TYLOSIS PALMARIS ET PLANTARIS FAMILIARIS ASSOCIATED WITH CLINODACTYLY

GORDON K. KLINTWORTH, B.Sc., M.B., B.Ch. (RAND) and INGRAM F. ANDERSON, M.B., B.Ch. (RAND)

Department of Medicine, Johannesburg General Hospital

Tylosis palmaris et plantaris familiaris (hereafter referred to as tylosis) is a familial ectodermal anomaly of the palms and soles producing marked hyperkeratosis. It is to Thost[35] and Unna[37] that credit must be given for the original description of the disease. Since then numerous reports have appeared in the literature. The most comprehensive review of the whole subject, however, is that of Cockayne.[3] Several workers have noted the rare association between tylosis and other conditions. Among them are Howel-Evans *et al.*[9] who discussed the association of this disease with carcinoma of the oesophagus. Modern genetic studies have focussed attention on the co-existence of familial conditions. In view of this it was felt necessary to study, in more detail, the family of a patient who presented with a myocardial infarction and a family history of tylosis.

A family of 59 members through 5 generations was investigated. Wherever possible they were personally interviewed. Where this was not practicable a first-hand collaborative history was taken from several other family members. Particular attention was paid to the presence of tylosis and other ectodermal anomalies, arterial degenerative disorders, dysphagia, and other abnormalities. In those deceased the cause of death was ascertained.

CASE REPORT

Mr. C.P., aged 42 years, lorry driver, was admitted to the Johannesburg General Hospital on 12 September 1959 with a myocardial infarction following a period of angina of effort. Typical hyperkeratotic lesions of the soles and palms, with extension of the lesion to the dorsal surfaces of the index and little fingers, were present. Similar small areas of horny thickening of the skin were noted over the extensor aspects of both elbows, overlying the tendo Achillis, and to a lesser extent in the dorsal ankle crease. An interesting feature was anhydrosis of the affected areas. The patient gave a good description of tylosis in other members of his family. The condition apparently became evident when he began to crawl at the age of 6 months but had not really troubled him until he became engaged in manual labour. He noted that his skin was much improved in a humid atmosphere and that use

