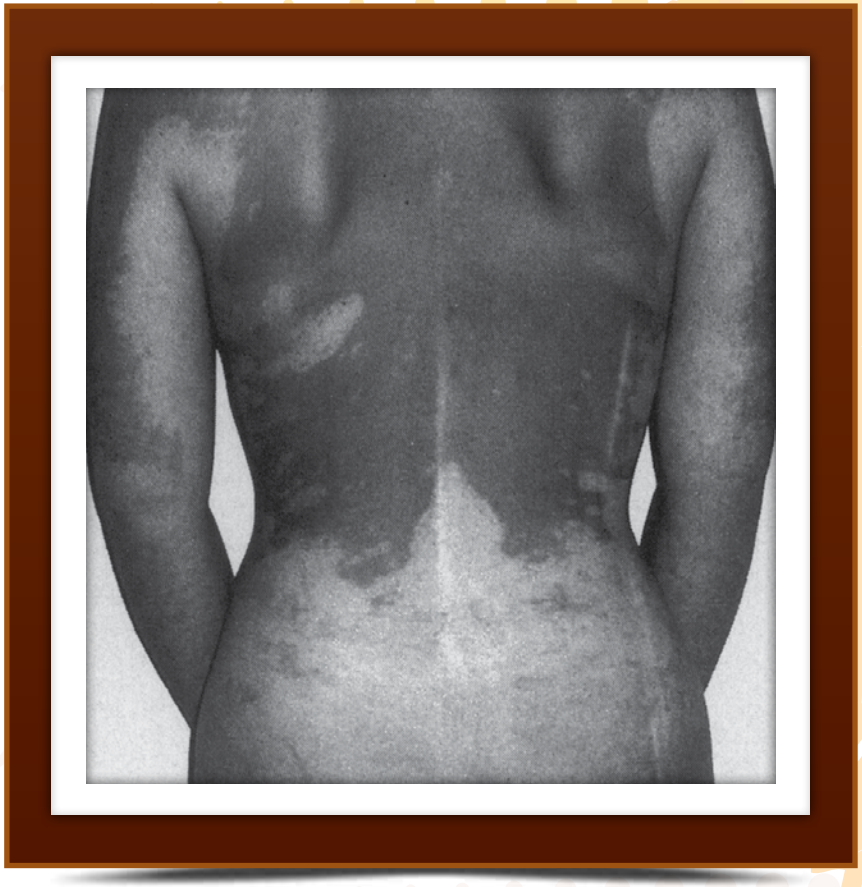
1987: Do all lamps have an equal therapeutic effect?

- First treatment of dermatosis with artificial ultraviolet radiation from carbon arc lamp was limited by noise, odour and sparks.
- While fluorescent lamps were developed in the late 1940s, metal halides were added too mercury lamps in the 1960s, to improve the emission in certain regions of the ultraviolet and visible spectra.
- Ultraviolet fluorescent lamp emitting a narrow band of radiation of 311 nm was therapeutically more effective in the treatment of dermatosis than a fluorescent sunlamp which emitted therapeutically-inactive UVC radiation.

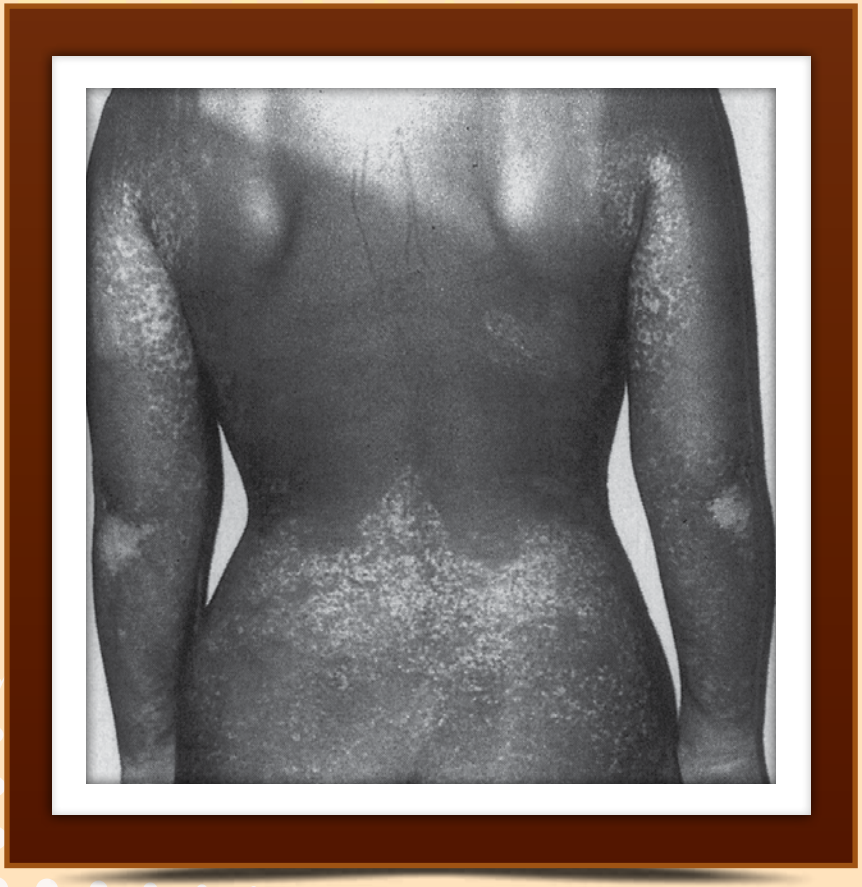
If patient can tolerate severe erythema then all of the lamps will be similarly effective. If mild erythema is chosen, then fluorescent lamps with negligible UVC emission is preferred. Medium-pressure mercury arc lamp is not effective.

Diffey BL. An appraisal of ultraviolet lamps used for the phototherapy of psoriasis. British Journal of Dermatology (1987) 117, 49-56.

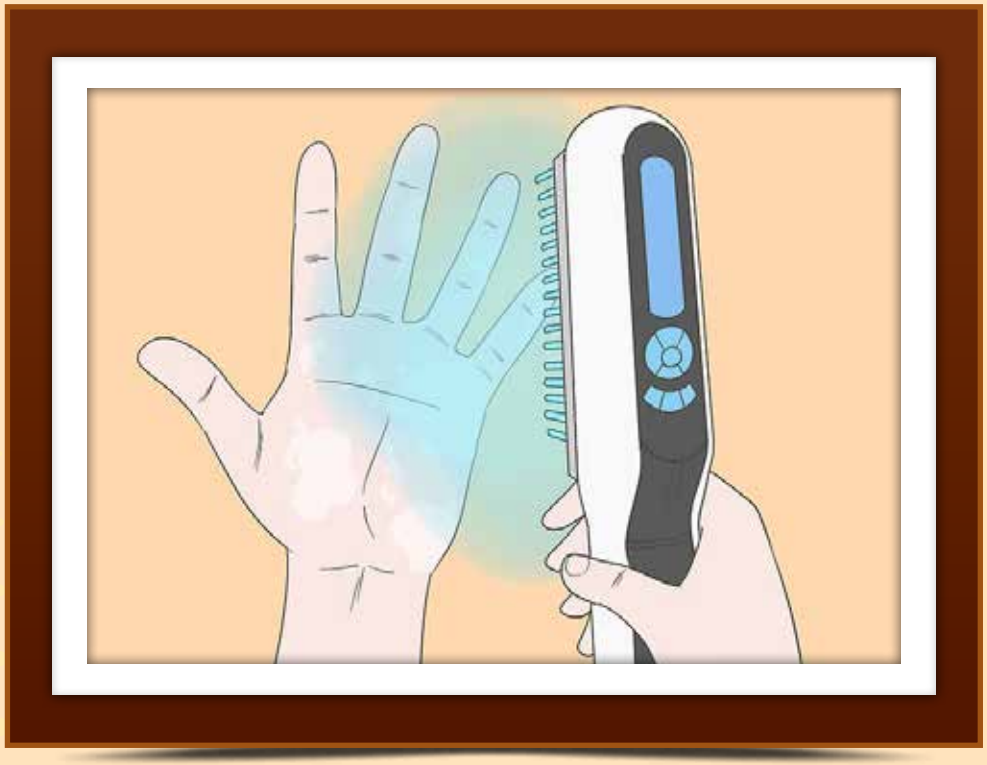
1997: First use of UVB radiation in the treatment of vitiligo



Patient with vitiliginous lesions on the back before treatment.



Repigmentation of vitiliginous lesions in the same patient after 1 year of treatment with 311nm UVB radiation.

