the man with Hb S and Hb K, and one of them showed the same picture—that is, Hb S and Hb K were found but Hb A was absent. All were natives of the British West Indies and of no other known origin except West African.

FIG. 3.—Hybridization of haemoglobins Beilinson and the present K (for details of technique see Raper, Gammack, Huehns, and Shooter, 1960). Hb Beilinson is an α -chain abnormal variant, and, after dissociation with Hb K and recombination, electrophoresis on starch gel clearly shows an additional fraction due to the formation of Hb A and Hb Beilinson/K; these two haemoglobins migrate as one fraction (see text). Left—before; right—after dissociation and recombination.

Discussion

The definition of Hb K is that it is a Mendelian co-dominant variant of adult haemoglobin which can be separated by electrophoresis from Hb A, where at pH 8.6 it moves just slightly ahead of Hb A and behind Hb J.

Electrophoretic and chromatographic properties are the outcome of molecular shape and the charges of the molecule. It is clear that the same electrophoretic properties can come about for different reasons. Thus amino-acid substitutions may occur in the α - or β -chain and yet the electrophoretic behaviour of the resulting haemoglobins may be the same. The Hb K found in East

Indians is an α -chain abnormal haemoglobin (K_α) whereas the haemoglobin at present under investigation is clearly a K_β .

The result of double heterozygosity for Hb S and Hb K falls well into the not unusual pattern of only mild sickle-cell disease arising from the combination of Hb S with another β -variant of Hb A. However, it is known in the case of sickle-cell/Hb C disease and sickle-cell/Hb E disease that the people affected, though apparently quite healthy, are liable to develop anaemia with clinical manifestations when exposed to stress of any kind.

Summary

In a West Indian and his maternal aunt, sickle-cell haemoglobin was found in the hitherto undescribed association with haemoglobin K. No haemoglobin A was present. Recombination experiments demonstrated that this haemoglobin K was a β -chain abnormal variant. There was no anaemia, and a history of occasional joint pains was the only complaint which might be related to "sickle-cell haemoglobin K disease."

We should like to thank Dr. G. Slot, under whose care the child who was investigated originally was admitted, for giving us the facilities to study its parents, and Dr. W. E. Miall and Dr. V. I. Massiah for helping us to trace relatives in the West Indies.

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SERUM-VITAMIN-A LEVELS IN TWO FAMILIES WITH TYLOSIS*

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Tylosis palmaris et plantaris, a disease inherited as an autosomal dominant, is characterized by varying degrees of hyperkeratosis of the skin of the palms of the hands and soles of the feet. Anderson and Klintworth (1961) reported on a family with tylosis and clinodactyly. They found an associated hypovitaminosis-A in eight members of the family. The authors speculated upon the relationship between vitamin-A levels and tylosis palmaris et plantaris,

although they recognized that their findings might have been purely coincidental.

We wish to present our findings of a study of two families in which tylosis was present and in which vitamin-A levels were determined in a total of 23 affected individuals. In all instances vitamin-A levels were found to be within normal range.

Material and Methods

The propositus of Family I (D.D., St. C.H.C. No. 612654), a 21-months-old white boy, came to our attention when he was admitted for evaluation of an episode of

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unconsciousness at another hospital during which time a low level of blood sugar was noted. In spite of numerous studies, including a six-hour glucose-tolerance test, intravenous tolbutamide test, and a 24-hour fast, the aetiology of the single hypoglycaemic episode was not established. Upon physical examination no abnormalities were noted other than hyperkeratosis of the palms of the hands and soles of the feet (see Fig. 1). This abnormality could be traced through six generations in a family comprising 83 individuals. Of these, 26 members were examined by us.

The proband of Family II (P.H., St. C.H.C. No. 600353), a 2½-year-old white girl, was admitted to St. Christopher's Hospital for Children in 1960 for the removal of a dermal sinus in the area of the first thoracic vertebra. Physical examination was within normal limits, except for hyperkeratosis of the palms of the hands and soles of the feet. In this family, which was of Irish descent, the disorder could be traced through four generations and contained 30 individuals. Of these, eight members were examined by us.

Serum from venous blood was used throughout. Beta-lipoproteins were determined immunochemically (Heiskell

et al., 1961). Beta-carotene and vitamin-A levels were determined with a Zeiss PMQ spectrophotometer after extraction of unsaponified serum with petroleum ether according to the method of Roels and Trout (1959), which is an adaptation of the standard Carr-Price reaction of vitamin A with antimony trichloride.

Results

Families I and II are depicted in Figs. 2 and 3, respectively. In Family I, 37 members were affected. In Family II, 15 members were affected. As can readily be appreciated in both pedigrees, the trait is inherited as an autosomal dominant. There is no sex preference; both males and females transmitted the disorder; each affected individual had an affected parent; no set of unaffected parents had an affected child; and approximately one-half of the offspring, one of whose parents was affected, were themselves affected. This is in conformity with the previous description of the genetics of tylosis palmaris et plantaris (Cockayne, 1933; Anderson and Klintworth, 1961).