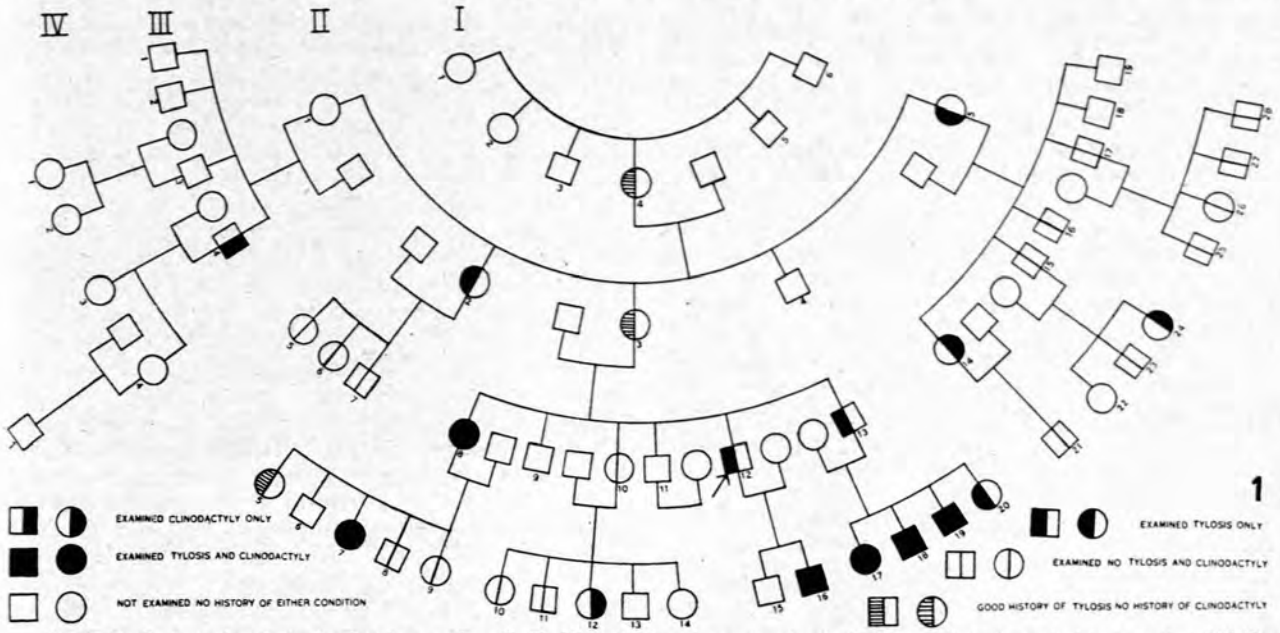


Fig. 1. Family tree of patient, showing 4 generations (I, II, III and IV) and one member in fifth generation. Arrow points to patient (III 12).

TABLE I. SUBJECTS WHO WERE PERSONALLY EXAMINED OR HAD HISTORY OF TYLOSIS

Family member†	*Sex*	*Age (years)*	*Examined or not*	*Living or deceased*	*Presence of tylosis*	*Distribution and severity of lesions*							*Presence of clinodactyly*	*Sweating of hands and feet*
						Soles	*Palms*	*Dorsum elbow*	*Tendo Achillis*	*Knee*	*Dorsum foot*	*Medial maleoli*		
I 4	F	95	N E	D	Yes	—	—							
II 2	F	50	E	L	Yes	++	++	—	—	+	—	—	—	Increased
II 3	F	51	N E	D	Yes	—	—	—	—	—	—	—	—	—
II 5	F	64	E	L	Yes	+++	+++	+	—	—	—	+	—	Decreased
III 4	M	50	E	L	No	—	—	—	—	—	—	—	Yes	Normal
III 5	F	11	E	L	No	—	—	—	—	—	—	—	No	Normal
III 6	F	9	E	L	No	—	—	—	—	—	—	—	No	Normal
III 7	M	7	E	L	No	—	—	—	—	—	—	—	No	Normal
III 8	F	38	E	L	Yes	++	+++	—	—	+	+	—	Yes	Decreased
III 10	F	33	E	L	No	—	—	—	—	—	—	—	No	Normal
III 12	M	42	E	L	Yes	+++	+++	+	+	—	+	—	No	Decreased
III 13	M	35	E	L	Yes	++	+++	—	+	—	—	—	No	Decreased
III 14	F	24	E	L	No	—	—	—	—	—	—	—	Yes	Normal
III 15	M	41	E	L	No	—	—	—	—	—	—	—	No	Normal
III 16	M	18	E	L	No	—	—	—	—	—	—	—	No	Normal
III 17	M	42	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 5	F	17	N E	L	Yes	—	—	—	—	—	—	—	—	—
IV 7	F	14	E	L	Yes	++	++	—	+	—	—	+	Yes	Decreased
IV 8	M	13	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 9	F	7	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 10	F	14	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 11	M	12	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 12	F	10	E	L	No	—	—	—	—	—	—	—	Yes	Normal
IV 16	M	5	E	L	Yes	+++	+++	+	+	—	+	—	Yes	Decreased
IV 17	F	12	E	L	Yes	++	++	—	+	—	—	+	Yes	Normal
IV 18	M	10	E	L	Yes	++	++	+	+	+	+	+	Yes	Decreased
IV 19	M	7	E	L	Yes	++	++	—	+	—	—	+	Yes	Normal
IV 20	F	3	E	L	Yes	++	++	—	—	—	—	—	No	Normal
IV 21	M	1	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 23	M	9	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 24	F	5	E	L	No	—	—	—	—	—	—	—	Yes	Normal
IV 25	M	10	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 26	F	6	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 27	M	8	E	L	No	—	—	—	—	—	—	—	No	Normal
IV 28	M	2	E	L	No	—	—	—	—	—	—	—	No	Normal

F=female, M=male, NE=not examined, E=examined, D=deceased, L=living, +=slight, ++=more pronounced, and +++=severe.
† For numbers refer to Fig. 1.

of the hands, especially in cold dry weather, resulted in gross thickening, cracking and even bleeding of the palmar skin. Except for the presence of tylosis and evidence of acute myocardial infarction, general examination of the patient was essentially normal.