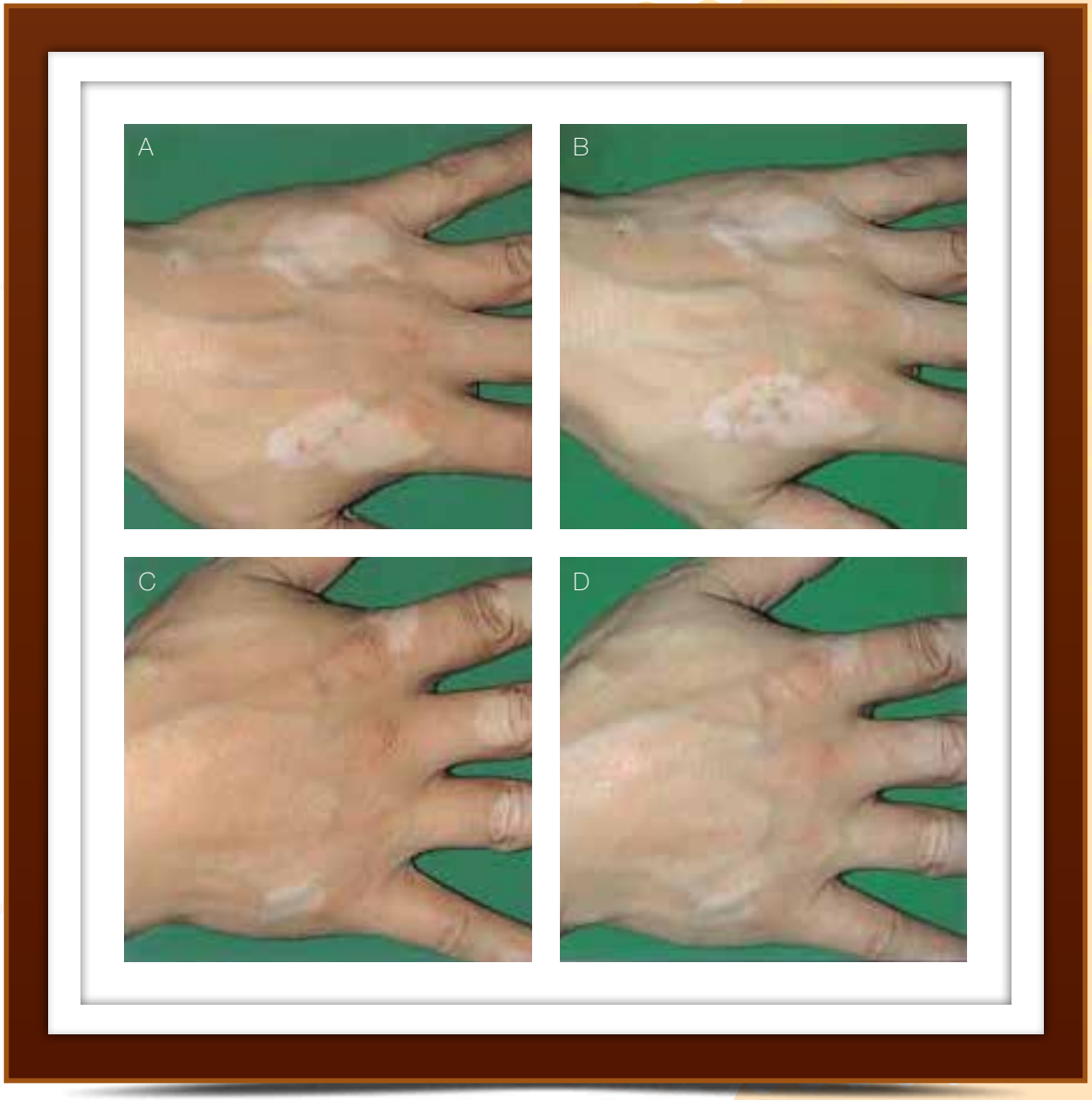


- In 1997, treatment of vitiligo with narrowband UVB was first used by Westerhof and Nieuweboer-Krobotova from the Netherlands Institute for Pigmentary Disorders, University of Amsterdam.

- Treatment of vitiligo with 311nm UVB radiation was found to be as efficient as topical psoralen plus UVA (PUVA) and with fewer adverse effects.

Westerhof W. et al, Treatment of vitiligo with UVB radiation vs. topical psoralen plus UVA. Arch Dermatol.1997;133:1525-1528.

1997: First use of 308-nm Xenon-chloride Excimer (XeCl) Laser in the treatment of vitiligo



Vitiligo patches on the left side of the hand (A) prior to the 308-nm XeCl excimer laser treatment and (B) at 20 treatments. Vitiligo patches on the right side of the hand (C) prior to NB-UVB phototherapy and (D) at 20 treatments.

Xenon–chloride laser light advantage in vitiligo

- Use of topical psoralen plus ultraviolet UVA (PUVA), the most frequently used forms of phototherapy in vitiligo, is limited by increased risks of cancer and premature ageing of the skin.

- Narrow-band UVB (NB-UVB) phototherapy is as effective as PUVA therapy but with lower risk of skin cancer.

- XeCl UVB laser is highly effective in the treatment of vitiligo. As only the vitiligous areas are treated by UVB, there is little risk of cancer occurring in the surrounding skin. XeCl UVB laser does not cause perilesional hyperpigmentation, which results in a better cosmetic appearance.

Similar to NB-UVB, XeCl UVB laser exerts immunomodulatory effects and may also stimulate the melanocytic reserves in the hair sheaths, as repigmentation occurs in a perifollicular pattern.

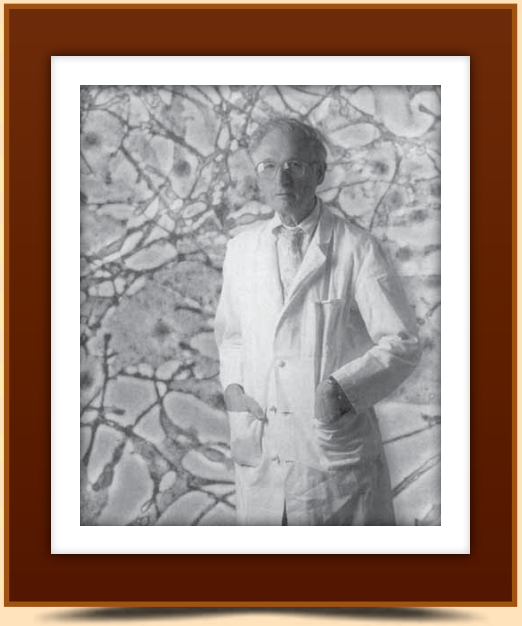
Baltás E et al Repigmentation of localized vitiligo with the xenon chloride laser. Br J Dermatol. 2001 Jun;144(6):1266-7.

Evolution of narrow band UVB therapy for vitiligo

Year	Event
1400 BC	First use of light therapy in vitiligo in 1400 BC with use of plant concentrates of *Psoralea corylifolia* in India and *Ammi majus* Linnaeus in Egypt in topical or oral forms followed by Sun exposure.
19th century	Real use of UV therapy in skin diseases started. Niels Finsen received Nobel Prize in 1903 for its use in lupus vulgaris.
1974	Use of PUVA by Parrish in psoriasis.
1977	Fischer found that 313 nm UV light cleared psoriatic plaques.
1978	Introduction by Wiskemann of cabin with broadband UVB tubes for psoriasis. Lack of efficacy in psoriasis. Broadband UVB went into disrepute.
1987	Diffey and Farr found UVB to be most effective and viable at 311 nm.
1990	It was established that 313 nm was the most reduced and effective wavelength and least erythemogenic-ideal “phototherapy index” for psoriasis.
1997	NB-UVB first used in vitiligo by Westerhof and Nieuweboer-Krobotova.
1997	Use of 308 nm excimer XeCl lasert.

Khanna U et al, What is new in narrow-band ultraviolet-B therapy for vitiligo? Indian Dermatol Online J 2019;10:234-43.

Aaron B. Lerner, in approximately 1944 (age 23).



1996: Aaron Lerner standing in front of an enlarged photograph of normal human melanocytes.

Dr. Lerner and Marge at Marge's graduation, 1945.

"Lerner had three major disappointments, other than that he would have liked to receive the Nobel Prize. First, he was upset that he never got to meet his dad. Second, if not for developing Parkinson's, he would have continued to see patients, might have cured vitiligo, and would have tinkered in his workshop forever."... Marguerite Rush Lerner, M.D

Aaron B. Lerner (1921-2007)

The man known as the “dean of pigmentation,” Aaron Bunsen Lerner, spent three years in Oregon doing research that proved vital in understanding mammalian skin color. The color of skin was a lifelong fascination for Lerner. He believed that the twenty-first century would bring cures for vitiligo, melanoma, and many other pigmentary disorders and that someday people would be able to change the color of their skin at will.

In 1957, Lerner and his colleagues isolated and determined the molecular structure of melatonin; they published their results in 1958.

Lerner AB. My 60 years in pigmentation. Pigment Cell Res 1999; 12:131-144.

1955: University of Oregon Medical School. Isolation of melanocyte stimulating hormone.

Standing left to right: Thomas Fitzpatrick; Howard Mason; Aaron Lerner; and Kazuo Shizume.

Isolation of melanocyte stimulating hormone

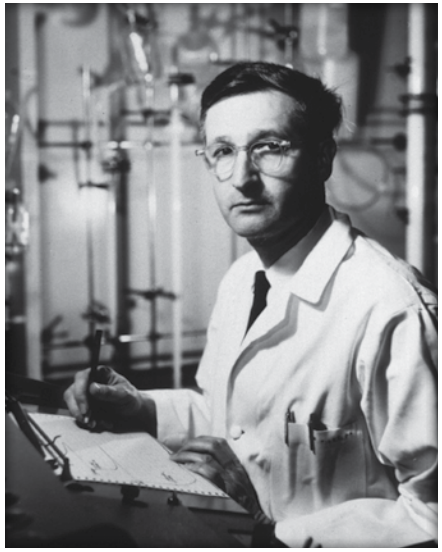
Excerpts from “My 60 Years in Pigmentation” by Aaron B. Lerner.

