International Journal of Research in Dermatology
Wang V et al. Int J Res Dermatol. 2026 Jan;12(1):119-124
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20254135

Review Article

Updates in paleodermatology: revisiting ancient skin disease through modern lenses

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Received: 26 September 2025
Accepted: 15 November 2025

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ABSTRACT

Paleodermatology is the study of ancient skin diseases via preserved human remains. This review builds upon Dr. Eve Lowenstein's foundational 2004 work on paleodermatoses, summarizing new discoveries, techniques, and insights gained about infectious disease, neoplasms, and tattoos over the past twenty years. This review also addresses the controversial identification of melanoma in ancient Incan remains. Much of what has been analyzed about past skin conditions have been misconceptions based upon our modern biases and assumptions, so we highlight these cases as well as provide new analyses. This provides insight into not only historical epidemics and lifestyles, but also the relationship between modern disease and our environments.

Keywords: Paleodermatology, Paleopathology, Mummies, Pseudopathology, History

INTRODUCTION

Paleodermatology is the study of ancient skin diseases through the examination of preserved human remains.[1] It provides valuable insights into the evolution of various dermatological conditions, including infectious, heritable, nutritional, hormonal, acquired, iatrogenic, and neoplastic disorders. This paper updates Dr. Eve Lowenstein's 2004 work on paleodermatology in 2004.[1] Our goal is to highlight discoveries and lessons learned over the subsequent twenty years from the publishing of her work. Paleodermatology has previously been defined by some as anything skin related prior to the advent of hydrocortisone.[1] Lowenstein preferred the definition offered by Sir Marc Ruffer, the "father of modern paleopathology": "Paleodermatology is the study of the integument and associated diseases as demonstrated in the remains of former times".[2] We focus on pre-industrial revolution findings to add to arguments for, and against, modernity and post industrial revolution lifestyles in skin conditions.

METHODS

A literature search was conducted on PubMed using the terms "paleodermatology," and "mummy skin disease" yielding 69 results. After excluding sources prior to 2005, 49 results remained. These were then narrowed to papers updating prior misconceptions or addressing novel topics, yielding nine papers. Commonly cited literature and specific cases from Lowenstein's article regarding history of paleodermatology were also included.

HISTORY OF TECHNIQUES

Sir Marc Armand Ruffer (1859-1917) made significant contributions to paleodermatology through his pioneering work on mummified tissues. While working in Egypt, he developed a softening fluid that revolutionized the rehydration of brittle mummy tissues, enabling detailed histological studies of ancient remains.[3]

Paleodermatology faces many challenges, such as misinterpretation of pseudopathology and the sparse

evidence for many skin diseases. Commonplace findings such as rope marks, post-mortem infections, and rodent infestations can be mistaken for pathological lesions.[4] In paleodermatology an ulcus rodens (rodent ulcer: the original proposed name of basal cell carcinoma), may indeed be just that–an ulcer from chewing rodents.[5] Modern biases can also affect interpretation, such as the portrayal of Ötzi the IceMan along the Austro-Italian border, who was traditionally believed to have had light skin given the geographical area where his body was recovered. But in a 2023 study, he was confirmed to have had darker skin.[6] Evidence for inflammatory diseases like eczema or psoriasis is also rare due to the difficulty in preserving specific histological features.[1]

Histological findings in mummified tissues have shown remarkable preservation of various skin structures. Predictably, the numerous types of collagen are often well preserved and abundant due to their lasting structural integrity. The preservation of nuclei, pigmentation, and skin structures such as the stratum corneum, keratinocytes, and pilosebaceous units is common.[7,8] Electron microscopy has revealed well-preserved collagen fibrils, elastic fibers, and chromatin density in mummified tissues.

