Hereditary Palmoplantar Keratoderma and Dermatophytosis in the Northernmost County of Sweden (Norrbotten)

by

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ABSTRACT

Clinical reports of hereditary palmoplantar keratoderma are generally based on a limited number of patients. In 1967 the prevalence in the northernmost county of Sweden (Norrbotten) was shown to be 0.55%. In 1982 it was possible to trace half of the original propositi from that study. Among these families, a severe clinical form with a presumed recessive inheritance could be distinguished. The clinical pictures in relatives of the original propositi were described, and other diseases were listed together with those in patients from previously performed studies.

The frequency of dermatophytosis was 36.2%, which was equal to a prevalence of 37.6%. *T. mentagrophytes* occurred significantly more often and immunological factors, such as increased presence of blood group A, specific dermatophyte IgG antibodies, precipitating antibodies and an immunological in vitro reaction to keratin, supported differences in the distribution of dermatophytes. However, the amount of keratin was considered the most important factor for the affinity of dermatophytes to the palms and soles.

A vesicular eruption along the hyperkeratotic border and a mononuclear cell infiltrate were often reported. Such reactions were interpreted as immunological reactions to dermatophytosis. Scaling and fissuring were considered clinical signs of dermatophyte infections and not a part of the originally reported clinical picture.

Results of the histopathological study corresponded to previously reported descriptions of the Unna-Thost variety. However, it has recently been reported that the histopathological picture of this variety was based on histopathological features of epidermolytic palmoplantar keratoderma. The existence on the Continent of the Unna-Thost variety was therefore questioned. Histopathological features of epidermolytic palmoplantar keratoderma were not found in the County of Norrbotten and the designation "Diffuse HPPK type Norrbotten" has therefore been proposed.

The histopathological picture of the presumed recessive variety did not differ from that of the dominant variety but ultrastructural characteristics differentiated it from Mal de Meleda and the dominant variety. It was therefore concluded that a new variety with a presumed recessive inheritance was found.

Key words: Hereditary palmoplantar keratoderma; dominant; presumed recessive; dermatophytosis; histopathology.

This thesis is based on the following publications, which will be referred to by their Roman numerals:

I.   Gamborg Nielsen P. Hereditary palmoplantar keratoderma in the northernmost county of Sweden. *Acta Derm Venereol (Stockh) 1985; 65: 224-229.*

II.   Gamborg Nielsen P. Immunological aspects of dermatophyte infections in hereditary palmoplantar keratoderma. *Acta Derm Venereol (Stockh) 1984; 64: 296-301.*

III. Gamborg Nielsen P, Faergemann J. Dermatophytes and keratin in patients with hereditary palmoplantar keratoderma. A mycological study. *Acta Derm Venereol (Stockh) 1993; 73: 416-418.*

IV. Gamborg Nielsen P, Hofer PÅ, Lagerholm B. The dominant form of hereditary palmoplantar keratoderma in the northernmost county of Sweden. *Dermatology 1994; 188: 188-193.*

V.   Gamborg Nielsen P, Mölne L. A comparative histopathological examination of biopsies from patients with either the dominant or the Gamborg Nielsen type of hereditary palmoplantar keratoderma. *Dermatology 1994; 188: 333-334.*

VI. Kastl I, Anton-Lamprecht I, Gamborg Nielsen P. Hereditary palmoplantar keratosis of the Gamborg Nielsen type. Clinical and ultrastructural characteristics of a new type of autosomal recessive palmoplantar keratosis. *Arch Dermatol Res 1990; 282: 363-370.*

VII. Gamborg Nielsen P, Brändström A. Adoption of a demographic data base for family studies of palmoplantar keratoderma of the Gamborg Nielsen type. *Dermatology 1994; 188: 194-199.*

CONTENTS

RESULTS contd

Dedicated to the memory of

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ABBREVIATIONS

HPPK	Hereditary palmoplantar keratoderma
PPK	Palmoplantar keratoderma
TR	T. rubrum / Trichophyton rubrum
TM	T. mentagrophytes / Trichophyton mentagrophytes
EF	E. floccosum / Epidermophyton floccosum
H&E	Hematoxylin & eosin
PAS	Periodic acid Schiff

NOMENCLATURE

The nomenclature of the different keratinization disorders has unfortunately not attained uniformity during the last century and the synonymous names in this study and in the reference literature should therefore be mentioned:

1. TYLOSIS. Descriptive term, generally used for the description of increased keratinization in eczema of the palms and soles. Occasionally used in older literature for the description of diffuse palmoplantar keratoderma.
2. KERATOMA. A description of isolated or solitary hyperkeratosis. However, also used in older descriptions of diffuse palmoplantar keratoderma.
3. KERATOSIS. Generally found in older literature in connection with keratosis palmo-plantaris.
4. KERATODERMIA. Latin nomenclature found only in keratodermia palmaris et plantaris.
5. PALMO-PLANTAR KERATOSIS. Generally used together with descriptive terms such as diffuse palmo-plantar keratoderma or punctate palmo-plantar keratoderma.
6. PALMO-PLANTAR HYPERKERATOSIS. As above.
7. PALMOPLANTAR KERATOSIS. As above.
8. KERATODERMA. Generally used descriptive term in modern literature.
9. HEREDITARY PALMOPLANTAR KERATODERMA. A designation, which has gained ground during the last decades, to differentiate between the acquired and the inherited keratinization disorders.

GENERAL INTRODUCTION

Definition

The palmoplantar keratodermas are heterogeneous groups of inherited or acquired keratinization disorders with different modes of inheritance, clinical features and micromorphological characteristics, generally confined to the palms and soles.

During the past century, these keratinization disorders have been grouped according to their clinical features, modes of inheritance, histopathological characteristics or biochemical defects. This inevitably resulted in much confusion about their classification. Although some have a distinctive appearance and mode of inheritance, considerable variations have been reported to exist among the individual families and inherited forms. Such variations involve both severity and age of onset. Transitional cases are often encountered and not infrequently impossible to classify at present (1).

History

Although Stullie (1828), in a letter, reported Mal de Meleda as a lepra variety, located to the Isle of Mljet in Dalmatia, the first detailed description of HPPK appeared in the dissertation: "Über erbliche Ichthyosis palmaris et plantaris cornea" by A. Thost in 1880 (2, 3). Three years later P.G. Unna clearly separated the clinical picture of HPPK from a localised form of ichthyosis, with which it had been connected (4). He stressed that HPPK was a separate disease not belonging to other keratinization disorders in 1883 in his fundamental paper: "Über das Keratoma palmare et plantare hereditarium appeared" (5, 6). In 1921 the Unna-Thost variety was included among the genodermatoses, which was further confirmed in 1922 and 1924 (7, 8, 9). The geneology of the Unna-Thost variety was considered to be a classical example of dominant inheritance.

In 1898 Mal de Meleda was no longer considered a form of lepra, and owing to the resemblance to the variety described by Unna and Thost, included among the HPPKs. Mal de Meleda was at that time considered to have an irregular dominant inheritance. However, during the succeeding years, an autosomal recessive mode of inheritance was confirmed.

In 1901 Vörner described the histopathological findings which are now designated epidermolytic PPK. It was found in one member of a family suffering from the Unna-Thost variety (10, 11). In 1970 his histopathological description was confirmed by others (12, 13, 14).

Buschke and Fischer, in 1910, described a variety of HPPK with punctate or macular keratosis, which was named Punctate PPK, Buschke-Fischer (15, 16, 17). Brauer, Brunauer and Fuhs reported a similar variety and during the following decades

it was also named keratodermia hereditarium dissipatum palmare et plantare. However, in modern literature this type is generally named punctate PPK.

In 1924 the keratosis of Papillon-Lefevre appeared in the dermatolgical literature and the same year a new variety with striate or areate hyperkeratosis was reported also by Brünauer and Fuhs, although it is generally known as striate PPK, Siemens (18, 19, 20, 21). In 1924 Vohwinkel also described a remarkable form of keratoderma with constricting hyperkeratotic bands resulting in strangulation of distal phalanges of the digits. This phenomenon is also called Ainhum constriction (22, 23).

Richner and Hanhart described a new syndrome with HPPK and tyrosinaemia in 1947 and Greither a transgredient or progredient variety in 1952 (24, 25, 26, 27).

During the twenties several attempts were made to classify the PPKs. For this purpose, three main properties were taken into account: 1/ clinical; 2/ morphological; and 3/ genetic (28, 29, 30, 31). The clinical and morphological classification included three different groups with characteristic clinical features and, with a few exceptions, significant histopathological findings: 1/ diffuse HPPK; 2/ punctate or striate PPK; and 3/ disseminated HPPK (32, 33). As clinically similar HPPKs have been proved to possess either a dominant or a recessive mode of inheritance, it was considered necessary to adopt genetic principles for correct classification. For biological reasons and for the purpose of genetic counseling, it was also considered important that all inherited diseases should be classified according to this principle.

In the thirties and fourties, extensive efforts were therefore made to classify the HPPKs according to genetic principles. However, it was not possible without constraint to arrange them in a genetic system. Classification according to their macro- and micromorphology presented similar difficulties.

The micromorphology appeared to be the same for most of the keratodermas and often indistinguishable from each other. It was therefore considered necessary to adopt a genetic as well as a clinical and morphological type of classification. The first attempt to classify the HPPKs according to genetic principles with assistance of clinical characteristics was published in 1953 by Kogoj (30).

Even though clinical and morphological principles were taken into account for disorders with unknown inheritance, it was not possible to arrange them in a classification based only on one of these principles. It was especially important on a genetic basis to separate the Unna-Thost variety from Mal de Meleda, as it is often impossible to distinguish these two forms in early childhood.

Franceschetti and Schnyder published in 1960 a consistent classification based on mode of inheritance, clinical features and histopathological findings (34). This classification is still used in dermatological literature but most often with modifications and simplifications. However, classifications based on clinical and morphological principles seem also to have been established in the literature (1). A genetic classification based on the principles of Franceschetti and Schnyder with support of a modern clinical and morphological classification is shown in Table I. With a large group of genetically determined diseases, it is not suprising that many other diseases affecting patients with HPPK have been reported, especially from areas with a high

Table I. Classification of hereditary palmoplantar keratoderma based on the original genetic principles published by Franschetti and Schnyder in 1960, commented on by Rook, Wilkinson and Ebling: Textbook of Dermatology, p 1370-1371, Vol. 2, 5th ed., 1992.