“In 1952, Fitzpatrick, as Professor, and I, as Associate Professor, set up the first Section of Dermatology in the Department of Medicine at the University of Oregon in Portland. Fitzpatrick was 32 years old and I was 31 years old. We were joined by Dr. Howard Mason, a biochemist, and by Dr. Kazuo Shizume, a young physician from Japan who was interested in endocrinology.

A year later, Teh Lee, after getting his Ph.D. degree, also joined us. Shizume and I perfected the assay for MSH by measuring the darkening of small pieces of frog skin. The work on isolation was going well.

Injections of MSH to patients produced darkening. Fitzpatrick and I were beginning to see and treat patients with pigment problems - especially vitiligo and melanomas.”

Harris JL, Lerner AB. Amino acid sequence of alpha-melanocyte stimulating hormone. Nature. 1957;179:1346–7.



In the Lab.

1957: Amino-acid sequence of the alpha melanocyte-stimulating hormone.

J. Leuan Harris and Aaron Lerner determining the amino acid sequence of α-MSH in Frederick Sanger's laboratory in the Biochemistry building at Cambridge University, England.

"Our research on MSH was always on a broad base, going from the chemistry to clinical studies. Others, such as Joe Bagnara and his students, also worked on a broad base, particularly on the various chromatophores in tadpoles, frogs, lizards, and other animals. It was always fun to overlap with the biologists.

There are three melanocyte-stimulating hormones (α-, β-, and γ-MSH) in the pituitary gland. These three neuropeptides, together with ACTH, are contained in the precursor molecule, pro-opiomelanocortin (POMC), from which they must be processed.

γ-MSH, the peptide that we first isolated and sequenced, is the first third of the ACTH molecule with an acetyl group at the N-terminal end. These peptides appear to play important roles in inflammation and pigmentation. We also determined the sequences of monkey and sheep MSH. As a by-product of the MSH work, we determined most of the sequence of human ACTH"

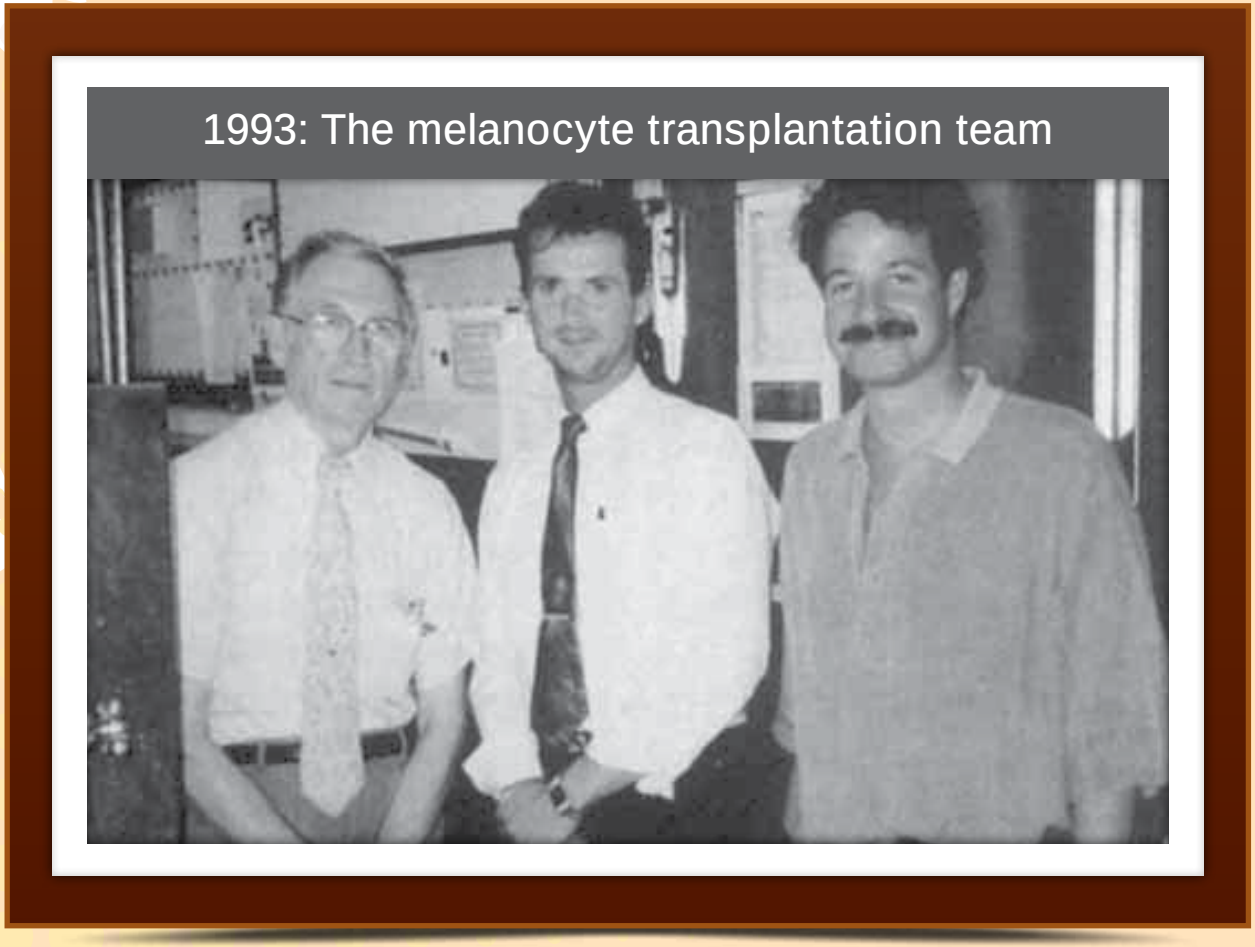
Harris JL, Lerner AB. Amino acid sequence of alpha-melanocyte stimulating hormone. Nature. 1957;179:1346–7.

1986: Melanocytes in culture and transplantation

Aaron Lerner in the lab with Ruth Halaban (left) and Gisela Moellmann.

"Ruth Halaban advanced our knowledge on the culturing of melanocytes and on growth factors for pigment cells. She determined the cDNA sequence for human tyrosinase. Gisela studied the ultra structure of pigment cells, and established the internalization of receptors. She found extracellular granular material in skin of patients with vitiligo."... Aaron Lerner

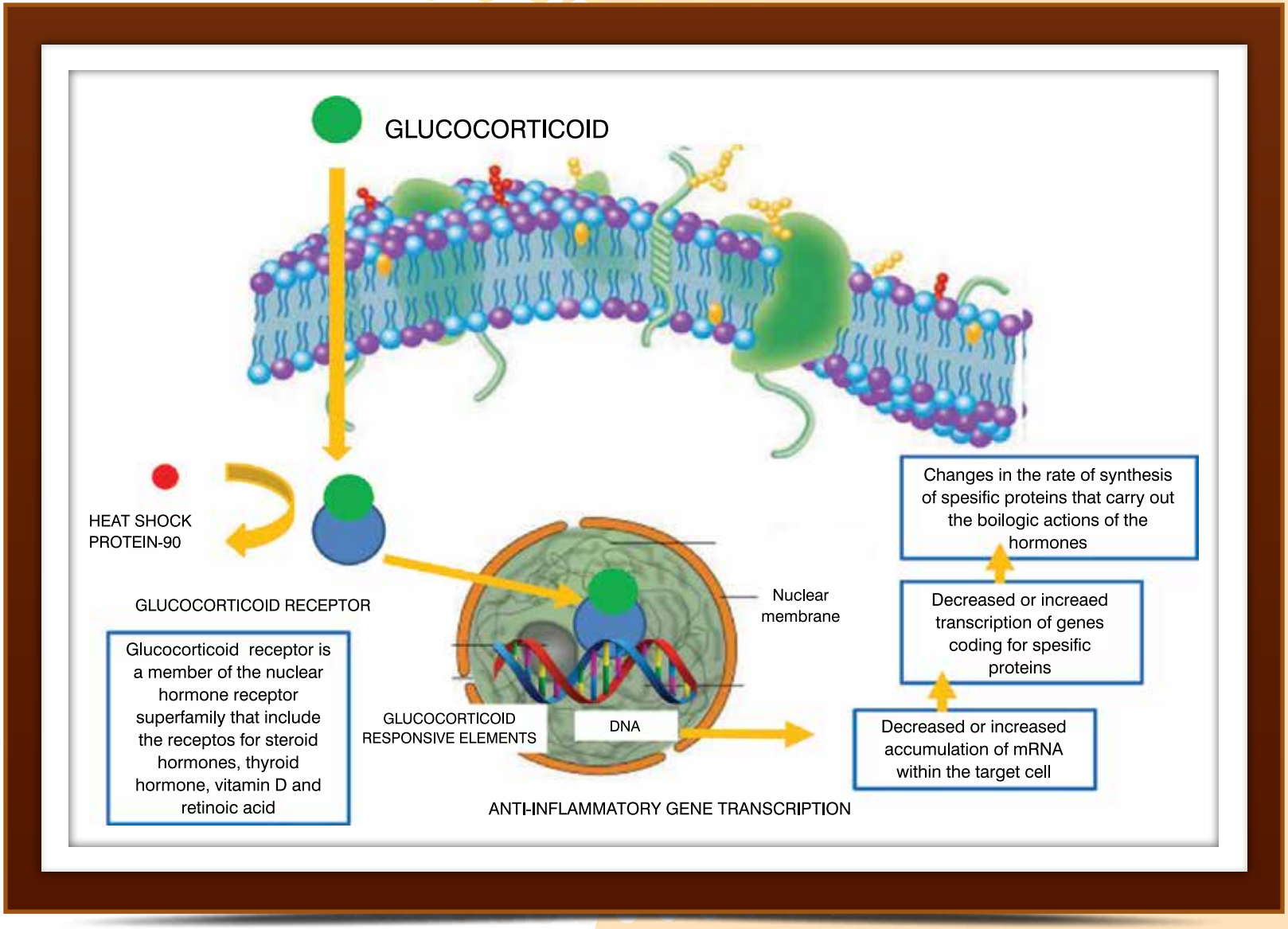
"The field of pigmentation has provided me with many good peers, teachers, students, and fellows. I dedicated my work to them"... Aaron Lerner



Aaron Lerner; Mats Olsson (Sweden); and Werner Lontz (Germany).

