causing death. Experimentally, Bywaters and Stead (1944) showed that myoglobin injected into healthy rabbits caused no renal damage unless the urine was acidified. It is therefore unlikely that the myoglobin released in sea-snake poisoning is solely responsible for the renal lesions. Is the venom nephrotoxic? Reid and Jenkins (1948) showed that cobra venom acted directly on the kidney of eviscerated adrenalectomized cats, causing liberation of rennin. Hypertension was observed in Case 1 and 3; progressive hyperkalaemia was the immediate cause of death in Cases 1 and 5. Renal damage may be mainly responsible for these two features—a renal pressor factor leading to hypertension while progressive hyperkalaemia arose because diminished renal excretion failed to cope with the extra load from cellular release of potassium. Against this concept of sea-snake venom being directly nephrotoxic is the paucity of visible damage in patients dying within 24 hours of the bite. By analogy with the skeletal-muscle lesions so evident in sea-snake poisoning one would certainly expect to find renal necrosis even when death occurs shortly after the bite. We have been unable to demonstrate the fine fatty globules which Graber and Seviitt (1959) found in the glomerular tufts and which they thought might be a histological sign of structural changes affecting glomerular filtration in burned patients.

The liver may appear distinctly pale at necropsy. Feldberg and Kellaway (1938a) described depigmentation and release of adenyl compounds from the liver experimentally perfused with cobra venom. Similar depigmentation occurred with staphylococcal toxin, mercuric chloride (Feldberg and Kellaway, 1938b), and clostridial toxin (Kellaway, Reid, and Trethewie, 1941). The centrilobular degeneration in sea-snake poisoning may therefore be due to direct venom damage. In Case 2 there was no obvious clinical explanation why death occurred when it did (Reid, 1961): in such cases liver damage may be an important factor.

Clearly, there are important differences in pathology between sea-snake poisoning in man and in the animals so far reported. Myonecrosis was not found at necropsy on a goat which died 30 hours after injection of *E. schistosa* venom; rabbits dying acute deaths showed no lesion in muscle, liver, or kidney (Carey and Wright, 1960). Possible explanations for these discrepancies include: (1) species may differ in their reactions; (2) some change occurs in sea-snake venom during desiccation; and (3) myonecrosis has been overlooked. To elucidate the problem we have recently injected dogs with *E. schistosa* venom, both freshly obtained and reconstituted from dried venom. In each case typical widespread necrosis of skeletal muscle was histologically evident. This suggests that myonecrosis has previously been overlooked.

Summary

The principal pathological lesion of sea-snake poisoning in man is necrosis of skeletal muscle.

As with other types of myonecrosis, renal damage often results.

Histological changes in the nervous system and in smooth and cardiac muscle are notably absent.

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HYPOVITAMINOSIS-A IN A FAMILY WITH TYLOSIS AND CLINODACTYLY

BY

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Tylosis palmaris et plantaris constitutes one of the group of polykeratoses (Touraine, 1954) and is a rare familial ectodermal anomaly of the palms and soles characterized by marked hyperkeratosis. The most comprehensive review of the subject is that of Cockayne (1933).

The association between various hyperkeratotic and dyskeratotic skin diseases and hypovitaminosis-A has been noted (Rapaport *et al.*, 1942; Peck *et al.*, 1943a, 1943b; Leitner and Moore, 1946; Leitner and Ford, 1947). Low blood levels of vitamin A were found in tylosis (Porter, 1951) and some improvement in the skin lesions occurred on giving high doses of the vitamin.

The present report is a study of a tylosic patient who was admitted to hospital with a myocardial infarction and a good description of tylosis in the family. The histopathological and clinical features of tylosis in this family have been more extensively dealt with in an earlier publication (Klintworth and Anderson, 1961).

Materials and Methods

A family of 59 members through five generations was investigated. Wherever possible they were personally interviewed. Where this was not practicable a first-hand collaborative description was taken from several other members of the family. Particular attention was paid to the presence of tylosis, cardiovascular disorders, manifestations of hypovitaminosis-A, and dysphagia. In those deceased the cause of death was ascertained. Specimens of blood were taken from willing members for estimation of the serum vitamin A, carotene, and lipid.

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The levels of serum vitamin A and carotene were estimated by the method of Pett and LePage (1940). Lipoprotein partitions were carried out on fasting specimens of blood. A dietary history was obtained, and special attention was paid to the carotene and vitamin-A content of the diet.