AUTOSOMAL DOMINANT INHERITANCE

Preferred name	Eponym	Other terms
Diffuse	Thost-Unna	Keratoma palmare et plantare heriditarium
Punctate	Buschke-Fischer	Keratodermia maculosa disseminata palmaris et plantaris
	Brauer Brunauer-Fuhs	Keratodermia hereditarium dissipatum palmare et plantare
Areata/striata/liniaris	Siemens Varians type of Wachters	Keratosis palmoplantaris areata Keratodermie en aires
Transgredient or disease	Greither	Keratosis extremitatum Greithers's hereditaria progrediens. Progressive keratoderma
Mutilating	Vohwinkel	Keratodermia hereditaria mutilans
Epidermolytic hyperkeratosis	Vörner	
Focal acral hyperkeratosis	Acrokeratoelastoidosis de Costa	

AUTOSOMAL RECESSIVE INHERITANCE

Preferred name	Eponym	Other terms
Meleda disease	Mal de Meleda Mljet	
Palmoplantar keratoderma with periodontosis	Papillon-Lefevre	
Oculocutaneous Tyrosinaemia Type II	Richner-Hanhart	
Papuloverrucous	Jakac-Wolf	Polykeratosis of Touraine

prevalence of HPPK. Some are isolated cases and probably fortuitous, but others, which occur repeatedly, may be significant. In older literature such repeatedly occurring diseases often designated as familiar cases have been reported as syndromes and therefore a classification of HPPKs may include a varying number of syndromes.

The acquired keratodermas constitute a special group and are divided into three sub-groups (5). 1/ PPK caused by mechanical, chemical or thermal influences; 2/ PPK caused by infections (Syphilis, Gonorrhoea and Reiter's syndrome) and endocrine disturbances (Keratoderma Climacterum, Haxthausen) (35); 3/ PPK caused by neurological diseases (Peripheral nerve lesions and diseases of the central nervous system, Poliomyelitis, Syringomyelia and Tabes dorsalis).

To make this classification complete, conditions giving rise to associated PPK should be mentioned. Atypical psoriasis of the pustular and arthropathic variety may present hyperkeratosis of the palms and soles. Darier's disease, pityriasis rubra pilaris, lichen planus, contact dermatitis and mycotic infections may demonstrate a complicating hyperkeratosis on the palms and soles of varying intensity (36).

The following sections deal exclusively with the diffuse PPKs. Therefore, it is also considered logical only to discuss the diffuse HPKKs and other diseases affecting these patients in the northernmost county of Sweden (Norrbotten).

Hereditary palmoplantar keratoderma Unna-Thost

In all pedigrees published, it has been proved that HPPK of the Unna-Thost variety possesses an autosomal dominant inheritance with high penetrance. In 1921 it was included among the genodermatoses and the enumeration was repeatedly confirmed in the literature during the succeeding years (37, 38). Specific HLA linkage has not been found (39).

Histopathology. The histopathological picture is, according to most dermato-pathologists, non-specific. Orthohyperkeratosis associated with hypergranulosis and moderate acanthosis is generally the only constant findings (40, 41). A mild perivascular infiltrate is also usually found. Older descriptions of the histopathology have not increased our knowledge of the disorder, even though they were meticulously performed.

Prevalence. HPPK of the Unna-Thost variety occurs in all races. The prevalence most often quoted is that of Northern Ireland of 1:40,000 (42). The prevalence in Slovenia (Yogoslavia) has been estimated to be 1:12,000 (39). In isolated provinces and in admission areas for dermatological departments, the prevalence may be much higher than that of countries or larger areas with a high population density. In 1938 it was 0.0113 per cent in Zurich (43) and in 1980 it was 0.3 per cent in the county of Västerbotten, Sweden (44).

Clinical picture. According to the description published by A. Thost in his thesis, the onset of the keratinisation disorder was insidious and progressive through the first three postnatal months. During the following months, a narrow purple zone develops towards normal skin. The hyperkeratosis starts in the periphery and propagates towards the

11

centre of the palms and soles. This initial course has essentially been confirmed by others. With increasing age, it becomes thicker, until it occupies the entire affected surface. The disease is generally completely developed at the age of 14-16 years. Hyperkeratosis is diffuse, smooth and uniform and strictly limited to palmar and plantar surfaces. The sharply demarcated margin towards normal skin may be surrounded by a band of erythema. About two thirds of the cases appear before the age of 2 years and the remaining third at varying ages (5). Extension of lesions to other parts of the skin may be found.

Two distinct clinical forms of HPPK of the Unna-Thost variety were reported in 1967 (45). The first is a rough-surfaced form, which is often characterised by fissuring and deepening of the major palmar and plantar creases. An exudate is often found together with such fissures. The second is a smooth-surfaced form, which lacks fissuring, but characterised by a yellow colour intermixed with black discolourations.

Hyperhidrosis of the palms and soles is the most common accompanying symptom, but it usually decreases after 50 years of age. Despite the thickness of the horny layer, sensibility is completely normal (45). The thickening persists throughout life, but spontaneous remissions have been reported (36). Variations of the clinical picture may be seen, depending on local traumata or secondary infections.

Other diseases

An increasing number of case reports and family reports have been published about other diseases in HPPK of the Unna-Thost variety. Such reports depend on the frequency of the keratoderma and the prevalence of other acquired or inherited diseases and inbreeding of the population. Sporadic and familial other diseases features are listed in Table II (46-77).

Mal de Meleda

In the past, several authors have included Mal de Meleda with the Unna-Thost variety and have used these two terms synonymously. However, during the last half century an increasing number of reports have appeared indicating a recessive trait.

Clinical picture. The age and mode of onset does not differ from that of the Unna-Thost variety, but hyperkeratosis is much more impressive, with extension to the dorsal aspects of the hands and feet. On the feet, it may extend to the Achilles tendon and extrapalmar and plantar lesions are common clinical findings. Lesions on the knees and elbows are seen in most cases. Hyperkeratosis is most often canary yellow but may be yellowish-green, depending on the thickness. Hyperhidrosis is invariably present.

Table II. Diffuse hereditary palmoplantar keratoderma with dominant inheritance and other accompanying diseases. Ref: Gamborg Nielsen P. Diffuse palmoplantar keratoderma associated with acrocyanosis. Acta Derm Venereol (Stockh) 1989; 69: 156-161 (Table 1).

Sporadic	Familial
SKELETON	
Clinodactyly (47)	Clubbing and skeletal deformity of end
Mutilating palmoplantar	phalanges of hands and feet (67)
keratoderma (48)	
SKIN, HAIR AND NAILS	
Hailey-Hailey disease (49)	Hyperpigmented spots (68)
Ichthyosis vulgaris (50)	Vitiligo (69)
Psoriasis vulgaris (51)	Heliotrichie (54)
Atopic dermatitis (I, 59)	
Darier's disease (52)	
Incontinentia pigmenti (53)	
Alopecia areata (9)	
Heliotrichie (54)	
Hydrocystoma, miliary cysts,	
xanthelasmas, nail and dental	
dystrophies (25)	
Basal cell epitheliomas (25)	
Multiple lipomas (25, 55)	
Knuckle pads, leukonychia and	
deafness (56)	
Onychodystrophy (9)	
EAR AND EYE	
Perceptive hearing loss and atopic	Progressive sensory-neural hearing
dermatitis (57)	loss (70)
Grey cataracht (58, 59)	Deafness (71, 72)
	Corneal dystrophy (73, 74)
MUCOUS MEMBRANES	
Reticular degeneration (60)	Oral leukoplakia (75)
Lip keratosis (61, 62)	Carcinoma of esophagus (76, 77)
Esophageal carcinoma (63)	
MICELLANOUS TYPE	
Charcot-Marie Tooth's disease (64)	Acrocyanosis (46)
Winer's calcinosis (65)	
Spinal myoclonus with dermal and	
retinal changes affected by	
myelitis (66)	

Histopathology. The histopathological changes are mainly confined to the epidermis. Marked acanthosis with rete pegs 4-5 times as long as normal, together with a greatly thickened horny layer, are the most prominent histopathological findings. An insignificantly mononuclear cell infiltrate at the dermo-epidermal junction has been reported from time to time. Sweat glands are usually twice their normal size (78, 79).

Frequency. Outside the isle of Mljet, the frequency of Mal de Meleda is not known. It occurrs so infrequently that studies are meaningless. Cosanguinity in the population of Mljet is high but it is not known if cosanguinity has any direct etiological significance.

Other diseases. Mal de Meleda is a very rare keratinization disorder outside the isle of Mljet and, together with its recessive inheritance, genuine other diseases are few and difficult to assess. A few reports have appeared but the reliability of such reports is doubtful (31, 80).

Genotype and environmental factors

Not only genetic factors seem to be of importance in the etiology of HPPK. Latent constitutional factors and the results of exogenic influences have also proved to affect the clinical picture. From a pathogenic point of view, there seems to be a dual influence of genetic and ecological factors, i.e. latent hereditary factors in co-operation with the environment, which may provoke the onset of the disease. Concerning HPPK, this second factor is considered mechanical. It has been reported that heavy work not only aggravates the clinical picture, but may also influence the onset of the keratinization disorder (32, 81, 82). A similar geno-ecological complex has been demonstrated for other geno-dermatoses, the environmental factors being alimentary, geographic, actinic, metabolic, enzymatic, ionising, terratogenic or toxic. Such factors always influence the disease in predisposed individuals. The type of work and the age at which work has started are therefore of importance in patients with HPPK.

Treatment

The symptomatic treatment of HPPK with warm soap baths, urea creams, salicylic ointments, sodium chloride-containing creams and ointments of different concentrations, salicylic adhesive plaster and manual removal of the horny layer has only proved to have only a transitory palliative effect (83). In 1951 treatment with 100,000-200,000 IU Vitamin A was introduced, but permanent improvement could not be shown (84, 85). High dose Vitamin B12 and treatment with orally administered magnesium were in 1962 added to the list of dubious therapeutic methods (86). X-ray radiation of the palms and soles was introduced in 1967 but without therapeutic effect; on the contrary, secondary side-effects appeared years later (87). Topical application of ointments with retinoic acid was introduced in 1975 with conflicting therapeutic results and gradually replaced by orally administered aromatic retinoids (88, 89, 90). After 2-3 weeks' treatment the thickness of the horny layer of the palms and soles was reduced to that

of normal individuals but normal function of the hands and feet was restricted, due to increased sensitivity and vulnerability (91, 92). Long-term treatment did not reduce these disagreeable symptoms. However, excellent therapeutic results have been observed among the localised keratodermas (93).

Several attempts have been made to treat HPPK with reconstructive surgery. Total excision of hyperkeratotic skin of the palms and soles to the level of palmar and plantar aponeurosis, followed by grafting, has been the principle method used (94, 95). However, plastic surgery has not achieved any significance and therapy of the diffuse PPK's is mainly concentrated to the older procedures, principally salicylic ointments, which unfortunately have little or no effect.

AIMS OF THE STUDY

In previously performed studies of HPPK, descriptions of clinical, morphological and genetic features are generally based on a limited number of patients. They often belong to families from isolated communities with different living conditions, which may influence the clinical picture and the onset of the disorder and interfere with the classification of the PPKs. The prevalence of HPPK in the northernmost county of Sweden is probably the highest in the world. Therefore, it was possible to include a great number of patients with a uniform symptomatology in the study.

The aim was to study:

1. the clinical characteristics of the dominant and the presumed recessive variety of HPPK,

2. dermatophytosis in HPPK,

3. the affinity of dermatophytes to the horny layer of the palms and soles in patients with HPPK,

4. histopathological features of the dominant and the presumed recessive variety of HPPK,

5. and ultrastructural characteristics of the presumed recessive variety of HPPK,

6. and to propose a new classification of the diffuse HPPKs.