"For the first time it was shown that transplantation of autologous melanocytes that were expanded in number in culture can be used to treat some patients with vitiligo or other forms of hypopigmentation" ... Aaron Lerne

Harris JL, Lerner AB. Amino acid sequence of alpha-melanocyte stimulating hormone. Nature. 1957;179:1346–7.



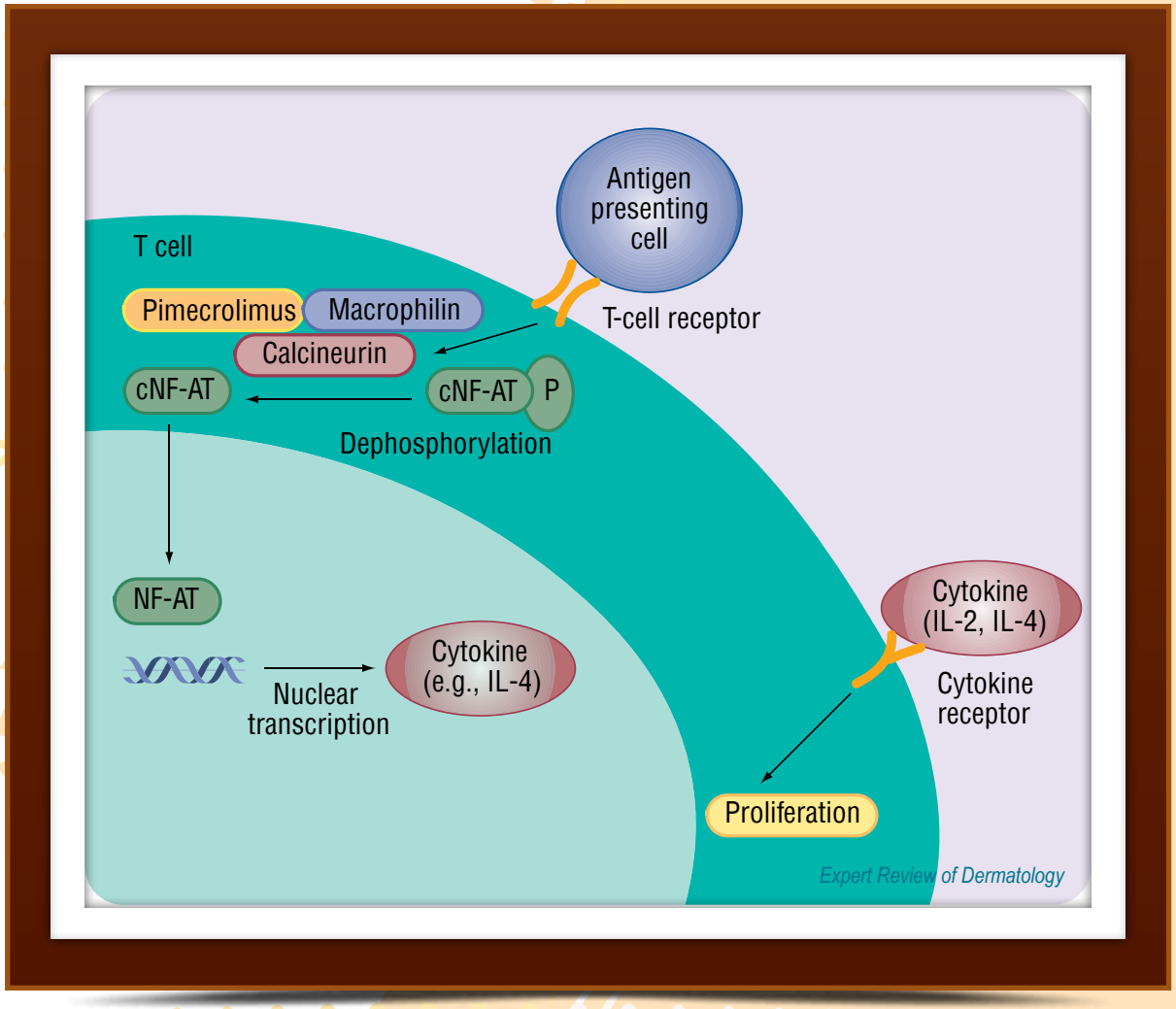
Mechanisms of actions of glucocorticosteroids.

Topical therapies in vitiligo

Corticosteroids

- Since its introduction in 1950's, glucocorticosteroids have been used widely as topical and sometimes intralesional therapy in vitiligo.
- At gene level, glucocorticoid acts by (a) transrepression, which is responsible for a large number of desirable anti-inflammatory and immunomodulating effects and by (b) transactivation, which is associated with frequently occurring side effects.
- Topical glucocorticosteroids, used as adjunctive treatment after skin grafts, can increase UV repigmentation efficacy.

Kim SM et al, The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patients. Int J Dermatol. 1999 Jul;38(7):546-50.



Mechanism of action of the calcineurin inhibitor Pimecrolimus

By binding with high affinity to macrophilin-12, pimecrolimus inhibits phosphatase activity of calcineurin, responsible for the dephosphorylation of cytosolic NFATs, thereby blocking nuclear translocation of the cNFAT subunit, and preventing the transcription and synthesis of inflammatory cytokines.

c: Cystolic; IL: Interleukin; NF-AT: Nuclear factor activated T cell; P: Phosphate.

Topical therapies in vitiligo

Topical Calcineurin inhibitors

- Topical calcineurin inhibitors (TCIs) have been specifically developed for the treatment of inflammatory skin diseases and are recommended as first-line treatments for vitiligo.

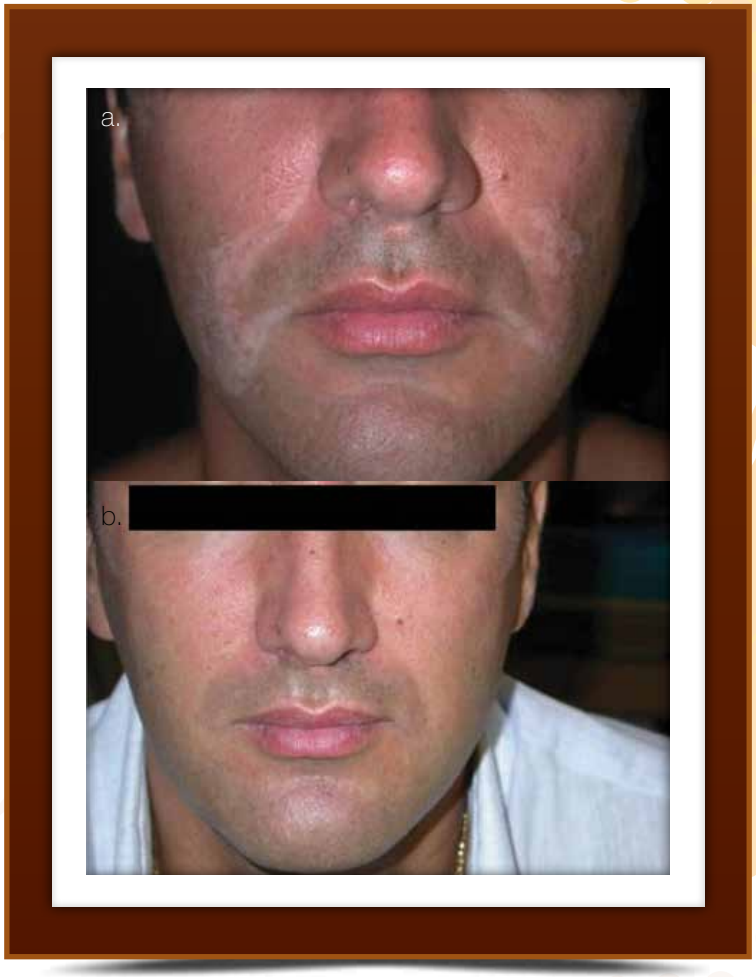
- Compared with topical corticosteroids, TCI do not have the risk of local side effects, such as skin atrophy, telangiectasia, and glaucoma after prolonged use.

- TCIs use is preferred in areas more susceptible to corticosteroids-associated side effects, such as the head and neck region, flexures andgenital area.