The propositus was in addition tested for dark-adapted visual acuity, using a Feldman adaptometer; his protein-bound iodine and vitamin-A uptake were determined; skin was biopsied for histology and vitamin-A autofluorescopy.

Results

The family tree is illustrated in Fig. 1. There were at least 14 members with tylosis (9 female, 5 male). Of the 32 members personally examined 11 were affected; a good description was obtained regarding three others. The extent and severity of the skin lesions were largely determined by occupational and climatic factors. Thus there was an aggravation of the skin condition during cold dry weather or, in the case of the hands, after prolonged manual labour. In addition, 10 members (6 female, 4 male) had clinodactyly—a curving-in of the little finger. This was associated with tylosis in six of the 10 cases.

Two other members besides the propositus had sustained a myocardial infarction. Of the seven known deaths, three were due to "heart disease" and none to malignancy. None of the family complained of night blindness, but this was not unexpected, as all were city dwellers.

Vitamin A.—The results of the biochemical findings are given in Table I. The fasting values of vitamin A were subnormal in the eight cases with tylosis, while the carotene levels were within normal limits. Two members (III 17 and III 14), although in the direct line of descent, did not have tylosis, but were hypovitaminotic-A. The propositus and his affected child did not benefit from vitamin-A therapy in high doses.

Lipoprotein Partition.—The results are shown in Table II. Several members exhibit evidence of hyperlipaemia, hypercholesterolaemia, and raised beta-lipoprotein fractions. There is, however, no constant association with either clinodactyly or tylosis.

The protein-bound iodine in the blood of the propositus was normal and his dark-adapted visual acuity was at the lower limit of normal. Autofluorescence of the skin showed the presence of carotene in the epithelium, especially in the stratum corneum. Vitamin A was absent in the skin.

Histologically the skin showed considerable hypertrophy of all its layers, more especially of the stratum corneum, which was greatly thickened. The stratum granulosum was normal in appearance and there was no change in the stratum spinosum. The papillae were increased in depth. The dermis was unaffected.

TABLE I.—Vitamin A and Carotene Levels

Family Member	Vitamin A I.U./100 ml.	Carotene mmg./100 ml.	Family Member	Vitamin A I.U./100 ml.	Carotene mmg./100 ml.
Average normal	70	60-300	III 12	3	112
II 2	15	72	III 13	43	138
II 5	6	102	III 14	32	65
III 4	79	65	III 17	0	123
III 8	22	72	IV 17	0	146
			IV 18	21	82
			IV 19	0	150

TABLE II.—Lipoprotein Partition

Family Member	Total Lipid mg./100 ml.	Total Cholesterol mg./100 ml.	Cholesterol		Cholesterol %		Lipoprotein %	
			Free mg./100 ml.	Esters of mg./100 ml.	$\alpha_1\alpha_2$ Lipo-protein	β Lipo-protein	$\alpha_1\alpha_2$ Lipo-protein	β Lipo-protein
Adult average normal	400-600	160-250	45-65	115-185	15-33	67-85	25-50	50-75
II 2	813	172	52	120	19	81	21	79
II 5	956	372	114	258	19	81	26	74
III 4	1,109	263	78	185	24.5	75.5	—	—
III 8	1,287	331	97	234	12.5	87.5	18.5	81.5
III 12	1,415	392	104	288	10	90	7	93
III 13	1,207	242	68	174	15	85	11	89
III 14	567	172	46	126	26	74	34	66
III 17	891	272	69	203	18	82	17	83
IV 17	665	228	58	170	22.5	77.5	26.5	73.5
IV 18	701	232	55	177	19	81	32	68
IV 19	591	209	—	—	—	—	—	—

Discussion

Vitamin A and Carotenoids

Vitamin A has an inhibiting effect on keratinization in epithelial cells. Defective metabolism of vitamin A, or hypovitaminosis-A, seems to be causally related to hyperkeratosis and other disorderly behaviour of

FIG. 1.—Family tree

epithelial tissues. Despite its importance to the skin, vitamin A is not present in the normal epidermis (Popper, 1941, 1944; Cornbleet and Popper, 1942), and this finding was confirmed in the hyperkeratotic skin of our case. Porter (1951) found the serum-vitamin-A levels to be low in the six cases of tylosis which he studied, while the carotenoids were normal. This is in accord with our findings. Hypovitaminosis-A has been described in Darier's disease (Peck *et al.*, 1943b), and several authors have used massive doses of vitamin A in their cases. Although there was some improvement the skin did not become quite normal, suggesting that there may be other factors besides the impaired vitamin-A metabolism involved in the aetiology of Darier's disease (Barwasser, 1941; Michelson, 1942; Abramovitz, 1942; Peck *et al.*, 1943b).