Confirmatory evidence for skin conditions in ancient remains is quite limited. And distinguishing among skin diseases in ancient times remains challenging due to the potential for pseudopathology and the limitations of preservation techniques.[1]

INFECTIOUS DISEASES

Since Lowenstein's publication regarding paleodermatoses, the mummies of Arezzo in Tuscany have been further studied. Of these sixteenth century Renaissance mummies, Maria d'Aragona (1503-1568) sheds light on sexually transmitted diseases. Researchers noted a pedunculated skin tumor affecting the paravulvar region that revealed a thickened epidermis and dilated vessels. The presence of HPV type 18, an oncogenic strain, was confirmed. Additionally, a 15×10 mm cutaneous ulcer of her left arm was found to be most consistent with a third-stage luetic gumma of syphilis. This early example of syphilis may help clarify the historic epidemic phase of the infectious disease, as her case occurred roughly a mere 50-75 years after its eruption in Europe. Her body also showed edema of the left leg believed to be lymphogenic metastases from metastatic vulvar cancer, her possible cause of death.[9]

Among the Arezzo mummies there is also a 2-year-old boy who presented with a diffuse vesiculo-pustular eruption. Light microscopy and indirect immunofluorescence with anti-vaccina virus antibody revealed this child died of a severe form of smallpox. Results and antigenic structure of the viral particles were confirmed with protein A-gold.[10]

The shared ancestral lineage of the smallpox virus (variola virus, VARV) has been traced back to approximately 1580 AD, suggesting that the strains circulating during the 20th-century eradication efforts stemmed from a common ancestor in the late 16th century.[11] A 2016 study by Duggan et al emphasized that these lineages emerged during a period of rapid human migration, population growth, and widespread inoculation and vaccination efforts, stating that "the VARV lineages eradicated during the 20th century had only been in existence for ~200 years." Earlier cases of smallpox attributed to VARV may have involved lineages that were no longer in circulation by the 1970s.[12]

The potential risk of re-exposure to smallpox from ancient remains has raised concerns about the viability of ancient pathogens. Although smallpox scabs may remain viable for up to 13 years, studies on mummies over 100 years old have consistently indicated nonviable virus.[13]

NEOPLASTIC EVIDENCE

Ancient evidence of skin cancers is often cited; however, they require closer examination. Many articles contend they are first mentioned in ancient Egyptian papyri from 2500 BCE.[14] Hippocrates wrote of ulcerative and non-ulcerative tumors that he coined as carcinos, or crab-like.[15] Literature, religious texts, and art also are often cited as examples of various cancers or dermatoses. However, without definitive pathology, all of this "evidence" is potentially specious. While Laennec, Jacob, and Bowen are historically credited with the first descriptions of melanoma (1804), basal cell carcinoma (1827), and squamous cell carcinoma in situ (1912) respectively, these tumors have likely existed far into antiquity.[16-18] Identifying histological evidence of how ancient, or not, these tumors are a goal of paleodermatology. Neoplastic tissue in mummified remains are scant and limited to, arguably, 15 cases ranging from true malignancies to calcified benign tumors.[9]

The emergence of artificial intelligence (AI) has further complicated research into the subject, as it often conjures its answers from a bulk of incorrect findings that have been simply copy and pasted into decades of papers. The best example of this is a report in Cancer from 1966, which claimed that nine grouped Incan mummies demonstrated "diffuse metastases to bone" from melanoma of unknown primary foci.[19] This claim has been widely cited without the deserved scrutiny. The isolation of nine mummies with malignant melanoma in such a concentrated context alone raises significant doubts. Lowenstein expressed skepticism in her 2004 paper as the current location of the bones is not known and cannot be subjected to study.[1] In 2006, Rothschild and Martin outright rejected the diagnosis of melanoma in a review of the 1966 paper; attributing the dubious diagnosis to postmortem changes, likely fungal, and a reminder that standards are higher for publication today".[20] In 2016, Mark reviewed six photographs from the original article and also concluded the young age of one of the individuals, as well as the size and locations of the lesions do not suggest melanoma.[21] Despite

Hippocrates' writings regarding various black entities, the first solid evidence we have for melanoma is a specimen from 1787. At that time, surgeon John Hunter excised and preserved a mass from the jaw of a male and in the late 1960's researchers established it was melanoma.[22] This specimen is still on display in the Hunterian Museum at the Royal College of Surgeons of England in London (Figure 1).[23] Nevertheless, the tale of the Incan mummies has so widely populated the literature that it is conflated as being factual. At the time of this writing, numerous AI search engines will offer it as an answer. As discussed previously, it appears melanocytes themselves are more subject to degradation over time as the earliest known melanocyte is from the Greenland mummies a mere 500 years ago. It will likely be proteinomic or genetic data that will eventually push back our timeline for melanoma.