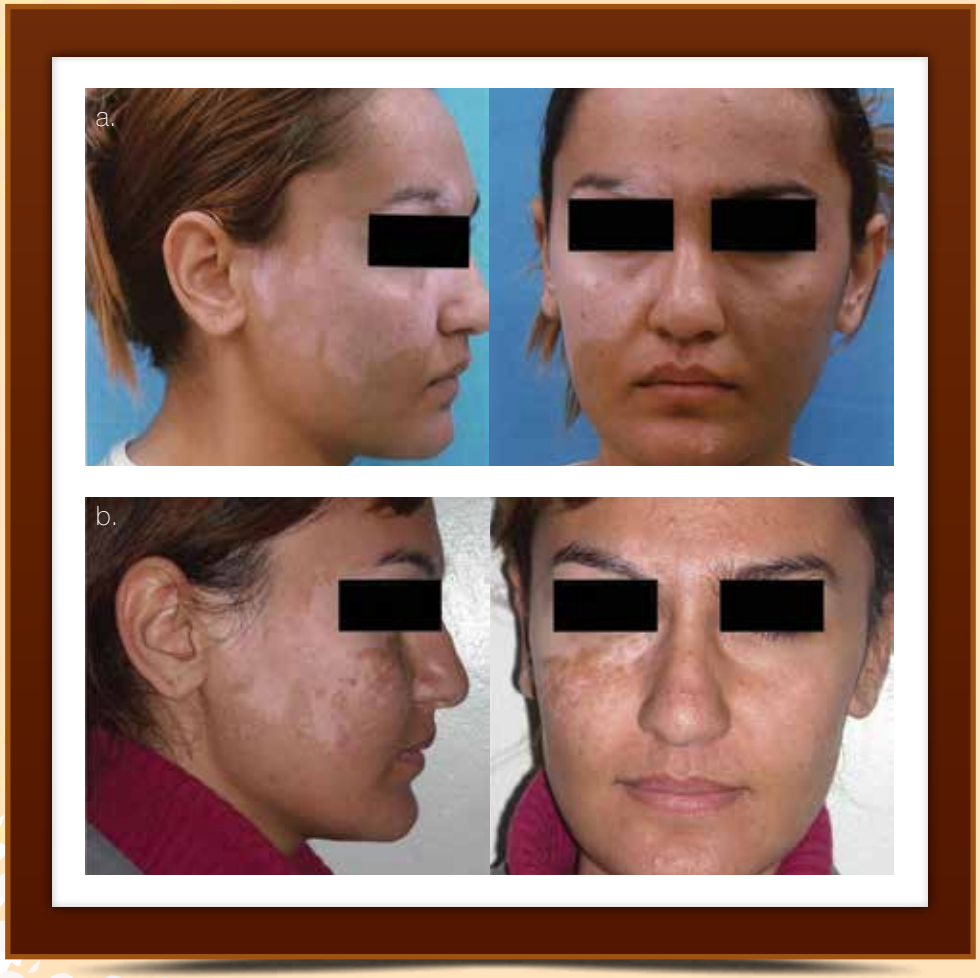
- TCIs have limited percutaneous penetration and therefore do not cause significant systemic absorption following normal use.

M. Picardo, A. Ta eb (eds.), Vitiligo, https://doi.org/10.1007/978-3-319-62960-5_35.

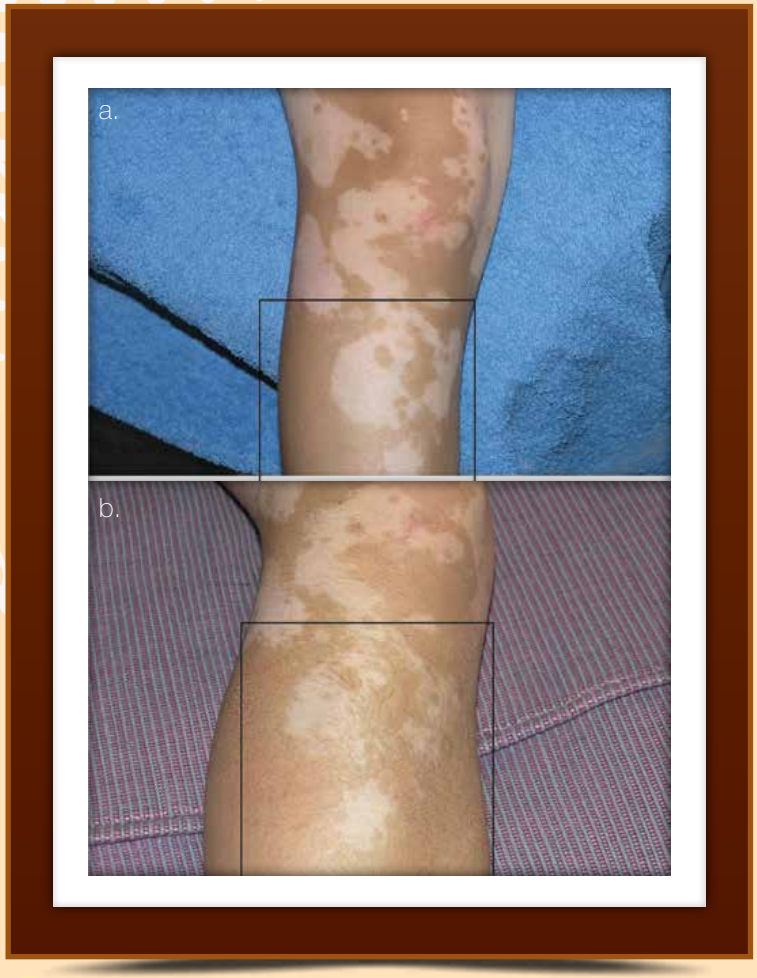
Efficacy of pimecrolimus in the treatment of vitiligo



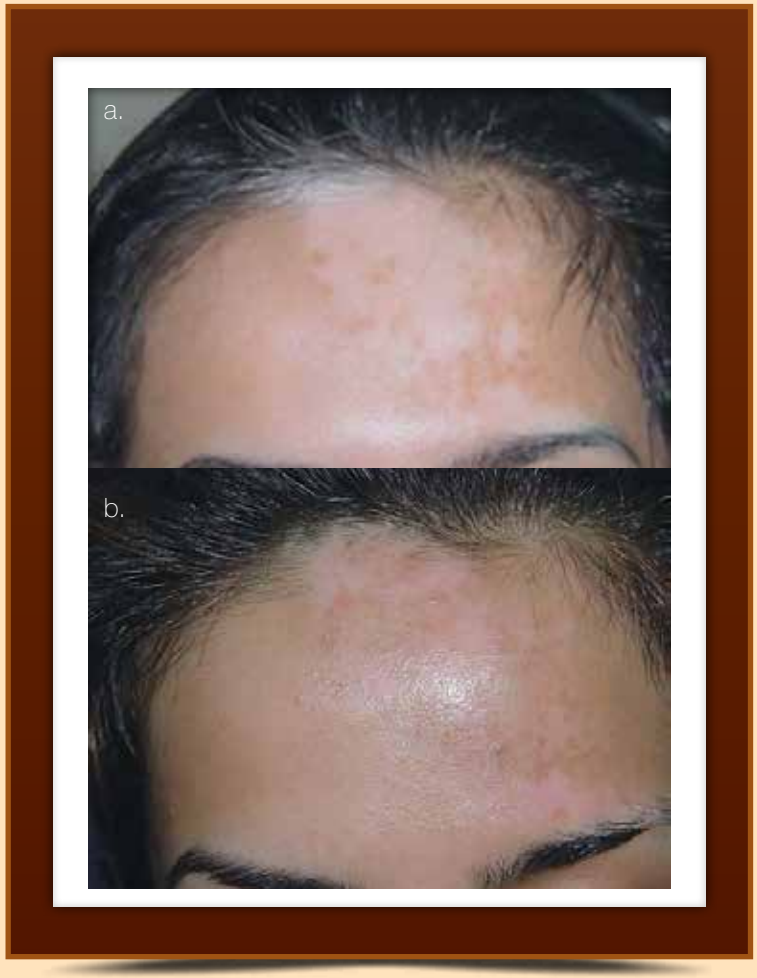
Facial vitiligo before (a) and after (b) treatment with Pimercrolimus.



Improvement in segmental vitiligo in patient treated with topical pimercrolimus for 6 months, before (a) and after (b) treatment.



Before (a.) and after (b.) pimercrolimus treatment under occlusion (hydrocolloid dressing) for 7 weeks.



Twenty-year-old female with marked vitiligo response before (a) and after (b) 12 weeks of treatment with pimecrolimus cream 1%.