Low levels of serum vitamin A have also been noted in ichthyosis (Rapaport *et al.*, 1942; Peck *et al.*, 1943a; Leitner and Moore, 1946), pityriasis rubra pilaris (Leitner and Moore, 1946; Leitner and Ford, 1947)—the similarity of the latter to the lesions found in vitamin-A deficiency has been stressed by Pettler (1936) and by Sutton and Sutton (1949)—and less frequently in commoner skin diseases such as eczema and psoriasis (Marchionini and Patel, 1937). Moore (1957) differentiates between skin lesions due to "dietary" and those due to "secondary" vitamin-A deficiency. Representatives of the latter are the conditions noted above. The dietary type—phrynoderma of Nicholls (1933)—takes the form of hyperkeratosis of the hair follicles, which become hard and protuberant. Such follicular hyperkeratosis due to vitamin-A deficiency is rare in Britain (Bicknell and Prescott, 1953), but is not uncommon in the African (Loewenthal, 1933).

The reason for the low levels of serum vitamin A in tylosis is not known. A deficient intake has been postulated, but the members of the family studied by us were all on a normal adequate diet. In areas in the Far East where the diet is low in vitamin A, tylosis is not more frequent than in any other part of the world (Dencer, 1953).

In regard to poor absorption, no members took liquid paraffin, which hinders uptake of vitamin A, and the vitamin-A-absorption test carried out on the propositus after fasting was normal, suggesting that intestinal absorption was adequate. However, defective absorption has been described in various skin lesions (Ruch *et al.*, 1946).

Carotene estimation alone is of value only in showing that carotene absorption is unimpaired. When vitamin A is estimated at the same time, an indication of the efficiency of conversion of carotene to vitamin A is gained (Bicknell and Prescott, 1953). In our study normal carotene with low levels of serum vitamin A was present, and poor conversion of provitamin to the vitamin should be considered.

Reduced storage capacity of the liver has been cited as a possible mechanism. In view of the incidence of heart disease and hyperlipaemic tendency in our family, it is interesting to note Moore's (1957) finding that the livers of people dying of coronary artery disease contain 100 I.U./g. of vitamin A as opposed to the approximate normal average of 200 I.U./g.

Increased utilization of vitamin A was excluded, as no member had any disease in which hypovitaminosis-A is known to occur as a complication, such as febrile conditions (Moore, 1957). However, the possibility of

increased katabolism of vitamin A by the hyperkeratotic skin should be borne in mind.

The association between tylosis and low serum vitamin A may be purely coincidental, but, since we are dealing with a primary genetic condition, an explanation in this field may be sought, as suggested by Jeghers (1943).

It is possible that there is a genetic disturbance involving a single gene which has led to a metabolic defect producing on the one hand tylosis and on the other low serum vitamin A. Such a mechanism would illustrate the pleiotrophic effect of a single gene. Two genes situated on one chromosome—that is, linked genes—may be involved, the one resulting in tylosis, the other in low serum vitamin A. Another possibility is that of a single gene leading to a metabolic disturbance which results in a low serum vitamin A—the latter ultimately manifesting as tylosis. However, no clear relationship exists between the vitamin-A level and the severity of the disease, and this was shown in our cases. Moreover, work in the experimental field does not support the idea of a primary causal relationship (Moore *et al.*, 1935; Hale, 1937; Davis and Madsen, 1941), and the skin lesions of dietary vitamin-A deficiency are quite distinct from tylosis.

Finally, the theoretical possibility of a gene resulting in some metabolic disturbance with production of tylosis must be considered. In this case there may be a disturbance in the function of the epithelial cells with consequent defective metabolism of vitamin A. The low levels of the latter therefore are the end-result of the skin disorder and not the primary cause. This would explain the finding that the level of vitamin A does not always correlate with either the severity or the extent of the skin lesion (as shown in our cases) and for the difficulty the epidermal cells seem to have in utilizing vitamin A normally (Fraser, 1949).