INTRODUCTION

The northernmost county of Sweden (Norrbotten), which is located near to the arctic circle, covers 98,900 km^2, and at the end of 1980 the total population was about 267,000, resulting in a density of three persons per km^2. During the past 20 years this population has been relatively constant, due to emigration to other parts of Sweden. At the same time, immigration from isolated villages and hamlets to larger towns of the county resulted in change of the original population structure. The mean annual temperature ranges from minus 0.8°C to plus 2.4°C, and from the middle of October to the middle of May the average depth of snow cover is about 50 cm. The relative humidity in the winter season is low compared with that of other parts of Sweden (96, 97). The main branches of employment are mining, crafts and industries, agriculture, military and medical service and local government. Hereditary palmoplantar keratoderma of the northernmost county of Sweden (Norrbotten) was first described in 1967 by Curt Bergström and was interpreted as a typical Unna-Thost variety. The frequency of this inherited disorder was 0.55% and was, compared with earlier reports, probably the highest in the world. Results of the study were based on examination of 15,569 schoolchildren, or 42% of the total number of 37,104 pupils attending the schools at that time. Among these children, 47 girls and 40 boys suffered from HPPK and they constituted the 87 propositi. It was proved that HPPK in the northernmost county of Sweden (Norrbotten) had an autosomal dominant inheritance. Eighteen children came from 6 families in which both parents suffered from HPPK. However, a more serious form of keratoderma could not be documented. Two propositi had healthy parents but brothers and sisters with HPPK (98, 99).

During 1977-1981, 38,136 dermatological outpatients attended the Department of Dermatology, Boden Central Hospital. Two hundred and eighty of these suffered from HPPK, corresponding to a visiting frequency of 0.73%. Of the known cases of HPPK, 19.1% visited the Department of Dermatology at that time. Simultaneously, the frequency of dermatophytosis in patients with HPPK was found to be 35.0% (100, 101).

Based on these reports, it was considered of interest to re-examine the original propositi and their family members to verify the studied dominant inheritance. It was thought especially important to study those two propositi who had healthy parents but brothers and sisters with HPPK and their families as well.

To study the development of the keratinization disorder, it was considered important in the same patients to compare the first clinical description, published in 1967, with the picture 18 years later. The clinical picture was also studied in relatives of the original propositi with HPPK.

From the patients' personal histories, the influence of employment on onset of HPPK and roughness and thickness of the hyperkeratosis on the palms and soles was assessed. At the histopathological examination, the thickness of the stratum corneum in patients with HPPK and dermatophytosis was compared with that in those without. The stratum corneum of the palms and soles of patients with HPPK is thicker than that of normal individuals. It was therefore found of interest to measure cell turnover time on the soles to specify the type of hyperkeratosis (102, 103).

In a 5-year survey of dermatophyte infections in the northernmost county of Sweden (1977 - 1981), dermatophytosis in patients with HPPK was found in 35.0%

(100, 101). At a meeting arranged by the northern Swedish Dermatological Society in 1980, the association between dermatophyte infections and HPPK in the northernmost county of Sweden (Norrbotten) was first reported (104). Dermatophyte infections in HPPK have later been investigated in relatively limited studies and in those studies the frequency was found to range between 30 and 60 per cent (90, 105, 106). The prevalence of dermatophytosis in patients with HPPK was later on investigated in a well defined area of the county of Norrbotten named "the Quadrangle" (107). Dermatophyte infections were therefore accorded special interest, as well as factors concerning their affinity to the horny layer.

An extracellular keratinase which in purified form can digest keratin has been isolated from different dermatophyte species, and it has been shown that it possesses an alkaline pH optimum (108, 109, 110). The normal pH of human skin ranges from 4.2 to 5.6 and this acid mantel has been proved to have a protective function against chemicals and microorganisms (111, 112). Changes in this defence mechanism might enhance the pathogenicity of dermatophytes. The pH of the soles of patients with HPPK and dermatophytosis was therefore measured and compared with that of patients without dermatophytosis and with normal individuals (113). The amino acid composition of keratin was also studied to determine whether any qualitative differences between keratin from patients with HPPK and healthy individuals existed (114, 115, 116, 117).

As the affinity of dermatophytes to the horny layer of the palms and soles in patients with HPPK might depend on fungal characteristics, the macro- and micro-morphology of the involved dermatophyte species were investigated. At the same time, minimal inhibitory concentrations (MIC) of a generally used antimycotic substance were measured.

As increased susceptibility to dermatophyte infections confined to the palms and soles in patients with HPPK has repeatedly been shown, it was considered natural to study patient factors which might influence this affinity to dermatophytes. A personal and family history of atopy has been found to be almost three times more common in chronically dermatophyte-infected patients compared with control subjects (118, 119). Likewise, a high total serum IgE level could be correlated to chronic fungus infections (120). Immunological cross-reactivity between a glycoprotein isolated from T.mentagrophytes and human isoantigen A has been demonstrated in in vitro samples taken from patients who were continuously infected, as has the presence of IgG antibodies against dermatophytes (121, 122, 123). It was therefore considered of interest to study the relationship between dermatophyte infections in patients with HPPK and immunological aspects, such as the ABO blood groups, family and personal histories of atopy, total serum IgE levels, specific dermatophyte IgE and IgG RAST, crossed immunoelectrophoresis and trichophytin reactions. To study tissue response to the invading dermatophytes, histopathological examination of biopsies from soles stained with H&E and PAS was performed in patients with dermatophytosis and compared with those without.

During the last decades, a still growing number of cases with a clinical picture similar to that of HPPK of the Unna-Thost variety, but with histopathological features of epidermolytic HPKK of the Vörner type, have been reported (124). Re-examination of the family originally studied by A Thost in 1880 demonstrated histopathological characteristics of epidermolytic PPK. Therefore, not only a high frequency of HPPK

of the Unna-Thost variety but also the existence of two separate entities of dominant inherited diffuse HPPK has been doubted (125). It was therefore considered important to examine biopsies from patients with HPPK in the northernmost county of Sweden (Norrbotten) to ascertain whether or not epidermolytic PPK could be demonstrated in the county.

A comparative histopathological examination of biopsies from patients with the common dominant variety and the rare presumed recessive variety of HPPK (Gamborg Nielsen type) was performed to assess whether any histopathological differences existed.

Ultrastructural examination of biopsies taken from patients with the presumed recessive variety of HPPK (Gamborg Nielsen type) was performed and the findings compared with those in biopsies taken from patients with Mal de Meleda and the dominant Unna-Thost variety on the Continent.

Family studies of patients with the presumed recessive variety of HPPK (Gamborg Nielsen type) in the two northernmost counties of Sweden (Västerbotten and Norrbotten) were performed by means of a demographic data base.

MATERIAL AND METHODS

Patients

Studies included in this thesis were performed during a number of years. Therefore, the patient groups, number and distribution of dermatophytes varied in the different publications. Patients included in the different sections of the thesis are consequently described according to the individual publications.

PUBLICATION No. I. Two groups of patients with HPPK were included in the material of the clinical description.

A: The original 87 propositi derived from the study reported in 1967 were traced with the assistance of the county registration office, and it was possible to re-investigate 44 (51%) of these; 17 men, average age 33 years (range 33-41 years) and 27 women, average age 35 years (range 33-38 years). Of the remaining 43 propositi, 34 lived outside the county, 4 did not keep their appointment at the Department of Dermatology, 2 were dead, 1 had emigrated to the USA and 2 could not be found (99).

B: Ninety-one relatives of the original propositi with HPPK were randomly selected: 31 men, average age 43 years (range 16 - 70 years), 36 women, average age 42 years (range 17 - 68 years) and 24 children, average age 7 years (range 1-15 years) constituted the second group of patients.

PUBLICATION No. II. Patients included in this publication were identical with those of publication No. I: 48 men, average age 43 years (range 16 - 70 years), 63 women, average age 42 years (range 17 - 68 years) and 24 children, average age 7 years (range 1 - 15 years).

The entire patient material was included in the study of ABO blood groups. Distribution of ABO blood groups was related to that of 13,319 individuals attending

the Blood Donor Centre of Boden Central Hospital during 1982. For the personal and family histories of atopy and serum levels of IgE, 85 patients with HPPK were included: 37 men, average age 48 years (range 43-70 years), and 48 women, average age 41 years (range 26-63 years).

Specific dermatophyte IgE and IgG RAST was investigated in 20 patients with HPPK: 15 men and 5 women, average age 37 years (range 26 - 65 years). Ten healthy individuals served as controls.

Precipitating dermatophyte antibodies determined by crossed immunoelectro-phoresis were studied in 24 patients: 13 men and 11 women, average age 44 years (range 22-67 years). Previously performed immunoelectrophoretic studies served as controls (Rigshospitalet, Copenhagen, Denmark).

Trichophytin reactions were assessed in 37 patients: 19 men and 18 women, average age 42 years (range 15 - 65 years). Twenty-five healthy persons without dermatophyte infections and 11 patients with dermatophytosis but without HPPK served as controls.

Fig. 1. The northernmost counties of Sweden in which this study has taken place related to the rest of Sweden. "The Quadrangle" and the "Skellefteå Triangle" are indicated on the map.

PUBLICATION No. III. Patients included in this study consisted of 14 patients with HPPK: 8 men and 6 women, average age 49 years (range 22-79). Five healthy subjects (2 women and 3 men) who had never suffered from dermatophytosis served as controls.

PUBLICATION No. IV. Patients were divided into two groups. Group A comprised fourty-four of the original 87 propositi. Thirty-nine of these were included in this part of the study. Group B consisted of 52 grown-up family members with HPPK derived from the original propositi, 25 men and 27 women, average age 43 years (range 17 - 68 years).

PUBLICATION No. V. The same 14 patients with HPPK of the dominant variety as studied in publication No. III were included in this study. Five patients with the presumed recessive variety of HPPK (Gamborg Nielsen type), 4 women and 1 man, average age 42 years (range 40 - 49 years), were also included.

Fig. 2. Distribution in the County of Norrbotten of patients with the dominant variety of hereditary palmoplantar keratoderma. ○ The original propositi (44). □ Relatives of the original propositi (91). ● Patients derived form "the Quadrangle" (60). ▲ Patients included in Publications III and V (14).

21

PUBLICATION No. VI. This study, performed at the Department of Dermatology, Ruprecht-Karls Universität, Heidelberg, Germany, included 3 affected and 5 unaffected members of one family in which the presumed recessive variety of HPPK (Gamborg Nielsen type) was found and 2 solitary cases. Five patients with the presumed recessive variety of HPPK (Gamborg Nielsen type) were consequently included: 4 women and 1 man, average age 42 years (range 18 - 49 years).

PUBLICATION No. VII. Eight patients, 6 women and 2 men, average age 42 years (range 18 - 49 years), derived from 4 different families, were included in the study. One patient from each family constituted the proband.

Altogether 209 patients with HPPK of the dominant variety were included in different parts of the thesis, that is to say 14.2% of the calculated number in the county at that time (Figs 1 and 2). However, two patients with the presumed recessive variety of HPPK (Gamborg Nielsen type) belonged to the original propositi. Therefore, 207 patients with the common dominant variety of HPPK and 8 patients with the rare presumed recessive variety of HPPK (Gamborg Nielsen type) were included in the studies.