M. Picardo, A. Ta eb (eds.), Vitiligo, https://doi.org/10.1007/978-3-319-62960-5_35.

Clinical studies on topical pimecrolimus in the treatment of vitiligo

Study design	N	Study duration
Case report (Boone 2006)	1	5 months
Case report (Seirafi H 2007)	2 children	3–4 months
Retrospective study (Lepe V, 2003)	8	11 months
Open prospective study (Castanedo-Cazares JP, 2003)	26	6
Open prospective study (Ostovari N 2006)	30	12 weeks
Open prospective study (Passeron T, 2004)	19	6 months
Comparartive prospective, non blind trial (Coskun B, 2005)	10	2 months
Case report (Coskun B, 2005)	1	5 months

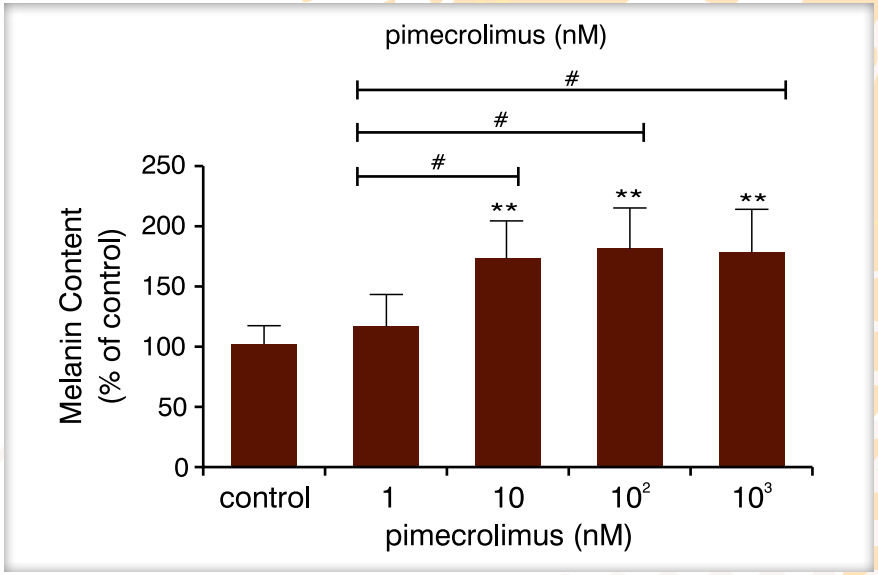
Treatment regimen	Results
5 months	Significant improvement with both, but mainly with pimecrolimus of facial lesions.
3–4 months	Almost complete repigmentation of eyelid and genital lesions.
11 months	Mean percentage repigmentation in face 72.5%.
6	Repigmentation in 57.7% of lesions. Mean repigmentation of 62% head and neck region.
12 weeks	Repigmentation in 57.7% of lesions. Best results face and truck (mean repigmentation 31% and 36% respectively).
6 months	>25% repigmentation in 68% of patients.
2 months	Comparable rate of repigmentation in non facial areas.
5 months	Percentage of repigmentation: >90%.

Pimecrolimus increases melanogenesis and migration of melanocytes

Study design	TCI Used	Brief Description	Conclusion	Ref
In vitro, cultured melanocytes	Pimecrolimus	Pimecrolimus significantly increased intracellular tyrosinase activity, and content of melanin	Increased melanin contents, tyrosinase, and MITF	Xu P et al Korean J Physiol Pharmacol. 2017 May;21(3):287-292.

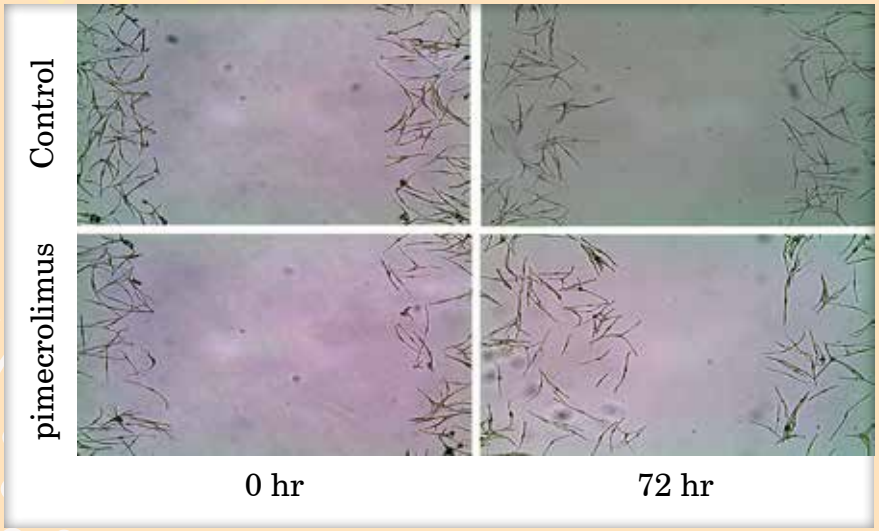
MITF: microphthalmia associated transcription factor.

Effect of pimecrolimus on melanin content



Addition of pimecrolimus at 10, 10^2 and 10^3 nM significantly increased intracellular tyrosinase activity, which was consistent with the elevated melanin content. *p<0.05 compared with control.

Effect of pimecrolimus on melanocytic migration



Migration was measured by scratch assay. Pimecrolimus rapidly reduced scratch size (67% wound gap size after 3 days) vs. control (83% wound gap size after 3 days), indicative of enhanced migration (p<0.05).

Repigmentation of vitiligo with pimecrolimus cream: Case report

Study design	TCI Used	Brief Description	Conclusion	Ref
Case report	Pimecrolimus 1% cream	Vitiligo lesions on the face, scalp, trunk. Treatment was given for 5 months	Percentage of repigmentation: >90%. No adverse effect	Mayoral FA, et al, Dermatology 2003; 207: 322-3.

Presented is a 19-year-old female patient with vitiligo since 11 years of age. Depigmentation initially began in her left perioral area and subsequently spread to involve the right side of her face and entire forehead. She had no significant past medical history and was not on any medication at the time of presentation. Patient was seen three months after the birth of her second child, with confluent patches of depigmentation on her face (Fig. 1a). Wood's lamp examination also revealed mild involvement of the trunk with a total body surface area of approximately 10%. Pimecrolimus cream twice a day, was applied to affected areas. After 3 months of treatment, the patient had 50% repigmentation of her vitiligo. Within 5 months of therapy, the patient had almost complete repigmentation of her facial skin (Fig. 1a–c). There were no treatment-assocaited adverse effects.

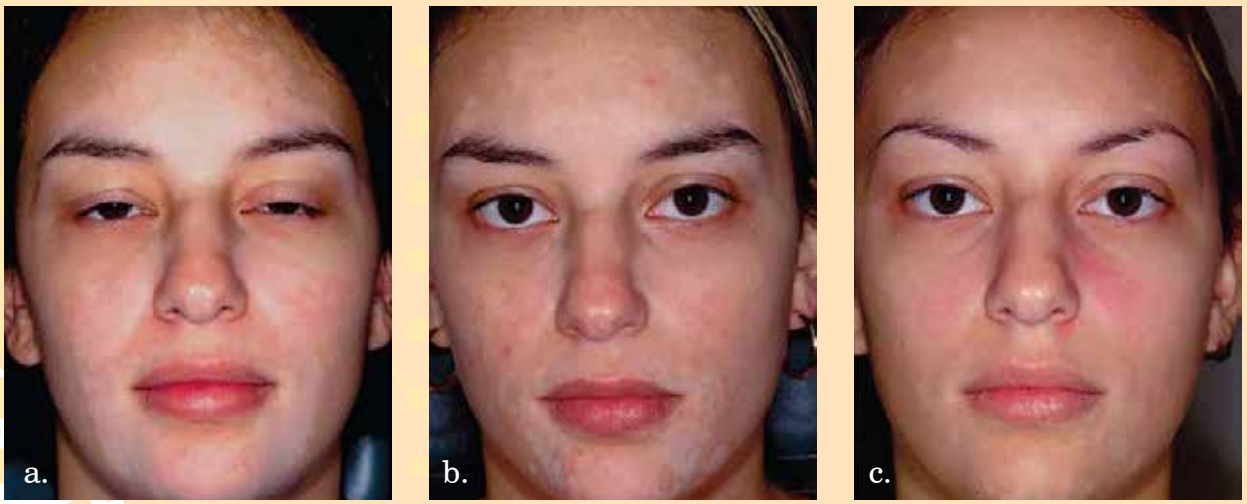
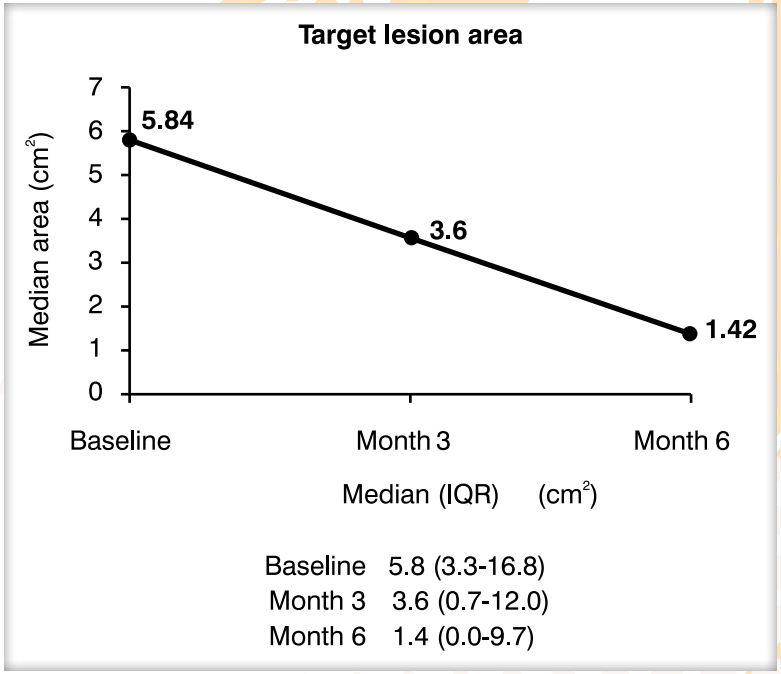


Fig. 1. A 19-year-old female patient with vitiligo treated with pimecrolimus.
(a.) Before treatment
(b.) After 3 months, and
(c.) after 5 months of treatment.

