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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
HYPERKERATOSIS OF THE LARGE TOE-NAILS AND SEBACEOUS CYSTS

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The accompanying pedigree, showing the inheritance of two interesting human conditions, is noteworthy because the traits in question are first met with separately for two generations in independent branches of the family and are then found associated in a number of persons of the third and fourth generations. Since several of the affected individuals were doctors and kept careful family records there is every reason to believe the pedigree is a highly accurate representation of the occurrence of the traits in the family.

Hyperkeratosis of the nails is a defect that exhibits a number of clinically distinct forms. Usually it involves keratinization of both finger and toe nails and may or may not be accompanied by shedding. In a large collection of cases by Cockayne,4 included under the title, "Hypotrichosis et Dystrophia Ungium," the nails of fingers and toes are very thick, longitudinally striated and discoloured while the hair on the body is usually very fine and slow growing. Presumably no shedding occurs. According to Clousten5 there are more than 6,000 Canadians with this defect, probably largely descendants of a French family that came to Canada about 180 years ago. Cockayne's collected data show that this condition is inherited as a simple dominant trait. There are a number of closely related forms of hyperkeratosis of the nails in which the finger and toe nails are extremely thick and cylindrical in form, assuming the shape of a claw and standing out at about a 45 degree angle when long. The thickened nails are brittle and dry, readily becoming infected, after which shedding usually occurs. In the family described by Walter and Bradford6 there were 27 affected persons in five generations. In 20 of these the keratosis involved only the thumb and index finger nails. In a pedigree given by Clemente7 an affected father transmitted the defect to five of his nine children. In this family the condition is present in all the finger and toe nails, but shedding does not occur.

In a case of onychomadesis in a French family described by Montgomery,8 the nails became yellowish in color over the lunula and gradually loosened and came out. Within from three to eight months new nails, normal in appearance, grew in. These in turn were shed within a few months. The condition was present in a woman, her son and her two brothers. Other pedigrees of hyperkeratosis, onychomadesis and onychogryphosis of the nails have been published.1,4,8 A study of these leads to the conclusion that probably large numbers of genes are concerned in the development of the nails, and that mutation in these may result in a variety of nail abnormalities, often associated with other ectodermal defects.

The condition described here differs from all of the above and probably represents a genetically distinct abnormality. In all of the affected persons the hyperkeratosis involved only the nails of the larger toes. This may be seen in Figure 6. The condition usually makes its appearance shortly after puberty, prior to which time the nails appear normal and no shedding occurs. With the onset of the trait, the large toe-nails become from two to five millimeters thick and can be cut only with great difficulty. One of the affected persons uses bone scissors, although soaking in warm water is the most frequent method used to facilitate cutting. There is no keratinization of the nail bed. The thickened nails are yellowish in color, so that the lunula does not show, and have a tendency to become
BIG TOENAILS AFFECTED

Figure 6

Individuals in this family affected with hyperkeratosis have thick bone-like nails of the big toes, which are shed periodically. The other toenails are normal and the trait varies in time of onset and severity of expression.

In most of the cases the nails of the large toes are shed from time to time, new nails making their appearance soon afterward. These become just as thick as the old ones and in turn are also shed. The length of the cycle of shedding and regeneration varies from individual to individual; thus III-8 shed his nails about four times yearly, whereas his son (IV-8) sheds only about once a year. The onset of the condition in the father was in the sixteenth year of life and in the son in the eleventh year. On the other hand, IV-4 did not manifest the thick nails until after he was twenty and he never shed them. The trait thus appears to be variable both in its time of onset and in its expression. In one instance it was transmitted by an apparently normal individual (III-2). It is possible that the manifestation of the condition in this person was so slight that it escaped detection but this could not be ascertained. In none of the cases were the nails known to exhibit a cylindrical form or to assume the shape of a claw. As far as could be determined no other defect, ectodermal or otherwise, was associated with the condition. Inheritance appears to be that of an incomplete dominant, the vari...
ability in the trait probably being the result of the influence of other genes and extrinsic factors.

Description of Cysts

The second condition exhibited by the pedigree is commonly known in the family as wens or sebaceous cysts. A sebaceous cyst is a retentitum cyst of a sebaceous gland. Since the description of the cysts in this family closely follows that given by Cockayne for epidermoid cysts it is possible they belong in that category. Such growths are generally between a pea and a hen's egg in size and are frequently found in the scalp alone but may appear on other parts of the head and body as well. In the cases being considered here the cysts are found only in the scalp in all but one case. In this person (IV-4) there was one in the scalp and another on the lower third of the neck. In at least eight persons in the pedigree the cysts were large and severe enough to necessitate surgical removal. Individual II-4 had a multilocular cyst the size of a large hen's egg. This was removed and never occurred again. The cysts were always few in number and the time of appearance of the first one ranged from the eleventh year of life in IV-5 to the 35th year in III-5. Cockayne states that epidermoid cysts may not make their first appearance until the 40th or 50th year of life and that in one instance a cyst developed in a man 65 years old.