Family

In the 59 members of the family there were at least 14 with tylosis (9 female, 5 male). Of the 32 members personally examined, 11 were affected; a good description was obtained regarding 3 others (Fig. 1 and Table I). In all affected cases the age of onset was in the first year of life. In 10 of the subjects clinodactyly was noted. In this condition the little finger is curved inwards towards the other fingers. No other abnormality of skin or skeleton was noted nor were there any abnormalities of hair or teeth. Besides the patient, 2 (II5, III11) of the 33 living members had sustained myocardial infarctions. No other members gave a history of cardiovascular disease. There was no history of dysphagia or buccal leukoplakia and as far as could be ascertained no one had died of oesophageal carcinoma. Of the 7 in whom the cause of death was known (I4, II1, II3, II4, III9, III18, and III19), 3 were due to cardiac disease (I4, II1, and II3). None of the 7 had died of malignant disease.

DISCUSSION

Tylosis

Much confusion exists in the literature regarding the terminology of the group of hyperkeratoses. Tylosis palmaris et plantaris has the following synonyms:[23] keratosis palmaris et plantaris, hyperkeratosis palmaris et plantaris, ichthyosis palmaris et plantaris, keratoderma palmare et plantare, and symmetrical keratoderma.

The condition has been described as rare.[22] In Northern Ireland the incidence was calculated to be 1 in 40,000.[24]

Histopathologically,[10] the skin usually shows considerable hypertrophy of all its layers, more especially the stratum corneum, which is grossly thickened. The stratum granulosum is normal in appearance and there is no change in the stratum spinosum. Occasionally there is flattening of the papillary body. These papillae may be increased five-fold in depth. The dermis is unaffected, except outside the area of horny thickening or where fissures are present, when mild inflammatory changes may be noted. The sweat glands and their ducts may be hypertrophied. The histopathological section in the present case is shown (Fig. 2) compared with a normal section (Fig. 3).

Clinically tylosis is rarely manifest at birth and is usually not recognized until the third or fourth month. In exceptional cases the onset may be delayed until the age of 6 years.[19,23] The lesions are bilateral, symmetrical, and situated almost exclusively on the palms and soles (Figs. 4 and 5) either of which may be predominantly involved. Occasionally the hyperkeratosis is noted on the dorsum of the hands, feet and phalanges. In some cases it is present on the extensor surfaces of the elbows, over the knees and about the ankles.[15,19] The nails may be involved and become thickened and opaque and are raised up from the nail bed by a horny accumulation beneath them. This complication may result in more severe symptoms than those produced by the skin lesions.

The distribution is determined to a large extent by physical factors such as pressure and friction. Thus, in infants, the lesions will be on the knees; on beginning to walk the feet are most involved in the weight-bearing areas of the soles; the manual labourer exhibits gross