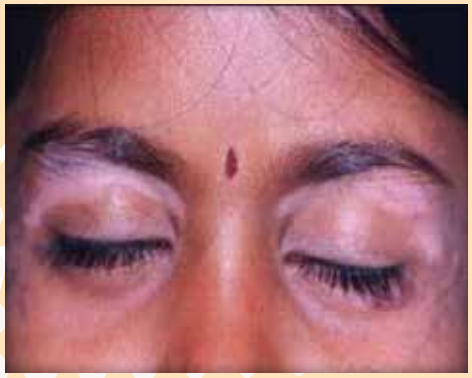
Efficacy of pimecrolimus in the treatment of vitiligo: Proof of concept study

Study design	N	Study Duration	Treatment regimen	Results	Ref
Case report	1	5 months	1% pimecrolimus versus calcipotriol cream	Significant improvement with both, but mainly with pimecrolimus of facial lesions	Boone et al Eur J Dermatol 2006; 17 (1): 1-7.

Assessment of repigmentation: target lesion area measurement.



Vitiligo lesion	Baseline	At 3 months	At 6 months	Reduction (%) from baseline
Median surface area in head and neck region	5.8 cm^2	3.6 cm^2	1.4 cm^2	72%

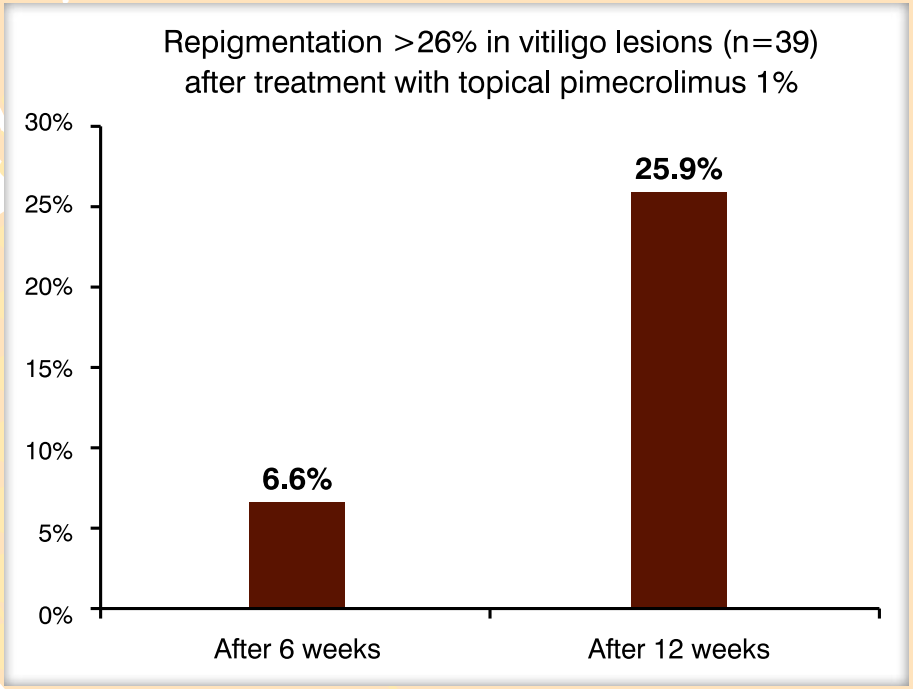


Baseline

After 6 months

Efficacy of topical pimecrolimus 1% in patients with vitiligo affecting <20% of body surface area

Study design	*N*	Study Duration	Brief Description	Conclusion	Ref
Case report	2 children	3-4 months	1% pimecrolimus twice daily	Almost complete repigmentation of eyelid and genital lesions	Seirafi H, et al. Dermatology. 2007;214:253–9.



Twenty-year-old female with marked response before (a) and (b) after 12 weeks of treatment with pimecrolimus cream 1%.

Monotherapy with topical pimecrolimus 1% cream resulted in moderate to excellent response (repigmentation >26%) in 6.6% and 25.9% of vitiligo lesions after 6 and 12 weeks of treatment, respectively. Greater response occurred in lesions located on the trunk, face and elbow, (85.7%, 75% and 70%, respectively.

Efficacy of topical pimecrolimus 1% in patients with vitiligo compared with clobetasol

Study design	N	Study Duration	Treatment regimen	Results	Ref
Comparative, single blinded trial	52	6 months	1% pimecrolimus twice daily vs. 0.05% clobetasol cream	Topical 1% pimecrolimus was as effective as clobetasol but more preferred due to lower side effects	Sharquie KE et al Journal of Cosmetics, Dermatological Sciences and Applications, 2015, 5, 107-115.

Cohort Characteristics

Males	Females	Age	Disease duration	Total numbers of lesions
22 (42.3%)	30 (57.7%)	3-40 years	6-84 months	144 (mean 2.2 lesions per patient)

Location of vitiliginous patches: Face 42.1%, Lower limbs 30.7%

Study Allocation & Outcome

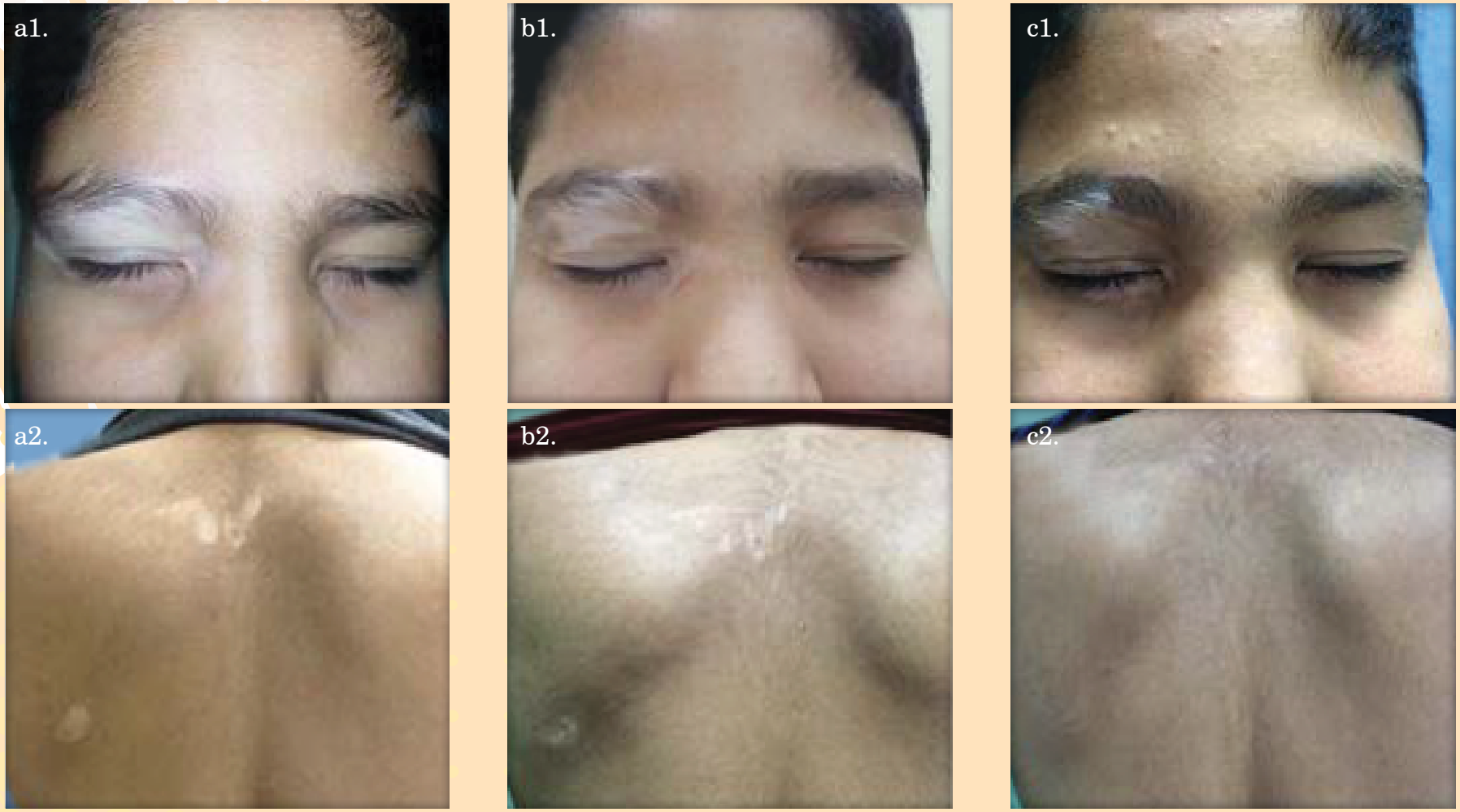
Group A (n=25, 52 lesions) treated with 1% pimecrolimus cream, bid	Group B (n=27, 62 lesions) treated with 0.05% clobetasol propionate cream, bid

Reduction in surface area of vitiligo after 6 months of treatment

Groups	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit	P value
Group A	18.91%	22.70%	35.65%	54.38%	68.86%	79.67%	0.263
Group B	19.29%	24.97%	36.48%	55.26%	70.18%	82.59%	**NOT SIGNIFICANT**

After 6 months of treatment there was 79.67% reduction in the surface area of lesions in ***Group A***, while in ***Group B*** there was 82.59% reduction in the surface area. ***There were no statistically significant differences between the two groups.***

Topical 1% pimecrolimus was as effective as 0.05% clobetasol propionate in treatment of localized vitiligo. Pimecrolimus was preferred to clobetasol due to lesser incidence of adverse effects.