Mycological methods (I-V)

Speciments for direct microscopic examination of skin scales were collected from palms and soles with a curette and stained with Schwartz-Lampkins staining solution (126).

Cultures were performed on Sabouraud's glucose agar without cycloheximide as additive and were incubated at 27°C for 3 weeks (127). Cultures were read once a week and discarded after 3 weeks (128). The identification of fungi was performed by macroscopic examination and microscopic examination of material collected with adhesive tape from cultures and stained with Lactophenol-Cotton-Blue (129, 130). Dubious cases were identified by use of selective culture methods. To prevent growth of saprophytic fungi, the palms and soles were washed with ethanol ether before specimens for culture were taken (131, 132, I, II, III, IV, V).

Study III. In the study of dermatophytes and keratin dermatophytes from the initial cultures were transfered to Sabouraud's glucose agar with cycloheximide as additive and inoculated at 32°C for up to 3 weeks. Laboratory dermatophyte cultures served as controls.

Specimens from the second culture of dermatophytes isolated from patients with HPPK and control dermatophytes were again inoculated on Sabouraud's glucose agar. Sterilised curreted keratin from patients and controls was placed in the centre of the plates. The study was performed as follows: A/ Dermatophytes isolated from patients were inoculated together with the corresponding patients keratin. B/ Control dermatophytes were inoculated together with keratin from all the patients. C/ Dermatophyptes from patients were inoculated together with pooled keratin from healthy individuals. Cultures were incubated at 32°C and macroscopically and microscopically read after one week.

Two preparations from each colony were made for the microscopic examination,

one with slight pressure on the fluffy mycelium and one with more vigorous pressure to attach keratin to the tape.

For the estimation of minimal inhibitory concentration (MIC) of ketoconazole 6 isolates of *T. rubrum* and 1 of *T. mentagrophytes* from the soles of patients with HPPK were included. Laboratory dermatophytes served as controls. The test medium was DST (Oxoid UK) and ketoconazole was dissolved in DMF (dimethylformamide) in a concentration of 1000 µg/ml. Decreasing concentrations of the stock solution were added to DST medium and controls were made with DMF and sterile water. Dermatophytes were harvested after 1 week of growth and 0.1 ml of a prepared dermatophyte suspension was inoculated on DST medium at 32°C and read after 4 days (133). MIC was assessed as the concentration of ketoconazole at which total inhibition of growth was seen (III).

Immunological methods (II)

ABO blood groups. Blood types were determined according to the ABO system and related to blood types of individuals attending Boden Central Hospital during 1982.

Family and personal histories of atopy. Patients with HPPK were questioned about family and personal histories of atopy and it was ascertained whether any of them suffered from atopic diseases (134).

IgE levels in serum. Total IgE levels in serum were determined using the Phadebase radio-immunoassay method (135, 136).

Specific IgE RAST. Specific IgE antibodies against *T. rubrum*, *T. mentragrophytes* and *E. floccosum* were determined by the Phadebas RAST method (137). Dermatophyte antigen extracts 1/30 w/v of the species *T. rubrum* (CBS 363.62), *T. mentagrophytes* (CBS 426.70) and *E. floccosum* (CBS 233.69) were prepared by extraction of homogenised mycelia from the individual species in 0.05 M sodium phosphate buffer pH 7.4. The extraction was performed during 16 hours at 4°C. The discs for the RAST assay were prepared by covalent coupling of the dermatophyte extract to the activated paper discs. The dermatophyte raw materials were purchased from Allergon AB, Ängelholm, Sweden. Sera from patients who had a total igE > 100 kU/ml were investigated for IgE antibodies against a reduced RAST panel,consisting of 10 common extrinsic allergens, which frequently elicit positive reactions in patients with allergic rhinitis and bronchial asthma. The allergens tested were Phleum pratense, Betula verrucosa, Artemisia vulgaris, egg-white, milk, cat epithelium, horse dandruff, dog dandruff, Dermatophagoides farinae and Chladosporium herbarum.

Specific IgG RAST. Specific IgG antibodies were determined by RAST assay, using the Phadebas IgG RAST reagents together with specifically prepared dermatophyte allergen discs (138). The same extractions of dermatophytes as were used for the determination of specific IgE antibodies were also used for this test and the results compared with those in healthy controls. Dermatophyte antibodies against *T. rubrum*, *T. mentagrophytes* and *E. floccosum* were related to their homologous species and to

23

the total number of dermatophytes, irrespective of their species.

Crossed immunoelectrophoresis (CIE). Precipitating dermatophyte antibodies were investigated by crossed immunoelectrophoresis with an intermediate gel (139, 140). Blood samples were taken from patients as soon as the diagnosis dermatophytosis was established by direct microscopic examination of skin scrapings. Results of CIE were correlated to the definite diagnosis after examination of the corresponding cultures. Results were compared with those of previously performed investigations of blood samples from patients with acute or chronic dermatophytosis without HPPK, performed at the same laboratory using the same method.

Trichophytin reactions

A commercial antigen with purified trichophytin prepared on extract from *T. mentagrophytes* (Trichophyton®, Miles and Dome) as adopted for this part of the study. A prick test was performed with a dilution containing 5000 nitrogen units per ml, preserved in 0.4% phenol with the addition of 50% glycerin. Histamine 1 mg/ml and 0.9% sodium chloride constituted the controls. Immediate reactions were read after 20 minutes and delayed reactions after 72 hours. An immediate or delayed reaction consisting of erythema and induration of at least 5 mm was considered positive. Reactions measuring less than 5 mm were registered as negative (141, 142).

Histopathology (IV, V)

Histopathology of the dominant variety of HPPK. Two groups of patients were included in the study and biopsies were taken from two different regions of the soles. Biopsies of Group A were taken from the medial aspect of the foot, 1 cm within the demarcation of the hyperkeratosis, corresponding to the metacarpophalangeal joint of the first toe. Biopsies from group B were taken from the plantar surface, about 1 cm in front of the heel. Biopsies were fixed and stained with hematoxylin and eosin (H&E) and periodic acid Schiff (PAS) (143, 144, 145).

Histopathology of the dominant variety of HPPK and dermatophytosis. In PAS-stained sections the micromorphology of the tissue response to dermatophyte infections was described (IV).

Comparative histopathological description of the dominant and the presumed recessive variety of HPPK (Gamborg Nielsen type). Two biopsies from each patient with the dominant variety of HPPK were taken, one from the medial aspect of the foot, 1 cm within the demarcation of the hyperkeratosis, corresponding to the 1st toe, and one from the plantar surface, about 1 cm in front of the heel. Biopsies from the soles of the presumed recessive variety of HPPK (Gamborg Nielsen type) were only taken from the plantar surface, 1 cm in front of the heel. Sections were fixed and stained with H&E and PAS and a comparative histopathological examination was performed with a blind design. The thickness of the epidermal cell layer, the stratum granulosum cell

layer, the stratum corneum thickness and acanthosis (length of rete pegs) was expressed in number of cell layers (V).

Ultrastructural examinations (VI)

Punch biopsies were obtained from the heels, within the involved hyperkeratotic skin of the soles of affected and unaffected family members. Samples were treated as follows: fixation with 3% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4, partial oxidation by addition of hydrogen peroxide modified after Peracchia and Mitler (146) for 2 hours at room temperature, further fixation in 3% glutaraldehyde without hydrogen peroxide and mailing from the northernmost county of Sweden (Norrbotten) to Heidelberg. The samples were then postfixed with 1% osmium tetroxide, dehydrated in graded ethanols and embedded in epoxy resin (Epon 812, now termed glycid-ether 100); semi-thin sections were stained with methylene blue; ultra-thin sections, mounted on copper grids, were treated with uranyl acetate and lead citrate. The electron microscropic investigations were performed using a Siemens Elmiskop Ia and a Philips EM 400 electron microscope (VI).

Family studies of the presumed recessive variety (VII)

The Swedish National Registration System includes different registers and lists. To simplify management of this complex information, the University of Umeå, Sweden, instituted a production unit in which the registers and lists were computerized. The computerised material, which covered areas in and between the counties of Västerbotten and Norrbotten, was organised as a structured query language (SQL) relational data base running on an IBM minicomputer system. The size of the data base at this point in time is 1.5 gigabytes, with information on approximately 365,000 individuals.

Four selected probands from the 4 families included in the study were traced in the computerised registration system as far back as possible. The relationship in different generations was tabulated. Birthplaces of the integrated family members and marital distance of unaffected relatives was mapped. The total number of patients with HPPK who had attended the Departments of Dermatology in Umeå and Boden was adjusted to the computerised material. Pedigrees for each of the 4 families were set up according to their personal and family histories (VII).

RESULTS

Clinical description of the dominant variety (I)

Two hundred and seven patients included in different studies of the thesis suffered from the autosomal dominant variety of HPPK, corresponding to the clinical description given by Thost and Unna in 1880 and 1883. It was also shown that this inherited keratinization disorder possessed a strong penetrance (Fig. 3).
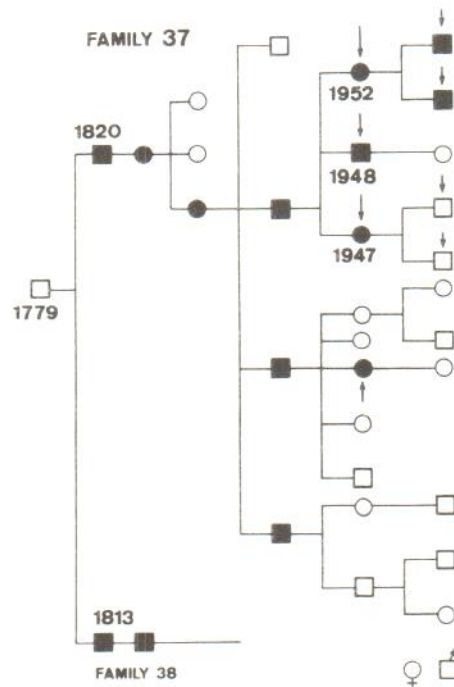

Fig. 3. Pedigree of one of the families with hereditary palmoplantar keratoderma of the dominant variety in the northernmost county of Sweden (Norrbotten).

Two clinical forms of the dominant variety of HPPK could be distinguished; a diffuse form with gradual transition from hyperkeratotic to normal skin on the hands and feet (I, Fig. 1b), and a form characterised by a papular border between hyperkeratotic and unaffected skin (I, Fig. 1a). Generally confined to the joints, this latter form frequently produced knuckle pads on dorsal aspects of the fingers (I, Fig. 1c). The papular form was more often observed among children, developing into the diffuse form with increasing age (I, Table 1). It was shown that about 25% of adult patients suffered from the papular form and about 75% from the diffuse. In both forms, hyperkeratosis was smooth and uniform (I, Fig. 1d). Depending on the thickness of the horny layer, the

colour ranged from yellow to that of normal skin.

A bluish-red demarcation zone between hyperkeratotic and normal skin has been described in patients with HPPK of the Unna-Thost variety (147. However, personal and family histories and clinical examinations did not indicate such a transition in patients with HPPK from the northernmost county of Sweden.