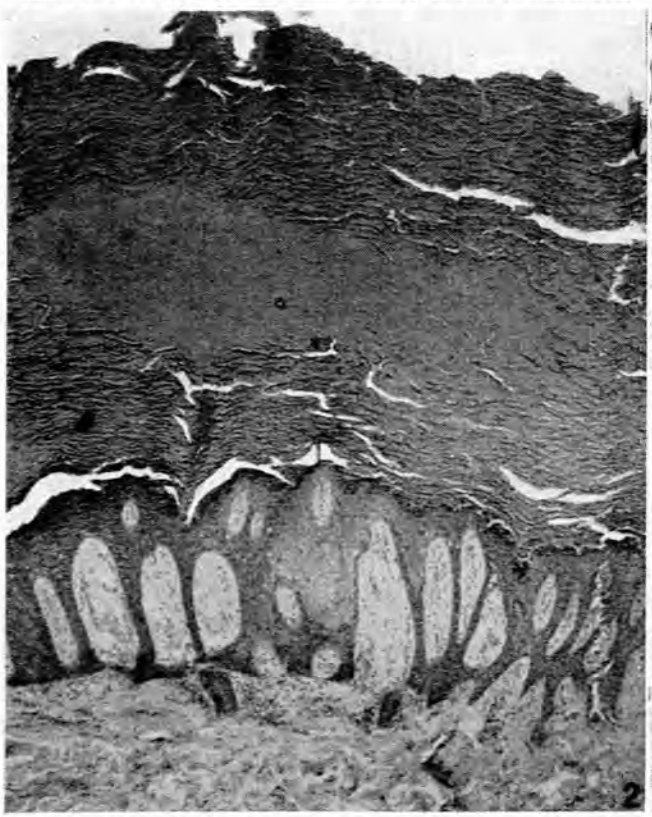


Fig. 2. Low-power section of hyperkeratotic palmar skin (× 45).

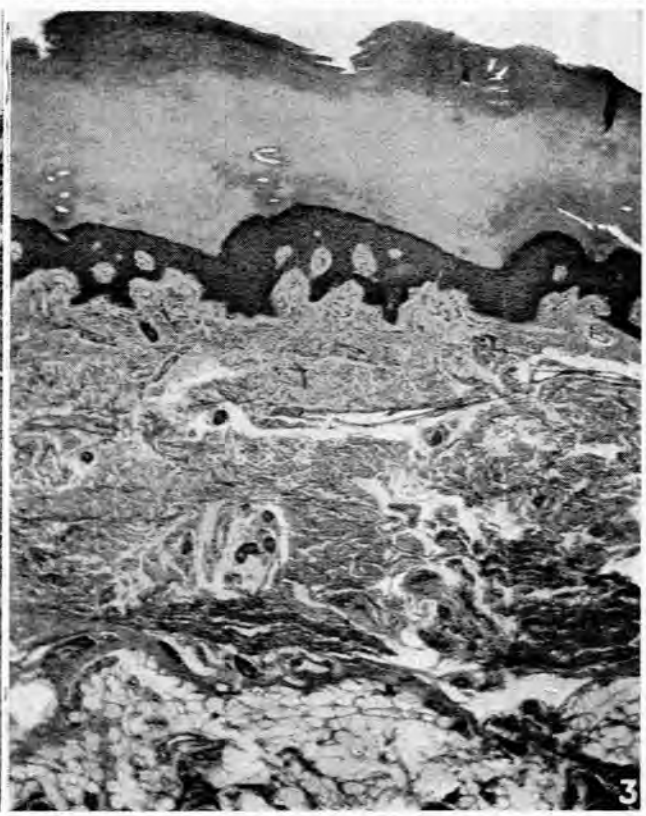


Fig. 3. Low-power section of normal palmar skin (× 45).

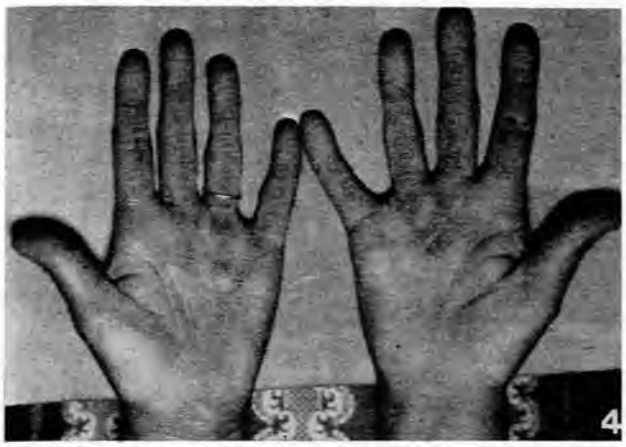


Fig. 4. This shows the bilateral lesions of tylosis on the palms.

lesions of the palms, and the office worker may have a predominant affection of the elbows.