Blood Lipids

Blood cholesterol levels in patients recovering from various diseases were noted to increase after large doses of vitamin A (Lasch, 1934). Josephs (1944) observed a rise in lipids and cholesterol after vitamin-A administration and felt that vitamin A had an important and specific effect on the metabolism of lipids. Recent workers could find no abnormality in the levels of cholesterol in the plasma or livers of rats deficient in vitamin A (Green *et al.*, 1955). In our family, however, several members with hyperlipaemia, hypercholesterolaemia, and elevated beta-lipoprotein fractions (to which carotene and vitamin A attach in the serum) had very low levels of vitamin A. In these instances the vitamin had not "drifted with the metabolic tide" (Moore, 1957). Sinclair (1953) felt that the possible deficiency of an essential fatty acid in tylosis should be considered. He has postulated a similar mechanism in the genesis of atherosclerosis (Sinclair, 1956).

Genetics

Tylosis is inherited as a Mendelian dominant with a high degree of penetrance. It appears to be controlled by a single autosomal gene. The sexes are equally affected and no race is immune (Cockayne, 1933; Sutton and Sutton, 1949; Scott, 1953). Lawler and Renwick (1957) believe that there are at least two types of inherited tylosis. These forms have been differentiated clinically, apparently run true to families, and

appear to be due to different genes. The lesions vary not only at different times in an affected individual but also in intensity and extent in members of the same family. Such differences are largely determined by genetic and environmental modifiers.

Tylosis and other ectodermal dysplasias have on rare occasions been found together with mucosal leucoplakia (Kumer and Loos, 1935; Touraine, 1954). The development of carcinoma in this premalignant lesion may be expected. Howel-Evans *et al.* (1958) noted a significant association between carcinoma of the oesophagus and tylosis in two families. There was no mention of leucoplakia in their cases. We found no evidence of leucoplakia or of oesophageal malignancy in our family. The possible relationship between ectodermal anomalies, various hyperkeratotic skin lesions, and low serum vitamin A has been alluded to by Porter (1951). Serum vitamin A was not estimated in the cases studied by Howel-Evans *et al.* (1958). It is well recognized that vitamin A is concerned with the integrity of epithelial structures and that in states of deficiency hyperkeratosis or squamous metaplasia may occur. Boyd (1947) has pointed out that squamous carcinoma may develop from squamous metaplasia. Regarding the participation of vitamin A in carcinogenesis there is no complete agreement.

Early workers in the experimental field (Fujimaki, 1926; Saiki and Fujimaki, 1927; Goldblatt and Benischek, 1927) indicated that while vitamin A did not appear to have a primary participation in carcinogenesis it was an important factor. However, other workers (de Ruyter, 1934; Fridericia *et al.*, 1940; Brunschwig and Rasmussen, 1941) could not substantiate this claim. On the basis of histological observations and a review of the literature, Popper and Ragins (1941) concluded that vitamin A had no bearing on the causation of tumour. The relationship between vitamin A and carcinoma has been extensively reviewed by Stern and Willheim (1943).

Clinodactyly was observed in our family (Fig. 1), and we can find no previous literature reporting the association of this condition with tylosis. Clinodactyly comprises a shortening of the middle phalanx of the fifth finger, mainly on its radial aspect, resulting in a radial deflection of over 15 degrees of the terminal phalanx (Figs. 2 and 3).

The term "clinodactyly" should be confined to those cases of crooked little finger due to incomplete ossification. There is no flexion deformity and the rest of the digits are normal (Hersh *et al.*, 1953). Transmission is via an autosomal dominant. Incomplete penetrance was noted in that in at least eight cases the parents did not have the anomaly. In one of these cases (IV 24) there was no clinodactyly in the parents or grandparents.

The presence in a family of two genetically determined abnormalities is an uncommon finding (Roberts, 1959). Accepting Swan's (1956) incidence for tylosis as 1 in 40,000 and that of the more common clinodactyly as 1 in 1,000 (Hersh *et al.*, 1953), it will be realized that the probability of these two conditions occurring together by chance is of the order of 1 in 40 million.