Hyperhidrosis of the hands and feet generally accompanies HPPK of the Unna-Thost variety (1). However, in this material hyperhidrosis occurred more often in men than in women and children. In the majority of cases, it disappeared with increasing age (I, Table 1). Pitted keratolysis was observed in 4 men, 7 women and 5 children, all of whom had hyperhidrosis (148) (Fig. 4).

Fig. 4. Pitted keratolysis on the soles of a patient with the dominant variety of hereditary palmoplantar keratoderma.

A constant clinical finding in patients with HPPK is the hydrophilic character of the horny layer. When the hands and feet are immersed in water for 5-10 minutes, the colour of the hyperkeratosis turns to white and the consistency becomes spongious (IV, Fig. 1). Differences in the clinical appearance of the hyperkeratosis between patients with hyperhidrosis and those without could not be documented. The nails were not

affected and the sensibility of the skin on the palms and soles did not differ from that of normal individuals. Hyperkeratotic lesions outside the palms and soles were not found.

Genotype and environmental factors

The influence of employment on the roughness and thickness of the hyperkeratosis on the palms according to the personal history of relatives to the original propositi is shown in Table III. The age of onset is shown in Table IV and the clinical picture of a newborn infant in Figure 5. It could not be proved in patients with late onset that heavy manual work induced the keratinization disorder. In 4 patients with heavy manual work a thicker hyperkeratosis was found on the right hand, but similar variations have been observed in workers without HPPK. A constant clinical sign was the hydrophilic character of the horny layer, which troubled all patients with wet work. However, an increase of the thickness was not clinically demonstrated in patients who constantly came into contact with fluids (IV, Fig. 1).

Fig. 5. Hereditary palmoplantar keratoderma of the dominant variety in a 6- weeks-old child.

Table III. *Influence of employment on the thickness of hyperkeratosis in the dominant variety of hereditary palmoplantar keratoderma.*

Employment groups	Number of patients	Impairment	Unaffected
Children < 16 years	24	0	24
Pensioners > 65 years	5	0	5
Farmers	5	3	2
Medical care personnel	8	1	7
Military personnel	3	0	3
Labourers	26	11	15
Desk-workers	20	1	19
Total	91	16 (17.6%)	75 (82.4%)

Table IV. *The age of onset of hereditary palmoplantar keratoderma in men, women and children.*

		0-10 years		10-30 years		> 30 years	
		n	%	n	%	n	%
Men	(n = 31)	21	67.7	8	25.8	2	6.5
Women	(n = 36)	23	63.9	11	30.6	2	5.5
Children	(n = 24)	24	100.0	0	0.0	0	0.0
Total	(n = 91)	68	74.4	19	20.9	4	4.4

Clinical description of the presumed recessive variety

Patients included in this part of the study were derived from 4 different families and considered to suffer from the presumed recessive variety of HPPK (Gamborg Nielsen type). From their personal and family histories, ordinary pedigrees for each of the four families were drawn up (VII, Fig. 3). By means of a demographic data base, it was

shown that these four families belonged to the same family and were integrated at different generation levels. However, it was not possible to trace a single ancestor who directly connected all four families (VII, Table 1). It was shown that the origin of family members was concentrated to areas which are generally known to harbour other inherited disorders (149, 150). (Fig. 6). The origin of probands and the marital distance of non-affected relatives is shown in Figure 6 (VII).
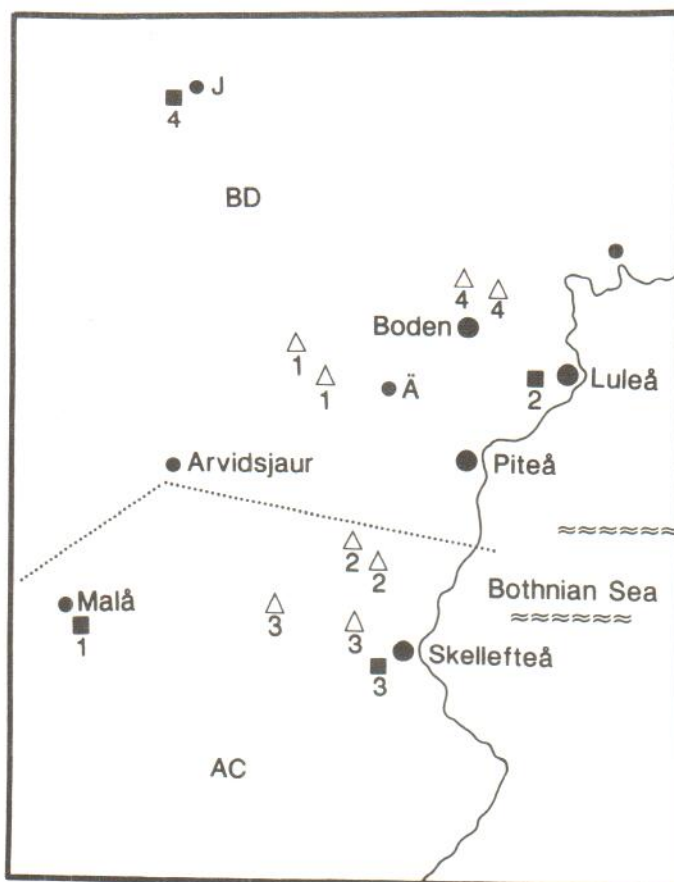

Fig. 6. Origin of probands and the marital distance of parents of the presumed recessive variety of hereditary palmoplantar keratoderma outlined on a map of the counties of Västerbotten and Norrbotten. △ Marital distance of parents in families 1-4. ■ *Origin of probands 1-4.*

The clinical picture was characterised by a very thick horny layer and a distinct demarcation to normal skin (VI, Fig. 1 a-d; VII, Fig. 1). In most patients hyperkeratosis was bordered by a bluish-red demarcation zone towards normal skin and knuckle pads were generally found on dorsal aspects of the finger joints. Apart from one patient, who had extension of hyperkeratosis to the dorsum of the hands, it was not found on other parts of the skin. The colour was described as canary yellow, due to the thickness of the horny layer. All patients had hyperhidrosis but the nails and sensibility of the palms and soles were normal.

Genotype and environmental factors

According to the personal history, patients' employment did not influence the severity of the hyperkeratosis. One patient, a 36-year-old carpenter, who at the age of 16 years developed fibrous digital constrictions which deteriorated with increasing age was found among these patients. This case has previously been reported as a type of mutilating PPK type Vohwinkel (48). Radiological examination of the fingers showed abnormally pointed end phalanges. However, such findings could not be demonstrated among the remaining patients or family members. Constricting keratotic bands may develop in patients with severe forms of diffuse HPPK when exposed to heavy manual work (151,152). Pointed end phalanges have never been reported in relation to HPPK and heavy manual work.

Clinical description of dermatophytosis in the dominant variety (I)

This part of the study was based on the original propositi (44 patients) and relatives of the original propositi (91 patients) (I). However, as the differentiation between the two varieties of HPPK at that time was uncertain, two propositi with the presumed recessive variety were included.

According to a 5-year survey of fungal infections performed in the northernmost county of Sweden (Norrbotten), the frequency of dermatophytosis in patients with HPPK was reported to be 35.0% during 1977-1981. Results were based on 280 consecutive patients, of whom 98 had dermatophytosis (100, 101) (Fig. 8). Later on the prevalence of dermatophytosis in patients originating from the "Quadrangle" (Fig. 1) was shown to be 36.7% with reference to conventional culture and 41.7% with reference to direct microscopic examination of skin scales (107) (IV, Fig. 2).

The distribution of dermatophytes compared to that of the 5-year survey of dermatophyte infections in patients without HPPK is given in Table V. It was shown that *T. mentagrophytes* occurred significantly more often in patients with HPPK than in those without (p < 0.01).

Table V. Distribution of dermatophytes in 135 patients with hereditary palmoplantar keratoderma (original propositi and relatives of the original propositi 1985 (I) and 1984 (II), compared with a 5-year survey of dermatophyte infections in patients without hereditary palmoplantar keratoderma.

	HPPK (I)	HPPK (II)	5-year survey
T. rubrum	21 (44.7%)	20 (39.2%)	213 (62.0%)
T. mentagrophytes	17 (36.2%)	18 (35.3%)	68 (19.9%)
E. floccosum	9 (19.1%)	13 (25.5%)	63 (18.1%)
Total	47 (100.0%)	51 (100.0%)	344 (100.0%)

Clinical signs related to results of conventional culture of dermatophytes and direct microscopical examination of skin scrapings in patients with HPPK and dermatophytosis are shown in Table VI. Erythema, vesicles, scaling and fissuring occurred significantly more often in patients with dermatophytosis (Fig. 7). It has previously been shown that treatment of dermatophyte infections resulted in a smooth and uniform hyperkeratosis and, therefore, eczema, scaling and fissuring should be interpreted as clinical signs of dermatophytosis (153). Personal history of recurrent vesicular eruptions along the hyperkeratotic border was found statistically more often in patients with dermatophytosis than in those without ($p < 0.01$) (Table VI).
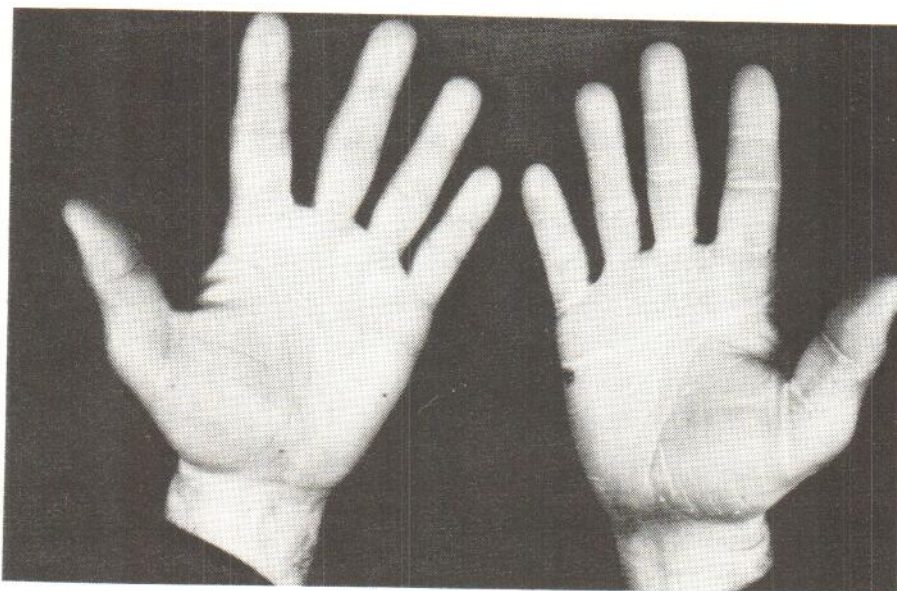
Fig. 7. *The dominant variety of hereditary palmoplantar keratoderma with dermatophytosis on the left palm (T. rubrum) and without on the right.*

Table VI. Clinical signs related to mycological procedures in 91 patients with hereditary palmoplantar keratoderma with or without dermatophytosis.

