PSEUDOXANTHOMA ELASTICUM

IN SOUTHERN AFRICA

BY

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A thesis submitted to the University of Cape Town in fulfilment of the requirements for the degree of Doctor of Medicine.

January 1991

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University of Cape Town

FOR

DIANE,

my parents

and my children

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DECLARATION

This project was undertaken under the guidance of Professor Peter Beighton during the tenure of a scholarship from the Medical Research Council of South Africa from July 1985 - June 1987, and thereafter while appointed as a Senior Lecturer and Senior Specialist. The investigation was performed in the Medical Research Council Unit for Inherited Skeletal Disorders, Department of Human Genetics, University of Cape Town.

Molecular linkage studies were conducted in collaboration with Professor C Boyd and his staff, in the laboratories of the Department of Human Genetics of the University of Cape Town Medical School, and the University of Medicine and Dentistry of New Jersey and the Robert Wood Johnson Medical School (formerly Rutgers Medical School).

I certify that this thesis is my own work and that it has not been presented for a degree at any other university.

Denis Lowe Viljoen

January 1991

PREFACE

Within weeks of entering the field of human genetics, I was given the opportunity of investigating a family with pseudoxanthoma elasticum (PXE). The findings fired my interest in the disorder and led to the clinical appraisal of a further 19 patients with PXE. It became apparent that several new manifestations were present in a form of the disorder which was prevalent within the Afrikaner community and the data were published locally **(Viljoen et al, 1984).** Thereafter, a study was conducted involving many facets of PXE; the findings form the basis of this doctoral thesis.

Throughout the following chapters several terms are used frequently and require clarification. The abbreviated term "PXE" is used in preference to the full expression "pseudoxanthoma elasticum" for the sake of brevity and because it has become scientifically acceptable.

Four major ethnic groups are present in South Africa:

a. White or Caucasian persons whose ancestors were derived from Western Europe.

b. Black or Negro persons who are indigenous to this region of Africa.

c. Individuals of Mixed Ancestry. These persons are an admixture of Caucasian/Khoisan (Hottentot and Bushmen)/ Malay (Javanese and Sumatran)/Black (West African and Madagascan) ancestry.

d. Asian individuals whose ancestors are of Indian or Sri Lankan stock.

Several references are made to PXE in these ethnic groups in the text as the clinical manifestations, implications and prognosis varies considerably according to ancestral derivations (Sections II, III, IV and V). In each instance, in accordance with currently acceptable terminology, the groups are referred to as Caucasian, Black, Mixed Ancestry and Asian, respectively.

Recently, four clinically distinct forms of PXE have been recognised (Pope, 1974 (a) and (b)). In the research undertaken for this study, a further subcategory of PXE became apparent, the features of which have been highlighted in Chapter 10. Nosological considerations regarding all five types of PXE are fully discussed in Chapter 4. For reasons of brevity and clarity in the writing of this thesis, each PXE entity will be designated as follows:

(i)	AD I	(autosomal dominant type I)
(ii)	AD II	(autosomal dominant type II)
(iii)	AR I	(autosomal recessive type I)
(iv)	AR II	(autosomal recessive type II)
(v)	"Afrikaner"	type. (Newly described autosomal recessive form of PXE found exclusively in the Afrikaner population).

On several occasions in the forthcoming chapters the term "peau d'orange" is used to describe both the dermatological and ophthalmological changes seen in PXE. When the description concerns the skin, the literal translation of "orange-peel texture and colour" is implied. In its use for the eye findings, however, the term traditionally describes the "mottled" appearance of the fundus seen early in the course of the disorder.

The layout of this thesis has been planned to facilitate ease of reading and to avoid unnecessary duplication of data. For this reason, the Tables and Figures pertinent to each chapter are interspersed within the text and extensive cross-referencing between chapters has been employed. Protocols of investigation, previously published manuscripts and papers presented at scientific meetings which relate to patients in this study are assembled in the Appendix.

This investigation was undertaken with the approval of the Research and Ethics Committee of the University of Cape Town Medical School.

DENIS VILJOEN

ABSTRACT

Pseudoxanthoma elasticum (PXE) is a rare heritable disorder of elastin with major manifestations in the cardiovascular system, skin and eyes. The disorder is heterogeneous, but the underlying genetic defects remain unresolved.

The study was undertaken to evaluate the frequency, clinical presentation, natural history, medical complications and therapeutic options for individuals with PXE in Southern Africa. During the investigation, in which 86 patients in 58 families were studied, it became apparent that in addition to the 4 previously delineated forms of the disorder, there was an autonomous entity confined to individuals of Afrikaner stock in which serious ophthalmological sequelae occurred. Detailed genealogical studies were performed in this group, common ancestors were identified and a high prevalence of the condition was discovered.

The dermatological, cardiovascular and ophthalmological manifestations of PXE were investigated at a clinical, biochemical and ultrastructural level. Restriction fragment length polymorphisms related to type I collagen and to the human elastin gene were used in linkage studies in an attempt to resolve the question of possible heterogeneity. Therapeutic options for the ophthalmological and cosmetic complications were evaluated.

As a result of this investigation and subsequent publications, information regarding the clinical consequences of a new form of PXE within the Afrikaner community has been disseminated to colleagues in the dermatological, genetic, medical, cardiac and ophthalmological fields in South Africa and abroad. In the light of my observations, antenatal diagnosis and carrier detection are likely to be feasible in the foreseeable future.

ACKNOWLEDGEMENTS

I am most grateful to Professor Peter Beighton, my supervisor and mentor whose guidance, constructive criticism and inspiration were major stimuli which ensured completion of this project. I am deeply indebted to him for giving me this opportunity.

I wish to express my thanks to the patients and their referring doctors for their active participation in the study.

My many friends and colleagues within the disciplines of ophthalmology, dermatology, cardiology and radiology assisted me through patient referrals and good advice. In particular I would like to thank Prof A Murray, Dr Ken Woods, Dr Clive Straker and Dr Roderick McKenzie (ophthalmology), Prof Norma Saxe, Dr E Swart, Dr E Benjamin, Dr P Strauss (dermatology), Prof B Bloch (obstetrics), Prof C Bloch (plastic surgery), Prof B Cremin and Dr S Wynshank (radiology), and Dr T Mabin (cardiology).

Many members of the Department of Human Genetics contributed significantly to my work and I would like to thank my medical colleagues Jack Goldblatt, Colin Wallis, Molly Nelson, Ingrid Winship and Lawrence Stevens for their friendly advice. To the Genetic Nursing Staff, Sisters Sue Beatty, Luzanne Boyes, Lesley Merckel, Gail Ross and Janis Shapera, I extend my grateful thanks for their assistance with patients, clinics and illustrations.

To Sue Thorne, who has worked with great patience, good humour and tolerance in typing this thesis, I am especially thankful. Many other persons provided secretary assistance including Elaine Lavin, Gillian Shapley, Cathy Ross, Phillippa Webster, Dianne Cannell, Sandi Gunst and Jane Vink.

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Mr Colin Clow and the Graphics Department of Groote Schuur Hospital provided excellent service for illustrating this work.

My wife Diane was always patient, loving and supportive as were my family and friends. I am extremely grateful to them all for their understanding and good humour.

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SECTION 1

THE PROJECT

In this section, historical and contemporary concepts relating to pseudoxanthoma elasticum are presented and the aims and methodology of the project are discussed:

CHAPTER 1: HISTORICAL PERSPECTIVES OF PSEUDOXANTHOMA ELASTICUM

CHAPTER 2: THE AIMS OF THE STUDY

CHAPTER 3: METHODOLOGY

SECTION 1

CHAPTER 1

HISTORICAL PERSPECTIVES OF PSEUDOXANTHOMA ELASTICUM

1.1 ORIGINAL DERMATOLOGICAL DESCRIPTIONS

1.2 EARLY OPHTHALMOLOGICAL INVESTIGATIONS

1.3 ORIGINAL CARDIOVASCULAR STUDIES

1.4 CURRENT CONCEPTS

CHAPTER 1

HISTORICAL ASPECTS OF PSEUDOXANTHOMA ELASTICUM

1.1 Original Dermatological Descriptions

The distinction of being the first to describe a case of pseudoxanthoma elasticum (PXE) in the medical literature is attributed to **Dr D Rigal** from the Faculty of Medicine, University of Lyon, France. In **1881**, he described the skin changes in a soldier from the 12th Battalion de Chasseurs who presented with diffuse cutaneous manifestations which were likened to that of the xanthomatoses (lipid storage disorders). The progressive nature of the skin lesions was stressed by **Rigal.**

The next significant contribution in the elucidation of PXE was made by **Dr FA Balzer (1849–1929)**, a French physician and histologist.

> *Balzer was born to Swiss parents in Rennes, Brittany, and he received medical training both in Rennes and Paris. He was a contemporary of Charcot and, at the great physician's instigation, Balzer presented an inaugural thesis on bronchopneumonia in 1878. Among Balzer's many contributions were studies on venereal diseases, the discovery of the streptococcus in the causation of impetigo and the use of bismuth as an antisyphilitic agent (1889). He also wrote an excellent textbook on syphilis and venereal diseases.*
>
> *Balzer became Chief of Service successively at the Broca, Record and Saint Louis Hospitals. He was elected to membership of the Academy of Medicine in 1908 and later was its vice-president. Balzer had many honours bestowed upon him including the presidency of the French Society of dermatology and Syphiligraphy and the rank of Officer of the Legion of Honour. He was said to be a "most kindly man whose clinics were popular.". (FA Balzer : an obituary, 1929).*

Among the plethora of research endeavours, **Balzer** performed an autopsy on a patient with PXE and described some of the other systematic manifestations associated with the disorder. Like **Rigal**, he mistakenly concluded that the disorder was a xanthomatosis.

A short time later, while investigating a young man with recurrent haematemeses, **Anatole Chauffard (1955–1932),** an outstanding French physician, made a major contribution towards the medical understanding of the disorder by correctly recognising the characteristic raised, yellow, flexural lesions as those of the condition which is now known as PXE. **Chauffard (1889)** brought this patient to the attention of his medical colleagues, and **Darier** later described the histopathology while **Hallopeau** and **Laffitte (1903)** reported the dramatic ocular changes in the same individual.

> *Anatole Chaffard was born in Avingnon on August 22, 1855 to medically distinguished parents. His father, Emile, was professor of general pathology in Paris. Chauffard junior had a brilliant career and made several original contributions to medicine including the first description of hereditary spherocytosis (familial haemolytic jaundice). He pioneered the use of emetine in the treatment of amoebic dysentry and was among the first to describe bovine tuberculosis infections in man. Chauffard also contributed to knowledge of the pathogenesis of jaundice in carcinoma of the pancreas. He was honoured as president of the International Congress of Medicine in 1900 and as President of the French Academy of Medicine in 1923. He died of bronchopneumonia on November 1st, 1932, aged 77 years. (WR Bett : Historical note, Anatole Chauffard, 1955).*

Despite the contributions made by **Chauffard,** it remained for his colleague, **Dr J Darier (1896),** to demonstrate that PXE was histopathologically distinct from the lipid storage disorders and had the pathognomonic features of clumped, calcified elastin. He offered the name "pseudo-xanthome elastique" or "elastorrhexis" for the condition.

> *Ferdinand Jean Darier was born of French parents on April 26, 1856, in Budapest. (WR Bett, 1956). He was educated in Geneva and then emigrated to Paris at the age of 20 years. After graduating MD in 1885, he worked in Louis Antoine Ranvier's laboratory (of the "Nodes of Ranvier") at the College de France. He became one of the immortal "Big Five" who made the Paris School of dermatology world renowned - the other four members were Ernest Henri Besnier, LAJ Brocq, Raymond Sabouraud and Alfred Fournier.*

Darier described keratosis follicularis and acanthosis nigricans in 1889, and 1909 his masterpiece, "Precis de dermatologie", was translated into English, German, Spanish and Japanese. The doyen of international dermatology, he was described as "highly cultured, urbane, modest, full of fun and perennially young...". A man of great energy, Darier began his eight volume work, "Nouvelle pratique dermatologique" (Paris, 1936) at the age of 80, only 2 years before he died after a protracted illness.

The histopathological changes of pseudoxanthoma elasticum in Chauffard's patient were first reported by Darier in 1896 at the Third International Dermatological Congress held in London. Only then was PXE recognised as being distinct from the xanthomatoses.

1.2 Early Ophthalmological Investigations

Although **Doyne (1889)** first reported the characteristic changes in the fundus in a person with PXE, he wrongly attributed the pathogenesis of these lesions to recurrent trauma. Shortly afterwards, the term "angioid streak" was coined by **Knapp (1892).** This terminology reflected contemporary opinion that these abnormalities were vascular in origin. Later on, **Hallopeau** and **Laffite (1903)** demonstrated chorioretinitis in **Chauffard's** patient with PXE and the same authors went on to describe the severe fundal changes which are frequently associated with the disorder. However, it remained for **Kofler (1917)** to correctly recognise that the streaks were at the level of **Bruch's membrane,** a fact subsequently confirmed at autopsy independently by **Böck (1938)** and Hagedoorn (1939). Although **Hallopeau** and **Lafitte** speculated that there might be a connection between the fundal and dermatological findings, it was left to **Esther Grönblad** and **James Victor Strandberg (1929),** two Swedish investigators, to propose that angioid streaks and the skin changes represented manifestations of the same disease.



Figure 1.1 ESTER ELIZABETH GRÖNBLAD (1888-1963)

Esther Elizabeth Grönblad (Figure 1.1) was born in Uppsala, Sweden in August 1888. She qualified in medicine in Stockholm in 1916 and later specialised in ophthalmology. A PhD degree was awarded to her for her research on angioid streaks in pseudoxanthoma elasticum. Further papers on eye disorders with skin manifestations followed, including investigations in collaboration with Sjogren and the subsequent delineation of the syndrome named after him.

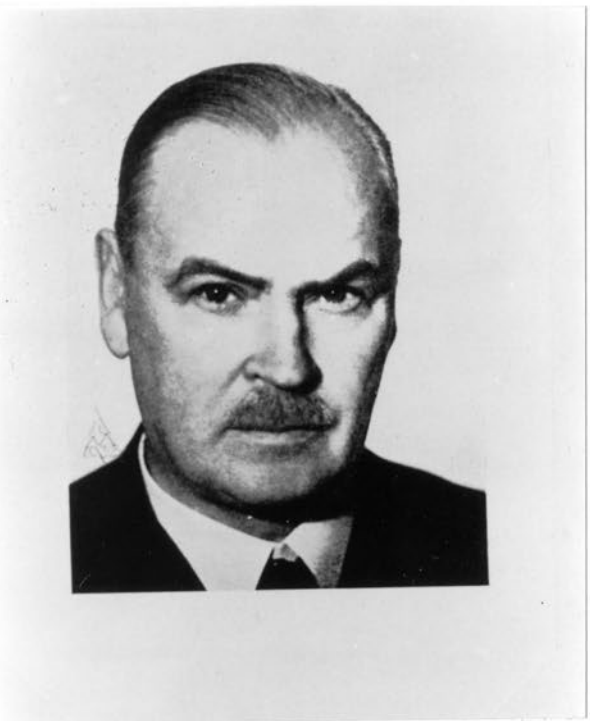


Figure 1.2 JAMES VICTOR STRANDBERG (1883–1942)

James Victor Strandberg (Figure 1.2) was born in Stockholm on March 9th, 1883. He was educated in that city and graduated in medicine in 1909. As a private practitioner, he was the first to diagnose smallpox in the great epidemic of 1920. He became a dermatology registrar at the Royal Caroline Institute in 1922 and was appointed to the full chair of dermatology and syphilology in 1936. He held this position until his death in 1942 from a cerebral haemorrhage.

Strandberg was an exceptional diagnostician and teacher with research interests in occupational eczema, solar elastosis and tuberculosis of the skin. Although he published widely in dermatological subjects, he will be best remembered for his combined contribution with Esther Grönblad in the description of pseudoxanthoma elasticum.

The conjoined eponym **"Grönblad-Strandberg syndrome"** is still occasionally applied to PXE, especially in Europe, but this practice is gradually falling into disuse.

1.3 Original Cardiovascular Studies

The peripheral vascular involvement in PXE has been investigated since the end of the nineteenth century. All the early reports, including those by **Rigal, Darier, Balzer** and **Chauffard** documented a decrease in the amplitude of peripheral pulses in affected individuals. The additional feature of recurrent haematemeses was also described, as were various stroke and embolic phenomena.

It was not until **1944**, however, that **Carlborg** demonstrated narrowing of the small- and medium-sized arteries by means of pulse-wave velocity studies and arteriogams. This classic work also confirmed the relative immunity of large blood vessels to this arteriosclerotic process; subsequent histological studies demonstrated disruption and calcification of elastin in the intimal and medial layers of smaller arteries.

Many other authors have contributed to the understanding of the physiological basis of the cardiovascular complications of PXE, namely **Urbach and Wolfram (1938), Kat and Prick (1940), Schele and Freeman (1946), Wolff et al. (1952)** and **van Embden Andres (1952).**

1.4 Current Concepts (1960 - To date)

Several comprehensive studies into the clinical and investigative aspects of PXE have been undertaken during the past three decades. In an excellent study, **Connor et al., (1961)** reported data relating to angioid streaks in 106 patients. These authors stressed the progressive nature of the retinal lesions which lead to loss of visual acuity, and in some instances, blindness.

Goodman et al., (1963) performed a clinical and histopathological study on 25 individuals at the Johns Hopkins Hospital, Baltimore; their detailed findings are incorporated into the chapter on pseudoxanthoma elasticum in **McKusick's** monograph entitled **"Heritable disorders of Connective Tissue" (1972).**

The most comprehensive investigation relating to PXE is a study conducted by **FM Pope.** He investigated 180 patients in a national survey which extended throughout England and Wales, and presented the data as an MD thesis to the University of Wales in 1972. **Pope** distinguished four groups of patients, two in which the disorder was inherited as an autosomal dominant **(Pope, 1974a)** and two where autosomal recessive inheritance was likely. In this way, he suggested for the first time that PXE might be heterogenous **(Pope, 1974b). Pope** also conducted a retrospective literature study encompassing all the previously published cases of PXE and demonstrated similar heterogeneity in these individuals **(Pope, 1975).**

In recent years, many important contributions have been made in the further understanding of PXE through studies such as the ultrastructural appearance of skin **(Reeve et al., 1979),** mitral valve anomalies in PXE **(Lebwohl et al., 1982)** and the role of calcium in the

diet (Renie et al., 1984). However, no major breakthroughs have been made in the elucidation of the biochemical or genetic defects, or in the understanding of the pathogenetic mechanism of the disorder.

SECTION 1

CHAPTER 2

THE AIMS OF THE STUDY

SECTION 1

CHAPTER 2

THE AIMS OF THE STUDY

Pseudoxanthoma elasticum (PXE) is a heterogeneous, heritable disorder of elastin which mainly involves the eye, cardiovascular system and skin. Many other body systems may be affected including the skeleton, reproductive tract, lungs, central nervous system and teeth. The condition is rare and, prior to this study and excluding my own publication (**Viljoen et al., 1984**), only three brief reports have appeared in the South African literature. (**Nellen & Jacobson, 1958; Przybojewski et al., 1980; Jacyk et al., 1988**).

The aims of this investigation were as follows:

1. To determine the prevalence of PXE among different ethnic groups in South Africa.

2. To establish the mode of genetic transmission in affected families.

3. To clinically appraise and investigate all affected individuals and their kindreds with special attention to the investigation of the ophthalmological, dermatological and cardiovascular systems. Other clinical aspects such as neurological complications, obstetric and gynaecological sequelae, bleeding diatheses and gastrointestinal problems were also documented. In this way, the incidence and age relationships of these manifestations could be determined.

4. To further delineate and document the recently recognised form of PXE found in Afrikaner kindreds and to conduct genealogical studies in affected families.

5. To delineate and document the rare occurrence of PXE in Black individuals in South Africa.

6. To undertake molecular linkage analysis studies using Restriction Fragment Length Polymorphisms (RFLPs) for the collagen and elastin genes, in an attempt to determine which connective tissue element is involved and to confirm heterogeneity in PXE.

7. To assess the efficacy of current therapeutic options in the management of PXE patients. These include plastic surgery and laser photocoagulation for retinal haemorrhage.

8. To enlighten affected individuals and their families as to the medical and genetic implications of the disorder, and to inform medical colleagues of recent developments in the field.

SECTION I

CHAPTER 3

METHODOLOGY

3.1 ASCERTAINMENT OF AFFECTED PERSONS

3.2 CLINICAL EVALUATION OF PATIENTS

3.3 SPECIAL INVESTIGATIONS

3.3.1 Histopathological examination

3.3.2 Evaluation of the cardiovascular system

3.3.3 Ophthalmological examination.

3.3.4 Radiological evaluation.

3.3.5 Computerised tomography and magnetic resonance imaging.

3.3.6 Linkage analysis using RFLP's.

3.3.7 Patient summary.

CHAPTER 3

METHODOLOGY

3.1 Ascertainment of Affected Persons

An attempt was made to identify all patients in South Africa with PXE through the following resources:

a. The record system established since 1972 in the Department of Human Genetics, University of Cape Town and subsequently in the MRC Unit for Inherited Skeletal Disorders.

b. The computerised record system for the Groote Schuur and Red Cross War Memorial Children's academic hospitals in the Western Cape.

c. The record systems from other major hospitals throughout the country.

d. Colleague referrals from the Departments of Human Genetics, Dermatology and Ophthalmology at South African Medical Schools and Teaching Hospitals.

e. A review article entitled "Pseudoxanthoma elasticum in South Africa - genetic and clinical implications" (Viljoen et al., 1984) (Appendix: Publication I) was published in the South African Medical Journal, in which a request for patient referral appeared.

f. Papers on the ophthalmological, dermatological, genetic and surgical aspects of PXE were delivered at the appropriate South

African congresses, during which appeals for patient referral were made. (See Appendix).

g. A circular requesting patient referral was sent to all dermatologists and ophthalmologists on the South African Medical & Dental Register.

3.2 Clinical Evaluation of Patients

All patients referred for study were assessed, where possible, by a multidisciplinary team of consultants including specialists in medical genetics (the author), cardiology, dermatology, radiology and ophthalmology. For logistical reasons a minority of individuals were fully appraised in their home solely by the author. Each patient was evaluated according to a set protocol, a copy of which is included in the Appendix (Protocol 1).

The patients were initially interviewed and detailed genealogical data were recorded. A thorough medical history was obtained. Special emphasis was given to establishing details of ophthalmological, cardiovascular, dermatological, gynaecological and obstetric sequelae in affected patients. The proformata which were used in the latter investigations are presented in the Appendix (Protocol 2).

Physical examination was performed using standard clinical procedures. A detailed appraisal of each body system was made by the author and the information was augmented by evaluations from colleagues who specialised in the skin, eye and cardiovascular systems.

The pedigree data assembled during the investigation of 86 affected persons from 58 kindred served as a basis for further extensive genealogical studies. These were performed by Dr Marie Torrington and her staff at the Genealogy Unit of the Medical Research Council, Tygerberg. Through the data bases of the Mormon Church Archives, the Cape Town Museum, the Dutch Reformed Church, Cape Town Municipal Archives and many private sources, pedigrees of affected families with the Afrikaner form of PXE were extended back 13

generations to the arrival of the original Cape Settlers at the end of the 17th century.

3.3 Special Investigations

Special investigations were performed on many patients, the sophistication of each study depended upon the medical expertise available in the locality in which they lived. Where possible, it was arranged for affected individuals and their families to be examined in major centres with tertiary medical facilities. Informed consent was obtained from each adult investigated or from the parents or guardians of minor children.

The studies on affected individuals included histopathological evaluation of a skin biopsy in every instance in order to confirm the diagnosis of PXE. Thereafter cardiovascular appraisal, ophthalmological investigations with fluorescein angiography, radiological evaluation, molecular linkage analysis, computerised tomography and magnetic resonance imaging were performed.

3.3.1 Histopathological Examination

An elliptical skin sample measuring 3-4mm in diameter was removed from the lateral aspect of the neck region in all affected individuals. This area was chosen as it is the usual site at which pathognomonic skin changes first appear in individuals with PXE. (Figure 3.1) The skin was anaesthetised using 2% lignocaine (without adrenaline) after cleansing with an ethanol swab, and a 23-gauge needle was inserted through the skin. The sample portion was then excised using a scalpel and a Betadine occlusive dressing applied.

The skin sample was placed into a 2% formalin fixative solution and sent for examination by a dermatopathologist. In a few persons, an area of "normal" skin from an apparently unaffected area of the forearm was biopsied for comparative purposes.



Figure 3.1 SKIN BIOPSY SITE IN THE NAPE OF THE NECK

In 7 persons, an additional ellipse of skin from a severely affected region was biopsied, placed in gluteraldehyde solution, prepared in standard fashion and examined using a Phillips 420 transmission electron microscope.

The diagnosis of PXE was confirmed in every instance by the demonstration of the pathognomic histological changes of the skin specimens visualised on light microscopy. Other conditions such as

senile elastosis and penicillamine toxicity, which are known to mimic the phenotypic findings of PXE, were thereby excluded.

3.3.2 Evaluation of the Cardiovascular System

Conventional electrocardiographic and echocardiographic studies were performed in 27 individuals. In the former, a standardised Marquette Mac 15 machine was used and a continuous 9-lead tracing obtained. A 2M mode echocardiograph (Advanced Technical Laboratory - Ultra Mark 8) was employed to assess cardiac parameters. Where clinically indicated, stress electrocardiography was also performed.

3.3.3 Ophthalmological Examination

Visual acuity was assessed in 77 individuals, 49 of whom were also evaluated by slit-lamp examination. Retinal photography was undertaken in the majority of these persons and fluorescein angiography was also performed in 12 adults with severe retinopathy. In each instance, the study was undertaken in a specialised ophthalmology unit of a major hospital.

3.3.4 Radiological Evaluation

A limited radiological skeletal survey was performed on 24 affected persons using conventional equipment. This comprised anterior-posterior views of:

a. Both hands and feet.

b. Both knees, including the upper tibiae and fibulae.

c. The pelvis to show the hip joints and upper femora.

d. Both elbows.

In addition, anterior-posterior and lateral views of the chest and skull were obtained, together with a lateral view of the thoraco-lumbar spine.

3.3.5 Computerised Tomography and Magnetic Resonance Imaging

Computerised tomography of the cranium with enhancement using contrast material was carried out in 10 persons.

Magnetic Resonance Imaging (MRI) scans were performed in a further 3 persons using a Gyrex 5000 Elscini (5 Tesla, super-conducting magnet) scanner at the Medical Research Council facilities at Tygerberg, Cape Town.

The radiographs, computerised tomography scans and magnetic resonance images were analysed by the author in conjunction with Professor B J Cremin (Head of Radiology, Red Cross War Memorial Children's Hospital, Cape Town).

3.3.6 Linkage Analysis using Restriction Fragment Length Polymorphisms (RFLP's)

Two molecular genetic approaches were employed in 2 large Afrikaner families with PXE:

1. Linkage analyses with two type 1 collagen probes.
2. Linkage analyses with two human elastin gene probes.

Details of the materials and methods employed in the above investigations are given in Section V.

3.3.7 Patient Summary

The clinical and investigative findings were recorded and a medical report was compiled and sent to the patient, the referring specialist and the general practitioner. In this summary, the problem medical areas were outlined, guidance for further management was provided and prognostic and genetic counselling was given. Recent medical reviews concerning PXE were listed for easy reference by the patient's own physician.

SECTION II

GENETICS

Although it is customary in a project of this nature to present the clinical data prior to an analysis of genetic aspects, convincing evidence of an autonomous form of PXE within the Afrikaner community emerged as the investigation proceeded. These findings were intensively studied and are presented in Chapter 10. As the new entity was confined to the Afrikaner segment of the population, it was appropriate to first analyse the genealogical data from different ethnic groups in South Africa.

Aspects of nosology are presented in this section and the current situation relating to PXE is discussed. A detailed analysis of the affected kindreds has been undertaken and evidence for autosomal dominant and autosomal recessive inheritance is reviewed. In addition, calculations of the prevalence of PXE and the gene frequency within different ethnic groups have been made. The geographical distribution of patients with PXE in this study is outlined.

CHAPTER 4 : NOSOLOGICAL CONSIDERATIONS IN PXE

CHAPTER 5 : ANALYSIS OF PEDIGREES

CHAPTER 6 : EPIDEMIOLOGY

CHAPTER 7 : POPULATION GENETICS

SECTION II

CHAPTER 4

NOSOLOGICAL CONSIDERATIONS IN PSEUDOXANTHOMA ELASTICUM

SECTION II

CHAPTER 4

NOSOLOGICAL CONSIDERATIONS IN PSEUDOXANTHOMA ELASTICUM

CHAPTER 4

NOSOLOGICAL CONSIDERATIONS IN PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum has long been considered a heritable disorder of connective tissue and, in most literature contributions prior to 1970, the condition was thought to be inherited as an autosomal recessive trait. Increased frequency of parental consanguinity (McKusick, 1972), the occurrence of multiple affected sibs and the rarity of the disorder in successive generations (Hubler, 1944; Coffman and Sommers, 1959; McKusick, 1972) supported this supposition.

Discussion regarding possible heterogeneity in PXE followed several reports describing affected individuals in two generations of a single kindred (Berlyne et al., 1961; Gills and Paton, 1965; Wise 1966). In the opinion of Wise (1966) who found 20 examples of parent-child transmission, this indicated the existence of a dominant form of PXE. McKusick (1972) postulated that these individuals may have represented "quasi-" or "pseudo-dominance" or be due to mating of a homozygote with a heterozygous carrier of the gene. An alternative explanation was "the occasional expression in the heterozygote".

It remained for Pope's extensive studies in the populations of England and Wales to demonstrate that PXE truly is a genetically heterogeneous entity. Pope was able to clinically differentiate two autosomal recessive (Pope 1974(a)) and two autosomal dominant (Pope 1974(b)) forms of the disorder. The characteristic features of the more common type I recessive form of PXE (AR I) were moderate eye, cardiac and skin manifestations whereas the rare type II recessive group (AR II) had severe cutaneous features only. Individuals with autosomal dominant

type II PXE (AD II) delineated by Pope had mild cardiac manifestations associated with a marfanoid habitus. The less prevalent autosomal dominant type I PXE (AD I) manifested with severe cardiac complications but lacked the marfanoid features. To substantiate his findings, Pope was able to confirm genetic heterogeneity in previously reported PXE patients by means of a retrospective search of the literature (Pope, 1975).

A further autonomous entity in which serious ophthalmological complications occurred was later described in the Afrikaner population of South Africa by Viljoen et al., (1987) (Appendix: Publication 2). These studies were undertaken during the initial phase of the current project. Through pedigree analysis of 58 affected persons, it is apparent that this latter condition is inherited as an autosomal recessive trait and occurs with a high prevalence in the Afrikaner population (Chapter 7 and Section III).

The Afrikaner antecedents were derived from Western European countries and consisted mainly of Dutch, German and French Huguenot settlers. It is therefore of interest that De Paepe et al., (1990) (Appendix : Publication 5) confirmed the occurrence of this form of PXE in patients of Belgian stock. The founder effect in the Afrikaner population is thought to account for the high prevalence of PXE in this subgroup (Chapter 9.3). The distinctive clinical features of the "Afrikaner" type of PXE are detailed in Table 11.1.

In the light of the foregoing there would currently appear to be five autonomous entities which are classified as "pseudoxanthoma elasticum". Three of these disorders are inherited as autosomal recessives while two are apparently transmitted as autosomal dominant traits.

A summary of the clinical features are presented in Table 4.1.

TABLE 4.1

A COMPARISON OF CLINICAL FEATURES WITHIN TYPES OF PXE

CLASSIFICATION OF PXE	CLINICAL FEATURES
AD type I	severe retinal and cardiovascular features; classical flexural changes
AD type II	mild retinal and cardiovascular changes; marfanoid features: high-arched palate, joint laxity, blue sclerae, arachnodactyly.
AR type I	moderate retinal and vascular lesions; classical peau d'orange skin manifestations.
AR type II	severe generalised cutaneous lesions only.
AR "Afrikaner" type	severe retinal complications; moderately-severe cardiovascular lesions; mild cutaneous features.

No biochemical or histopathological abnormalities are presently able to separate these conditions. It will remain for elucidation of the genetic defect at a molecular level to determine whether true heterogeneity exists or whether epistatic or other influences are responsible for the variable clinical manifestations.

SECTION II

CHAPTER 5

ANALYSIS OF PEDIGREES

5.0 INTRODUCTION

5.1 ETHNIC DISTRIBUTION OF PEDIGREES

5.2 SEGREGATION ANALYSIS

5.2.1 Method for testing autosomal recessive inheritance

5.2.2 Autosomal dominant PXE

CHAPTER 5

ANALYSIS OF PEDIGREES

5.0 Introduction

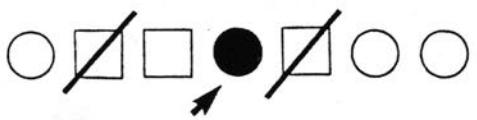
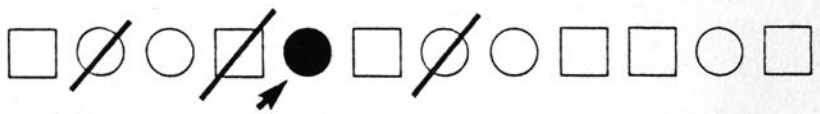
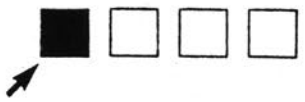
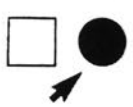
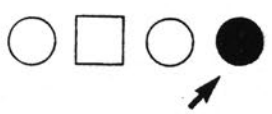
During the initial interview with each affected patient, historical data regarding details of the family tree were obtained. In this way information concerning 58 kindreds with a histologically confirmed diagnosis of PXE was compiled. These data are shown in abbreviated form in Table 5.1. The symbols used to characterise individuals are those used in standard genetic texts; a key to the pedigrees and the abbreviations used is given at the foot of Table 5.1.

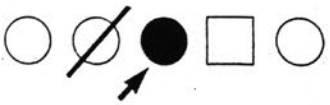
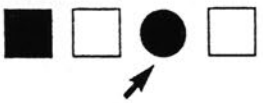
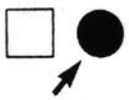
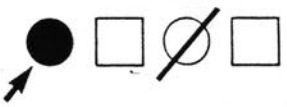
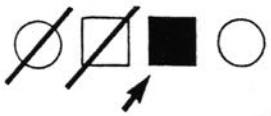
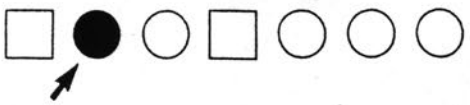
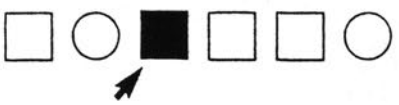
Four pedigrees are presented in a formal manner as they contain aspects of special interest. (Figures 5.1 - 5.4).

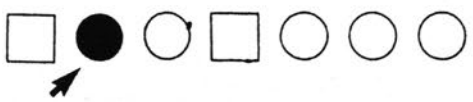
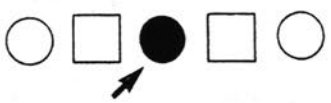
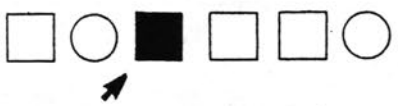
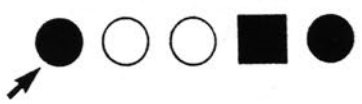
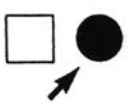
In the 58 kindreds under scrutiny, generation-to-generation transmission or presumed autosomal dominant inheritance of PXE occurred in 3 large families. (Figures 5.1 - 5.3). This latter group comprised a total of 16 affected and 32 unaffected siblings, all of whom were Afrikaner in descent. In addition 44 sporadically occurring persons with PXE (and 142 unaffected siblings) were ascertained where either autosomal dominant or autosomal recessive inheritance may have occurred.

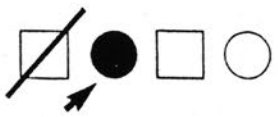
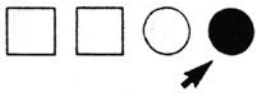
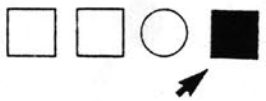
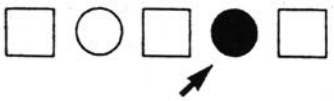
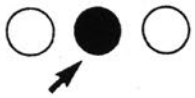
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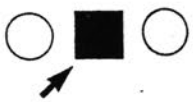
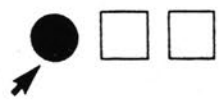
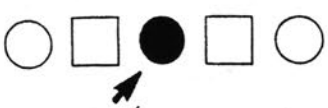
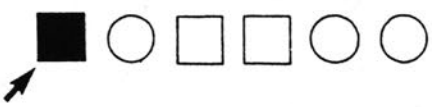
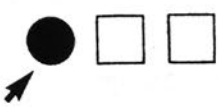
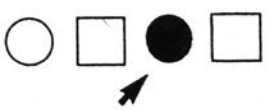
ABBREVIATED PEDIGREE DATA

ETHNIC GROUP	PEDIGREE NUMBER	PATIENT SYMBOL
E	1 + 2	
A	3 - 9	See Figure 5.1
MA	10	
E	11	
MA	12	
A	13	
A	14	
MA	15	
A	16	
A	17	
E	18	

ETHNIC GROUP	PATIENT NUMBER	PEDIGREE SYMBOL
A	19 - 21	
A	22	
A	23 - 24	
E	25 - 26	
A	27	
A	28	
A	29	
B	30	
A	31	
MA	32	
C	33	
MA	34	

ETHNIC GROUP	PATIENT NUMBER	PEDIGREE SYMBOL
A	35 - 38	See Figure 5.2
A	39	
E	40 - 41	
MA	42	
MA	43	
MA	44	
MA	45	
A	46 - 50	See Pedigree 5.3
A	51 - 53	
A	54	
A	55	
C	56	

ETHNIC GROUP	PATIENT NUMBER	PEDIGREE SYMBOL
A	57	
A	58 - 59	
A	60	
A	61 - 63	See Figure 5.4
E	64 - 65	
A	66	
A	67	
A	68 - 70	
B	71	
MA	72	
A	73	
A	74	

ETHNIC GROUP	PATIENT NUMBER	PEDIGREE SYMBOL
A	75 - 76	
A	77	
B	78	
E	79	
A	80	
A	81	
A	82	
E	83	
E	84	
A	85	
B	86	

ETHNIC GROUP

E: British

A: Afrikaner

MA: Mixed ancestry

B: Black

C: Caucasian (non-Afrikaner & non-English speaking)

KEY TO PEDIGREES

Normal female

Normal male

Affected female

Affected male

Deceased individuals

Proband

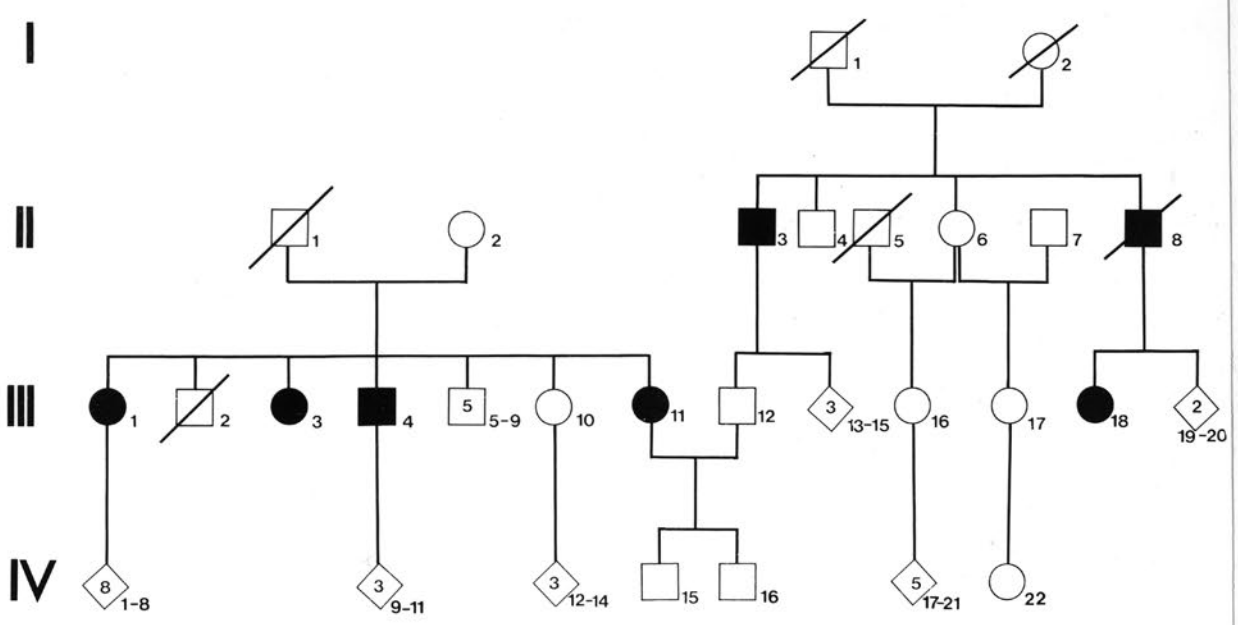


Figure 5.1 PEDIGREE OF A KINDRED WITH PXE WHO WERE ORIGINALLY DOMICILED IN WORCESTER, CAPE PROVINCE

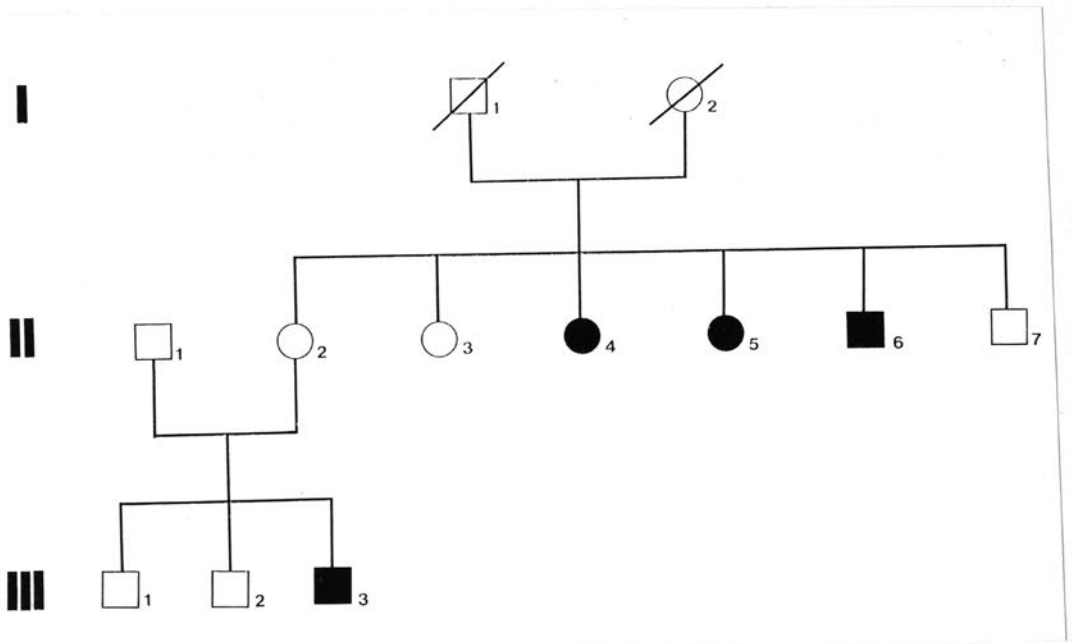


Figure 5.2 PEDIGREE OF A FAMILY WITH PXE FROM THE WESTERN TRANSVAAL

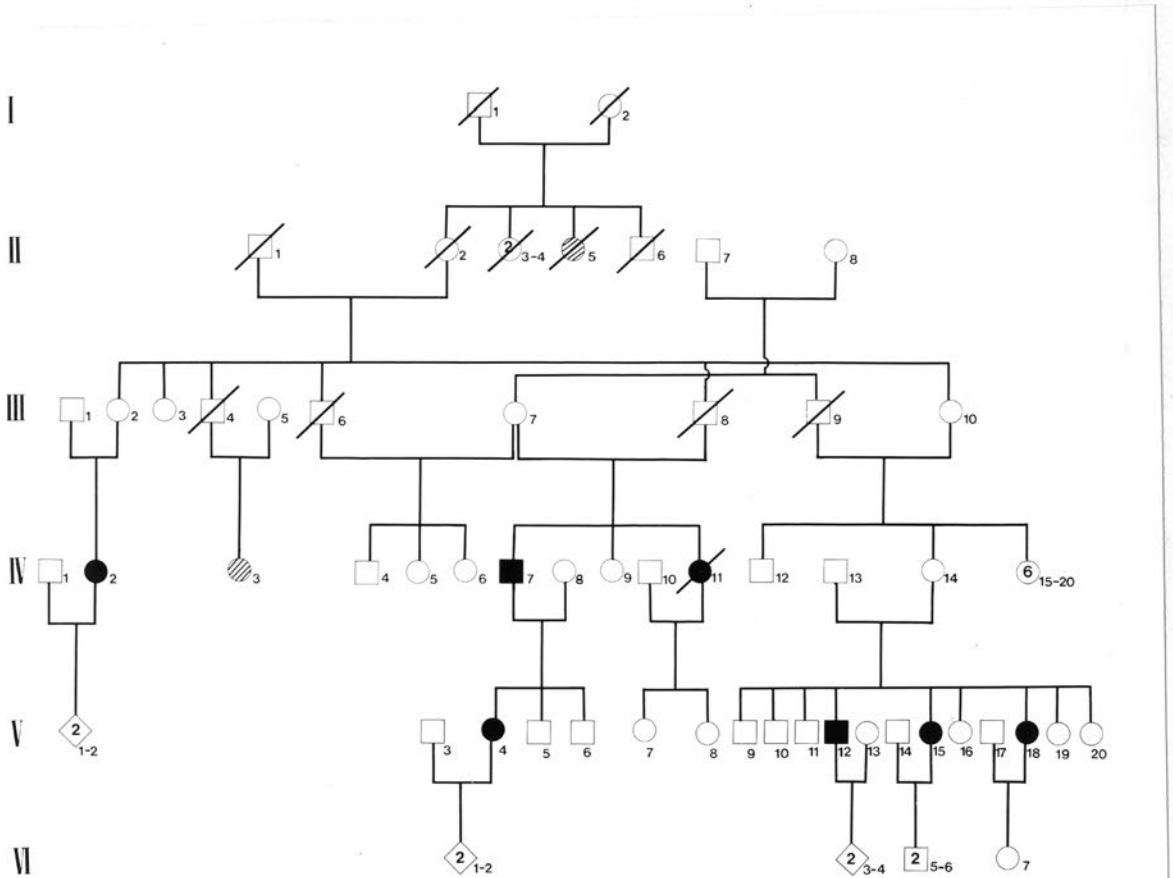


Figure 5.3 PEDIGREE OF A KINDRED WITH PXE ORIGINALLY DOMICILED IN VELDDRIFT, WESTERN CAPE PROVINCE

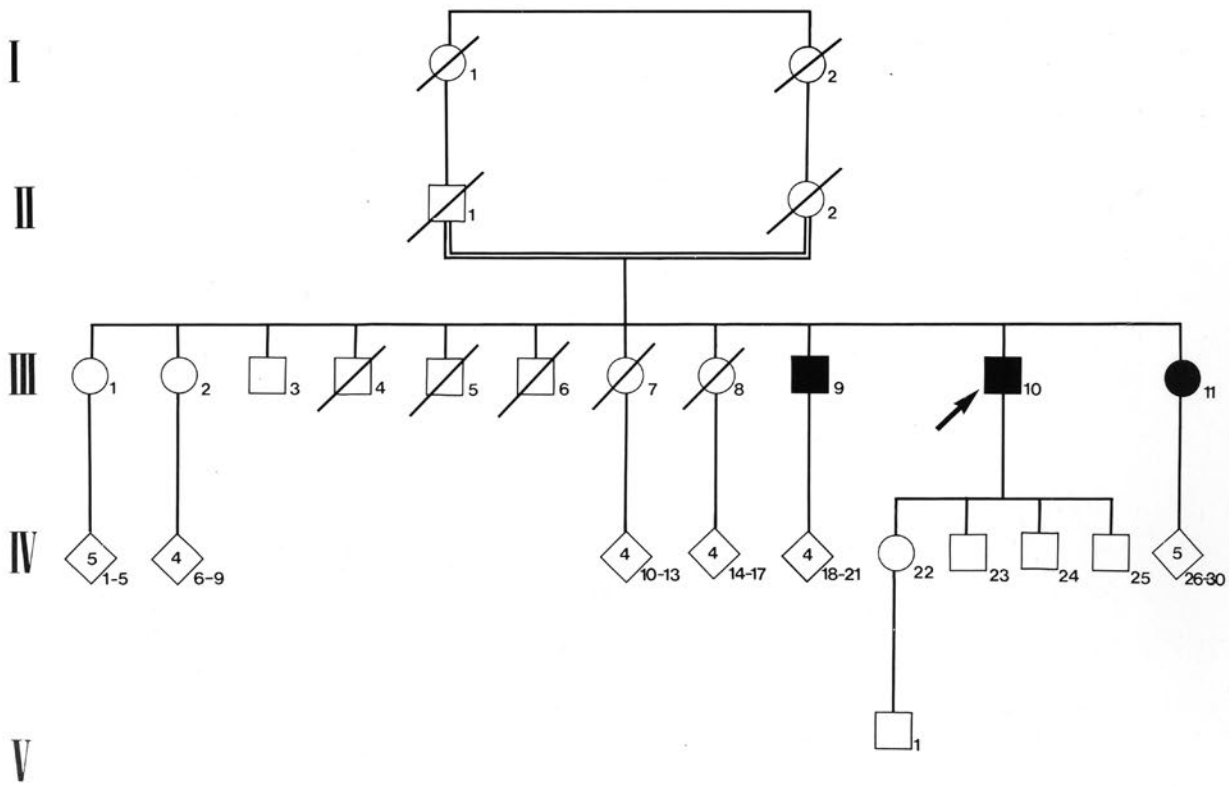


Figure 5.4 PEDIGREE OF A CONSANGUINEOUS FAMILY DOMICILED IN DURBAN

5.1 Ethnic Distribution of Pedigrees

Fifty-eight families were analysed in this investigation from which 86 individuals with PXE were positively identified. Their ethnic derivations are outlined in Table 5,2.

TABLE 5,2

THE ETHNIC ORIGINS OF 58 FAMILIES WITH PXE

	Ethnic Origins	No. of Kindreds	No. of Affected Individuals
Caucasian	British	9	12 (15)
	Afrikaner	33	58 (135)
	Other	2	2 (1)
Mixed Ancestry		9	9 (36)
Asian		1	1 (6)
Black	Xhosa	3	3 (10)
	Zulu	1	1 (3)
	Total	58	86 (206)

(Figures in brackets = unaffected siblings)

5.2 Segregation Analysis

In view of the nosological debate currently underway in the literature regarding possible genetic heterogeneity in PXE, it was deemed necessary to perform an analysis of the segregation ratios in our families. This study would indicate whether heterogeneity exists in PXE within South African populations.

5.2.1 Method for Testing Autosomal Recessive Inheritance

The expected risk to each offspring of heterozygous parents is p = 0.25; correction for complicating factors such as non-paternity and late onset may yield a lower expected p value.

Due to ascertainment bias alluded to in Chapter 6, in order to estimate the frequency of PXE amongst offspring of heterozygous parents and to compare it with the expected value, the Davie (1979) modification of the Singles Method of Segregation analysis (derived by Gart, 1967 and Li and Mantel, 1968) was employed. The reasoning behind the method is as follows:

Consider an individual X who has a sib Y who is a proband. Then X has a probability P of being affected; moreover, since Y is a proband the family will be ascertained whether or not X is affected. Thus if all the members of the sample who have a sib as a proband are considered, on average a proportion p is expected to be affected.

Formula :

T = Total number of individuals in sample

R = Number with PXE

J = Number of sporadic PXE individuals without sib

$$P = \frac{(R - J)}{(T - J)}$$

Analysis of PXE patients

A. All affected individuals

$$P = \frac{(86 - 44)}{(294 - 44)} = 0.168 \text{ (expected 0.25)}$$

B. Exclusion of pedigrees with possible dominant inheritance

$$P = \frac{(70 - 44)}{(224 - 44)} = 0.144 \text{ (expected value = 0.25)}$$

Comment

Segregation analysis of PXE patients under investigation both when analysed as a whole and when possible dominant pedigrees are excluded reveal similar, lower than expected results (p = 0,168 and p = 0,144 respectively). Complicating factors in the analysis are:

1. **Late onset of clinical signs**

   The clinical manifestations of PXE usually become evident in the early teenage years. However, many affected persons escape clinical detection well into adulthood. In this investigation, the earliest age of diagnosis was 9 years and in one person PXE was only confirmed at 64 years. Although the majority of siblings in affected families were clinically appraised by the author, it is possible that in some instances individuals will develop signs of

PXE later in life. The probability ratios calculated for autosomal recessive inheritance might then approximate the expected figure (P=0,25). However, the author has maintained close contact with affected families over the past five years and thus far not a single instance of a "missed" diagnosis has occurred. It would seem that the effect of undetected, late-onset disease is likely to be minimal.

2. Non-paternity

Non-paternity can introduce an error in underestimating the probability of autosomal recessive inheritance. Although figures for non-paternity are unavailable for the various ethnic groups in South Africa, it would seem unlikely that the low probability found in this study can be solely attributed to this factor.

3. "Sporadic" cases

If segregation analysis of a genetic disease believed to be inherited as an autosomal recessive trait results in an estimated probability significantly less than expected, then a possible explanation is that other inheritance patterns have been included in the sample. Such skewing of the data can be derived from the presence of "sporadic" or "isolated" cases, where only a single individual in a family is affected. (The terms are not used interchangeably in this context. True "sporadic" individuals are taken to represent new autosomal dominant mutations. The term "isolated" is used to refer to individuals who are the sole affected person in their family and are homozygous for the recessive gene.).

As "isolated" individuals represent the homozygous recessive state, they may be differentiated from "sporadic" cases by testing for consanguinity in their parents.

In this investigation, parental consanguinity was recorded in only two of the kindreds studied. Nevertheles it has been shown that earlier generations of Afrikaner families in particular were extensively intermarried (Chapter 9). Thus the separation of true "isolated" from "sporadic" cases of PXE is impossible.