Twelve-year-old male patient with history of localized vitiligo for 4 years treated by Pimecrolimus cream. Lesions (a1, a2) at baseline visit; (b1, b2) after 3 months and (c1, c2) after 6 months.

Combination of 308-nm excimer laser with topical 1% pimecrolimus for the treatment of vitiligo

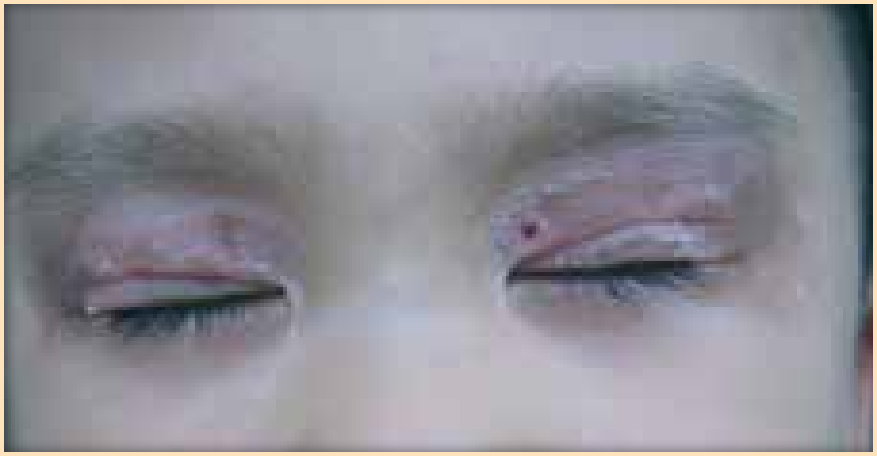
Study design	N	Study Duration	Treatment regimen	Results	Ref
Single blinded, randomized trial	48	30 weeks	**Group A**: 308-nm excimer laser therapy + topical 1% pimecrolimus cream twice daily. **Group B**: 308-nm excimer laser therapy only	Combination of topical 1% pimecrolimus and excimer laser is statistically better than excimer laser alone	Lan HY et al, Pediatr Dermatol. 2009;26(3):354-6.

Results of two treatment groups after 30 treatment sessions

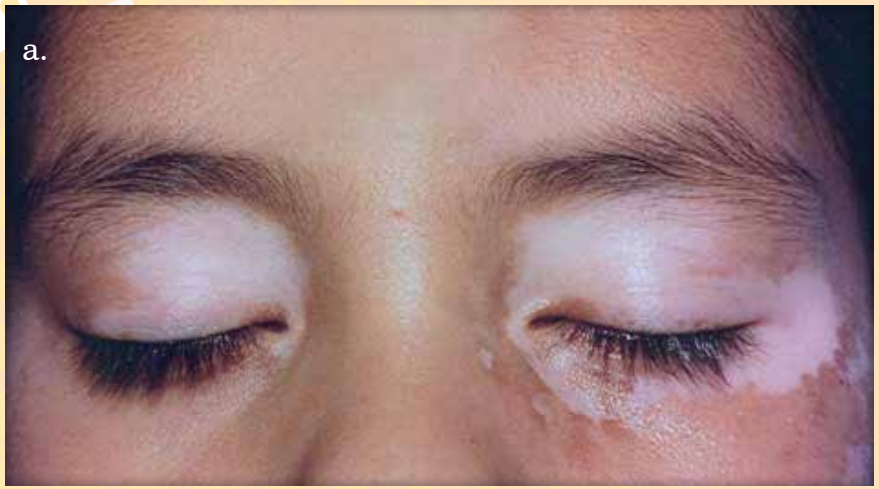
Study design	15th treatment session		30th treatment session	
	Group A	Group B	Group A	Group B
Grade 4 repimentation, n (%)	1 (2.1)	1 (2.1)	21 (43.75)	13 (27.1)
Grade 3 repimentation, n (%)	8 (18.8)	6 (12.3)	13 (27.1)	16 (33.3)
Grade 2 repimentation, n (%)	17 (35.4)	12 (25)	6 (12.5)	9 (18.75)
Grade 1 repimentation, n (%)	19 (39.6)	26 (54.2)	6 (12.5)	10 (20.8)
Mean cumulative dose (mJ / cm^2)			8,484.78	8,134.13
Treatment to Achieve Grade 4 Repimentation, *n*			27.1	25.4
Treatment to Achieve Grade 1 Repimentation, *n*			9.3	10

Grade 4 repimentation: ≤75% improvement, Grade 3: 51% to 75% improvement, Grade 2: 26% to 50% improvement, Grade 1: ≥25% improvement. No statistically significant difference of efficacy between the two groups at the way of mean cumulative dose ($t = 0.149$, $p = 0.085$).

Before treatment (308-nm laser plus pimecrolimus was applied on the right side, 308-nm laser was applied on the left side).



After 30 treatment sessions, vitiligo on the left had Grade 4 repigmentation, whereas the vitiligo on the right side had Grade 3 repigmentation.



(a), Vitiligo depigmentation is apparent on the brows and lids of this patient before treatment. (b) The condition is much improved after 30 treatment sessions.

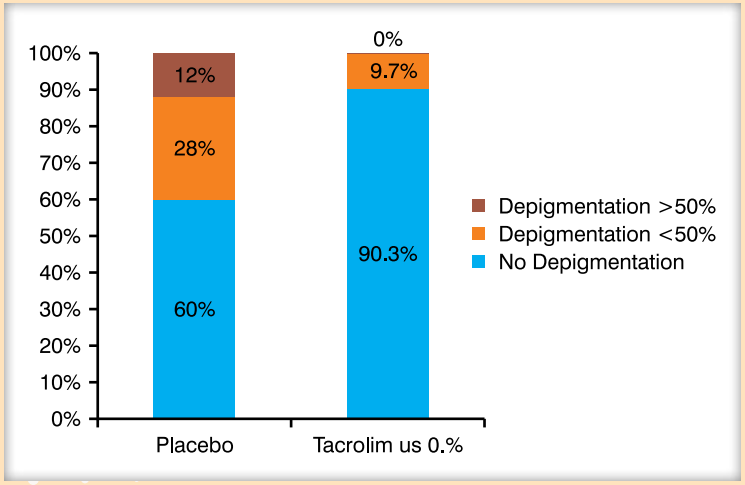
Maintenance therapy of adult vitiligo with topical 1% pimecrolimus in previously successfully repigmented patients

Study design	N	Study Duration	Treatment regimen	Results	Ref
Randomized, Double Blind, Placebo–Controlled Study	35	30 weeks	16 patients with 31 patches assigned to placebo and 19 with 41 patches assigned to topical 1% pimecrolimus	Maintenance with topical 1% pimecrolimus can reduce recurrences of previously repigmented vitiligo lesions	Cavalie M et al Journal of Investigative Dermatology (2015) 135, 970–974.

Cohort Characteristics

Study design	Placebo group (n=16)		Tacrolimus 0.1% group (n=19)	
	n	%	n	%
Sex	16		19	
Male Female	10 6	62.5 37.5	11 8	57.9 42.1
Age (years) median (interquartile range)	16	43.0 (38.0–46.5)	19	44.0 (33.0–52.0)
Age at diagnosis	16	32.8 (17.0–40.8)	19	32.4 (25.2–43.2)
Previous repigmentation episodes, n (%)	16	62.5	10	52.6
Type of repigmentation				
Marginal Perifollicular Both	6 7 3	37.5 43.8 18.7	6 7 6	31.6 36.8 31.6
Koebner's phenomenon	6	37.5	6	31.6

Topical 1% Pimecrolimus prevents depigmentation of vitiligo



40.0% of lesions showed some depigmentation in the placebo group, whereas only 9.7% did in the 1% pimecrolimus group (P=0.0075). Depigmentation superior to 50% was observed in 12% of the lesions in the placebo group and 0% in the 1% pimecrolimus group.

Labial vitiligo associated with a factice disorder treated with topical 1% pimecrolimus cream

A 17-year-old young woman, with no previous medical and surgical history, was consulted for labial depigmentation. Initially, the lesion affected the left part of the upper lip for which she was recommended treatment with vitamin C and folic acid. This treatment was continued for a month without any noticeable result. Subsequently, the lesion had spread to the entire upper lip with lesions on the left labial commissure and the skin facing the lip. Patient revealed that she chronically bit her lips.

Examination of the oral mucosa revealed a linear depigmentation of the vermilion border of the upper lip with peripheral pigment enhancement. Examination of the skin revealed a centimeter-sized depigmented area of the ring finger of her right hand. Laboratory evaluations for thyroid stimulating hormone, anti-thyroglobulin, and antithyroperoxidase antibodies showed no anomalies.

Based on the clinical profile, treatment with twice daily local application of 1% pimercrolimus was prescribed and patient advised to discontinue the lip-biting habit. Protection from the sun was also advocated.

Lip depigmentation

Cutaneous depigmentation

Fricain M et al, J Oral Med Oral Surg 2018;24:167-169.

Vitiligo has been recognized and feared over centuries. Even though modern treatment represents a vast improvement from ancient herbal techniques, eradication of vitiligo continuous to be fraught with challenges. Undoubtedly, humanity has much to learn, both from the sociologic and medical impact of vitiligo, if we are to progress in managing this ancient disease in the modern world.

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