	With dermato-phytosis (N = 33)		Without dermato-phytosis (N = 58)	
	No.	%	No.	%
Eczema	23	70.0	4	6.9
Scaling/Fissuring	23	70.0	2	3.4
Vesicular eruptions	26	78.8	10	17.4
Hyperhidrosis	21	63.6	34	58.6
Culture of dermato-phytes (feet)	33	100.0	0	0.0
Culture of dermato-phytes (hands)	5	15.2	0	0.0
Direct microscopy (feet)	31	93.9	5	8.6
Direct microscopy (hands)	4	12.1	0	0.00

Hyperhidrosis was found just as often in patients with dermatophytosis as in those without and dermatophyte infections did not appear to depend on the existence of hyperhidrosis. It has previously been reported that treatment of dermatophytosis reduced hyperhidrosis but this could not be confirmed in this study (154).

Onychomycosis was found in 18.2% of cases with dermatophytosis and *T. rubrum* was cultured exclusively from the soles of these patients. Surprisingly, positive direct microscopy of skin scales from patients with HPPK without dermatophytosis, as shown by conventional culture, was demonstrated in 8.6 per cent (Table VI). However, it has been reported on more than one occasion that the number of positive direct microscopical examinations may exceed that of conventional culture (100, 155). As shown in Table VI, symptomless carriers of dermatophytes and patients with erythema, vesicles, scaling and fissuring without corresponding positive mycological cultures were found. The distribution of patients with dermatophytosis with or without HPPK among different employment groups, compared with a 5-year survey of dermatophyte infections in the county, is shown in Table VII (I). However, no significant difference was found in the distribution of patients with dermatophytosis (156, 157, 158). Influence of dermatophytosis on the extension or thickness of hyperkeratosis could not be demonstrated.

Table VII. Distribution of patients with hereditary palmoplantar keratoderma and dermatophytosis derived from the original propositi and their relatives, among different employment groups, compared with that of a 5-year survey of patients without hereditary palmoplantar keratoderma in the northernmost county of Sweden (Norrbotten) (1977-1981).

	Dermatophytosis in patients with HPPK		Dermatophytosis in patients without HPPK	
	N	%	N	%
Children < 16 years	5	10.6	24	7.0
Pensioners > 65 years	3	6.4	8	2.3
Farmers	2	4.3	5	1.5
Medical care personnel	4	8.5	20	5.8
Military personnel	1	2.1	30	8.7
Labourers	19	40.4	131	38.1
Desk-workers	13	27.7	126	36.6
Total	47	100.0	344	100.0

Clinical description of dermatophytosis in the presumed recessive variety

In the presumed recessive variety of HPPK (Gamborg Nielsen type) dermatophytosis was found in 5 of 8 patients and dermatophytes were distributed as follows: *T. rubrum* 2, *T. mentagrophytes* 1 and *E. floccosum* 2. Clinical signs followed the same pattern as for that of the dominant variety. Apart from the thickness of the keratoderma, the course of dermatophyte infections in the presumed recessive variety was the same.

Immunological studies

Blood groups and dermatophytosis in HPPK. One hundred and thirtyfive patients with HPPK, of whom 51 had dermatophytosis, were included in the study. The distribution of dermatophytes is shown in Table V. The distribution of ABO blood groups was related to that of 13,319 individuals attending the Blood Donor Centre of the Boden Central Hospital during 1982. ABO blood groups of patients with HPPK were distributed as follows: A 53%, 0 37%, B 4% and AB 6%, which is similar to the distribution of blood groups of those attending the Blood Donor Centre: A 48%, 0 37%, B 10%, and AB 5%. The relationship between different blood groups of patients with HPPK and different dermatophyte species is shown in III, Table 2. It was also shown that *T. mentagrophytes* occurred significantly more often among patients with HPPK and blood group A than in the remaining blood groups ($p < 0.05$) (II).

Family and personal histories of atopy. Of 85 patients with HPPK a personal and/or family history of atopy was obtained in 32 patients, of whom 15 (44%) had dermatophytosis. Twenty-two had a family history of atopy of whom 10 (45%) had dermatophytosis. Ten patients had a personal history of atopic rhinitis or bronchial asthma, but none atopic dermatitis. Dermatophytes were isolated from 5 of these. Fifty-three patients had no personal and/or family history of atopy and dermatophytes was found in 24 (49%). Accordingly no difference between atopics and non-atopics was documented. Therefore, patients with HPPK, who had a personal and/or family history of atopy did not appear to have a higher frequency of dermatophyte infections than that found in non-atopics (II, Table 1).

IgE levels in serum. Total IgE levels in serum, correlated to different dermatophyte species are shown in III, Table 1. It was found that patients with serum IgE level > 100 kU/ml had a tendency to increased frequency of dermatophyte infections, when compared with patients with a serum IgE level < 100 kU/ml. This difference was not statistically significant, however.

Specific IgE RAST. Only one patient had specific IgE antibodies against *T. mentagrophytes* and *E. floccosum* and an IgE level in serum of 623.5 kU/ml. Results from testing with the reduced RAST panel of common extrinsic allergens showed raised values of circulating specific IgE antibodies against most antigens of the panel in all patients with an IgE level > 100 kU/ml (159, 160).

Specific IgG RAST. Significantly higher levels of *T. mentagrophytes* and *E. floccosum* antibodies could be shown to exist in patients with HPPK infected with *T. rubrum* and *E. floccosum* compared with healthy controls (III, Table 3) (p < 0.05). It was confirmed that *T. rubrum*, *T. mentagrophytes* and *E. floccosum* have at least one antigen in common. With this method, *T. mentagrophytes* appeared to be a weak homologous and heterologous antibody inducer compared with *T. rubrum* and *E. floccosum*, and patients infected with *T. mentagrophytes* did not produce higher levels of IgG antibodies against *T. rubrum*, *T. mentagrophytes* and *E. floccosum* than the control individuals (II) (161).

Crossed immunoelectrophoresis. Twenty-four patients with HPPK and dermatophytosis were included in the study and dermatophytes were distributed as follows: *T. rubrum* 14, *T. mentagrophytes* 6 and *E. floccosum* 4. Precipitating circulating antibodies determined by crossed immunoelectrophoresis were found in 13 of 24 (54%) sera (162). They were distributed as follows: *T. rubrum* 5 of 14 (36%), *T. mentagrophytes* 6 of 6 (100%) and *E. floccosum* 2 of 4 (50%).

Trichophytin reactions

Twentyfour of 37 patients had dermatophytosis (65%) (*T. rubrum* 12, *T. mentagrophytes* 7 and *E. floccosum* 5). The commercial antigen gave only 1 positive immediate reaction (*T. rubrum*) erythema and induration ≥ 5 mm and three with erythema and induration < 5 mm (*E. floccosum* 2 and *Candida albicans*). No delayed reactions were observed (II) (163).

Dermatophytes and keratin in patients with HPPK

Dermatophytes were isolated from 7 of 14 patients (50%) (*T. rubrum* 6 and *T. mentagrophytes* 1). When dermatophytes isolated from patients with HPPK were inoculated together with the homologous sterilised keratin, an inhibition zone was demonstrated in the centre of 5 of 6 cultures with *T. rubrum*, but not in that with *T. mentagrophytes*. No inhibition zone was seen with keratin from control individuals. Control cultures of *T. rubrum* and *T. mentagrophytes*, incubated together with keratin from 14 patients with HPPK, showed an inhibition zone in 6 cultures (III). Microscopic examination of tape specimens stained with lacto phenol cotton blue revealed no difference in growth pattern of dermatophytes between control keratin and keratin from patients with HPPK.

   The minimal inhibitory concentration (MIC) of ketoconazole against the 6 *T. rubrum* and 1 *T. mentagrophytes* from patients with HPPK was lower (0.767 SD $\pm$ 0.65) than the MIC against 6 *T. rubrum* and 1 *T. mentagrophytes* control isolates (2.56 SD $\pm$ 2.15). However, no statistically significant difference was found ($p = 0.1025$) (III).

Histopathological examinations

The dominant variety
The most important histopathological findings for both groups are shown in IV, Table 1. According to an accumulated description of biopsies from patients included in group B, areas of hypertrophic stratum granulosum and infrequently presence of clumsy keratin granules without giant granules were demonstrated. However, in none of the sections were histopathological features characteristic of epidermolytic PPK of the Vörner variety found (164, 165, 166) (Enerbäck L, Mölne L. Personal communication). The distribution of patients from whom biopsies representing both group A and B were taken is shown in IV, Figure 4.

The dominant variety and dermatophytosis
In PAS-stained sections, hyphae were demonstrated in the stratum corneum in 35.9% of group A and in 32.7% of group B (IV, Table 1). In group A the demonstration of hyphae and spores was related to results of culture, the individual species found and to direct microscopical examination of skin scrapings (IV, Table 2). A subepidermal mononuclear cell infiltrate was found in 28.2% of sections of group A and in 25.0% of group B (IV, Table 1). In group A, this mononuclear cell infiltrate at the dermo-epidermal junction was found in 9 of 11 (81.8%) sections in which hyphae were simultaneously demonstrated. In only 2 of 11 (18.2%) sections with this cell infiltrate were hyphae not found ($p < 0.05$) (IV).

   A personal history of relapsing vesicular eruptions along the hyperkeratotic border occurred significantly more often in patients with HPPK and dermatophytosis than in those without (I). However, in only 4 of 24 (16.7%) sections of both groups was a subepidermal mononuclear cell infiltrate found, together with spongiotic vesicules localised to the stratum granulosum and spinosum (IV, Table 1).

Comparative histopathological description of the dominant and the presumed recessive variety

Twentyeight biopsies were obtained from 14 patients with the dominant variety of HPPK and 5 biopsies from 5 patients with the presumed recessive variety of HPPK. Due to detachment of the stratum corneum, one biopsy was excluded.

Dermatophytes were cultured from the soles of 7 patients with the dominant variety (*T. rubrum* 6, *T. mentagrophytes* 1 and *C. albicans* 2). From the soles of the presumed recessive variety of HPPK, dermatophytes were isolated in 3 (*T. rubrum* 2, *E. floccosum* 1 and *C. albicans* 1).

The comparative histopathological examination of biopsies taken from patients with either the dominant or the presumed recessive variety of HPPK allowed no differentiation between them. Differences in thickness of cell layers and acanthosis (length of rete pegs) could not be demonstrated (V, Fig. 1) (Fig. 8).

Histopathological description of the presumed recessive variety

Light microscopical examination

The first light microscopical description of the presumed recessive variety of HPPK in the northernmost county of Sweden (Norrbotten) was performed by Kastl and Anton-Lamprecht (167). The epidermis was found to be extremely acanthotic with a focally broadened granular layer. Between the granular layer, several "clear cells" which showed a more loosely arranged cell content, compared with the adjacent granular cells, were seen. The horny layer was orthohyperkeratotic and cells were flattened. Occasional spine-like protrusions of granular cells into the horny layer occurred (168, 169).