Estimate of True Sporadic Cases

If, for the purposes of this investigation, it is assumed that of the 44 sporadic cases of PXE, half (22) represented "isolated" cases (or homozygous recessive persons) and the remainder were "sporadic" cases (new mutation for an autosomal dominant disorder) then the analysis for testing autosomal recessive inheritance would change as follows:

Formula :

$$P = \frac{(R - J)}{(T - J)}$$

Calculation :

$$P = \frac{(70 - 22)}{(224 - 22)} = 0{,}237$$

This estimate of the probability of autosomal recessive inheritance in our families with PXE would fit very well with the expected p value of 0,25.

Conclusion

The estimated number of individuals with PXE in this study inheriting the trait as an autosomal recessive is 48 persons, of which 26 have more

than one affected sibling per kindred and a further 22 persons occurred as isolated cases (assumed for the purposes of ascertainment to be homozygous for the trait). Almost 56 per cent of the cohort of affected persons thus had an autosomal recessive form of PXE.

5.2.2 Autosomal Dominant Pseudoxanthoma Elasticum

Generation-to-generation transmission occurred in 3 families investigated, and these individuals are assumed to be examples of autosomal dominant inheritance. Sixteen (16) affected persons fitted this category, accounting for 18.6 per cent of the total cohort. A further 22 persons were assumed, for the purposes of analysis, to represent true "sporadic" cases (or new autosomal dominant mutations). In total, therefore, 38 individuals were ascertained in this study as representing autosomal dominant PXE.

Comment

As can be observed from the pedigrees represented in figures 5.1 - 5.3, the generation-to-generation transmission of PXE in the 3 kindreds may conceivably represent quasi- or pseudo-dominant inheritance. Several other explanations, some of which have already been discussed in Chapter 4, are:

i. The occasional expression of the heterozygote in an autosomal recessive disorder.

ii. The existence of a true dominant form of PXE. The fact that no more than two generations are affected in any of the 3 pedigrees shown and the apparent skipping of generations may be due to variable penetrance of a dominant gene.

iii. A further possibility is that a high background frequency of the recessive gene for PXE exists in the South African population in which expressivity is so wide that many individuals escape clinical detection because the manifestations to the disorder blend with normality.

iv. Other modes of inheritance, such as polygenic, X-linked and epistatically-influenced transmission appear unlikely as a cause of this phenomenon, but remain possibilities. Mitochondrial inheritance and gonadal mosaicism would appear to be excluded by pedigree analysis, the relatively equal sex distribution and the high prevalence of the disorder.

Summary

Many reports in the literature have established generation-to-generation transmission of PXE. Yet, due to the frequent occurrence of sporadic cases, the exact prevalence of autosomal dominant PXE will only be resolved when molecular techniques allow accurate identification of the underlying gene defect.

SECTION II

CHAPTER 6

EPIDEMIOLOGY

6.1 INTRODUCTION

6.2 FREQUENCY OF PXE IN SOUTH AFRICA

6.3 MORTALITY RATE FOR PXE

6.4 GENDER OF PATIENTS WITH PXE

6.5 GEOGRAPHIC DISTRIBUTION OF PXE IN SOUTH AFRICA

6.1 Introduction

Epidemiology has been defined as the study of the distribution, frequency and natural history of disease in man (Barker and Bennett, 1973).

Several epidemiological studies on PXE have been previously performed, the most comprehensive of which formed part of a thesis by FM Pope for the University of Wales (1972). In this study, Pope attempted to ascertain all affected individuals in England and Wales. One hundred and eighty persons were appraised in all.

Apart from Pope's investigation, several other series of individuals with PXE have been reported (Connor et al., 1961; Goodman et al., 1963; Alinder and Bostrom, 1972; Neldner, 1988). These studies were usually hospital-based investigations, however, and thereby biased in their ascertainment. For these reasons, no attempts were made by the authors to assess prevalence of the disorder; estimates have ranged from 1/60 000 - 1 per million of the general population (McKusick, 1972).

6.2 Frequency of Pseudoxanthoma Elasticum in South Africa

Frequency of a disease may be expressed in terms of:

a. Prevalence: the total number of affected persons in a defined population at a specific time.

b. Incidence: The total number of affected persons newly ascertained in a given time period.

Although an earnest attempt was made at accurately assessing the prevalence of PXE within each ethnic group of the South African population, factors such as incomplete referral and the reluctance of individuals to be further investigated has almost certainly prevented complete ascertainment. Nevertheless, a minimum prevalence rate of occurrence of PXE for each population group could be calculated.

The prevalence of PXE in South Africa was established for 30th December, 1989. This date was arbitrarily chosen as the end of data collection for the purposes of the study, although an ongoing assimilation of data will continue as part of the service commitment of the Department of Human Genetics, University of Cape Town.

Prevalence was calculated according to the following formula:

$$\text{Prevalence} = \frac{A \times 10^6}{\text{Population}}$$

where A = total number of living affected persons on prevalence day.

The population figures are estimates based on the 1985 census figures, taking into account the average annual growth rate for each population group. (Department of National Health and Population Development, 1989; see Tables 6.1 & 6.2). It is estimated that sixty per cent of the Caucasian population of South Africa are Afrikaner in descent.

TABLE 6.1

THE ESTIMATED POPULATION OF SOUTH AFRICA BY GEOGRAPHIC AREA (1990)

(Totals and distribution based on the 1985 census - Epidemiological Comments Vol 14 No 1.)

REGION	POPULATION GROUP				
	ASIAN	BLACK	COLOURED	WHITE	TOTAL
Western Cape	21392	494339	1971968	861019	3348718
Northern Cape	2091	321465	297124	127127	747807
Eastern Cape	12737	1115059	393485	395788	1917069
Orange Free State	60	1902095	70089	380281	2352525
Natal	746960	1142211	106332	640842	2636345
S Transvaal	137286	5576636	291111	2607133	8612166
N Transvaal	5607	859481	9110	209402	1083600
Homeland States	3867	9466714	6781	6408	9483770
GRAND TOTAL	930000	20878000	3146000	5228000	30182000

TABLE 6.2

CURRENT ESTIMATED POPULATION FIGURES FOR SOUTH AFRICA (1990)

	MILLIONS
Caucasian	5.228
Mixed Ancestry	3.146
Asian	0.93
Black	20.878
	30.182

(Source: Epidemiological Comments Vol 16, No 11, pg 38, 1990)

Results

The number of living affected individuals with PXE on 30 December 1989 was 86. The prevalence of PXE in the various ethnic groups in South Africa is presented in Table 6.3. The minimum prevalence in both the English-speaking and Afrikaner groups of the Caucasian population is shown in Table 6.4.

TABLE 6.3

MINIMUM PREVALENCE OF PXE IN SOUTH AFRICAN POPULATIONS

	NUMBER	PREVALENCE X 10^{-6}
Caucasian	73	13.963
Mixed Ancestry	8	2.543
Asian	1	1.075
Black	4	0.192
TOTAL	86	

TABLE 6.4

PREVALENCE OF PXE IN THE CAUCASIAN POPULATION

	NUMBER	PREVALENCE X 10^{-6}
English-speaking	15	8.606
Afrikaner	58	16.643

When the prevalence rates for the 3 major ethnic groups are calculated for each of the provinces of South Africa, the highest prevalence was found in the Cape Province (Table 6.5).

TABLE 6.5

PREVALENCE OF PXE IN DIFFERENT PROVINCES OF SOUTH AFRICA

PROVINCE		NUMBER	POPULATION $x10^3$	PREVALENCE $x\ 10^{-6}$
Cape	Caucasian	38	1384	28,90
	MA	8	2663	3,00
	Black	3	1931	1,55
Natal	Caucasian	6	641	9,36
	MA	-	-	-
	Black	1	5831	0,17
Orange Free State	Caucasian	5	380	13,16
	MA	-	-	-
	Black	-	-	-
Transvaal	Caucasian	23	2817	8,17
	MA	-	-	-
	Black	-	-	-

MA : Mixed ancestry

Comment

The prevalence figures for the various ethnic groups are underestimates of the true frequency of PXE in South Africa and represent minimum prevalences for the disorder.

Ascertainment for all groups was highest in the Cape Province as the study was undertaken from a base in Cape Town. It is likely that almost complete ascertainment of PXE amongst the Caucasian population

of the Cape Province was achieved because of the author's interest in the disorder and close contact with medical colleagues, especially those in the specialities of genetics, ophthalmology, cardiology and dermatology.

The minimum prevalence of PXE for the Afrikaner population varied from 1/23,066 in the Cape Province (Calculation D, Chapter 7) to 1/60,008 for the Afrikaner population as a whole in South Africa. The former is the highest prevalence rate for the disorder reported anywhere in the world. The implications and gene frequency are discussed in Chapter 7.

The prevalence for English-speaking Caucasians in South Africa is 1/120,000 while that for the mixed ancestry population in the Cape Province is 1/330,000 (Calculation E, Chapter 7). The prevalence of the disorder in Blacks in the Cape Province is almost 1/650,000 (Calculation F, Chapter 7).

It is unlikely that all affected individuals from the Black and Mixed Ancestry group in the Cape Province were assessed, unless complications of PXE had drawn attention to the diagnosis in the affected persons. Nevertheless, the prevalence figures do indicate a strong probability that PXE is less frequent by far in these populations. However, assigning statistical significance to these findings is not valid.

6.3 Mortality Rate for PXE

McKusick (1972) calculated survivorship of 52 patients with PXE from the Johns Hopkins Hospital records (Baltimore). He showed that after 62 years of age only 4% of males survived, whereas the figure approached 20% for females of the same age.

Mortality rates for PXE in South Africa are impossible to calculate due to the under-ascertainment of the disorder in past years and incorrect recording of cause of death on death certificates.

During the period of study, no individual identified as manifesting the signs of PXE died. Three persons with PXE had demised prior to the commencement of this investigation. (Figure 5.1, patient II,8; Figure 5.3, patients IV,2 and IV,11). Their deaths occurred at the ages of 46 years, 35 years and 38 years respectively and in two instances, were related to the complications of ischaemic heart disease. Stroke phenomena are frequent in PXE and this complication may have contributed to the death of patient II,8 (Figure 5,1). However, ischaemic heart disease for other reasons is common in the Afrikaner, so that retrospective determination of the factors causing death is impossible in these instances.

The oldest affected person in the current investigation is a male aged 82 years while eight other persons exceed 60 years. The average age of the 86 affected individuals is 38.4 years.

The number of affected persons aged 60 years and over is in concordance with the mortality figures published by McKusick (1972). Nevertheless, mortality rates for individuals with PXE in South Africa

are currently impossible to calculate although increasing awareness of the disorder may allow estimates of mortality in future years.

6.4 Gender of Patients with PXE

There has been a female preponderance in all large series of patients with PXE (Connor et al., 1961; Goodman et al., 1963; Alinder and Bostrom, 1972; Pope, 1972; Neldner, 1988). This gender discrepancy has been attributed to women seeking medical attention at an earlier age for cosmetic reasons. There is no evidence that increased male mortality in PXE contributes to the sex differences in patients.

Females with PXE were more common than males for all ethnic groups in this investigation (Table 6.6). The complications of PXE relating to the cardiac and ophthalmological systems were similar between the sexes (Chapters 13 & 14). However, females appeared to have more severe dermatological sequelae attributable to PXE than their male counterparts (Chapter 12) and this finding may account for the 52:34 female/male preponderance in this series.

TABLE 6.6

GENDER OF PATIENTS AFFECTED WITH PXE

		MALE	FEMALE	TOTAL
Caucasian	British	5	7	12
	Afrikaner	25	33	58
	Other	1	1	2
Mixed Ancestry		3	6	9
Asian		0	1	1
Black		0	4	4
TOTAL		34	52	86

6.5 Geographic Distribution of Patients with PXE in South Africa

The populations of South Africa are concentrated in greatest density in the urban areas of major cities in the 4 provinces. In the Transvaal, the highest population density occurs in the metropolitan areas of Johannesburg and Pretoria, whereas the focus in Natal is mainly around Durban. The populations of the Cape Province are concentrated mainly in Cape Town, Port Elizabeth and East London and in the Orange Free State, Bloemfontein and Welkom have the largest populations.

The geographic distribution of patients with PXE is shown in a map of Southern Africa illustrated in Figure 6.1. The highest proportion of affected individuals were investigated in Cape Town (38 persons). A large proportion of the remainder were drawn from the cities mentioned previously in the three other major provinces. There were few referrals of affected persons from rural areas. This situation may reflect lack of awareness of my research interest by colleagues in these areas together with the low population density outside the major centres of South Africa.

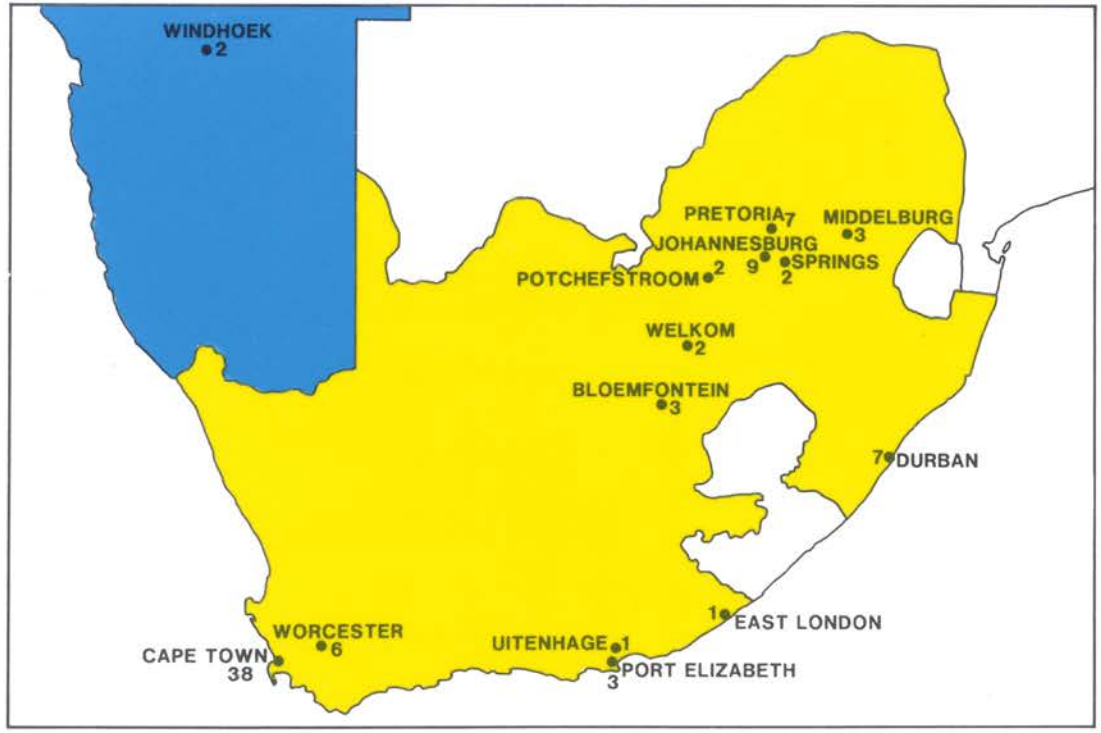


Figure 6.1 THE GEOGRAPHIC DISTRIBUTION OF PATIENTS WITH PXE IN SOUTHERN AFRICA

SECTION II

CHAPTER 7

POPULATION GENETICS

7.1 THE GENE FREQUENCY OF PXE IN SOUTH AFRICA

7.2 ESTIMATES OF UNDIAGNOSED PATIENTS IN DIFFERENT ETHNIC GROUPS

CHAPTER 7

POPULATION GENETICS

7.1 The Gene Frequency of PXE in South Africa

Introduction

Pseudoxanthoma elasticum is a heterogenous disorder. Evidence for this fact derived from previously published reports has been discussed in Chapter 4, and the prevalence of recessive and dominant PXE in South African populations has been analysed in Chapter 6. In South Africa the most prevalent mode of inheritance, calculated from segregation analysis of affected persons, is as an autosomal recessive trait.

Autosomal dominant inheritance implies phenotypic expression in the heterozygous state. In this situation the contribution to the gene pool is immediately apparent and, in the South African context, small. For this reason, affected individuals from kindreds where autosomal dominant inheritance was likely were excluded from the calculations of gene frequency. Similarly, the "true sporadic" or "assumed autosomal dominant" individuals were not included in this estimation.

Due to the small number of affected individuals in the Black and Asian ethnic groups of South Africa, estimates of the gene frequency were confined to Caucasian and Mixed Ancestry groups, together with the Black population of the Cape Province. The latter group was selected as ascertainment was more complete than in the other Provinces in South Africa.

Method

The Hardy-Weinberg formula was used in the calculation of gene frequency in patients found to have the autosomal recessive form of PXE. The Hardy-Weinberg principle is true only for large populations where there is no migration or selection against a particular genotype and where there is random mating and a constant rate of mutation (Emery and Mueller, 1988). The limitations of applying the Hardy-Weinberg calculation for the patients in this investigation will be alluded to in "Discussion".

Formula

$$p + q = 100\% \text{ (or } 1)$$

where p + q represents the sum total of the PXE genes at the recessive gene locus.

q^2 = prevalence of PXE homozygote in the population

but $p = 1 - q$ (q is extremely small)

Therefore 'p' approximates 1

The frequency of carriers = 2pq

Calculations

A. Frequency of PXE Recessive Gene in the Caucasian Population of South Africa. (Excluding possible autosomal dominant pedigrees).

Total number of Caucasians affected = 35

Total Caucasian population = $5{,}228 \times 10^6$

Prevalence = $35/5{,}228 \times 10^6$

Gene frequency = $35/5{,}228 \times 10^6 = 0{,}002569$

Heterozygous rate = 2 x 0,002569 = 0.005138

No of carriers = 26 860

Carrier frequency = 1/195 of population

B. **Frequency of PXE Recessive Gene in the Afrikaner Population. (Excluding possible autosomal dominant pedigrees).**

Total number of Afrikaners affected: 30

Estimated total Afrikaner population: 3 485 x 10^6

Prevalence = 30/3, 485 x 10^6

Gene frequency = 30/3, 485 x 10^6 = 0,0029325

Heterozygous rate = 2 x 0,0023325 = 0,005865

Number of carriers = 20 440

Carrier frequency = 1/170 of population

C. **Frequency of PXE Recessive Gene in the Afrikaner Population (Assuming all pedigrees are recessive).**

Total number of Afrikaners affected = 58

Estimated total Afrikaner population = 3,485 x 10^6

Prevalence = 58/3,485 x 10^6

Gene frequency = 58/3,485x10^6 = 0,00407

Heterozygous rate = 2 x 0,00407 = 0,00815

Number of carriers = 28 400

Carrier frequency = 1/123 of population

D. **Frequency of Recessive Gene for PXE in Afrikaner Population of the Cape Province (Assuming all pedigrees are recessive).**

Total affected	**= 40**
Estimated Afrikaner population of the Cape	**= 922 666**
Prevalence	**= 40/922 666**
Gene frequency	**= 40/922 666 = 0.00658**
Heterozygous state	**= 2 x 0,00658 = 0,01316**
Number of carriers	**= 12 140**
Carrier frequency	**= 1/76 of population**

E. **Frequency of Recessive Gene for PXE in Mixed Ancestry Population in the Cape Province.**

Total affected	**= 8**
Estimated Mixed Ancestry population of the Cape	**= 2,643 x 10^6**
Prevalence	**= 8/2,663 x 10^6**
Gene frequency	**= 8/2,663 x 10^6 = 0,001732**
Heterozygous state	**= 2 x 0,001732 = 0,03464**
Number of carriers	**= 9 225**
Carrier frequency	**= 1/289 of the population**

F. **Frequency of the Recessive Gene for PXE in the Black Population of the Cape Province.**

Total affected	= 3
Estimated Black population of the Cape	= 1 931 x 10^6
Prevalence	= 3/1 931 x 10^6
Gene frequency	= 3/1 931 x 10^6 = 0,001225
Heterozygous state	= 2 x 0,001225 = 0,002450
Number of carriers	= 4730
Carrier frequency	= 1/408 of the population

Discussion

Due to the wide ethnic differences and disparate ancestral origins of the population groups in South Africa, it is important for future medical planning to assess the impact of an inherited disorder such as PXE for each population. In this context, the genealogical origins of the Afrikaners will be discussed in Chapter 10.

The ethnic distribution of the 3 major groups (Caucasian, Black and Mixed Ancestry) varies in each of the 4 major provinces. For instance, the Black population is concentrated mainly in Natal, Transvaal and Orange Free State whereas the largest mixed ancestry population is found in the Cape Province (see Table 6.1). As the investigation of patients with PXE originated in Cape Town, it would be reasonable to expect that the ascertainment of affected individuals would be most complete in the Cape Province. Also, as the Caucasian group generally have a higher standard of living and tend to seek medical attention earlier than the other populations, estimates of prevalence and gene frequency are likely to be more reliable in this group.

The use of the Hardy-Weinberg principle to calculate gene frequency in the recessive form of PXE in the Afrikaner population is contentious, given the ancestral origins of this population. Many factors mitigate against the use of this means of analysis, namely:

1. The Afrikaner population was originally small and intermarried frequently. It was also isolated for cultural, religious and geographical reasons.

2. Small isolates of the Afrikaner population were decimated by epidemics of measles and smallpox which swept through the land during the 18th century.

3. It has been proven that the founder effect has occurred in several heritable disorders in the Afrikaner community (Brink and Torrington, 1989; Torrington and Viljoen, 1990).

Despite these limitations, the H-W principle remains the most convenient and widely use tool in the assessment of the gene frequency of a disorder within a given population.

The gene frequency distribution of the recessive form of PXE within the major South African ethnic groups suggests that the heterozygous state occurs most commonly in the Caucasian population (carrier frequency = 1/195) and less frequently in the Mixed Ancestry population (carrier frequency in the Cape = 1/289). The heterozygote frequency within the Afrikaner subgroup is more common (carrier frequency = 1/123) when calculated over the extent of the whole country. However, the frequency in the Cape Province where ascertainment of individuals affected with PXE is most complete, is even higher (carrier frequency =

1/76). This latter figure reflects the most likely carrier frequency within the Afrikaner population throughout South Africa, assuming an even distribution of the PXE gene in this group.

7.2 Estimated Number of Undiagnosed Patients with PXE in South Africa

The gene frequency for PXE in various ethnic groups in South Africa has been calculated in Chapter 7.1. As previously indicated, ascertainment of PXE in all population groups is probably incomplete. Analysis of data reflects minimum prevalence rates of homozygous affected persons (Chapter 6) and the minimum gene frequency for the recessive gene.

The morbidity in individuals with PXE is considerable (Section IV: Clinical Manifestations) and the mortality rate is elevated in affected persons (McKusick, 1972). For these reasons, it was considered important to estimate the number of undiagnosed individuals with PXE in South Africa. Awareness of PXE and its potential complications could then be increased in the South African medical community and the benefits of better management thereby made available to affected persons.

Analysis

The number of expected homozygotes within each ethnic group was calculated using the highest gene frequency determined in Chapter 7.1.

Estimated Undiagnosed PXE in the Afrikaner Populations in the Transvaal, Orange Free State and Natal:

Transvaal

Afrikaner population	$= 1{,}878 \times 10^3$
Estimated carrier frequency	$= 1/76$
Number of expected homozygotes	$= \frac{1{,}878 \times 10^3}{(76)^2 \times 4} = 81$

Orange Free State

Afrikaner population = $427{,}3 \times 10^3$

Estimated carrier frequency = 1/76

Number of expected homozygotes = $\frac{253{,}5 \times 10^3}{(76)^2 \times 4} = 11$

Natal

Afrikaner population = $427{,}3 \times 10^3$

Estimated carrier frequency = 1/76

Number of expected homozygotes = $\frac{427{,}3 \times 10^3}{(76)^2 \times 4} = 18$

Cape Province

Number of Afrikaners affected = 40

TOTAL ESTIMATED AFRIKANER PXE PATIENTS = 150

TOTAL AFRIKANER PATIENTS CURRENTLY DIAGNOSED = 58

TOTAL UNDIAGNOSED PATIENTS (ESTIMATED) = 92

The calculations are made in full (*vide supra*) in the case of the Afrikaner population to demonstrate the mode of analysis. For the remaining population groups the estimated number of affected persons is summarised in Table 7.1.

TABLE 7.1

NUMBER OF UNDIAGNOSED PATIENTS WITH PXE IN SOUTH AFRICA

ETHNIC GROUP	NUMBER OF CONFIRMED CASES	ESTIMATED NUMBER OF UNDIAGNOSED PXE CASES
AFRIKANER	58	92
ENGLISH-SPEAKING CAUCASIAN	15	16
MIXED ANCESTRY	9	10
BLACK	4	31
TOTAL	86	149

Comment

The calculation of the number of undiagnosed cases of PXE within the various ethnic groups of South Africa is, by necessity, an estimate. A major assumption is that the recessive gene for PXE within each population is spread uniformly throughout the community. This assumption is likely to be correct in both the Black and Caucasian (Afrikaner and English-speaking) groups, but may differ in the mixed ancestry population. The so-called "Cape Coloured" (Cape Mixed Ancestry) community is derived from the indigenous Khoisan peoples, Caucasian settler groups of the 17th century, Malay immigrants from Java and Sumatra, and Blacks from West Africa and Madagascar. By contrast, Mixed Ancestry populations elsewhere in South Africa (Transvaal, Free State and Natal) are principally an admixture of Caucasian and local Black ancestry. It is therefore unlikely that the gene frequency for PXE is uniform in this latter diverse population group.

The analyses give an estimate of 149 individuals undiagnosed in the South African population. This figure is probably considerably underestimated. Nevertheless, some idea of the health burden of PXE to the community can be calculated and medical strategies can be devised to cope with the affected persons. Some of these aspects are discussed in Section VI.

SECTION III

PSEUDOXANTHOMA ELASTICUM IN THE AFRIKANER POPULATION

Section III is exclusively devoted to the genealogical and clinical findings of PXE within the Afrikaner community of South Africa. A unique form of PXE was discovered within the Afrikaner population group during the current investigation. For this reason, historical and demographic aspects which have relevance to the high prevalence of the disorder within the Afrikaner group are discussed.

CHAPTER 8 : HISTORICAL AND DEMOGRAPHIC ASPECTS OF THE AFRIKANER COMMUNITY IN SOUTH AFRICA

CHAPTER 9 : GENEALOGICAL ASPECTS RELATING TO THE AFRIKANER POPULATION

CHAPTER 10: CLINICAL MANIFESTATIONS OF PXE IN THE AFRIKANER POPULATION

CHAPTER 11: AN AUTONOMOUS FORM OF PXE IN THE AFRIKANER POPULATION

SECTION III

CHAPTER 8

HISTORICAL AND DEMOGRAPHIC ASPECTS OF THE AFRIKANER COMMUNITY IN SOUTH AFRICA

CHAPTER 8

On Christmas Eve, 1651, Commander Jan van Riebeeck sailed from Texel in Holland with the purpose of establishing a small settlement at the Cape of Good Hope for the provision of supplies to passing ships of the Dutch East India Company. He arrived with a small party in Table Bay on 6 April 1652. From that time further settlers journeyed from Holland to the Cape at regular intervals; for instance, 344 people survived the 130 day voyage on the ship "Dordrecht" and arrived in Table Bay on 25 April 1658. A further 200 Huguenot settlers escaped religious persecution in France and joined the Cape settlement in 1688. By 1700 the total Caucasian community of the Cape numbered 1,265 individuals.

The Dutch and French Huguenot settlers in the Cape were soon in close contact with the indigenous peoples comprising the San (formerly called "Bushmen") and Khoikhoi (formerly "Hottentot"). The former pursued a hunter-gatherer existence, while the latter were pastoralists. Both communities were largely nomadic and did not establish fixed settlements.

Very little immigration to the Cape occurred in the succeeding 100 years, but due to a phenomenally high rate of natural increase, the Caucasian population numbered 13,028 by 1790 (Theal, 1922). Large families with 10 or more children were common in early generations (de Villiers, 1893). The average fertility rate exceeded 5 per family (Schmidt, 1955) and the ratio of deaths to baptisms was approximately 100:261 during this period (Theal, 1922). These factors combined to ensure a doubling of the settler population every 30 years.

Having taken firm root in the Cape Peninsula region, the new immigrants spread mainly eastwards and to the north. Almost 100 years after the original settlement and after journeying more than 800 kilometers, they first encountered the Black indigenous peoples (Xhosa tribal groups) at the Kei river, north of present-day East London (Figure 6.1).

Further waves of immigration to the Cape continued in the 19th century mainly from Dutch, German and French sources. Negro slaves from Madagascar and West Africa were also brought to the Cape and a sizeable community of "Malay" slaves from Java and Sumatra was established at the foot of the African continent. During this time several "treks" or migrations into the hinterland were made by the settlers or burghers, and geographically isolated, small communities were established in many areas. It was from these ethnic sources that the white Afrikaans-speaking people had their genealogical roots. According to genealogical estimates, the ethnic composition of the Afrikaners in 1867 was as follows:-

Dutch	34.8%
German	33.7%
French	13.2%
Mixed ancestry	6.9%
British	5.2%
Other nationalities	2.7%
Unknown	3.5%

(Heese 1972)

As stated previously, the settler population increased rapidly in the favourable climatic and nutritional circumstances. However, outbreaks of smallpox and possibly, plague, reduced the Caucasian population from 1,939 in 1712 to 1,697 in 1716. Considering the rapid population growth

at that time, these diseases resulted in a reduction in excess of 15 per cent in the Caucasian group. In 1755 a further 963 Caucasians died and lesser epidemics in the 18th century accounted for several hundred deaths in this community (Thom, 1952; Moodie, 1960). Malaria was also a considerable health hazard to isolated establishments in the northern regions.

A further minor influence on the gene pool of the Afrikaans-speaking Caucasian community of South Africa occurred as a result of gene flow following the British occupation which commenced in 1795. Up until that time the church registers contain the names of 1,526 male immigrants who had produced children in South Africa. It is from these latter individuals that nearly all of the present-day Afrikaners are descended. For reasons of culture, religion and geographic isolation (see Chapter 9), the gene pool of the Afrikaner has remained relatively stable since that time.

At present 40 per cent of all Afrikaans-speaking Caucasians in South Africa share 40 surnames, mainly of Dutch, French and German origin. The current estimate of the Afrikaner population is 3,485,000 individuals. This is a 2,500-fold increase in a period of 300 years following the original settlement of the Cape.

SECTION III

CHAPTER 9

GENEALOGICAL ASPECTS RELATING TO THE AFRIKANER POPULATION

9.1 AN APPROACH TO GENEALOGICAL STUDIES IN SOUTH AFRICA

9.2 A GENEALOGICAL INVESTIGATION OF 23 AFRIKANER KINDREDS WITH PXE

9.3 EVIDENCE FOR FOUNDER EFFECT

CHAPTER 9

GENEALOGY

9.1 An Approach to Genealogical Studies in South Africa

The Afrikaans-speaking Caucasian population originated mainly from Dutch (about 35%), German (about 34%) and French (13%) stock (Chapter 8). Several factors, including religious, cultural, and geographic circumstances have ensured this community has remained isolated. Accurate records of births and deaths are available in this population from the time of the original Dutch settlement of the Cape in 1652. These are ideal circumstances for intensive genealogical investigations of a disorder such as PXE.

Reference Books

The prime genealogical reference book was written in 1893 by **Christoffel Coetzee de Villiers** entitled ***"Geslacht-Register der Oude Kaapsche Familien"***. It is a record of old Afrikaner families extending back in time from the early 19th century to the original settlers more than 150 years previously. A revised and updated version of this book was published in 1966 (De Villiers CC, Parma C).

Several other books tracing the origins of individual family surnames, such as Roux and Viljoen, have been compiled by interested family members within the Afrikaner community. These provide additional sources of information for genealogical reserch.

The Family Bible

It is common practice for the pedigree of an Afrikaner kindred to be recorded in the family Bible. This heirloom is conventionally passed from a father to his eldest son through the generations. The record

was updated at regular intervals and, together with church registers of baptisms and deaths, provides considerable information for genealogical research.

Naming of Afrikaner Children

Until the mid-20th century it was traditional in Afrikaner families to name children in a conventional manner. The first son was named after his paternal grandfather; the second born male was named after the maternal grandfather and the third son was called after his father. Similarly, in the female line, the first born daughter was named after her maternal grandmother, and so on. These traditions allow rapid identification of family lines in pedigrees under study.

Archival Sources

Several sources for archival research are available to the genealogist. The most important are the files of the Master of the Supreme Court, the State Archives and the Dutch Reformed Church Archives. A lesser source for research in Afrikaner families, but of inestimable value for other family data, is the archival and computer records of the Genealogical Library of the Church of the Latter Day Saints in Mowbray, Cape Town.

9.2 A Genealogical Investigation of 23 Afrikaner Kindreds with PXE

At the completion of the investigation of patients with PXE in South Africa, a total of 33 Afrikaner kindreds were identified in which 58 individuals were positively diagnosed as having the disorder. Twenty-three families were selected for further genealogical evaluation as data relating to their pedigrees was readily accessible for archival research.

The findings formed the basis of a paper by **Torrington and Viljoen (1990)** in which founder effect in Afrikaner families with PXE was documented. **(Appendix: Publication 6).**

Methods

Once the proband had been identified by the author within each of the 23 pedigrees under scrutiny, Dr Marie Torrington or a member of her staff from the Genealogy Unit of the Medical Research Council of South Africa, visited and interviewed these individuals. Working on the hypothesis that each proband was homozygous for the recessive PXE gene, the lineage was sought from both the paternal and maternal branches of each kindred. Data relating to 3-5 previous generations was obtained in this fashion. Thereafter, archival research traced the family ancestors back and linked them to previously researched genealogies or to the **De Villiers and Parma** record of genealogies of old South African families **(1966).**

Findings

Through the archival sources previously described, it was possible in 14 instances to gather data relating to 13 generations of both ancestral lines, i.e. a total of 28 parental ancestral lines. In a further 6

pedigrees, either the maternal or paternal lines could not be completed. The reasons for these difficulties were varied :-

a) The family records in 4 paternal lines were located in the Orange Free State where archive sources have not yet been researched.

b) Data relating to one maternal line was located in Namibia (formerly the South African Protectorate of South West Africa) and were inaccessible to research.

c) In one instance records of a paternal line were overseas and could not be accessed.

Essential elements were absent in 3 pedigrees under investigation and these kindreds were not analysed further. In all, a total of 34 (out of a possible 40) ancestral lines were fully appraised in 20 kindreds.

The investigation was able to identify the original settler ancestors in all 20 kindreds. On compilation of a table of these individuals (Table 9.1), 4 surnames predominated namely, van der Merwe (M), Burger (B), Visser (V) and Smit (S). The pedigrees listed in Table 9.1 are numbered I - XX and coded to protect the identity of individuals currently afflicted with PXE.

TABLE 9.1

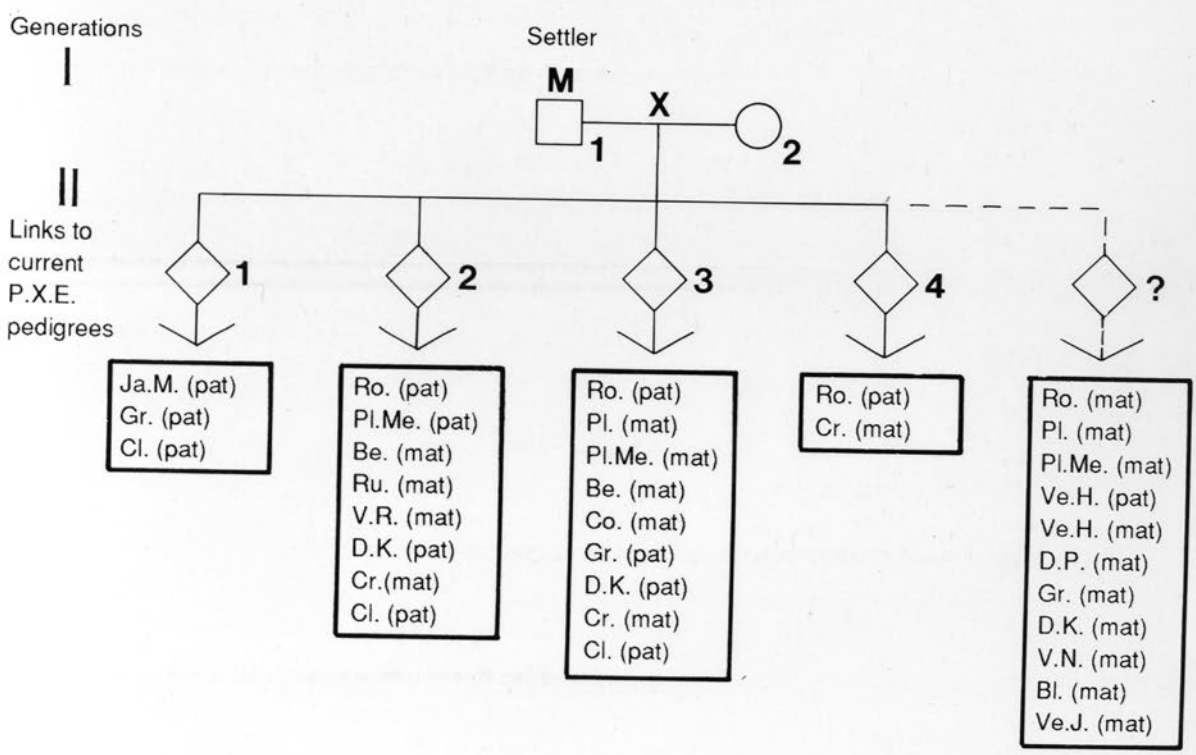
ORIGINAL SETTLER LINKS IN 20 PROBANDS WITH PXE

PEDIGREE NUMBER	CURRENT FAMILY (CODED)	PATERNAL ANCESTORS		MATERNAL ANCESTORS	
		M/B	V/S	M/B	V/S
I.	Ped. Ro	X	X	X	-
II.	Ped. Pi.	X	X	X	X
III.	Ped. Pi/Me.	X	X	X	X
IV.	Ped. Be.	X	-	X	-
V.	Ped. Ru.	X	X	X	X
VI.	Ped. V.R.	X	-	X	X
VII.	Ped. Ja.M.	X	X	-	X
VIII.	Ped. Co.	-	X	X	X
IX.	Ped. Te.	-	X	X	-
X.	Ped. Ve H	X	X	X	-
XI.	Ped. D.P.	-	X	X	X
XII.	Ped. Gr.	X	X	X	X
XIII.	Ped. D.K.	X	X	-	X
XIV.	Ped. V.N.	-	X	X	X
XV.	Ped. Bi.	Overseas		X	X
XVI.	Ped. Cr.	O.F.S.		X	X
XVII.	Ped. Cl.	X	X	S.W.A.	
XVIII.	Ped. Bo.	O.F.S.		-	X
XIX.	Ped. Op.	O.F.S.		-	X
XX.	Ped. Ve.J.	O.F.S.		X	X

Surnames : M : Van der Merwe
B : Burger
Ped : pedigree
V : Visser
S : Smit

The links between the original settlers and present-day persons with PXE are shown in Figures 9.1 - 9.4. In addition, within each pedigree a column of proband names has been listed as II, ? In the latter instance, definite genealogical evidence of linkage to each of the four surnames M,B,V and S could be found but researchers were unable to determine at which generation level this had occurred.

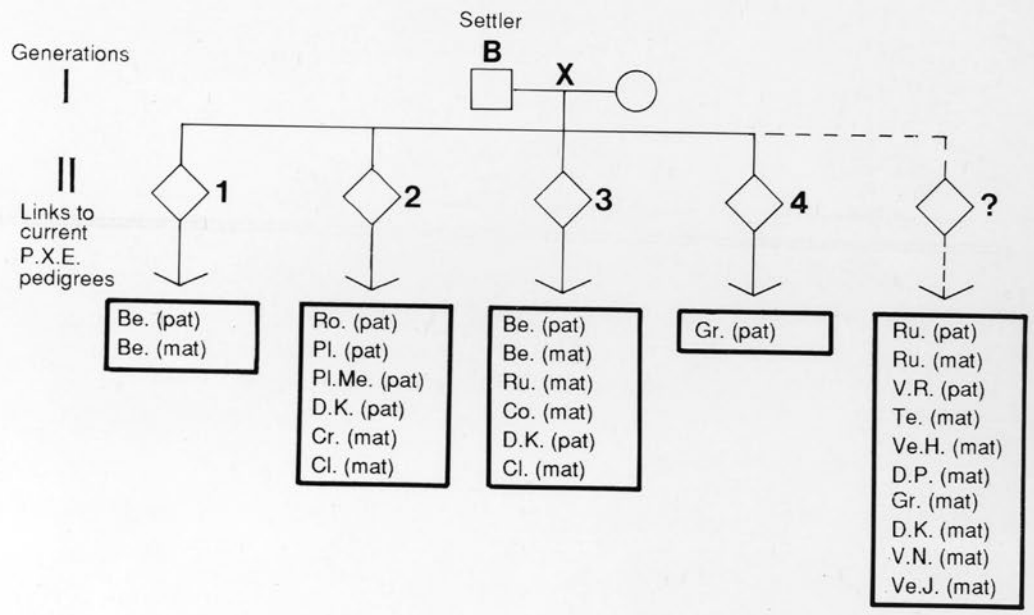
Figure 9.1 PEDIGREE DEMONSTRATING LINKS BETWEEN SETTLER M (SURNAME VAN DER MERWE) AND CURRENT PXE FAMILIES



In Table 9.1 the paternal and maternal ancestors are grouped in the combinations M/B (van der Merwe/Burger) and V/S (Visser/Smit). As has been demonstrated in Fig 9.5 considerable intermarriage occurred between the offspring of the ancestor settlers van der Merwe and Burger. This continued into successive generations and occurred to an

extent where it became impossible to trace the lineage. Therefore, the heterozygous carrier for PXE may have emanated from either settlers van der Merwe or Burger. Similarly, the offspring of settlers Visser and Smit were extensively intermarried making the identification of the source of the PXE gene between these two forefathers impossible.

Figure 9.2 PEDIGREE DEMONSTRATING LINKS BETWEEN SETTLER B (SURNAME BURGER) AND CURRENT PXE FAMILIES



In all, 15 male- and 19 female-ancestral lines were studied (total 34). The combination of the surnames M/B (van der Merwe/Burger) appeared a total of 24 times, whereas the V/S (Visser/Smit)-linked surnames appeared 28 times. The frequency at which each of the 4 ancestral names appeared in PXE kindreds both individually and linked to the other common surname are shown in Table 9.2.

Figure 9.3 PEDIGREE DEMONSTRATING LINKS BETWEEN SETTLER V (SURNAME VISSER) AND CURRENT PXE FAMILIES

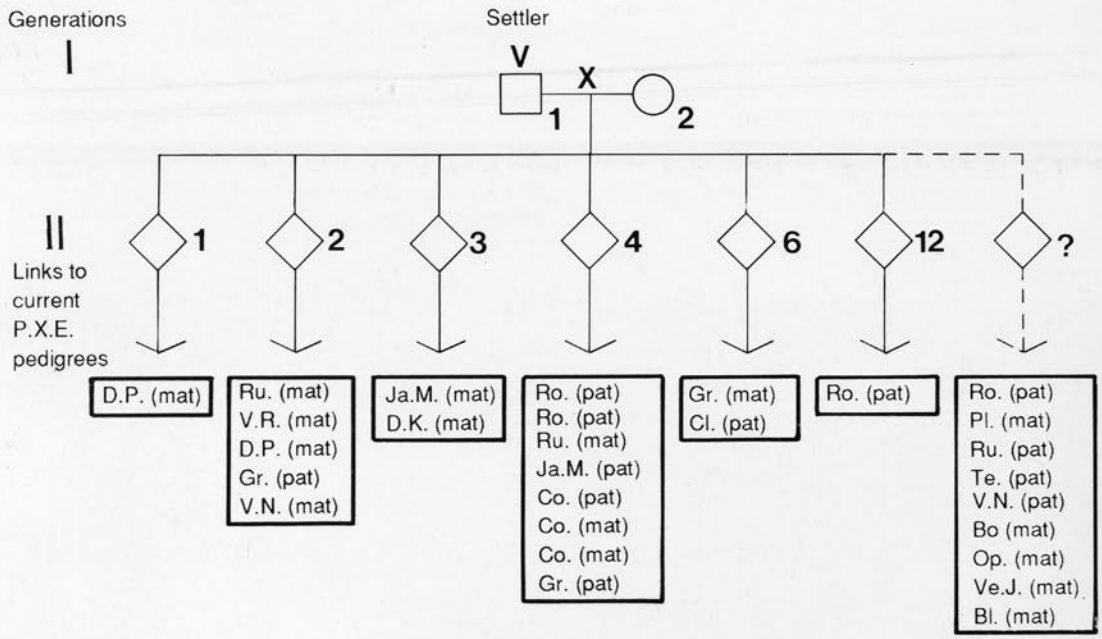


Figure 9.4 PEDIGREE DEMONSTRATING LINKS BETWEEN SETTLER S (SURNAME SMIT) AND CURRENT PXE FAMILES

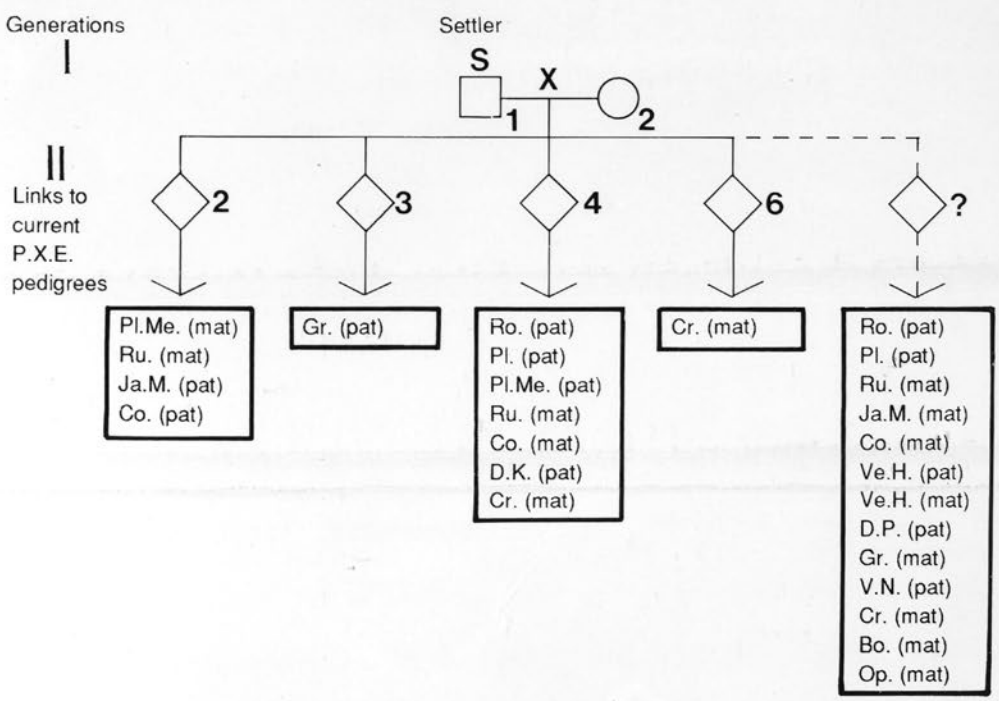
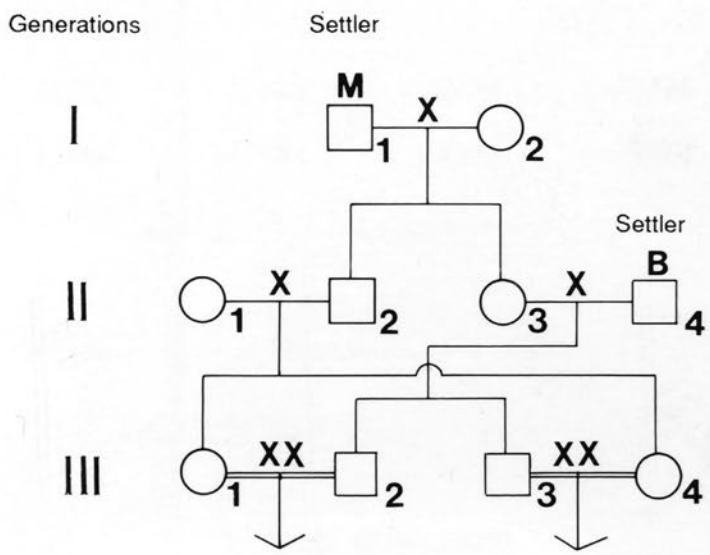


Figure 9.5 PEDIGREE DEMONSTRATING EXTENSIVE CONSANGUINEOUS MARRIAGES BETWEEN OFFSPRING OF SETTLER M (SURNAME VAN DER MERWE) AND SETTLER B (SURNAME BURGER)



Comment

The current genealogical study suggests that any or all four ancestral settlers may have been heterozygous for the PXE recessive gene. However, the extensive intermarriage between the offspring of settlers Van der Merwe and Burger, and those of settlers Visser and Smit supports the hypothesis that two settlers (either M or B, or V or S) were most probably heterozygous for the PXE gene.

TABLE 9.2

LINKAGE OF PRESENT-DAY PXE PATIENTS WITH SETTLER ANCESTORS

INDIVIDUAL SURNAMES

M	B	V	S
33/34	25/34	28/34	26/34
(98%)	(74%)	(82%)	(76%)

LINKED SURNAMES

	Maternal line (N = 15)	Paternal line (N = 19)
M/B	11 (73%)	15 (79%)
V/S	13 (87%)	15 (79%)

Key

M : van der Merwe
B : Burger
V : Visser
S : Smit

9.3 Evidence for Founder Effect

Founder effect occurs when one of the original members of a small isolated population carries an otherwise rare gene which then becomes disseminated throughout the population.

The above description of the founder effect can readily be applied to several heritable disorders found more commonly in the Afrikaner population than in other groups. (see Table 9.3).

TABLE 9.3

DISORDERS OF HIGH PREVALENCE IN THE AFRIKAANS-SPEAKING POPULATION OF SOUTH AFRICA

Porphyria variegata

Lipoid proteinosis

Sclerosteosis

Familial hypercholesterolaemia

Progressive familial heart block (Types I and II)

Cystic fibrosis

Colonic polyposis

Huntington disease

Fanconi anaemia

Spondylo-epimetaphyseal dysplasia with joint laxity

Oudtshoorn skin disease

(Source : Botha and Beighton, 1983)

Of these disorders, founder effect has already been established in porphyria (Dean, 1972), Huntington disease (Hayden et al., 1980)

progressive familial heart block - two types (Brink and Torrington 1977), cystic fibrosis (Super, 1978), colonic polyposis (Louw et al., 1972) and, more recently, PXE (Torrington and Viljoen, 1990) (Appendix: Publication 6).

The essential attributes necessary for invoking founder effect in Afrikaner kindreds with PXE are present, namely:-

1) A small founding settler population (Chapter 8).

2) Evidence of extensive intermarriage (Figure 9.5).

3) A large natural population increase (Chapter 8).

4) A closed or isolate community for reasons of religious beliefs, geographic isolation, cultural ideologies and language differences (Chapter 8).

5) A high gene frequency (PXE is more common in the Afrikaner than in any previously reported ethnic group : Chapter 7.1).

PXE in Belgium

Further evidence supporting the contention that founder effect is present in the Afrikaner with PXE emanates from a conjoined study of PXE in Belgium and South Africa (De Paepe, Viljoen et al., 1990). This research has confirmed the presence of a form of PXE in the Belgian population which is clinically indistinguishable from that described in the Afrikaner. These findings support the hypothesis that the abnormal gene originated in the Low Countries of Europe. Indeed, the founder ancestors identified in South Africa (van der Merwe, Burger, Visser and Smit) were immigrants from Oud-Beyerland, Lubeck, Maastricht and Ommen, respectively, all of which are in the "Low Countries". Further

studies on the gene frequency of PXE in this European community are underway.

Implications

The strong evidence for a founder effect of the PXE gene in Afrikaner kindreds in South Africa is an important observation as it has implications for health planning and PXE-awareness programmes within the South African medical fraternity. As has been shown recently by the example of cystic fibrosis (CF), the cloning of the PXE gene, knowledge of the exact mutation and use of the polymerase chain reaction, may make population screening feasible. Possible screening for PXE is discussed in Section VI.

SECTION III

CHAPTER 10

CLINICAL MANIFESTATIONS OF PSEUDOXANTHOMA ELASTICUM IN THE AFRIKANER POPULATION

10.1 INTRODUCTION

10.2 GENERAL INFORMATION

10.3 OPHTHALMOLOGICAL COMPLICATIONS

10.4 DERMATOLOGICAL MANIFESTATIONS

10.5 CARDIOVASCULAR MANIFESTATIONS OF PXE

10.6 INVOLVEMENT OF OTHER ORGAN SYSTEMS

CHAPTER 10

CLINICAL MANIFESTATIONS OF PXE IN THE AFRIKANER POPULATION

10.1 Introduction

During the early part of this investigation I had the opportunity of appraising a large Afrikaner kindred with PXE, most of whom lived in Worcester, Cape Province (see pedigree, Fig. 5.1). The striking clinical finding in affected individuals in this family was the presence of severe ophthalmological complications attributable to PXE. The cardiovascular and dermatological findings usually associated with PXE and previously reported in the literature (Pope 1974a, 1974b) were present but to a very mild degree. In one person (Patient III,3) the cutaneous manifestations were, even to experienced dermatological colleagues, indistinguishable clinically from the normal ageing process. In this instance the diagnosis was confirmed by histological studies on a skin biopsy.

Further clinical evaluation of 39 Afrikaner individuals with PXE convinced me that a previously undescribed, autonomous entity was present in this section of the South African population and these findings were subsequently published (Viljoen et al., 1987). At a later stage comparisons between affected Afrikaner individuals and Belgian patients with similar clinical manifestations were reported (De Paepe, Viljoen et al., 1990). The latter study confirmed impressions that a unique form of PXE existed in both the Afrikaners and their genealogical antecedents in Europe.

In this chapter, data relating to the clinical manifestations in 58 affected individuals of Afrikaner stock are analysed. The unique characteristics

of PXE in the Afrikaner are stressed and compared to the clinical features in other populations.