The condition varies not only in intensity in different individuals of the same family but also at different times in an affected individual. The condition is aggravated during very warm or very cold weather and also during manual labour, especially if the work involves exposure of the hands to moisture and cold.[24] The influence of climatic and occupational factors was also well illustrated in members of the family we studied.

Many subjects may be so slightly affected that they do not realize that they have the condition until their attention is drawn to it. On the other hand, marked thickening of the palmar skin may reduce tactile sensibility and

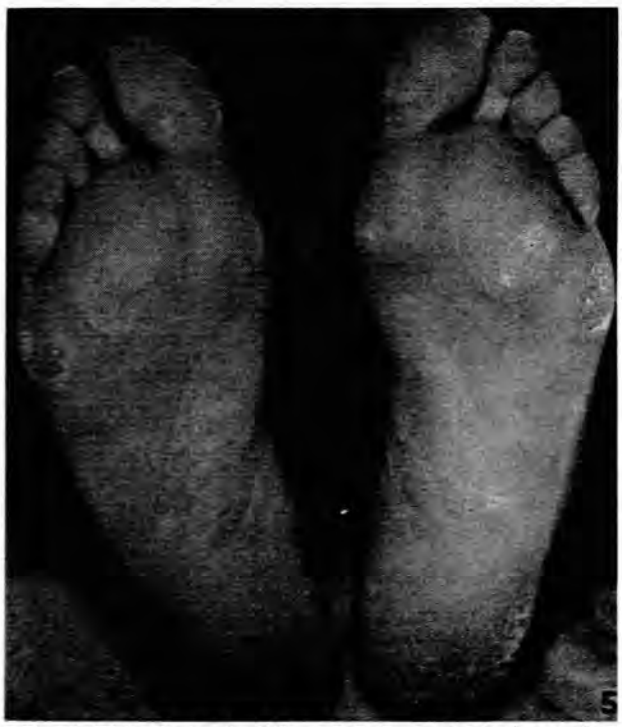


Fig. 5. This shows the bilateral lesions of tylosis on the soles. Note symmetry of the lesions.

interfere with the finer finger movements. Pain is not usually a marked feature of the hand lesions, although Anderson[1] reported a case with extremely painful lesions of the hands. The soles tend to be more painful than the palms and this may interfere with normal walking. Affected areas are predisposed to fissuring because of a lack of normal elasticity.[22,23] The normal fissures are exaggerated and produce a mosaic-like appearance. Involvement of the dermis by the fissures causes pain and sometimes haemorrhage.

Hyperhydrosis is present in the majority of cases reported in the literature. Families are on record in which sweating was diminished.[3] In the family under consideration both states obtained. There appeared to be an inverse relationship between the degree of hyperkeratosis and the amount of sweating, and we suggest that the hypohydrosis in severely affected cases may be due to obstruction of the sweat-gland ducts by the thickened and hyperkeratotic skin. Sweat-gland hypertrophy is not an uncommon feature and may account for the increased sweating noted in milder cases.

Tylosis should be differentiated from the acquired types of hyperkeratosis, notably lichen simplex (neurodermatitis), contact dermatitis, psoriasis, tertiary syphilis, fungal infections (particularly *Trichophyton rubrum*), volar verrucae, calluses, and the now rarely-seen arsenical keratoderma.[19,23,28]