This being the case, it is possible for an individual to transmit the gene for the condition and die before reaching the age at which the defect might have appeared in him. Siemens,8 in a study of 109 cases of epidermoid cysts, found that in 34 there was a record of one or more relatives affected, while in 75 there were no known relatives who had the condition. Data collected from sibships belonging to families in which there is a history of the disease gives a ratio of 97 affected to 195 normal, a wide deviation from the 1:1 ratio expected for a dominant trait. In these families there are nine unaffected persons who had affected offspring. In the pedigree given here there is only a single conductor. The data for the family cases, therefore, tends to follow the pattern expected for incomplete dominant heredity. In a pedigree of what was called sebaceous tumours by Sedgwick,7 but believed to be epidermoid cysts by Cockayne, affected females transmitted the condition to all of their daughters and none of their sons, while males never showed the condition and never transmitted it. This has been considered to be a possible case of attached-X chromosome inheritance in man.

It should be noted that V-1 and V-2 are still in their teens and may yet have cysts, and that V-3 and V-4 are still too young to show either condition. In contrast with most pedigrees of cysts of this sort the present one is marked

POOING OF GENETIC DEFECTS

Figure 7

One branch of the family transmitted a gene for defective toenails; the other a gene for sebaceous cysts. Several individuals in the fourth and fifth generations showed both defects, but there is no indication that they are linked in inheritance.
by the apparently high penetrating power of the dominant gene. This also appears to hold for hyperkeratosis of the nails. This may be shown by examining the ratios for each trait. Assuming that the matings giving rise to affected individuals are between heterozygotes and recessives, a 1:1 ratio of affected to normal is to be expected in the offspring. The actual ratio for sebaceous cysts is 20 affected to eight normal, and for hyperkeratosis nine affected to five normal. In either case it is apparent that probably few persons carry one of the genes and fail to be affected. As we have already seen there are two persons who presumably fall into this category. Here it must be emphasized that for traits like these, that show great variability in time of onset and in degree of severity, great care must be taken in assembling pedigrees and making genetic analyses. Allowance must also be made for the fact that in all such material pedigrees with an excessive number of affected individuals are the ones which will be most likely to come to the attention of an investigator.

**Linkage Improbable**

Insufficient evidence is available to determine whether or not the two traits are linked. The facts, however, would seem to point against such a possibility or at least against close linkage. If we let $H$ represent the gene for hyperkeratosis and $h$ its normal allele; and $C$, the respective alleles for cysts and absence of cysts, then the mating between $H$ and $h$ can be represented by the linkage formula $(HC) (hc) \times (hc) (hc)$. The four offspring, $H$ and $h$, (assuming he carries the gene for hyperkeratosis), $H$ and $h$, (assuming he carries the gene for cysts), $H$ and $h$, and $H$ and $h$, would be genetically $(HC) (hc)$. All of them presumably mate with $(hc) (hc)$ individuals. If linkage were close such matings would rarely give the cross-over type $(HC) (hc)$ showing both traits. Of the six offspring resulting from these unions, one has hyperkeratosis, three have cysts and two show both traits. It therefore appears unlikely that any close linkage exists.

**Literature Cited**


**Effects of the War on British Fertility**

The birth rate has fallen to a level which in the near future means a decline of population. The number of persons in this country between the ages of 14 and 64 is 33 million, and two thirds of them are engaged in the war effort, whether in the armed forces, civil defense or war industries. No country has ever before mobilized its man power to the extent we have. The effect of the war on the birth rate is interesting. Except as it causes a temporary loss of births by separation of man and wife and a permanent loss of potential fathers and mothers by violent deaths, it seems that the war may have a favorable effect on fertility in the long run by bringing about a change in values and removal of some of the deterrents to childbearing. There has been a remarkable increase in marriages. This is in part due to the large number of girls reaching the ages of 19 and 20 owing to the high birth rate which followed the last war. But more important are the allowances provided for the wives of the fighting men. The birth rate for the first quarter of 1942 was higher than for any other first quarter since 1931, in spite of the disruption of family life produced by the war, including the bombing of our cities and their evacuation on a large scale.—LONDON LETTER, J. A. M. A., July 25, 1942.