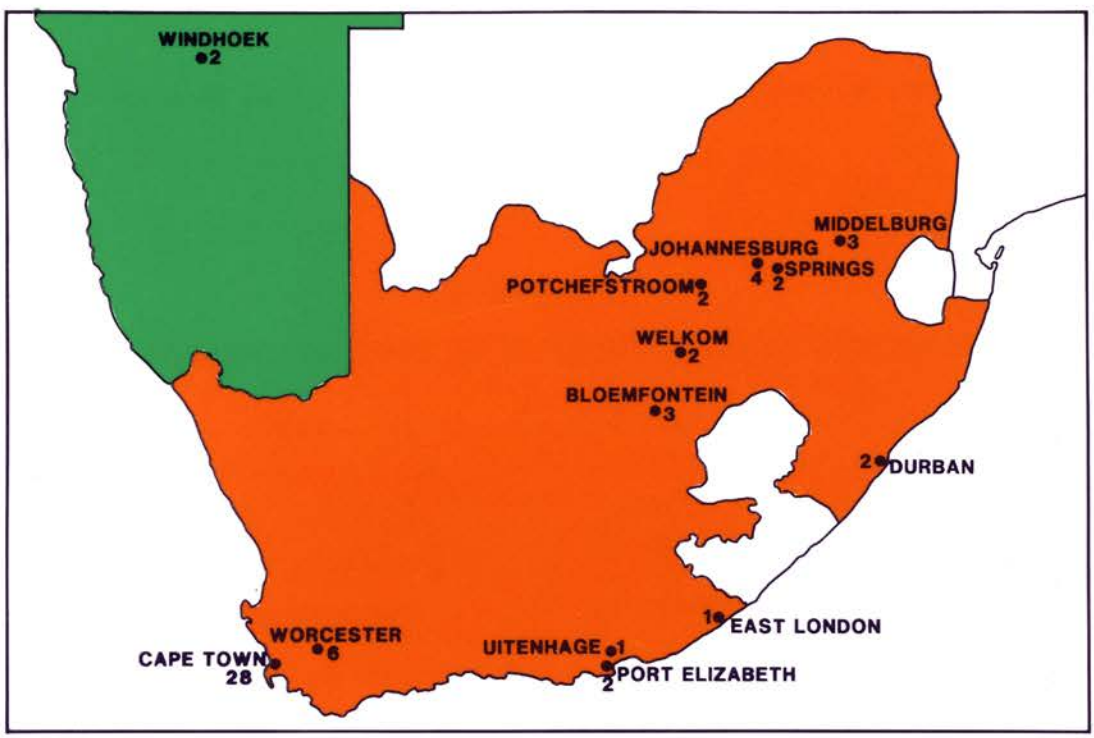


Figure 10.1. THE DISTRIBUTION OF 58 AFRIKANER PXE PATIENTS IN SOUTH AFRICA

10.2 General information

The patients in this study were examined according to a protocol (**Appendix : Protocol 1**) previously approved by the Ethics and Review Committee of the University of Cape Town Medical School. The methodology of clinical evaluation and special investigations carried out on the affected persons are detailed in Chapter 3.

The female-to-male ratio, age of presentation and age at the time of appraisal in this investigation are shown in Table 10.1.

TABLE 10.1

BACKGROUND DATA RELATING TO 58 AFRIKANER PATIENTS WITH PXE

Female : Male ratio	=	33:25 (1.32:1)
Average age at presentation	=	21.4 yrs (range 4-71 yrs)
Average age at time of study (1990)	=	41.7 yrs (range 14-82 yrs)

The female to male ratio of 1.32:1 is in keeping with general experience in other large series (**Neldner, 1988**), but not as disparate as that reported by **McKusick** in 1972 (2:1). The preponderance of females has been attributed to the fact that they seek medical attention for cosmetic reasons earlier than their male counterparts. Supportive evidence for this supposition in Afrikaner patients is presented in part 10.3 of this chapter.

The average age of affected persons at the time the data were analysed in 1990 was 41.7 years, with a range of 14 - 82 years. However, the

average age of initial presentation to a medical practitioner was 21.4 years (range 4 - 71 years).

The geographical distribution of affected Afrikaans-speaking individuals is illustrated in the map of South Africa in Fig. 10.1. As expected, the majority of the patients (N = 40) were resident in the Cape Province, while 11 lived in the Transvaal, 2 in Natal and 5 were domiciled in the Orange Free State. The reasons for the biased geographical distribution have been fully discussed in Chapter 7.

10.3 Ophthalmological Complications

The foremost feature of PXE which distinguishes the Afrikaner form of PXE is the severity of the ophthalmological complications. Blindness by the age of 50 years (see page 103) is present in the majority of patients.

In this investigation, ophthalmological data was available from 54 of the 58 Afrikaans-speaking PXE patients; there were 32 females and 22 male individuals and their ages ranged from 14 - 82 years (mean = 40.5 years).

In order to analyse the ophthalmological complications found in these patients, and for the sake of clarity, the current understanding of the evolution of the retinal lesions in PXE is described.

Pathogenesis of retinal lesions in PXE

The fundamental defect in PXE results in the production of abnormal elastin fibres.

Bruch's membrane of the retina separates the pigmentary epithelium and the choroid. It is derived from both the retina and the choroid plexus and has an inner layer without elastin fibres and an outer layer consisting of densely matted elastin and collagen fibres **(Neldner, 1988).** In its normal state, the membrane is impervious to fluid and provides structured support for the ganglion cells, blood vessels and rods and cones of the retina. In PXE, breaks which appear within this structure result in the fundal changes and complications commonly seen in the affected persons.

The earliest ophthalmological manifestation attributed to PXE is a peculiar stippled appearance of the fundus which begins in the polar regions and gradually extends to the macula (Krill et al., 1973) These lesions are referred to as "peau d'orange" changes or "retinal mottling" (see Figure 10.2) and are thought to represent loss of regularity of the elastin bundles in Bruch's membrane.



Figure 10.2 RETINAL MOTTLING IN THE FUNDUS OF A PATIENT WITH PXE

Further elastin degeneration and fragmentation of the fibres leads to thickening of Bruch's membrane and short interruptions in its integrity. These events give rise to the formation of "salmon spots" which are circular, light-coloured lesions scattered initially in the fundal peripheries but later becoming more central in location. Salmon spots are considered to be the precursors of angioid streaks. (Figure 10.3).

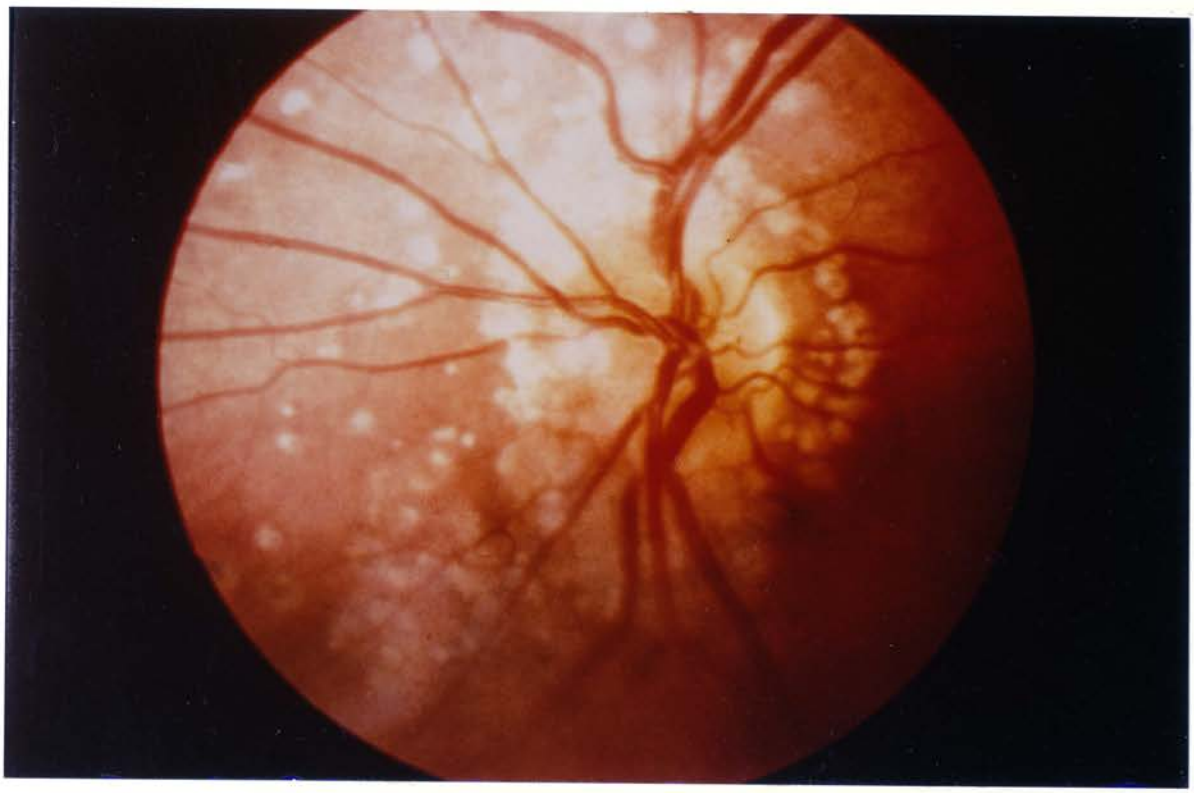


Figure 10.3 "SALMON SPOTS" IN THE FUNDUS OF A PXE PATIENT

It is postulated that further disruption of the elastin fibres in Bruch's membrane results in the formation of angioid streaks (**Hagedoorn, 1939; Verhoeff, 1948; McKusick, 1972; Neldner, 1988**). The term was coined initially by **Knapp (1892)** and reflected the mistaken view that these abnormalities were vascular in origin. Angioid streaks vary in colour from dusky-red or maroon to nearly black. They radiate out from the optic disc like spokes of a wheel or may encircle the disc; they are then termed peripapillary streaks. (Figure 10.4). Histological studies have confirmed that breaks in Bruch's membrane, which is thickened and calcified are, in fact, angioid streaks **(Klein, 1947)**. Angioid streaks may cross the macula and fovea and number more than 50 in a single eye **(Neldner, 1988)**. They, in themselves, cause no visual disturbance but fundamentally weaken the retinal structures.

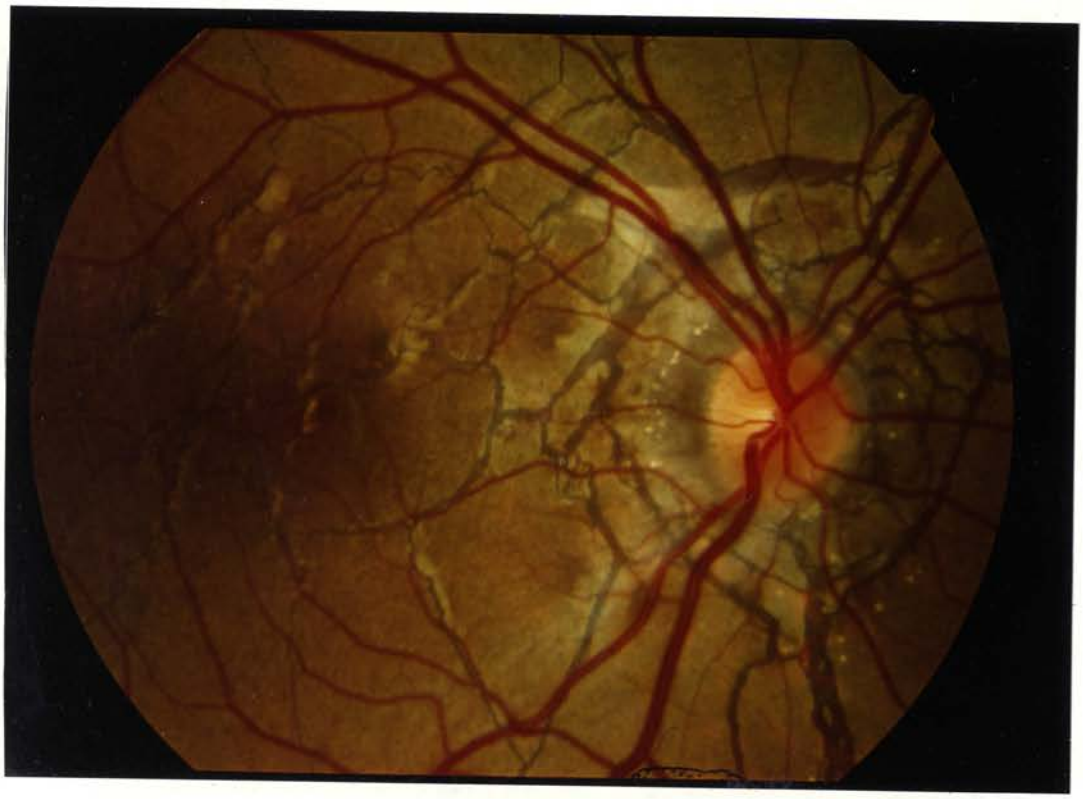


Figure 10.4 ANGIOID STREAKS IN PXE

Secondary changes within angioid streaks are commonplace in patients with PXE. Fibrovascular tissue from the underlying choriocapillaris layer may grow into the breaks (angioid streaks) and beyond the edges causing "cuffing" which may become apparent at fundoscopy (McKusick, 1972; Dreyer and Green, 1978). These channels from the choriocapillaris allow the formation of neovascular membranes which may leak and cause retinal detachment. There is also a tendency for frank retinal haemorrhage and subsequent disciform scarring. (See Figure 10.5). The latter sclerotic changes are probably the combined consequences of fibrous "cuffing" and resolution of retinal haemorrhages, and culminates in derangement of the light-sensitive rods and cones with eventual loss of central vision if the macula and fovea are involved.

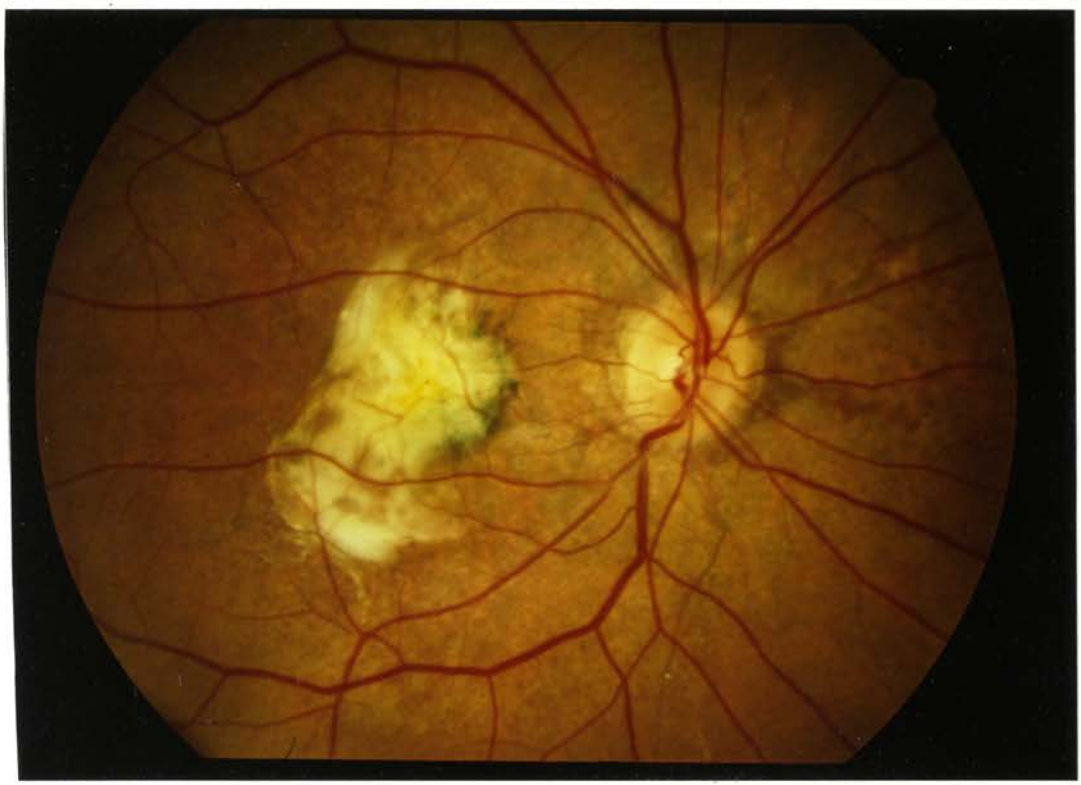


Figure 10.5 DISCIFORM SCARRING IN THE MACULAR REGION OF A PATIENT WITH PXE

Ophthalmic features in 54 patients

The ophthalmological sequelae of PXE in 54 Afrikaner patients is summarised in Table 10.2.

TABLE 10.2

OPHTHALMOLOGIC FEATURES OF 54 AFRIKANER PATIENTS WITH PXE

OPHTHALMOLOGIC MANIFESTATIONS		NUMBER OF PATIENTS (%)
Visual acuity -	7/10 - 10/10	18 (33.3)
	2/10 - 6/10	14 (25.9)
	1/10 or less	22 (40.7)
Angioid streaks		54 (100)
Peau d'orange fundal changes		41 (75.9)
"Salmon" spots		7 (13.0)
Macular degeneration		36 (66.7)

Visual loss as a consequence of trauma

Affected persons of Afrikaner descent under the age of 30 years seldom had loss of visual acuity although they all had angioid streaks, regardless of age. However, vision was lost in one or both eyes in 3 young individuals as a consequence of trauma. In view of the important implications of this problem, case histories are provided below:-

CASE 1

At the age of 15 years, an adolescent girl of Afrikaner descent was struck in the right eye with a squash ball. Visual acuity was diminished in the affected eye after the injury. The diagnosis of PXE had previously been confirmed following dermatological appraisal and skin biopsy at the age of 12 years. Ophthalmological investigation, including fluorescein angiography, demonstrated a large retinal

haemorrhage partially involving the macula of the right eye. Angioid streaks were evident in both eyes at this time. No therapy was undertaken and serial clinical appraisal showed gradual resolution with mild scarring. Eventually visual acuity was partially regained for the affected eye (6/10 in right eye, 9/10 in left).

This patient continued to play squash using protective lenses and has had no further visual deterioration in the succeeding 11 years.

CASE 2

A man aged 25 years was perfectly well with normal vision until he was struck with a tennis ball over the left temporal region. He had been aware of his skin lesions from the age of 14 years and a diagnosis of PXE had been confirmed in his younger sister, although he had not as yet sought medical attention for himself.

The temporal blow resulted in sudden blurring of vision in the left eye. Appraisal by an ophthalmologist several days following the trauma revealed an extensive retinal haemorrhage involving the macular region of this eye. Resolution was accompanied by retinal sclerosis and there was no improvement in visual acuity.

He is presently 48 years of age and has visual acuity of 9/10 and 1/10 in the right and left eyes respectively. Clinical appraisal has revealed disciform maculopathy in the left eye, and extensive angioid streaks are visible in both eyes.

CASE 3

A male aged 19 years sustained a kick to the right side of his head during a rugby match while completing national service in the army; thereafter he complained of "double vision". Clinical examination demonstrated mild dermatological features suggestive of PXE and angioid streaks were visible on fundoscopy. In addition, he had developed an extensive retinal haemorrhage involving the right macula. Gradual resolution of this lesion occurred but at the age of 27 years he had a visual acuity of 6/10 in the right eye. Following his injury, he was medically boarded from the armed services and financially compensated for his visual loss.

Comment

The onset of visual symptoms after head injury in PXE has been well described in the literature. (Grönblad, 1954; Britten, 1966; Levin and Bell, 1977). In fact, Doyne in 1889 ascribed the retinal changes he visualised solely to trauma and not to the underlying disorder of PXE. Fine (1977) described 28 patients with PXE and macular haemorrhages, 7

of whom sustained trauma to the orbit 24 hours prior to the onset of visual loss. It is unusual, however, for young persons with PXE to develop retinal haemorrhage following injury and only 6 individuals have been previously reported (Levin and Bell, 1977; Tanenbaum and de Margerie, 1966; Neldner, 1988). The finding of 3 young Afrikaner patients with retinal haemorrhages following trauma is remarkable especially as no other instances were recorded in persons with other forms of PXE in this investigation (Chapter 14). The finding suggests that the ophthalmological sequelae in the "Afrikaner" type of PXE are more severe than in the other forms and that activities involving repetitive blows to the head such as contact sports, should be avoided in affected persons.

Only one of three young patients with retinal haemorrhage had complete restoration of visual acuity and the other two suffered profound loss of acuity in the affected eye. Previous literature reports suggest that normal visual acuity was usually restored in such circumstances and the outcome in the South African patients further emphasises the severity of the disorder in the Afrikaner population.

Retinal Haemorrhage

The occurrence of retinal haemorrhages was a common, age-related event in Afrikaner patients. (see Table 10.3). Haemorrhages were associated with trauma in 12 persons of differing ages. In 7 instances, the lesion was initially unilateral but 5 persons later developed bilateral haemorrhages. The nature of traumatic events included road traffic accidents (3), sporting injuries (4), a fall (1), a blow to the head (2) and chronic cough (2). In the latter instance, both patients had parapertussis-like infections which resulted in prolonged periods of

coughing over several weeks. It is well recognised that raised vascular pressure occurs in association with the Valsalva manoeuvre and this factor was probably responsible for the retinal haemorrhages.

Blindness in terms of the legal definition (visual acuity 1/10 or less), was present in more than 73 per cent of individuals after 50 years of age. When compared with patients with other forms of PXE, the rate of blindness after the 5th decade of life is appreciably higher in the Afrikaner (73% versus 50%). Few comparisons can be made with previous literature reports, but **Neldner (1988)** reported that 5 of his 10 patients in the over 50 year old age group were legally blind in his series.

TABLE 10.3

RETINAL HAEMORRHAGES ACCORDING TO AGE IN 54 AFRIKANER INDIVIDUALS WITH PXE

AGE GROUP (YEARS)	NO. OF PATIENTS	RETINAL HAEMORRHAGES (%)	LEGAL BLINDNESS
0 - 9	0	0 (0)	0 (0)
10 - 19	4	2 (50)	0 (0)
20 - 29	11	5 (45)	0 (0)
30 - 39	14	8 (57)	4 (29)
40 - 49	10	9 (90)	6 (60)
50 - 59	8	8 (100)	6 (75)
60 - 69	6	6 (100)	4 (66)
>70 yrs	1	1 (100)	1 (100)

Comment

The findings of this investigation confirm that the ophthalmological prognosis in patients with the Afrikaner form of PXE is poor and that the majority of affected persons will be legally blind after the fifth decade of life. Furthermore, moderate head or eye trauma, even in very young patients, is very likely to result in retinal haemorrhage and severe loss of visual acuity in the affected eye.

The fundal changes of Afrikaner individuals with PXE are characteristic of the disorder and similar to those described previously in the literature. However, the frequency and severity of complications is considerably greater than previously documented, and suggests a fundamental weakness in Bruch's membrane which is not present in other forms of the disorder. No pathological specimens were available for study from affected individuals in this investigation so that the cause of the possible increase in fragility of Bruch's membrane is not known. Further ophthalmological findings in the "Afrikaner" form and other subtypes of PXE are discussed in Chapter 14.

10.4 Dermatological Manifestations

The cutaneous manifestations of PXE were directly responsible for 46 of 58 patients of Afrikaner stock initially seeking medical guidance. A further 5 persons were discovered only when other family members already known to be affected were examined and found to have the characteristic skin lesions. Disturbances in vision were responsible for 7 individuals first seeking medical advice.

Age at presentation

The average age at which dermatological features were first noted was 11.6 years (range 2 - 37 years) (Figure 10.6). As stated previously, 12 (20.5%)individuals were completely unaware of any clinical involvement of their skin. The latter persons had an average age of 56.6 years (range 27 - 82 years); this fact supports the contention that the dermatological features in Afrikaner patients are generally mild.

Sex differences

The female preponderence over males in all large published series of patients with PXE has been previously mentioned. In Figures 10.7 and 10.8 the ages of initial presentation in females and males are compared. In each group 6 individuals were unaware of their skin disorder and are not shown in the histograms. The female PXE patients sought medical attention far earlier than their male counterparts. At the age of 15 years, 86 per cent of females had visited their doctor, compared with 72 per cent of males at the same age.

Figure 10.6

THE AGES AT WHICH DERMATOLOGICAL CHANGES WERE FIRST NOTED IN 46 AFRIKANER PXE PATIENTS

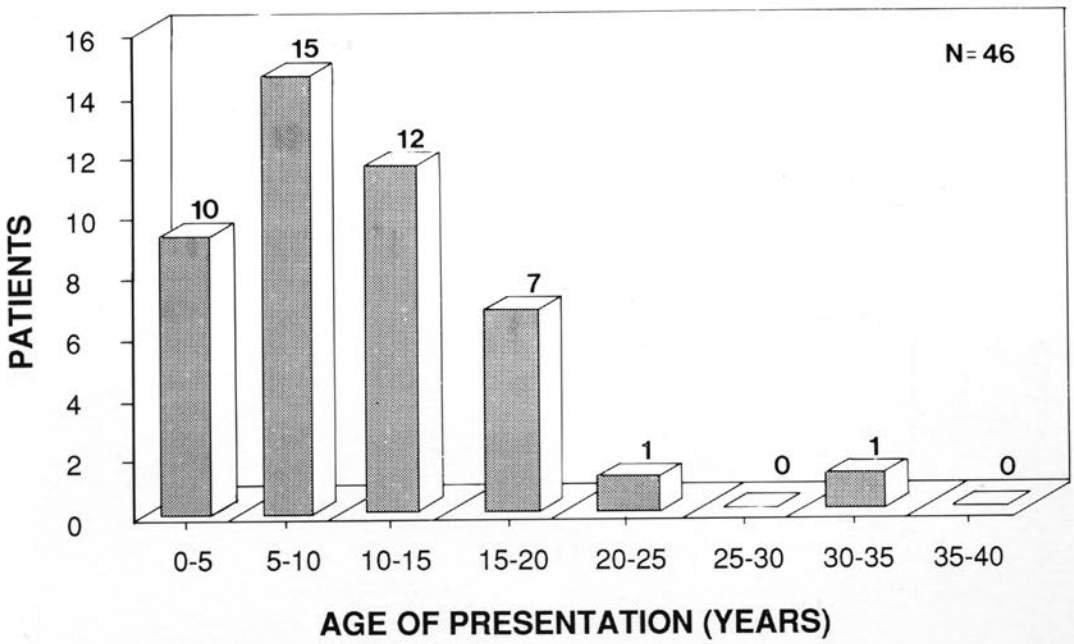


Figure 10.7

THE AGES AT WHICH DERMATOLOGICAL FEATURES WERE FIRST EVIDENT IN 28 FEMALE AFRIKANER PATIENTS WITH PXE

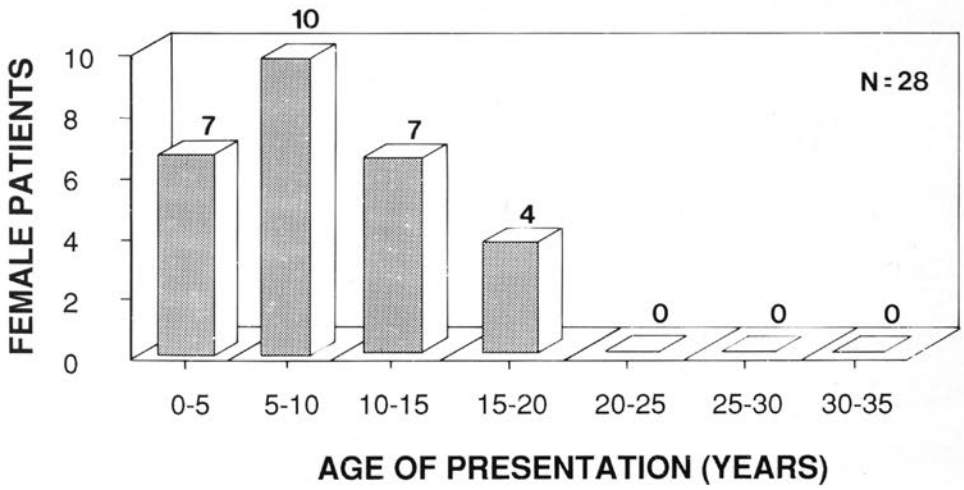
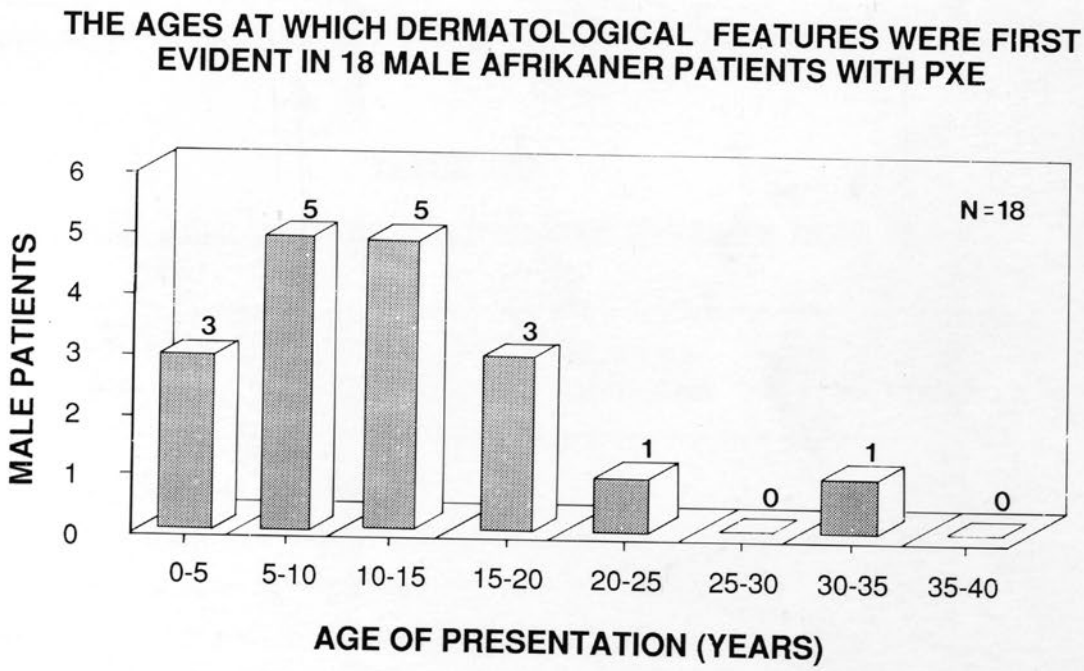


Figure 10.8



Distribution of skin lesions

In all except 2 persons with dermatological involvement, the lesions first appeared in the nape of the neck. The affected skin was initially noted to be darkened and coarse. In several instances, patients remembered bath times during their childhood years with considerable clarity and they recalled the painful experience of their mothers endeavouring to scrub the "filth" from their "dirty" necks!

The lesions tended to progress slowly, become more extensive and thickened, and then gradually took on a yellowish, cobblestone appearance. In most affected persons involvement of the skin was confined to the cervical region until the age of 20 years. Thereafter, the axillary region tended to be involved and the skin developed an element of redundancy. In women, the next area of predeliction was the inguinal region, whereas in males, the antecubital fossa was more likely

to be affected. The dermatological manifestations of 58 affected individuals of Afrikaner descent are summarised in Table 10.4.

TABLE 10.4

DERMATOLOGICAL DATA IN 58 AFRIKANER PATIENTS WITH PXE

CLINICAL MANIFESTATIONS	NUMBER AFFECTED	% AGE OF TOTAL
Classical, peau d'orange lesions	58	100
Yellow, reticular rash	11	19
Unusual cutaneous site involvement	8	14
Buccal mucous membrane involvement	20	34
Telangiectatic lesions of lip and mucous membranes	14	24

The classical, peau d'orange skin lesions were present in all 58 affected persons. These manifestations were usually plainly seen in the collar area of the neck, the axilla, antecubital fossae, groin areas and, in severely affected persons, over the trunk and popliteal regions (Figures 10.9 and 10.10). These raised, cobblestone-like lesions often gave way to a more reticular, yellow rash, particularly in the antecubital fossa (Figure 10.10), over the trunk and mucous membranes. The sites and frequency of skin involvement are depicted in Figure 10.11.

A site of unusual involvement was the peri-umbilical region in a minority of patients (14%). Telangiectasiae of the lip and buccal mucous membranes were found relatively commonly. In 7 of 33 affected females, their dermatological lesions were so severe that cosmetic surgery was performed on one or more occasions with generally satisfactory results (see Chapter 20).



Figure 10.9 THE PEAU D'ORANGE CHANGES AND LAXITY OF THE CERVICAL SKIN ARE EVIDENT IN A WOMAN AGED 28 YEARS



Figure 10.10 THE RETICULAR RASH OF PXE IN THE ANTECUBITAL REGION

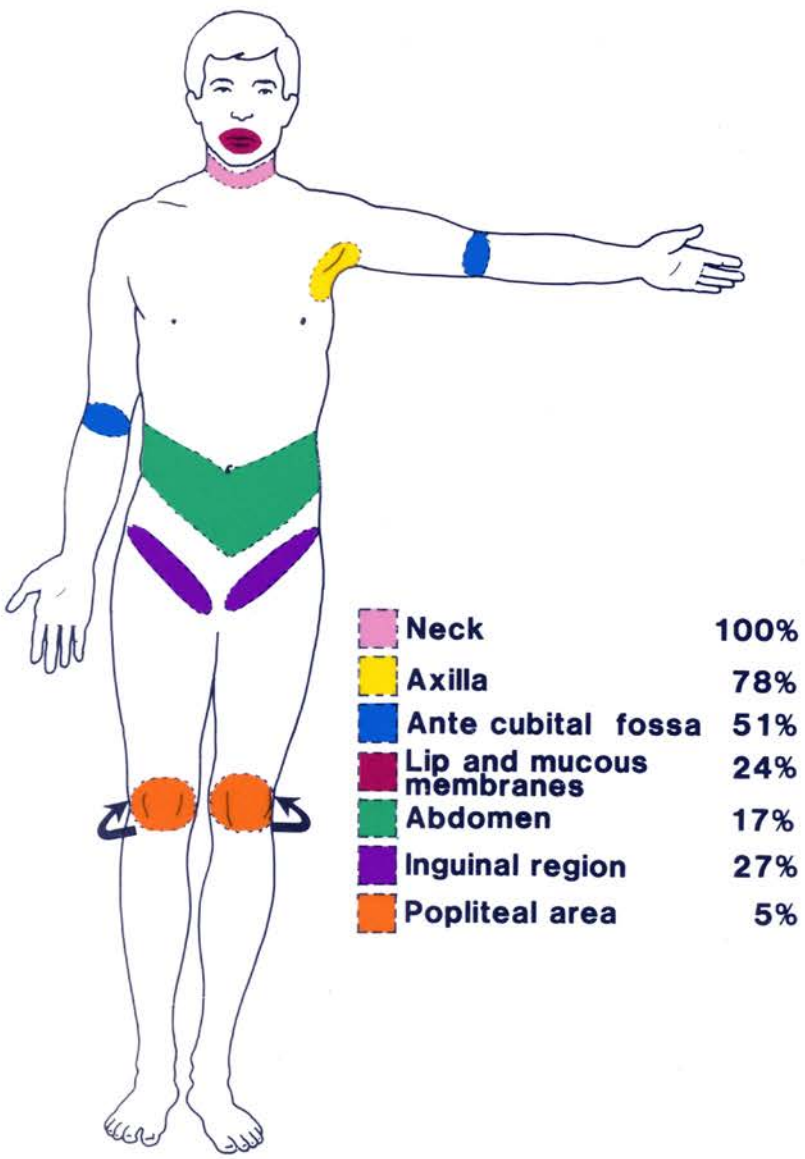


Figure 10.11 THE SITES AND FREQUENCY OF CUTANEOUS LESIONS IN AFRIKANER PATIENTS WITH PXE ARE DEMONSTRATED

Summary

The cutaneous manifestations in affected Afrikaners were generally milder than those in other ethnic groups but on an individual basis, the lesions could not readily be distinguished from those of other common forms of PXE. Exceptions are the rare individuals with AR II PXE who have very severe cutaneous involvement (Chapter 12).

The histological and electron microscopic changes in skin biopsy specimens from Afrikaner patients could not be distinguished from the features seen in other patients with PXE. A comprehensive histological description of affected skin is given in Chapter 12, together with a review of factors which tended to aggravate and cause deterioration in the cutaneous lesions.

10.5 Cardiovascular manifestations of PXE in the Afrikaner population

Introduction

Cardiovascular manifestations have been reported in all forms of PXE except the rare AR II form described by Pope (Chapter 4). The vascular lesions are particularly prominent in the AD I form, but are less prevalent or severe in the AD II and AR I categories of PXE. The cardiovascular manifestations in Afrikaner PXE patients have been summarised in two previous publications (Viljoen et al., 1987; De Paepe, Viljoen et al., 1990); these features are intermediate in severity between those recorded for the AD I form and the more frequently occurring AD II and AR I subtypes.

A detailed analysis of the vascular features found in Afrikaners with PXE is described in this section.

Vascular lesions

The small- and medium-sized arteries are predominantly affected by a process of atheromatous occlusion in patients with PXE. There appears to be a predeliction for vessels of the upper limb but the smaller arteries of the lower limb and virtually every organ system may also be involved. (Carlborg, 1944; Goodman et al., 1963; McKusick, 1972; Neldner, 1988) Calcification of the elastic media is probably the primary event followed by elastic tissue degeneration and compensatory muscular hypertrophy of the media. The vessel lumen thus becomes progressively obliterated and eventually the degenerative process extends to the elastic intima. Arteriosclerosis then develops and atheromatous plaques are formed.

The above processes are indistinguishable from non-PXE atherosclerosis except that the age of onset is earlier in PXE. McKusick (1972) attributes many of the changes to an abiotrophy of elastin fibres in the media and intimal layers of the arteries. Paradoxically, the aorta which is laden with elastin, is largely unaffected in the degenerative process. The clinical complications attributable to arterial occlusive disease in PXE are the same as for other forms of arteriosclerosis namely, diminished peripheral pulses, intermittent claudication, hypertension, haemorrhage, aneurysm formation, thrombosis and ischaemia.

Cardiovascular findings in Afrikaner patients with PXE

Fifty-three patients of Afrikaner stock with PXE were investigated. There were 32 females and 21 males and ages ranged from 14-82 years. (mean : 40.1 years). The vascular manifestations are summarised in Table 10.5.

TABLE 10.5

CARDIOVASCULAR MANIFESTATIONS IN 53 AFRIKANER PATIENTS

VASCULAR FEATURE	NO OF PATIENTS	(%)
Diminished peripheral pulses	40	(75.5)
Hypertension	18	(34.0)
Intermittent claudication	11	(20.8)
Angina	5	(9.4)
Ischaemic leg ulcers	1	(1.9)
Cerebrovascular accident	1	(1.9)
Gastro-intestinal haemorrhage	1	(1.9)

Affected individuals were investigated according to the cardiovascular protocol outlined in Chapter 3. No sex differences were apparent. Diminished peripheral pulses were recorded in 40 subjects (75.5%), 39 of whom were older than 20 years of age. The most frequently affected arterial systems were those around the wrist (82.5%) while diminution in amplitude of pulses was recorded in nearly 70% of the peripheral arteries of the leg. (Table 10,6).

TABLE 10.6

DECREASED PERIPHERAL ARTERIAL PULSES IN 40 AFRIKANER PXE PATIENTS

ARTERY	NO OF PATIENTS (%)
Radial/Ulnar	33 (82.5)
Brachial	14 (35.0)
Axillary	4 (10.0)
Dorsalis Pedis	27 (67.5)
Posterior Tibial	28 (70.0)
Popliteal	17 (42.5)

Intermittent claudication was a feature in 11 persons (20.8%) and angina was recorded in 5 individuals. To date, no patient with PXE in the Afrikaner group has experienced a myocardial infarction although 3 individuals with the disorder and related to persons in this project may have had a coronary thrombosis (Chapter 5). The latter individuals had died as a result of their illness prior to the onset of this study. Among the study cohort, one person experienced ischaemic changes with ulcer

formation of her right leg; gangrene and infection of the surrounding skin eventually warranted amputation of the compromised limb. Another affected person aged 55 years suffered frequent transient cerebral ischaemic attacks and then developed a dense left hemiplegia.

Hypertension

Moderate to severe hypertension defined as a systolic pressure in excess of 160mm Hg and a diastolic pressure exceeding 110mm Hg was a feature of more than 33 per cent of the Afrikaner PXE patients. In 7 individuals severe elevation of blood pressure was unrecognised prior to this investigation. In every instance the problem was well controlled using conventional therapy with thiazide diuretics and beta-blockade. The youngest individual with hypertension requiring therapy was 27 years of age.

Gastro-intestinal haemorrhage

The characteristic gastric mucosal bleeds reported in many literature articles in patients with PXE (**Edwards, 1958; Fisher et al., 1958; Goodman et al., 1963; Cunningham et al., 1980; Neldner, 1988**), especially those associated with pregnancy in young women (**McCaughey et al., 1956**), were not features of Afrikaner patients in this study. Indeed, only 1 affected person had episodes of gastro-intestinal haemorrhages. This woman had oesphageal varices due to alcoholic cirrhosis.

Cardiac manifestations

Few patients with PXE from the Afrikaner community had cardiac manifestations attributable to the disorder. (Table 10,7). Two individuals received antifailure therapy as a consequence of undefined cardiomyopathy and chronic hypertension. Mitral valve prolapse was a feature in 6 persons (11%) but this was an incidental finding of no apparent clinical significance. Two affected individuals had bifid aortic valves while in 3 others non-specific cardiomegaly was demonstrated on radiographic examination.

TABLE 10.7

CARDIAC MANIFESTATIONS IN AFRIKANER INDIVIDUALS WITH PXE

MANIFESTATION	NO OF PATIENTS (%)
Congestive Cardiac failure	2 (3.8)
Mitral valve prolapse	6 (11.3)
Bifid aortic valve	2 (3.8)
Undefined cardiomegaly	3 (5.7)

Comment

The cardiovascular manifestations in Afrikaans-speaking PXE patients are similar to those described in other large series of patients (Eddy & Farber, 1962; Goodman et al., 1963; Pope, 1974; Neldner, 1988). According to Pope's classification (chapter 4), the severity of findings in Afrikaner patients fall between the AD I form and the AD II and AR I subtypes. i.e. the cardiovascular manifestations are moderately-severe.

Interestingly, none of the patients studied developed typical gastric mucosal bleeds said to be experienced in 8 - 10 percent of affected individuals in other series. **(McKusick, 1972).** This disparate finding is unexplained but lends credence to the claim that the Afrikaner form of PXE is an autonomous entity.

The hypertension which occurred in more than thirty per cent of the patients has important implications for management of affected persons. For this reason, all patients were advised to have a thorough annual appraisal from their family physician.

Mitral valve prolapse (MVP) has been reported in individuals with PXE with a prevalence which varied between 4 per cent **(Neldner, 1988)** and 71 per cent **(Lebwohl et al., 1982).** Six patients in this series were diagnosed as having MVP but no adverse clinical sequelae were associated with this diagnosis.

A remarkable finding was the absence of proven myocardial infarction in any person affected with PXE, although 5 individuals were on therapy for recurrent angina. Familial hypercholesterolaemia and several other factors have contributed to the highest rate of ischaemic heart disease within the Afrikaner community in the Western World. **(Seftel et al., 1980).** Thus the arteriosclerotic tendencies in affected individuals with PXE would have been expected to have had an additive effect for poor cardiovascular prognosis in Afrikaner individuals. There is no explanation for this negative finding.

10.6 Involvement of Other Organ Systems

As previously stated, the basic defect in PXE is currently considered to be a mutation in the gene coding for elastin. This structure forms a vital component of connective tissues in many body organ systems; for instance, it is an integral part of synovial membranes, tendon structures and lung tissue. It is, therefore, remarkable that apart from the eye, skin and cardiovascular system, there are few sequelae in other organs which are attributable to PXE.

During an in-depth investigation of 58 Afrikaner patients, anomalies were found in the central nervous system, musculoskeletal system, female genital tract and teeth of a few persons with PXE. These complications, which tended to be minor, are briefly detailed in this section.

Central nervous system

Neurological and neuropsychological abnormalities have previously been reported in up to 5 per cent of patients with PXE. (Eddy & Farber, 1962; McKusick, 1972; Goto, 1975; Neldner, 1988). Given the arteriosclerotic changes affecting small- and medium-sized arteries in PXE, the consequences of various stroke phenomena would be expected. Only one patient, however, sustained a hemiplegia following recurrent episodes of transient ischaemic attacks. Two Afrikaner women, aged 48 and 62 years respectively, required regular psychiatric consultations for emotional problems, episodes of depression and anxiety neurosis. "Antisocial" behaviour was present in several female patients and a minority of male individuals. Two women were confirmed alcoholics. In addition, 14 marriages involving individuals afflicted with PXE ended in divorce. Ten persons in the latter category were of the female sex. The frequency of divorce in individuals with PXE exceeded the generally

accepted rate of 1:3 for divorce in Caucasian South African couples. Factors other than neuropsychological problems may be responsible for divorce in these couples; for instance, it may be the consequence of deteriorating cosmetic appearance and poor self-image, particularly in female patients.

Musculoskeletal involvement

There were no instances of major arthropathy or severe bony lesions in patients with PXE. Ligamentous calcification and mineralisation of the pineal gland, falx cerebri and arterial blood vessels were recorded. These radiological changes are discussed in Chapter 17.

Gynaecological and obstetric implications

Comprehensive gynaecological histories were obtained in 20 Afrikaner women. The clinical details are discussed at length in Chapter 15. The important findings were a propensity for menorrhagia and evidence of pelvic ligamentous laxity in a minority of affected individuals.

The obstetric details regarding 34 pregnancies in Afrikaner PXE patients are described in Chapter 16. Two adverse sequelae were apparent; firstly, there was a moderately increased risk of first trimester abortion and secondly, cosmetic deterioration of the abdominal skin frequently accompanied advanced pregnancy.

No differences in the obstetric and gynaecological findings were apparent between patients with varying forms of PXE. This may be due to the small number of individuals represented in each group. The latter argument is more fully explored in chapters 15 and 16.

Dental deterioration

Complete dental clearance had frequently been undertaken in patients with PXE because of excessive caries and 30 of 39 individuals over the age of 30 years (77%) wore dentures. No data are available to substantiate whether this high proportion of individuals with dentures is excessive for the Afrikaner community as a whole.

As the teeth are largely comprised of type I and type II collagen which appears to be unaffected in PXE, it would seem unlikely that affected individuals would be susceptible to dental caries. However, the small nutrient arteries of the tooth may be compromised by arteriosclerosis and lead to enamel deterioration and decay. Further data are required to elucidate this aspect of PXE.

Summary of the phenotypic manifestations of the "Afrikaner" form of PXE

In Afrikaner patients with PXE, the ophthalmological sequelae were severe and culminated in legal blindness in a majority of individuals exceeding 50 years of age. Trauma to the eye or head was directly responsible for retinal haemorrhages in more than thirty per cent of affected persons. In addition, moderately-severe cardiovascular complications consisting mainly of hypertension, minor stroke phenomena, angina and claudication were common. In general, the cutaneous manifestations of affected persons were mild although the cosmetic deterioration, skin redundancy and premature-ageing effect caused 7 women to undergo cosmetic surgery. Other organ systems were affected to a lesser extent; neuropsychological sequelae were occasional events while obstetric and gynaecological manifestations were infrequent but

noteworthy. A new finding, namely increased propensity to dental caries, may reflect poor nutrient blood-supply to teeth in affected individuals. Calcification of various elastin-rich structures such as arterial vessels, juxta-articular ligaments and falx cerebri were recorded.

The clinical manifestations in Afrikaner PXE patients are unique. These findings, which have considerable implications for affected individuals and for health planning in South Africa, are discussed in Chapter 11.

SECTION III

CHAPTER 11

AN AUTONOMOUS FORM OF PSEUDOXANTHOMA ELASTICUM IN THE AFRIKANER POPULATION

11.1 AN AUTONOMOUS FORM OF PXE

11.2 IMPLICATIONS OF PXE IN THE AFRIKANER COMMUNITY

CHAPTER 11

AN AUTONOMOUS FORM OF PSEUDOXANTHOMA ELASTICUM IN THE AFRIKANER POPULATION

During the early phases of the current project, it became apparent that a clinically distinct form of PXE existed in the Afrikaner community of South Africa. The findings became the subject of two papers (Viljoen et al., 1984; Viljoen et al., 1987). Since that time, further evidence has accumulated and has been described at length in the preceding chapters and in several literature reports, (Viljoen, Beatty and Beighton, 1987; Viljoen, 1988; Torrington and Viljoen, 1990; De Paepe, Viljoen et al., 1990).

The purpose of this chapter is to compare and contrast the clinical and genealogical data of the Afrikaner form with established types of PXE. (See chapter 4). This was done to establish the credentials of PXE in the Afrikaner community as an autonomous entity. The implications for these affected persons are discussed in the light of management and possible preventative strategies.

11.1 An Autonomous Form Of PXE

The principle clinical features of 58 affected persons of the Afrikaner stock are summarised in Table 11.1 and compared with the PXE categories previously described by Pope (1975).

TABLE 11.1

COMPARISON OF CLINICAL FEATURES WITHIN TYPES OF PXE

		Study reported by Pope (1975)				AR "Afrikaner"
	Clinical characteristics	AD I (N=12)	AD II (N=52)	AR I (N=54)	AR II (N=3)	form (N=58)
Skin	Classical flexural	100%	24%	77%	-	100%
	Generalised	-	-	-	100%	-
Cardio-vascular system	Hypertension	75%	7.8%	19.7%	-	34%
	Angina/claudication	56%	-	-	-	22.4%
Ophthalmic manifes-tations	Angioid streaks	34%	47%	47%	-	100%
	Severe choroiditis	75%	7.8%	35%	-	66.7%
Marfanoid features	High arched palate, loose jointedness, blue sclerae	-	50%	10%	-	-

As has been previously shown in Chapter 5, PXE in the Afrikaner is almost always inherited as an autosomal recessive trait. This consistent inheritance pattern is in contradistinction to the patients studied by Pope, in whom there were two autosomal dominant and two autosomal recessive forms of PXE.

In the more common AR I form of PXE described by Pope, ophthalmological manifestations were observed in less than 50 per cent of individuals compared with 100 per cent of the affected Afrikaners.

More than sixty per cent of the latter patients had choroiditis and the same proportion of persons were blind, according to the legal definition, after the fifth decade of life. Other differences between AR I PXE and the Afrikaner patients were found in the cardiovascular system where hypertension and signs of ischaemia were more frequent in the latter group.

Patients with the rarely diagnosed AR II form of PXE (Pope, 1974), had severe, generalised cutaneous manifestations in the absence of other stigmata and were easily identifiable as a separate entity.

Apart from the different inheritance pattern, patients with Afrikaner PXE were readily distinguishable from the more frequently occurring AD II individuals described by Pope. Fully fifty per cent of the latter group had marfanoid features, in which blue sclerae, loose jointedness, highly-arched palate and limb : body-length disproportion were variably present. These manifestations were not observed in Afrikaner patients who had more severe ophthalmological and cardiovascular complications.

Patients with the AD I disorder delineated by Pope had clinical manifestations most akin to those seen in the Afrikaner. Both groups of affected persons had severe ophthalmological features together with moderately severe cardiovascular complications. In addition, the cutaneous lesions were similar. However, the inheritance patterns between the two disorders were dissimilar, indicating that both are autonomous entities. Given the spectrum of severity of clinical signs which may occur within a single kindred with PXE and the paucity of patients in the AD I group (N=12), it is likely that these individuals may merely represent the severe end of the spectrum of the AD II patients. In any event, the hereditary characteristics readily distinguish the

dominant PXE disorders described by Pope from the Afrikaner PXE patients in whom the disorder is inherited as an autosomal recessive trait.

Additional factors which suggest an autonomous form of PXE exists within the Afrikaans-speaking community of South Africa are :

1. The evidence of a similar condition in European antecedents of the original Cape settlers (De Paepe, Viljoen et al., 1990). These authors confirmed the high prevalence of an autosomal recessive form of PXE in Belgium in which patients have severe ophthalmological complications, moderately-severe vascular sequelae and mild cutaneous lesions. The clinical presentation and natural history precisely parallels that of Afrikaner patients.

2. The isolation of the Afrikaner community for religious, cultural and geographic reasons is likely to have preserved homogeneity of PXE in this group. Calculations of the gene frequency of PXE in the Afrikaner community are the highest for any ethnic group previously reported. (Chapter 7).

Although the arguments for autonomy of PXE within the Afrikaner community of South Africa are based on sound biological precepts, the ultimate proof will only be forthcoming once the precise genetic defect is identified at the molecular level. From previous experience in autosomal recessive disorders with protean clinical manifestations such as cystic fibrosis, it is likely that PXE is a heterogeneous disorder with homogeneity of a specific form in the genetic isolate formed by the Afrikaner population.

11.2 Implications of PXE in the Afrikaner Population

The minimum gene frequency for PXE within the Afrikaner community of South Africa has been shown to be as high as 1/76 (Chapter 7), with an estimated number of 150 homozygous individuals. When compared with other recessive disorders within this population group (estimated number of persons with cystic fibrosis is 1400), the number of individuals with PXE is small. However, the prevalence is most likely grossly underestimated (Chapters 6 & 7), and may approach 1/10,000 of the population with almost 500 affected persons.

According to the data accumulated in this investigation, a large proportion of patients with PXE were unaware of the medical implications of their disorder and a readily treatable complication such as hypertension had not been given attention in 7 of 53 affected persons. In order to redress the lack of knowledge of this disorder among the medical and ancilliary professions in South Africa, a process of education is warranted. Communications through local medical journals, the press, medical congresses and hospital meetings should be directed primarily at physicians, ophthalmologists, dermatologists, plastic surgeons, cardiologists and general practitioners.

In the process of accumulating data for this investigation, papers on various aspects of PXE were delivered by the author to colleagues at several medical congresses. The subject titles are listed in the Appendix. **(Papers Delivered at Local and International Congresses).**

Part of the committment which the author undertook when this project was initiated was to "enlighten affected individuals and their families as to the medical and genetic implications of (PXE)..." (Chapter 2). At the time each affected person was investigated, the family were extensively

counselled and a detailed medical report with literature references was forwarded to their medical practitioner. The likely prognosis and future complications were described so that preventative measures could be instituted. Annual medical and ophthalmological appraisal was advised for affected persons. These measures are discussed further in Section VI.

Although PXE in the Afrikaner remains a relatively minor disorder when considering the health problems of South Africa in general, the total costs to the country due to loss of manpower and use of medical facilities are heavy while the burden to affected families is enormous. In such analyses, the following aspects require consideration :

1. Sixty-five percent of adults with PXE over the age of 50 years are legally blind. These persons are unable to work and require the provision of State funded facilities for the Blind.