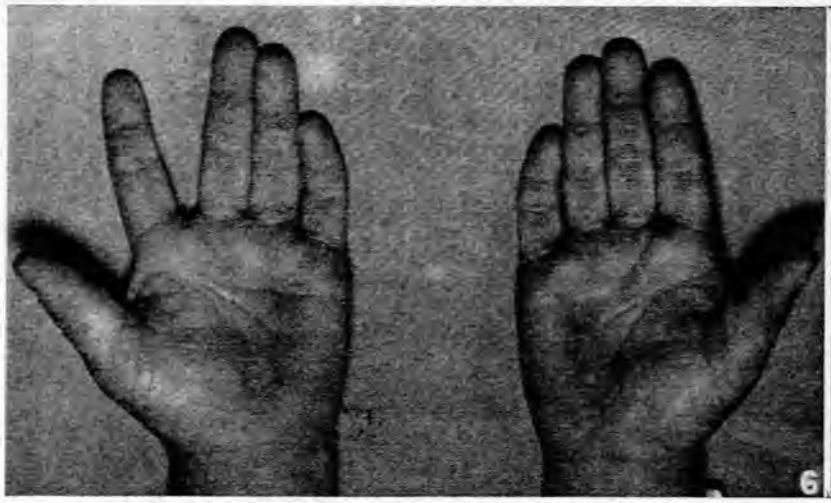
Certain familial skin conditions resembling tylosis must be differentiated. Hereditary disseminate keratoderma palmaris et plantaris consists of multiple, symmetrical, discrete plaques on the palms and soles. The lesions do not coalesce and the onset usually occurs at adolescence but is sometimes delayed until adulthood.[21]

Mal de Meleda[3] is a rare type of palmar and plantar hyperkeratosis described only on the island of Meleda off the Dalmatian coast. Most of the inhabitants are consanguinously related; this favours transmission of the disease by what is considered to be a recessive gene. In addition to the usual sites the hyperkeratosis involves the dorsum of the hands and feet, and may extend up the legs and forearms to the elbows and knees. Hyperhydrosis is present.

There is no known cure for tylosis. Amelioration may occur with change of occupation or during humid weather. Treatment is purely palliative and numerous therapeutic measures have been employed with variable temporary benefit. Keratolytics such as salicylic-acid preparations are employed to soften and remove the horny layers. Superficial X-ray therapy has been advocated by some but has not met with general approval, mainly because of the risk of causing carcinoma and because effective dosage may lead to cicatricial atrophy with telangiectasis.[10] Various hormones, notably thyroid extract and oestrogens, have been tried. The use of large doses of vitamin A has been reported to control the gross manifestations of the disease.[16] Its use is purely empirical and no satisfactory explanation of the mechanism is forthcoming. Sandpapering and mechanical abrasion of the affected areas has been used. In severe cases benefit has been claimed by complete excision and grafting.[4,13,19,29]

Tylosis and Associated Abnormalities

Many abnormalities associated with tylosis have been



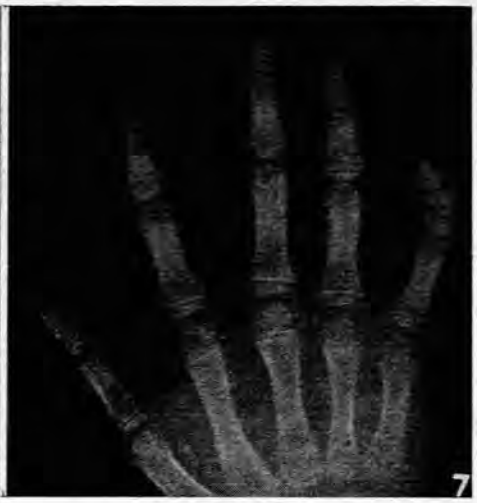


Fig. 6. Tylosis and clinodactyly. Note radial deflection of both little fingers.
Fig. 7. Clinodactyly. X-ray showing sloping of the distal surface of the middle phalanx of the little finger due to shortening of the radial surface of the phalanx.

described in isolated instances. Howel-Evans *et al.*[9] reported the association of carcinoma of the oesophagus and tylosis in 2 families. There was unequivocal evidence that carcinoma of the oesophagus was associated with tylosis in 17 of their cases, and in only 1 case in which the neoplasm was found was it impossible to establish that tylosis was present. Members of the family unaffected by tylosis were unaffected by carcinoma. In the cases of carcinoma of the oesophagus in which the oesophageal epithelium adjacent to the tumour was examined histologically, no evidence of hyperkeratosis was found. The association between palmar and plantar hyperkeratosis and leukoplakia of the mouth has been recorded.[12,23,25] Malignant degeneration in areas of hyperkeratosis has been considered likely by some dermatologists,[15] and Ingram and Brain[10] mentioned a case in which squamous carcinoma developed in tylosis.