The second light microscopical examination was performed by Mölne (V), designed as a blind comparative study between the dominant and the presumed recessive variety of HPPK. Orthohyperkeratosis, hypergranulosis and acanthosis were the most important findings, and it was not possible to separate the dominant from the presumed recessive variety of HPPK.

In PAS-stained sections from patients with dermatophytosis, hyphae and spores were found together with parakeratosis and a dermo-epidermal mononuclear cell infiltrate. However, "clear cells" were not observed.

Ultrastructural findings

The results of ultrastructural examination of biopsies from the presumed recessive variety of HPPK were compared with those of biopsies from patients with Mal de Meleda. Biopsies from unaffected family members without clinical symptoms of HPPK were also compared with those of the affected family members with the presumed recessive variety of HPPK. Several ultrastructural features were common to those of Mal de Meleda.
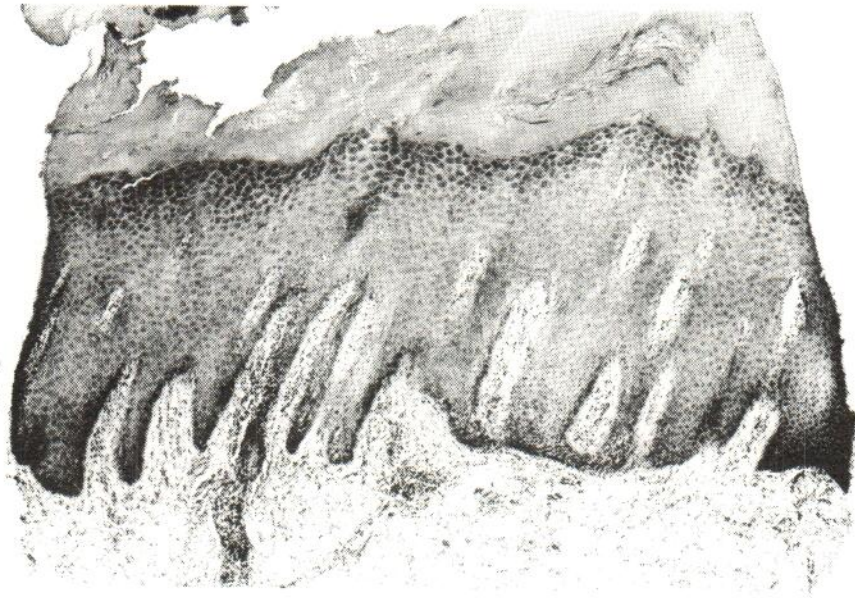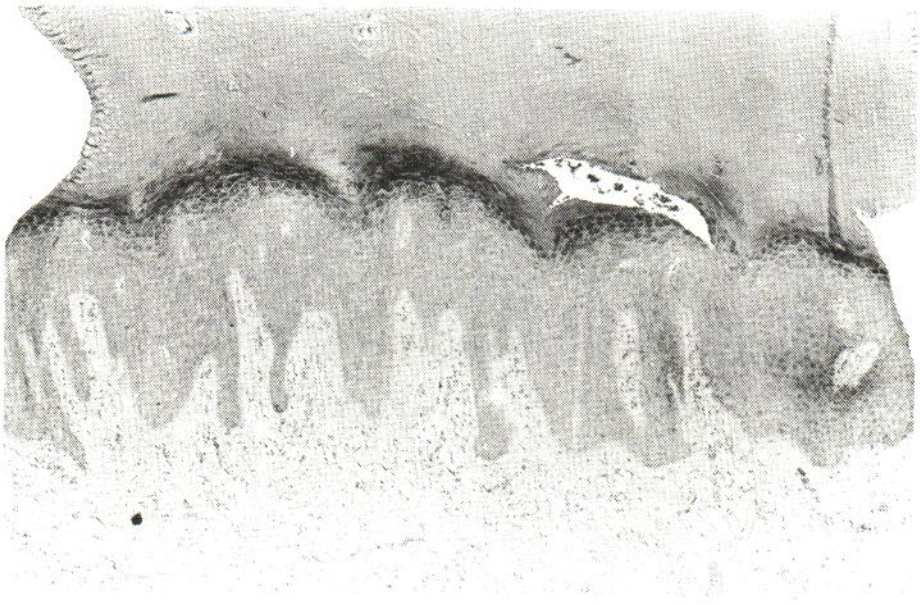
Fig. 8. Histopathological sections stained with PAS showing the dominant (A) and the presumed recessive variety (B) of hereditary palmoplantar keratoderma in the northernmost county of Sweden (Norrbotten) (x 100).

Mal de Meleda. Only a few ultrastructural studies of Mal de Meleda have been reported (170, 171). The findings could be summarised as follows: a broadened granular layer, a transitory region consisting of cells with a marginal envelope and considerable hyperkeratosis with composite keratohyalin granules (172).

Affected family members with the presumed recessive variety of HPPK. In contrast to the normal appearance of keratohyalin granules found in Mal de Meleda, keratohyalin granules showed different degress of spongiosity and electron density and sometimes a granular border. The remainding findings did not differ from those of Mal de Meleda (VI, Figs 3 and 4).

Unaffected members of the family with the presumed recessive variety of HPPK. In 4 of 5 unaffected family members different degrees of spongiosity in keratohyalin granules could be demonstrated. Keratohyalin granules had a different electron density and sometimes a granular border. These findings corresponded to those found in biopsies from the affected family members but they were less impressive.

GENERAL DISCUSSION

Diffuse HPPK of the Unna Thost variety occurs in all races. The prevalence most often quoted is that of Northern Ireland of 1:40,000. In 1967 C. Bergström reported a prevalence of 1:200 in the northernmost county of Sweden (98). Based on genetic observations by C. Bergström, the autosomal dominant inheritance was confirmed 18 years later (I, 99). The distribution of patients in the county did not differ substantially from that of the first study in 1967 (I) (Fig. 2). Among these patients, a severe form of HPPK with a presumed recessive inheritance and with a calculated frequency of 0.002% was found. From a clinical point of view, it was easy to differentiate between the common dominant and the severe recessive variety of HPPK. Compared with Mal de Meleda, the presumed recessive variety differed only in the extension of the hyperkeratosis. Patients were derived from 4 families, who at different generation levels belonged to the same family (VII). The families originated from an area called the "Skellefteå Triangle", which is generally known to harbour inherited disorders (Fig. 1).

Clinical description. Two different forms of the dominant variety of HPPK could be distinguished: a diffuse form, with gradual transition from hyperkeratotic to normal skin on the palms and soles, and a papular form characterised by a papular border between hyperkeratotic and normal skin. The papular form was more often observed among children and generally developed into the diffuse form with increasing age (I).

The onset of the keratinization disorder varied between 0 and 30 years of age, and hyperhidrosis occurred more often in men than in women and children and disappeared with increasing age in the majority of cases. The hydrophilic character of the hyperkeratosis was a constant clinical finding among patients with HPPK (I). It was not possible to apply geno-ecological principles to the onset, severity or clinical appearance. The keratoderma was assessed as a retention hyperkeratosis and persists throughout life, even though spontaneous remissions have been reported (101).

Other diseases affecting inherited disorders are generally subdivided into two groups, sporadic and familial. Among patients with the dominant variety of HPPK in the northernmost county of Sweden (Norrbotten), sporadic other diseases, such as mutilating PPK, ichthyosis vulgaris, psoriasis vulgaris and atopic dermatitis have been reported (48, 50, 51, 104, 173). A familial case of HPPK associated with acrocyanosis was also reported from the County of Norrbotten (46). Dermatoses with a polygenic or dominant inheritance occur relatively often and it was therefore not surprising that such associated disorders were found among patients with HPPK. Accompanying diseases usually affect ectodermally derived tissues and more seldom tissues generated from mesoderm or entoderm (Table II).

Dermatophytosis. Previously performed investigations, based on a limited number of patients, have shown a frequency of dermatophytosis in patients with HPPK of 30-60 per cent (90, 105, 106). In these studies, *T. rubrum* and *E. floccosum* occurred significantly more often. According to a 5-year survey of dermatophyte infections in the northernmost county of Sweden (Norrbotten) performed in 1977-1981, the frequency of dermatophytosis among patients with HPPK was 35.0% (102). This figure could be confirmed during repeatedly performed studies (I, II, 101, 104). The

prevalence of dermatophytosis was 36.7% with reference to conventional culture, and it was statistically proved that *T. mentagrophytes* more often occurred in patients with HPPK than in those without (I, 107). Predominant clinical symptoms were itching and scaling, while fissuring was more seldom observed (I). Among patients with HPPK, symptomless carriers or latent dermatophytosis could also be demonstrated (I).

It is a general clinical experience that topical and systemic antimycotics have poor therapeutic efficacy on dermatophytosis in patients with HPPK. Therefore, from a clinical and pathogenetic point of view, it was interesting that a cream containing 1% econazole and 50% propylene glycol was reported effective in the treatment of dermatophyte infections in HPPK (133, 174, 175, 176). This cream was signifcantly more effective than 1% econazole cream (Pevaryl®, Cilag AG, Schaffhausen, Switzerland) alone (p < 0.001) (153). Scaling, itching and fissuring disappeared and hyperkeratosis became smooth and uniform. It was therefore tempting to maintain that scaling, itching and fissuring should be considered symptoms of dermatophytosis and not part of the clinical picture.

Previously, two clinical forms of HPPK of the Unna-Thost variety have been reported on the Continent, a rough-surfaced form, characterised by scaling, fissuring and deepening of the major palmar and plantar creases, and a smooth-surfaced form with uniform hyperkeratosis with black discolourations (45). Cultures for dermatophytes were not performed and these two clinical descriptions of HPPK might therefore be interpreted as varieties with and without dermatophytosis.

Personal history of recurrent vesicular eruptions along the hyperkeratotic border occurred significantly more often in patients with HPPK and dermatophytosis than in those without (I, II). Such eruptions were considered a pathogenomic sign of dermatophyte infection and interpreted as an immunological reaction to dermatophytosis. Histopathological examination of biopsies from patients with dermatophytosis showed a mononuclear cell infiltrate at the dermo-epidermal junction which occurred significantly more often in patients with dermatophytosis than in those without. Depending on the intensity of the inflammatory reaction spongiosis and spongiotic vesicules were found together with hyphae and spores. However, a subepidermal mononuclear cell infiltrate is part of the classical histopathological description of HPPK, but the presence of hyphae and spores has not earlier been described.

Vesicular eruptions at the transition zone between hyperkeratotic and normal skin might explain why spreading of dermatophytosis never occur. Erythema, vesicles, scaling and fissuring localised to the transition zone between hyperkeratotic and normal skin is generally the result of this immunological reaction.

Experimental studies. The composition of keratin in patients with HPPK was assessed from the amino acid composition of guanidine-extracted alpha-protein (117). The replacement time of the stratum corneum on the heels of patients with HPPK of the dominant variety was not significantly different from that of healthy control individuals (102, 103). The pH on the soles of patients with HPPK and dermatophytosis did not differ from that of normal control individuals or other patients with dermatophytosis (108, 109, 112, 113).