2. More than one third of patients required treatment for hypertension.

3. Complications such as stroke phenomena (7 per cent), ischaemia (10 per cent) and intermittent claudication (21 per cent) required therapy and, apart from visual deterioration, were the main indications for early retirement from productive labour.

4. Numerous operative procedures for PXE complications are undertaken on affected persons; namely cosmetic surgery (13 per cent), laser ophthalmological treatment (8 per cent), vesico-uterine prolapse (5 per cent of women) and vascular surgery (3 per cent).

5. Although no data are available for this population, the life-span of affected persons has been shown to be considerably reduced compared with the normal population. (Chapter 6).

Given the morbidity and mortality and high prevalence of PXE within the Afrikaner community, the possibility of antenatal and pre-symptomatic diagnosis would have real benefits and may be cost-effective. The future prospects regarding these strategies are discussed more fully in Section VI.

SECTION IV

ANALYSIS OF CLINICAL MANIFESTATIONS IN PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum is a multisystem disorder in which the eye, heart and skin are principally involved. Other organ systems may be affected to a lesser extent with minor sequelae. Data relating to the clinical manifestations and complications occurring in 86 patients encoutered during the investigation and affected by all forms of PXE, are analysed in this section.

PXE is heterogeneous and data have been previously presented in Chapter 10 on an autonomous form of the disorder found within the Afrikaner population. Due to the small number of patients in other subcategories of PXE, the clinical manifestations have been analysed together so as to derive more meaningful conclusions.

CHAPTER 12: **DERMATOLOGICAL FEATURES IN PXE**

CHAPTER 13: **CARDIOVASCULAR MANIFESTATIONS OF PXE**

CHAPTER 14: **OPHTHALMOLOGICAL FEATURES OF PXE**

CHAPTER 15: **GYNAECOLOGICAL FINDINGS IN WOMEN WITH PXE**

CHAPTER 16: **OBSTETRIC IMPLICATIONS OF PXE**

CHAPTER 17: **RADIOLOGY AND MAGNETIC RESONANCE IMAGING IN PATIENTS WITH PXE**

CHAPTER 12

DERMATOLOGICAL FEATURES IN PSEUDOXANTHOMA ELASTICUM

12.1 HISTOLOGICAL CHANGES IN PXE

12.2 CUTANEOUS MANIFESTATIONS IN PXE

12.3 CUTANEOUS AR II PXE

12.4 FACTORS ADVERSELY AFFECTING THE SKIN IN PXE

12.5 DIFFERENTIAL DIAGNOSIS OF CUTANEOUS PXE

CHAPTER 12

DERMATOLOGICAL FEATURES IN PSEUDOXANTHOMA ELASTICUM

The cutaneous manifestations of PXE may vary from very mild changes which are indistinguishable from the normal ageing process to severe, unsightly, redundant lesions which are cosmetically unacceptable.

The skin lesions in the Afrikaner form of PXE have already been described in Chapter 10.3. In this chapter, the light- and electron-microscopic findings of biopsy material from the skin in PXE patients are reported, as are the unique clinical manifestations of PXE in Black patients. In addition, factors which aggravate and cause the dermatological lesions to deteriorate will be highlighted as will other diseases processes which mimic PXE.

12.1 Histological Changes in PXE

The method and site of skin biopsy has been described in Chapter 3.3.1. All 86 affected persons in the study were biopsied in order to confirm the diagnosis. With prior consent, multiple biopsies were performed in affected areas and in apparently normal skin in 3 adults so that the natural history of cutaneous deterioration could be determined. In each instance the biopsy material was conventionally stained with haematoxylin and eosin, Verhoeff and von Kossa stains and 7 specimens were placed in gluteraldehyde solution for electron microscopic examination. The specimens were appraised by histopathologists from the Department of Pathology of the University of Cape Town Medical School.

Light-microscopic Findings

The use of haematoxylin and eosin (H&E) for staining biopsy material is able to demonstrate fragmentation, disruption and calcification of the elastin fibre of the lower papillary dermis in PXE lesions that are well-established. Lesser affected elastin fibres with mild calcification can more readily be detected with the von Kossa stain which is specific for carbonate or phosphate radicals of calcium. The Verhoeff-van Gieson stain is specific for elastin but will only take up the stain after fragmentation of the fibre occurs, late in the pathogenesis of the disorder. By using these three basic stains, a positive diagnosis of PXE can be made at any stage of the disease process and differentiated from solar elastosis, the normal ageing process and other mimics of PXE.

The classical light-microscopy findings in a biopsy from the PXE-affected skin of the cervical area are demonstrated in Figure 12.1. The stained elastin fibres in the middle and deep dermis are readily visible.

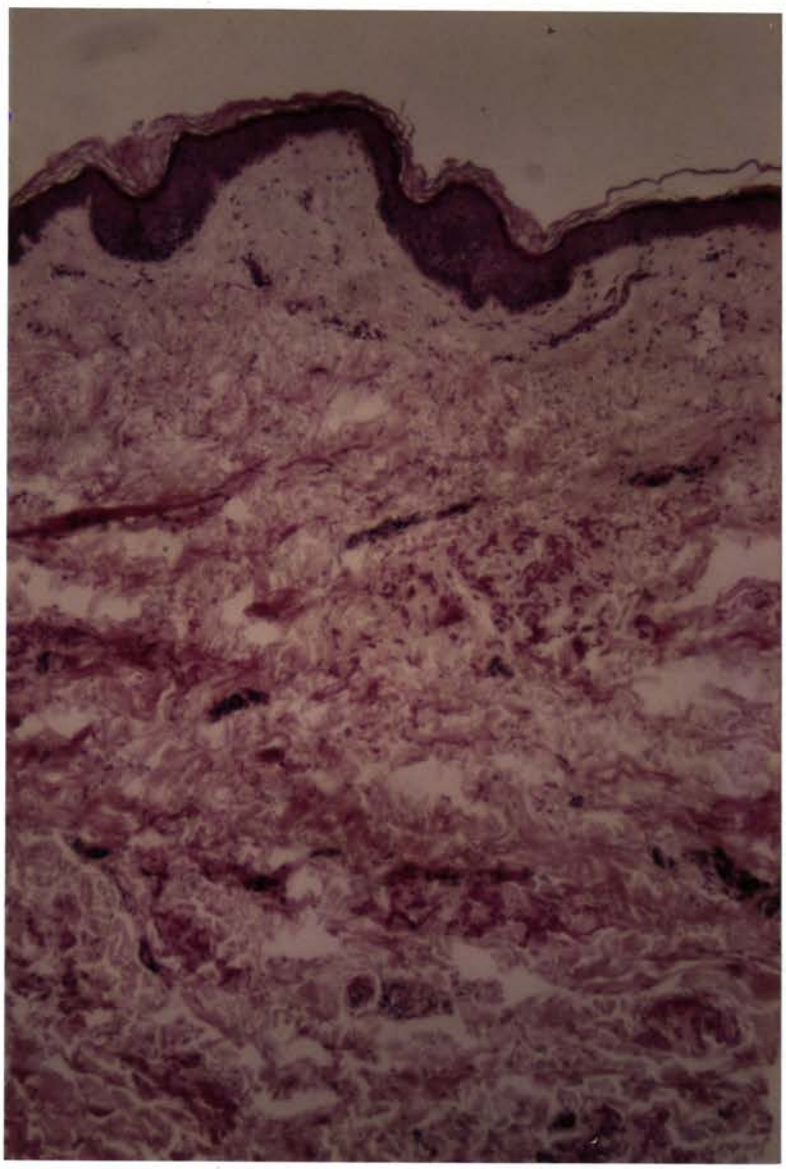


Figure 12.1 A LOW POWER VIEW OF THE FRAGMENTED AND IRREGULARLY CLUMPED ELASTIN FIBRES IN THE MID-DERMIS (H&E X 100).

During the pathological process, the elastin fibres initially are thickened and later become clumped and fragmented. Specific staining for calcium has shown that the earliest histological change in the elastin fibre is a process of calcification (Goodman et al., 1963). Typically clumped elastin fibres from the skin of a patient with long-standing PXE and stained with H & E stain are seen under high magnification (x 200) in the dermis in figure 12.2. The "coiled" appearance of the fragmented elastin fibres is evident in the high magnification view in Figure 12.3.

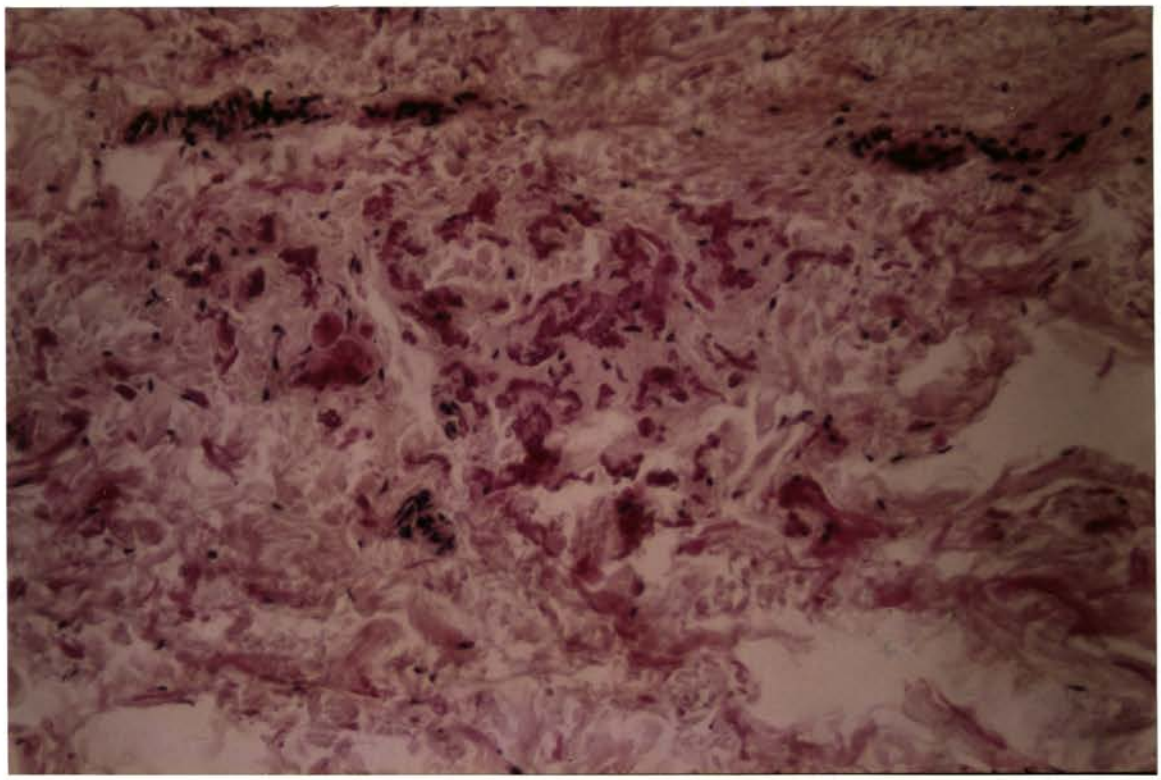


Figure 12.2 CLASSICAL CLUMPING AND THICKENING OF ELASTIN FIBRES IN THE DERMIS OF A PATIENT WITH PXE. (H&E X 200)

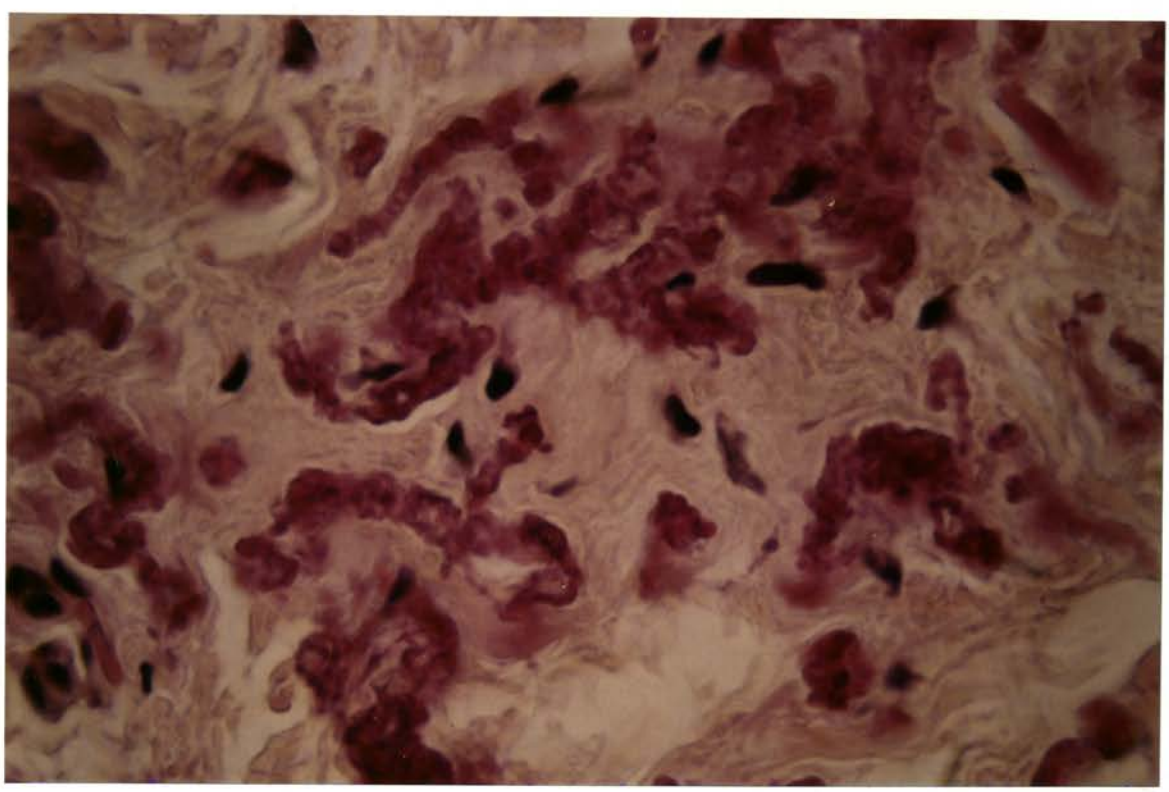


Figure 12.3 PSEUDOXANTHOMA ELASTICUM. THE "COILED" APPEARANCE OF THE FRAGMENTED ELASTIC FIBRES IS EVIDENT. THESE CHANGES, DUE TO MINERALISATION WITH CALCIUM SALTS, ARE SEEN STAINED WITH H&E X 400

Other, less specific dermatological findings may be evident in patients with PXE. Small foci of histiocytic and giant foreign body reactions in association with calcified elastin tissue have been observed by **Heyl (1967), Lombardo, (1969), Blumcke et al., 1974** and **Dupre et al., (1979).** Eccrine sweat glands may undergo distortion as a consequence of calcification of surrounding elastin fibres **(Goodman et al., 1963)** and degeneration of the elastin of the media in small skin arteries may also be seen **(Neldner, 1988).**

The histological features described above were seen to some degree in the biopsy material of all the patients investigated. The extent of the degenerative process was dependent on the duration and locality from which biopsy material was derived. Individuals from whom multiple biopsies were taken demonstrated a range of changes from severe elastin calcification and distortion in the skin biopsied from the cervical region to minor degrees of calcification in biopsies taken from the mildly affected skin of the back and chest.

Following careful examination of the skin biopsies by two histopathologists, no distinguishing features were found in the histological appearances between the different clinical forms of PXE. In each instance, the clinical severity of the skin lesion was matched by a similar degree of pathological change.

Electron Microscopy Findings

The ultrastructural composition of PXE skin has been examined repeatedly by numerous investigators using transmission and scanning analysis techniques **(Huang et al., 1967; Hashimoto and Dibella, 1967;**

Dawber and Shuster, 1971; Ross et al., 1978). All 7 individuals examined in this investigation demonstrated similar lesions.

Electron microscopic studies demonstrate that the site of primary involvement in PXE is the elastin fibre and that a process of degeneration ensues which is unique to the disorder. The normal elastin fibre is a non-homogeneous structure with peripheral microfibrils and small, electron-dense deposits throughout the fibre. In PXE, a characteristic solid, central-core of material appears which represents mineralization by carbonate and phosphate calcium salts. The process progresses in the central core and thickening of the outer rim of the fibre occurs. Eventually the elastin fibre becomes enormously enlarged to the point of rupture and fragmentation, discharging its contents into the surrounding dermis.

Natural History

From the gradual degeneration of elastin fibres described previously, the clinical and histological correlations in PXE become apparent :

a) The skin initially is discoloured and a reticular rash then appears. This clinical stage correlates with early elastin mineralisation.

b) Raised, cobblestone-like lesions develop in the flexural areas probably as a consequence of thickening of the elastin fibres seen at an ultrastructural level.

c) Skin laxity then becomes more noticeable. This feature may correlate with fragmentation and rupture of the elastin fibres evident on electron- and light-microscopy.

d) Progressive calcification within the dermis occurs as the calcified salts are released into these tissues.

12.2 Cutaneous Manifestations in PXE

The skin lesions in 86 patients described in this investigation are summarised in Table 12.1. Due to the small number of patients in each group, no attempts were made to separate the clinical findings into the categories of PXE advised by Pope (1975). The clinical manifestations within the Afrikaner subgroup have been included in this appraisal. Clinical details regarding 4 individuals with the autosomal recessive type II form of PXE in which generalised severe skin manifestations only are apparent, have been described separately. (See Chapter 12.3).

TABLE 12.1

CUTANEOUS LESIONS IN 86 PATIENTS WITH PXE

CLINICAL MANIFESTATION	NUMBER AFFECTED	% AGE OF TOTAL
Classical flexural peau d'orange	84	97.6
Yellow, reticular rash	30	34.9
Acneiform lesions	8	9.3
Unusual cutaneous site involvement	11	12.8
Mucous membrane involvement	29	33.7
Periumbilical PXE	3	3.5
Keloid scarring	4	4.7

The cutaneous lesions were responsible for 71 of the 86 affected persons (82.5%) first seeking medical advice. The average age at which the 86 PXE patients were first appraised by a medical practitioner was 13.2 years (Range 0-37 years). Interestingly, only one non-Afrikaner individual from a cohort of 28 (3.5%) affected persons, was unaware that he had the disorder. This contrasts sharply with 12 of 58 persons (20.7%) in the Afrikaner subgroup and supports the contention that

latter persons have milder dermatological features. The female preponderance in patients in this study is 52:34 (or 3:2). The reasons for this finding have been discussed elsewhere. (See chapters 6.4, 10.3 and 21.1).

The initial site of appearance and distribution of skin lesions in the affected patients is similar to that described in the Afrikaner subgroup (Chapter 10.3). In general, the cervical region was initially involved followed by the axillary area, the antecubital fossa, inguinal region, and popliteal and periumbilical areas. Telangiectasiae of the buccal and vaginal mucous membranes were infrequent. The dermatological sequelae in non-Afrikaner patients tended to be severe and generalised with profound cosmetic consequences (see Figures 12.4 and 12.5).



Figure 12.4 SEVERE PEAU D'ORANGE CHANGES IN THE CERVICAL REGION OF A WOMAN OF MIXED ANCESTRY



Figure 12.5 SEVERE CUTANEOUS LAXITY AND THICKENING IN AN AFFECTED WOMAN AGED 37 YEARS

Acneiform lesions were present in 8 severely affected individuals with PXE in the non-Afrikaner group. These occurred in the cervical and axillary regions predominantly and occasionally over the abdomen. The lesions were sharply demarcated, whitish and scarred and covered with soft crusts which exuded pus. Such findings are unusual in individuals with PXE **(Goodman et al., 1963; Heyl, 1967)**. They are thought to be induced by PXE and consist of comedones, cysts and inflammatory nodules.

Histologically, there are no transepithelial elimations or folliculitis but granulomatous tissue with epithelioid cells and giant cell reaction is apparent. The latter cells contain degenerating bundles of elastin fibres in the dermis which have been invaded by inflammatory cells, and then phagocytosed.

The pathogenesis of acneiform lesions in PXE patients appear to be similar to that of perforans serpiginosa, but is histologically distinct. None of the patients in this study had lesions suggestive of the latter disorder.

An additional cutaneous manifestation in 4 patients with PXE was the formation of keloids in surgical (2 individuals) and traumatic (2 persons) scars. These findings may be fortuitous as keloids are a relatively common complication of wound healing. There are indications, however, that the healing process in individuals with PXE may be abnormal because of degenerating dermal elastin and this factor may induce keloid formation **(Danielson and Kobayasi, 1974; Lebwohl et al., 1987)**.

12.3 Cutaneous AR II Pseudoxanthoma Elasticum

A severe form of PXE in which only the skin is affected was delineated by Pope in 1974. (AR II PXE). The disorder is exceedingly rare and is inherited as an autosomal recessive trait. Pope described 3 persons in this category all of whom had marked peau d'orange lesions in the flexural areas accompanied by a generalised reticular rash over the back, chest and abdomen. Despite the profound skin involvement, none of the eye or cardiovascular complications normally associated with PXE could be demonstrated in these patients.

Four of 86 persons in the current investigation had clinical manifestations similar to those of AR II PXE. All were adults aged between 24-56 years, and 3 were female. Two persons were of mixed ancestry and 2 were Blacks from the Xhosa tribal group. The affected individuals were sporadic and no parental consanguinity was recorded.

The dermatological manifestations varied in severity in each person. Marked peau d'orange lesions occurred in the flexures of all these individuals while gross skin laxity was documented in two of them. A hyperpigmented, generalised rash over the trunk and back was present in all four persons and acneiform changes occurred in one severely affected woman. (See Figures 12.6 - 12.8). The characteristic histological changes normally found in PXE were detected on skin biopsy. No other systemic involvement was present.



Fig 12.6 **SEVERE CUTANEOUS LESIONS OF PXE ARE EVIDENT IN A PATIENT AGED 56 YEARS**



Figure 12.7 AR II PXE; PROFOUND SKIN LAXITY IS EVIDENT



Fig 12.8 A YOUNG MAN OF MIXED ANCESTRY WITH AR II PXE; A HYPERPIGMENTED RETICULAR RASH IS EVIDENT OVER HIS CHEST

Comment

The skin lesions reported in the 4 patients in this study are far more severe than those described by Pope in 3 affected Caucasian patients. On this basis it is possible that yet another distinct form of PXE has arisen which is confined to individuals of negro stock in South Africa. A recent report by **Jacyk et al., (1988)** concerning 7 Black patients from tribal groups domiciled in the Northern areas of South Africa supports this contention. Three of these persons had extensive dermatological lesions similar to those observed in this study. As the black population of Southern Africa are thought to be derived from common central African ancestors **(Beighton, 1978)** it is likely that the same genetic defect is responsible for PXE in the black population. Further investigation to determine the validity of these comments is required.

12.4 Factors Adversely Affecting the Skin in PXE

It has become apparent through several reports that the cutaneous stigmata of PXE progress in an erratic manner. (Goodman et al., 1963; McKusick, 1972; Neldner, 1988). Several factors may influence the severity and spread of skin lesions. A positive correlation between skin deterioration and advancing age, duration of the lesions, tobacco use and childhood dietary intake of calcium has been demonstrated in patients with PXE (Renie et al., 1984; Neldner 1988). There is said to be no correlation with the cutaneous manifestations and alcohol use, diabetes mellitus, sex, hypercholesterolaemia and hypertriglyceridaemia (Neldner, 1988).

In the 86 individuals with PXE in this study, 10 women underwent cosmetic surgery for severe skin manifestations. No males sought plastic surgery and, in general, their dermatological sequelae were considerably less severe than in affected women. This finding contradicts prior reports where no sex differences could be demonstrated in the severity of skin manifestations. Further substantiation of the claim that females have a worse cosmetic prognosis comes from 5 sibling pairs in this study where, in each instance, the females had more severe skin stigmata than their brothers, irrespective of age differences of 2-5 years.

Other adverse prognostic indicators for the integument determined through this investigation were obesity, rapid changes of body mass, frequent sun exposure, and pregnancy. In the history obtained from each patient during the initial interview (Chapter 3), factors affecting the progression of the skin lesions were sought. In 16 instances, patients experienced rapid deterioration following strict dieting or when eating binges produced large increases in body mass. Skin changes

were particularly noted during pregnancy in multiparous women (Chapter 16). In addition, severe dermatological stigmata were evident in 3 very overweight women, suggesting that obesity per se was an adverse factor (Figure 12.9). Two women who habitually sun-tanned during the summer months and 3 men who were farmers and chronically exposed to sunlight, also experienced rapid skin deterioration.



Figure 12.9 THE CUTANEOUS FEATURES IN AN OBESE WOMAN WITH PXE

Comment

Although some of the prognostic factors pertaining to skin changes in PXE are probably anecdotal, several are likely to induce rapid deterioration, namely :

1. Frequent, rapid changes in body mass.
2. Multiple pregnancies.
3. Prolonged exposure to ultraviolet light.
4. Obesity.

In these examples, undue stretching of elastin fibres is most likely the principal event leading to calcification and fragmentation. In solar elastosis, the histological changes also involve elastin fibre fragmentation and, in an individual also affected by PXE, are likely to induce rapid deterioration. Patients in this investigation were advised to avoid undue exposure to sunlight and rapid changes in body mass (Chapter 19).

12.5 Differential Diagnosis of Cutaneous Pseudoxanthoma Elasticum

As the name "pseudoxanthoma elasticum" implies, physicians at the end of the nineteenth century had difficulty in distinguishing the condition from the xanthomatoses and other lipid storage disorders (Chapter 1). The later discovery of eye and vascular manifestations in many patients with PXE has reduced the number of conditions with which it may be confused, and most are now easily identified. The most important disorders in which the dermatological features are similar to those of PXE are listed in Table 12.2.

TABLE 12.2

DISORDERS MIMICKING CUTANEOUS PXE

Solar/actinic elastosis
Ageing process
Penicillamine therapy
Tumoral calcinosis
Hypervitaminosis D
Cutis laxa
Exogenous exposure to calcium salts
Periumbilical perforating PXE
Elastosis perforans serpiginosa (EPS)
Elastic tissue nevus

Solar or actinic elastosis is an acquired process in which the skin degenerates due to excessive and prolonged exposure to sunlight. In this disorder, large amounts of amorphous elastin-staining material accumulates in clumps in the upper dermis; this appearance contrasts with the histological features seen in PXE where the changes in elastin occur predominantly in the middle and deep dermal structures. Clinically, the stigmata of actinic elastosis and mild PXE are very similar, especially in sun-exposed flexural regions. However, patients

can usually be differentiated by peau d'orange changes which occur in non-exposed areas, and by the associated characteristic changes in the retina and cardiovascular system.

The normal ageing process of skin can closely mimic the changes seen in PXE. The elastin fibres in the former tend to mineralise and swell with age, but frank disruption, calcification and clumping of these structures occurs infrequently.

Patients with Wilson's disease, a hereditary disorder of copper metabolism, are frequently treated with penicillamine for prolonged periods of time. The drug is a potent chelator of copper and, through disruption of lysyl oxidase links in the tropoelastin molecule, produces a generalised, yellowish, papular rash and a tendency for the skin to become lax.

Case Report

A patient with Wilson's disease and a provisional diagnosis of PXE was investigated during the course of this project. She was the product of a first-cousin marriage between parents of Indian stock. Her brother had died from the complications of cirrhosis due to Wilson's disease, which had been confirmed by biochemical tests in early childhood.

Large doses of penicillamine had been administered to the young woman for the past 13 years in order to promote copper excretion. Her dermatological lesions were consistent with those seen in PXE. Skin biopsy confirmed the presence of the "serrated" or "bramble bush" lesions of the elastic fibres which are pathognomonic for penicillamine therapy. These differ from PXE and, in addition, do not undergo calcification (Hashimoto et al., 1981). The skin lesions in this patient were later reported by a dermatological colleague (Bentley-Phillips, 1985) who stressed the difficulty of distinguishing the clinical features from those of PXE.

Tumoral calcinosis, hypervitaminosis D and other disorders of calcium and phosphate metabolism have been occasionally found in association

with PXE. These conditions have elevated calcium-phosphate products (Ca X P) and manifest with soft tissue calcification. In isolation, they do not produce the classical peau d'orange changes seen in PXE, but are of interest as they induce elastin calcification. Clinical differentiation from PXE is usually simple and the exact diagnosis can be confirmed using standard biochemical tests.

The cutis laxa group of disorders may occasionally mimic PXE as skin redundancy is sometimes a prominent feature in the latter condition. Differentiation is usually easy as the former lacks the skin discolouration, eye manifestations and cardiovascular changes usually seen in PXE patients.

Exposure to exogenous calcium salts, especially calcium chloride in road workers and coal miners, have very infrequently produced localised PXE-like lesions (**Zacheim and Pinkus, 1957; Clendenning and Auerbach, 1964**). This condition is easily differentiated by the history of exposure and localised nature of the lesions.

An unusual and infrequent disorder occurring predominantly in multiparous, obese, black women was described by **Hicks (1979)** and designated "periumbilical perforating PXE". The affected persons developed periumbilical lesions resembling PXE with several instances of perforating transepidermal elimination papules. Apart from a high incidence of hypertension in these individuals, none of the eye and cardiovascular stigmata associated with PXE were apparent.

Occasionally the condition of elastosis perforans serpiginosa (EPS) may be confused with PXE. EPS has been described in isolation and in association with PXE (**Reed et al., 1973**) and in disorders such as Ehlers-

Danlos syndrome, cutis laxa and scleroderma (**Thomas and Kirby, 1985**). The lesions usually occur in the cervical region and consist of grouped, slightly keratotic, shiny papules which are readily differentiated histologically from PXE lesions.

Comment

Although the dermatological manifestations of PXE may be difficult to distinguish from those of solar elastosis, a common finding amongst Caucasians living in the sunny South African climate, the presence of the associated eye and cardiovascular features in the former condition and typical biopsy findings firmly clinch the diagnosis. The other disorders described in this section seldom pose a problem of differentiaton for medical practitioners familiar with PXE.

SECTION IV

CHAPTER 13

THE CARDIOVASCULAR MANIFESTATIONS OF PSEUDOXANTHOMA ELASTICUM

13.1 CARDIOVASCULAR FEATURES

13.2 PERIPHERAL ARTERIOGRAPHY IN PATIENTS WITH PXE

13.3 COMMENT

CHAPTER 13

Cardiovascular manifestations have been reported in all forms of PXE except the rare AR II type (See Chapter 11.1). The vascular lesion in PXE is the basis for many of the pathophysiologic findings which occur in the disorder including retinal haemorrhage, stroke, ischaemic phenomena, hypertension and perhaps even some dermatological changes.

The basic defect which occurs in small- to medium-sized arteries has been described in Chapter 10.5, as have the cardiovascular lesions which are prevalent in affected individuals of Afrikaner descent. The purpose of this chapter is to describe and depict the vascular lesions occurring in the 86 persons with all forms of PXE who were investigated in this study. In addition, the arteriographic findings in 2 persons are reported in detail.

13.1 Cardiovascular Features

A total of 80 individuals from the initial cohort of 86 persons in this investigation were analysed regarding their vascular status according to the protocol outlined in Chapter 3. There were 48 females and 32 males whose ages ranged from 14-82 years (mean 40.6 years).

The clinical features are summarised in Table 13.1 and affected Afrikaner patients are compared with 27 individuals with other forms of PXE in Table 13.2.

TABLE 13.1

CARDIOVASCULAR MANIFESTATIONS IN 80 PXE PATIENTS

VASCULAR FEATURE	NO. OF PATIENTS (%)
Diminished peripheral pulses	53 (66.3)
Hypertension	26 (32.5)
Calcification of vessels	22 (27.5)
Intermittent claudication	17 (21.3)
Redundant mitral valve chords	10 (12.5)
Angina	7 (8.8)
Cardiomegaly	4 (5.0)
Congestive cardiac failure	3 (3.8)
Bicuspid aortic valve	3 (3.8)
Cerebrovascular accident	2 (2.5)
Thickened aortic valve leaflet	1 (1.3)
Gastro-intestinal haemorrhage	1 (1.3)

TABLE 13.2

COMPARISON OF THE CARDIOVASCULAR FEATURES BETWEEN 53 AFRIKANER PATIENTS AND 27 INDIVIDUALS WITH OTHER FORMS OF PXE

VASCULAR FEATURE	AFRIKANER (%)	OTHER FORMS (%)
Diminished pulses	40 (75.5)	13 (48.1)
Hypertension	18 (34.0)	8 (29.6)
Intermittent claudication	11 (20.8)	6 (22.2)
Mitral valve prolapse	6 (11.3)	4 (14.8)
Angina	5 (9.4)	2 (7.4)
Cardiomegaly	3 (5.7)	1 (3.7)
Congestive heart failure	2 (3.8)	1 (3.7)
Bicuspid aortic valve	2 (3.8)	1 (3.7)
Cerebrovascular accident	1 (1.9)	1 (3.7)
Gastro-intestinal haemorrhage	1 (1.9)	- (-)

It was noteworthy that the vascular sequelae in the latter patients were, in the main, far less severe than those recorded in the Afrikaner. Only 48 percent of non-Afrikaner patients had diminished peripheral pulse pressures in contrast to 75 per cent of those of Afrikaner descent. Fewer non-Afrikaners had hypertension (29.6% versus 34%) but the incidence of other vascular features and complications were similar.

13.2 Peripheral Arteriography in Patients with PXE

Two Caucasian women of Afrikaner descent, aged 46 and 54 years respectively, were investigated by cardiological colleagues by means of brachial and femoral arteriograms. Both individuals had clinical diminution of peripheral pulses, intermittent claudication, moderate hypertension and complained of easy fatiguability. The investigations were performed in order to determine the extent of their peripheral vascular disease.

Peripheral arterial narrowing was present in the two women and both had complete stenosis of the radial artery (Figure 13.1). The interosseous circulation of the forearm appeared normal.



Figure 13.1 NORMAL CIRCULATION THROUGH THE RIGHT ULNA ARTERY IS DEMONSTRATED (ARROWS) BUT THERE IS COMPLETE OCCLUSION OF THE RADIAL VESSEL

In both affected individuals, calcification of the lower aorta was evident (Figure 13.2), as were lesser degrees of calcification in the femoral and popliteal arteries.



Figure 13.2 CALCIFICATION OF THE ABDOMINAL AORTA IS APPARENT IN THIS PATIENT AGED 46 YEARS

In the older patient, complete occlusion of the right femoral artery was observed in association with a good collateral circulation (Figure 13.3). The larger arteries were in the main unaffected and no pathological narrowing of the renal arteries was demonstrated.

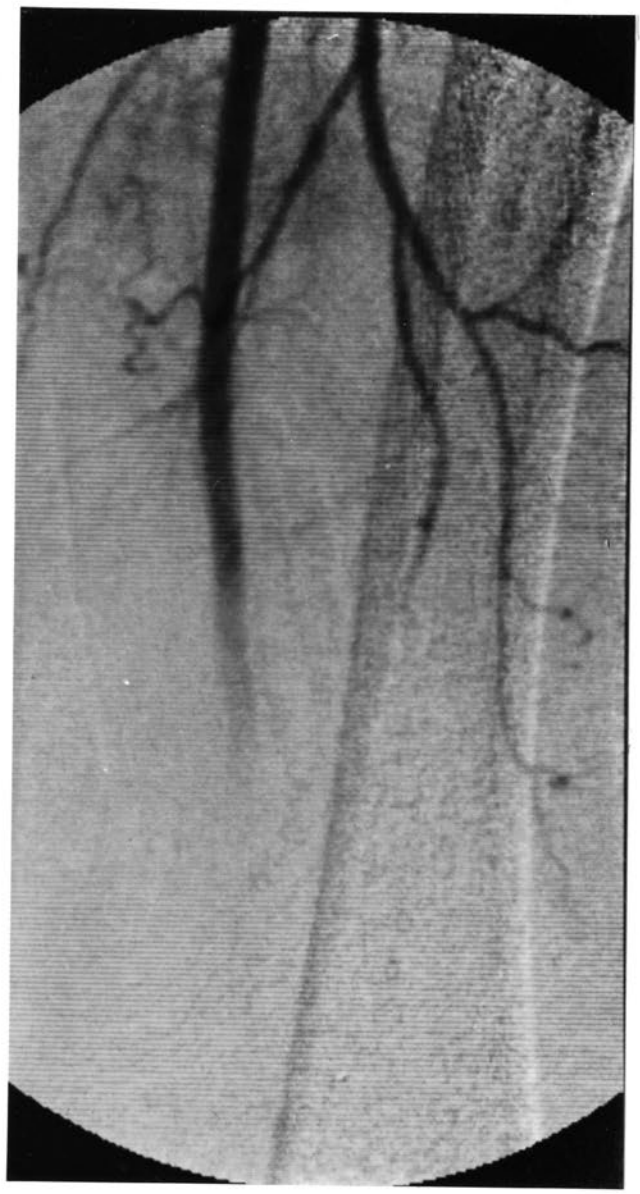


Figure 13.3 ARTERIOGRAM DEMONSTRATING OCCLUSION OF THE RIGHT FEMORAL ARTERY. AN EXCELLENT COLLATERAL CIRCULATION IS EVIDENT

Although arteriography in two patients revealed the presence of luminal narrowing within the smaller arteries, the information obtained from the investigation was limited and of no direct benefit to them. Due to the discomfort, expense and risks of haemorrhage, sepsis and reaction to the radio-opaque dye inherent in arteriographic procedures, only individuals with vascular compromise where embolectomy or graft-surgery are contemplated are now investigated through these means by the vascular surgeons.

13.3 Comment

The cardiovascular manifestations in PXE have been the subject of several detailed investigations (**Carlborg, 1944; Goodman et al., 1963; McKusick, 1974; Pope, 1974; Mendelsohn et al., 1975**). The clinical consequences of PXE, given the tendency for premature arteriosclerosis, are commonly intermittent claudication, angina pectoris, hypertension, myocardial infarction, and congested cardiac failure. These features have been previously described in the literature and were present in many patients in this investigation. However, several more-recently reported clinical manifestations of PXE have come to light as detailed below:-

a) "Idiopathic" cardiomegaly

Cardiomegaly for which no cause could be determined was present in 4 (5%) of the patients reviewed in this series. Similar findings have been reported in other large series (**Eddy & Farber, 1962; Goodman et al., 1963; Neldner, 1988**). In most patients with PXE cardiomegaly is the consequence of myocardial ischaemia and prolonged hypertension. However, in recent years postmortem studies and antemortem endomyocardial biopsy have revealed evidence of myocardial involvement in several patients with PXE (**Przybojewski et al., 1981**). **Huang et al. (1967)** commented on autopsy evidence of localized endomyocardial fibrosis. Other authors described endocardial lesions consisting of internal fibro-elastotic thickening, disorganisation, calcification and fragmentation of the elastic fibres of the deep endocardial layers (**Carlborg et al., 1959; Coffman and Sommers, 1959; Goodman et al., 1964; Akhtar and Brody, 1975**).

It is now evident that pan-myocardial dysfunction occurs in patients with PXE. The cause is unknown but according to **Przybozewski et al. (1981)** it is due to "a diffuse arteriopathy involving the small coronary vessels ('intramyocardial'; 'intramural') which was not visible angiographically."

According to most authorities, patients with unexplained cardiomegaly and PXE should be digitalised as a precaution against incipient heart failure.

b) **Coronary artery involvement**

Although a total of 7 (8.8%) of the patients analysed in this investigation had symptoms of angina, no episode of myocardial infarction had been recorded in any living persons with the disorder up to the time of writing. Three persons from an Afrikaner kindred studied in this project who were ostensibly affected with PXE, have died as a result of myocardial infarcts. Their deaths had occurred prior to 1984 when this investigation was instituted and medical details of their illness were fragmentary and incomplete. The paucity of individuals with proven myocardial infarction in this study is surprising and unexplained, especially as the risk of coronary thrombosis in the Afrikaner population due to other medical causes is the highest in the Western world **(Seftel et al., 1980).**

After scrutinizing the literature, it became apparent that coronary artery involvement with calcification is relatively common in adults with PXE **(Nellen and Jacobson, 1958; Eddy and Farber, 1962; Goodman et al., 1963; Mendelsohn et al., 1978; Neldner, 1988).** Sudden death has also been described during strenuous exercise in 3 teenage boys with PXE, in whom autopsy-verified myocardial infarction and coronary

atheroma had occurred **(Wilhelm and Paver, 1972).** Selective coronary arteriography was first carried out in a patient with PXE by **Bete et al. (1975)** in an 18 year old girl who was demonstrated to have significant triple vessel coronary artery disease. She later underwent a successful grafting operation.

Przybojewski et al. (1981) described a black man with angina and PXE in whom coronary arteriography was performed. No atherosclerosis or calcification could be demonstrated. Endocardial biopsy showed an absence of coronary arterioles, and the authors postulate that much of the mechanical and electrical disturbance of cardiac function in patients with PXE can be attributed to "small coronary arteriopathy" and not involvement of the larger epicardial coronary arteries. Their hypothesis may explain the dearth of individuals in this study with "true" myocardial ischaemia in the face of fairly frequent anginal attacks. In addition, it would explain the finding of "idiopathic cardiomegaly" described earlier in this chapter.

c) **PXE and Mitral Valve Prolapse**

Mitral valve prolapse (MVP) was confirmed in 6 Afrikaners with PXE (11.3 per cent) and in 4 non-Afrikaners (14.8 per cent) in the study cohort. No complications attributable to this finding were evident in the affected persons.

It has been long debated as to whether MVP has any pathological significance and more than 90 references on this subject were listed by **Cheitlin et al. (1975).** It is generally accepted, however, that in connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta and PXE, MVP is common and not always innocuous **(Perloff, 1982; Lebwohl et al., 1982).** Several

complications which may have severe consequences for affected persons may arise in association with MVP; these include supraventricular tachycardia, cerebral ischaemic events and mitral incompetence (**Devereux et al., 1976**).

The reported frequency of MVP in patients with PXE has varied from 4 per cent (**Neldner, 1988**) to 71 per cent (**Lebwohl et al., 1982**). The latter authors have been subsequently criticised for selecting patients almost exclusively with AD II PXE (**Pope, 1974**), in which marfanoid features predominate. MVP would be more frequently expected in this form of PXE where laxity of soft tissues is prevalent.

Summary

The cardiovascular manifestations of patients with PXE in this study are in accordance with previous literature reports. The predominant complications are due to premature atherosclerosis in small- to medium-sized arteries. Patients of Afrikaner stock have more vascular sequelae than individuals with PXE from non-Afrikaner origins, probably reflecting the severe nature of the disease in the former.

The relative paucity of coronary thrombosis in patients with PXE in this investigation is probably explained by the newer concept of "small coronary arteriopathy" which would, nevertheless, cause anginal symptoms and eventually lead to a cardiomyopathic state. The relative frequency of MVP in PXE is of practical significance in the management regime and it is appropriate that the complications of arrhythmia and cerebral ischaemia should be actively treated at an early stage.

SECTION IV

CHAPTER 14

OPHTHALMOLOGICAL FEATURES IN PSEUDOXANTHOMA ELASTICUM

14.1 OPHTHALMOLOGICAL LESIONS IN PXE

14.2 THE NATURAL HISTORY OF RETINAL HAEMORRHAGE IN PATIENTS WITH PXE

14.3 OTHER SYSTEMIC DISORDERS WITH ANGIOID STREAKS

CHAPTER 14

Pseudoxanthoma elasticum usually manifests with a triad of clinical signs, namely skin changes, features attributable to premature arteriosclerosis of small arteries, and progressive visual disturbance. The latter feature has already been described in 54 Afrikaner patients with PXE (Chapter 10.3), in whom the ophthalmological manifestations are particularly severe. The pathogenesis of the characteristic retinal changes was depicted and outlined in the same section. In addition, retinal haemorrhages associated with trauma were also reported in case studies of young patients.

In this chapter, the ophthalmological features in a total of 77 persons with all forms of PXE are described and the sequence of changes following a retinal haemorrhage is illustrated. Other disorders in which angioid streaks commonly occur are listed and their clinical manifestations have been briefly contrasted with the findings in PXE.

14.1 Ophthalmological Lesions in PXE

The study cohort consisted of 77 persons in whom 41 were female and 36 were male patients. Their ages ranged from 14-82 years (mean 40.1 years). The ophthalmological manifestations are listed in 2 groups in Table 14.1 so as to contrast the signs found in Afrikaner patients and those who were non-Afrikaners. Although the general features within the two groups were similar, the Afrikaner patients had more severe visual disturbances (40.7 percent versus 26 per cent were deemed legally blind) and macular degeneration occurred more frequently in the former individuals.

TABLE 14.1

OPHTHALMOLOGICAL MANIFESTATIONS IN 77 PATIENTS WITH PXE

CLINICAL MANIFESTATION	23 NON-AFRIKANER PATIENTS (%)	54 AFRIKANER PATIENTS (%)	COMBINED TOTAL (%)
Visual acuity			
7/10-10/10	14 (60.9)	18 (33.3)	32 (41.6)
2/10-6/10	3 (13.0)	14 (25.9)	17 (22.1)
1/10 or less	6 (26.0)	22 (40.7)	28 (36.4)
Angioid streaks	20 (87.0)	54 (100)	74 (96.1)
Peau d'orange fundal changes	14 (60.9)	41 (75.9)	55 (71.4)
"Salmon" spots	3 (13.0)	7 (13.0)	10 (13.0)
Macular degeneration	9 (39.1)	36 (66.7)	45 (58.4)

Despite the wide age range of the patients who were investigated, more than 96 per cent had evidence of angioid streaks. In other literature reports (Connor et al., 1961; Goodman et al., 1963; Clarkson and Altman, 1982; Neldner, 1988) the proportion of patients with angioid

streaks varied from 50-87 per cent. These authors stressed the age-related onset of this feature; in this context **Neldner (1988)** found only 30 percent of his patients under 10 years had angioid streaks. In the latter investigation, however, 100 per cent of persons with PXE in the 50-59 year age group had angioid streaks. As there was a relatively even distribution of patients from all age groups in the South African investigation, the high proportion of persons with angioid streaks compared with other studies further confirms the severity of eye involvement found principally in the Afrikaner group.

In the current study, more than 36 per cent of persons were blind according to the legal definition (visual acuity of 1/10 or less). These affected individuals were mainly aged 40 years and older, and were principally derived from the Afrikaner group (40.7 per cent versus 26 per cent for the non-Afrikaner patients). Visual deterioration was the consequence of retinal haemorrhage and subsequent macular degeneration. The ages at which Afrikaner and non-Afrikaner patients were found to have these severe complications are shown in Table 14.2.

In this study, only one individual of non-Afrikaner stock became blind prior to the fifth decade of life (9 per cent) whereas 10 Afrikaner patients were legally blind by this age (25.6 per cent). By comparison, **Neldner (1988)** found blindness in 3 of 75 persons (4 per cent) under the age of 50 years. The more frequent severe ophthalmological sequelae in South African patients are again demonstrated in these findings. This is particularly true in Afrikaner PXE individuals and, to a lesser extent, in the non-Afrikaner persons.

TABLE 14.2

RETINAL HAEMORRHAGES ACCORDING TO AGE IN 77 PATIENTS WITH PXE

Age group (years)	AFRIKANER PATIENTS (N=54)		NON-AFRIKANER PATIENTS (N=23)	
	Retinal haemorrhages (%)	Legal blindness (%)	Retinal haemorrhages (%)	Legal blindness (%)
0-9	0 (0)	0 (0)	0 (0)	0 (0)
10-19	2 (50)	0 (0)	0 (0)	0 (0)
20-29	5 (45)	0 (0)	1 (25)	0 (0)
30-39	8 (57)	4 (29)	1 (20)	0 (0)
40-49	9 (90)	6 (60)	2 (40)	1 (20)
50-59	8 (100)	6 (75)	4 (57)	3 (43)
60-69	6 (100)	4 (66)	3 (100)	2 (66)
> 70	1 (100)	1 (100)	-	-

The figures in brackets represent the percentage of patients affected.

14.2 The Natural History of Retinal Haemorrhage in Patients with PXE

The propensity for visual deterioration in Afrikaner individuals with PXE has been previously emphasised. The progression of the retinal lesions through clinically recognisable stages from a peau d'orange mottling of the fundus to the development of "Salmon spots", angioid streaks and eventual retinal haemorrhage has been illustrated and described in Chapter 10.3. As the macular area of the retina provides maximal visual acuity, haemorrhage in this region which results in sclerosis tends to eventual blindness. An understanding of the natural history following retinal haemorrhage is crucial if optimal results from argon laser therapy are to be obtained. For this reason the sequence of events in a typical patient with PXE is described and depicted below.

Case Report

A 40 year old man of Afrikaner descent with confirmed PXE complained of sudden deterioration of vision in his left eye. He consulted an ophthalmologist 48 hours later and a subretinal haemorrhage was found in the macular region of the left fundus (Figure 14.1).

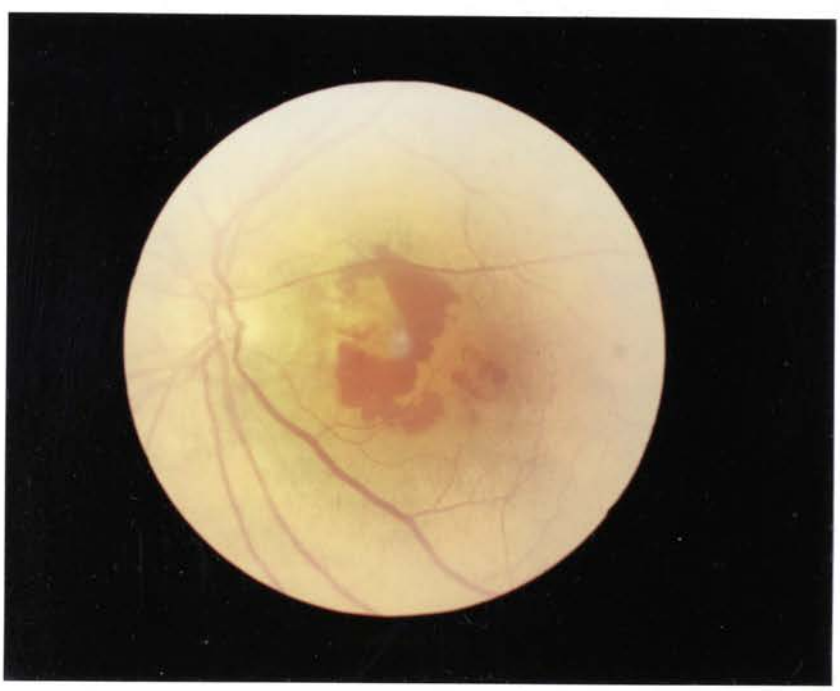


Figure 14.1 LEFT MACULAR SUBRETINAL HAEMORRHAGE

Fluorescein angiography was undertaken and demonstrated that diffuse leakage of the dye had occurred due to the presence of a neovascular membrane. The area of hypofluorescence correlated to the subretinal haemorrhage, thereby masking the underlying choroidal fluorescence (Figure 14.2).

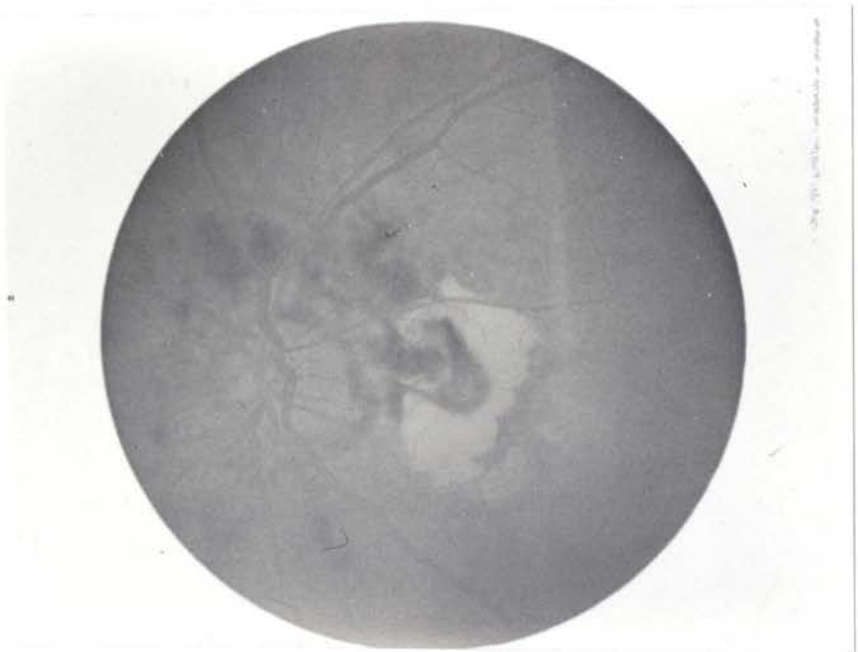


Figure 14.2 FLUORESCEIN ANGIOGRAPHY CONFIRMS LEAKAGE OF DYE DUE TO A NEOVASCULAR MEMBRANE

Six weeks following the initial event, the subretinal haemorrhage had become smaller and a greyish neovascular membrane was evident. Visual acuity at this stage had diminished to the ability to count fingers at 2 metres (Figure 14.3).



Figure 14.3 THE SUBRETINAL HAEMORRHAGE IS SMALLER 6 WEEKS AFTER THE INITIAL BLEED

Four months later, a further haemorrhage had occurred and extended to involve the whole macular area (Figure 14.4).

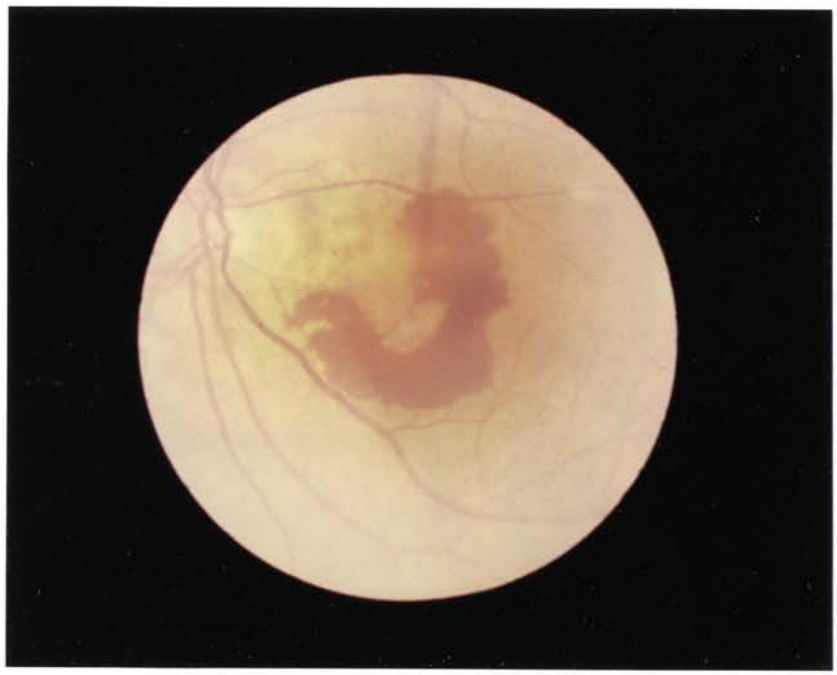


Figure 14.4: A MASSIVE MACULAR HAEMORRHAGE IS EVIDENT

Fluorescein angiography was again performed and demonstrated diffuse leakage of the dye due to a neovascular membrane. Again the area of hypofluorescence correlated to the subretinal haemorrhage which masked the underlying choroidal fluorescence (Figure 14.5).