Hanhart (quoted by Cockayne[3]) described a Swiss family in which the affected members developed tylosis and multiple lipomata during late adolescence. Cockayne[3] commented that the late age of appearance of tylosis made it doubtful whether it was the ordinary form of the disease.

Tylosis has been reported to occur occasionally with extensive ichthyosis hystrix or with epidermolysis bullosa.[10] It has been found associated with other ectodermal abnormalities[3,10,23] or with hypogenitalism, oxycephaly, clubbing of the fingers, or mental retardation.[2,3]

Clinodactyly, as described in our cases, is a shortening of the middle phalanx of the fifth finger, mainly on its radial aspect, which results in a radial deflection of the terminal phalanx of from 15° to 30° (Fig. 6). The remaining digits are normal and there is no flexion curvature.[8] On X-ray (Fig. 7), the middle phalanx of the little finger is slightly shorter on the radial side, thus forming an appreciable slope on its distal surface. X-ray observations indicate that this seems to be caused by a slowing-down process of ossification, specifically at the upper radial part of the middle phalanx of the fifth finger. Due to this slanting, the distal phalanx is inclined inwards towards the other fingers. The rest of the phalanges are normal. The incidence has been calculated at 1 in 1,000 in Northern Ohio.[8] Hersh *et al.*[8] feel that the term clinodactyly should be limited to those cases which are due to incomplete ossification and should not be confused with other causes of familial crooked little fingers such as those due to abnormal tendons[5-7] and to fused ossification.[11]

Genetic Transmission

Tylosis is inherited as a Mendelian dominant with high penetrance. It appears to be controlled by a single autosomal gene. Cockayne[3] reviewed 47 families in the literature and the proportion of affected to normal members was 594 : 483. The sex ratio was 318 males to 284 females. He reported 2 small families in whom the lesion only occurred in the females and not in the males. Subsequent studies, however, indicated that the two sexes are equally affected and no race is immune.[20,23]

Lawler and Renwick[14] are of the opinion that there are at least 2 types of inherited tylosis which apparently run true in families and appear to be due to different genes. The 2 forms have been differentiated on clinical grounds. Type A has a variable age of onset ranging from 5 to 15 years, whereas Type B is recognizable during the first year of life. The latter is clinically distinguishable from Type A by the uniform thickness of the keratosis, by the sharply delimited edges of the lesion, and by the rare incidence of painful fissuring. Both types are inherited as a Mendelian dominant. This clear-cut distinction was not a feature of our cases, since fissuring was not an uncommon finding in lesions which had been noted in the first year of life with relatively sharply demarcated edges and in which keratosis was of uniform thickness.

Tylosis is due to a mutant gene and the extent, distribution and severity are independent aspects which are largely determined by composite genetic and environmental factors. Thus the same mutant gene may cause several distinct clinicopathological pictures and this difference in expressivity may be evoked to explain the large and varied nomenclature applied to the hyperkeratoses.

Clinodactyly has not previously been described asso-

ciated with tylosis. The only reported association of clinodactyly is that with webbing of the toes.[8] In the family we studied there were 10 members with clinodactyly — 6 female and 4 male. In 8 cases the curving of the little finger was bilateral but in 2 this curving was only present in the left hand. Of those with clinodactyly, 6 were affected with tylosis as well. Clinodactyly is transmitted as an autosomal dominant. Lack of complete penetrance was shown by the fact that in 6 cases the parents did not have the condition. In 1 case (IV24) neither the parents nor the grandparents had clinodactyly. These features of dominant transmission with incomplete penetrance have been reported by others.[8]

Is there a genetic linkage between clinodactyly and tylosis, or is the association purely one of chance? We were unable to obtain statistically significant results in favour of genetic linkage, using the sibling pair method of Penrose.[17,18] However, assuming that the incidence of tylosis and clinodactyly in South Africa is 1 in 40,000[24] and 1 in 1,000[8] respectively, the probability of these 2 conditions occurring together is in the region of 1 in 40 million.