Figure 1: Melanoma from jaw mass excised by John Hunter in 1787, on display at the Hunterian Museum at the British Royal College of Surgeons in London.

The earliest histologic evidence of basal cell carcinoma is from the body of Ferdinando Orsini, Duke of Gravina. Having passed away in 1549, there was a wide erosion of the upper orbital margin and glabella and complete destruction of the retro-orbital bones. Staining strongly with pancytokeratin, there were palisading and clefting chords of basaloid cells invading compact and spongy bone.[24] The southern Italian sun likely played a role in this pathology. Two Egyptian skeletons from the dynastic period, and believed to be brothers, demonstrate the candidates for basal cell nevus syndrome. Bifid ribs, mandibular cysts, shortening of the 4th metacarpals, and fusion anomalies of the sacrum noted on the bodies support this diagnosis. Unfortunately, no cutaneous structures were intact or were not noted in the report.[25]

The paleodermatological trail for squamous cell carcinoma is scant. The first clinical description of squamous cell carcinoma was by Sir Percivall Pott in 1775. He identified a link between scrotal cancer and chimney sweeps' exposure to soot, marking the first documented instance of occupational cancer.[26] There are no paleoncological records of squamous cell carcinoma before this instance.

From the Cabuza culture (300-600 AD) in Chile, there is an example of a facial rhabdomyosarcoma. The skull of a 12-18-month male child demonstrates a 5×2 cm hard mass that resulted in closure of the eye. It is preserved to the extent that nuclear material is observable.[27] It is curious that examples of squamous cell carcinomas are lacking given the high prevalence of these today while a rare tumor such as a rhabomyosarcoma is recorded. There are also cases of lipomas, fibrous histiocytomas, verruca, and other benign findings that Lowenstein covers, as well as, mentioning the dubious nature of reports of many others.[4]

MUMMIES OF INTEREST TO THE DERMATOLOGIST (ADDENDUM TO LOWENSTEIN 2004)

Since Lowenstein's original article in 2004, numerous mummies of dermatological interest have been reported. Perhaps no mummy has excited pathologists more than the Tylorean IceMan, nicknamed Otzi. Accidently discovered by hikers in 1991 along the Austro-Italian border, he is the oldest, most complete intact human body, dating to approximately 5,300 years ago. Otzi had three Beau's lines that represented unknown physiological stress that corresponded to around 16, 13, and 8 weeks prior to death.[28] Literature regarding the nails of mummies is quite scant, with only another article describing Mee's lines secondary to arsenic poisoning.[29] Genetic material from Lyme causing bacteria *Borrelia burgdorferi* was also isolated from Otzi.[30] It is unknown if he actually suffered from Lyme disease but this does make him the first known carrier of the bacteria in history.[31] Until researchers compare his sample with the modern strain there will not be a clear story of how Lymes has evolved.

The first female ruler of ancient Egypt, Pharaoh Hatshepsut, reigned from 1479-1458 BCE. A small flask of what had been believed to have been her perfume was re-examined at the University of Bonn in 2009. It was revealed to have been a skin cream containing palm oil, apple nutmeg oil, unsaturated fats, and various hydrocarbons derived from creosote. The researchers hypothesised that this was used to treat dermatoses, as skin problems were known to exist in her family.[32] This flask of Pharaoh Hatshepsut demonstrates the need to interrogate previously held beliefs in archeology, as her female sex may have led earlier researchers to assume it was a perfume. Another Egyptian female mummy, from 3,500 years ago) has been found to have exogenous ochronosis that was confirmed by confocal and electron microscopy. Although ultimately unknowable, researchers believe it likely the result of heavy cosmetic usage containing lead or mercury.[33]

In 2003, two male bog bodies from Ireland were recovered from separate bogs by peat cutters that dated from 400-175 BCE. As expected for bog bodies, the skin was stained tea-colored but both were subjected to a 'spectacular variety

of depredations', including the amputation of the nipples.[34,35] Eamonn Kelly, an expert in Irish archeology, proposes that these Celtic bodies were those of kings who had failed their subjects by not providing milk and cereals. The king would enter into a ceremonial marriage with a goddess of fertility and of the land itself. Kelly points out that St. Patrick reported sucking of the king's nipples as a rite of fealty; so no nipples meant no crown, either here or in the afterlife.[36]