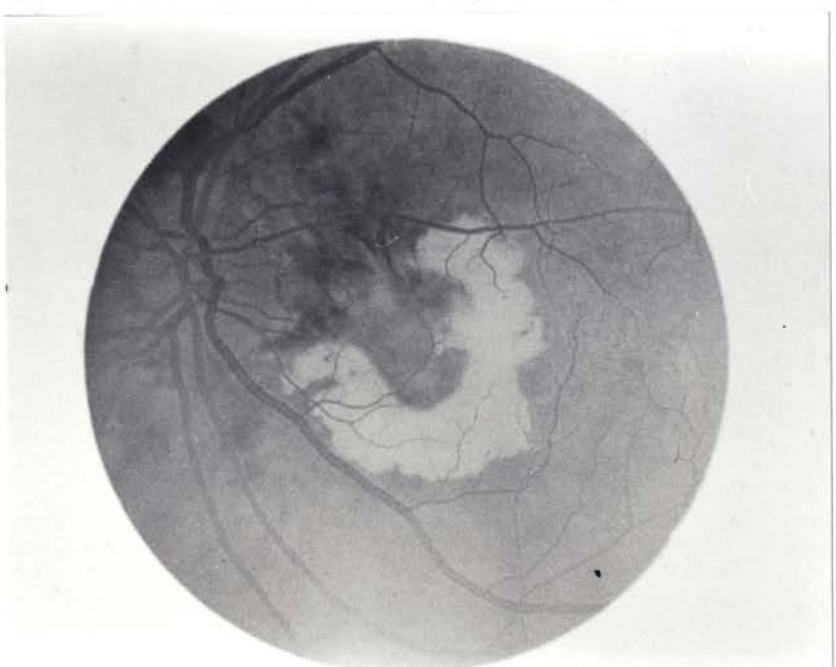


Figure 14.5: FLUORESCEIN ANGIOGRAPHY REVEALS THE EXTENT OF THE SUBRETINAL HAEMORRHAGE

Five months later, a fundal photograph of the left eye showed an old disciform scar or subretinal fibrosis. At this stage, the patient's sight was reduced to the visualisation of hand movements only at 3 metres (Figure 14,6).

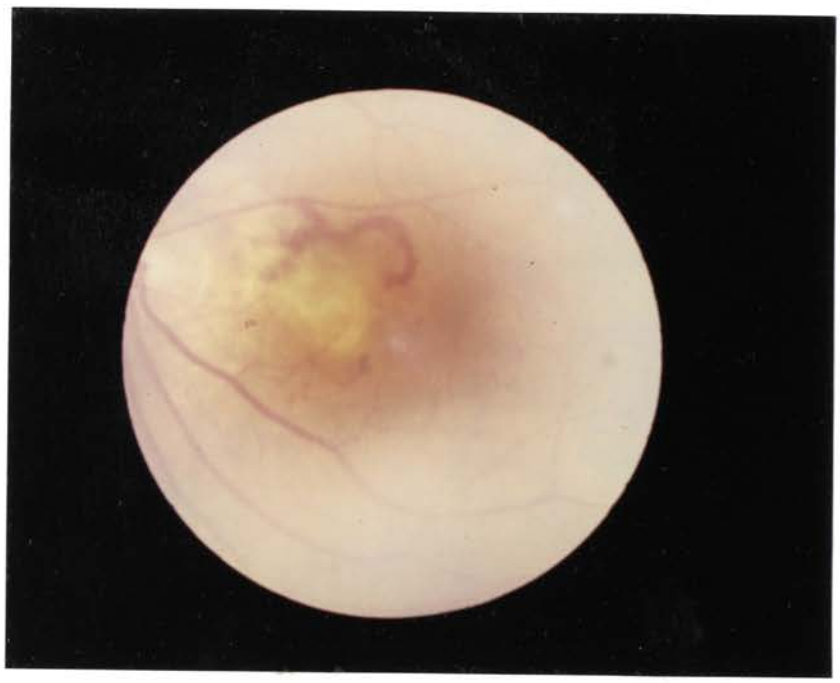


Figure 14.6: A DISCIFORM SCAR HAS FORMED FIVE MONTHS LATER

One year afterwards, a large fibriotic scar remains and the affected person was effectively blind (Figure 14.7).

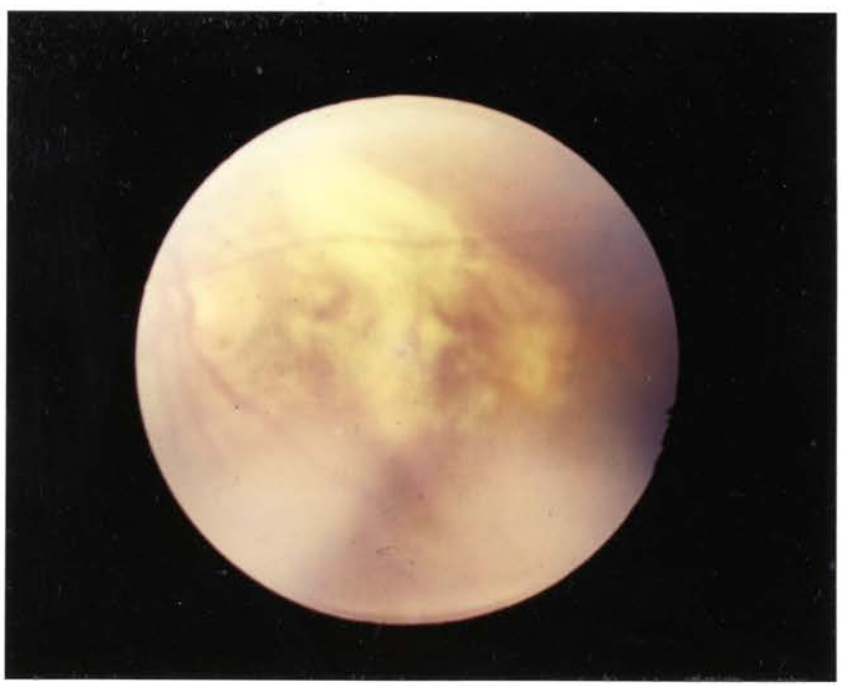


Figure 14.7: THE MACULA IS CONTRACTED BY A FIBROTIC SCAR

Comment

The frequency of retinal haemorrhage in both eyes exceeds 90 per cent in Afrikaner patients after 40 years of age (see Table 14.2) and is associated with blindness in more than 50 per cent of individuals due to the predilection for occurrence in the macular region. Although less common in non-Afrikaner individuals with PXE, blindness also occurs following bilateral retinal haemorrhage.

In some individuals, the use of xenon photocoagulation or argon laser therapy for the treatment of neovascular membrane formation appears to have beneficial effect. Conversely, prophylactic photocoagulation of the angioid streaks may make the situation worse **(Clarkson & Altman, 1982)** The treatment of the ophthalmological complications of PXE is more fully dealt with in Section VI.

14.3 Other Systemic Disorders With Angioid Streaks

Angioid streaks are frequently found in patients with PXE but have also been reported in many other conditions (see Table 14.3). Apart from PXE, the most commonly associated disorders are Paget's disease of bone and the sickle cell haemoglobinopathies.

TABLE 14.3

SYSTEMIC CONDITIONS WITH ANGIOID STREAKS

Acromegaly
Ehlers-Danlos syndrome
Diabetes mellitis
Haemochromatosis
Acquired haemolytic anaemia
Hypercalcinosis
Hyperphosphatasia
Lead poisoning
Neurofibromatosis type I
Paget's disease
Senile elastosis
Sickle cell haemoglobinopathies
Sturge-Weber syndrome
Tuberous Sclerosis

(Clarkson & Altman, 1982)

Paget's disease of bone, in which progressive bony deformity develops and in which serum alkaline phosphatase is elevated, is usually easily distinguishable from PXE. However, calcification of small- and medium-sized arteries is common to both disorders. Angioid streaks usually appear after 60 years of age in about 8-15 per cent of patients **(Terry, 1934; Scholz, 1941; Clarkson and Altman, 1982).** The progression to retinal haemorrhage and retinal sclerosis occurs in a minority of individuals.

Retinopathy in sickle cell disease has been recognised since 1959 **(Lieb et al.)** and is said to occur in 1-2 per cent of affected individuals **(Clarkson and Altman, 1982).** The incidence of angioid streaks increases

with age and they are seldom apparent before 25 years. Complications of haemorrhage and retinal detachment seldom occur.

Comment

Angioid streaks are rarely seen in individuals without evidence of systemic disease, but do occasionally occur in persons with senile elastosis (Clarkson and Altman, 1982). The frequency of angioid streaks in patients with PXE exceeds 85 per cent, but this finding is age related. Although not pathognomonic, the majority of patients with angioid streaks will have PXE. Other much less-likely diagnoses are Paget's disease and sickle cell haemoglobinopathy.

SECTION IV

CHAPTER 15

GYNAECOLOGICAL FINDINGS IN WOMEN WITH PXE

15.1 GYNAECOLOGICAL INVESTIGATIONS

15.2 DISCUSSION

CHAPTER 15

GYNAECOLOGICAL FINDINGS IN WOMEN WITH PXE

Several large scale investigations in persons with PXE have been undertaken in the past three decades **(Connor et al., 1961; Pope, 1974; Neldner, 1988).** Despite frequent reports of haemorrhagic gastrointestinal and central nervous system complications, only isolated case reports on the gynaecological sequelae have been documented **(Giesen, 1936; Touraine, 1940).**

To gain a perspective as to the gynaecological implications in PXE, a retrospective, interview-based study was undertaken in 52 affected women. These findings, together with the obstetric aspects of 54 pregnancies, formed the basis of a publication in the obstetric literature **(Viljoen et al., 1987) (Appendix: Publication 3).**

15.1 Gynaecological Investigations

At the initial visit each female patient with PXE was interviewed using a standardised protocol regarding the gynaecological history. **(APPENDIX: Protocol No 2).** The individual's age at menarche and menopause were documented as well as details of her menstrual history. Any episodes of abnormal vaginal bleeding were recorded as were symptoms such as dysmenorrhoea or menorrhagia. The previous methods of contraception were noted in each woman together with details of any adverse sequelae associated with their use. All previous gynaecological operative procedures were recorded.

Retrospective data were deemed sufficiently complete and reliable in 27 of the 52 women for further analysis.

Findings

The women with PXE were grouped according to the classification system devised by **Pope (1975).** In the total cohort, most individuals were Caucasian (23) while 2 each were from the Black and Mixed Ancestry population groups. At the time of the study, their ages ranged from 14 to 71 years. Their menstrual histories are summarised in Table 15.1.

The number of patients with PXE in each group were too small for meaningful statistical analysis and for these reasons their data is considered together. The mean age at menarche was 13.4 years (range 11.3-15.4 years) and that of 7 individuals at menopause averaged 48 years (range 46-51 years). The mean duration of the menstrual cycle was 28.6 days (range 12-32 days) with menstrual bleeding lasting, on average, 4.6 days (range 2-11 days).

TABLE 15.1

MENSTRUAL HISTORY OF 27 PATIENTS WITH PXE

	AR 1	AR II	"AFRIKANER" FORM	AVERAGE
PATIENT NUMBERS	5	2	20	Total = 27
AVERAGE AGE AT MENARCHE (Yrs)	14.4	12.5	13.2	13.4
MENSTRUAL CYCLE (RANGE)	29.6 (28-32)	28 (28)	28.4 (12-32)	28.6 (12-32)
DURATION (RANGE IN DAYS)	4.6 (3-6)	7 (6-8)	4.4 (2-11)	4.6 (2-11)
AGE (YRS) AT MENOPAUSE RANGE	49 (49)	46 (46)	48.2 (47.1-51)	48 (46-51)
NUMBER OF MENOPAUSAL WOMEN	1	1	5	7

On direct questioning 7 women experienced menorrhagia regularly at the time of menstruation while 11 complained of dysmenorrhoea (Table 15.2).

TABLE 15.2
GYNAECOLOGICAL SYMPTOMS IN 27 WOMEN

SYMPTOMS	AR I (5)	AR II (2)	"AFRIKANER" FORM (20)	TOTAL (27)
MENORRHAGIA	1	1	5	7 (25.9%)
INTERMENSTRUAL BLEEDING	2	1	14	17 (63.6%)
DYSMENORRHOEA	2	0	9	11 (40.7%)

More than one half of the 27 patients were receiving oral contraceptives at the time of the study and the majority claimed to have used this form of contraceptive for a period exceeding 6 months (Table 15.3).

TABLE 15.3

THE METHODS OF CONTRACEPTION EMPLOYED BY 27 WOMEN

METHOD OF CONTRACEPTION	AR I (5)	AR II (2)	"AFRIKANER" FORM (20)	TOTAL (27)
ORAL CONTRACEPTIVES	4	1	11	16
INTRAUTERINE DEVICE	0	1	8	9
TUBAL LIGATION	3	1	7	11

Nine women had had an intrauterine device fitted and 11 eventually opted for tubal ligation. No complications from the use of oral contraceptives were recorded apart from the previously reported problem of intermenstrual bleeding.

Very few of the women investigated had required operative gynaecological procedures (Table 15.4).

TABLE 15.4

OPERATIVE GYNAECOLOGICAL PROCEDURES UNDERTAKEN IN 27 WOMEN WITH PXE

OPERATIVE PROCEDURES	AR I (5)	AR II (2)	"AFRIKANER" FORM (20)	TOTAL (27)
SALPINGECTOMY & OOPHORECTOMY	1	0	3	4
HYSTERECTOMY	1	0	3	4
REPAIR OF PROLAPSE	0	0	4	4

A total hysterectomy had been undertaken in 4 women. In two patients the procedure was ostensibly for dysfunctional uterine bleeding associated with a fibroid uterus. In a further individual, the preceding factors were persistent lower abdominal pain associated with chronic salpingitis, vaginal discharge and uterine fibroids. In the fourth woman the procedure was advised for ovarian carcinoma. In the latter instance post operative radiotherapy had been instituted and she has remained well and disease-free five years later.

Four other individuals with PXE had undergone salpingectomy and oophorectomy for ovarian cysts and chronic tubal sepsis. Surgical repair of a cystocoele (3 persons) and rectocoele (1 individual) were required when bladder or rectal prolapse developed in the fourth and fifth decades of life causing urinary incontinence. In every instance the operations, anaesthetic procedures and post-operative course were uneventful.

15.2 Discussion

As elastin is a component of most tissues, many body organs may be pathologically affected in patients with PXE. Previous investigators have reported a propensity for epistaxis, gastrointestinal haemorrhage (Carlborg 1944, Loria et al., 1957, Goodman et al., 1963, McKusick 1972), ovarian haemorrhage (Giesen, 1936) and uterine haemorrhage (Touraine, 1940). Surprisingly only isolated reports of gynaecological complications have appeared in the literature and no previous evaluation of a large cohort of women have been undertaken.

The gynaecological histories of the patients are unremarkable in that the average ages of menarche and menopause occurred at the appropriate time, menstruation was normal and there was no apparent increase in episodes of menorrhagia. However, wide ranges for each of these parameters were recorded so that although a minority of patients did display an increased propensity of bleeding, they escaped detection in the data analysis.

Intermenstrual bleeding was a feature in 63% of patients. Despite these findings no instances of exceptional bleeding were identified, and it seems likely that haemorrhagic complications, previously reported in the literature in patients with PXE, were isolated events (Giesen, 1936; Touraine, 1940).

A feature of concern in women with PXE was the frequent use of oral contraceptives. The risk of thromboembolic episodes is known to increase amongst individuals using high-dose oestrogen oral contraceptives and, in a disorder such as PXE where stroke and hypertension are more frequent, the likelihood of a vascular accident is likely to be increased even if low-dose oestrogen compounds are used.

Although no complications of this type were encountered, it would seem reasonable for other means of contraception to be advocated for women with PXE.

Four women in this series required surgical repair of a rectocoele and cystocoele. The development of redundant skin folds due to loss of elasticity in PXE would suggest that other structures, such as pelvic ligaments, may also become lax particularly in multiparous women. This may account for a tendency to prolapse the bladder, rectum or uterus in affected females.

Comment

Although PXE is a heterogeneous disorder, separate analysis of patients in the investigation is impossible due to the small numbers within each group.

Major gynaecological complications, apart from an apparent slight propensity for vaginal bleeding, were not prevalent in the 27 women with PXE analysed in this investigation. However, evidence of pelvic ligamentous redundancy was documented in 4, suggesting that abiotrophy of elastin fibres does occur in women with PXE, particularly following recurrent pregnancies. **McKusick (1972)** is a proponent of the hypothesis that elastin fibres degenerate through a process of abiotrophy in PXE. In support of this concept, one of the patients with vesicovaginal prolapse in this investigation had completed 4 pregnancies.

It has been advocated that women receiving oestrogenic compounds in any form should be carefully evaluated for embolic sequelae. In view of the additional risks of the latter complication in women with PXE,

methods of contraception other than oral contraceptives would seem appropriate.

SECTION IV

CHAPTER 16

OBSTETRIC IMPLICATIONS OF PSEUDOXANTHOMA ELASTICUM

16.1 OBSTETRIC INVESTIGATION AND FINDINGS

16.2 DISCUSSION

CHAPTER 16

OBSTETRIC IMPLICATIONS OF PSEUDOXANTHOMA ELASTICUM

The potential problems for both mother and fetus during pregnancy in patients with PXE are many. Hypertension, intrauterine growth retardation, thromboembolic phenomena and gastrointestinal haemorrhage are some previously reported complications. **(Eddy & Farber, 1962; Goodman et al., 1963; McKusick, 1972).** Nevertheless, in an extensive literature search, only 28 pregnancies in 10 women with PXE could be identified. **(Berde et al., 1983; Lao et al., 1984; Elejalde et al., 1984).** In 1987, the author published his findings in 54 pregnancies in 20 women with PXE **(Viljoen et al., 1987) (Appendix: Publication 3).** In order to elucidate these aspects further, the medical aspects of 64 pregnancies in 22 affected women are now reviewed.

16.1 Obstetric Investigation and Findings

A standardised obstetric history was obtained from each patient at the initial interview. **(APPENDIX: Protocol No.2).** Questions regarding parity, previous miscarriages, illnesses and drugs in pregnancy were posed. In addition information concerning maternal hypertension, mode of delivery, duration of labour, maternal complications and fetal outcome was collected. Where possible, details were corroborated by the attending obstetrician or from hospital records.

A total of 64 pregnancies were recorded in the 22 women studied. The affected individuals were classified according to PXE type in the standard manner (Chapter 4). None of the patients were from autosomal dominant kindreds. Due to the small subgroup numbers, the patients have generally been assessed together. Only where obvious differences between PXE types were present have separate data analyses been performed.

TABLE 16.1

FETAL OUTCOME OF 64 PREGNANCIES IN WOMEN WITH PXE

	AR I (N=4)	AR II (N=2)	"AFRIKANER" FORM (N=16)	TOTAL (N=22)
Live Births	6	10	32	48
Abortions	5	2	9	16
No. of Pregnancies	11	12	41	64

In the 64 pregnancies, there were 48 live births and 12 first trimester spontaneous abortions. One woman with cervical incompetence had 2

miscarriages in the second trimester. Her subsequent pregnancies were managed successfully with a Shirodkar suture. Two terminations of pregnancy were performed at 8 weeks gestation for psychiatric reasons in one patient. Data relating to all the abortions is summarised in Table 16.2. It would appear that the women with AR I form of PXE had a higher risk which was significantly increased compared with the other two groups.

TABLE 16.2

DATA RELATING TO 16 ABORTIONS IN WOMEN WITH PXE.

PXE TYPE	NO. OF PREGNANCIES	ABORTIONS	GESTATION	% FETAL LOSS
Autosomal Recessive I	11	5	2 x 6 weeks 2 x 8 weeks 1 x 14 weeks	45,5%
Autosomal Recessive II	12	2	2 x 6 weeks	16.7%
Afrikaner Form	41	9	1 x 6 weeks 5 x 8 weeks 2 x 12 weeks 1 x 14 weeks	23.1%

Hypertension, which occurred during 9 pregnancies, was treated with bed rest in 5 individuals and with antihypertensive and diuretic therapy in the other 4 patients (Table 16.3). No instances of antepartum haemorrhage or diabetes mellitus were recorded in any patients.

TABLE 16.3

MATERNAL COMPLICATIONS IN 64 PREGNANCIES

	AR I	AR II	AFRIKANER	TOTAL
No. of patients	4	2	16	22
No. with Hypertension	2	0	7	9

Routine antenatal ultrasound studies in 12 pregnancies detected no congenital fetal abnormalities. Evidence for intrauterine growth retardation was found in 2 fetuses whose mothers were hypertensive. Their birth weights were 2.36kg and 2.18kg respectively. Both were gestationally scored at 39 weeks using the Dubowitz criteria (1970). The ultimate outcome for these babies was good.

A detailed history of labour was available for 47 pregnancies. Duration for the first stage of labour varied between 3-12 hours (mean 7.3 hours) and the length of the third stage of labour averaged 30 minutes for all mothers (Table 16.4). Forty-two babies were delivered vaginally while the remaining 5 were delivered by caesarian section. Surgical intervention was deemed necessary in 2 of these mothers for cephalopelvic disproportion and in one instance of fetal distress. Two patients with failure to progress in labour also underwent caesarian section.

TABLE 16.4

DURATION OF LABOUR IN 47 PREGNANCIES

	AR I	AR II	AFRIKANER
No. of pregnancies	5	8	34
Length of 1st Stage (Hours)	3	12	12.3
Length of 3rd Stage (Minutes)	30	30	30

The mean birth weight of the live born infants was 3.16kg (range 1.37 - 3.92kg). Three babies were born pre-term at estimated gestational ages of 32-34 weeks. No complications were associated with prematurity in these infants apart from mild respiratory distress in one individual. As mentioned previously, 2 babies were small for gestational age, but there were no adverse sequelae.

Data were available concerning 3 placentas; apart from a slightly excessive degree of calcification in two and a mildly elevated placental-fetal mass ratio of 1:8 (Normal 1:5 - 1:7), no macroscopic or histological abnormalities were detected.

Postpartum haemorrhage or sepsis were not features of any delivery. One baby died at 4 days of age from a complex cyanotic cardiac malformation. All the remaining live born babies, many of whom are already adults, have thrived.

There was no deterioration in the general health of the 22 women and specifically no ophthalmological or gastrointestinal symptoms were reported during pregnancy.

Striae and the peau d'orange mottling of the skin typical of PXE became more prominent late in the gestational period, particularly in women who gained weight excessively and in some multiparas. The skin lesions did not regress after delivery and several women complained of persistence of an abdominal "apron" of lax skin. Cosmetic surgery was performed with good results in one such person (See Chapter 20, Figure 20.8). The appearance and severity of other flexural skin lesions remained constant.

16.2 Discussion

Little has been published regarding pregnancy in women with PXE. In a review of the literature, **Berde et al. (1983)** documented a total of 24 pregnancies in 7 women. Gastrointestinal haemorrhage was a prominent feature which was reported in 8 of 20 pregnancies in 5 women. **Berde et al., (1983)** also described in detail a further uneventful pregnancy in a 28-year-old woman. **Lao et al. (1984)** briefly outlined the case histories of 2 pregnant women with PXE, one of whom had mild hypertension and **Elejalde et al. (1984)** described in detail a pregnancy with special emphasis on the ultrasonographic findings. Other authors have alluded to obstetric complications in patients with PXE **(Altman et al., 1974; Hall, 1981)** but the data presented have been insufficient for analysis. Prior to this study, a total of only 28 pregnancies in women with PXE have been documented. These reports are probably biased in that mainly abnormal confinements would have been described. For this reason, the author published his findings regarding 54 pregnancies in 20 women with proven PXE **(Viljoen et al., 1987).** Subsequently, a further two detailed obstetric histories became available.

The rate of spontaneous abortion in patients with PXE (25%) is slightly higher than the rate in the general population **(Gustaavi, 1984).** The two second trimester miscarriages in a woman with cervical incompetence may reflect a previously undescribed manifestation of PXE. Both miscarriages had been preceded by a normal vaginal delivery and it could be speculated that the incompetent cervix was the result of abnormal elastic fibres. However, there have been no other similar reports in the literature to support this suggestion.

The patients in this investigation had surprisingly normal pregnancies. Hypertension occurred in 7, but the level and control of blood pressure

improved with duration of the pregnancy, suggesting that the increasing low resistance vascular bed provided by the placenta may have helped in lowering blood pressure. Despite the fact that the small and medium-sized blood vessels are involved in PXE, no adverse cardiovascular events related to PXE were recorded during any of the pregnancies.

Labour and delivery were unremarkable in the 22 women except that there were 3 preterm births and 2 babies which were small for gestational age. This rate of premature delivery is within the normal range. Two of the 3 placentas examined showed mildly excessive calcification for which no reason was apparent.

An important finding was that only one of the 48 live babies had a congenital malformation (a severe cardiac anomaly) which led to death at 4 days of age (rate of 2%). As the rate of congenital abnormalities in the general population is considered to be 1-2 per cent, it appears from these data that maternal PXE does not increase the risk of congenital malformations.

During pregnancy, no progression occurred in the ophthalmic and cardiovascular features attributable to PXE. In multiparous women, abdominal striae and marked skin laxity developed, the severity of which correlated with the number of pregnancies and excessive weight gain during pregnancy. The flexural skin lesions were unaffected during this period.

Comment

From the accumulated data, two adverse factors regarding pregnancy in women with PXE have emerged. Firstly, there is a moderately increased risk of first trimester miscarriage in women with PXE. Secondly, most affected women claimed a deterioration in the cosmetic appearance of the abdominal skin during pregnancy.

A potentially severe complication, that of gastointestinal haemorrhage due to abnormal blood vessels, was not encountered in this investigation. It can be concluded, therefore, that despite many possible maternal and fetal hazards, most pregnancies in females with PXE have a normal course and outcome.

SECTION IV

CHAPTER 17

RADIOLOGY AND MAGNETIC RESONANCE IMAGING IN PATIENTS WITH PXE

17.1 CONVENTIONAL RADIOGRAPHIC EVALUATION

17.1.1 Radiological findings; soft tissue calcification

17.1.2 Radiological findings; musculoskeletal system

17.1.3 Comment on the conventional radiological findings

17.2 ARTERIOGRAPHY

17.3 COMPUTERISED AXIAL TOMOGRAPHY

17.4 MAGNETIC RESONANCE IMAGING

CHAPTER 17

Pseudoxanthoma elasticum is a disorder with protean clinical manifestations in which calcification of elastin-containing tissues frequently occurs. This factor makes the disorder readily amenable to investigation by a variety of radiological techniques.

In this chapter, descriptions of the findings in 24 individuals with PXE who underwent limited radiological skeletal survey are detailed. In addition, arteriographic findings in a further 2 affected persons are reported together with the changes seen in 10 individuals in whom computerised axial tomography (CT) of the skull was performed. Finally, the characteristics of magnetic resonance imaging (MRI) in 3 persons with PXE are detailed. In each instance, informed consent was obtained prior to undertaking the radiographic and MRI procedures.

17.1 Conventional Radiographic Evaluation

A limited skeletal survey was performed in 24 patients with PXE in order to evaluate the radiological changes associated with the disorder. There were 16 women and 8 men in the study whose ages ranged from 27-62 years. The following radiographic views were obtained:

1) Skull (both anterior-posterior (AP) and lateral views)
2) Chest (AP and lateral)
3) Pelvis including both hip joints (AP only)
4) Thoraco-lumbar spine (lateral only)
5) Both hands and feet (AP only)
6) Elbow including lower humerus (AP only)
7) Knee including lower femur (AP only).

17.1.1 Radiological findings; soft tissue calcification

Calcification was seen in the aorta and peripheral vessels, skin, ligmentous structures, falx cerebri and in the lungs of several patients. The degree of calcification was dependent on the severity of systemic involvement with PXE and age of the patient.

Arterial Calcification

Calcification of the lower aorta was a common feature (see Figure 13.2) and age related. It occurred in 17 individuals in this investigation but was not responsible for major occlusive symptoms in affected persons. Specifically, no vascular surgery or embolectomy procedure of the aorta was required in any person and there appeared to be no sex-related differences in occurrence or severity.

Other blood vessels which frequently exhibited calcification were the femoral artery (6 of 24 patients) (See Figure 17.1), radial artery (2

persons), aortic arch (4 individuals), and internal carotid artery (2 persons).

In this context, an unusual situation arose in a 2 year old male who was admitted to hospital with septicaemia. During the illness, he developed swelling and tenderness of his forearms and radiographs of the radius and ulna were taken to exclude osteomyelitis. Calcification of the radial and ulna arteries was demonstrated; this disappeared within 4 weeks of resolution of his illness. He later developed typical dermatological and vascular signs of PXE. The occurrence of calcification in this infant is unexplained but presumably related to PXE.



Figure 17.1 CALCIFICATION OF THE RIGHT FEMORAL ARTERY IN A FEMALE WITH PXE AGED 42 YEARS

Skin calcification

Four severely affected female patients with PXE who formed part of this survey were coincidentally found to have evidence of calcinosis cutis. An irregular calcified border was demonstrated in the breast outline of one woman on a routine chest radiograph (Figure 17.2). The other 3 patients were less markedly affected; minor skin calcification was evident in the axillae (2 persons) and cervical skin (1 individual).

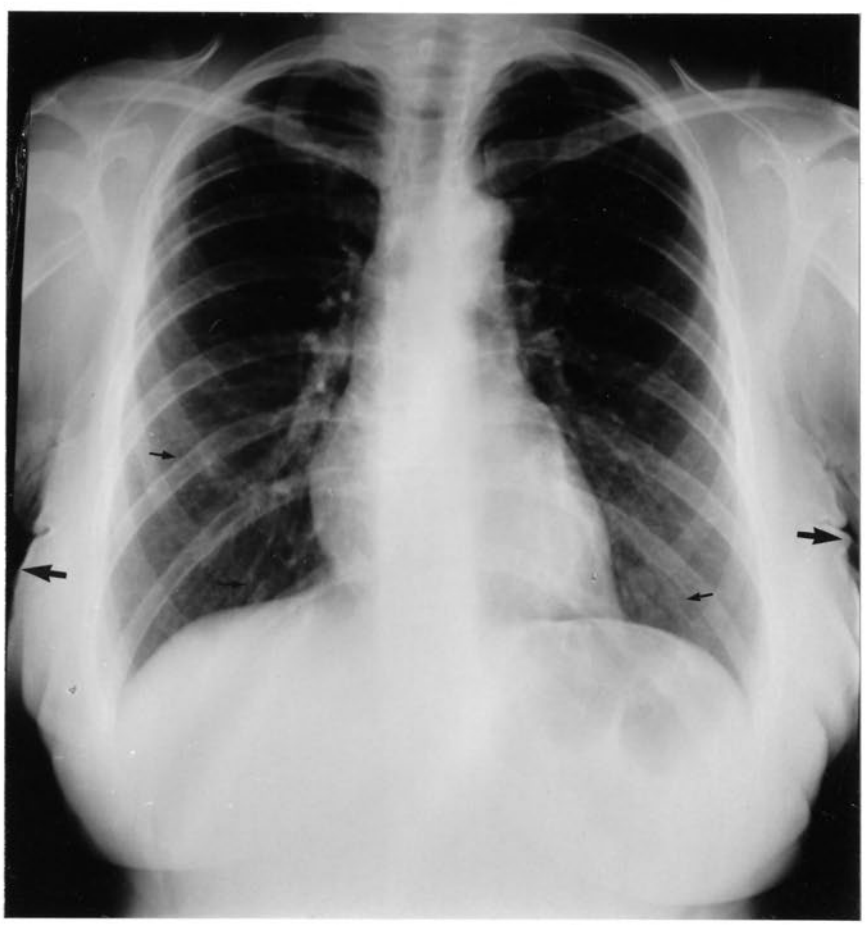


Figure 17.2 CALCINOSIS CUTIS OF THE BREASTS IS EVIDENT IN THE CHEST RADIOGRAPH OF A WOMAN AGED 38 YEARS WITH PXE (LARGE ARROWS). RETICULAR LUNG OPACITIES ARE ALSO APPARENT (SMALL ARROWS).

Intracranial calcification

Calcification of structures within the cranium was seen in several patients after the age of 45 years. The most common of these was mineralisation in the falx cerebri in 5 persons (Figure 17.3).

In 2 persons, there was evidence of calcification of the petroclinoid ligaments (Figure 17.4) and thickening of the base of the skull. A further affected person demonstrated calcification of the pineal gland (Figure 17.5).



Figure 17.3 CALCIFICATION OF THE FALX CEREBRI



Figure 17.4 CALCIFICATION OF THE PETROCLINOID LIGAMENTS IN A PATIENT WITH PXE



Figure 17.5 CALCIFICATION OF THE PINEAL GLAND IN AN INDIVIDUAL WITH PXE

17.1.2 Radiological findings; musculoskeletal System

Minor anomalies were frequently visualised in the skeletal structures of patients with PXE. Transverse "growth-lines" were present in the femoral and tibial metaphyses of 6 patients. They are probably the consequence of intercurrent afflictions in the growth period of long bones, and unrelated to PXE.

Resorption of the tufts of the terminal phalanges were evident in 8 PXE patients, most of whom were over 50 years of age (Figure 17.6). Occlusive changes to small arteries and subsequent ischaemia are probably responsible for the resorption. The only other significant abnormality in the musculoskeletal system was juxta-articular calcification which was noted in 3 individuals around the hip, elbow and knee joints, respectively.

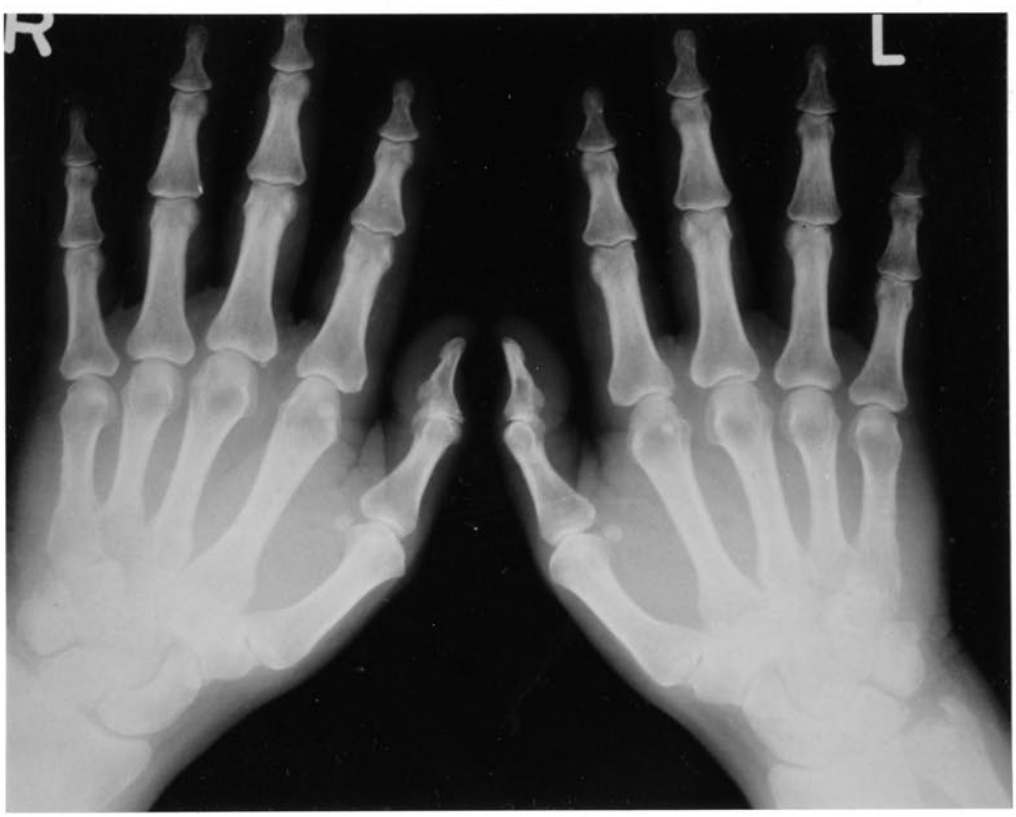


Figure 17.6 RESORPTION OF THE TUFTS OF THE TERMINAL PHALANGES IN A PATIENT WITH PXE

17.1.3 Comment on conventional radiographic findings

The radiological changes in PXE are numerous but usually incidental findings. Few reviews on the subject are available but the best and most concise is that of **Prick and Thijsson (1977).** These authors found calcification in one or more of the larger arteries occurred in 14 per cent of all patients with PXE. Other investigators had previously reported similar findings **(Goodman et al., 1963; Everette et al., 1969).** In addition, calcinosis cutis was demonstrated by several authors in well established cases of PXE; techniques of xeroradiography and mammography using a low-dose film system were employed for this purpose **(Goodman et al., 1963; Everette et al., 1969; Prick and Thijssen, 1977).** The latter procedures were not used in any of the patients in this investigation.

Calcification of the falx cerebri, pineal gland and petroclinoid ligaments, and thickening of the base of the skull has been previously reported in individuals with PXE **(Messis and Buzilovich, 1970; Prick and Thijssen, 1977).** This finding probably reflects the high elastin content of these structures and their subsequent degeneration and mineralisation in persons with PXE. In addition, juxta-articular calcification in patients with PXE is said to be commonplace **(Everette et al., 1969),** although seen in a minority of patients in this investigation.

Reticular opacities in the lungs was found in one individual in this series and a similar finding in 3 patients described in the literature has been attributed to haemosiderosis following multiple small haemorrhages **(Wolff et al., 1952; Mamtora and Cope, 1981).**

The radiological changes found in individuals with PXE reflect the multisystem nature of the disorder. Although many of these findings do not have immediate clinical relevance, the extent of calcification is an indication of the severity of the condition in an affected person.

17.2 Arteriography

It has long been known that the peripheral arteries are involved in the pathological process underlying PXE. Angiography has been performed on many affected individuals and reported in the literature **(Carlborg, 1944; Goodman et al., 1963; McKusick, 1972; Mendelsohn et al., 1975; and others).** Narrowing and, occasionally, occlusion of peripheral vessels are the most frequently demonstrable lesions.

During the current study, two women with the Afrikaner form of PXE were investigated by means of femoral and brachial arteriography. (Some of the angiographic findings were previously addressed in Section 13.2.) The two females who underwent investigation had symptoms of occlusive vascular disease in that they complained of easy fatiguability, intermittent claudication and had demonstrable diminution of their peripheral arterial pulses. Conventional retrograde femoral and brachial angiography was performed (See Figure 17.7) and demonstrated luminal narrowing of the peripheral arteries in one individual and complete occlusion of the radial artery (Figure 13.1) in the other. Good collateral circulation was evident proximal to the occluded vessels in each instance. No vertebral or carotid angiograms were undertaken.

Comment on the Arteriographic Findings

The angiographic changes in patients with PXE are age related. **Bafverstedt and Lund (1955)** found no abnormality in the brachial arteriogram of a 9 year old affected child. However, after this age narrowing of blood vessels has been demonstrated by this means **(Prick and Thijssen, 1977). Carlborg** and co-investigators **(1959)** found arterial narrowing in the forearm of 25 per cent of patients studied. Similar findings were reported by **Goodman et al. (1963)** who found abnormalities in the upper extremities in 6 of 12 individuals and in the lower limbs of

3 of 6 patients investigated. Good collateral circulation was reported in most cases of complete obstruction which suggests that vascular changes in PXE are chronic in nature and slowly progressive, allowing ample time for compensatory vessels to develop. Only one person of 86 studied in the current investigation developed severe ischaemic changes (Chapter 10.5). The low incidence of this complication may be due to the development of a good collateral circulation in most instances.

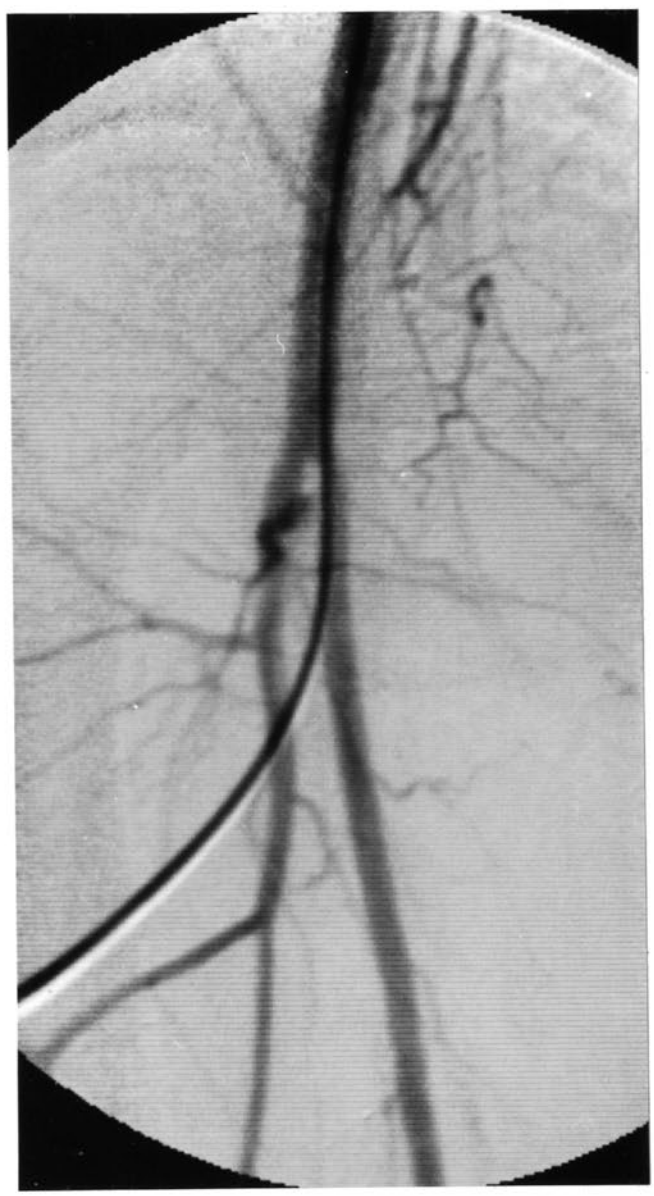


Figure 17.7 ANGIOGRAPHY OF THE RIGHT FEMORAL ARTERY IN A WOMAN AGED 46 YEARS WITH PXE. THE EXCELLENT COLLATERAL CIRCULATION IS EVIDENT

Intracranial aneurysms have been reported relatively commonly in individuals with PXE **(Dixon, 1951; McKusick, 1972; Goto, 1975)**, and include berry and carotid artery aneurysms **(Scheie and Hogan, 1957)**. Unilateral carotid artery-cavernous sinus fistula has also been documented **(Koo and Newton, 1972; Rios-Montenegro, 1972)**. It is a matter of concern that subarachnoid and intracerebral haemorrhages may result from these lesions **(Sharma et al., 1974; Iqbal et al., 1978)**. One 55 year old woman in the current study developed a dense hemiplegia following an intracerebral bleed (See Chapter 10.6); the rarity of this complication is surprising considering the high incidence of hypertension and peripheral vascular disease in patients with PXE.

Angiographic studies may be helpful in PXE patients where renal artery stenosis has occurred. **Dymock (1979)** described a child with hypertension in whom unilateral calyceal dilatation was demonstrated on intravenous pyelography. Renin output was significantly different between the kidneys. Left nephrectomy was performed and histological evidence of calcification of the renal arteries was obtained. Other reports of hypertension and renal artery calcification have been published **(McKusick, 1972)** and hypertension due to a congenital angiomatous lesion has been described **(Farreris-Valenti et al., 1965)**.

Coronary artery calcification and obstruction has been documented in patients with PXE **(Nellen and Jacobson, 1958; Eddy and Farber, 1962; Goodman et al., 1963; Mendelsohn et al., 1978; Neldner, 1988)**. Selective coronary arteriography was first undertaken on a girl aged 18 years with PXE who had significant triple-vessel disease **(Bok, 1975)**. This procedure is now performed routinely in patients with angina in PXE to enable grafting operations to be undertaken timeously.

Angiographic studies are seldom helpful in the investigation of abnormalities in the abdominal blood vessels of patients with PXE as the microaneurysms in the gastric mucosa are not well demonstrated by these means **(Kaplan and Hartman, 1954; Woo and Chandler, 1958).** It is noteworthy that gastrointestinal haemorrhage occurred in only one individual in this investigation. Bleeding in this instance was due to oesophageal varices on the basis of cirrhosis and probably unrelated to PXE (Chapter 13.1). In the context of abnormalities of the abdominal vasculature, angiomatous malformations of the hepatic and splenic arteries **(Prick and Thijssen, 1977)** and tortuosity of the superior mesenteric artery **(Bardsley and Koehler, 1969)** are infrequently reported in PXE. No examples of these anomalies were encountered in patients in this investigation.

In general, there is limited place for routine angiographic studies in the management of patients with PXE. Nevertheless, in selected individuals with angina, suspected intracranial aneurysm or hypertension attributable to unilateral renovascular disease, angiographic studies may allow early, life-saving vascular surgery or nephrectomy to be performed.

17.3 Computerised Axial Tomography

As part of the radiological appraisal of 10 patients with PXE, computerised axial tomography was performed in order to ascertain whether minor central nervous system changes were present. None of the individuals investigated had clinically apparent neurological deficits. Seven of the patients were female and the ages of the cohort ranged from 27-62 years. Contrast material was injected intravenously to enhance the quality of the image obtained.

There were no abnormal scans although several minor changes were demonstrated. Calcification of the falx cerebri and/or pineal gland was apparent in 7 persons (Figure 17.8).

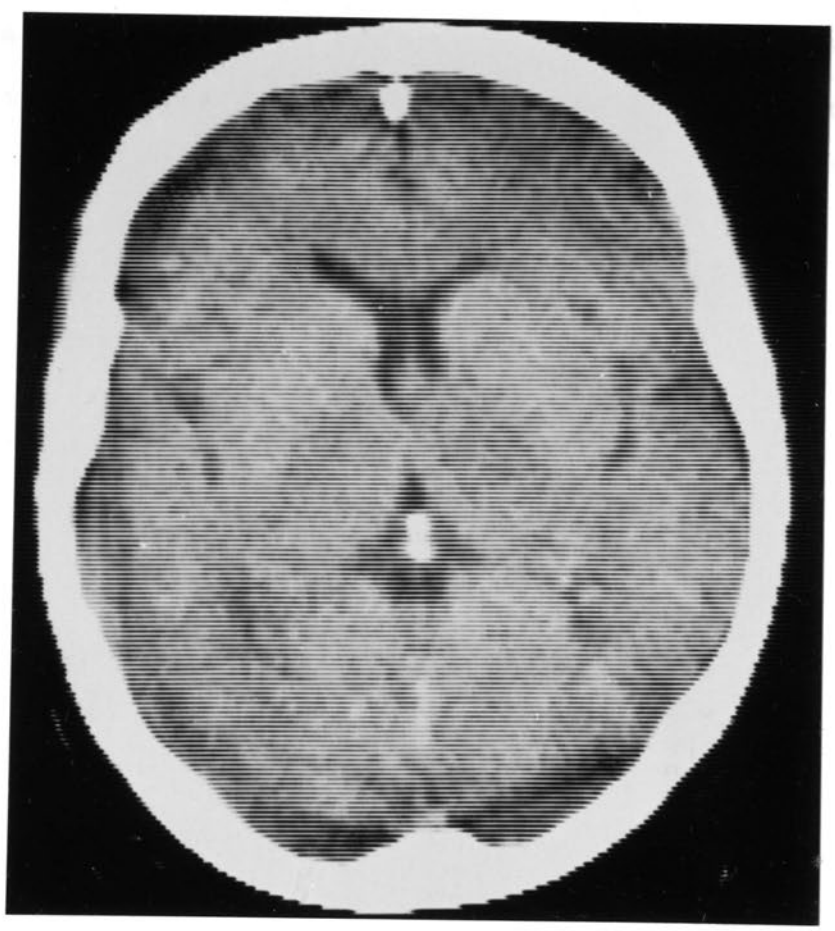


Figure 17.8 CT SCAN: CALCIFICATION OF THE FALX CEREBRI AND PINEAL GLAND IS EVIDENT

In one 60 year old woman, there was a 10mm poorly defined high attenuation area visible in the left lower parietal region. This area became more readily recognizable after contrast administration and had the characteristics of a granuloma which was probably unrelated to PXE. In 3 other persons, widening of the sulci indicative of mild cerebral atrophy was present. The latter findings seemed appropriate for the patients' ages.

Comment

This is the first report of cranial tomographic images in patients with PXE. Apart from premature calcification of elastin-rich structures such as the falx cerebri, the investigation results were normal. It is, therefore, apparent that in the absence of neurological signs, no additional information helpful to patient management can be derived from routine cranial tomography in PXE patients.

17.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), was employed to evaluate the central nervous sytem and intracranial contents in 3 individuals with PXE. In two persons, the MRI scan was totally normal. The scan of a 62 year old man with PXE demonstrated mild cortical atrophy, widening of the sulci and slight dilation of the lateral and third ventricles (Figures 17.9 and 17.10). These features were thought excessive merely for the normal ageing process and were probably due to generalised ischaemia from poor intracranial blood flow. However, the patient had no demonstrable central nervous system signs and the true significance of these observations is uncertain.

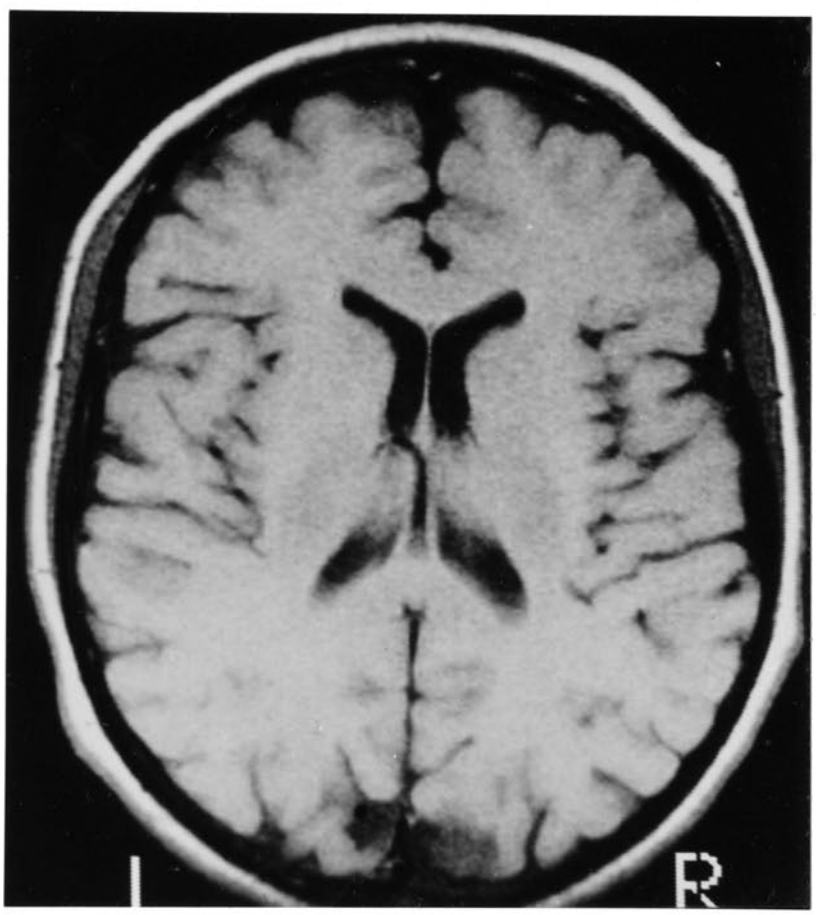


Figure 17.9 MRI SCAN OF 62 YEAR OLD PATIENT WITH PXE DEMONSTRATING MILD VENTRICULAR DILATATION

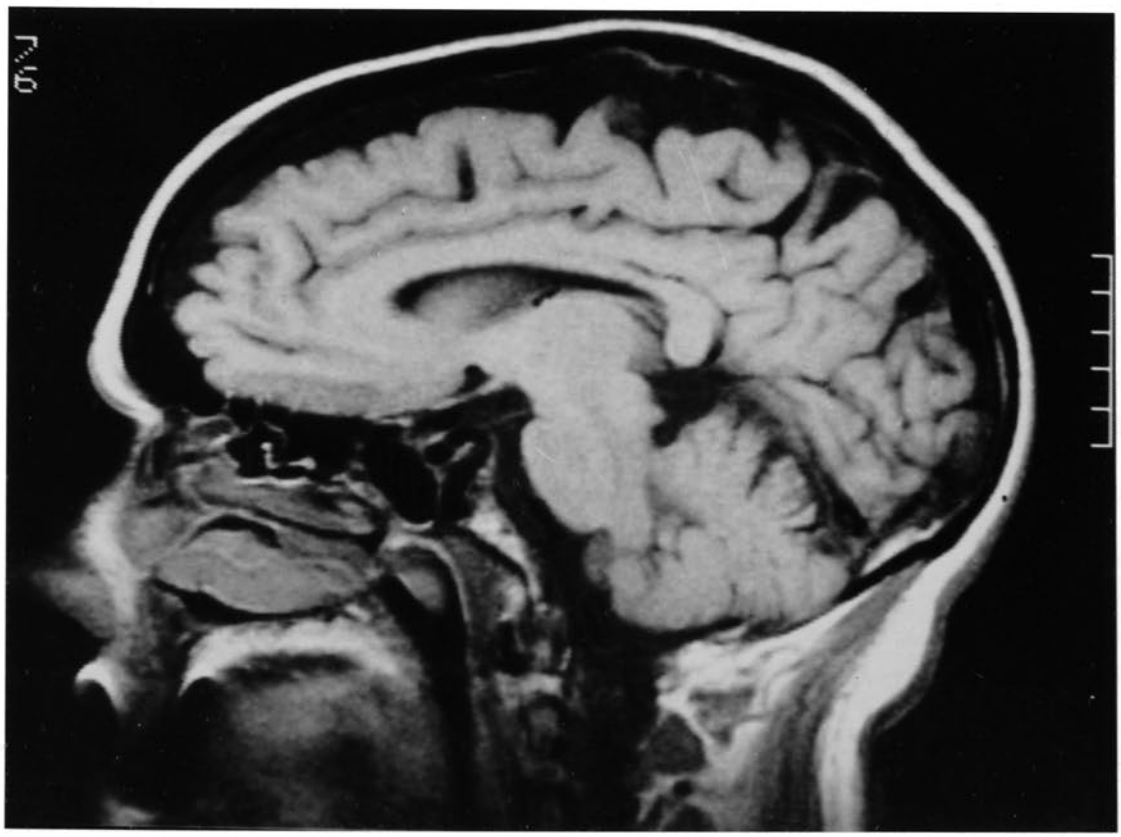


Figure 17.10 **MRI SCAN SHOWING MILD CORTICAL ATROPHY IN A 62 YEAR OLD MAN WITH PXE**

Comment

MRI is an excellent modality for investigating the brain and intracranial contents and would be recommended in any patient with PXE in whom localising central nervous system signs are present. Areas of infarction, aneurysmal dilatation and ventricular expansion are well demarcated by these means. The scans of 3 patients in the current investigation were essentially normal and the routine use of MRI in individuals with this disorder is not warranted. Nevertheless, this form of investigation is invaluable in the appropriate circumstances; this report documents its use in PXE patients for the first time.