SUMMARY

In a family affected with tylosis palmaris et plantaris 59 members were studied. The family tree and the mode of genetic transmission are outlined. The incidence, histopathology, clinical features, differential diagnosis and treatment of tylosis are discussed. The association of tylosis and clinodactyly is noted. In addition some of the reported abnormalities occurring with tylosis are reviewed.

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REFERENCES

1. Anderson, I. (1951): Brit. J. Derm., **63**, 127.
2. Bureau, G., Horeau, M., Barriere, H. and DuFage, C. (1958): Bull. Soc. franç. Derm. Syph., **65**, 328.
3. Cockayne, E. A. (1933): *The Inherited Abnormalities of the Skin and its Appendages*. London: Oxford University Press.
4. Dencer, D. (1953): Brit. Plast. Surg., **6**, 130.
5. Heffner, R. A. (1924): J. Hered., **15**, 323.
6. *Idem* (1929): *Ibid.*, **20**, 395.
7. *Idem* (1941): *Ibid.*, **32**, 37.
8. Hersh, A. H., De Marinis, F. and Stecher, R. M. (1953): Amer. J. Hum. Genet., **5**, 257.
9. Howel-Evans, W., McConnell, R. B., Clarke, C. A. and Sheppard, P. M. (1958): Quart. J. Med., **27**, 413.
10. Ingram, J. T. and Brain, R. T. (1957): *Sequeira's Diseases of the Skin*, 6th ed. London: Churchill.
11. Koenner, D. M. (1934): J. Hered., **25**, 329.
12. Kumer, L. and Loos, H. O. (1935): Wien. klin. Wschr., **48**, 174.
13. Landazuri, H. F. (1958): Plast. Reconstr. Surg., **22**, 557.
14. Lawler, S. D. and Renwick, J. H. (1957): Personal communication to Howel-Evans *et al. loc. cit.*[9]
15. Ormsby, O. J. and Montgomery, H. (1948): *Diseases of the Skin*, 7th ed. Philadelphia: Lea and Febiger.
16. Porter, A. D. (1951): Brit. J. Derm., **63**, 123.
17. Penrose, L. S. (1935): Ann. Eugen., **6**, 133.
18. *Idem* (1938): *Ibid.*, **8**, 233.
19. Pupo, J. A. and Farina, R. (1953): Plast. Reconstr. Surg., **12**, 446.
20. Scott, O. L. S. *In* Sorsby, A. ed. (1953): *Clinical Genetics*. London: Butterworth.
21. Scott, M. J., Costello, M. J. and Simuangco, S. (1951): Arch. Derm. Syph., **64**, 301.
22. Semon, H. C. G. (1953): *An Atlas of the Commoner Skin Diseases*, 4th ed. Baltimore: Williams and Wilkins.
23. Sutton, R. L. and Sutton, R. L., jun. (1939): *Handbook of Diseases of the Skin*, 10th ed. St. Louis: C. V. Mosby.
24. Swan, H. P. (1956): Ulster Med. J., **25**, 27.
25. Thost (1880): Dissertation, Heidelberg. (Quoted by Cockayne, E. A. *loc. cit.*[3]).
26. Touraine, A. (1954): Brit. J. Derm., **66**, 294.
27. Unna, P. G. (1886): *Histopathology*. Edinburgh: Walker. (Quoted by Cockayne, E. A. *loc. cit.*[3]).
28. Vickers, H. R. (1960): Practitioner, **184**, 350.
29. Wynn-Williams, D. (1953): Brit. J. Plast. Surg., **6**, 123.