TATTOOS OF ANTIQUITY

Humans on every continent have been tattooing their skin since time immemorial, however when Lowenstein first published her article in 2004, no tattoos were known to exist on Egyptian mummies. It is now recognized that tattooing was likely commonplace in antiquity across all societies on earth.[37]

Tools believed to have been used in tattooing date back to the Paleolithic Era.[38] Obsidian tools (Solomon Islands, 3,000 years old), Turkey bones (Tennessee, USA, 5,000 years old), shark teeth, and even bird and human bones (Tonga, circa 2,500 years old) are some of the more notable.[39-41] A site in Grotte du Mas-d'Azil, France produced possible tattoo tools dating back 12,000 years. Archaeologists have discovered two probable tattoo kits from ancient Egypt: the Abydos kit (3,000 BCE) and the Gurob kit (1,450 BCE), made of metal points with wooden handles and bronze needles respectively.[42]

The oldest tattoos are from the body of Otzi which held 61 charcoal dermal deposits in curious patterns that many have speculated represent an early form of acupuncture, although the true purpose cannot be known.[37] Another example of tattooing was in the Chancay culture in Peru, where over 100 mummies had tattoos.[43]

Ancient tattoos still influence the choices people seeking designs make today. The "Mark of Otzi" has been tattooed on the actor Brad Pitt and others. The Siberian Ice Maiden (circa 2,500 years old), from Scythian culture, has inspired people today to recreate her ornate deer tattoo that incorporates elements of ice crystals and frost.[44]

It is difficult to know how prevalent tattoos were in ancient cultures. Traditionally, researchers have not either noticed or known how to look for tattoos. Despite the centuries of study around Egyptian mummies, relatively few tattoos had been discovered. In 2014, archaeologist Anne Austin simply attached an infrared camera to an iPad at the Deir el-Medina site, near the Valley of Kings. She immediately discovered 30 tattoos that were not visible to the naked eye.[45] Since then, infrared examination has revealed tattoos dating back approximately 5,000 years in Egypt, almost rivaling the date of Otzi's.[46] The fact that these tattoos have been literally right under the noses of archeologists for hundreds of years is humbling and a reminder that lessons from mummified skin are still to be learned.

FUTURE OF PALEODERMATOLOGY

The future of paleodermatology lies in molecular studies such as proteomics. In 2016, Jones et al, analyzed skin and muscle tissue from three 4,200-year-old mummies using high-resolution liquid chromatography-mass spectrometry (LC-MS). They identified over 230 unique proteins, including large amounts of collagen, confirmed by scanning electron microscopy.[47]

The protein profiles of Khepeshet, a female included neutrophil-associated proteins that indicate tissue inflammation and a severe immune response to infection at death, likely from a bacterial pulmonary infection.[47] This is further supported by the identification of proteins indicative of innate immune system activation and severe tissue inflammation. Hydroxyproline cross-linking, which contributes to the longevity of the tissue, was noted in the collagen. SEM images revealed the preservation of skin structures, including collagen fibrils and elastic fibers, despite some unraveling of the lattice arrangement.[47]

These findings highlight the potential of proteomics in uncovering ancient immune responses and infections. However, no studies have yet investigated tumor necrosis factor, interleukins, or other mediators for conditions like psoriasis or atopic dermatitis. The absence of such definitive evidence underscores the challenges in diagnosing specific skin diseases in ancient remains and illustrates the massive potential of proteomics for the future of paleodermatology.[1,47]

CONCLUSION

Since Lowenstein published her original article on paleodermatoses in 2004, there have been advances in our understanding of a wide range of dermatological issues from antiquity. The paucity of cases for inflammatory disease and malignant neoplasms is particularly vexing. The introduction of proteomics will hopefully shed more light on these subjects. Researchers should also not be reluctant to reexamine previously known facts, as our modern culture biases have led to misunderstanding of the evidence in cases.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Wang V, Adams D. Updates in paleodermatology: revisiting ancient skin disease through modern lenses. Int J Res Dermatol 2026;12:119-24.