SECTION V

MOLECULAR INVESTIGATIONS

The basic defect responsible for PXE is currently unknown. Clinical and histological findings in affected individuals suggest that the condition is a disorder of connective tissue, and that the moeity almost exclusively involved in the pathogenetic process is elastin.

The purposes of this study were to investigate large kindreds with PXE using collagen type I and elastin probes in an attempt to establish linkage, and thereby elucidate the genetic defect.

CHAPTER 18 : COLLAGEN TYPE I AND ELASTIN PROBES IN FAMILIES WITH AUTOSOMAL RECESSIVE PXE

SECTION V

CHAPTER 18

COLLAGEN TYPE I AND ELASTIN PROBES IN FAMILIES WITH AUTOSOMAL RECESSIVE PXE

18.1 LINKAGE ANALYSIS OF PRO ALPHA 1(1) AND PRO ALPHA 2(1) COLLAGEN GENES IN AFRIKANER KINDREDS WITH PXE

18.1.1 Materials and methods

18.1.2 Results

18.1.3 Comment

18.2 HUMAN ELASTIN PROBES IN AFRIKANER FAMILIES WITH PXE

18.2.1 Method

18.2.2 Results

18.2.3 Comment

CHAPTER 18

The genetic defect in PXE is unknown although histological evidence would suggest mutations within either the type I collagen gene or the human elastin gene may be responsible for the disorder. In the light of the intragenic heterogeneity within the type I collagen gene found in families with osteogenesis imperfecta (Byers et al., 1984; Sykes et al., 1986), it is possible that a similar scenario will be present in patients with PXE.

On the assumption that the disorder is genetically heterogeneous, investigations were undertaken using type I collagen and elastin probes in Afrikaner kindreds with autosomal recessive PXE in an attempt to establish linkage. These families were chosen for study as they were likely to be homogeneous (see Chapters 9-10) and most suitably structured for molecular analysis. The method of investigation and findings are reported in this chapter.

18.1 Linkage Analysis of pro alpha 1(1) and pro alpha 2(1) Collagen Genes in Afrikaner Kindreds with PXE

Two Afrikaner families with autosomal recessive PXE were investigated. In each instance 3 affected siblings and both parents were available for study. The molecular investigations were performed by the staff of the laboratories of the Department of Human Genetics, University of Cape Town Medical School, under the direction of molecular biologists, Dr Rajkumar Ramesar and Dr Gillian Wallis.

18.1.1 Materials and Methods

The method for isolation and separation of DNA described by **Vandenplas et al. (1984)** was employed. Ten ml of EDTA anticoagulated blood was used. Ten µg aliquots of DNA were digested with 30 units of the specific restriction enzymes, EcoRI or MspI as directed by the suppliers. Lamda DNA, supplied by BRL, digested with Hind III and end labelled with [ß-32P] using T4 DNA polymerase, was used as a molecular marker. After digestion at 37°C overnight, the DNA fragments were separated by electrophoresis in 0.6% (w/v) agarose gels. The fragments were transferred to Hybond N membrane (Amersham) as described by **Southern (1975).** The genomic probes were nick translated to a specific activity of at least 1 x 10^7 cpm/g, using the nick translation kit and protocol supplied by Amersham. The blots and corresponding probes were hybridized for 48 hours at 65°C, as previously described **(Brebner et al., 1985).** Some alterations as advocated by **Johnson et al. (1984)** were incorporated in the methodology:

(i) "Blotto" (Carnation low-fat powdered milk) was used instead of Denhart's solution.

(ii) Hybond N membrane (Amersham) replaced nitrocellulose to facilitate multiple rehybridization of the filters. Stringency washes used were 0.1xSSC and 0.1% SDS at 65°C. Autoradiography was done at -80°C using Cronex-4 X-ray film from Protea in waterproof, light-tight cassettes.

Probes

(i) A genomic clone p1A1H1 7526, detecting an MspI RFLP was used for the pro alpha 1(1) collagen gene.

(ii) A genomic clone NJ-3' detecting EcoRI RFLP in the human pro alpha 2(1) gene was used.

18.1.2 Results

The position of the RFLP linked to the human pro alpha 1(1) gene is shown in Figure 18.1. The MspI RFLP is detected by the genomic clone p1A1H1 7526. Similarly, the restriction map indicating the polymorphic sites in the human pro alpha 2(1) gene is shown in Figure 18.2. The EcoRI RFLP is detected with the genomic clone NJ-3'.

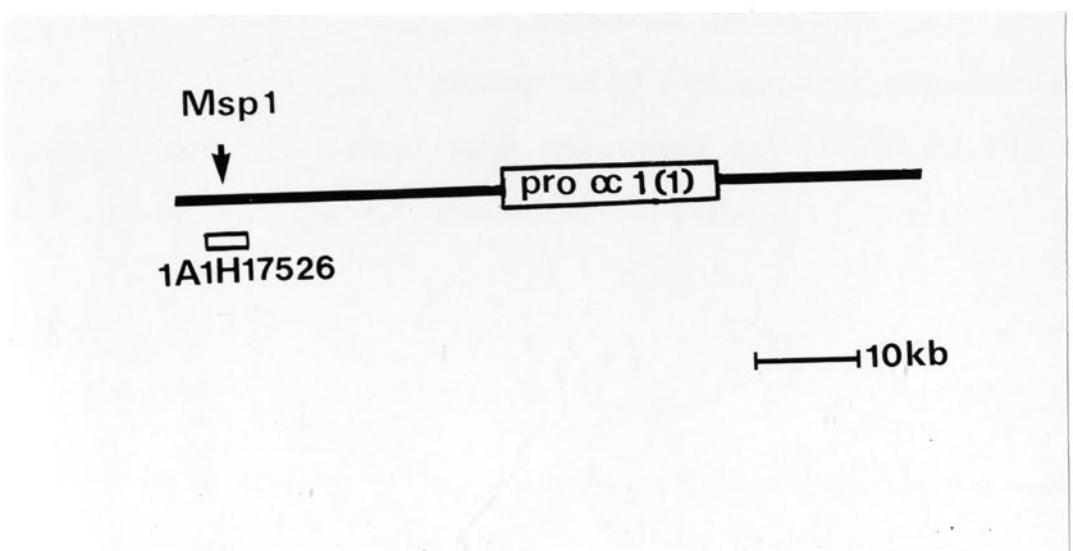


Figure 18.1 THE POSITION OF THE MspI RFLP LINKED TO THE PRO ALPHA 1(1) GENE IS SHOWN

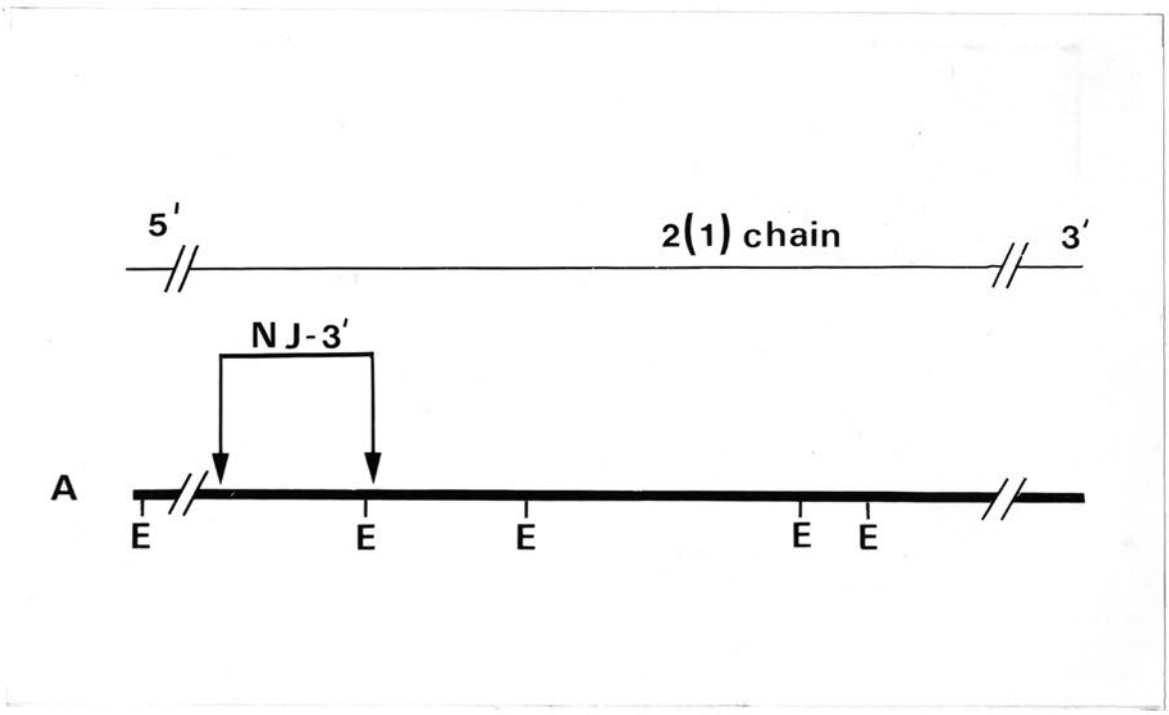


Figure 18.2 THE POSITION OF THE EcoRI RFLP DETECTED WITH THE GENOMIC CLONE NJ-3' IN THE HUMAN PRO ALPHA 2(1) GENE IS SHOWN

Families A and B, with the "Afrikaner" form of PXE, showing haplotypes using the enzymes EcoRI(E) and MspI(M) are illustrated in Figures 18.3 and 18.4, respectively. In family A, the EcoRI RFLP was uninformative. With regard to the MspI RFLP, no consistent segregation of a set of genotypes with the phenotypic expression of PXE could be demonstrated. Similarly in family B, using both the EcoRI and MspI RFLPs, no cosegregation of genotype and phenotype was evident.

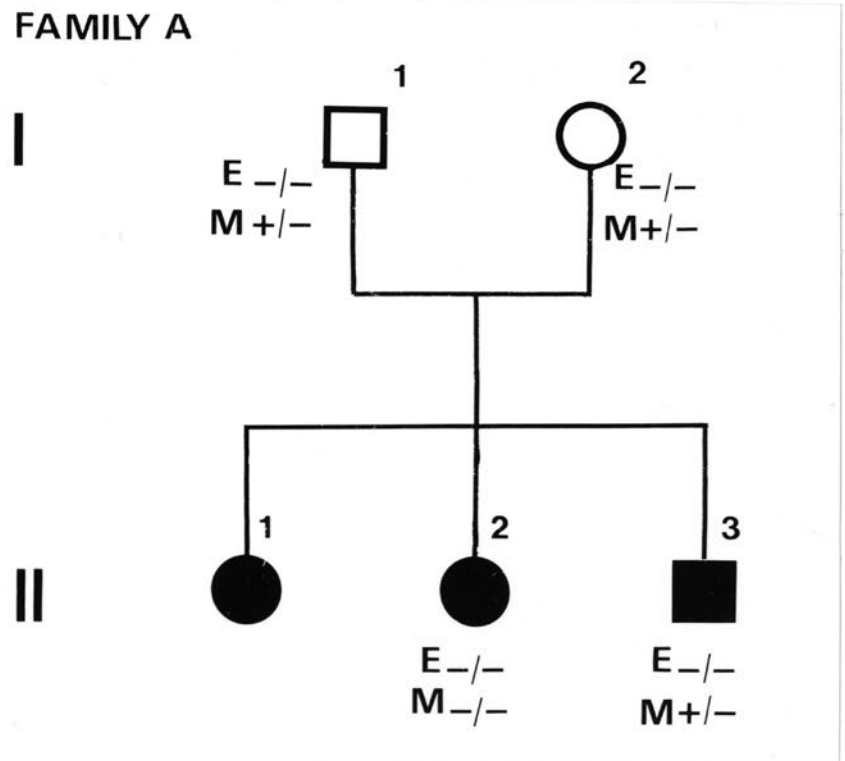


Figure 18.3 PEDIGREE OF FAMILY A WITH THE "AFRIKANER" FORM OF PXE SHOWING HAPLOTYPES USING THE EcoRI(E) AND MspI(M) ENZYMES

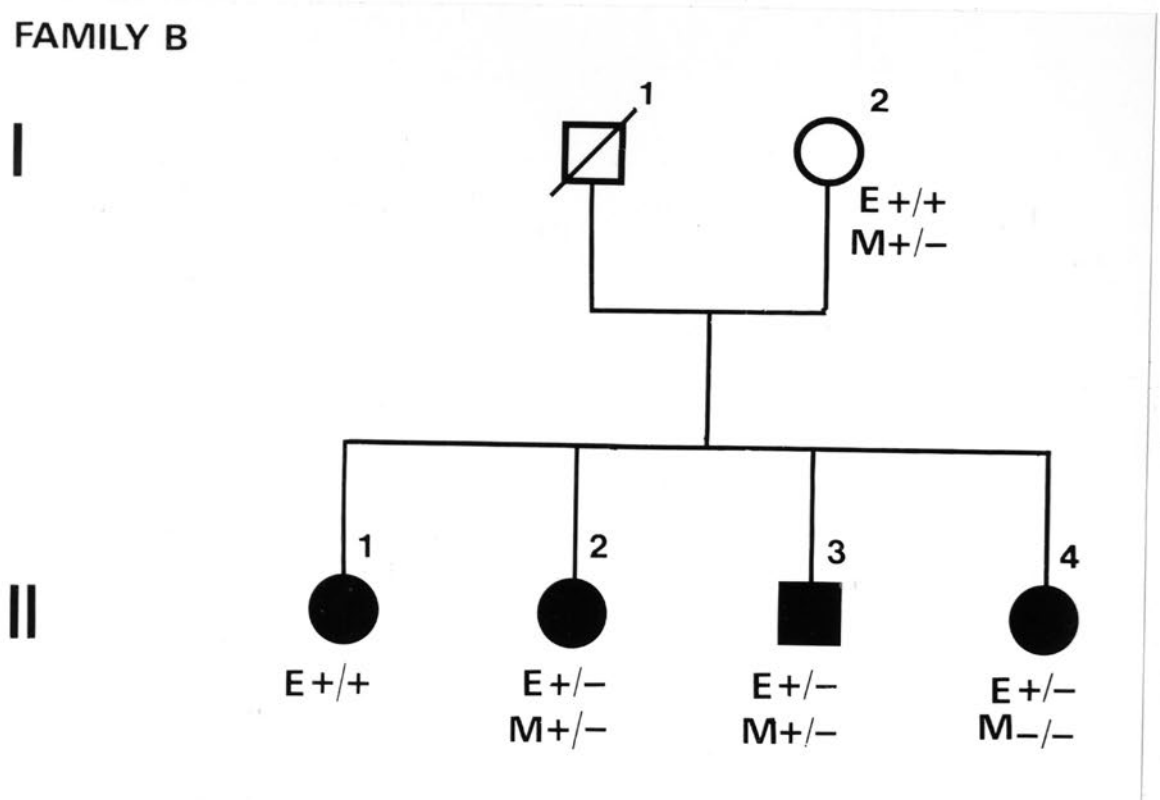


Figure 18.4 PEDIGREE OF FAMILY B WITH "AFRIKANER" TYPE PXE SHOWING HAPLOTYPES USING THE EcoRI(E) AND MspI(M) ENZYMES

18.1.3 Comment

Given the limited data available, no linkage between the COL1A1 or COL1A2 probes and affected individuals with PXE could be demonstrated in this study. In order to completely exclude linkage of type 1 collagen genes and the "Afrikaner" form of PXE, many informative families would need to be studied; this is beyond the scope of this investigation.

18.2 Human Elastin Probes in Afrikaner Families with PXE

A preliminary investigation to ascertain whether the basic defect of PXE at the molecular level involved elastin, was undertaken by a collaborative study involving two laboratories:

1) The Molecular Laboratory of the Department of Human Genetics, University of Cape Town Medical School; Chief Scientist, Dr Rajkumar Ramesar.

2) The Molecular Laboratories of the University of Medicine and Dentistry of New Jersey and the Robert Wood Johnson Medical School (formerly Rutgers Medical School); Head of Department, Professor Charles Boyd.

In this investigation, RFLPs within the human elastin gene were sought in the Afrikaner population.

18.2.1 Method

One hundred chromosomes were analysed for RFLPs with the pcHELI **(Emanuel et al., 1985)** and pcHEL2 **(Indik et al., 1987)** probes using the standard techniques described by **Vandenplas et al. (1984)** and **Southern (1975).** The following restriction enzymes were used in the investigation:

i) Taq I
ii) Rsa I
iii) Hind III
iv) Msp I
v) BamH I
vi) Bgl II
vii) Pst I
viii) Nco I

18.2.2 Results

No RFLPs were detected in individuals within the Afrikaner population by these means. The association between defects in the elastin gene and PXE could, therefore, not be determined within this group at the genetic level.

18.2.3 Comment

The inability to detect RFLPs with the human elastin probes pcHELI and pcHEL2 within the Afrikaner community is disappointing but not surprising. Previous investigations have shown remarkable conservation of the human elastin gene within Caucasian populations world-wide, with the exception of the Finnish population **(Boyd, personal communication).** Several laboratories in the United States and Europe are currently addressing the problem and only recently, has a VNTR polymorphism at the 3' end of the human gene been detected **(Boyd, personal communication).** This RFLP occurs at a very high frequency in the Caucasian population of New York, and is currently being used in American and British families with autosomal dominant PXE. It is intended to investigate suitable families with "Afrikaner" type PXE once this probe is available.

SECTION VI

MANAGEMENT OPTIONS

PXE is incurable in terms of current medical knowledge; nevertheless, strategies are available which may modify the natural history of the disorder. These include general measures such as genetic counselling, dietary advice, general health programmes and regular ophthalmological and cardiovascular appraisal. These issues will be discussed in Chapter 19 of this Section on patient management. In view of the important practical implications, the role of cosmetic surgery in patients with PXE will be addressed separately. The future prospects for management and antenatal diagnosis are discussed in Chapter 21.

CHAPTER 19 : GENERAL MANAGEMENT OF INDIVIDUALS WITH PXE

CHAPTER 20 : PLASTIC SURGERY IN PATIENTS WITH PXE

CHAPTER 21 : FUTURE PROSPECTS

SECTION VI

CHAPTER 19

GENERAL MANAGEMENT OF INDIVIDUALS WITH PSEUDOXANTHOMA ELASTICUM

19.1 LIFESTYLE AND DIETARY ADVICE

19.2 OPHTHALMOLOGICAL MANAGEMENT

19.2.1 Annual Appraisal

19.2.2 Role of Laser Therapy

19.3 CARDIOVASCULAR EVALUATION

19.4 GENETIC COUNSELLING

CHAPTER 19

During the current investigation it became apparent that most patients were not fully aware of the natural history, complications and prognosis of PXE. In addition, in some instances, faulty information amongst members of the medical profession had resulted in an erroneously poor prognosis being given to affected persons and their families.

Eighty-six persons with PXE in 58 kindreds were clinically appraised by the author during this investigation and the individual clinical findings were discussed in detail personally with each patient. Thereafter a medical report with recommendations for further investigation and management was sent to the general practitioner and medical specialists involved in the care of the patient.

Specific aspects of management drawn from the collective experience obtained during the current study will be addressed in this Chapter.

19.1 Lifestyle and Dietary Advice

As detailed previously, individuals with PXE are prone to cosmetic deterioration of their skin, hypertension with vascular stroke phenomena, and subretinal haemorrhages with consequent visual loss. Changes in general lifestyle and a healthy diet can help modify the severity of these complications.

As was stressed in Chapter 12, the major adverse prognostic factors associated with skin deterioration in individuals with PXE are obesity, frequent and rapid changes in body mass, prolonged exposure to ultraviolet light and multiple pregnancies in females. In order to minimise cosmetic deterioration, affected women were advised to limit their family size. The use of ultraviolet-screening lotions when in the sun were advocated and a calorie restricted diet was recommended in order to avoid obesity and weight fluctuations.

Affected persons were advised to undergo annual medical examination in order to detect hypertension and other cardiovascular sequelae of the disorder. Dietary restriction of polyunsaturated fatty acid intake, regular exercise and avoidance of cigarette smoking is well known to limit the onset and consequences of atherosclerosis, and the importance of this appraisal was emphasised. Affected persons were advised not to partake in contact sports such as boxing, rugby, soccer and the martial arts so as to limit the risks of retinal haemorrhage and subsequent blindness. Other sporting activities including swimming, running (not ultra-distance), tennis and golf were strongly encouraged in order to enhance cardiovascular fitness.

Two previous investigations **(Renie et al., 1984; Neldner, 1988)** have suggested that dietary calcium intake in childhood and adolescence

correlated positively with severity of clinical manifestations in patients with PXE. These authors claimed that dietary restriction of calcium may, in some instances, be associated with regression of the cutaneous stigmata of PXE. However, the problems associated with retrospective dietary studies were emphasised in both papers, and the benefits of a calcium restricted diet in PXE patients, particularly in the elderly who are at risk for osteomalacia, must remain doubtful. A prospective dietary calcium analysis in affected persons would resolve the issue but would involve a long-term investigation which would be outside the scope of the current project.

19.2 Ophthalmological Management

In the current investigation, the most debilitating and serious complications of PXE which were encountered were the severe ophthalmological sequelae occurring in the majority of patients with the "Afrikaner" form of the disorder after 50 years of age (Chapters 10 and 14). Similar changes also occurred in patients with other forms of PXE although the consequences tended to be less severe. In most instances, affected individuals were aware of the potential complication of blindness but were uninformed as to how to reduce the risks of adverse sequelae. Two strategies were advocated:

19.2.1 Annual Ophthalmological Appraisal

Patients with PXE were advised to undergo an annual ophthalmological appraisal by a specialist with experience and knowledge of the disorder. Ideally, the clinical evaluation should be undertaken within the Ophthalmological Department of a tertiary institution. Depending on the clinical findings, any of a variety of specialized investigative procedures could be undertaken on affected patients during this appointment; these might include fundal photography, slit-lamp examination and fluorescein angiography.

At the ophthalmological consultation the patient would be informed regarding any clinical deterioration of visual acuity or extension of angioid streaks, presence of retinal haemorrhage or scarring. In this context, a photographic record of the fundal changes was found to be especially helpful in assessing any deterioration. This appraisal also provided continuity of care, especially if a patient changed location for work or other reasons; retinal photographs could then be sent to the new medical attendant as an objective retrospective record.

19.2.2 Role of Laser Therapy

The structure of Bruch's membrane and its anatomical relationships to the retinal pigment epithelium and choriocapillaris has been discussed previously (Chapters 10.3 and 14). In patients with PXE, neovascularisation occurs into the angioid streaks forming subretinal "nets" or membranes. Oedema fluid may leak from these areas (exudative maculopathy) which then become highly susceptible to haemorrhage, particularly after head trauma. At this stage argon or krypton-red laser therapy can obliterate the neovascular membrane and, it is generally believed, prevent imminent or subsequent retinal haemorrhage.

Once haemorrhage has occurred, laser therapy is thought to be of little value and may be contra-indicated **(Neldner, 1988)**. Laser therapy should never involve the fovea as sites of photocoagulation heal by a process of gliosis and scotoma results with consequent blindness.

Patients were encouraged to immediately call on their ophthalmologist should they become aware of the early signs of exudative maculopathy, such as sudden onset of blurring of vision. Ophthalmological expertise in the use of laser therapy in these situations can most likely preserve vision in the short term; however, long term, controlled studies are required to assess the real value of this therapeutic modality.

19.3 Cardiovascular evaluation

The vascular complications of PXE have been discussed in detail in Chapters 10.5 and 13 and are the same as for arteriosclerosis of any aetiology (ie. hypertension, myocardial ischaemia, stroke, intermittent claudication and vascular occlusion). PXE patients were advised to undergo an annual medical examination through a specialist physician specifically to seek out and treat early signs of cardiovascular complications. At these consultations, non-specific measures such as weight control, a balanced diet, a regular exercise programme and avoidance of smoking, could be emphasised.

Following regular full clinical examination, further special investigations could be performed as indicated; these might include lipid profile analysis, electrocardiogram, exercise tolerance tests, and echocardiography. Drug therapy for hypertension in most instances is commenced using thiaside diuretics and propranalol. This choice of diuretic is contentious as thiazides may induce hypercalcaemia in a minority of individuals. **Neldner (1988)** has advocated furosemide as the diuretic of choice in PXE as this drug promotes calcium excretion in the urine. As the role of calcium in the pathogenesis of PXE is still unknown, the use of thiazide diuretics, which are less costly and generally have fewer other side-effects, is probably warranted.

Pentoxyfylline can be used for improving vascular flow in patients with intermittent claudication associated with PXE. The drug is effective by lowering blood viscosity and enhancing erythrocyte flexibility.

Early bypass surgery in patients with chronic angina has been advocated in PXE. In the present investigation, cardiac surgery has not been required for any patient to date.

19.4 Genetic Counselling

Affected individuals were usually aware that PXE was a heritable disorder, although the risks of transmission to future progeny were unknown in most instances.

The majority of persons counselled were affected by the "Afrikaner" form of PXE which is inherited as an autosomal recessive trait. In accordance with conventional genetic principles, the transmission of the faulty gene from phenotypically-normal but heterozygous 'carrier' parents was explained to the patients and the one-in-four risk to further progeny of such a union was emphasised. For affected individuals, the risk of producing affected children was given as low. However, they were advised to seek a spouse from outside of the family in order to decrease the risk of marrying a heterozygous carrier of the PXE gene. Clinically normal siblings who were at risk of being carriers of the abnormal gene, were given similar guidance regarding spouse selection.

Autosomal dominant inheritance was apparent in three families with PXE (see Chapter 5). These individuals were advised that there was a 50 per cent recurrence risk for the progeny of affected persons. In a few families the clinical features of PXE had only become apparent in the affected adult after the birth of their children. Skin biopsy of clinically normal individuals within such kindreds was advised in order to exclude the diagnosis of PXE, prior to their embarking on a family.

In general, patients were immensely relieved to find that the risk of producing affected children was slight. Nevertheless, in the absence of confirmatory diagnostic tests for PXE, complete reassurance for affected

families was impossible, especially in those individuals where the disorder occurred sporadically.

Currently, no presymptomatic or antenatal diagnostic tests are available for families with PXE. There is, however, potential for the future and new molecular findings and their possible applications in this context will be discussed in Chapter 21.

Summary

Despite the severity of cardiovascular and ophthalmological complications in patients with PXE, non-specific measures such as weight control, smoking avoidance, dietary measures and a regular exercise programme, can enhance the quality of life of affected persons. These measures, together with early antihypertensive drug therapy, cosmetic and cardiac surgery and argon laser therapy for retinal haemorrhage prevention, can reduce morbidity and, in some instances, mortality in individuals with PXE.

SECTION VI

CHAPTER 20

PLASTIC SURGERY IN PATIENTS WITH PSEUDOXANTHOMA ELASTICUM

20.1 INTRODUCTION

20.2 PATIENTS AND METHODS

20.3 RESULTS

20.4 DISCUSSION AND COMMENT

CHAPTER 20

PLASTIC SURGERY IN PATIENTS WITH PSEUDOXANTHOMA ELASTICUM

20.1 Introduction

The dermatological features of pseudoxanthoma elasticum are the most clinically obvious sequelae of this disorder. In all large series to date **(Connor et al., 1961; Goodman et al., 1963; Alinder and Bostrom, 1972; Pope, 1974)** a female preponderance has been noted, sometimes outnumbering men by a ratio of 2:1 **(McKusick, 1972).** This finding has been attributed to women seeking medical advice earlier than men for cosmetic reasons and was also noted in the current investigation where the female to male ratio was determined to be 3:2 (see Chapter 6).

The dermatological findings in more than 80 persons with PXE have previously been discussed in Chapters 10.4 and 12. It is apparent that the clinical sequelae in women appear to be more severe than those experienced in men. Several reasons may account for this:

1. The higher body fat composition in women than men may predispose to skin laxity and eventual redundancy.

2. The high oestrogen level found in adult women is said to increase joint and ligament laxity, and may have a similar effect on dermal elastin thereby increasing skin laxity.

3. Acute changes in body mass and configuration during pregnancy may predispose women with PXE to increased skin laxity, redundancy and striae formation.

4. Women who are exposed to excessive ultra-violet radiation, usually from sun-tanning, are more likely to experience a rapid ageing

process known as "senile elastosis". When this recreational activity is actively pursued in females with PXE, elastotic changes may be excessive.

Although cosmetic creams containing ultra-violet blocking agents, lanolin, vegetable oils, perfumes and vitamin E have all been advocated in patients with PXE **(Stout, 1951)**, there is little clinical evidence of their efficacy. Plastic surgery would appear to offer a more definitive therapy but a thorough literature search revealed only three previous reports concerning the use of plastic surgery in PXE **(Pickrell et al., 1948; Crickelair, 1953; Kaplan & Henjyoji, 1976).**

The purpose of this study was to investigate the effects of cosmetic surgery in 10 severely affected women. Some of the findings have already formed the basis of a recent publication **(Viljoen et al., 1990)** **[Appendix: Publication 7].** The further outcome, complications and subsequent course of the disorder following plastic surgery in these individuals is depicted and discussed in this chapter.

20.2 Patients and Methods

Ten women with PXE who had undergone cosmetic surgery were studied. These patients were derived from a total cohort of 86 individuals with biopsy-proven PXE, and data relating specifically to the dermatological and cosmetic surgery aspects was collected.

A detailed history regarding the onset, anatomical site, progression and management of the skin lesions was obtained. The respective medical practitioners and plastic surgeons of each affected person were contacted and information regarding the type of anaesthetic, intra- and post-operative complications, surgical techniques employed and outcome were documented. Pre- and post-operative photographic slides were available in many instances from which serial records of the skin lesions were compiled. The response of affected individuals to surgery and the further progression of the cutaneous features were recorded.

20.3 Results

The 10 female patients investigated ranged in age from 25-56 years at the time of surgery. The surgical procedures, cosmetic result, length of follow-up and current clinical status of the patients are summarised in Table 20.1.

The most frequent sites of surgery involved the posterior aspect of the neck (7 persons), both axillae (3 women), abdomen (2 individuals), thighs (2 persons), breasts (1 patient) and lower limb (1 individual). Two persons had undergone plastic surgery on more than one occasion, while in several, two procedures had been performed (eg. axillae and cervical area) during the same operation. General anaesthesia was used in every instance and no complications arose despite the potential cardiovascular hazards of premature arteriosclerosis which are prevalent in PXE.

Large portions of redundant skin were exised in the majority of patients, resulting in considerable cosmetic improvement. (See Figures 20.1-8). There were no reports from the surgeons of technical difficulties during the operation. Excessive cutaneous laxity and a "gritty" sensation (due to intradermal calcification) when excising affected skin was described in all patients. The other tissues appeared normal. Untoward haemorrhage did not occur and specifically, no oozing from small arteries was noted.

TABLE 20.1

PLASTIC SURGICAL ASPECTS OF TEN PATIENTS

Patient	Age at Time of Surgery	Surgical Procedure	Cosmetic Result	Follow-up Period
1	31	Thigh lipectomy	Excellent	3 years; no regression
2	33	Excision of skin in cervical region	Keloid formation in scar	4 years; no change
3	22	Skin excision in cervical region	Good	1 year; no change
4	32	(1) Breast reduction (2) Excision of lax cervical skin	(1) Satisfactory (2) Good	4 years; mild skin redundancy in cervical region
5	(1) 25	(1) Lax cervical and axillary skin excised	(1) Good	(1) 15 years; mild deterioration of cervical skin; no regression in axillae
	(2) 33	(2) Abdominal lipectomy and excision of the lax abdominal skin	(2) Large, unsightly scars	(2) 7 years; no regression
6	23	Lax skin on inner thigh excised	Good	2 months; normal wound healing
7	56	Skin graft of varicose ulcer	Satisfactory initially	Subsequent below-knee amputation for peripheral gangrene
8	(1) 28	(1) Redundant skin of neck and stomach excised		8 years; moderate keloid formation
	(2) 31	(2) Lax skin of axillae excised	(2) Fair result	5 years; no regression
9	32	Lax cervical skin excised	Good	6 months; no regression
10	26	Lax cervical and axillary skin excised	Fair	4 months; no regression



Figure 20.1 THE ACCENTUATED NASOLABIAL FOLDS ARE EVIDENT IN A PATIENT WHO HAD PREVIOUSLY UNDERGONE COSMETIC SURGERY TO THE CERVICAL REGION



Figure 20.2 A WOMAN, AGED 25 YEARS (PATIENT NO.4), PRIOR TO COSMETIC SURGERY



Figure 20.3 PATIENT NO.4 FOUR YEARS AFTER SURGERY



Figure 20.4 LATERAL VIEW OF PATIENT NO.4 PRIOR TO SURGERY



Figure 20.5 PATIENT NO.4 FOUR YEARS POST SURGERY. CONSIDERABLE IMPROVEMENT IN CERVICAL SKIN LAXITY IS EVIDENT



Figure 20.6 CUTANEOUS LAXITY AND THICKENING IS PRESENT IN THE AXILLA PREOPERATIVELY IN PATIENT NO.8

Wound healing was slower than usual in most instances and keloid formation was a problem in 2 persons. Extrusion of calcium particles through the healing scars was a feature in two other patients. Considerable delay in healing occurred in the abdominal wound of one individual and sepsis caused unsightly scarring in another patient. Patient 10 developed wound sepsis, dehiscence and experienced considerable post-operative pain.

One patient underwent reduction mammoplasty and a good cosmetic result was achieved (Figure 20.9). There were no complications following the procedure apart from some wound thickening between the breasts.



Figure 20.7 POST-OPERATIVE IMPROVEMENT IS EVIDENT (PATIENT NO.8)

The post-operative follow-up period ranged from 4 months to 15 years and, although progression of the skin lesions was noted, it had been unnessary to repeat any surgical procedure. By and large, all the patients were satisfied with the cosmetic improvement which had been attained.



Figure 20.8 THE POSTOPERATIVE APPEARANCE FOLLOWING EXCISION OF THE ABDOMINAL "APRON" IN A WOMAN AGED 36 YEARS



Figure 20.9 THE RESULTS OF REDUCTION MAMMOPLASTY IN A PATIENT WITH PXE

20.4 Discussion

Pseudoxanthoma elasticum inevitably causes considerable psychological stress and a poor self-image in affected women because of progressive deterioration of skin cosmesis.

The group of patients described in this investigation generally exemplify the range of severity and potential distribution of the stigmata of PXE. They form a select subgroup by the very nature of their severe dermatological sequelae. These features are usually found in the AR II PXE (**Pope, 1974**). However, the majority of the patients had the AR I form of PXE, in which moderate skin manifestations in association with mild ophthalmological and cardiac involvement are the usual clinical findings (Chapter 4). This contrasts with the AD I and "Afrikaner" forms of PXE where eye and cardiovascular lesions tend to be more severe.

One of the few therapeutic options available to individuals with PXE is that of plastic surgery. Surprisingly, few reports on the subject have appeared in the literature. **Pickrell et al. (1948)** were the first to demonstrate cosmetic benefit from surgery in a woman with PXE. **Crickelair (1953)** documented a similarly treated individual, **Kaplan & Henjyoji (1976)** described a further affected person and **McKusick (1973)** alluded to the use of cosmetic surgery in his monograph on connective tissue disorders.

The main indication for cosmetic surgery is undoubtedly the correction of unsightly creases in the nasolabial folds and cervical region. Laxity of the facial skin produces a characteristic "hound-dog" appearance which is evident in Figure 20.1. Figures 20.2-5 portray a 25-year old

woman with changes of this type, before and following surgery. The cosmetic appearances achieved were consistently good in the seven individuals who had surgery to the cervical region.

Other areas of significant disfigurement in patients with PXE are the axilla, abdomen and thighs. The axillary repair procedure was successfully undertaken in 3 patients with good cosmetic results and little subsequent skin deterioration (Figures 20.6-7). Extensive excision of redundant abdominal skin with lipectomy were performed in two persons (Figure 20.8). In these persons the lax tissue formed an "apron" which was thought to be due to repeated stretching and disruption of elastin fibres as a consequence of multiple pregnancies and obesity. Cutaneous laxity in the thigh areas was corrected in two severely affected women without complication.

Spontaneous haemorrhage is reported to be a major complication of PXE, particularly from the gastro-intestinal tract, **(Eddy & Farber, 1962; McKusick, 1973; Cunningham et al., 1980)** and into the subarachnoid space **(Sharma et al., 1974).** Bleeding into the skin was described by **Marchesani & Wirtz (1931)** and **Franchetti & Roulet (1936).** The bleeding is entirely due to changes in the blood vessels, and there is no disturbance of the clotting mechanism. Haemorrhage at operation was not a problem in any of the 10 persons described in this investigation. This appears to hold true even in instances of major surgery as demonstrated in the patient described by **McKusick (1972)** with atherosclerotic occlusion at the aortic bifurcation due to PXE, who underwent successful homograft operation.

Tissue fragility due to calcification and slow healing are important complications of patients with PXE who undergo surgery. Extrusion of

calcium in the form of 'spicules' or 'granules' through surgical scars was noted in two individuals. This unusual manifestation has been previously reported in one instance. **(Kaplan & Henjyoji, 1976).** Both patients in this study with this complication had very severe skin manifestations of PXE and small areas of wound dehiscence, delayed healing and unsightly scars where calcium was extruded. Mild keloid formation was a feature in two persons following surgery, but the finding may be coincidental and not related to the underlying disorder.

Post-operative deterioration of the skin was not a prominent feature in our patients and none had required repeated cosmetic surgery. However, in several women progressive widening of surgical scars occurred with time suggesting that a process of ongoing degeneration of elastin was present. Scars due to trauma and other surgical procedures reacted similarly. Individuals with more severe dermal manifestations of PXE and those who were obese tended to fare worse in this respect.

Six of the patients who underwent cosmetic surgery were highly satisfied with the outcome, but 4 persons expected more improvement and admitted disappointment with their results. Those with a reserved response had severe cutaneous stigmata of PXE and 2 of these individuals required abdominal lipectomy as well as skin excision.

Plastic surgery in individuals with PXE is a highly effective therapeutic option which is warranted where the cutaneous stigmata of the disorder are unacceptable for psychosocial reasons. The benefit to the affected person is usually considerable and few operative risks or complications are encountered. The tendency for regression of the skin manifestations in pregnancy or in obese individuals warrants careful

consideration and cosmetic surgery reserved for patients who have completed their families.

SECTION VI

CHAPTER 21

FUTURE PROSPECTS

21.1 MOLECULAR INVESTIGATIONS

21.2 FUTURE DIRECTIONS

21.3 FINAL COMMENTS

CHAPTER 21

The increased morbidity and mortality in individuals with PXE places heavy social and economic burdens on both the affected family and the community at large (Chapters 10-16). Currently, no cure is available for the disorder, and the prognosis regarding the eye and cardiovascular sequelae is poor, particularly in the Afrikaner form of PXE (Chapter 10.3 and 10.5). In addition, the cosmetic complications have considerable psychological and social implications in affected women.

The purposes of this chapter are to highlight areas of future research and development which will allow improved clinical management and the formulation of techniques for antenatal and presymptomatic diagnosis.

21.1 Molecular Investigations

It is currently thought that PXE is a heterogeneous disorder of elastin. Support for this concept is provided by the involvement in the disorder of elastin-rich tissues such as Bruch's membrane of the retina and the medial and intimal layers of arterial blood vessels. Equally, elastin fibres in skin undergo degenerative changes and calcification. Histological evidence of widespread elastin involvement can be demonstrated both by light microscopy and through ultrastructural investigations.

Until recently, molecular studies with human elastin probes have been hampered by the inability to detect RFLPs in affected families due to the remarkable conservation of the elastin gene. **Boyd** and his co-workers have now proven linkage between two Caucasian families with autosomal dominant PXE and a VNTR polymorphism at the 3' end of the human elastin gene **(Boyd, 1990; personal communication).** The implications are considerable in that, for the first time, PXE has been linked to abnormalities in the elastin gene in some autosomal dominant families. In the future, the discovery of other RFLPs will increase the prospects of linkage in other kindreds with a similar inheritance pattern, and eventually allow haplotype analysis of families with autosomal recessive PXE. Thereafter, molecular techniques previously employed in the elucidation of the mutations of other recessive disorders such as cystic fibrosis, can be applied in order to determine mutations in the elastin gene in all forms of PXE.

In a homogeneous population such as the Afrikaners, it is very likely that affected persons are homozygous for a single mutation. Once the faulty gene has been identified, antenatal diagnosis could be offered to at-risk individuals. Identification of heterozygotes in families, screening

of couples before they have declared themselves to be at risk by producing an affected child and assessment of the gene frequency of PXE would then be feasible.

The prevalence of the abnormal genes for PXE, even within the Afrikaner population, is likely to be low. Given these circumstances, population screening programmes would probably not be warranted or cost-effective.

The human elastin gene has previously been completely sequenced and the entire structure of elastin is already known **(Cicila et al., 1985; Bashir et al., 1989).** As elastin is a structural rather than regulatory protein, it will require the future development of techniques of successful gene therapy to correct mutations in the elastin gene in man. Although this achievement appears unlikely in the near future, it may eventually provide an effective cure for persons with PXE.

In the South African context and in the light of the findings of this investigation, it is suggested that future molecular studies in PXE should be directed toward the following aspects:

i) The detection of RFLPs to human elastin in families with PXE, particularly those from the Afrikaner and Black populations in whom clinically distinct forms of PXE appear to be segregating.

ii) The elucidation of the most frequently occurring elastin gene mutations in each population group.

iii) Analysis of the gene frequency of PXE within each population group.

iv) Presymptomatic and antenatal diagnosis of PXE in at-risk kindreds.

v) Family screening for heterozygous carriers of PXE.

21.2 Future Directions

The major clinical manifestations in patients with PXE, namely those in the skin, eye and cardiovascular system, have been extensively investigated during this century. However, important aspects remain to be elucidated:

i) The use of the argon laser in the prevention of retinal haemorrhages is contentious; some investigators are proponents of its use while others claim it may aggravate the visual disturbances **(Clarkson & Altman, 1982)**. A prospective, randomised trial is required to resolve this problem.

ii) Several investigators **(Renie et al, 1984; Neldner, 1988)** have suggested that excessive ingestion of calcium during the childhood and adolescent period is associated with increased severity of PXE later in life. These conclusions have followed retrospective dietary analyses of affected individuals. A prospective study is necessary to establish the validity of these claims.

iii) In the South African context, PXE is rare in Black persons. Clinical studies within this population group are recommended in order to determine the spectrum of manifestations and natural history of PXE in affected individuals.

iv) Other aspects which require investigation are:-

   a) the efficacy of vitamin E preparations in skin care in PXE

   b) calculation of mortality attributable to PXE in South Africa

   c) assessment of the effectiveness of early preventative management strategies on the life expectancy in PXE.

Final Comments

The scope for further molecular and clinical studies in individuals with PXE is large but prospective investigations in this rare disorder are generally time-consuming and costly. In these circumstances collaborative studies between interested colleagues offer the best prospects for a successful outcome. During this project, international collaborative investigations were established between the Department of Human Genetics in Cape Town and colleagues in America, the United Kingdom and Belgium on aspects of genealogy and molecular studies of PXE. It is anticipated that these links will be strengthened and broadened in the future.

PXE is a serious disorder which has major implications for affected persons and their families. The condition occurs in a relatively low prevalence in all communities throughout the world but nevertheless, demands the disproportionate expenditure of medical and financial resources in order to provide appropriate care for affected individuals and their families. For these reasons all efforts to determine the basic defect in order to alleviate patient morbidity and mortality are fully warranted.

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APPENDIX

SECTION A : PUBLICATIONS

SECTION B : PAPERS DELIVERED AT LOCAL AND INTERNATIONAL CONGRESSES

SECTION C : RESEARCH PROTOCOLS

SECTION A:

PUBLICATIONS

1. Viljoen DL, Beighton P, Mabin T, Woods K, Saxe N, Bonefede P (1984)
2. Viljoen DL, Pope FM, Beighton P (1987)
3. Viljoen DL, Beatty S, Beighton P (1987)
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5. De Paepe A, Viljoen DL et al. (1990)
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Pseudoxanthoma elasticum in South Africa — genetic and clinical implications

D. L. VILJOEN, P. BEIGHTON, T. MABIN, K. WOODS, N. SAXE, P. BONAFEDE

Summary

After investigation by a multidisciplinary team, 19 cases of biopsy-proven pseudoxanthoma elasticum are described. Evidence for an increased gene frequency in the Afrikaner population was found, as was support for the claim of genetic heterogeneity in the disorder. The well-described clinical manifestations involving the eyes, skin and cardiovascular system were seen, as were more rarely reported features such as acne, telangiectasia of the lips and bilateral cataracts. Mitral valve prolapse and gastro-intestinal haemorrhage were not found in our patients, although there are several reports in the literature.

S Afr Med J 1984; **66**: 813-816.

The cutaneous manifestations of pseudoxanthoma elasticum (PXE) were first described by Rigal in 1881.[1] The characteristic skin lesions consist of raised yellow papules and their appearance led to the erroneous conclusion that the condition was related to the xanthomatoses. However, in 1896 Darier[2] described the histological changes and demonstrated that it was a separate disorder, for which he offered the name 'pseudoxanthoma elasticum' or 'elastorrhexis'.

Considerable evidence has accumulated which suggests that PXE is a heritable defect of connective tissue with a consequent wide clinical spectrum in which the skin, eyes and cardiovascular system are principally involved.[3] Lesions of lesser significance have been detected in the stomach, central nervous system, skeleton and other organs.

This rare disorder is probably heterogeneous[4,5] and the medical prognosis and genetic basis varies in the different forms of the condition. To obtain a perspective of the clinical and genetic implications of PXE in the RSA, we investigated 19 affected persons.

Patients and methods

The individuals studied were derived from three principal sources. Some were referred to genetic clinics by colleagues who knew of our interest in the disorder, while others were found in the diagnostic register of the MRC Unit for Inherited Skeletal Disorders, Department of Human Genetics, University of Cape Town. In addition, several patients were found after computer searches of the records at the Groote Schuur and Red Cross War Memorial Children's Hospitals. In each instance the diagnosis was confirmed by examination of a skin biopsy specimen.

In all except 4 patients a thorough genetic history was obtained, together with details of the age of onset and development of symptoms and clinical signs. After careful physical examination, patients were categorized in the manner advocated by Pope.[3] Limited radiographic skeletal surveys were performed in 15 individuals and in 8 of these computed tomographic studies of the cranium were undertaken using contrast material.

A detailed ophthalmological examination, including fluorescein angiography of the retina, was performed in 15 patients and they were also assessed by a cardiologist through clinical examination, chest radiography, ECG and echocardiography. These patients were also investigated by a dermatologist who obtained biopsy specimens, which were studied by light and electron microscopy, from areas of normal and affected skin.

Classification

Four categories of PXE have been described by Pope:[3-5]

Autosomal recessive type I. This group had moderate vascular and retinal degeneration accompanied by flexurally distributed *peau d'orange* cutaneous lesions.

Autosomal recessive type II. This is a very rare variant presenting with generalized skin manifestations and no systemic involvement.

Autosomal dominant type I. This is characterized by severe retinal and cardiovascular degeneration, accompanied by classic cutaneous features. Early blindness and coronary artery disease frequently result.

Autosomal dominant type II. Mild cardiovascular and retinal changes, together with marfanoid features of hyperextensible joints, blue sclerae and a high arched palate, characterize this form.

Four affected individuals in our series could not be categorized. Nevertheless, using Pope's classification, the distribution frequency of our patients is similar to his report, except that there were fewer people with autosomal dominant type II PXE.

Results

Nineteen patients with PXE were studied, their ages ranging from 7 to 59 years, with an average age at assessment of 31 years. The average age of onset of symptoms was 15 years with a range of 3 - 42 years. Three children aged 8 - 10 years were investigated; the condition was first recognized in these individuals at 3,5 and 6 years. There was a female preponderance (7 males and 12 females). Fifteen patients were White, 1 was Black and 3 were of mixed ancestry.

The clinical features of the affected individuals are analysed in Table I. All showed the classic *peau d'orange* flexural skin lesions, while a high percentage (42%) presented with acne.

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TABLE I. ANALYSIS OF CLINICAL FEATURES OF PATIENTS IN STUDY GROUP

Clinical features	No.	%
Dermatological		
Classic *peau d'orange* flexural lesions	19	100
Macular cutaneous lesions	9	47
Acne	8	42
Other cutaneous lesions		
Telangiectasia of lip	6	32
Papular truncal lesions	1	5
Cosmetic surgery	2	11
Ophthalmological		
Myopia	5	26
Angioid streaking	13	68
Chorioretinal atrophy	4	21
Peau d'orange pigmentation	9	47
Retinal haemorrhages	1	5
Bilateral cataracts	1	5
Cardiovascular		
Hypertension	6	32
Diminished pulses	5	26
Angina	3	16
Calcification of vessels	5	26
Congestive cardiac failure	1	5
Redundant mitral valve chords	1	5
Bicuspid aortic valve	1	5
Thickened aortic valve leaflet	1	5

Cosmetic surgery had been performed on 2 patients. Angioid streaking was the most common ophthalmological feature; it was found in almost 70% of the patients. Severely impaired vision due to PXE was found in 4 individuals. The cardiovascular manifestations reflected intimal calcification with resultant hypertension in 6 patients (32%), diminished peripheral pulses in 5, angina in 3, and calcification of major vessels (seen on radiographs) in 5.

In terms of the genetic classification established by Pope,[3] 10 patients (53%) were thought to have the characteristic features of the autosomal recessive type I form of PXE. The autosomal dominant type II form was next most frequent (3 patients, 16%), while there was 1 individual in each of the autosomal recessive type II and autosomal dominant type I subgroups. In 4 individuals categorization was uncertain.

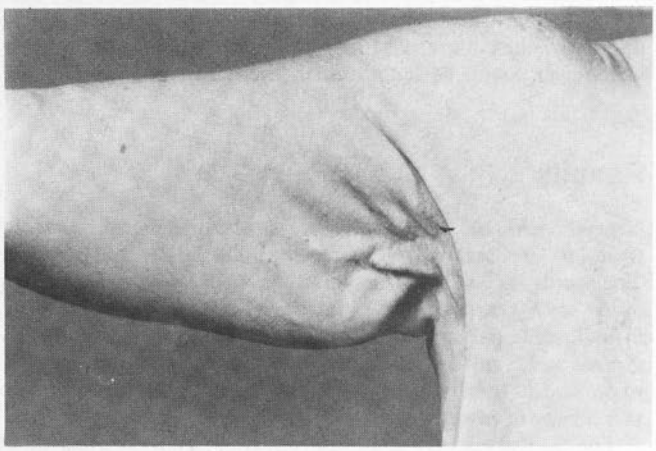


Fig. 1. Axillary lesions and redundant skin folds in a patient with PXE.

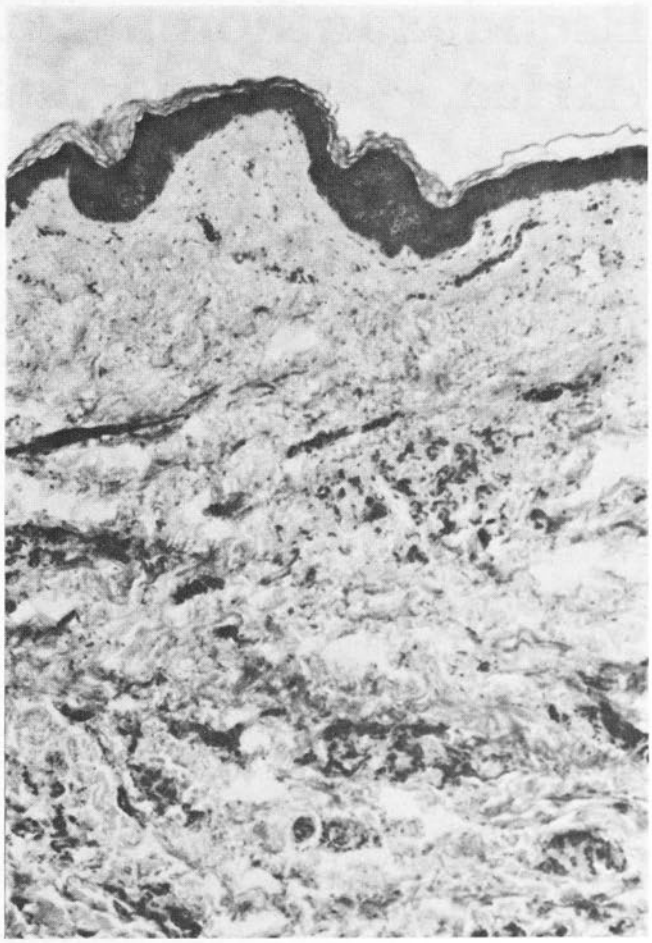


Fig. 2. Histological section of skin demonstrating disruption of elastin fibres.

