Pseudoxanthoma elasticum (PXE) is a hereditary disorder of elastin first described by Rigal in 1881. On histological examination, the elastin fibres of sufferers are fragile, tend to fragment and undergo a process of calcification resulting in loss of tissue elasticity. The disorder, although rare, has been described in many different ethnic groups and populations; the estimated incidence in the populations of the USA is 1:100 000. The clinical manifestations are usually evident from late childhood. The cutaneous lesions are progressive and result in a peau d'orange mottling of the flexural areas of the neck, axilla, antecubital fossa, popliteal area and groins. The skin usually becomes lax, thickened, and cosmetically unsightly. Angioid retinal streaks usually appear in the 2nd decade of life. These lesions weaken the vascular infrastructure and increase the risk of haemorrhage and neovascular changes. Gradual visual loss may occur, leading to severe handicap after the third decade of life. In addition, intimal degeneration of small- and medium-sized blood vessels contributes to loss of peripheral pulses, hypertension, intermittent claudication, coronary insufficiency and various stroke phenomena.

In a nation-wide survey of PXE in England and Wales, Pope was able to differentiate clinically two autosomal recessive and two autosomal dominant forms of the disorder. A further autonomous entity in which profound ophthalmological sequelae occurred was later described in the Afrikaner population of South Africa by Viljoen et al. From pedigree analyses of over 60 individuals it is apparent that this latter condition is autosomal recessive and the prevalence is remarkably high in this group. For cultural, religious and geographical reasons the Afrikaner is an isolate population.
Fig. 1. Ancestral links to current PXE families (Settler M).

Fig. 2. Ancestral links to current PXE families (Settler B).
shown at gen II. The position of the child within the sibship has been given within the symbol. Thus in Fig. 1 II4 is the 10th child of settler M. Two current PXE pedigrees, namely Ro and Cr, have this child as their common ancestor, Ro through the paternal line and Cr through the maternal line. The 34 PXE ancestral lines (15 paternal lines and 19 maternal lines) were found to be linked to some of the children of each ancestor M, B, V and S.

Occasionally the retrospective tracing of a PXE proband lineage was linked to an individual with surname M, B, V, or S, but linkage could have occurred at any generation level. In these instances factors such as migration, wars and unrecorded births made the tracing of records linking the latter individual and the original ancestor impossible. This necessitated the grouping of such individuals into columns headed “S?” and “7?” in Figs 1 - 4. Although the link to the founder had not been established, it is certain that at this early stage of Afrikaner history the individuals listed in column “??” were from the
original founder(s). Most pedigrees extended to 13 generations with the probands appearing at generations XI and XII, respectively.

The 4 identified surnames, however, did not appear as free independent family names because of recurrent consanguinity. For example, there were several instances of intermarriage between families M and B in the late 17th century (Fig. 5). At generation II, settler M’s daughter II3 had married settler II4. Their children at generation III married first-degree cousins, III2 and III4 being 2 sisters marrying 2 brothers III2 and III3 respectively. Too complex to demonstrate, consanguineous marriages occurred frequently in each pedigree over several generations and were also observed between surnames V and S. These intermarriages obscured the identification of two independent founder members and made it necessary to group the four surnames into two sets, M/B and V/S (Table I). In the 15 PXE male ancestral lines studied and the 19 PXE female lines, the surnames M/B appeared 11 and 15 times, respectively (73% and 79%). The surnames V/S appeared 13 and 15 times, respectively (87% and 79%). Even taken individually, these 4 surnames were shown to link up as follows: surname M appeared in 33 of the possible 34 ancestral lines;
surnames B in 25 of 34 lines; surname V in 28 of 34 lines; and surname S in 26 of 34 lines.

Discussion

PXE is a disorder with protean clinical manifestations and severe ophthalmological, cardiac and cosmetic implications. The disorder has been intensively investigated in South Africa and it has been recognised that an autonomous, autosomal recessive form occurs relatively commonly in the Afrikaner community. At present no biochemical or molecular markers are available for the identification of heterozygous carriers or preclinical homozygous individuals.

Twenty Afrikaner probands were genealogically investigated. The history of Afrikaner settlement in the subcontinent of Africa lends understanding to the dissemination of the gene for PXE in this population. In the late 17th and early 18th centuries, the original Dutch settlers migrated northwards from the Cape and followed a nomadic existence until a suitable habitat was found. Great distances had to be covered due to the shortage of water, and the communities that were eventually established were geographically isolated. Other factors, such as cultural considerations, language differences and religious practices, further maintained the isolation of the Afrikaner. Consanguineous marriages were common and the frequency of rare homozygous affected individuals increased in this community.

In the 19th and 20th centuries, large urban communities arose and the social organisation of the Afrikaner community changed. Cross-cultural admixture occurred freely and randomly, and there were fewer consanguineous matings. Family size also decreased. All these factors tended to 'dilute' the abnormal gene pool established earlier through various selection forces and founder effect.

In this study, it was possible — by constructing genealogical pedigrees — to identify both the common ancestors in the kindreds with PXE and the original founder members of PXE in South Africa. Figs 1 - 4 illustrate the manner in which each ancestor (designated M, R, V and S) had specific children who were identified and from whose descendants the maternal and/or paternal branches were linked to individuals with PXE.

During this investigation it was not possible to separate the families M and B, and V and S. There are two possible explanations for this finding. Firstly, that two of the original four settlers fortuitously brought the PXE gene to South Africa. Secondly, a single individual heterozygous for PXE may have settled in the Cape and the high prevalence of consanguinity together with large family numbers may have increased the abnormal gene frequency rapidly.

The identification of M/B and V/S as the founder individuals in PXE adds to the growing list of genetic disorders that have been studied from a genealogical viewpoint in the Afrikaans-speaking community. Founder members have already been identified for familial polyposis of the colon and familial heart block. Familial hypercholesterolaemia in a religious isolate has been described in this group. The current search for founder members of PXE has also led to the unexpected finding of an association between familial cancers and some PXE families. This finding forms part of a thesis to be submitted by one of the authors (D.L.V.) to the University of Cape Town in the near future. In addition, the other author (M.T.) has identified the PXE founder individuals as those in whose descendants familial pre-menopausal breast cancer has occurred. These findings have as yet to be published but substantiate the association between familial cancer and/or familial breast cancer and PXE.

The identification of families at risk for various genetic disorders will allow preventive programmes to be instituted in South Africa when appropriate molecular markers become available. These findings can also be extended to the European countries of origin of the Cape settlers. Recent collaborative research with geneticists in Belgium has confirmed the presence of a form of PXE in that community, which is clinically indistinguishable from that described in the Afrikaners. This supports the hypothesis that the abnormal gene originated in the Low Countries of Europe. Indeed, the four ancestors identified in South Africa were emigrants from Oud-Beyerland, Lübeck, Maastricht and Ommen respectively.

At present, heterozygous carriers of PXE cannot be identified clinically or through the use of sophisticated biomolecular techniques. However, investigations are under way using elastin and collagen molecular probes, which may eventually allow elucidation of the defective gene. When the technology becomes available to identify either heterozygous carriers or homozygous affected individuals, then at-risk families identified in this study can be appropriately investigated and counselled.

REFERENCES