The coexistence of two genetically determined entities may be due to genetic linkage of the two abnormal genes. Genes are called linked when they are situated at loci on the same chromosome pair. The problem of linkage studies in man is complicated by the extreme

difficulty of obtaining pedigrees of a sufficient magnitude to be statistically significant. Another hazard is the phenomenon known as "crossing over," which may allow dissociation of the genes if they are not closely situated on the chromosomes. Methods of determining genetic linkage by comparison of siblings with one another were developed by Penrose (1935, 1938). These techniques are based on the fact that if the siblings receive the same chromosome from a parent there will be an increased probability that the siblings will be phenotypically alike. Furthermore, they will more probably be alike in any trait determined or influenced by a gene located on that chromosome. Ultimately a correlation is established between sibling likeness in

FIG. 2.—Photograph showing clinodactyly.

FIG. 3.—Radiograph of right hand showing clinodactyly.

one trait and sibling likeness in the second trait, genetically linked to the first. By means of such methods in the present family we were unable to obtain results which were statistically significant for linkage. These results, however, do not exclude the likelihood of the two mutant genes being situated on the same chromosome. The possibility of tylosis and clinodactyly being due to the pleiotropic effects of a single gene seems unlikely, as this association of the two conditions has not been previously reported. Finally, their association may be the result of genes situated on different chromosomes.

Summary

A family exhibiting tylosis plantaris et palmaris and clinodactyly was investigated. At least 14 of the 59 members had tylosis and 10 had clinodactyly. Six cases had both conditions.

In eight of the members with tylosis the values of serum vitamin A and carotene were estimated. In all

cases the serum vitamin A was subnormal while that of carotene was within normal limits. The role of vitamin A in tylosis and various other skin conditions and its possible relationship to squamous metaplasia and carcinoma are discussed. The metabolism of vitamin A and its functions in maintaining the integrity of epithelial structures is still poorly understood. Some of the possible genetic mechanisms underlying this association between low serum vitamin A and familial skin diseases are outlined.

In addition to the propositus, two other living members had sustained a myocardial infarction. Hypercholesterolaemia and hyperlipaemia were noted in several members, but were unrelated to tylosis, clinodactyly, or serum vitamin A.

Tylosis is transmitted via a monomeric autosomal dominant gene with a high degree of penetrance. The expressivity of the condition is governed to a large extent by environmental modifiers. Clinodactyly is inherited as a non-sex-linked Mendelian dominant with low penetrance. The explanation for the coexistence of two genetically determined entities is considered, and in the case of tylosis and clinodactyly we feel that the association is due either to distant linkage or to the genes being on different chromosome pairs.

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HEREDITARY BRANCHIAL DEFECTS IN A HAMPSHIRE FAMILY

BY

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This paper records the occurrence of multiple congenital branchial defects in several members of a family covering four generations. A number of similar inherited anomalies have been described previously, but in this particular group multiple lateral cervical sinuses were associated with maxillary malformations and ear-pits, a combination which does not appear to have been reported before.

The grandfather of the propositus was a Wiltshire man. His daughter married a Hampshire farm labourer, moved to a small village near Winchester, and with her increasing progeny has remained in this area ever since. The family group comprised 21 members; 15 were blood relatives, and eight of these possessed abnormalities. The affected persons were the grandfather himself, two of his daughters and one of his sons, and three grandsons and one granddaughter. I examined four normal and three affected relatives. The remaining 14 members, including five affected persons, were either dead or untraceable at the time of inquiry. The descriptions of these are thus unfortunately only second-hand, being provided from the memories of the relatives personally examined; but, since these tallied though supplied without prior collusion, they are probably reliable. These people were uncertain about the presence of ear-pits in the other affected relations, but this is not surprising, as these small malformations are quite unobtrusive.

The ear-pits when present were situated in the upper anterior end of the helix, being about 1 mm. wide and 1 mm. deep. They were observed only in the propositus and his brother. There were two maxillary abnormalities, always coexistent. The upper front teeth projected forward at an angle of some 20 to 30 degrees from the vertical, giving a slightly simian cast to the facies. The hard palate was high and arched, equally on both sides. The lateral cervical sinuses were typical of their kind. Their openings in the skin were 2 to 3 mm. in diameter and were always located in the anterior line of either sternomastoid muscle at various levels. Their depth was not probed. They usually caused little trouble, but when a collar was worn were inconvenient