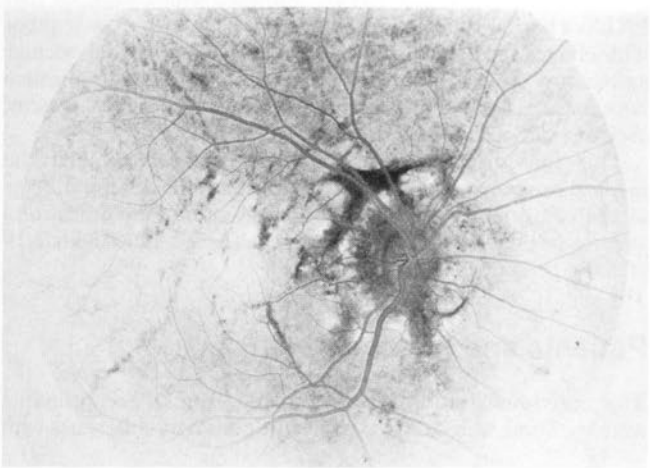


Fig. 3. Fundus of a patient with PXE showing angioid streaking.

Cutaneous manifestations

The early cutaneous features of PXE are relatively subtle and very often confused with the normal ageing processes of the skin in adults. Not infrequently the cutaneous features may be so mild as to escape clinical recognition. This was so in 3 individuals from one family in whom routine investigation was performed after the discovery of one affected sibling. The diagnosis was

subsequently confirmed by the examination of skin biopsy specimens.

The classic cutaneous features are xanthoma-like papules or plaques affecting all the flexural areas, but predominantly those of the neck, axilla, groin and antecubital fossa. The lesions resemble 'plucked-chicken skin' and may be sparse or confluent. Severely affected areas of skin become lax and hang in folds. Acneiform lesions were common in our patients (42%), as was telangiectasia of the lips and mucous membranes (32%). Both these cutaneous manifestations of PXE have been described previously, although the former is uncommon.[11] Cosmetic surgery had been successfully performed on 2 patients in our series. The initial cosmetic results were good but the long-term outlook is uncertain.

Ophthalmological manifestations

The characteristic ophthalmological finding in PXE is angioid streaking of the retina, i.e. breaks in Bruch's membrane due to weakening of the elastic lamina. These lesions are not pathognomonic since they also occur in other disorders, including Paget's disease, sickle-cell anaemia and haemochromatosis.[12] Angioid streaks were present in 13 of our patients (68%), while 4 had severe chorioretinal atrophy which had resulted in visual impairment. *Peau d'orange* pigmentation, said to be the precursor of angioid streaks,[7] was found in 9 patients and a further 5 were myopic. In our series the ophthalmological manifestations were responsible for more morbidity than the involvement of any other organ system.

Cardiovascular manifestations

The cardiovascular manifestations of PXE are well described.[7,13] The most common findings in our study group were hypertension in 6 patients, diminished peripheral pulses in 5, and radiographically apparent calcification of blood vessels in 5. Interestingly, no instances of mitral valve prolapse were found, despite a previous report by Lebwohl *et al.*[14] in which 71% of their patients had this anomaly. The significance of this observation is uncertain, since in the series of 28 patients investigated by Pyeritz *et al.*[15] only 6 individuals had prolapse of the mitral valve. This figure only just exceeds the confidence interval for the accepted prevalence of the anomaly in the general population (5 - 8%).[16] This discrepancy may be due to the predominance of autosomal dominant type II patients in Lebwohl's study group and would also explain the absence of the condition in our group, in which only 3 patients (16%) had the dominant type II variety of PXE.

Other systems

In the assessment of other organ systems it was surprising that none of our patients gave a history of gastro-intestinal haemorrhage, although this problem is frequently reported in the literature.[17] Such rare occurrences as pulmonary opacities,[18] subarachnoid haemorrhage[19] and other neurological presentations[20] were also not observed. Significant radiological abnormalities of the skeleton and soft tissues were found in several affected individuals and will be described in detail elsewhere.

Discussion

PXE is a rare, multisystem disorder with a variably reported incidence of between 1/160 000 and 1/1 000 000,[6] although McKusick[7] claims that the condition is probably more common. It can be estimated that approximately 100 - 150 affected people live in South Africa if the prevalence rate is similar to that reported above.

Of the 19 individuals in the study group 16 resided in the Cape Peninsula and immediate vicinity and a minimum prevalence of approximately 1/220 000 can be estimated for this region. Although no racial predilection has been reported, only 3 of the Cape patients (18%) were non-White. This may reflect failure of referral in the Black and mixed-ancestry populations, or a genuine increase of gene frequency in the White group, in which the calculated prevalence rate is 1/115 000. However, it is probable that not all affected individuals within each ethnic group have been identified, thereby supporting McKusick's[7] supposition that previously reported prevalence rates in PXE are underestimated. It is noteworthy that 11 of the 16 patients (69%) in the Cape were of Afrikaner descent, suggesting an increased gene frequency in this group similar to that found in several other heritable disorders.[8,9]

Three people were unaware of their condition and were first diagnosed at the initial investigation by the multidisciplinary team. As in other studies[7,10] females outnumbered males. This fact may reflect a tendency for women to seek medical attention for cosmetic reasons more frequently than men.

Histological appearances in elastin are pathognomonic of PXE, although there is dispute as to whether the primary defect lies in this tissue or in collagen. Owing to the complexity of the biochemical structure of these substances, it is likely that studies at the DNA level will prove to be more fruitful and in the current phase of our investigation we are now addressing the problem using the new molecular technology.

We are very grateful to all colleagues who referred case material to us and to Sisters Lesley Merckel and Gail Christy who co-ordinated the investigation of patients. We thank Gillian Shapley for typing the manuscript, Mr Colin Clow for the photographs and Mrs L. Horne for the retinal angiograms. This investigation was supported by grants from the South African Medical Research Council, the University of Cape Town Staff Research Fund and the Mauerberger Foundation Fund.

The principal author (Dr Denis Viljoen, Red Cross War Memorial Children's Hospital, Rondebosch, 7700 RSA) would be grateful for any information regarding patients or clinical experiences with PXE from medical colleagues within the RSA.

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PIONEER

Clinical Genetics 1987: **32**: 100–105

Heterogeneity of pseudoxanthoma elasticum: delineation of a new form?

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Sixty-four patients with pseudoxanthoma elasticum (PXE) were investigated in a nationwide study within South Africa and Zimbabwe. Thirty-nine individuals formed a distinct clinical subgroup. These persons were found exclusively among people of Afrikaner descent, whose origins are mainly derived from Dutch and French-Huguenot stock. This disorder was inherited as an autosomal recessive trait and presented mild to moderate cutaneous and cardiovascular manifestations. However, after the third decade of life severe visual impairment developed and culminated in blindness in 8 people by the age of 50. The cause of the visual defect was progressive extension of angioid streaks into the macula with neovascularization and haemorrhage. Laser therapy may have prevented further bleeding in 4 instances. The severity of ocular involvement contrasted with the mildness of the skin changes, and in this respect the condition seems to differ from previously delineated autosomal recessive forms of PXE.

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Key words: autosomal recessive inheritance; blindness; elastin; pseudoxanthoma elasticum.

Pseudoxanthoma elasticum (PXE) was first reported in 1881 by Rigal (Rigal 1881), who considered that the disorder was an atypical xanthoma. Derivation of the term pseudoxanthoma elasticum was ascribed to Darier (1896), who histologically demonstrated an abnormality in elastin in 1896. The eponym Grönblad-Strandberg syndrome (Grönblad 1929), named after two investigators who initially described the common association of ophthalmological and cutaneous features, is still used occasionally in the literature.

PXE is a rare, heritable disorder of elastin with protean clinical manifestations. The condition may be an abiotrophy of elastin fibres which undergo fragmentation and calcification (McKusick 1973). Skin over the joint flexures is most severely involved, as is the media of medium and small-sized arteries. The frequent involvement of the eyes in PXE is due to the preponderance of elastin fibres in Bruch's membrane of the retina. Degeneration at this site leads to angioid streak formation, weakened support for the retinal blood vessels, haemorrhage with neovascularization and visual impairment.

In a study of 200 affected individuals in England and Wales in 1973, Pope identified four distinct clinical types of PXE. Two of these were inherited as an autosomal recessive trait, while two were transmitted in an autosomal dominant mode (Pope 1974a, b).

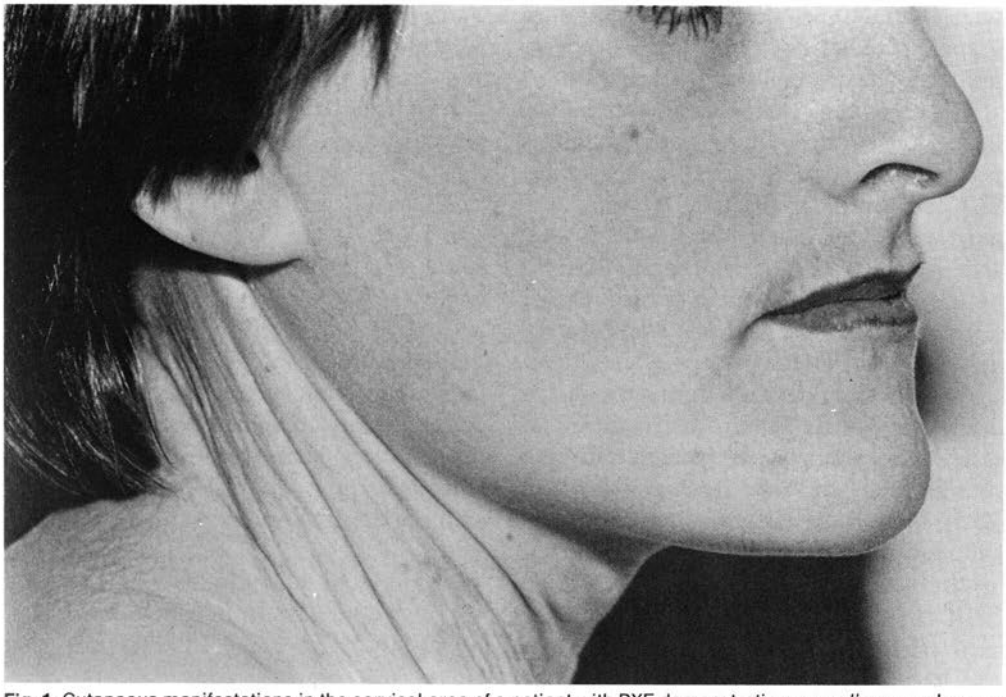


Fig. 1. Cutaneous manifestations in the cervical area of a patient with PXE demonstrating *peau d'orange* changes and laxity.

From careful pedigree analyses, together with the extent of the ophthalmic, dermatological and cardiovascular involvement, each form of PXE was clearly distinguishable. To support this contention Pope, in a historical survey of previously reported cases of PXE in the literature between 1896–1968, was able to categorize the reported patients into the 4 groups that he had identified (Pope 1975).

Sixty-four individuals from South Africa and Zimbabwe with histologically confirmed PXE have been appraised and a specific form of the disorder has been identified in 39 people of Afrikaner descent. The condition manifests with consistent and severe ocular signs and it is possible that this entity differs from established forms of PXE; the phenotypic and genealogical aspects are presented and discussed in this paper.

Material and Methods

Sixty-four patients with PXE were identified in a nationwide study within South Africa and Zimbabwe. Many of these individuals were referred to genetic clinics that are held throughout the country by colleagues who knew of our interest in the disorder. Other affected persons were ascertained as a result of a letter sent to dermatologists in hospital and private practice requesting patient referrals.

In all individuals a detailed family history was obtained together with information regarding the age of onset and development of symptoms and signs. Patients were physically examined and photographs of the dermatological manifestations were obtained. Limited skeletal radiographic surveys were performed in nearly all individ-

uals, and in 10 people computerized tomographic studies of the cranium were undertaken using contrast material.

Where possible, a detailed ophthalmological and cardiovascular examination was performed including chest radiographs, ECG, echocardiography and fluorescein angiography of the retina. Many patients were also examined by a dermatologist. Skin biopsy specimens were taken from areas of affected and normal skin, and studied using light and electron microscopy.

From the data obtained during this multidisciplinary investigation, we attempted to categorize each affected person into the classification advocated by Pope (1974a, b, 1975), by the criteria summarized below:

Autosomal Recessive Type I
Affected persons have moderate vascular and retinal degeneration accompanied by flexurally distributed *peau d'orange* cutaneous lesions.

Autosomal Recessive Type II
This i a very rare variant presenting generalized skin manifestations and no systemic involvement.

Autosomal Dominant Type I
Individuals from this group are characterized by severe retinal and cardiovascular degeneration, accompanied by classic cutaneous features. Early blindness and coronary artery disease frequently result.



Fig. 2. Typical findings of macular sclerosis in the "Afrikaner" form of PXE.

Table 1

Classification of patients with PXE

	Pope classification				"Afrikaner" Form	Total
	AD I*	AD II	AR I*	AR II		
No. of patients	3	3	15	4	39	64

* AD = Autosomal dominant
** AR = Autosomal recessive

Autosomal Dominant Type II
Mild cardiovascular and retinal changes, together with hyperextensible joints, blue sclerae and a high arched palate characterize this form.

Results

Sixty-four individuals with biopsy-proven PXE were identified, of whom 40 were female; their ages ranged from 12–63. Fifty-three affected persons were Caucasian, while 8 were of mixed ancestry. Only one Black with PXE was encountered.

Twenty-five persons in the study group were readily identified and grouped according to the classification advocated by Pope (Table 1). However, 39 individuals of Afrikaner descent had manifestations that were not in strict accordance with the criteria of any of Pope's subtypes. Pedigree analysis in these families was consistent with an autosomal recessive mode of inheritance.

In Table 2, a comparison is made between the clinical findings in the four types of PXE previously described by Pope (1975) and the 39 South Africans of Afrikaner descent. In this group, all affected persons had the classical flexural cutaneous manifestations consisting of yellowish papular lesions with mild redundancy of the skin, *peau d'orange* changes around the sides and nape of the neck and infiltration of the buccal mucosa of the lower lip. A total of 40% were hypertensive and a further 20% had arterial occlusion, as judged by either angina or intermittent claudication. There were no instances of gastro-intestinal haemorrhage, epistaxis or stigmata of other bleeding diatheses in affected individuals. Lax joints,

Table 2

Comparison of clinical features within types of PXE

		Study reported by Pope (1975)				Autosomal recessive "Afrikaner" form (N = 39)
	Clinical characteristics	AD I (N = 12)	AD II (N = 52)	AR I (N = 54)	AR II (N = 3)	
Skin	Classical flexural	100%	24%	77%	–	100%
	Generalized	–	–	–	100%	–
Cardiovascular system	Hypertension	75%	7.8%	19.7%	–	41%
	Angina/claudication	56%	–	–	–	20.5%
Ophthalmic manifestations	Angioid streaks	34%	47%	47%	–	76.9%
	Severe choroiditis	75%	7.8%	35%	–	51.3%
Marfanoid features	High arched palate, loose jointedness, blue sclerae	–	50%	10%	–	–

highly arched palate and blue sclerae as found in autosomal dominant Type II PXE were not seen in any of the patients from the "Afrikaner" group.

The physical signs of the autosomal recessive "Afrikaner" group more closely parallel autosomal dominant Type I PXE; in particular, ophthalmic sequelae were severe and were associated with moderate cardiovascular and cutaneous features.

Detailed results of the ophthalmological, cardiac, histological and radiographic studies performed on affected individuals will be published elsewhere.

Discussion

PXE is a multisystem disorder in which the structure of elastin is defective. The concept of heterogeneity is supported by its differing modes of inheritance and variable clinical expression (Pope 1974a, b, 1975, Viljoen et al. 1984). Although the human elastin gene is located on the short arm of chromosome 2, it has not been fully cloned and few restriction fragment length polymorphism (RFLP) markers are as yet available for linkage studies. It is therefore not possible to prove heterogeneity exists in PXE. Presently, the clinical presentation and mode of inheritance are the only discriminatory parameters available for the delineation of supposedly new forms of the disorder.

Pope subdivided PXE into two autosomal dominant and two autosomal recessive types. The dominant Type I group presented severe cardiovascular and eye manifestations, while in contrast, persons with the dominant Type II form had mild skin, eye and cardiovascular features together with cutaneous redundancy, high-arched palates, blue sclerae and loose-jointedness. These conditions were distinct from the "Afrikaner" type of PXE by virtue of the fact that they were both inherited as an autosomal dominant trait, whereas the latter is autosomal recessively inherited. However, the phenotype of the "Afrikaner" recessive and "British" dominant Type I patterns are remarkably similar.

The two autosomal recessive types of PXE described by Pope seemed to differ from the "Afrikaner" form, as his recessive Type I disorder less often had severe cardiovascular and eye signs, whereas his recessive Type II condition had only generalized cutaneous features and is clearly a distinct entity.

The "Afrikaner" form of PXE, with early and consistent retinal deterioration associated with eventual blindness, is an obvious discriminatory and poor prognostic feature. The ophthalmic features are age-related and severe visual impairment was usually apparent by the fourth decade of life. However, early angioid streaks occur soon after the first decade before any visual defect is detectable. In 40% of individuals, severe hypertension and occasionally angina or intermittent claudication were also present. Generally, the cutaneous manifestations were mild and did not cause significant cosmetic problems.

Since the "Afrikaner" form and other forms of PXE are indistinguishable on histology, electron microscopy or biochemistry, clinical separation of disease categories is at present the only feasible way of detecting genetic heterogeneity. Although the "Afrikaner" group does appear to have a frequency of ophthalmic retinal degeneration, hypertension and angina more like that of the "British" dominant Type I group, several comments are pertinent. Firstly, British patients with recessive Type I PXE are sometimes phenotypically indistinguishable from "British" Type I dominant patients. Secondly, there was a significant frequency of gastrointestinal bleeding (at least 10%) in the "British" Type I recessive group.

Time alone will tell whether these differ-

ences are specific, or are caused by sampling errors between the populations due to slightly different age distributions. Ultimately, gene clones for structural elastin genes and related microfibrillar components should allow formal linkage studies of PXE. This will resolve the question of whether true heterogeneity exists and allow specific antenatal diagnosis and definitive genetic counselling. Until such a discriminatory tool becomes available, categorization of the disorder and counselling for affected individuals and their kin will be based upon phenotypic and genealogical data.

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The obstetric and gynaecological implications of pseudoxanthoma elasticum

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Summary. The obstetric aspects of 54 pregnancies in 20 women with pseudoxanthoma elasticum (PXE) have been reviewed. Forty live births were delivered vaginally, three of them were preterm. Twelve pregnancies miscarried at between 6 and 14 weeks gestation and two were terminated in the 8th week for psychiatric reasons. Fetal losses in two instances were attributed to cervical incompetence. One baby died at 4 days of age from a complex congenital cardiac anomaly. No abnormal maternal genital or gastrointestinal bleeding was recorded. Hypertension complicated seven pregnancies. Abdominal striae developed in all patients, the severity of which correlated with weight gain and the number of pregnancies. All the women had normal gynaecological histories, none had excessive menstrual bleeding or increased episodes of menorrhagia. The eye, blood vessels and other organ systems involved in PXE were unaffected by pregnancy. Apart from the increased risk of first trimester miscarriage and the cosmetic deterioration of the abdominal skin, there are few serious complications in pregnancy in patients with PXE.

Pseudoxanthoma elasticum (PXE) is a rare, heritable disorder of elastic fibres which is found in all population groups throughout the world. Initially described by Rigal (1881), it was at first thought to be related to the lipid disorders. The name 'pseudoxanthoma elasticum' was suggested by Darier (1896) to describe the xanthoma-like plaques found in the skin flexures. Characteristic fragmentation and calcification of elastic fibres seen histologically is pathognomonic for the disorder.

PXE is heterogeneous and four clinically distinct types have been described, two of which are inherited as an autosomal dominant trait (Pope 1974*a*) and two are inherited as autosomal recessives (Pope 1974*b*). PXE is a multisystem disorder affecting predominantly small and medium-sized arteries, Bruch's membrane in the eye and the flexural skin creases. Episodes of epistaxis and gastrointestinal haemorrhage have been reported frequently (Eddy & Farber 1962; McKusick 1973).

The potential problems for both mother and fetus during pregnancy in this disorder are many. Hypertension, intrauterine growth retardation, thromboembolic phenomena and gastrointestinal haemorrhage are some complications reported previously. Yet in a thorough literature search, only 28 pregnancies in 10 women with PXE could be identified (Berde *et al.* 1983; Lao *et al.* 1984; Elejalde *et al.* 1984). No references to gynaecological sequelae in PXE were discovered. In an attempt to elucidate these aspects further we have reviewed in detail the gynaecological histories and medical aspects of 54 pregnancies in 20 affected women.

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Patients and methods

Sixty-four patients with PXE were studied in a nationwide, multidisciplinary investigation within Southern Africa. Patients were referred by colleagues, who knew of our special interest in the disorder, to genetic clinics held in the major population centres throughout the country.

The 64 affected persons, 40 of whom were female, were derived from 34 separate kindreds. A detailed history of the disorder was obtained and all persons were examined clinically by one author (D.V.). In addition, detailed studies were performed by colleagues in the cardiac, dermatological and ophthalmic specialties. Diagnosis was confirmed by skin biopsy in every instance. Other special investigations included a radiographic survey, cineangiography of the retina, electrocardiography, echocardiography and electron microscopic examination of biopsies of affected skin.

As part of this study, gynaecological and obstetric histories were obtained and, where possible, the information was verified with hospital records. In this manner, details on the obstetric aspects of 20 women and 54 pregnancies were retrospectively obtained together with information about three placentas which had been studied macroscopically and histologically.

Results

Retrospective data were deemed sufficiently well documented in 20 women with PXE for inclusion in the investigation. Genealogical data from respective kindreds indicated that all the patients had an autosomal recessively inherited form of the disorder. Eighteen women were of white European descent and two were of mixed ancestry. At the time of the study, their ages ranged from 15 to 64 years.

Gynaecological aspects

The mean age at menarche was 13·2 years (range 11·5–15·0 years). Only five women claimed to have had menorrhagia and the average menstrual cycle was 28·2 days (range 12–32 days) with bleeding for 4·6 days (range 2–9 days). On direct questioning, eight women complained of dysmenorrhoea.

More than one third of the 20 patients were receiving oral contraceptives at the time of the study and half those questioned had previously used this form of contraception for a period exceeding 6 months. Seven women had had an intrauterine device fitted and nine women eventually opted for tubal ligation. No complications from the use of oral contraceptives were recorded.

Few of the women investigated had required operative gynaecological procedures. Three women had had a total hysterectomy; in two this was ostensibly for dysfunctional uterine bleeding in association with a fibroid uterus. In the third the procedure was advised for ovarian carcinoma with postoperative radiotherapy. She has remained well and disease free 5 years later. Surgical repair of a cystocoele and rectocoele was required in two women following the development of urinary incontinence in the fourth decade of life. In every instance the operations, anaesthesia and postoperative courses were uneventful.

Obstetric aspects

A total of 54 pregnancies were recorded in the 20 women studied. There were 40 live births and 10 first trimester spontaneous abortions. One woman with cervical incompetence had two abortions both in the second trimester. Her subsequent pregnancies were managed successfully with a Shirodkar suture. Two terminations of pregnancy were performed at 8 weeks for psychiatric reasons in one patient. Hypertension, which occurred in seven women, was treated with bed-rest alone in three and with antihypertensive and diuretic therapy in the other four. No instances of antepartum haemorrhage or diabetes mellitus were recorded in any patients. Routine antenatal ultrasound studies in seven pregnancies detected no fetal abnormalities.

A detailed history of labour was available for 38 pregnancies. Duration of the first stage of labour varied between 3 and 12 h (mean 7·3 h). All the babies were born vaginally and their mean birthweight was 3·16 kg (range 1·37–3·92 kg). Three babies were born preterm at estimated gestational ages of 32–34 weeks. No complications were associated with prematurity in these infants. Data were available for three placentas; apart from a slightly excessive degree of calcification in two and a mildly elevated placental–fetal mass ratio of 1:8 (normal 1:5–1:7), no macroscopic or histological abnormalities were detected.

Postpartum haemorrhage was not a feature of any delivery. One baby died at the age of 4 days from a complex cyanotic cardiac malformation. All the remaining live born babies, many of whom are already adults, have thrived.

There was no deterioration in the general health of the 20 women and no ophthalmological symptoms were reported during the pregnancy. Striae and the peau d'orange mottling of the skin typical of PXE became more prominent during the pregnancy, particularly in women who gained excessive weight and in some multiparas. The skin lesions did not regress after delivery and several women complained of persistence of an abdominal 'apron' of lax skin. The appearance and severity of other flexural skin lesions remained constant (Fig. 1).

Discussion

PXE is a rare heterogeneous disorder of elastic fibres which has a wide ethnic and geographical distribution. The estimated prevalence varies but is thought to be in the region of 6 in 10^6 of the population. Multiple body systems are involved due to the presence of abnormally fragmenting elastic fibres within affected tissues but the sites of predilection are the skin, cardiovascular system and eye. The cutaneous features are yellow, maculopapular areas resembling 'plucked chicken-skin' or 'cobblestones' predominantly affecting the flexural areas. The lesions are progressive and the skin in the affected regions becomes lax. The cardiovascular manifestations are early arteriosclerotic changes in medium-sized arteries with the resultant propensity for hypertension, congestive cardiac failure and stroke. In the eye, the elastin-rich lamina within the retina known as Bruch's membrane is principally affected with resultant angioid streaks, retinal haemorrhages, macular degeneration and eventual blindness.

Little has been published about pregnancy in women with PXE. In a review of the literature, Berde *et al.* (1983) documented a total of 24 pregnancies in seven women. Gastrointestinal haemorrhage was a prominent feature which was reported in 8 of 20 pregnancies in five women. Berde *et al.* (1983) also described in detail one further uneventful pregnancy in a 28-year-old woman. Lao *et al.* (1984) briefly outlined the case histories of two pregnant women with PXE, one of whom had mild hypertension, and Elejalde *et al.* (1984) described in detail one pregnancy with special emphasis on the ultrasonographic findings. Other authors have



Fig. 1. Patient demonstrating the classical cutaneous laxity and peau d'orange changes of pseudoxanthoma elasticum (PXE).

alluded to obstetric complications in patients with PXE (Altman *et al.* 1981; Hall 1981) but the data presented have been insufficient for analysis. Thus far, a total of only 28 pregnancies in women with PXE have been described and these reports are probably biased in that mainly abnormal confinements would have been described.

In this paper we describe 54 pregnancies in 20 women with PXE who were part of a larger cohort of 64 affected patients, 40 of them women. The 20 women were selected for this study because detailed obstetric and gynaecological histories were available. In all these women, the medical condition was inherited as an autosomal recessive trait and the diagnosis was established by skin biopsy.

The gynaecological histories of our patients are unremarkable in that menarche occurred at the appropriate time, menstruation was normal and there was no apparent increase in episodes of menorrhagia. In view of the previously reported propensity for epistaxis, gastrointestinal haemorrhage (Carlborg 1944; Loria *et al.* 1957; McKusick 1973), ovarian haemorrhage (Giesen 1936) and uterine haemorrhage (Touraine 1940), the absence of bleeding problems in our patients suggests that these complications may have been over-reported previously in comparison to the number of normal pregnancies which take place. However, the possibility of bleeding diathesis in individuals with PXE has important implications for obstetric management.

A feature of concern in our patients was that oral contraceptives were frequently used. The risk of thromboembolic episodes is known to increase in women using high dose oestrogen oral contraceptives and in a disorder such as PXE where stroke and hypertension are more frequent, the likelihood of a vascular accident may be increased even if low dose oestrogenic compounds are used. Although we did not encounter complications of this type it would seem reasonable that other means of contraception should be advocated for these women.

Two women in our series required surgical repair of a rectocoele and cystocoele. The development of redundant folds of skin due to loss of elasticity in PXE would suggest that laxity of pelvic ligaments and tissue may also occur in multiparas, thus accounting for prolapse of bladder, rectum or uterus.

The rate of abortion in our patients (about 26%) may be slightly higher than the rate in the general population (Gustavii 1984). The two second trimester miscarriages in one woman with cervical incompetence may reflect a previously undescribed manifestation of PXE. Both miscarriages had followed a normal vaginal delivery and it could be speculated that the incompetent cervix was due to the presence of abnormal elastic fibres. However, there have been no other similar reports in the literature to support this suggestion.

Our patients had surprisingly normal pregnancies. Hypertension occurred in seven but the level and control of blood pressure improved with duration of the pregnancy suggesting that the increasing low resistance vascular bed provided by the placenta may have helped in lowering blood pressure. Despite the fact that the blood vessels are involved in PXE, no adverse cardiovascular events related to PXE were recorded during any of the pregnancies.

Labour and delivery were unremarkable in the 20 women except that there were three preterm births. This rate of premature delivery is within the normal range. Two of the three placentas examined showed mildly excessive calcification for which no reason was apparent. An important finding was that only one of the 40 babies was born with a congenital malformation; a severe cardiac anomaly which led to death at 4 days of age.

During pregnancy, no progression of the ophthalmic and cardiovascular features attributable to PXE occurred. In multiparous women, abdominal striae and marked skin laxity developed, the severity of which correlated with the number of pregnancies and excessive weight gain during pregnancy. The flexural skin lesions were unaffected during this period.

In conclusion, there was an increased risk of abortion and most women claimed a deterioration in the appearance of their abdominal skin. The potential for gastrointestinal haemorrhage due to abnormal blood vessels is present but rarely occurs in our experience. We can confirm the clinical impression that despite the potential maternal and fetal hazards, most pregnancies complicated by PXE have a normal course and outcome.

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Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome)

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Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome)

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Pseudoxanthoma elasticum (PXE) is a rare disorder of elastin which primarily involves the skin, cardiovascular system, and eyes, but also manifests in the central nervous system, skeleton, and gastrointestinal tract. Rigal[1] first described the cutaneous lesions of PXE in 1881 and thought the disorder was akin to the xanthomatoses. In 1896, Darier[2] showed the typical histological changes in elastin fibres, thus proving that PXE was a separate condition. Grönblad and Strandberg subsequently recognised the association between ophthalmological and dermatological features in PXE and their names are sometimes eponymously applied to the disorder.[3]

Incidence

The true frequency of PXE is unknown but estimates range from 1:160 000 to 1:1 000 000 of the population.[4] There appears to be no specific ethnic or population predilection, but more affected females than males have been reported. This probably reflects an ascertainment bias as women are more likely to seek medical attention for cosmetic reasons.

Clinical aspects

SKIN

The typical manifestations of PXE are yellowish papular lesions in the flexures associated with mild skin redundancy. The nape of the neck is the most frequently affected, followed by the axillae, groins, and antecubital fossae (fig 1). A rare, generalised form of PXE has been described in which the skin is very lax and non-flexural areas are involved.[5]

EYE

Although not pathognomonic of PXE, angioid streaks or breaks in Bruch's membrane of the retina occur in 85% of affected subjects. These lesions tend to extend radially from the optic disc (fig 2). Neovascularisation, oedema, haemorrhage, and eventual fibrosis lead to visual deterioration which may be profound when the macula is involved.[6]

CARDIOVASCULAR SYSTEM

Premature obliterative arteriosclerotic changes of the medium and small sized arteries result in diminished pulses, cold peripheries, intermittent claudication, renovascular hypertension, angina, and cerebrovascular accidents. Mitral valve prolapse is reported to be common in one form of PXE.[7]

GASTROINTESTINAL

Despite a plethora of single case reports, GIT haemorrhage is an infrequent complication of PXE. When it occurs, bleeding is probably the result of structural weaknesses in the submucosal blood vessels of the stomach.[3]

OTHER FEATURES

Clinical features less frequently reported are presenile dementia, peripheral neuropathy, and an increased risk to the affected female of having a miscarriage in the first trimester.[8] Minor radiological changes include calcification of the falx cerebri.

Differential diagnosis

Solar and actinic (senile) elastosis have cutaneous features which are very similar to PXE. Occasionally, penicillamine and vitamin D toxicity can produce skin lesions which resemble those of PXE, but can be histologically differentiated. Patients with cutis laxa have skin redundancy but no other stigmata of PXE.

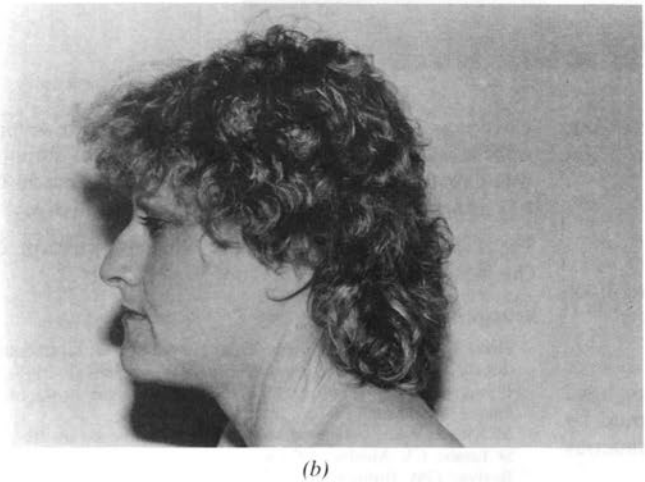
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(a)



(c)



(b)

1 *Loose, thickened skin folds in a patient with PXE (a) before surgery and (b) after surgery. (c) Marked cutaneous ity in the axilla.*

vestigations

in biopsy may be the only means of differentiating tween the aforementioned disorders and PXE. e characteristic skin changes occur in the deep d middle zones of the corium where large gregations of degenerate elastin fibres are found. lcification of elastin fibres is the earliest histo- gical abnormality in skin from affected subjects d this phenomenon is progressive. Collagen is said be unaffected in PXE.

Routine annual review of the cardiovascular and hthalmological status of affected persons is im- rative in order to treat early hypertension and also avoid the sequelae of angioid streaks extending into the macula of the eye area. Bleeding and neovascularisation in the latter lesions causes severe visual impairment and extension of angioid streaks may be prevented through the use of laser therapy.

Natural history and management

PXE is a progressive disorder and affected subjects have an increased propensity for ischaemic heart disease, cerebrovascular accidents, visual impairment, and cosmetic deterioration of the skin. Life expectancy is reduced as compared with the general population.

Early medical treatment of hypertension, cosmetic surgery, and laser therapy for eye complications

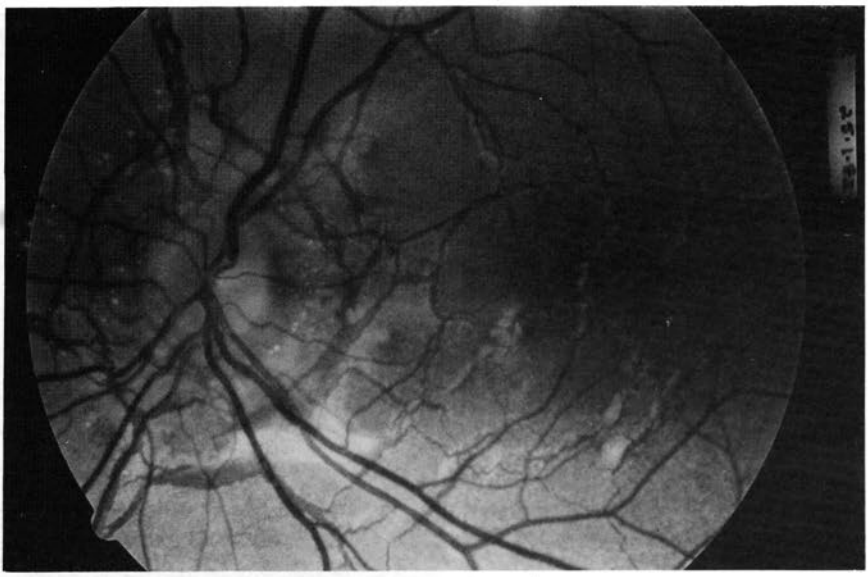


FIG 2 *Ocular fundus of a PXE patient showing angioid streaks and retinal sclerosis.*

are some of the therapeutic options. There is some evidence suggesting a beneficial effect from a low calcium diet.[9]

Inheritance

PXE is heterogeneous and five forms have been described which are phenotypically distinct.[5 10 11] Pope[10] delineated four types.

Autosomal recessive type I. These patients have vascular and retinal degeneration accompanied by flexurally distributed peau d'orange cutaneous lesions.

Autosomal recessive type II. This is a very rare variant presenting with generalised skin manifestations and no systemic involvement.

Autosomal dominant type I. This form is characterised by severe retinal and cardiovascular degeneration, accompanied by classic cutaneous features. Early blindness and coronary artery disease frequently result.

Autosomal dominant type II. Mild cardiovascular and retinal changes, together with Marfanoid features of hyperextensible joints, blue sclerae, and a highly arched palate, characterise this form.

A fifth distinct form of PXE has recently been described in 39 patients from 24 families in the Afrikaner community in Southern Africa.[11] Affected persons have mild to moderate cutaneous and cardiovascular manifestations together with severe ophthalmological lesions. Profound visual impairment or blindness occurs from the third decade of life onwards. Inheritance is autosomal recessive.

Fig 1 is reproduced with the kind permission of the editor of *Clinical Genetics*.

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Pseudoxanthoma Elasticum : Similar Autosomal Recessive Subtype in Belgian and Afrikaner Families

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RUNNING HEAD

De Paepe et al.. Pseudoxanthoma Elasticum

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ABSTRACT

A multidisciplinary survey of the clinical and genetic characteristics of 26 Belgian and 32 Afrikaner families with biopsy-proven pseudoxanthoma elasticum (PXE) was undertaken. The major PXE phenotype emerging from this study is very similar in both patient groups and is characterized by severe ophthalmologic manifestations with variable, mild cutaneous and vascular symptoms. In the families with more than one affected relative, segregation analysis is compatible with autosomal recessive inheritance in both groups. It is suggested that the PXE phenotype of these Belgian and Afrikaner patients is distinct from the other recognized PXE subtypes. The phenotypic resemblance in both patient groups raises the question whether a similar genetic mechanism is involved.

KEY WORDS : pseudoxanthoma elasticum, elastin, autosomal recessive inheritance, clinical and genetic heterogeneity, severe retinopathy.

INTRODUCTION

Pseudoxanthoma elasticum (PXE) is a rare heritable disorder of elastin mainly involving the skin, eyes and cardiovascular system.

Pope [1974 a and b] suggested that PXE is clinically and genetically heterogeneous and recognized two autosomal dominant (AD) and two autosomal recessive (AR) subtypes, which differed in severity of the ophthalmologic and vascular manifestations. Recent studies suggest that this classification warrants expansion [Viljoen et al., 1987; Neldner, 1988; Pope, 1988]. In particular, a new "Afrikaner" subtype, characterized by severe visual disturbances and AR inheritance has been reported [Viljoen et al., 1987].

In a Belgian study, the phenotype of a number of PXE patients resembled the Afrikaner form of the condition [De Paepe et al., 1988], raising the question whether they have a similar disorder. A comparative clinical evaluation of the Afrikaner and Belgian patient data is presented here.

MATERIAL AND METHODS

The Belgian group comprised 30 patients (from 26 families) which were seen in the Centre for Medical Genetics during a 6 months survey. The diagnosis of PXE had been established on clinical and/or histological grounds. Twenty of the index patients were referred from the Department of Ophthalmology, and 10 from the Department of Dermatology. There were 20 females and 10 males, between age 25 and 73 years, all

Caucasian and of Belgian descent. A detailed medical history, physical examination and photographs of the skin lesions were obtained in every patient.

In all 30 patients, a skin biopsy was taken from a predilection site, usually in the neck. In 22 of them an additional skin biopsy was obtained from an ostensibly normal non-predilection site. Specimens were sent for light- and electron microscopy and for fibroblast cultures. Sections were stained successively with hematoxylin and eosin, Von Kossa and also specifically for elastic tissue. Fibroblast cultures were stored at -196° C. Measurement of visual acuity, fundoscopy and photography, and fluorescein angiography were performed.

Besides a routine cardiovascular evaluation, a Doppler examination of the peripheral blood vessels was undertaken in 20 patients.

Accurate pedigree data comprising at least 3 successive generations were compiled. All first degree relatives were clinically examined and possible consanguinity was traced through civil registry files for 6 or more generations.

The South African group comprised 51 Afrikaner patients (belonging to 33 families), mainly derived from Dutch, Flemish and French-Huguenot stock, who were detected on the occasion of a nation-wide PXE survey in South Africa and Zimbabwe. These individuals had a distinct phenotype and good evidence for AR inheritance [Viljoen et al., 1987]. In every instance a detailed family history had been obtained together with

information regarding the time-of-onset and development of symptoms and signs. Clinical diagnosis was based on specialized dermatologic, ophthalmologic and cardiologic examination. Wherever possible, the diagnosis was confirmed by skin biopsy.

RESULTS

CLINICAL DATA

Belgian Patients

Dermatologic Findings (Table I). The typical flexurally distributed skin lesions, i.e. "peau d'orange" and yellow xanthoma-like papules with or without skinfolding were seen in 19 of the 30 patients. However, the distribution and severity of the lesions were extremely variable. The neck and axilla were most frequently involved, whereas the periumbilical or presternal areas were usually spared. Eight patients had only a discrete reticular yellowish rash and 3 had no visible skin lesions. Skin biopsies from the predilection sites showed characteristic fragmented and calcified elastic fiber clumps in the lower and middle dermis of all patients, except in 2 sisters born from consanguineous parents. Both had typical PXE eye lesions but no skin involvement, whereas their affected sister presented with typical clinical and histological PXE skinlesions (Fig. 1 pedigree Y., Si). The biopsies from non-predilection sites were normal in all except one patient where PXE lesions were found in the lower dermis. Mucosal involvement was mainly observed in patients with serious skin lesions and presented as yellow papules on the inner side of the lower lip.

Ophthalmologic Findings (Table II). The major visual complaints were metamorphopsia and visual loss. Visual acuity was severely decreased in 17/30 patients. In all of these the visual abnormalities had occurred before the fifth life decade. Moreover, once the visual abnormalities had occurred in one eye, involvement of the second eye usually followed within 2 years. In all 30 patients angioid streaks and pigment alterations were present in the fundus. Moreover, 20 patients had signs of macular degeneration which was of the exudative form in 17 patients and of the atrophic type in 3. None had high grade myopia.

Vascular Findings (Table III). The cardiovascular problems included occlusive vascular disease, manifesting as intermittent claudication or angina, hypertension or, rarely, gastrointestinal hemorrhages. However, in 2 patients hematemesis had been the first manifestation of the disease. Doppler examination performed in 11 patients with clinical symptoms of occlusive vascular disease showed decreased arterial flow in 7 but showed no abnormalities in the 4 others. Of the 7 PXE patients without clinical vascular symptoms, 4 had decreased arterial flow and 3 had normal Doppler findings.

Afrikaner Patients

Dermatologic Findings. The cutaneous manifestations of 51 Afrikaner patients (Table I) were extremely variable, but even in mild cases classical "peau d'orange" changes could be demonstrated in the skin flexures, especially those of the neck

and antecubital fossae. More unusual sites included the anterior chest wall and peri-umbilical region; occasionally the skin showed a generalized fine reticular rash. In severely affected individuals, the mucous membranes of the mouth were affected and telangiectasia of the lower lip sometimes present.

Ophthalmologic Abnormalities (Table II). Individuals under the age of 30 years seldom had loss of visual acuity, although all had angioid streaks. After the third decade of life retinal hemorrhages, macular degeneration and loss of visual acuity in one or both eyes was common and blindness occured in 65% of individuals over age 50 years.

Vascular Findings (Table III). Of the 51 Afrikaner patients 17 had hypertension while 15 had evidence of occlusive vascular disease in the form of intermittent claudication, angina, ischemic leg ulcers and strokes. Apart from one patient who had recurrent hematemeses from oesophageal varices due to cirrhosis, no instances of gastrointestinal hemorrhage were recorded.

GENETIC DATA

Belgian Patients

The 30 Belgian patients represented 26 different families. In 21 families there was only one affected patient while in the 5 others (Fig.1) 2 or 3 affected relatives were found. In 4 of these 5 families the affected relatives were sibs whose parents were found to be normal. In one family (Fig. 1 V.,El & V.K.Li) there were affected patients in two generations, i.e. the

index patient, her maternal uncle and a distant paternal cousin.

Consanguinity between the parents of affected patients was found in 4 of the 26 families, i.e. in 2 with sporadic and in 2 with familial occurrence (Fig. 1).

In total, 18 patients had already produced 40 children and 18 grandchildren, all of whom were healthy. However, 9 of the children and all the grandchildren were still too young to show symptoms of the disease.

Afrikaner Patients

The 51 Afrikaner patients represented 33 different families, of whom 22 had a single affected individual. In 1 patient, no family history was available. The remaining 10 kindreds contained from 2 to 6 affected individuals. Seventeen patients from 2 families, all affected relatives in each kindred were sibs whose parents were normal. In one family, two generations were affected (Fig. 2). It is assumed that the mother (II-2) and the father (II-1) were heterozygous carriers of the PXE gene. In a further kindred (Fig. 3), generation to generation transmission of the disorder had occurred and was interpreted as pseudo-dominant inheritance. Patient II-8, an affected individual, produced an affected daughter.

One hundred and thirty-eight children and numerous grandchildren have been born to the remaining 49 patients with PXE, in whom the genealogical data are complete. None of these offspring have shown signs of the disorder.

DISCUSSION

Phenotypical and Clinical Aspects

The Belgian and South African data further underline the phenotypic variability of PXE, as was already pointed out by Pope [1975]. Indeed the appearance and extent of the cutaneous lesions were very variable even among sibs of the same family (Y,Si in Fig. 1). In some patients the skin lesions were too mild or atypical for accurate diagnosis. In this respect, it is stressed that it is important to confirm the diagnosis of PXE histologically in patients with atypical skin lesions. Histological examination is also mandatory for differential diagnosis with disorders such as senile elastosis which can present similar cutaneous lesions and with conditions such as Paget disease in adults and children (osteoectasia), where angioid streaks can be found in the retina.

In both the Belgian and Afrikaner patient groups the ophthalmologic manifestations were frequently present and usually severe whereas the skin lesions were generally mild and did not cause significant cosmetic problems.

In the Belgian study, thorough search through all patient files from the last 10 years in the dermatologic and ophthalmologic clinics showed a much higher number of PXE patients in the latter department. This explains why most patients in the Belgian group were ophthalmological (20) rather than dermatological (10). This bias emphasizes the point that PXE patients mainly sought medical help for their ophthalmologic

problems. Also angioid streaks and "peau d'orange" changes in the fundus were sometimes detected only after careful fundus inspection following pupillary dilatation. There was no clear correlation between the extent of the skin lesions and the severity of the eye or vascular manifestations in either series of patients. Vascular manifestations, although common, were apparently less hazardous and troublesome than the ophthalmologic lesions. Gastrointestinal hemorrhage was a rare complication in both the Belgian and the South African patients.

Genetic Analysis.

In the Belgian patient group consanguinity between the parents of affected patients was increased (15%) compared to the rate of consanguineous marriages in the Belgian population. The latter is estimated to have been 2% in the early 20th century and to have decreased subsequently to less than 1% [Twiesselmann et al., 1962]. In none of the Belgian families there was any evidence for AD transmission: no father to son transmission and no multiple generation families were observed. The only 2 generation family (Fig.1, V.El. & V.K.Li) is still compatible with segregation of a recessive PXE trait. Indeed, the genealogical data in this family are highly suggestive of consanguinity between the maternal and paternal ancestors of the index patients. Also, the index patient's mother showed no clinical signs of PXE at the age of 60 years.

Evidence for AD transmission was also lacking in the Afrikaner families, with the exception of the kindreds illustrated in fi-

gures 2 and 3. In the first example, patient II-2 may represent non-penetrance of a dominant gene. However, her parents were unaffected. She also has affected sibs who have a total of 7 normal children. The evidence supports autosomal recessive inheritance with patients II-1 and II-2 representing heterozygous carriers for PXE.

In the second family, a patient with PXE (II-8) has produced an affected daughter. Given the pattern of inheritance in this kindred, it would appear that the wife of patient II-8 was a fortuitous PXE heterozygote resulting in apparent generation-to-generation transmission of the disorder. This is a probable example of pseudo-dominant inheritance.
The Ethnic origins of the spouses in each instance of "pseudo-dominant" inheritance were Afrikaner and no consanguinity was evident within the past 3 generations in each pedigree. However, in genealogical studies involving 14 generations from the time of early Cape settlement to date, considerable consanguinity was recorded within generations I - VI in these kindreds (Torrington and Viljoen, 1989). Indeed, in a recently completed genealogical study of the ancestors of Afrikaner PXE families [Torrington and Viljoen, 1989], founder effect was demonstrated. Considerable consanguinity was also evident in the isolated, culturally distinct Dutch settler population in the Cape resulting in an increased frequency of the PXE gene. Links to families in the low countries of Europe have been established through this study. Founder effect has also been

implicated in the increased incidence of several other heritable disorders in the Afrikaner [Louw and Torrington, 1968; Brink and Torrington, 1977; Torrington et al., 1984].

Testing of the family data for consistency with the segregation ratio for AR inheritance [Vogel and Motulsky, 1986] gave strikingly similar findings for both the Belgian and Afrikaner patient groups, assuming ascertainment to be either of the single selection or complete (truncate) selection type (Table IV). Under truncate selection the observed data fit the hypothesis of AR inheritance (the difference between observed and expected numbers of affected individuals is not statistically significant). However, under the assumption of single selection, the difference between observed and expected number of affected individuals in both groups is significant at the 0.05 level but not at the 0.1 level. The observed number of affected individuals is smaller than would be expected with AR inheritance. However, in practice ascertainment is somewhere between complete and single selection. The Belgian sample selection is certainly of the multiple incomplete ascertainment type, with 27 propositi having 61 sibs of whom 11 were affected.
Even though the possibility of a new dominant mutation must be considered in the sporadic patients, the familial occurrences point towards AR inheritance.
It was difficult to subdivide the patients rigorously into Pope's subtypes, because of lack of correlation between clinical severity and pattern of genetic transmission. Patients with

mild or no visual disturbances fitted most accurately into Pope's AR type I, although on the whole, the incidence of fundus alterations and cardiovascular symptoms was higher. Myopia was very occasional and mild.

The other patients presented a phenotype somewhat reminiscent of Pope's AD type I with respect to the severe ophthalmologic complications but AD transmission was evident in none of them. None of the patients were found to fit into the conventional AD type II or the AR type II subgroups.

CONCLUSIONS

The major PXE phenotype emerging from the Belgian and South African data is strikingly similar, i.e. severe ophthalmologic manifestations with variable but rather mild cutaneous and vascular symptoms. This clinical resemblance and recent genealogical studies raise the question whether the same mutation might be involved in the two patient groups, i.e. whether Belgian patients with PXE might be homozygous for the same genes that cause the Afrikaner form of PXE in South Africa.

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TABLE I. Dermatological Data

Clinical Manifestation	Belgian n=30 pat.	Afrikaner n=51 pat.
Classical peau d'orange lesions	19	51
Yellow, reticular rash	8	11
Unusual cutaneous site involvement	2	6
Buccal mucous membrane involvement	7	18

TABLE II. Ophthalmological Findings

Ophthalmologic Manifestation	Belgian n=30 pat.	Afrikaner n=51 pat.
Visual acuity - 7/10 - 10/10	10	18
2/10 - 6/10	3	13
1/10 or less	17	20
Angioid streaks	30	51
Peau d'orange fundal changes	30	38
Macular degeneration	20	33

TABLE III. Cardiovascular Problems

Cardiovascular Manifestation	Belgian n=30 pat.	Afrikaner n=51 pat.
Intermittent claudication	11	9
Angina	2	4
Ischemic leg ulcers	0	1
Cerebrovascular accident	0	1
Hypertension	9	17
Gastro-intestinal hemorrhage	3	1

TABLE IV. Segregation Analysis

		Selection					
			Single			Complete	
Sample	O	E	V		E	V	
Belgian	30	37.8	10.3	2.41(.015)	32.8	8.1	.99(.32)
Afrikaner	46	57.3	20.4	2.49(.014)	48.2	17.0	.54(.58)

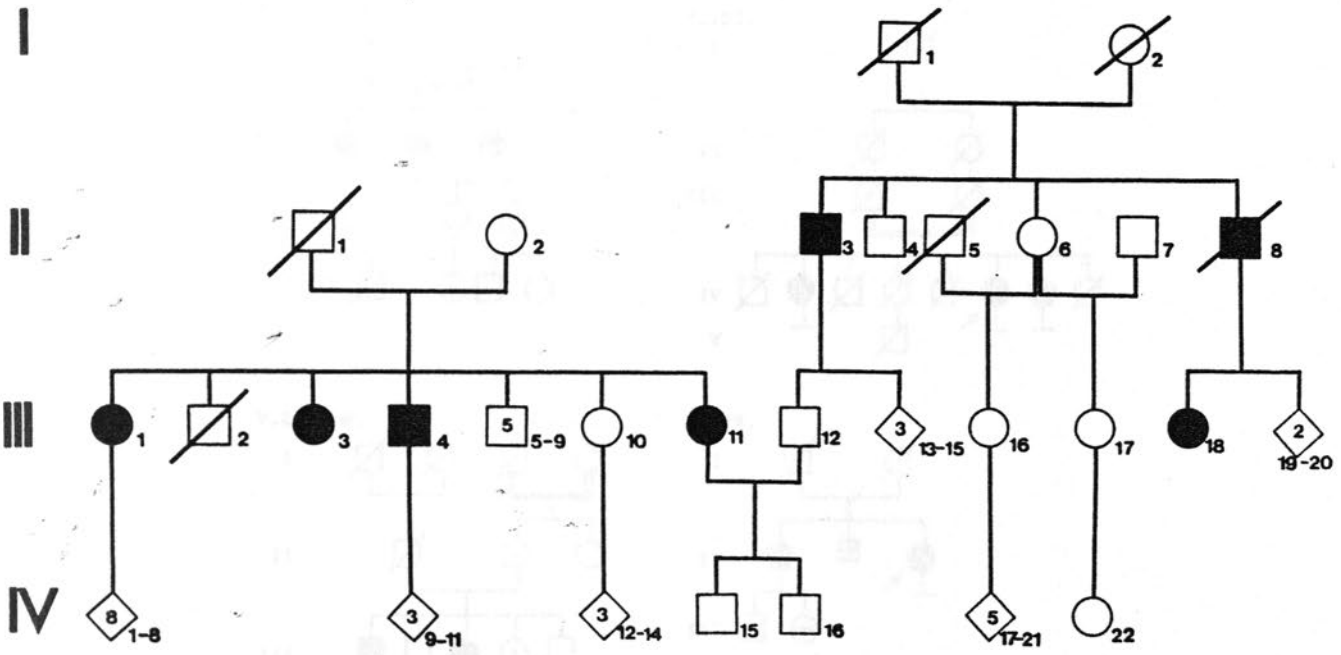
Observed (O), Expected (E) numbers of affected individuals, with its variance (V) in Belgian and South-African samples, together with the result of the χ-test($\chi = [O-E]/V^{1/2}$), and its p-value.