The Table lists these affected members of each family in whom chemical determinations were obtained. In Family I the vitamin-A levels ranged from 99 to 197 I.U./100 ml., with a mean of 134 I.U. ± S.E.M. of 8.1; beta-carotene levels ranged from 33 to 117 µg./100 ml., with a mean of 83 µg./100 ml. ± S.E.M. of 5.5; and the mean beta-lipoprotein level was 4% precipitate. In Family II the vitamin-A levels ranged from 70 to 191 I.U./100 ml., with a mean of 110 I.U./100 ml. ± S.E.M. of 19.8; beta-carotene levels ranged from 58 to 88 µg./100 ml., with a mean of 73 µg./100 ml. ± S.E.M. of 4.0; and the mean beta-lipoprotein level was 5% precipitate.

FIG. 1.—Hyperkeratosis plantaris of the proband of Family I and of his mother (right).

FIG. 2.—Pedigree of Family I.

FIG. 3.—Pedigree of Family II.

Chemical Determinations in Affected Individuals

Individuals	Serum		
	Vitamin A I.U./100 ml.	β -Carotene μ g./100 ml.	β -Lipoprotein Immunocrit Units
<i>Family I</i>			
III 3	134	79	5
IV 17	195	107	4.5
18	192	87	8
19	130	60	4
22	121	117	4.5
V 8	130	62	4
11	197	108	3
12	101	68	5
13	138	100	4
16	152	33	4
26	148	85	4
VI 5	99	88	3
6	109	75	4
9	103	98	3
10	101	50	2
12	107	86	4
27	124	100	4
Mean $\pm$ S.E.M.	134 $\pm$ 8.1	83 $\pm$ 5.5	4
<i>Family II</i>			
II 5	72	58	5
III 4	191	88	6
11	146	72	6
IV 4	82	69	3
12	70	71	—
13	99	77	5
Mean $\pm$ S.E.M.	110 $\pm$ 19.8	73 $\pm$ 4.0	5
Families I and II combined mean	128	80	4

Discussion

The levels of beta-carotene in each individual were within normal limits as determined in this laboratory and also as judged from the values obtained from a large number of normal individuals studied by Leitner, Moore, and Sharman (Moore, 1957, p. 361). Normal serum levels of beta-carotene imply an unimpaired absorption of lipids from the gastro-intestinal tract.

The levels of beta-lipoprotein were, with the exception of one member of Family I (IV 18), within normal limits as judged by our data on over 300 individuals without known metabolic disease in whom the beta-immunocrits ranged from 1.5 to 6.0, with a mean of 3.7 and mode of 4.0. Normal beta-immunocrits are indicative of normal beta-lipoprotein levels, which in turn indicate normal capacity of the blood to transport lipids.

The vitamin-A levels were also within normal limits as obtained in this laboratory and as given by Moore (1957,

p. 361) for 306 healthy individuals in whom the range was 40 to 320 I.U. vitamin A per 100 ml., with a mode between 140 and 160 I.U.

The data obtained from the two families studied by us do not reveal a correlation between tylosis and hypovitaminosis-A as reported by Anderson and Klintworth (1961). Although some of the values of vitamin-A levels in Family II were below the mode, they are within the normal range as defined by Moore (1957). Porter (1951) also observed lower than average values for serum vitamin A in six persons with tylosis; however, the values (tests performed by Moore) were still within the normal range as defined by Moore (1957). Perhaps one should not conclude, with certainty, that values well below the mode in six consecutive individuals are to be interpreted as being within the normal range.

In Anderson and Klintworth's (1961) series there were three instances in which no vitamin A was detected in the serum. The average of their normal value was given as 70 I.U./100 ml. These normal values are only half as high as those reported in the literature (Moore, 1957, p. 361) and found in our laboratory. The findings of zero I.U. of vitamin A per 100 ml. of serum in three of their patients is surprising when one considers that normal individuals deprived of vitamin A for periods of up to two years exhibited serum-vitamin-A levels which never fell below 20 I.U./100 ml. (Moore, 1957, p. 370). Even patients with marked inability to absorb lipids from the gastro-intestinal tract as judged by zero serum levels of beta-carotene after beta-carotene loading have not had zero vitamin-A levels. For example, patients with abeta-lipoproteinaemia have a marked inability to absorb lipids from the gastro-intestinal tract and have zero serum beta-carotene levels. The serum-vitamin-A levels of such patients have been reported as 35 I.U./100 ml. by Mabry *et al.* (1960) and as 19 I.U./100 ml. by Salt *et al.* (1960). Our data from two families fail to reveal a correlation between low serum levels of vitamin A and tylosis. We cannot explain the low normal values for serum vitamin A and the three instances of zero serum levels of vitamin A reported by Anderson and Klintworth.

Summary

Two families with tylosis palmaris et plantaris are presented in which the serum-vitamin-A, beta-carotene, and beta-lipoprotein levels were within normal limits. This observation is in contrast to the report by Anderson and Klintworth (1961), in which they found hypovitaminosis-A in a family with tylosis and clinodactyly.

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