Immunological cross-reactivity between a glycoprotein isolated from *T. mentagrophytes* and human isoantigen A has been demonstrated in *in vitro* samples

taken from patients who were continuously infected with this particular fungus. Surprisingly, *T. mentagrophytes* was more often isolated from patients with HPPK and blood group A (p < 0.05).

Neither personal nor family histories of atopy or serum IgE > 100 kU/ml were associated with a higher frequency of dermatophytes, even though it has previously been demonstrated in patients with dermatophytosis without HPPK. Specific IgE antibodies against *T. rubrum*, *T. mentagrophytes* and *E. floccosum*, determined by RAST assay, were negative. However, by determination of IgG antibodies against the same species a significantly higher level of *T. mentagrophytes* and *E. floccosum* antibodies could be shown to exist in patients infected with *T. rubrum* and *E. floccosum* (p < 0.05) measured with specific IgG RAST. *T. mentagrophytes* seems to be a weak antibody inducer compared with *T. rubrum* and *E. floccosum*, and patients infected with *T. mentagrophytes* did not produce higher levels of IgG antibodies against these dermatophyte species than control individuals (II). Precipitating antibodies determined by crossed immunoelectrophoresis were found in 54%, compared with 10% of patients with acute or chronic dermatophytosis without HPPK. Even though it was a limited material, it was with this method shown that precipitating antibodies against *T. mentagrophytes* occurred in 100%. Immediate and delayed trichophytin reactions were insignificant when a commercial antigen prepared from extract from *T. mentagrophytes* was used. In a subsequent study with a *T. rubrum* antigen, trichophytin reactions were the same (173). It has previously been reported that much fewer trichophytin reactions were found among patients in Scandinavia than in Central Europe and the USA. Accordingly, positive delayed reactions to *T. mentagrophytes* have been found in 70% and to *T. rubrum* in 12% of patients with chronic dermatophytosis, but such figures were not found among patients with HPPK and dermatophytosis (118, 163, 177, II).

Dermatophytes. Compared with laboratory dermatophytes, the micro- and macromorphology of dermatophytes isolated from patients with HPPK was identical and no difference was found in minimal inhibitory concentration of ketoconazole. When curetted keratin from patients, sterilised with ethylene gas, was placed in the middle of dermatophyte cultures isolated from patients and laboratory strains, an inhibition zone was observed in the centre of most cultures with *T. rubrum* but none with *T. mentagrophytes*. This reaction was unexpected and studies with keratin and dermatophytes from patients with dermatophytosis of the soles but without HPPK are now in progress. When sterilised, pooled keratin from control individuals was placed in the middle of cultures, no inhibition zone could be demonstrated (III). A possible interpretation for this phenomenon is based on reports dealing with immunoglobulins in sweat and sebum (178, 179). Most patients with HPPK suffer from hyperhidrosis and, due to the hydrophilic character of the horny layer, sweat should immediately be absorbed. Therefore, immunoglobulins could possibly be found in the outermost layers of the stratum corneum, reacting with the approaching antigenic invaders. Therefore, an immunological reaction might explain the inhibition zone found in cultures of *T. rubrum* (III).

Climatic conditions leading to special footwear during several months of the year and types of employment in the county did not explain a high frequency and the distribution of dermatophytes in patients with HPPK. It is generally accepted that the distribution of dermatophytes may vary from one area or country to another. However,

such variations could not account for the overrepresentation of *T. mentagrophytes*. Therefore, even though immunological factors may influence the defence mechanism of the hyperkeratosis, the affinity to the abundant horny layer should be considered the most important factor leading to dermatophytosis in patients with HPPK.

Histopathology. The histopathological picture of the dominant variety of HPPK in the northernmost county of Sweden (Norrbotten) was essentially characterised by orthohyperkeratosis, normogranulosis and hyperplasia (I, IV, V). The histological findings corresponded with the original report by A. Thost (3). However, at a follow-up examination of descendants of the original family, described by A. Thost in 1880, characteristic features of epidermolytic PPK, as first described by Vörner in 1904, could be demonstrated (124, 125). Likewise, re-evaluation of biopsies from other families with HPPK of the Unna-Thost variety on the Continent indicated a high frequency of epidermolytic PPK. The histopathological description of the Unna-Thost variety was consequently based on familial cases of epidermolytic PPK. However, this description agreed with that of patients with HPPK of the northernmost county of Sweden (Norrbotten). Biopsies taken from patients with the dominant variety of HPPK in the county constituted 6.2% of the calculated number, but histopathological features corresponding to epidermolytic PPK were not found (IV).

Transgredient or progressive PPK of the Greither variety was first described in 1952. It differed from HPPK of the Unna-Thost variety by hyperkeratotic lesions on the dorsal aspects of the hands and feet, together with hyperkeratotic lesions on the knees and elbows. Several cases on the Continent of the Unna-Thost variety have later been classified as the Greither variety (180). This variety has never been reported among patients with HPPK in the northernmost county of Sweden (Norrbotten). The histopathological picture corresponds to that of the Unna-Thost variety and the existence of the Greither variety as a separate nosological entity has therefore been questioned.

Mutations within the same gene, resulting in insignificant clinical differences in the group of dominant inherited diffuse PPKs, might be an explanation for confusions in the classification. Consequently, the Unna-Thost variety should be considered a non-epidermolytic PPK and the only dominant inherited variety in the County of Norrbotten. Therefore, according to Prof. S.H. Saurat, Editor of "Dermatology", Geneva, Switzerland, it appeared most logical to adopt the name "Diffuse HPPK type Norrbotten" for this keratinisation disorder (181).

Ultramicromorphology. Electron-microscopical examinations were performed in 3 affected and 5 unaffected members of one of the families with the presumed recessive variety of HPPK. Two additional cases, belonging to 2 different families, were also examined.

It was documented that keratohyalin granules with spongiosity, increased electron density and a granular border were characteristic features of the presumed recessive variety of HPPK. These characteristics were also found in keratohyalin granules of the heterozygous family members. Granular borders have also been found in HPPK of the Unna-Thost variety and in some cells of verrucae vulgaris (167, 182). However, ultrastructural characteristics were considered sufficient for a new type of recessive diffuse PPK, proposed by Prof. I. Anton-Lamprecht, Heidelberg, Germany,

to be named "Hereditary palmoplantar keratosis of the Gamborg Nielsen type" (VI).

Mal de Meleda with an established recessive inheritance, the "Gamborg Nielsen type" and the "Nagashima type" with presumed recessive inheritance (183) might be looked upon as allelic mutants which should be further characterised and differentiated as soon as the biochemical or genetic defects are identified. Until that time, they should be considered variations of a heterogeneous group of HPPK with probably a recessive inheritance, which might belong to the recessive inherited Mal de Meleda.

Based on results of the studies, a new classification of the diffuse HPPKs was proposed (Table VIII).

Table VIII. New classification of diffuse kereditary palmoplantar keratoderma.

AUTOSOMAL DOMINANT INHERITANCE	HPPK of the Unna-Thost variety?
	HPPK of the Greither type?
	Mutilating PPK Vohwinkel
	HPPK type Norrbotten
	HPPK type Vörner
AUTOSOMAL RECESSIVE INHERITANCE	Mal de Meleda
	"Nagashima" type?
	"Gamborg Nielsen type"?

CONCLUSIONS

This thesis, which includes seven studies, performed between 1984 and 1993, deals with different aspects of HPPK in the northernmost county of Sweden (Norrbotten). As long ago as in 1967, C. Bergström was able to show a prevalence of HPPK of 0.55%. In a solitary county, this prevalence should be considered the highest in the world.

About 20 years later, the original propositi from the first study were traced and 51% of these were examined at the Department of Dermatology, Central Hospital, Boden, Sweden. Relatives of the propositi were requested to visit the clinic and 14.2% of the calculated number of patients with the dominant variety of HPPK were examined. Two of the original propositi had a presumed recessive variety of HPPK and, together with 6 relatives from 4 families, they constituted 0.002% of the calculated number of patients.

The distribution of patients corresponded to the general population density of the county. The clinical picture of the dominant variety differed from that of the Unna-Thost variety of HPPK, being without a bluish-red demarcation between hyperkeratotic and normal skin. Hyperkeratosis was smooth and uniform and subdivision into a form characterised by scaling and fissuring and a smooth-surfaced form was not possible in patients without dermatophytosis. The presumed recessive variety of HPPK differed clinically from Mal de Meleda by absence of extra-palmary or extra-plantary lesions.

The frequency of dermatophytosis was 36.2%, corresponding to a prevalence of 37.6%, and it was shown that *T. mentagrophytes* occurred significantly more often in patients with HPPK than in those without. Scaling and fissuring were predominant features of dermatophytosis and treatment resulted in a smooth and uniform hyperkeratosis. It was therefore concluded that scaling and fissuring were not part of the clinical picture. A personal history of recurrent vesicular eruptions along the hyperkeratotic border was found significantly more often in patients with dermatophytosis. Symptomless carriers or latent dermatophytosis were also found. Influence of climatic or employment factors on the frequency and distribution of dermatophyte infections in patients with HPPK could not be documented.

The keratoderma was considered to be a retention hyperkeratosis, and the amino acid composition and pH on the soles of patients with HPPK and dermatophytosis did not differ from those without fungal infection or normal control individuals. Blood group A occurred significantly more often among patients with HPPK infected with *T. mentagrophytes*. This study was based on *in vitro* studies of cross-reactivity between a glycoprotein isolated from *T. mentagrophytes* and human isoantigen A. Family and personal histories of atopy, serum IgE levels and IgE RAST results did not differ from those of controls. IgG RAST and precipitating antibodies determined by crossed immunoelectrophoresis supported the mycological findings. Trichophytin reactions did not add any further information. The morphology and resistance of dermatophytes did not differ from those of laboratory strains but a sort of immunological reaction of keratin from patients with HPPK and dermatophytosis may indicate that an immunological reaction occurred. The affinity of dermatophytes and especially *T. mentagrophytes* to the horny layer of the palms and soles of patients with HPPK should so far be interpreted as depending on the great amount of keratin.

Re-examination of biopsies from descendants of the original family of Thost and likewise other families assessed as HPPK of the Unna-Thost variety showed that they

in fact had epidermolytic PPK type Vörner. Therefore, the dominant variety of HPPK in the northernmost county of Sweden (Norrbotten) should be considered an independent variety named "Diffuse HPPK type Norrbotten".

A mononuclear dermo-epidermal cell infiltrate belongs to the classical description of the Unna-Thost variety. It was shown that this cell infiltrate occurred significantly more often in patients with dermatophytosis than in those without, and it was therefore interpreted as an inflammatory reaction to dermatophyte infections.

The light microscopical picture of the presumed recessive variety of HPPK did not differ from that of the dominant variety but ultrastructural characteristics found in both unaffected and affected members of the families differed from those of Mal de Meleda and the dominant variety of HPPK. The ultrastructural features were interpreted as a new type of HPPK with a recessive inheritance, which differed from previously reported varieties. It was proposed to be named "HPPK type Gamborg Nielsen". Based on these findings, it was concluded that HPPK in the northernmost county of Sweden (Norrbotten) includes two new varieties of HPPK.

ACKNOWLEDGEMENTS

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