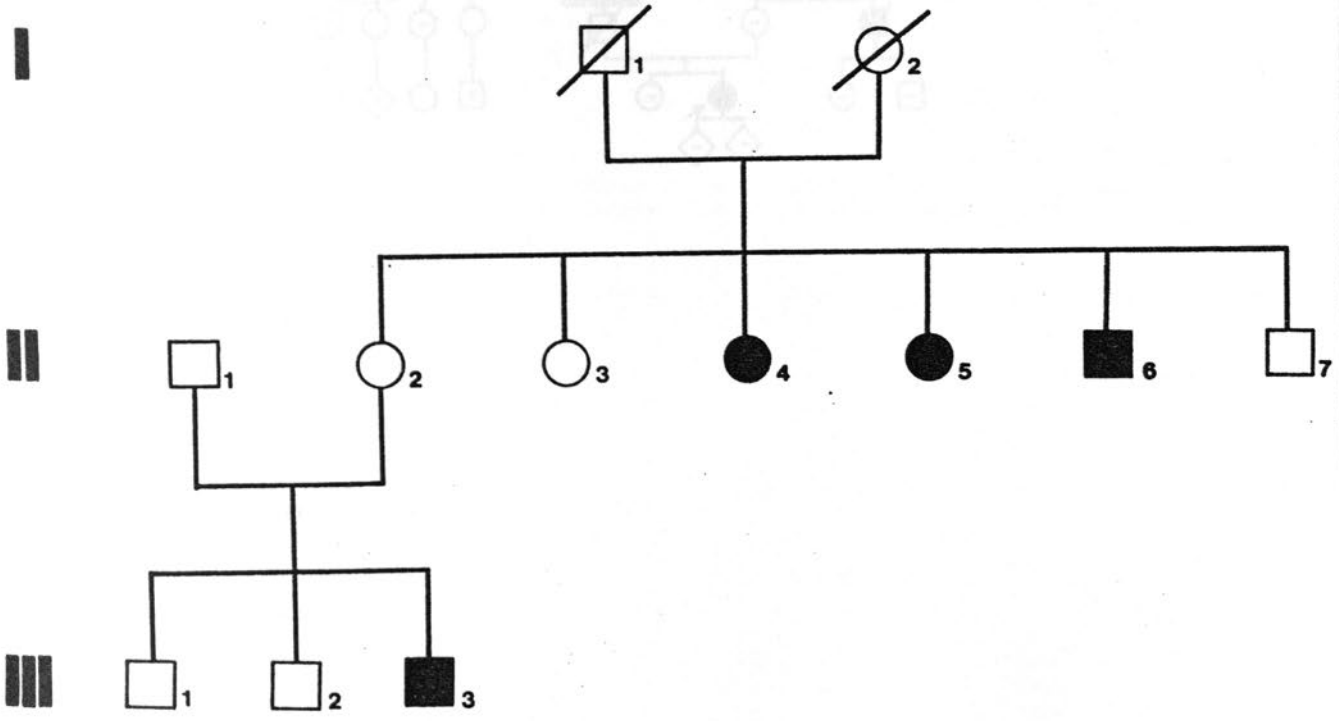
LEGENDS

Fig. 1 : Pedigrees of the Belgian PXE families with more than one affected relative (●■) ⌜- - - -⌝ = probably consanguineous. ⊖ ⊟ = individuals who were examined but showed no signs of PXE

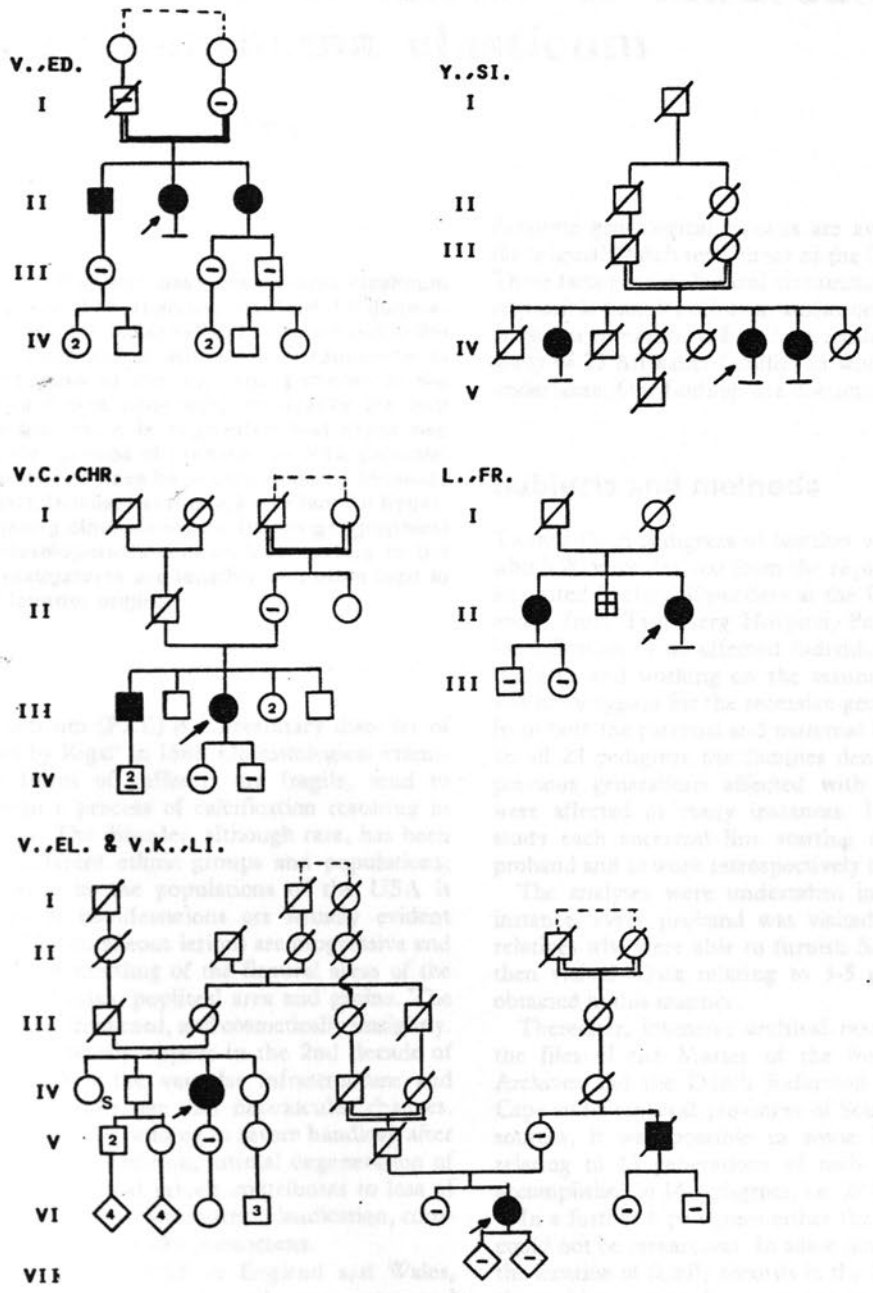
Fig. 2 : Pedigree of one Afrikaner family with affected relatives in two generations. Individuals II-2 and II-1 are assumed to be heterozygous carriers of the PXE gene.

Fig. 3 : Pedigree of second Afrikaner family where the occurrence of PXE in two generations could be explained by pseudo-dominant inheritance.


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FAMILIAL PXE CASES.



Founder effect in 20 Afrikaner kindreds with pseudoxanthoma elasticum

M. TORRINGTON, D. L. VILJOEN

Summary

The pedigrees of 20 families with pseudoxanthoma elasticum (PXE) were investigated. The analyses involved 13 generations up to and including the initial settlers, who arrived in the Cape before 1660. Four settler surnames predominate in these pedigrees. Because of the marriage patterns of the settlers' descendants it was necessary to classify the four surnames into two groups. It is suggested that these two groups are the founder groups of present-day PXE patients. Similar genealogical studies have been performed on kindreds with familial polyposis, familial heart block and familial hypercholesterolaemia, among other disorders. Due to geographical isolation, political developments and cultural factors in the Afrikaner, these investigations are feasible and often lead to the identification of founder origin.

S Afr Med J 1991; **79**: 7-11.

Pseudoxanthoma elasticum (PXE) is a hereditary disorder of elastin first described by Rigal[1] 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.[2] 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[3-5] 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.*[6] 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. Accurate genealogical records are available from the time of the original Dutch settlement of the Cape in the 17th century. These factors provide ideal circumstances for the investigation of possible founder effect in a disorder such as PXE within the Afrikaner community. For these reasons a detailed genealogical study of 23 Afrikaner families in whom PXE is prevalent was undertaken. Our findings are documented here.

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Accepted 29 Mar 1990.

Subjects and methods

Twenty-three pedigrees of families with PXE were studied of which 20 were derived from the records of the MRC Unit for Inherited Skeletal Disorders at the University of Cape Town and 3 from Tygerberg Hospital, Parowvallei, CP. After the identification of an affected individual (the proband) in each pedigree and working on the assumption that each proband was homozygous for the recessive gene, the lineage was sought from both the paternal and maternal branches of each kindred. In all 23 pedigrees the families denied having knowledge of previous generations affected with PXE, although siblings were affected in many instances. It was thus necessary to study each ancestral line starting from the parents of the proband and to work retrospectively through the generations.

The analyses were undertaken in two ways. In the first instance, every proband was visited and interviewed. Other relatives who were able to furnish further family details were then visited. Data relating to 3-5 previous generations was obtained in this manner.

Thereafter, intensive archival research was undertaken in the files of the Master of the Supreme Court, the State Archives and the Dutch Reformed Church Archives of the Cape and Transvaal provinces of South Africa. Through these sources, it was possible in some instances to gather data relating to 13 generations of each ancestral line. This was accomplished in 14 pedigrees, i.e. 28 parental ancestral lines.

In a further 6 pedigrees either the paternal or maternal line could not be researched. In some instances, failure was due to the location of family records in the Orange Free State, where the archive sources have not yet been researched (4 paternal lines). In another kindred, archival records were located in Namibia (1 maternal line) and, in a further family, the parental roots were overseas (1 paternal line). Thus 6 out of 12 possible ancestral lines in this group were studied. A total of 34 lines in 20 families were thus fully investigated.

Three pedigrees had to be discarded, primarily because the family data were logistically difficult to research.

Results

Archival searches were deemed to be complete once a link was made to previously researched family genealogies or to the De Villiers and Pama[7] record of genealogies of old South African families. These references allowed identification of the initial settlers/original ancestors in each of the 34 lines of the 20 probands under study. On compilation of a table of these individuals, 4 surnames predominated, namely M, B, V, and S (Figs 1-4). Each of these settlers had a number of children

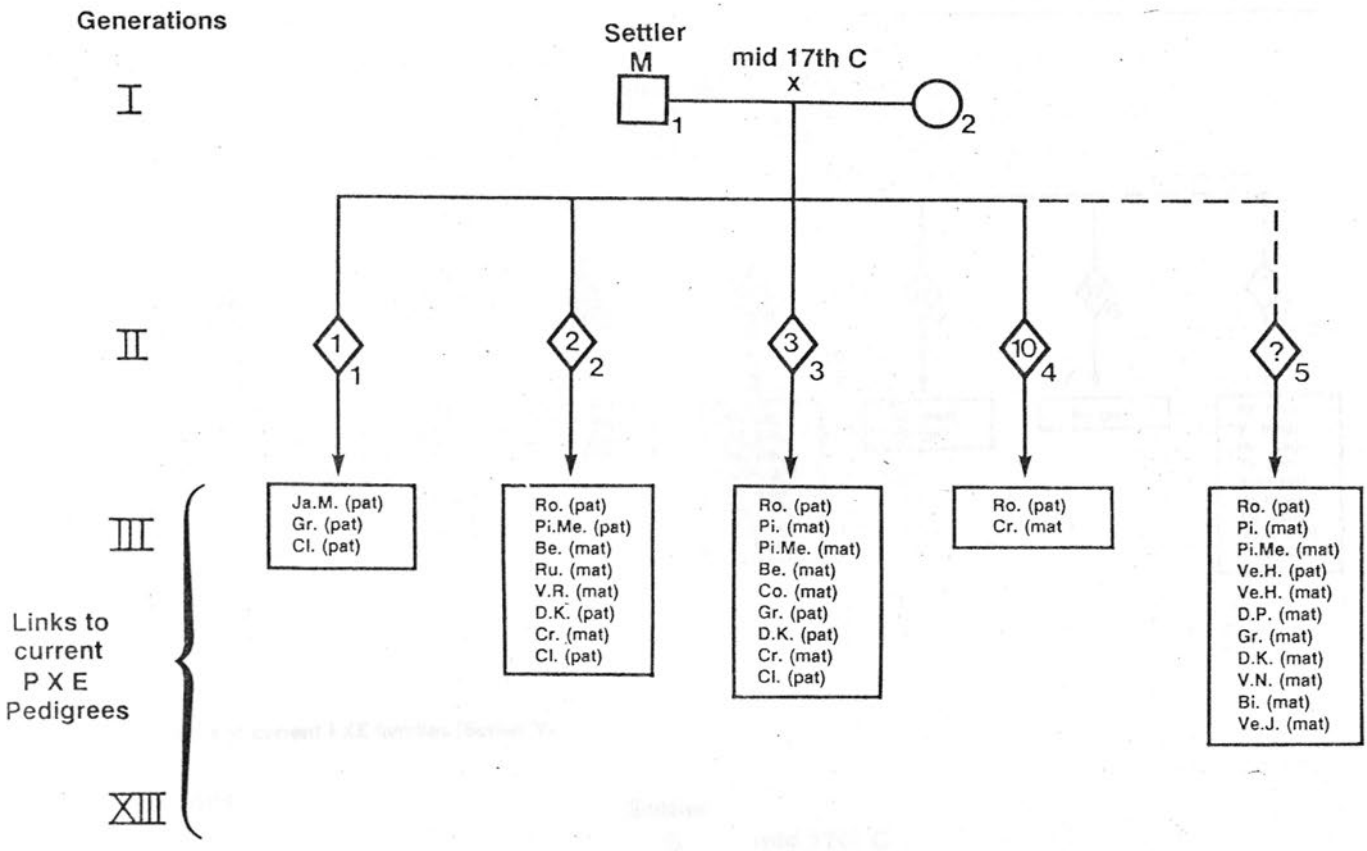


Fig. 1. Ancestral links to current PXE families (Settler M).

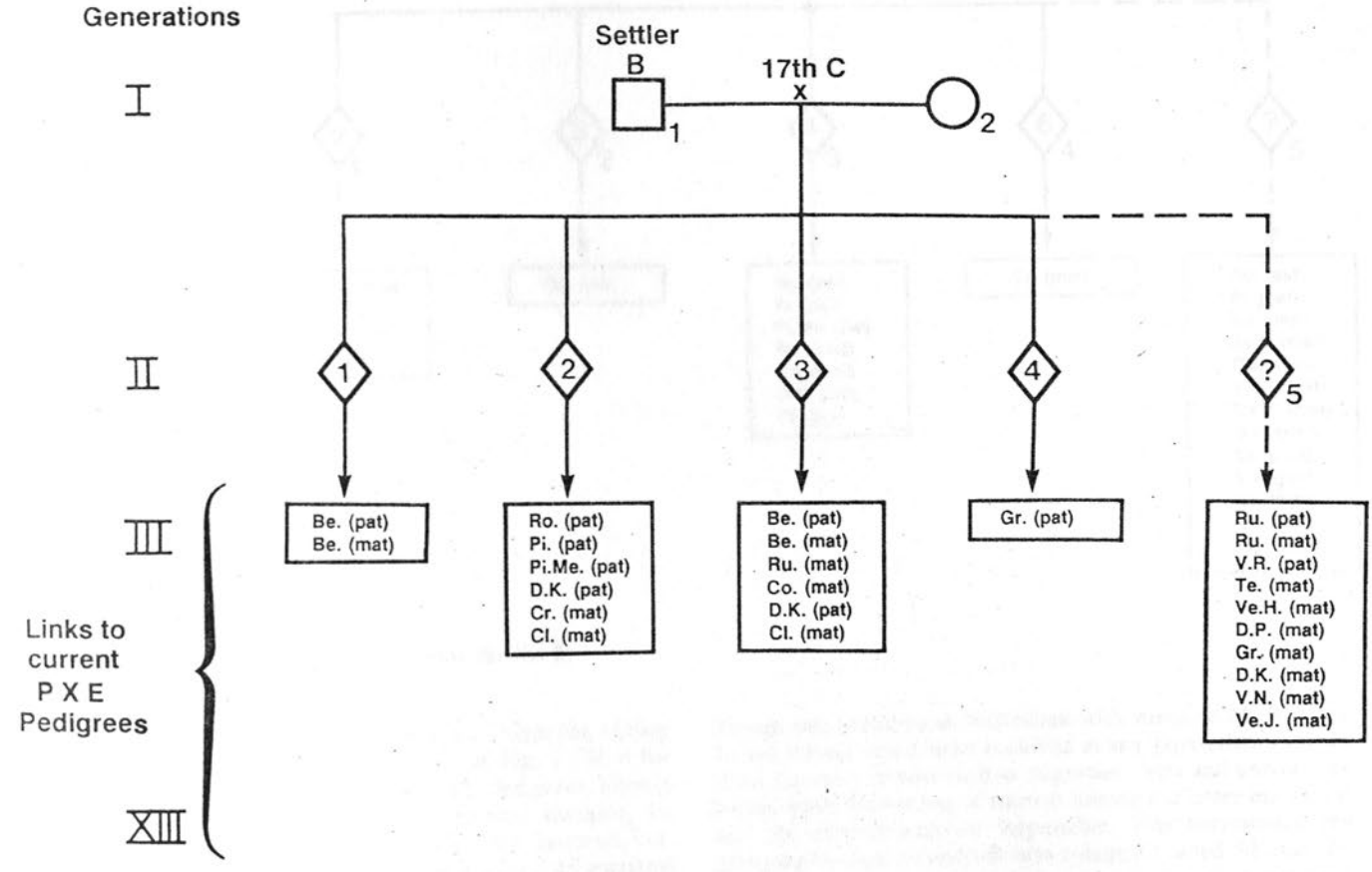


Fig. 2. Ancestral links to current PXE families (Settler B).

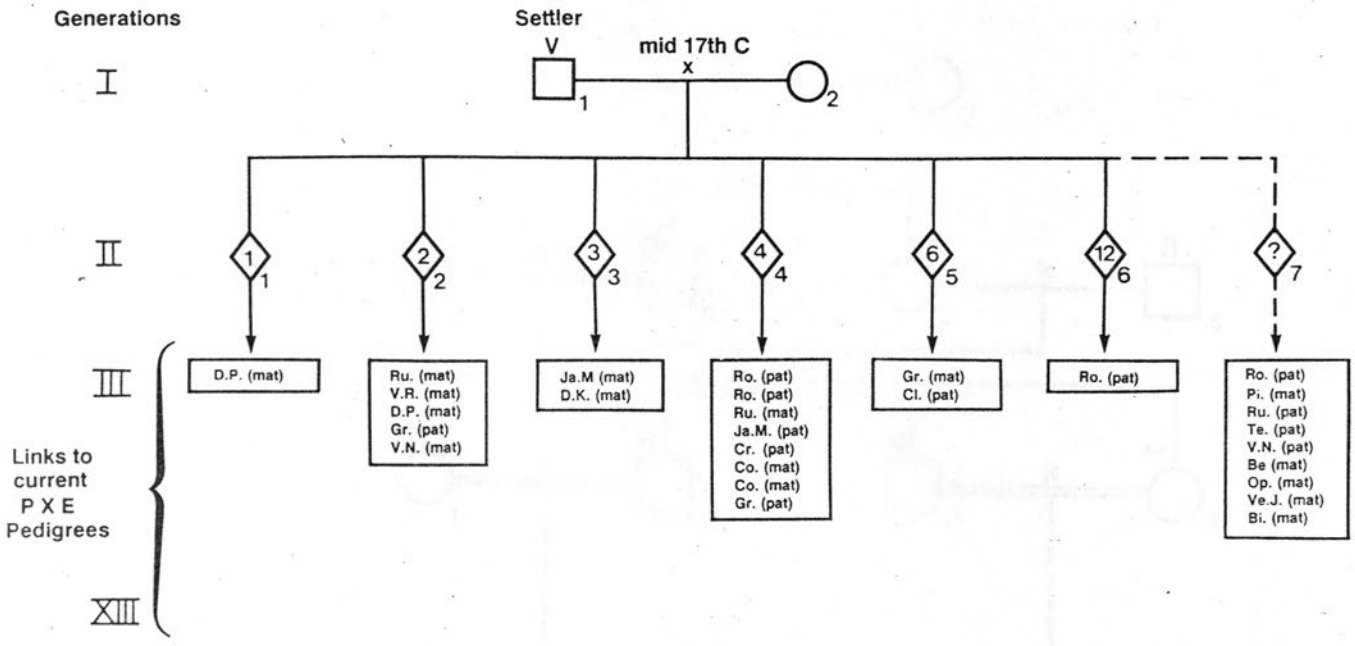


Fig. 3. Ancestral links to current PXE families (Settler V).

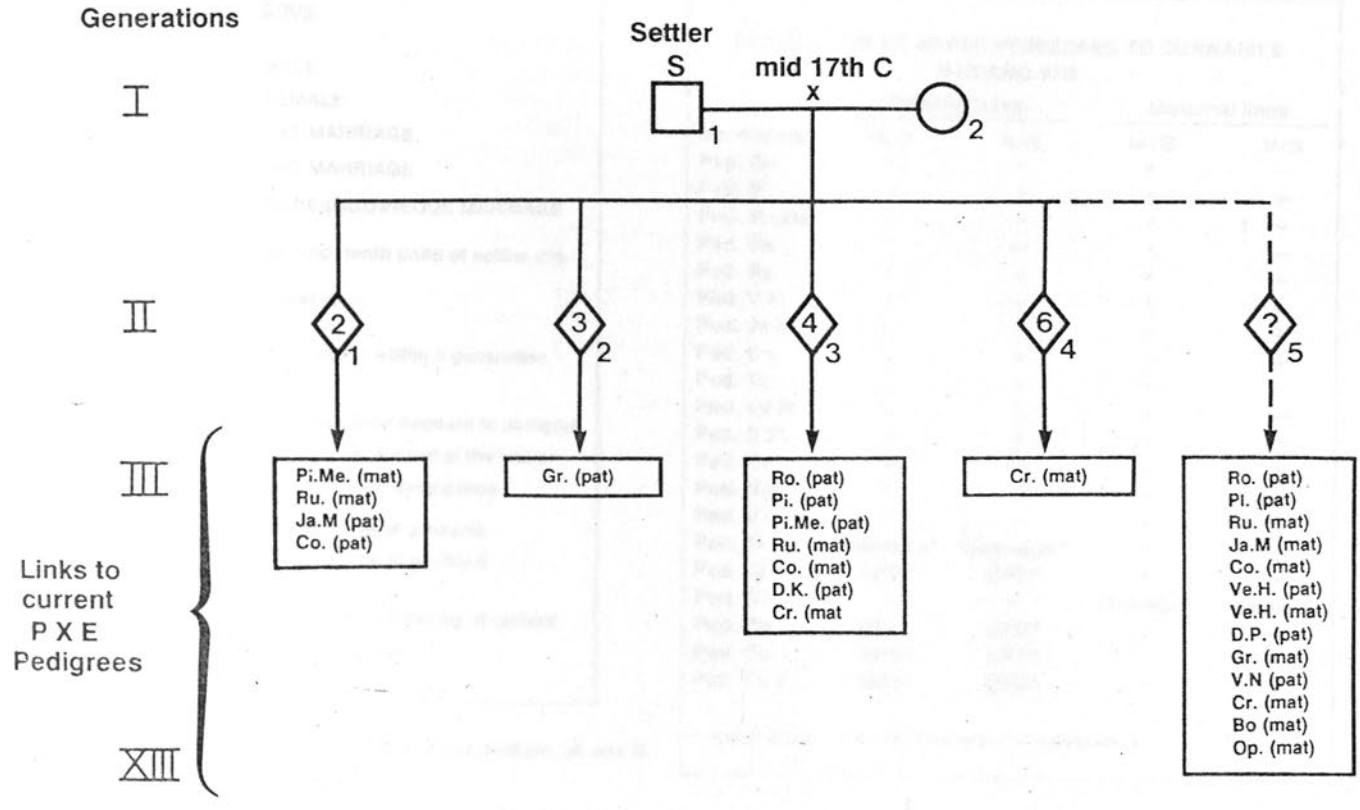


Fig. 4. Ancestral links to current PXE families (Settler S).

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 '5?' 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

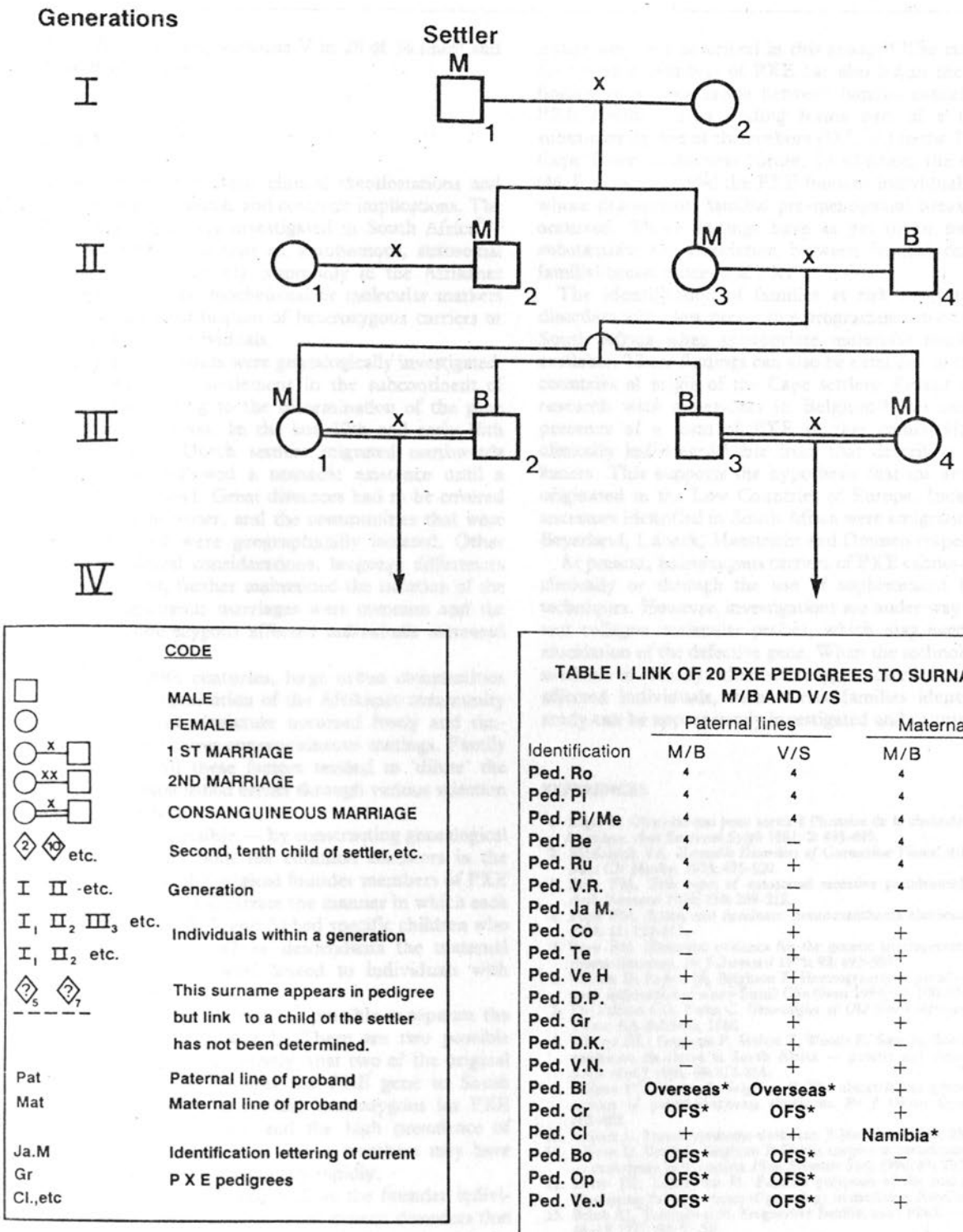


Fig. 5. Intermarriages in three generations of two settlers, M and B.

TABLE I. LINK OF 20 PXE PEDIGREES TO SURNAMES M/B AND V/S

	Paternal lines		Maternal lines	
Identification	M/B	V/S	M/B	V/S
Ped. Ro	⁴	⁴	⁴	–
Ped. Pi	⁴	⁴	⁴	+
Ped. Pi/Me	⁴	⁴	⁴	+
Ped. Be	⁴	–	⁴	–
Ped. Ru	⁴	+	⁴	+
Ped. V.R.	⁴	–	⁴	+
Ped. Ja M.	⁴	+	–	+
Ped. Co	–	+	+	+
Ped. Te	–	+	+	–
Ped. Ve H	+	+	+	–
Ped. D.P.	–	+	+	+
Ped. Gr	+	+	+	+
Ped. D.K.	+	+	–	+
Ped. V.N.	–	+	+	+
Ped. Bi	Overseas*	Overseas*	+	+
Ped. Cr	OFS*	OFS*	+	+
Ped. Cl	+	+	Namibia*	Namibia*
Ped. Bo	OFS*	OFS*	–	+
Ped. Op	OFS*	OFS*	–	+
Ped. Ve.J	OFS*	OFS*	+	+

+ = positive link; – = no link to ancestors; * = not traced.

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;

surname 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[8-11] 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, B, 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[12] and familial heart block.[13] Familial hypercholesterolaemia in a religious isolate has been described in this group.[14] 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[15] 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.

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Plastic Surgery in Pseudoxanthoma Elasticum: Experience in Nine Patients

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Nine women between the ages of 22 and 56 years underwent cosmetic surgery for correction of the severe cutaneous stigmata of pseudoxanthoma elasticum (PXE). The outcome was generally favorable, and follow-up for up to 15 years showed only moderate regression of the skin manifestations. No serious intraoperative or postoperative complications occurred, although tissue friability, poor wound healing, and keloid formation were noted in a minority of persons. An unexpected problem of extrusion of calcium particles through the surgical wound occurred in two individuals. This resulted in delayed healing and unsightly scars.

Pseudoxanthoma elasticum (PXE) is an uncommon heterogeneous heritable disorder of elastin.[1–3] Cutaneous, ocular, and vascular abnormalities become apparent during the second decade and may eventually cause serious disability and early demise.

The skin becomes progressively redundant and indurated, and the disfigurement may eventually prompt the patient to seek cosmetic surgery. A literature search revealed only three previous reports concerning the use of plastic surgery in pseudoxanthoma elasticum.[4–6] The purpose of this paper is to describe and illustrate the cardinal features of pseudoxanthoma elasticum in nine persons who underwent cosmetic surgery. The outcome, complications, and subsequent course of the disorder in these individuals is depicted and the implications for plastic surgery are discussed.

Patients and Methods

Nine women with pseudoxanthoma elasticum who had undergone cosmetic surgery were studied. These patients were derived from a total cohort of 82 individuals with biopsy-proven pseudoxanthoma elasticum, who formed part of a nationwide survey conducted throughout South Africa. Each affected individual was investigated by a multidisciplinary team comprising specialists in genetics, ophthalmology, cardiology, and dermatology. Data derived from these studies regarding nosology, incidence, genetics, gynecologic, and obstetric aspects have been published elsewhere.[3,7,8]

Since the cardiovascular system may be affected in individuals with pseudoxanthoma elasticum, preoperative evaluation was undertaken by a cardiologist, including full clinical assessment, chest radiograph, electrocardiogram, and ultrasonography of the heart.

In these nine women, data relating specifically to the dermatologic and cosmetic surgery aspects were collected. A detailed history regarding the time of onset, anatomic site, progression, and management of the skin lesions was obtained. The respective medical practitioners and plastic surgeons of each affected person were contacted, and information regarding the type of anesthetic, intraoperative and postoperative complications, surgical techniques employed, and outcome were documented. Preoperative and postoperative photographic slides were available in many instances, from which serial records of the skin lesions were compiled. The response of affected individuals to surgery and the further progression of the cutaneous features were recorded.

Results

The nine patients investigated each underwent skin biopsy to confirm the diagnosis of pseudo-

From the Research Unit for Inherited Skeletal Disorders, Department of Human Genetics, at the University of Cape Town Medical School and the Department of Plastic, Reconstructive, and Maxillofacial Surgery at the Groote Schuur Hospital. Received for publication June 29, 1987; revised January 23, 1989.

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TABLE I
Plastic Surgical Aspects of Nine Patients

Patient	Age at Time of Surgery	Surgical Procedure	Cosmetic Result	Follow-Up Period
1	31	Thigh lipectomy	Excellent	3 years; no regression
2	33	Excision of skin in cervical region	Keloid formation in scar	4 years; no change
3	22	Skin excision in cervical region	Good	1 year; no change
4	32	(1) Breast reduction (2) Excision of lax cervical skin	(1) Satisfactory (2) Good	4 years; mild skin redundancy in cervical region
5	(1) 25	(1) Lax cervical and axillary skin excised	(1) Good	(1) 15 years; mild deterioration of cervical skin; no regression in axillae
	(2) 33	(2) Abdominal lipectomy and excision of the lax abdominal skin	(2) Large, unsightly scars	(2) 7 years; no regression
6	23	Lax skin on inner thigh excised	Good	2 months; normal wound healing
7	56	Skin graft of varicose ulcer	Satisfactory initially	Subsequent below-knee amputation for peripheral gangrene
8	(1) 28	(1) Redundant skin of neck and stomach excised	(1) Good result	8 years; moderate keloid formation
	(2) 31	(2) Lax skin of axillae excised	(2) Fair result	5 years; no regression
9	32	Lax cervical skin excised	Good	6 months; no regression

xanthoma elasticum prior to surgery. Their ages ranged from 25 to 56 years. In all affected persons, the skin of the flexures was lax and had a yellowish, cobblestone-like appearance that was cosmetically unsightly. The surgical procedures, cosmetic result, length of follow-up, and current clinical status of the patients are summarized in Table I. Associated clinical findings relating to other body systems in the nine affected women are shown in Table II. Figures 1 to 8 portray some clinical manifestations and the effects of plastic surgery. The most common sites of surgery involved the posterior aspect of the neck (six patients), both axillae (two patients), abdomen (two patients), thighs (two patients), breasts (one patient), and lower limb (one patient). Four patients had undergone plastic surgery on more than one occasion, while in several two procedures had been performed (e.g., axillae and cervical area) during the same operation. General anesthesia was used in every instance, and no complications arose despite the potential cardiovascular hazards of premature arteriosclerosis that are prevalent in pseudoxanthoma elasticum.

Large portions of redundant skin were excised in the majority of patients, resulting in considerable cosmetic improvement. There were no reports from the surgeons of technical difficulties during the operation. Excessive cutaneous laxity and a "gritty" sensation (due to intradermal calcification) when excising affected skin was described in all patients. The other tissues appeared normal. Untoward hemorrhage did not occur, and specifically, no oozing from small calcified arteries was noted.

Wound healing was slower than usual in most

TABLE II
Other Clinical Manifestations of Pseudoxanthoma Elasticum in the Nine Patients

Clinical Manifestation	Number of Patients ($N = 9$)
Cardiovascular:	
Diminished peripheral pulses	8
Hypertension	3
Congestive cardiac failure	1
Mitral valve prolapse	1
Peripheral gangrene and limb amputation	1
Ophthalmologic:	
Angioid streaks	8
Retinal hemorrhages	3
Myopia	3
Gynecologic:	
Rectovesical prolapse	2

instances, and keloid formation was a problem in two patients. Extrusion of calcium particles through the healing scars was a feature in two other patients. Considerable delay in healing occurred in the abdominal wound of one patient, and sepsis caused unsightly scarring in another patient.

The postoperative follow-up period ranged from 2 months to 15 years, and although progression of the skin lesions was noted, it had been unnecessary to repeat any surgical procedure. By and large, all the patients were satisfied with the cosmetic improvement that had been attained.

DISCUSSION

Pseudoxanthoma elasticum is a heterogeneous disorder with protean clinical manifestations. There is still doubt as to the exact nature of the basic defect, although evidence suggests that the disorder is primarily an abiotrophy of elastin.[9] The main histologic changes involve the dermis, where calcium is deposited on aggregated elastin fibers. Although all body systems may be involved, elastin in the skin, eye, and arterial blood vessels is predominantly affected and becomes progressively fragmented and calcified.

The group of patients described in this paper generally exemplify the range of severity and potential distribution of the stigmata of pseudoxanthoma elasticum. However, they form a select subgroup by the very nature of their severe dermatologic sequelae, features that are usually found in the autosomal recessive type I pseudoxanthoma elasticum (Pope classification).[10] Mild ophthalmologic and cardiac involvements are the other clinical manifestations associated with this form of the disorder. This contrasts with the autosomal dominant type I[1] and Afrikaner varieties of pseudoxanthoma elasticum,[3] where eye and cardiovascular lesions tend to be more severe.

One of the few therapeutic options available to individuals with pseudoxanthoma elasticum is that of plastic surgery. However, surprisingly few reports on the subject have appeared in the literature. Pickrell et al.[4] were the first to demonstrate cosmetic benefit from surgery in a woman with pseudoxanthoma elasticum. Crikelair[5] documented a similarly treated individual, Kaplan and Henjyoji[6] described a further affected person, and McKusick[9] alluded to the use of cosmetic surgery in his monograph on connective-tissue disorders.

The main indication for cosmetic surgery is undoubtedly the correction of unsightly creases in the nasolabial folds and cervical region. Laxity of the facial skin produces a characteristic "hounddog" appearance, which is evident in Figure 1. Figures 2 and 3 portray a 32-year-old woman with cutaneous laxity before and following surgery. The cosmetic appearances achieved were consistently good in the six individuals who had surgery to the cervical region.

Other areas of significant disfigurement in patients with pseudoxanthoma elasticum are the axilla, abdomen, and thighs. The axillary repair procedure was successfully undertaken in two patients with good cosmetic results and little subsequent skin deterioration (Figs. 4 and 5). Extensive excision of redundant abdominal skin with lipectomy was performed in two persons (Fig. 6). In these individuals, the lax tissue formed an "apron" that was thought to be due to repeated stretching and disruption of elastin fibers as a consequence of multiple pregnancies



FIG. 1. *Patient 5.* The typical "hounddog" features of pseudoxanthoma elasticum are evident.

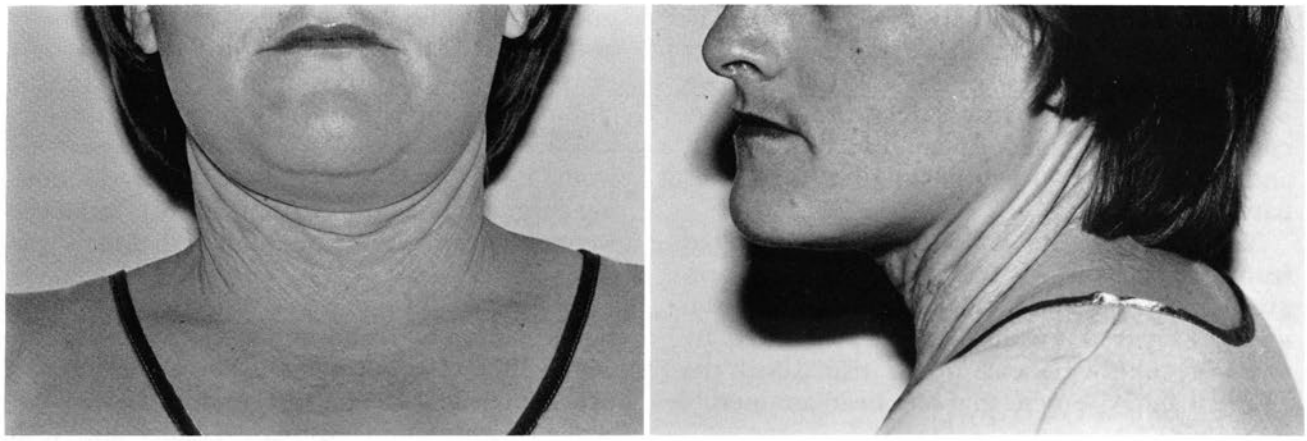


FIG. 2. Patient 4, aged 32 years, demonstrating cutaneous redundancy in the cervical region.



FIG. 3. Patient 4 following cosmetic surgery.

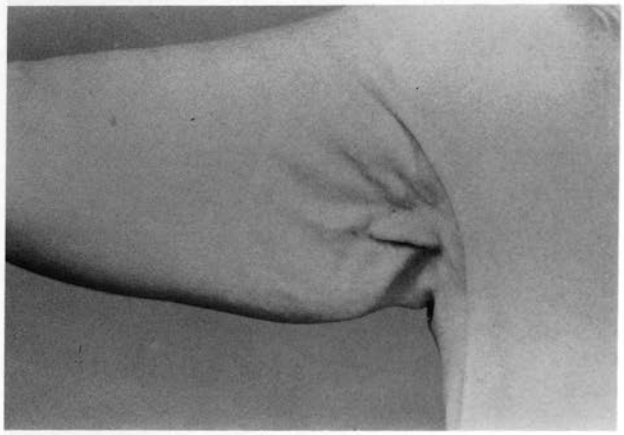


FIG. 4. *Patient 8.* Cutaneous laxity of the axilla is evident.

and obesity. Cutaneous laxity in the thigh areas was corrected in two severely affected women without complication. Breast reduction was successfully undertaken in one person, but was complicated by mild keloid formation (Fig. 7).

Spontaneous hemorrhage is reported to be a major sequela of pseudoxanthoma elasticum, particularly from the gastrointestinal tract[9,11,13] and into the subarachnoid space.[13] Two instances of cutaneous bleeding also have been described.[14,15] The hemorrhagic tendency is entirely due to changes in the blood vessels, and there is no disturbance of the clotting mechanism. Hemorrhage at operation was not a problem in any of the nine persons described in this report. This appears to hold true even in instances of major surgery, as demonstrated in the patient described by McKusick[9] with atherosclerotic occlusion at the aortic bifurcation due to pseudoxanthoma elasticum, who underwent successful homograft operation.

Tissue fragility due to calcification and slow healing are important complications of patients with pseudoxanthoma elasticum who undergo surgery. Extrusion of calcium in the form of spicules or granules through surgical scars was noted in two individuals. This unusual manifestation has been previously reported in one instance.[6] Both patients in this study had very severe skin manifestations of pseudoxanthoma

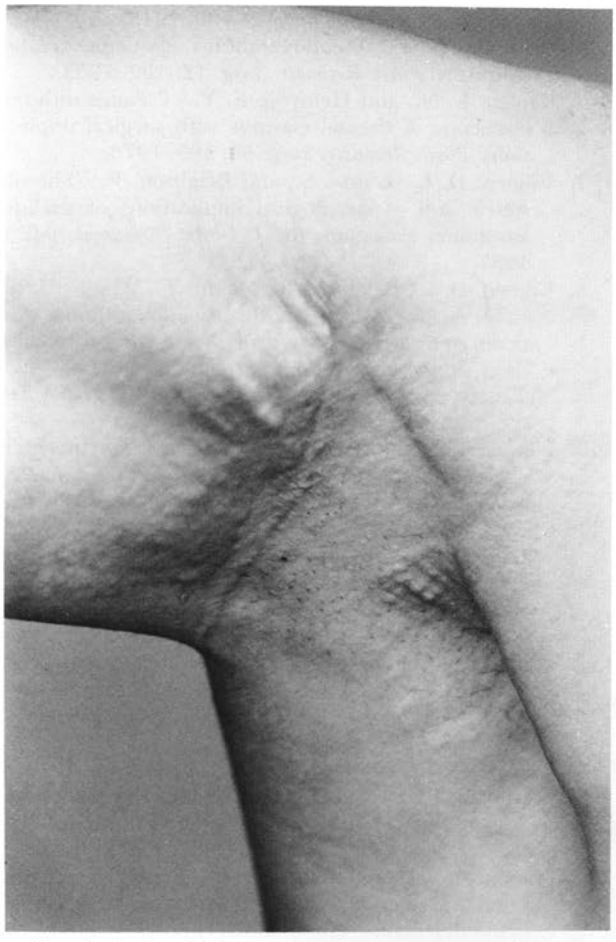


FIG. 5. *Patient 8.* Appearance 1 year postoperatively.



FIG. 6. *Patient 5.* Lipectomy and excision of lax abdominal skin were performed 7 years previously.

elasticum, and small areas of wound dehiscence, delayed healing, and unsightly scars occurred where calcium was extruded. Mild keloid formation was a feature in two persons following surgery, but the finding may be coincidental and not related to the underlying disorder.

Postoperative deterioration of the skin was not

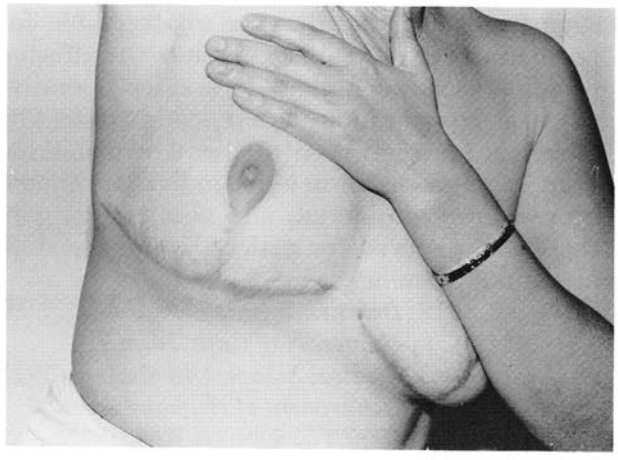


FIG. 7. Patient 4 following breast reduction surgery. The scars remained indurated 4 years later.

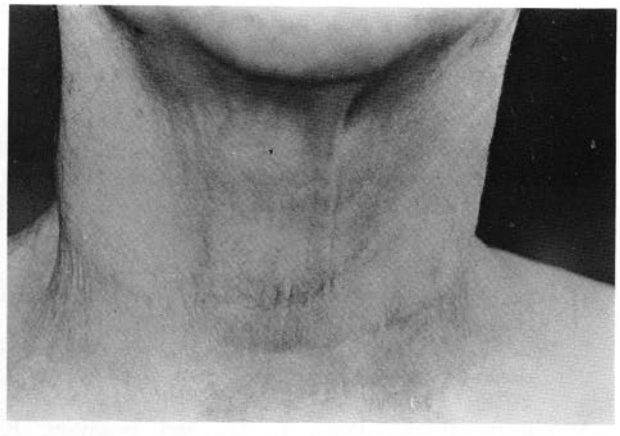


FIG. 8. Patient 5 demonstrating widening of the cervical scar 15 years postoperatively.

a prominent feature in our patients, and none required repeated cosmetic surgery. However, in several women, progressive widening of surgical scars occurred with time, suggesting that a process of ongoing degeneration of elastin was present (Fig. 8). Scars due to trauma and other surgical procedures reacted similarly. Individuals with more severe dermal manifestations of pseudoxanthoma elasticum and those who were obese tended to fare worse in this respect.

Five of the patients who underwent cosmetic surgery were highly satisfied with the outcome, but four persons expected more improvement and admitted disappointment in their results. Those with a reserved response had severe cutaneous stigmata of pseudoxanthoma elasticum, and two of these individuals required abdominal lipectomy as well as skin excision.

Plastic surgery in individuals with pseudoxanthoma elasticum is a highly effective therapeutic option that is warranted where the cutaneous

stigmata of the disorder are unacceptable for psychosocial reasons. The benefit to the affected person is usually considerable, and few operative risks or complications are encountered. The tendency for regression of the skin manifestations in pregnancy or in obese individuals should be carefully considered, and cosmetic surgery should be reserved for patients who have completed their families.

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SECTION B

PAPERS DELIVERED AT LOCAL AND INTERNATIONAL CONGRESSES

1. Paediatric Dermatology Congress (1985)
2. Plastic Surgery Congress (1985)
3. Rheumatology Congress (1986)
4. World Human Genetics Congress (1986)
5. March of Dimes Birth Defects Congress (1988)
6. Human Genetics Congress (1989)

PAPERS RELATED TO PXE DELIVERED AT

LOCAL AND INTERNATIONAL CONGRESSES

1) Paediatric Dermatology Congress: March 1985; Cape Town.
"Pseudoxanthoma elasticum: a potentially lethal genodermatosis."
Viljoen DL.

2) Congress of the Association of Plastic and Reconstructive Surgeons of Southern Africa: September 1985; Cape Town.
"Plastic Surgery in pseudoxanthoma elasticum."
Viljoen DL

3) Congress of the Rheumatism and Arthritis Association: March 1986; Johannesburg.
"An unusual complication of penicillamine therapy".
Viljoen DL

4) 7th International Congress of Human Genetics: September 1986; Berlin
"Heterogeneity of Pseudoxanthoma elasticum".
Viljoen DL

5) March of Dimes Birth Defects Congress: July 1988; Baltimore.
"Heterogeneity of Pseudoxanthoma elasticum in 80 Southern African patients".
Viljoen DL

6) Human Genetics Society of South Africa Congress: July/August 1989; Durban.
"Founder Effect in twenty Afrikaner kindreds with Pseudoxanthoma elasticum".
Torrington M, Viljoen DL

SECTION C

RESEARCH PROTOCOLS

1. **General Proforma for Patients**
2. **Obstetric and Gynaecological Protocol**

PROFORMA : PSEUDOXANTHOMA ELASTICUM

NAME:

DATE OF BIRTH:

ADDRESS:

TELEPHONE: WORK:

HOME:

OCCUPATION:

REFERING DOCTOR AND ADDRESS:

PEDIGREE:

HISTORY

A) DERMATOLOGY

AGE OF ONSET:

ANATOMICAL SITE:

PROGRESSION:

DISTRIBUTION OF LESIONS WITH AGEING:

SCARRING:

OTHER:

B) CARDIOLOGY

HYPERTENSION?

PERIPHERAL VASCULAR DISEASE SYMPTOMS (CLAUDICATION):

MURMURS:

ANGINA/I.H.D.:

VISITS TO A PHYSICIAN:

C) OPHTHALMOLOGY

VISUAL DETERIORATION:

RETINAL CHANGES:

RETINAL HAEMORRHAGE:

VISITS TO AN OPHTHALMOLOGIST:

OTHER:

D) BLEEDING DIATHESIS

EPISTAXIS:

GASTROINTESTINAL HAEMORRHAGE:

MENORRHAGIA:

TRAUMATIC BLEEDING EPISODES:

E) OPERATIONS

F) GENERAL MEDICAL HISTORY

EXAMINATION:

AGE/SEX: WEIGHT:

HEIGHT:

GENERAL:

DERMATOLOGICAL FINDINGS:

CARDIAC EXAMINATION: H/RATE: BP

PULSES:

OPHTHALMOLOGICAL ASPECTS:

OTHER SYSTEMS:

DIAGNOSIS:

INVESTIGATIONS

1) HISTOPATHOLOGY:

LIGHT MICROSCOPY:

ELECTRON MICROSCOPE:

2) CARDIOLOGY: CXR:

ECG:

ECHO:

3) OPHTHALMOLOGY: EXAMINATION:

CINEANGIOGRAPHY:

4) RADIOLOGY:

CT SCAN:

M.R.I.:

5) LINKAGE STUDIES:

6) PHOTOGRAPHS:

7) OTHER:

OBSTETRIC & GYNAECOLOGICAL PROTOCOL

FORM OF PXE: .....

GYNAECOLOGICAL PROTOCOL

AGE OF MENARCHE: .....

AGE OF MENOPAUSE: .....

MENSTRUAL HISTORY:
- Duration .....
- Cycle .....
- Dysmenorrhoea .....
- Menorrhagia .....
- Abnormal bleeding .....

FORM OF CONTRACEPTION:
- Contraceptive pill .....
- Type of pill .....
- I.U.D. .....
- Tubal ligation .....
- Other .....

OPERATIVE PROCEDURES (DATE):
- D & C .....
- Salpingectomy & oophorectomy .....
- Hysterectomy .....
- Repair of prolapse .....
- Other .....

OBSTETRIC PROTOCOL

GENERAL HISTORY
- Number of pregnancies .....
- Number of live infants .....
- Number of miscarriages .....
- Age (in weeks) at time of miscarriage .....
- Cause of miscarriage (if known) .....
- .....

PREGNANCY HISTORY

PREGNANCY NO: .....

NAME OF INFANT: .....

DATE OF BIRTH: .....

SEX: .....

WEIGHT OF PATIENT: Prior to pregnancy .....

1st trimester .....

2nd trimester .....

3rd trimester .....

INFECTION DURING PREGNANCY: .....

ILLNESSES DURING PREGNANCY: Hypertension (only) .....

Pre-eclampsia .....

Diabetes .....

Other .....

DRUGS OR TREATMENT DURING PREGNANCY: .....

VAGINAL BLEEDING: Stage in pregnancy (weeks) .....

Duration .....

Severity .....

Cause .....

Treatment .....

.....

.....

ABDOMINAL PAIN (PLEASE SPECIFY): .....

.....

INFLUENCE OF PREGNANCY ON EXISTING LESIONS:

Skin .....

Eyes .....

Other .....

PRE-TERM LABOUR (WEEKS) & MANAGEMENT: .....

DELIVERY

ONSET OF LABOUR: How many weeks pregnant? .....

Length of labour (hours) .....

DURATION OF SECOND STAGE: (i.e. time of bearing down) .....

BLEEDING POST-DELIVERY: Normal .....

IF ABNORMAL: Estimate loss and treatment given

EPISIOTOMY: .....

OTHER COMPLICATIONS OF DELIVERY: .....

BABY

BIRTH WEIGHT: .....

APGAR SCORE (IF KNOWN): .....

RESUSCITATION REQUIRED: (PLEASE DETAIL) .....

OTHER COMMENTS: .....